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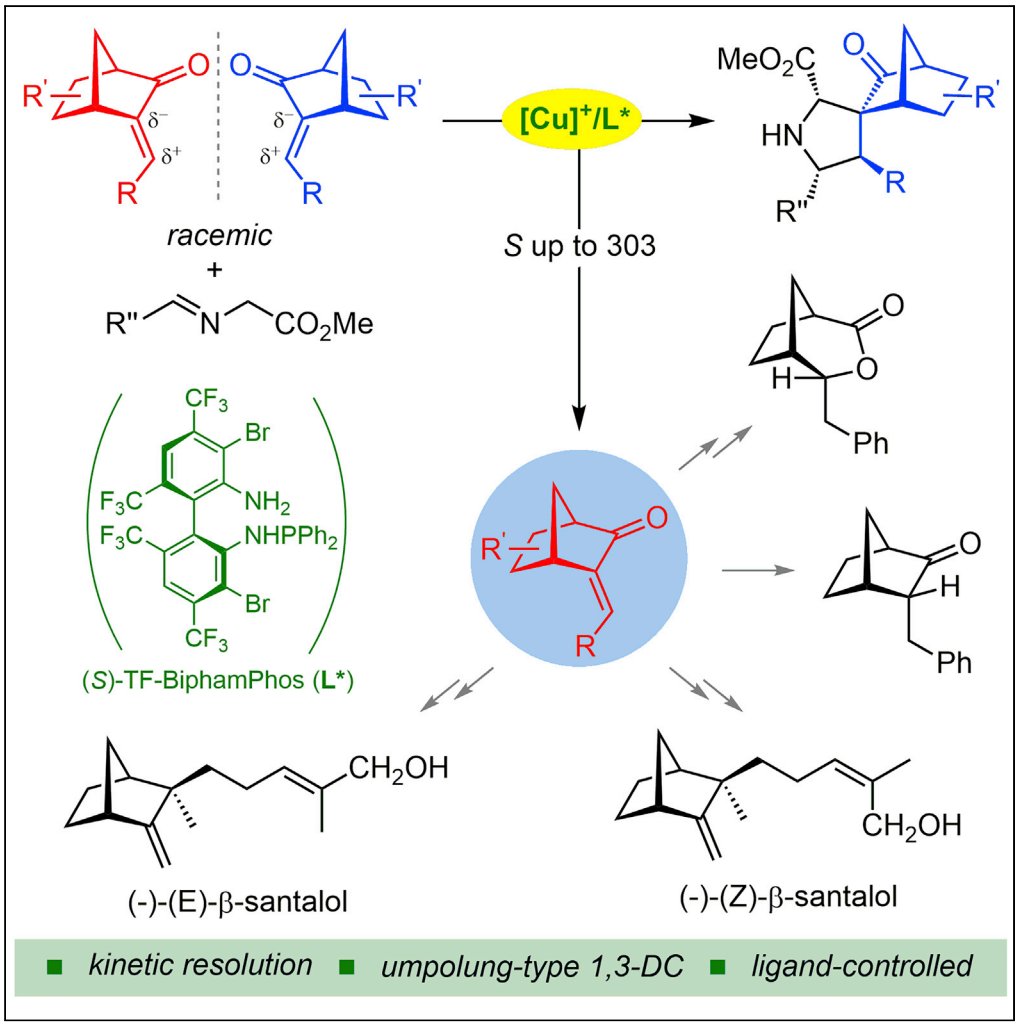

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HIGHLIGHTS

Kinetic resolution of racemic alkylidene norcamphors

Spiro architectures incorporating norbornane and pyrrolidine scaffolds

Unique ligand-enabled umpolung-type 1,3-dipolar cycloaddition

DATA AND SOFTWARE AVAILABILITY

www.ccdc.cam.ac.uk/getstructures

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Kinetic Resolution of Alkylidene Norcamphors *via* a Ligand-Controlled Umpolung-Type 1,3-Dipolar Cycloaddition

Chong Shen,[1,2,5] Yuhong Yang,[4,3,5] Liang Wei,[1] Wu-Wei Dong,[1] Lung Wa Chung,[3,*] and Chun-Jiang Wang[1,2,6,*]

SUMMARY

Development of a general catalytic and highly efficient method utilizing readily available precursors for the regio- and stereoselective construction of bioactive natural-product-inspired spiro architectures remains a formidable challenge in chemical research. Transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides produces numerous N-heterocycles, but reaction control with the regioselectivity opposite to the conventional fashion has rarely been demonstrated. Herein, we report a unique ligand-controlled Cu(I)-catalyzed umpolung-type 1,3-dipolar cycloaddition of azomethine ylide to realize efficient kinetic resolution of racemic alkylidene norcamphors with the concomitant construction of previously inaccessible spiro N-heterocycles with high levels of regio- and stereoselectivity. The success of this methodology relies on the strategy of kinetic resolution, and the serendipitous discovery of a unique ligand-enabled regiospecific cycloaddition, which not only provides evidence for the existence of the minor zwitterionic resonance form in metallated azomethine ylide but also diversifies the existing chemistry of azomethine ylide-involved 1,3-dipolar cycloadditions with rare polarity inversion.

INTRODUCTION

1,3-Dipolar cycloaddition reaction is one of the fundamental processes in organic chemistry (Huisgen, 1963; Padwa, 1984; Padwa and Pearson, 2003). In particular, catalytic asymmetric 1,3-dipolar cycloaddition of *in situ*-formed metallated azomethine ylides (dipoles) from readily available imino esters (Figure 1A) offers the most powerful and diversity-oriented synthesis (Schreiber, 2000) (DOS) for the convergent construction of numerous enantioenriched five- or six-membered nitrogen-containing heterocycles in stereocontrolled fashion (Hashimoto and Maruoka, 2015; Adrio and Carretero, 2011, 2014; Stanley and Sibi, 2008; Álvarez-Corral et al., 2008; Nájera and Sansano, 2005; Pellissier, 2007; Pandey et al., 2006; Coldham and Hufton, 2005), which are very important pharmaceuticals, natural alkaloids, and building blocks in organic synthesis. Metallated azomethine ylide has four π electrons spread over a C-N-C unit, which can be presented by the two most common zwitterionic resonance forms as shown in Figure 1B: the coordinated central N atom is positively charged, and the negative charge is distributed over the two adjacent carbon atoms (Pandey et al., 2006; Coldham and Hufton, 2005). In general, the major zwitterionic resonance form **I** makes greater contribution to the resonance hybrid structure because the negative charge of the intermediate is delocalized by the neighboring electron-withdrawing ester group, which accounts for the observed regioselectivity of the well-explored 1,3-dipolar cycloaddition controlled by the highest occupied molecular orbital (HOMO) of the azomethine ylide interacting with the lowest unoccupied molecular orbital of the electron-deficient dipolarophiles (Pandey et al., 2006; Coldham and Hufton, 2005; Houk, 1975; Houk et al., 1973). Although the umpolung-type 1,3-dipolar cycloaddition related with the minor zwitterionic resonance form **II** would give rise to the opposite regioselectivity and thus greatly enhance the diversity of product accessible from azomethine ylide, such polarity inversion reactivity remains elusive so far and was sporadically reported in limited examples (Barr et al., 1989; Kanemasa et al., 1990; Chen et al., 2009; Xu et al., 2018; Feng et al., 2018) or the intramolecular cycloaddition caused by conformational ring constrain (Stohler et al., 2005).

Kinetic resolution (Kagan and Fiaud, 1988; Vedejs and Jure, 2005; Pellissier, 2011) is one of the commonly used strategies to obtain the optically active compounds from racemic starting materials, which was recently also employed in cycloaddition reactions (Cardona et al., 2001; Yu et al., 2010; Takayama et al., 2013; Xu et al., 2016; Yuan et al., 2018). As part of our ongoing research interest in asymmetric 1,3-dipolar cycloaddition (Wang et al., 2008, 2012; He et al., 2013; Li et al., 2014), we considered employing kinetic

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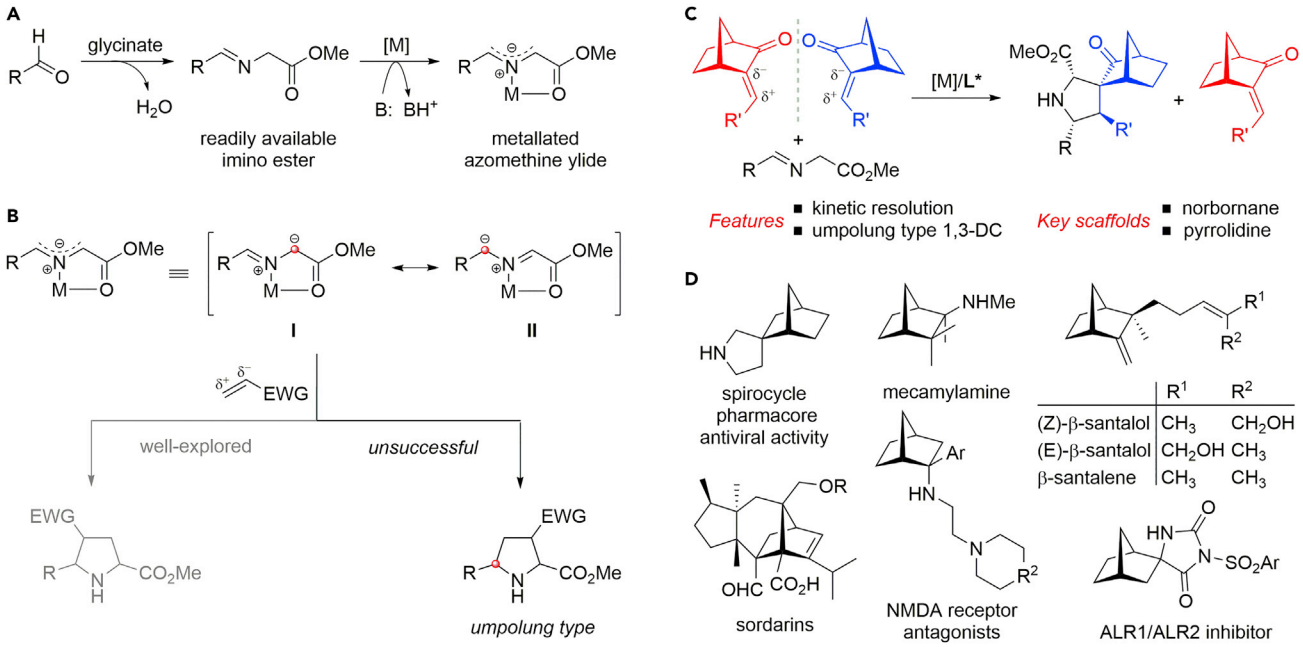


Figure 1. Rational Design and Serendipity

(A) *In situ*-formed metallated azomethine ylide from readily available imino ester (precursor).

(B) The two most common zwitterionic resonance forms (**I** and **II**) of metallated azomethine ylide and the 1,3-dipolar cycloaddition with different regioselectivities.

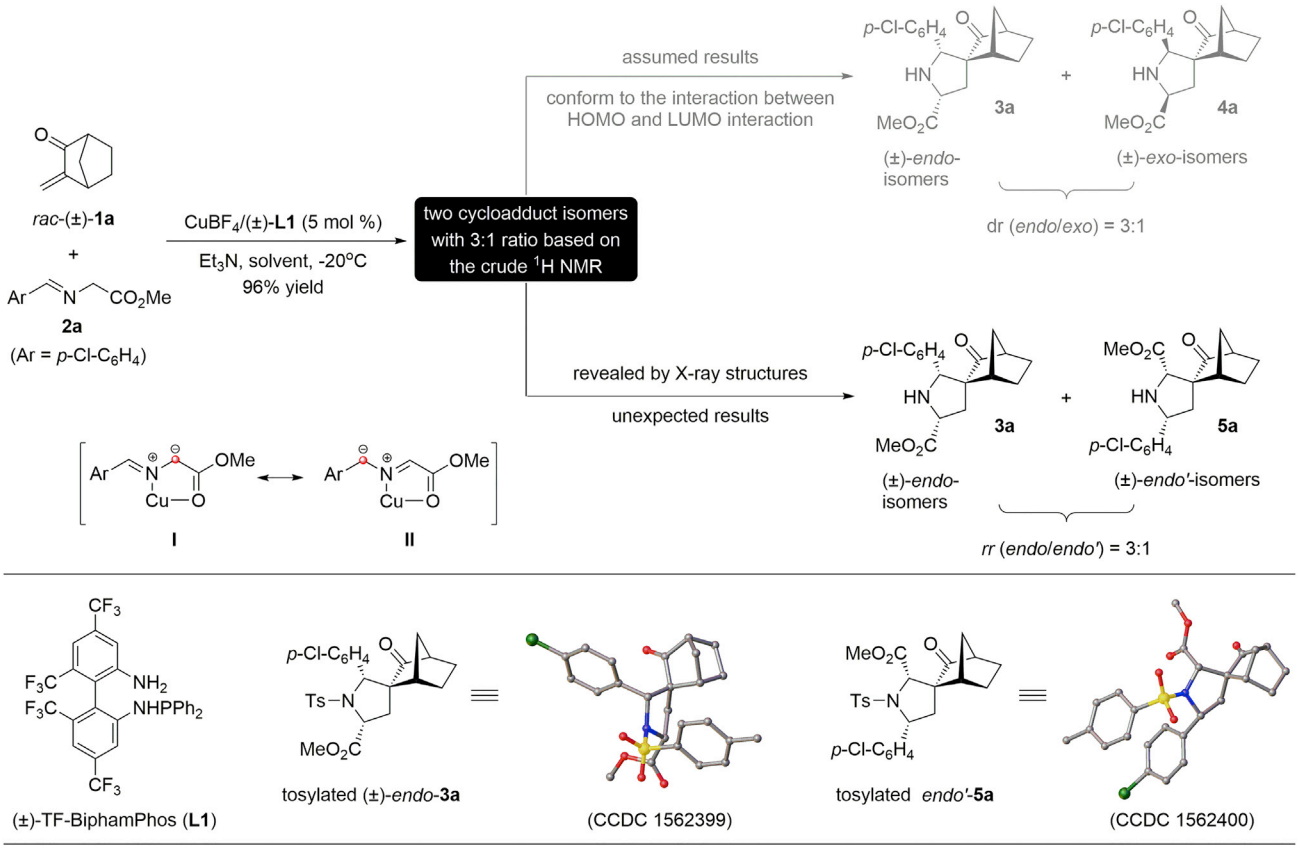
(C) Kinetic resolution strategy in catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide to efficiently construct the complex natural-product-inspired architectures incorporating norbornane and pyrrolidine scaffolds concurrently with a serendipitous polarity inversion of azomethine ylide.

(D) Selected bioactive natural products and synthetic drugs or drug candidates containing bicyclic norbornane scaffold.

resolution strategy to develop a new cycloaddition process with readily accessible racemic alkylidene norcamphors as dipolarophiles (Figure 1C). This methodology would not only provide a simple and efficient access to synthetically important chiral building block alkylidene norcamphors but also efficiently assemble complex natural-product-inspired polycyclic spiro architectures incorporating norbornane (bicycle[2.2.1] heptane) and pyrrolidine scaffolds, both of which are the core structures embedded ubiquitously in natural products and pharmaceuticals, and therefore much attention has been paid to synthetic and biological studies (Reinhard et al., 1992; Suchocki et al., 1991; Demole et al., 1976; Odds, 2001; Chen and Lipton, 2006; Iqbal et al., 2013) (Figure 1D). However, several significant challenges are associated with this design and differentiate it from the majority of azomethine ylide-involved cycloadditions described previously including (1) the lower reactivity of alkylidene norcamphors with the inherent convex skeleton as dipolarophiles because both the upper and lower sides of C=C bond are sterically hindered from a facial recognition standpoint, which would impede the approach of the dipole, and (2) a formidably challenging spiro quaternary stereogenic carbon center (Christoffers and Baro, 2005) is generated on the sterically congested pyrrolidines ring (having up to five substituents) with stereoselectivity control. The paucity of synthetic methodologies available in the literature for the efficient construction of enantioenriched alkylidene norcamphors and spiro[norbornane-pyrrolidines] encouraged us to launch this project. Herein, we report for the first time the highly efficient kinetic resolution of readily available racemic alkylidene norcamphors via Cu(I)-catalyzed 1,3-dipolar cycloaddition with concomitant construction of previously inaccessible spiroheterocycles. Notably, this rationally designed 1,3-dipolar cycloaddition is endowed with the serendipity of realizing the potential polarity inversion of metallated azomethine ylide (Figure 1C), which provides direct and convincing experimental evidence for the existence of the minor zwitterionic resonance form in metallated azomethine ylide.

RESULTS AND DISCUSSION

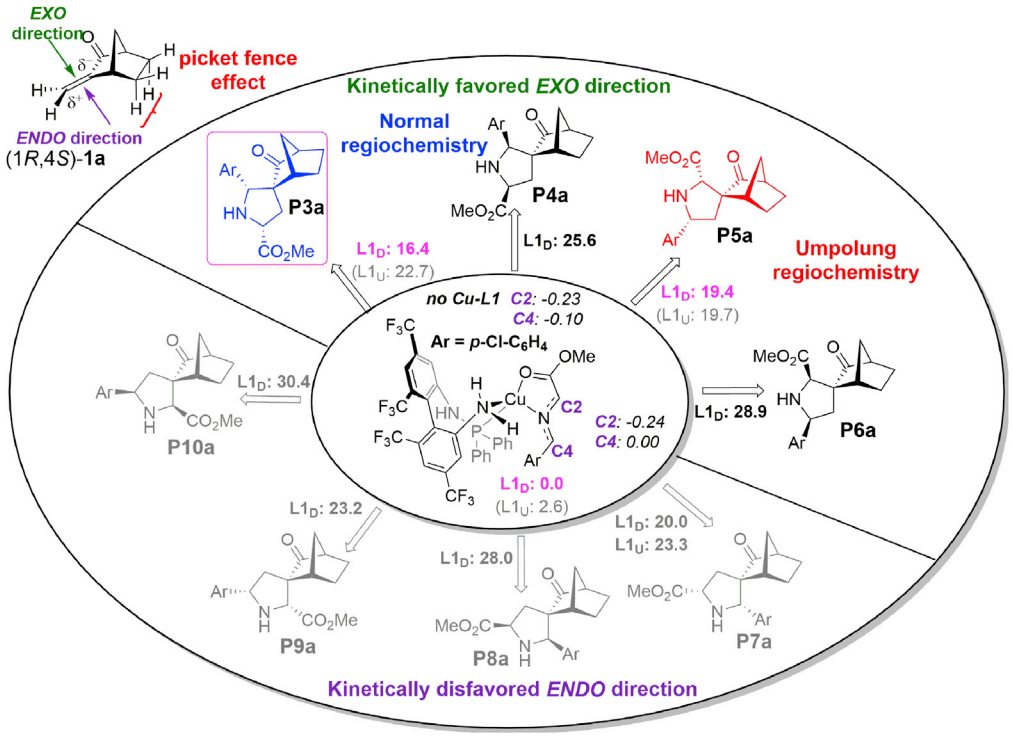
To test the feasibility of racemic alkylidene norcamphors as dipolarophiles, in preliminary experiments we examined the reaction of commercially available 3-methylene norcamphor **1a** and *N*-(4-chlorobenzylidene)-glycine methyl ester **2a** with Et_3N as the base in the presence of Cu(I)/*rac*-(±)-TF-BiphamPhos



Scheme 1. Initial Test Leading to the Discovery of This Ligand-Controlled Umpolung-Type 1,3-Dipolar Cycloaddition

Initial test on the regio-/diastereoselective control of the 1,3-dipolar cycloaddition of azomethine ylide *in situ*-generated from imino ester **2a** with 3-methylene-2-norbornanone **1a** catalyzed by $CuBF_4$/(±)-TF-BiphamPhos (**L1**). The crystal of tosylated *endo'*-**5a** for X-ray analysis was obtained from the corresponding enantioenriched cycloadduct with (*S*)-TF-BiphamPhos **L1** as the chiral ligand.

complex (Wang et al., 2008) as the catalyst (Scheme 1). In view of steric hindrance, terminal alkene moiety connected to the bulky norcamphor scaffold is believed to possess higher reactivity and therefore facilitate the potential cycloaddition process. Racemic TF-BiphamPhos (**L1**) was employed as the ligand to simplify the stereochemical analysis of the cycloadduct because only diastereoselectivity was considered in this case. TF-BiphamPhos, as one of the privileged ligands in 1,3-dipolar cycloaddition (Adrio and Carretero, 2014), exhibited exclusive *endo*-selectivity for a variety of pyrrolidine synthesis, which is the foundation of the hypothetic kinetic resolution of racemic alkylidene norcamphors. Initial experimental results were far from encouraging; full conversions of methylene norcamphor were observed at 5 mol % catalyst loading, but resulted in cycloadducts as two inseparable isomers in 3:1 ratio on silica gel column according to crude ^{1}H nuclear magnetic resonance, which at first was regarded as the diastereoselective ratio of the *endo*-adduct to the *exo*-adduct. This assumed diastereoselectivity is contradictable with the perfect *endo*-selectivity control exhibited by TF-BiphamPhos in our previous work. Therefore some verification experiments must be carried out to provide the irrefutable evidence on the stereochemical configurations of the two original isomers. Subsequent N-tosylation of the cycloadducts successfully converted the two isomers into separable and crystallizable compounds. To our surprise, X-ray diffraction analysis of the tosylated **3a** and **5a** revealed that both the cycloadducts are regioisomers rather than the assumed diastereomers (see Supplemental Information for the details). It is generally believed that the approach of the azomethine ylide to the methylene norcamphor would occur specifically from the *EXO*-direction due to the "picket fence effect" exhibited by norbornanone (Mangan et al., 2016; Corey et al., 1962) (Scheme 2). The major isomer was formed through the *endo*-selective 1,3-dipolar cycloaddition related with the major zwitterionic resonance form **I**, but the minor one with the opposite regioselectivity was formed via the umpolung-type *endo*-selective 1,3-dipolar cycloaddition related with the minor zwitterionic resonance form **II** (Scheme 1). Notably, this serendipitous finding regarding the minor isomer **5a** offers direct experimental

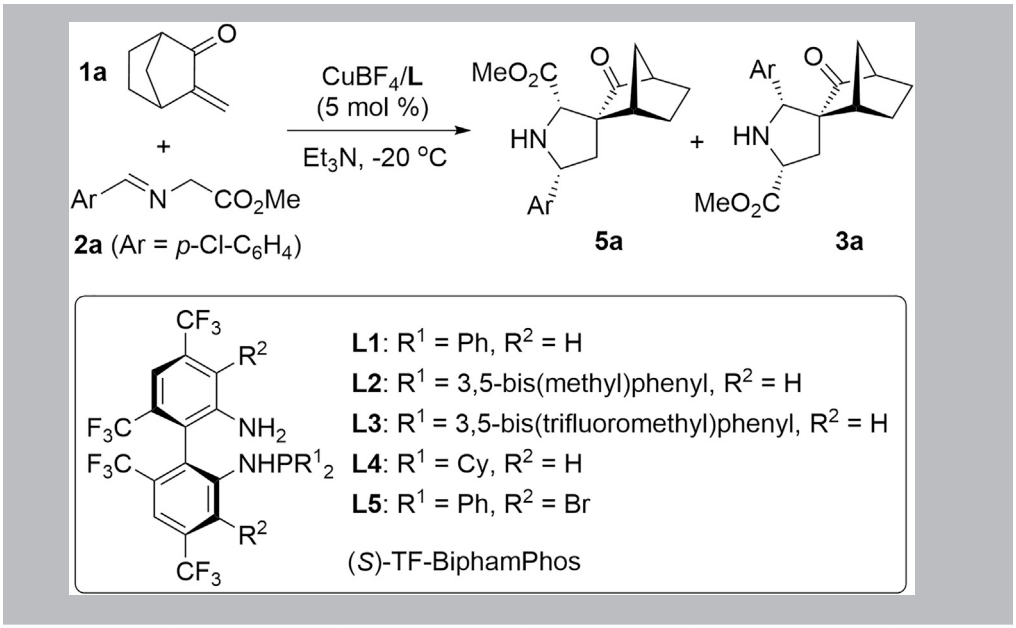


Scheme 2. Computed Overall Free-Energy Barrier of the Formation of Several Products from the Reaction of (1R,4S)-1a and 2a Catalyzed by Cu(I)-LI in Dichloromethane (DCM) Solution by the Polarizable Continuum Model (PCM)-B3LYP//B3LYP Method

The two coordination modes of Ph in the Cu-azomethine ylides ($L1_D$ and $L1_U$) were considered for the most important intermediates (D: Ar downward; U: Ar upward). The computed NBO charge for the two reacting carbon atoms is also given in an italic form.

evidence on the two zwitterionic resonance structures of a metallated azomethine ylide. Inspired by these promising results, we further investigated the potential regioselectivity and enantioselectivity control to realize the asymmetric variant of this umpolung-type cycloaddition with a series of chiral TF-BiphamPhos ligands, and the results are tabulated in Table 1. With Cu(I)/(*S*)-**L1** complex as the catalyst, cycloadducts (**3a** + **5a**) were separated in 96% yield with moderate regioselective ratio (rr) (3:1), and 73% enantiomeric excess (ee) for **3a** and 20% ee for **5a** (Table 1, entry 1). When the phenyl group on the phosphorus atom of ligand **L1** was replaced by bulky electron-donating 3,5-bis(methyl)phenyl (**L2**), or electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group (**L3**), however, the conventional cycloadduct *endo*-**3a** was formed predominantly in high yields with good to excellent *rr* and good ee (Table 1, entries 2 and 3). Chiral ligand **L4** containing cyclohexyl groups on the phosphorus atom also displayed normal regioselectivity control with a detrimental effect on the enantioselectivity. To our delight, further ligand screening revealed that ligand **L5** incorporating two bromine atoms at the 3,3′-positions of the biphenyl scaffold completely reversed the regioselectivity, affording *endo*-**5a** in 90% yield with exclusive diastereoselectivity and 92% ee (Table 1, entry 5). A subsequent solvent survey indicated that dichloromethane was the best solvent of choice in terms of regioselectivity and diastereo-/enantioselectivity (Table 1, entries 5–10). Lowering the reaction temperature was beneficial for enantioselectivity control, and high yield with 94% ee was achieved for *endo*-**5a** when the reaction was performed at −40°C (Table 1, entry 11).

Having the optimized reaction conditions in hand, we examined the substrate scope of the 1,3-dipolar cycloaddition by treating methylene norcamphor (*rac*-**1a**) with various imine esters **2** (Table 2). The representative results are tabulated in Table 2. A variety of glycine ester imines are compatible with this umpolung-type 1,3-dipolar cycloaddition reaction, providing the desired cycloadducts in excellent regio- and stereoselectivities. Aryl aldimine esters incorporating different substitution patterns on the phenyl ring were well tolerated in this reaction, and the corresponding cycloadducts **5** were obtained in acceptable yield (59%–94%) with exclusive regioselectivity (>20:1 *rr*), perfect diastereoselectivity (>20:1 dr) and



Entry[a]	Ligand	Solvent	*rr*[b] 5a:3a	Yield (%)[c]	ee (%)[b]
1	L1	CH_2Cl_2	1:3	96	73 (3a)
2	L2	CH_2Cl_2	1:14	94	84 (3a)
3	L3	CH_2Cl_2	<1:20	96	89 (3a)
4	L4	CH_2Cl_2	<1:20	83	46 (3a)
5	L5	CH_2Cl_2	>20:1	90	92 (5a)
6	L5	THF	8:1	92	86 (5a)
7	L5	EtOAc	4:1	94	86 (5a)
8	L5	CH_3CN	10:1	78	93 (5a)
9	L5	PhMe	18:1	93	88 (5a)
10	L5	$CHCl_3$	6:1	88	90 (5a)
11[d]	L5	CH_2Cl_2	>20:1	91	94 (5a)

Table 1. Optimization of 1,3-Dipolar Cycloaddition of Azomethine Ylide with 3-Methylene-2-Norbornanone 1a

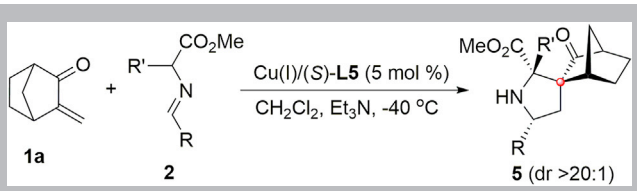
[a]All reactions were carried out with 0.20 mmol of **2a** and 0.40 mmol of **1a** in 2 mL solvent, 48–60 hr $CuBF_4$ = $Cu(MeCN)_4BF_4$.

[b]*rr* was determined by crude ^1H nuclear magnetic resonance, and ee was determined by high-performance liquid chromatography.

[c]Isolated yield of **3a** and **5a** based on **2a**.

[d]Carried out at −40°C.

excellent enantioselectivity (93%–97%) (Table 2, entries 1–14). It is worth mentioning that perfect regioselectivity and excellent stereoselectivity could be still achieved with the sterically hindered *ortho*-chloro (**2e**), *ortho*-methyl (**2l**), and 1-naphthyl (**2m**) imino esters (entries 5, 12, and 13). The electronic property of the substituent group on the aryl ring slightly affected the reactivity of this cycloaddition. The cycloaddition reaction furnished quickly with aldimine ester containing strong electron-deficient *p*-NO_2 or *p*-CN substitution on the phenyl ring (entries 6 and 7). Extended reaction time was needed for electron-rich aldimine esters, but the regioselectivity and stereoselectivity still maintained at the excellent level (Table 2, entries 9–12). Aliphatic aldimine esters were not compatible in this reaction, probably due to the reduced reactivity. Notably, α-methyl- or benzyl-substituted aldimine esters were tested to further investigate the



Entry[a]	R	R′	5	Yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4	H	5a	91	94
2	*m*-Cl-C_6H_4	H	5b	88	95
3	*p*-Br-C_6H_4	H	5c	84	95
4	*m*-Br-C_6H_4	H	5d	85	94
5	*o*-Cl-C_6H_4	H	5e	94	94
6	*p*-NO_2-C_6H_4	H	5f	72	98
7	*p*-CN-C_6H_4	H	5g	83	94
8[d]	Ph	H	5h	86	93
9[d]	*p*-MeO-C_6H_4	H	5i	59	95
10[d]	*p*-Me-C_6H_4	H	5j	74	93
11[d]	*m*-Me-C_6H_4	H	5k	66	94
12[d]	*o*-Me-C_6H_4	H	5l	64	97
13[d]	1-Naphyhyl	H	5m	73	95
14[d]	2-Naphyhyl	H	5n	88	93
15	*p*-Cl-C_6H_4	Me	5o	70	97
16[d]	*p*-MeO-C_6H_4	Me	5p	57	>99
17[d]	2-Thienyl	Me	5q	64	96
18[e,f]	*p*-Cl-C_6H_4	Bn	5r	68	>99

Table 2. Scope of Azomethine Ylides for Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition with 3-Methylene-2-Norbornanone 1a

[a]All reactions were carried out with 0.20 mmol of **2** and 0.40 mmol of **1a** in 2 mL CH_2Cl_2 in 8–12 hr.

[b]Isolated yield based on **2**.

[c]dr was determined by crude ^{1}H nuclear magnetic resonance, and ee was determined by high-performance liquid chromatography.

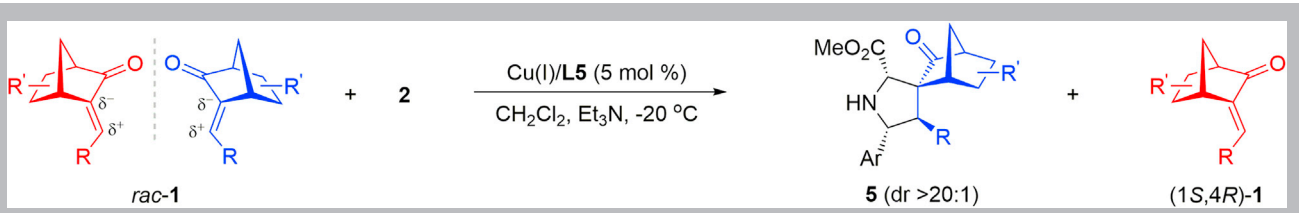
[d]Carried out at −20°C in 36 hr.

[e]Inorganic base Cs_2CO_3 was used.

[f]Carried out at −0°C in 48 hr.

generality of this methodology. The cycloaddition proceeded very well, affording the corresponding spiro [norbornane-pyrrolidines] decorated with one all-carbon and one N-containing quaternary stereogenic center in synthetically useful yields (57%–70%) with exclusive regioselectivity (>20:1 *rr*) and excellent stereoselectivities (>20:1 dr; 96%–>99% ee) (Table 2, entries 15–18).

The fact that enantioenriched spirocycloadduct **5a** could be formed regiospecifically in an exclusive diastereoselective fashion from racemic methylene norcamphor **1a** (Table 1, entry 11) shows that the two enantiomers of methylene norcamphor have significantly different reactivity in this catalytic system. Therefore kinetic resolution of alkylidene norcamphors employing Cu(I)/(*S*)-**L5**-catalyzed cycloaddition should be worthy of our further investigation. In the early study of treating 0.4 mmol of racemic methylene norcamphor **1a** with 0.2 mmol of glycine imino ester **2a** (Table 1, entry 11), when the spirocycloadduct **5a** was



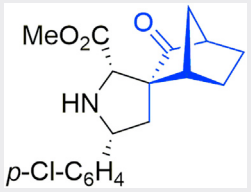
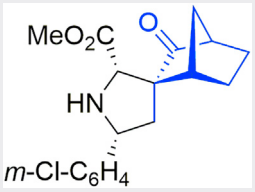
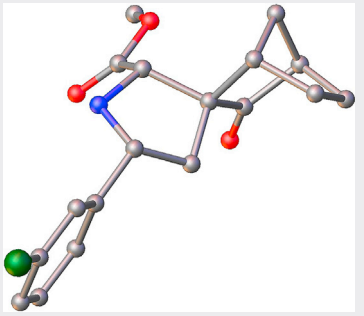
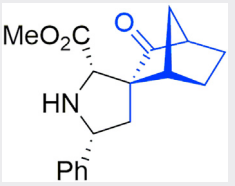
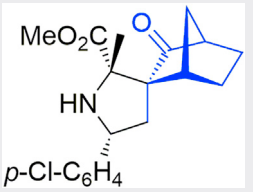
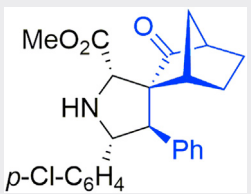
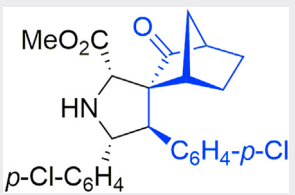
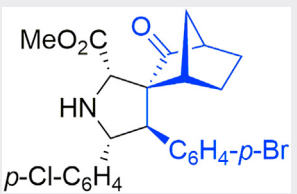
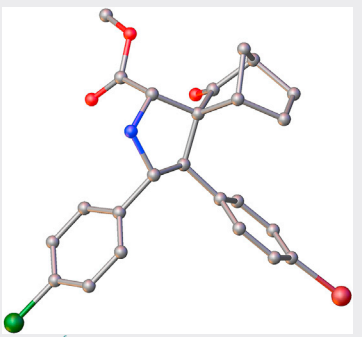
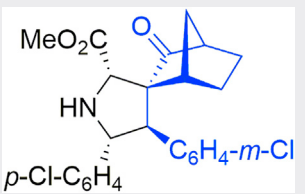
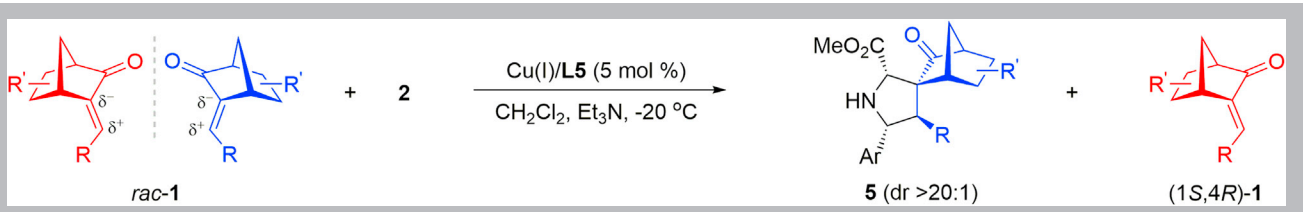
				
Entry 1[a,b] **5a:** 46% y, 94% ee **1a:** 44% y, 92% ee C = 49%,[c] *S* = 106[d]	Entry 2[a,b] **5b:** 47% y, 94% ee **1a:** 43% y, 97% ee C = 51%,[c] *S* = 136[d]	**5b** (CCDC 1562402)	Entry 3[a,e] **5h:** 43% y, 95% ee **1a:** 44% y, 93% ee C = 50%,[c] *S* = 103[d]	Entry 4[a,e] **5o:** 44% y, 94% ee **1a:** 45% y, 97% ee C = 51%,[c] *S* = 136[d]
				
Entry 5[a] **5s:** 48% y, 94% ee **1b:** 46% y, 94% ee C = 50%,[c] *S* = 115[d]	Entry 6[a] **5t:** 49% y, 93% ee **1c:** 45% y, 97% ee C = 51%,[c] *S* = 116[d]	Entry 7[a] **5u:** 50% y, 93% ee **1d:** 45% y, 97% ee C = 51%,[c] *S* = 116[d]	(±)-**5u**[f] (CCDC 1562405)	Entry 8[a] **5v:** 48% y, 93% ee **1e:** 45% y, 96% ee C = 51%,[c] *S* = 108[d]

Table 3. Kinetic Resolution of Various *rac*-Alkylidene Norcamphors 1

(Continued on next page)



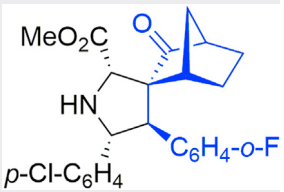
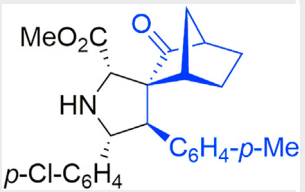
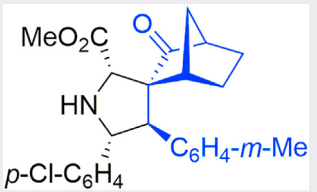
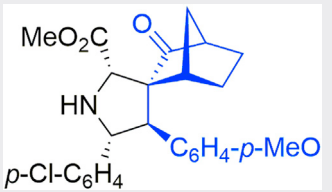
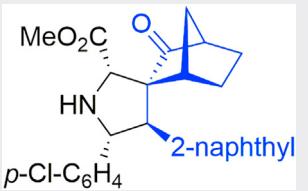
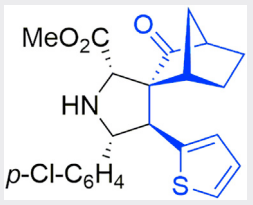
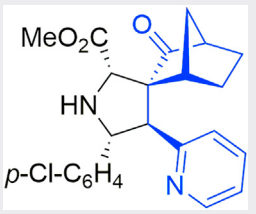
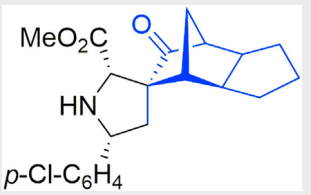
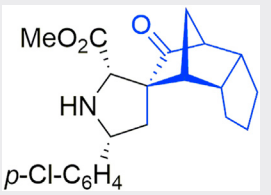
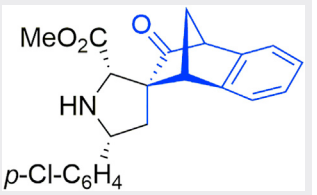
				
Entry 9[a] **5w+3w:** 51% y,[e]2:1 *rr* 83% ee (major) **1f:** 43% y, 99% ee	Entry 10[a] **5x:** 47% y, 93% ee **1g:** 46% y, 97% ee C = 51%,[c]*S* = 116[d]	Entry 11[a] **5y:** 46% y, 93% ee **1h:** 47% y, 94% ee C = 50%,[c]*S* = 98[d]	Entry 12[a] **5z:** 42% y, 97% ee **1i:** 50% y, 87% ee C = 47%,[c]*S* = 188[d]	Entry 13[a] **5A:** 46% y, 94% ee **1j:** 46% y, 95% ee C = 50%,[c]*S* = 121[d]
				
Entry 14[a] **5B:** 45% y, 94% ee **1k:** 46% y, 91% ee C = 49%,[c]*S* = 103[d]	Entry 15[a] **5C:** 46% y, 97% ee **1l:** 45% y, 98% ee C = 50%,[c]*S* = 303[d]	Entry 16[a] **5D:** 48% y, 96% ee **1m:** 45% y, 91% ee C = 49%,[c]*S* = 156[d]	Entry 17[a] **5E:** 45% y, 85% ee **1n:** 44% y, 90% ee C = 51%,[c]*S* = 38[d]	Entry 18[a] **5F:** 47% y, 92% ee **1o:** 46% y, 90% ee C = 49%,[c]*S* = 74[d]

Table 3. Continued

[a]Reaction conditions: *rac*-**1** (0.4 mmol), **2** (0.6 mmol), Et_3N (0.01 mmol), Cu(I)/(*S*)-**L5** (0.02 mmol) in 2 mL CH_2Cl_2 in 48 hr. Isolated yield was based on **1**, and the maximum possible yield of (1*S*,4*R*)-**1** is 50%. >20:1 dr of **3** was determined by crude ^1H nuclear magnetic resonance. ee of **5** and (1*S*,4*R*)-**1c**-**1o** was determined by high-performance liquid chromatography, and ee of (1*S*,4*R*)-**1a** and (1*S*,4*R*)-**1b** was determined by gas chromatography.

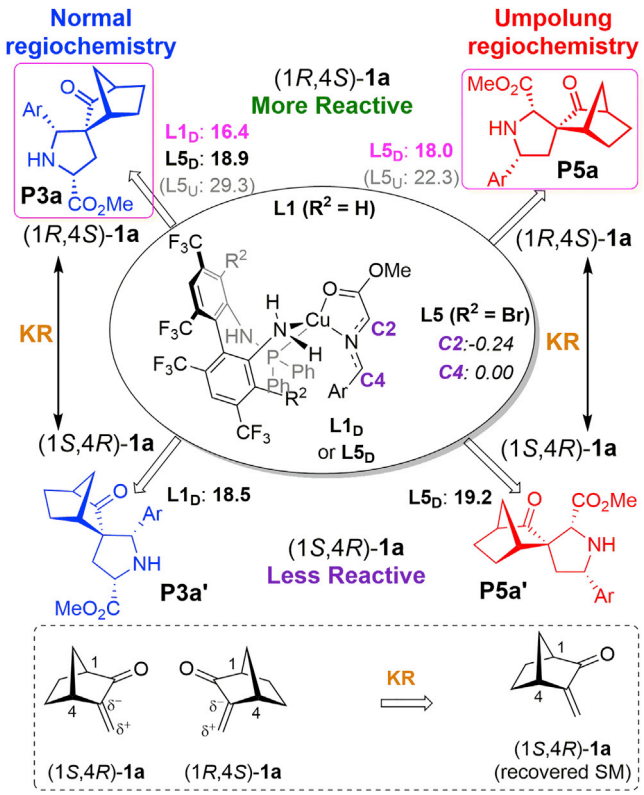
[b]Carried out at −60°C.

[c]Conversion of (*rac*)-**1** = $ee_1/(ee_1 + ee_3)$.

[d]*S*-factor = $\ln[(1 - conv)(1 - ee_1)/\ln[(1 - conv)(1 + ee_1)]$.

[e]Carried out at −40°C.

[f]The crystal of (±)-**5u** for X-ray analysis was obtained from the corresponding cycloadduct with (±)-TF-BiphamPhos**L5** as the ligand.



Scheme 3. Computed Overall Free Energy Barrier (in kcal/mol) of Formation of the Most Critical Products for the Reactions with 2a, (1*R*,4*S*)-1a, and (1*S*,4*R*)-1a Catalyzed by Cu(I)-LI ($L1_D$) or Cu(I)-L5 ($L5_D$) in Dichloromethane (DCM) Solution by the Polarizable Continuum Model (PCM)-B3LYP//B3LYP Method

The computed NBO charge for the two reacting carbon atoms in the Cu-azomethine ylide intermediate $L5_D$ is also given in an italic form.

separated in 91% yield (isolated yield based on imino ester **2a**) with >20:1 dr and 94% ee, methylene norcamphor **1a** was also recovered in 45% yield (isolated yield based on **1a** initially used) and 91% ee with high selectivity factor (*S* = 103) albeit within longer reaction time of up to 48 hr. In consideration of the fact that enantioenriched norcamphors are synthetically useful building blocks, we further re-optimized the reaction conditions to develop more efficient kinetic resolution protocol in terms of both the selectivity factor and reaction time. In short, by increasing the feed ratio of imino ester to alkylidene norcamphor and adjusting the reaction temperature (see Supplemental Information for the details), a variety of racemic alkylidene norcamphors could be resolved more reproducibly with high selectivity factors (*S* = 38–303) within reduced reaction time (18–24 hr) (Table 3). Under the re-optimized reaction conditions, terminal methylene norcamphor (*rac*-**1a**) was resolved efficiently via asymmetric Cu-catalyzed cycloaddition of different aldimine esters with selectivity factors of up to 136 and good yields (Table 3, entries 1–4). Notably, excellent ee values for both spiroadduct **5o** and recovered **1a** were achieved with high selectivity factors when alanine-derived imino esters **2o** were employed as the reaction partner. To better define the substrate scope and limitation with respect to the dipolarophiles, an array of more challenging trisubstituted alkylidene norcamphors were further investigated. (*E*)-benzylidene norcamphors containing various substituents at *para*- or *meta*-position of the phenyl ring were tolerated well, regardless of the electron properties (e.g., electron deficient, electron neutral, or electron rich), affording the desired spirocycloadducts with 93%–97% ee and the recovered norcamphors with 94–99% ee, corresponding to selectivity factors (*S*) of 98–188. Probably due to disfavored steric hindrance, *ortho*-fluoro-substituted benzylidene norcamphor has detrimental effect on the regioselectivity of the cycloadducts, but still furnishes the recovered norcamphor **1f** with an ee value of 99%. Heteroarylidene norcamphors were also well tolerated in this catalytic system (Table 3, entries 14 and 15). Remarkably, 3-pyridin-2-ylidene norcamphor **1l** could be resolved efficiently, producing the expected cycloadduct **5C** with 97% ee and recovered product **1l** with 98% ee, with the highest selectivity factor of 303. Alkyl-substituted alkylidene norcamphors were not viable substrates in this reaction, probably

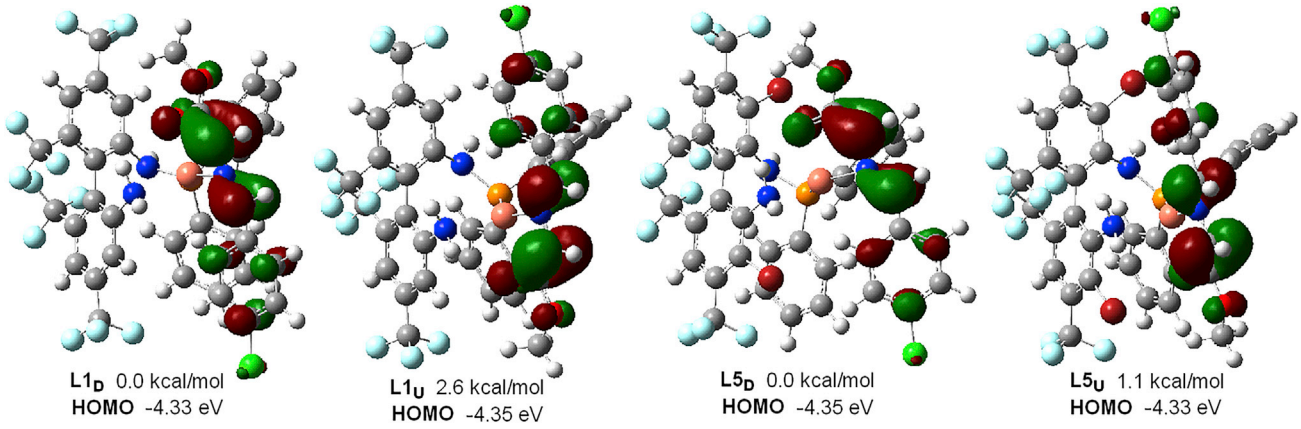


Figure 2. Computed Structure, the Relative Free Energy, and HOMO Energy of the Cu-Azomethine Ylide Intermediates $L1_D$, $L1_U$; $L5_D$, and $L5_U$

due to the pretty low reactivity. All the racemic trisubstituted alkylidene norcamphors tested in this work were obtained exclusively with more than 99% (*E*)-geometry via base-promoted condensation between norcamphor and the corresponding aldehyde. Considering that the geometry of C=C double bond has an important influence on the reactivity or stereoselectivity in alkene-involved asymmetric reactions, we further studied the performance of (*Z*)-benzylidene norcamphor **1b**, which could be obtained with 99% configurational purity upon UV light irradiation (Berthelette et al., 1997) of (*E*)-**1b**. Under the same reaction conditions, no reaction took place when racemic (*Z*)-benzylidene norcamphor was tested. No reaction occurred with the racemic methylene camphor as the dipolarophile presumably because the disfavored steric repulsion caused by the bridged 7,7-dimethyl group impedes the approach of the azomethine ylide from the *EXO*-direction. Both racemic methylene *exo*- and *endo*-tricycle[5.2.1.$0^{2,6}$]decan-8-one, containing a fused cyclopentane moiety on the norcamphor skeleton, were well tolerated and resolved to afford the corresponding spiroadducts containing seven stereogenic centers and the recovered fused norcamphors with selectivity factors of 156 and 38, respectively (Table 3, entries 16 and 17). *Exo*-**1m** displayed higher reactivity, furnishing the chiral spiro polycyclic adduct with better ee value. Racemic methylene 2-benzonorbornanone **1o** bearing a fused benzene ring was also a viable substrate for this kinetic resolution protocol, providing the cycloadduct **5F** and the recovered **1o** with high enantioselectivity and a selectivity factor of 74 (Table 3, entry 18). The absolute configuration of spirocycloadduct **5b** from methylene norcamphor and **5u** from *para*-bromobenzylidiene norcamphor was unambiguously determined by X-ray diffraction crystallography as (1*S*,2*S*,2′*S*,4*R*,5′*R*) and (1*S*,2*R*,2′*S*,4*R*,4′*R*,5′*R*), respectively (see Supplemental Information for the details). The absolute configuration of the recovered methylene norcamphors was assigned as (1*S*,4*R*), which was deduced from the stereochemistry result of kinetic resolution and further confirmed by comparing the optical rotation of **1a** with the data reported in the literature (Krotz and Helmchen, 1994). Those of other spiroadducts and recovered alkylidene norcamphors were deduced based on these results.

To understand the mechanism of the unusual ligand-controlled regioselectivity and kinetic resolution of the cycloaddition reaction, density functional theory (DFT) (B3LYP/6-31G(d)+SDD method) (Wang et al., 2012) calculations were carried out by using Cu(I), substrates **1a** and **2a,** as well as **L1** ligand (or **L5** for the most important cases) as our system (See Supplemental Information for the details). As shown in Schemes 2 and 3 and Figure 2, the reacting C2 atom of two Cu-azomethine ylide intermediates $\mathbf{L1_D}$ and $\mathbf{L5_D}$ had a more negative charge (−0.24) and contributed to slightly larger HOMO than the other reacting C4. This result supported the major resonance form **I** (Scheme 1). For the reaction with (1*R*,4*S*)-**1a**, our computational results showed that intermediate $\mathbf{L1_D}$ (using **L1** ligand) generally had lower barriers for the cycloaddition toward the EXO-direction to the methylene norcamphor than the ENDO-direction, owing to the above-mentioned "picket fence effect" (Scheme 2). Moreover, the most kinetically favorable pathway preferred the formation of the normal and major *endo*-selective cycloaddition product **P3a** other than the *exo*-selective **P4a** via the rate-determining Michael-addition-type transition state $\mathbf{3a\text{-}L1_D\text{-}TS1_{endo}}$ (Scheme 2 and Figure 3), which had a lower barrier than that for the umpolung-type and minor *endo*-selective cycloaddition product **P5a** via $\mathbf{5a\text{-}L1_D\text{-}TS1_{endo}}$ (Michael-addition type) by roughly 3.0 kcal/mol. The norcamphor approached the amine side of **L1** ligand and formed a strong hydrogen bond (NH–O: 1.78 Å) in $\mathbf{3a\text{-}L1_D\text{-}TS1_{endo}}$. However, when the norcamphor approached the phosphorus side of **L1** ligand to form **P5a**

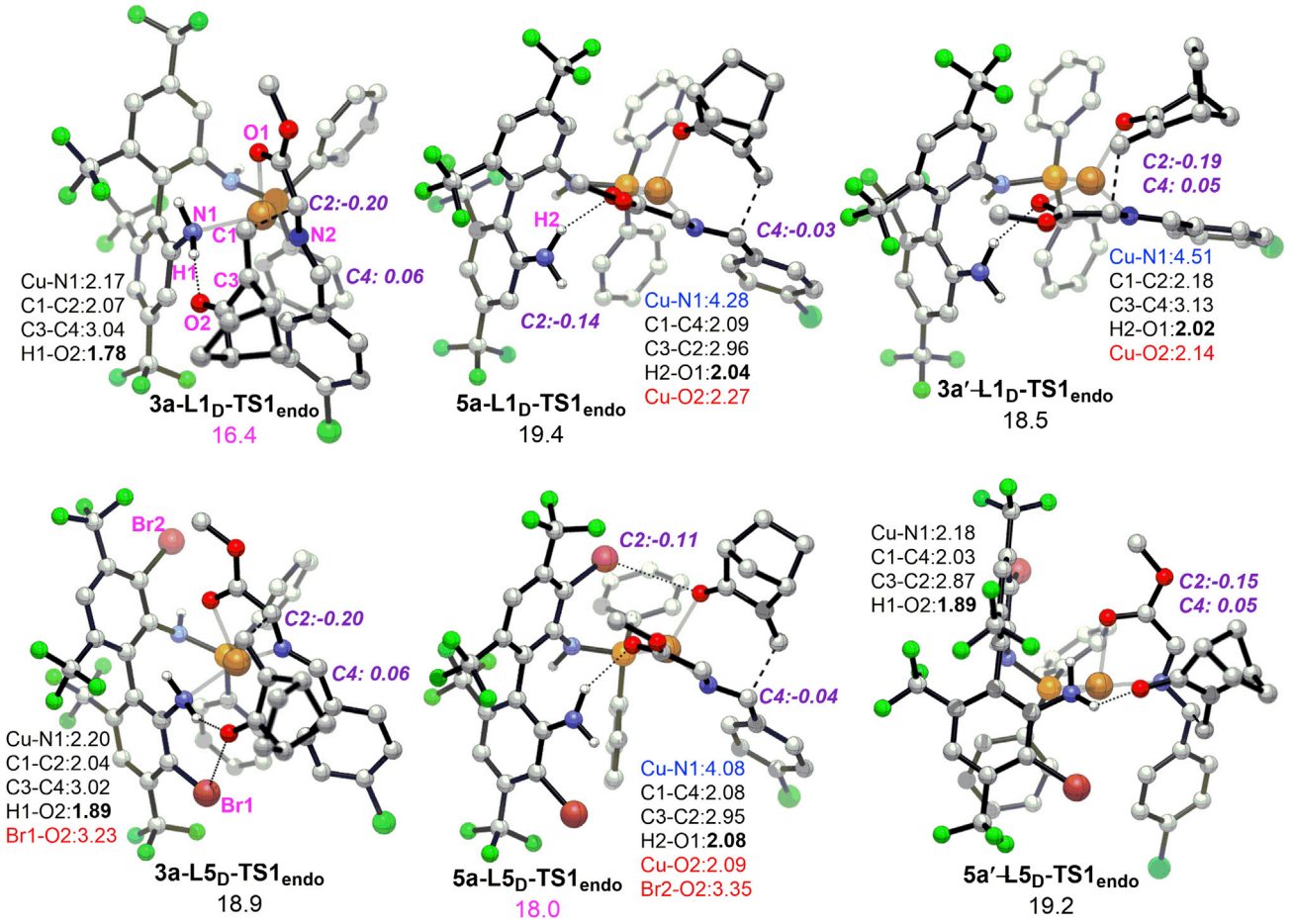
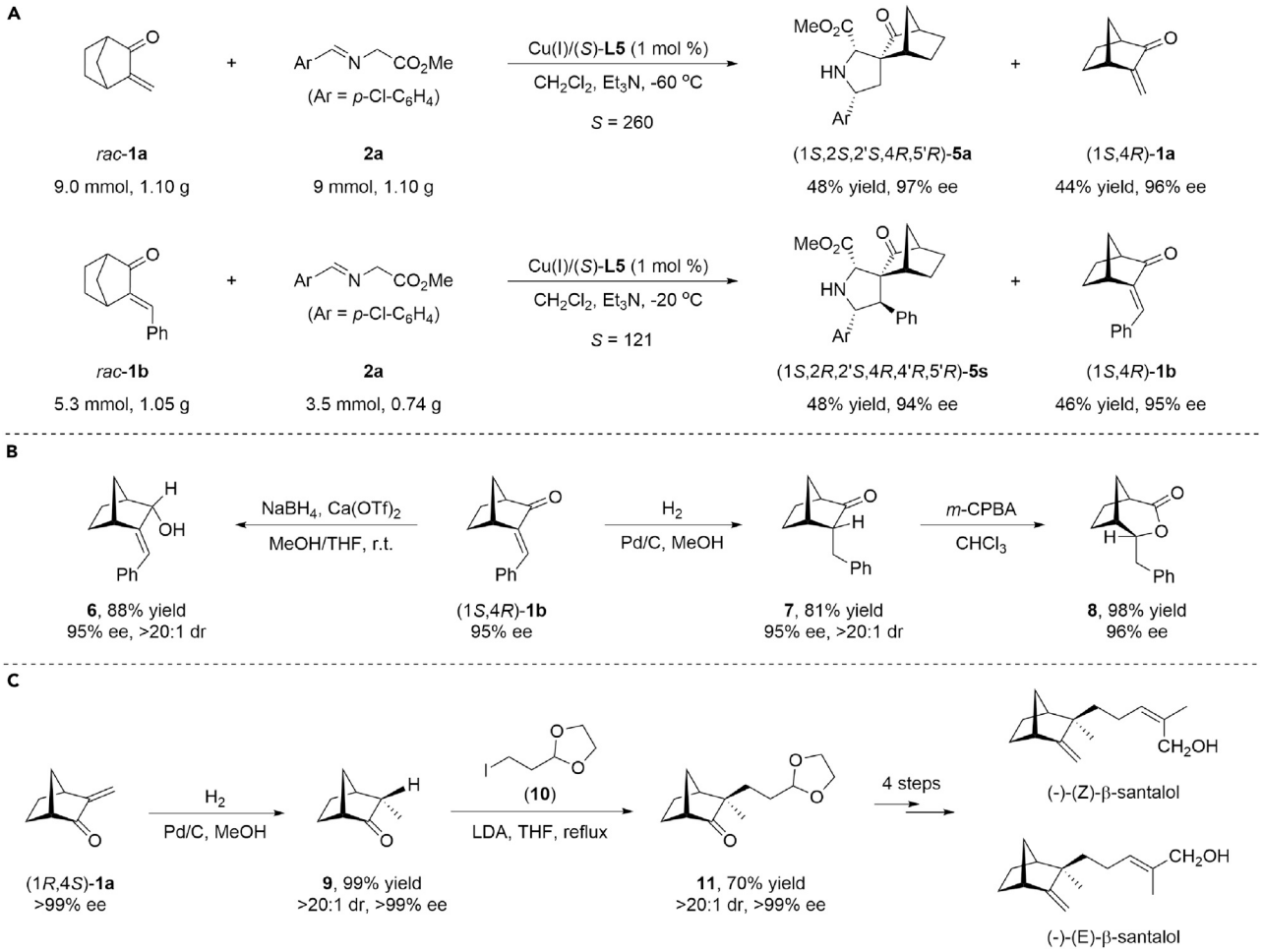


Figure 3. DFT Calculations

The computed most critical transition states with NBO charge for the two reacting carbon atoms (in an italic form), key bond lengths (in angstrom), and relative free energy (in kcal/mol) for the reactions with **2a**, (1*R*,4*S*)-**1a**, or (1*S*,4*R*)-**1a** catalyzed by Cu(I)-**L1** or Cu(I)-**L5** in Dichloromethane (DCM) solution by the polarizable continuum model (PCM)-B3LYP//B3LYP method.

in **5a-L1$_D$-TS1$_{endo}$**, the amine nitrogen of **L1** ligand was found to dissociate from the Cu center and the carbonyl oxygen of the norcamphor coordinated to the metal (Cu–O: 2.14 Å). As the norcamphor was required to approach the phosphorus side of the ligand to afford **P5a**, increasing steric repulsion between the norcamphor and the more bulky phosphine ligand (**L2**, **L3** or **L4**) should further disfavor the umpolung-type regioselectivity (Table 1). In addition, the reaction of intermediate **L1$_D$** with (1*S*,4*R*)-**1a** was computed to have a higher barrier to form **P3a′** by about 2.1 kcal/mol, which demonstrated a lower reactivity of (1*S*,4*R*)-**1a** and explained the observed kinetic resolution.

Interestingly, when replacing **L1** ligand by **L5** ligand, the most favorable pathway switched to the umpolung regiochemistry to give *endo*-selective **5a** via **5a-L5$_D$-TS1$_{endo}$**, which is lower in free energy than the normal regiochemistry to form *endo*-selective **3a** via **3a-L5$_D$-TS1$_{endo}$** by ~0.9 kcal/mol (Scheme 3). An electrostatic repulsion between the carbonyl oxygen of the norcamphor and one bromine (Br1) atom of the biphenyl ligand (O–Br: 3.23 Å in **3a-L5$_D$-TS1$_{endo}$**, shorter than the sum of their van der Waals radii [3.37 Å]; see Figure 3) was found to weaken the hydrogen bond between the substrate and ligand and, thus, should play a key role in inverting regiocontrol of the cycloaddition. Moreover, the natural bond orbital (NBO) charge of the reacting C2 and C4 atoms were found to become less negatively charged and more negatively charged, respectively, in the key umpolung-type transition states **5a-L1$_D$-TS1$_{endo}$** and **5a-L5$_D$-TS1$_{endo}$**, showing more contribution of the minor resonance form **II** (Scheme 1). Furthermore, the reaction of **L5$_D$** with (1*S*,4*R*)-**1a** leading to **P5a′** had to overcome a higher barrier height by 1.2 kcal/mol relative to the formation of **P5a** from (1*R*,4*S*)-**1a**. Overall, these computational results were



Scheme 4. Synthetic Versatility of the Present Catalytic System

(A) Scale-up of the kinetic resolution process with as low as 1 mol % catalyst loading.

(B) Derivatization of recovered optically active alkylidene norbornanone (1*S*,4*R*)-**1b**.

(C) Facile access to the key intermediate of chiral odorants (Z) and (E)-β-santalol.

qualitatively consistent with the observed ligand-controlled regioselectivity and kinetic resolution, and also showed the key role of the bromine atoms.

To demonstrate the scalability of this methodology, we carried out the gram-scale kinetic resolution of methylene norcamphor *rac*-**1a** (9.0 mmol, 1.10 g) with imino ester **2a** in the presence of as low as 1 mol % of Cu(I)/(*S*)-**L5** catalyst, which furnished (1*S*,4*R*)-**1a** (44% yield, 96% ee) and the spirocycloadduct **5a** (48% yield, 97% ee) with a selectivity factor of 260 at 50% conversion (Scheme 4A). In a similar fashion, benzylidene norcamphor *rac*-**1b** (5.3 mmol, 1.05 g) could also be efficiently resolved with a selectivity factor of 121 at 50% conversion. The synthetic transformations of the resolved benzylidene norcamphor were then evaluated. Luche reduction of the carbonyl group in (1*S*,4*R*)-**1b** with $NaBH_4/Ca(OTf)_2$ in a highly diastereoselective fashion led to compound *endo*-**6** in 88% yield with the maintained enantioselectivity. Direct hydrogenation of **1b** in the presence of catalytic amount of Pd/C in methanol gave compound *endo*-7 in 81% yield with exclusive diastereoselectivity control. Subsequent Baeyer-Villiger oxidation of **7** with *meta*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature afforded the previously inaccessible bridged lactone **8** in 98% yield without loss of enantiomeric excesses (Scheme 4B). To further demonstrate the potential utility of this methodology, the Cu(I)-catalyzed kinetic resolution of alkylidene norcamphor was successfully applied to the facile synthesis of the key intermediate of (*Z*) and (*E*)-β-santalol (Krotz and Helmchen, 1994) (Scheme 4C). A concise synthetic route was designed to those chiral odorants, which

relies on the highly efficient kinetic resolution of racemic methylidene norcamphor with Cu(I)/(*R*)-**L5** complex, leading to (1*R*,4*S*)-**1a** (40% yield, >99% ee) with excellent efficiency at 54% conversion. (1*R*,4*S*)-**1a** could be readily hydrogenated with Pd/C to deliver compound *endo*-**9** in 99% yield with the maintained enantioselectivity in an excellent diastereoselective manner (>20:1 dr). Treatment of compound **9** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by the addition of Stowell iodide (Stowell et al., 1983) **10** exclusively afforded the *exo*-alkylation product **11**, the key intermediate for (−)-(*Z*) and (*E*)-β-santalol.

Conclusion

We have developed an expedient kinetic resolution of synthetically important racemic alkylidene norcamphors by Cu(I)-catalyzed umpolung-type 1,3-dipolar cycloaddition of azomethine ylide with the DOS of natural-product-inspired spiro[norbornane-pyrrolidines] containing multiple stereogenic centers. The success of this methodology relies heavily on the rational design, which led to implement the strategy of kinetic resolution, and serendipity, which led to the discovery of a unique ligand-controlled regiospecific cycloaddition, which is especially notable and provides direct experimental evidence for the existence of two zwitterionic resonance forms in metallated azomethine ylide. Beyond the broad utility in organic synthesis, this protocol diversifies the existing chemistry of transition metal-catalyzed 1,3-dipolar cycloadditions of azomethine ylide with rare polarity inversion.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

DATA AND SOFTWARE AVAILABILITY

Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) as CCDC 1592399 (tosylated(±)-endo-**3a**), 1592400 (tosylated endo'-**5a**), 1562402 (**5b**), 1562404 (**5s**), 1562405 ((±)-**5u**), and 1562406 ((±)-**1d**), which can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/getstructures.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods, 183 figures, 10 tables, and 6 data files and can be found with this article online at https://doi.org/10.1016/j.isci.2018.12.010.

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AUTHOR CONTRIBUTIONS

C.-J.W. and C.S. conceived and designed the research. C.S., L.W., and W.-W.D. performed the research. Y.Y. and L.W.C. performed the DFT calculations. C.J.W., L.W.C., and C.S. co-wrote the paper. All authors analyzed the data, discussed the results, and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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ISCI, Volume *11*

Supplemental Information

Kinetic Resolution of Alkylidene Norcamphors *via* a Ligand-Controlled Umpolung-Type 1,3-Dipolar Cycloaddition

Chong Shen, Yuhong Yang, Liang Wei, Wu-Wei Dong, Lung Wa Chung, and Chun-Jiang Wang

Supplemental Figures for ^{1}H, ^{13}C and NOESY NMR Spectra and HPLC Spectra

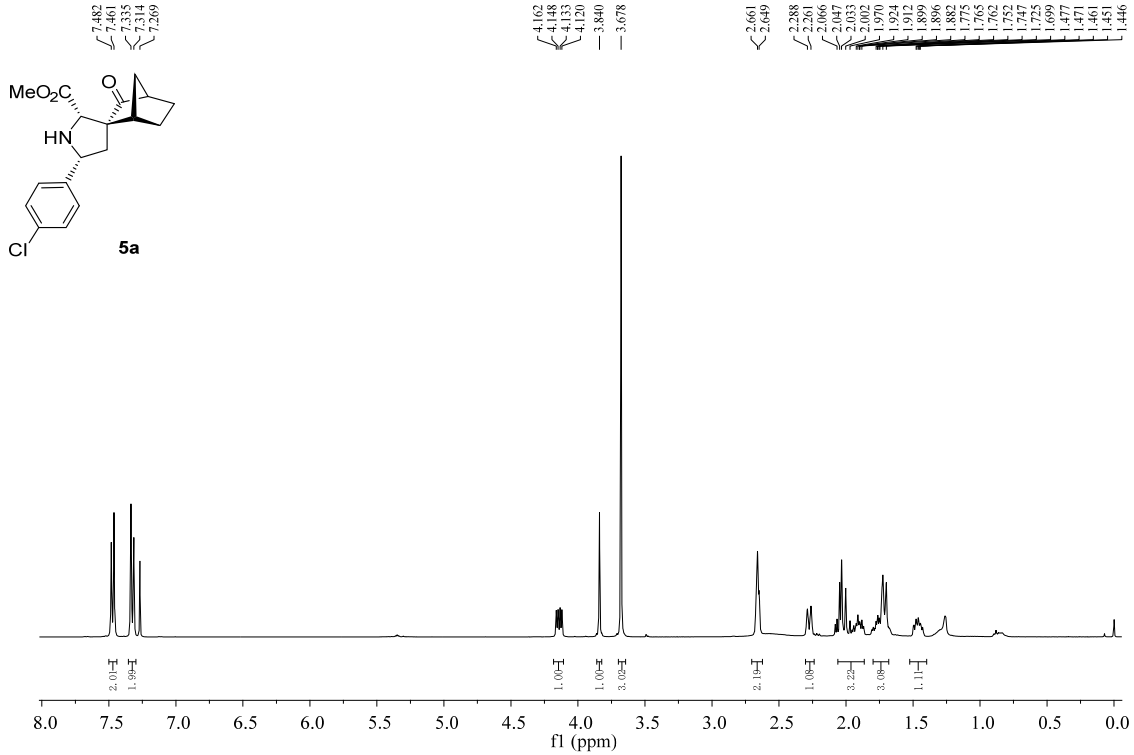

Figure S1. ^{1}H NMR spectrum of **5a**, related to **Table 2**.

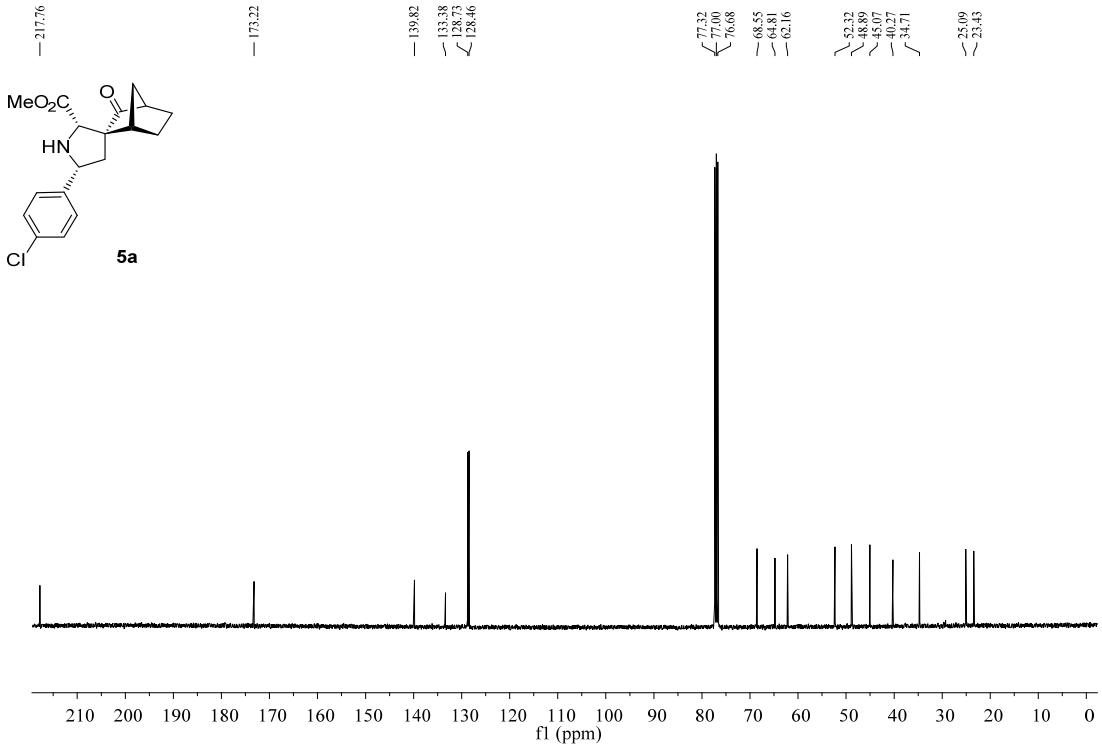

Figure S2. ^{13}C NMR spectrum of **5a**, related to **Table 2**.

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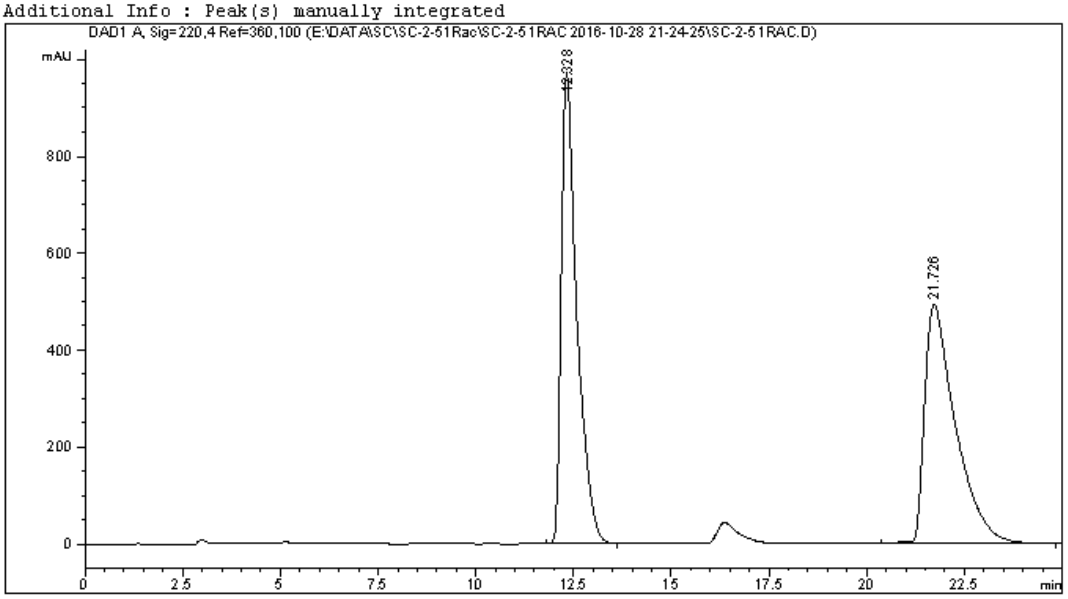


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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


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   1  12.328 BB    0.4036 2.69613e4   972.11151  49.8290
   2  21.726 BB    0.8053 2.71463e4   493.86307  50.1710

Totals :                  5.41076e4  1465.97458
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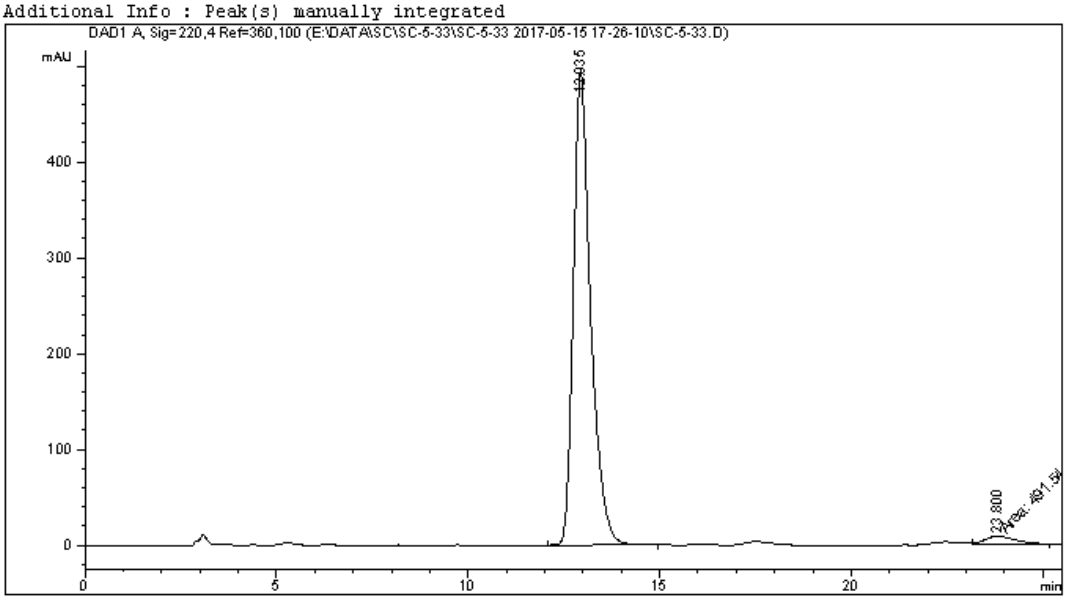


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Signal 1: DAD1 A, Sig=220,4 Ref=360,100

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Totals :                  1.59622e4   500.70549
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Figure S3. HPLC spectrum of **5a**, related to **Table 2**.

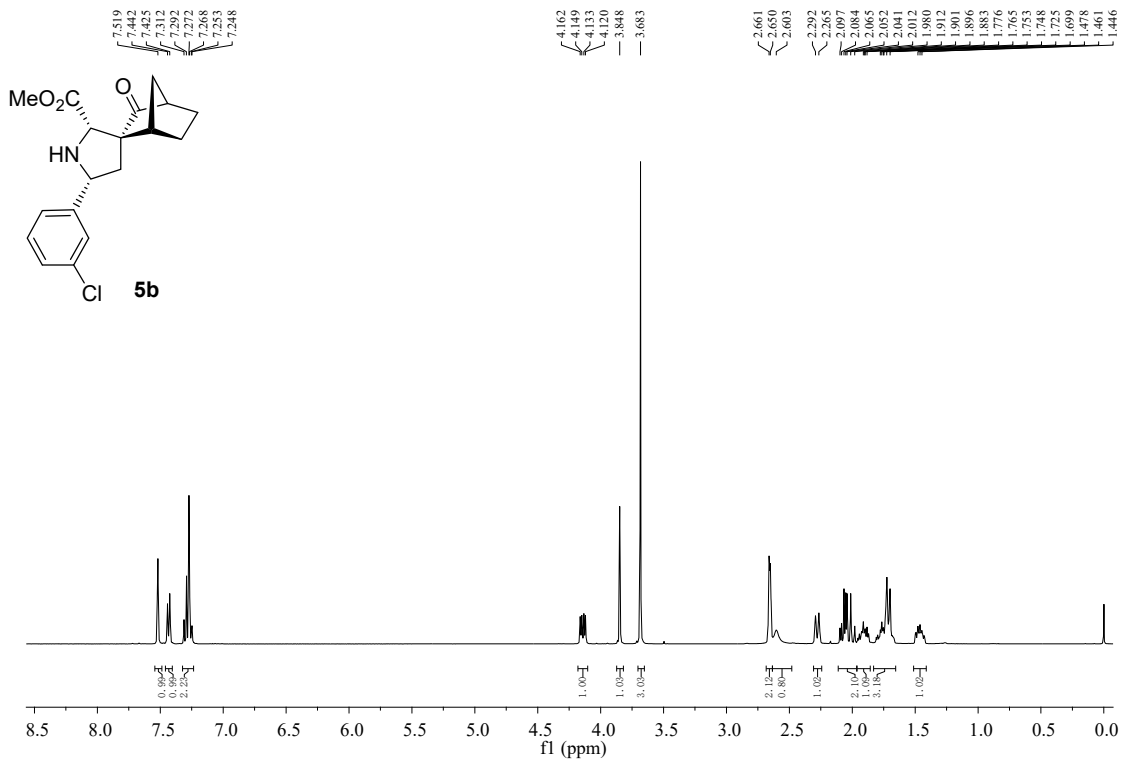

Figure S4. ^{1}H NMR spectrum of **5b**, related to **Table 2**.

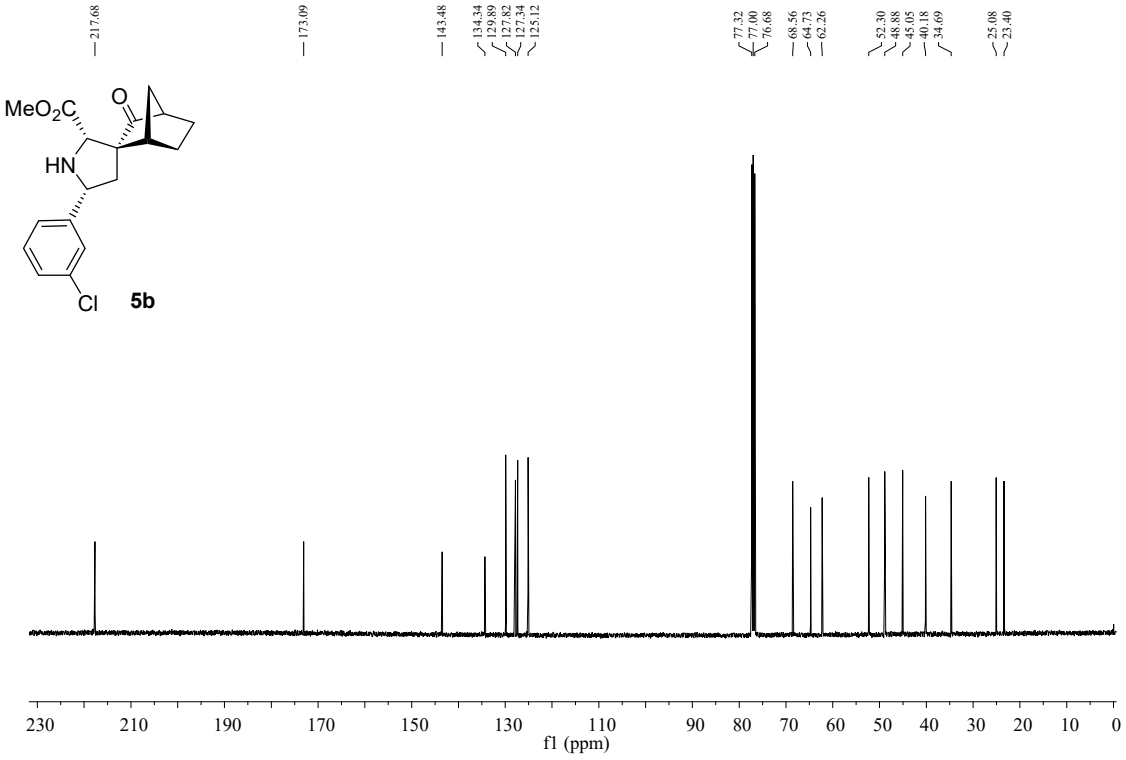

Figure S5. ^{13}C NMR spectrum of **5b**, related to **Table 2**.

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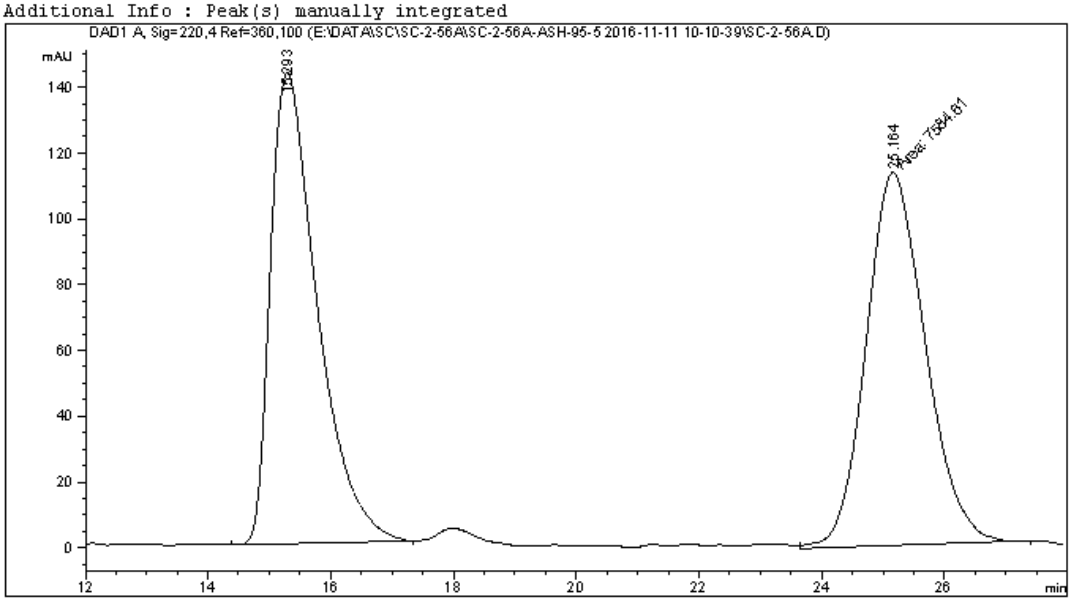


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    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

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       1  15.293 BB    0.7806 7588.30518  143.11862  50.0122
       2  25.164 MM    1.1146 7584.61230  113.41533  49.9878

    Totals :                  1.51729e4   256.53395
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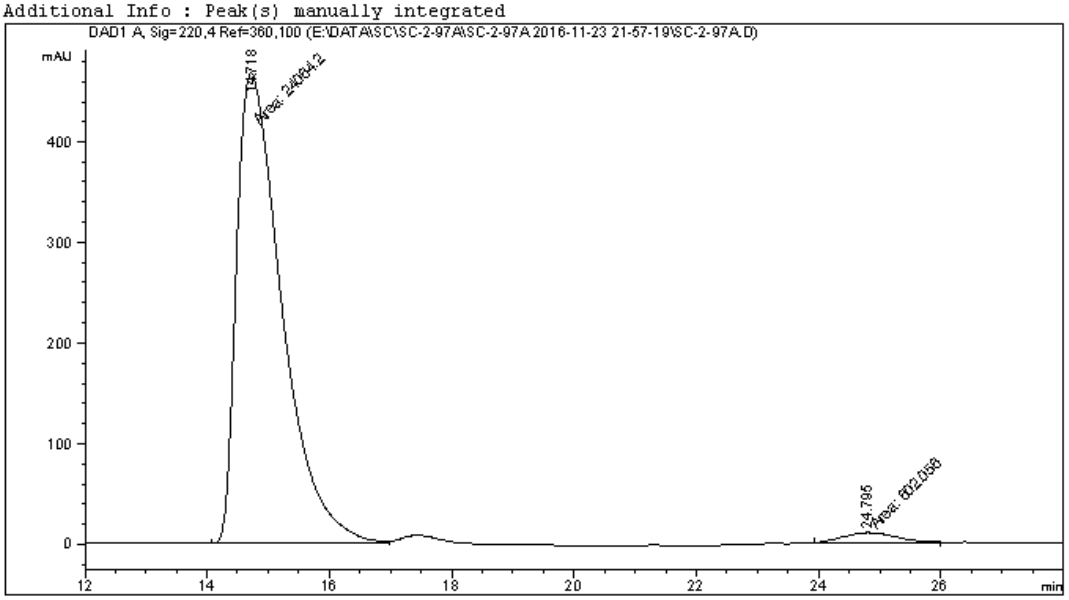


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Figure S6. HPLC spectrum of **5b**, related to **Table 2**.

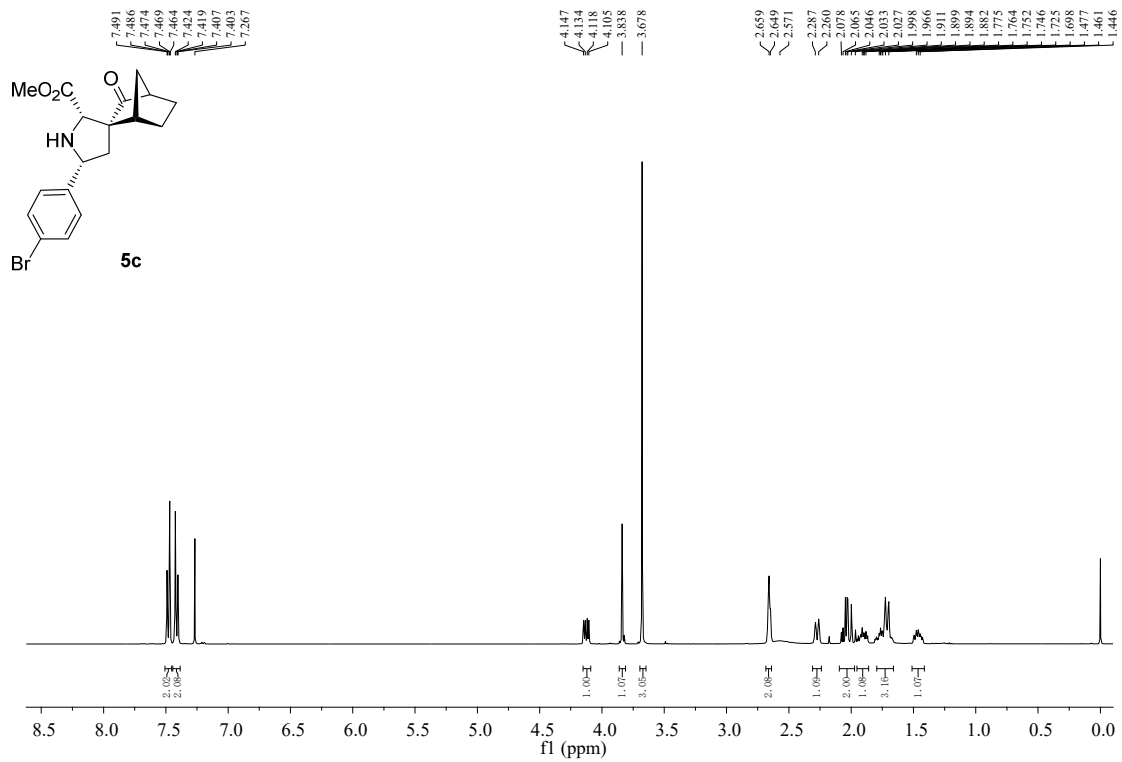

Figure S7. ^{1}H NMR spectrum of **5c**, related to **Table 2**.

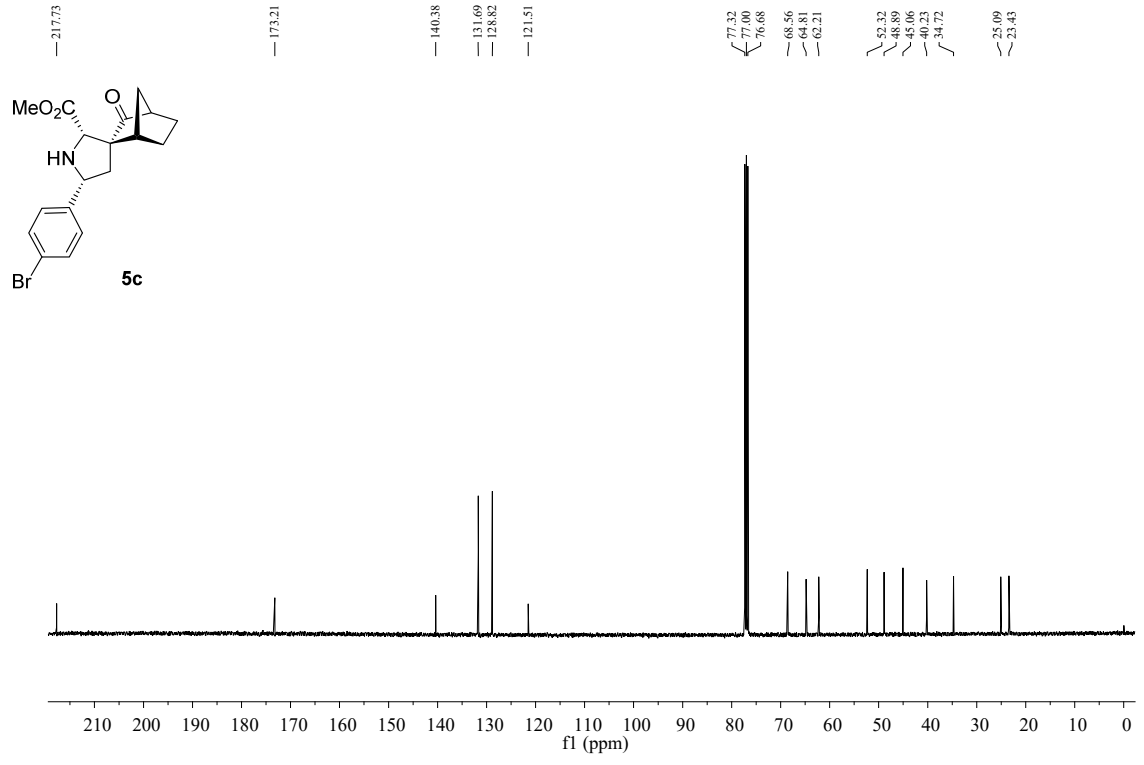

Figure S8. ^{13}C NMR spectrum of **5c**, related to **Table 2**.

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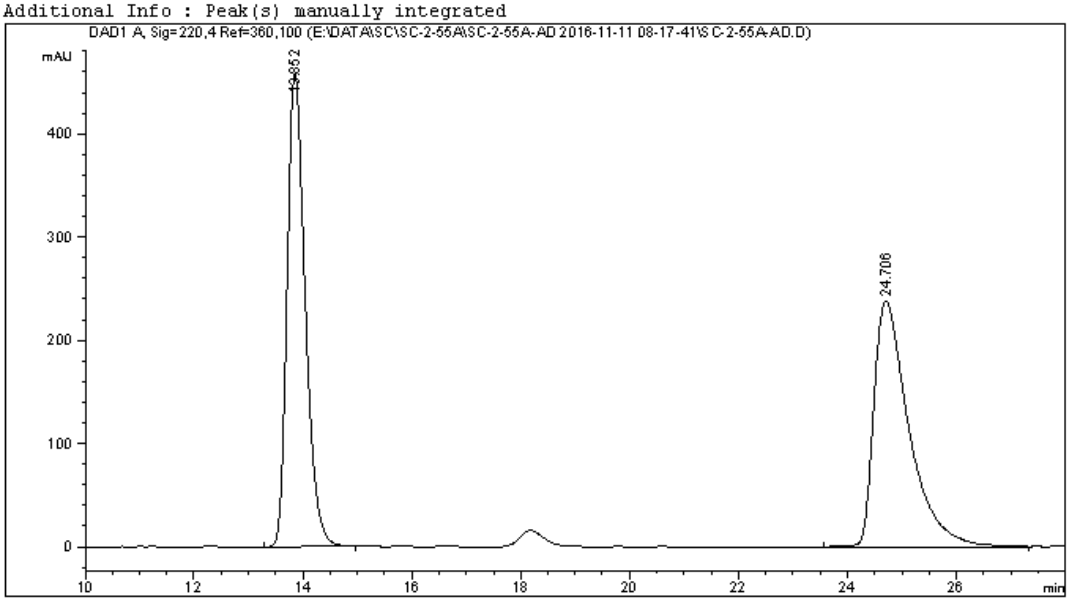


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       1  13.852 BB    0.3541 1.05875e4   459.02625  49.9002
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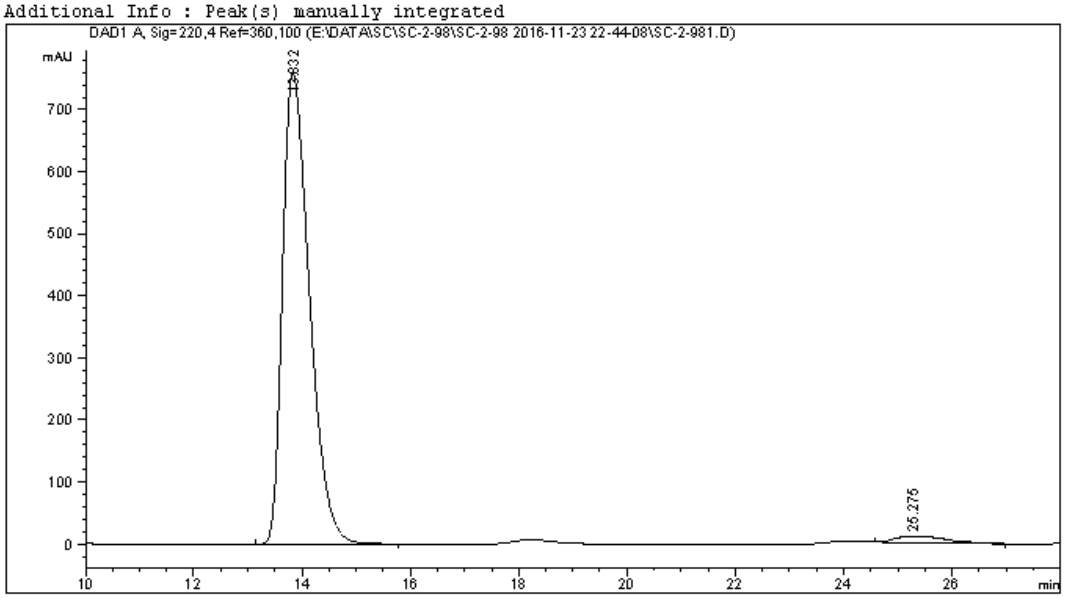


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Figure S9. HPLC spectrum of **5c**, related to **Table 2**.

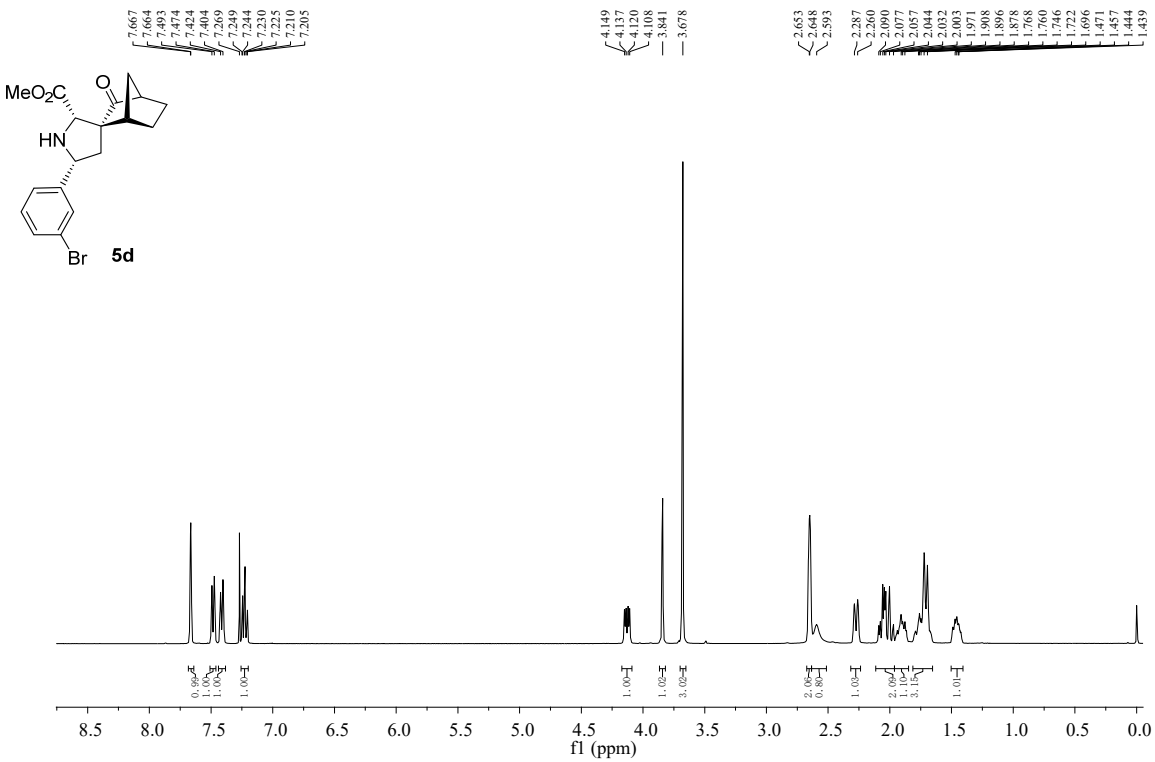

Figure S10. ^{1}H NMR spectrum of **5d**, related to **Table 2**.

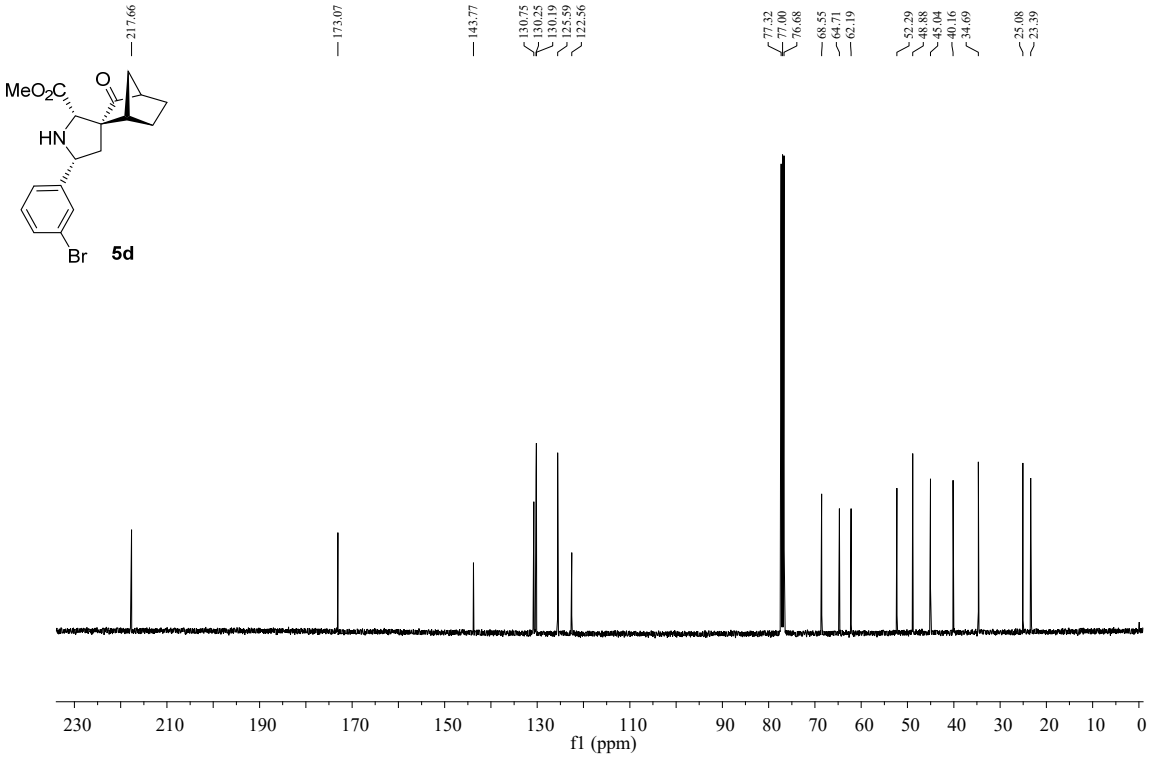

Figure S11. ^{13}C NMR spectrum of **5d**, related to **Table 2**.

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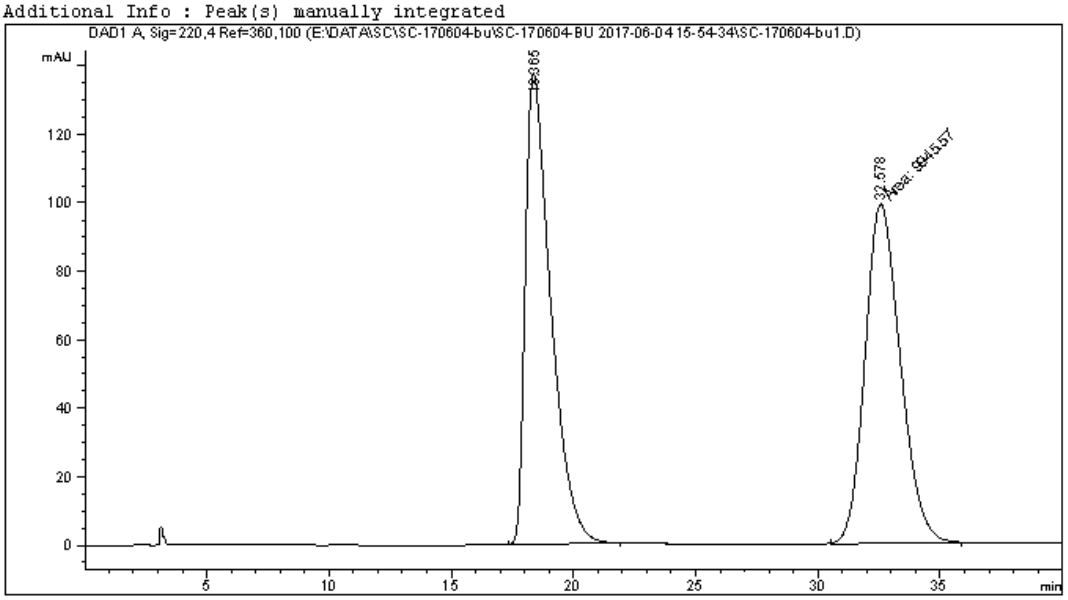


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Dilution              :      1.0000
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   2  32.578 MM    1.6737 9945.56934   99.03499  49.9809

Totals :                  1.98988e4   236.56915
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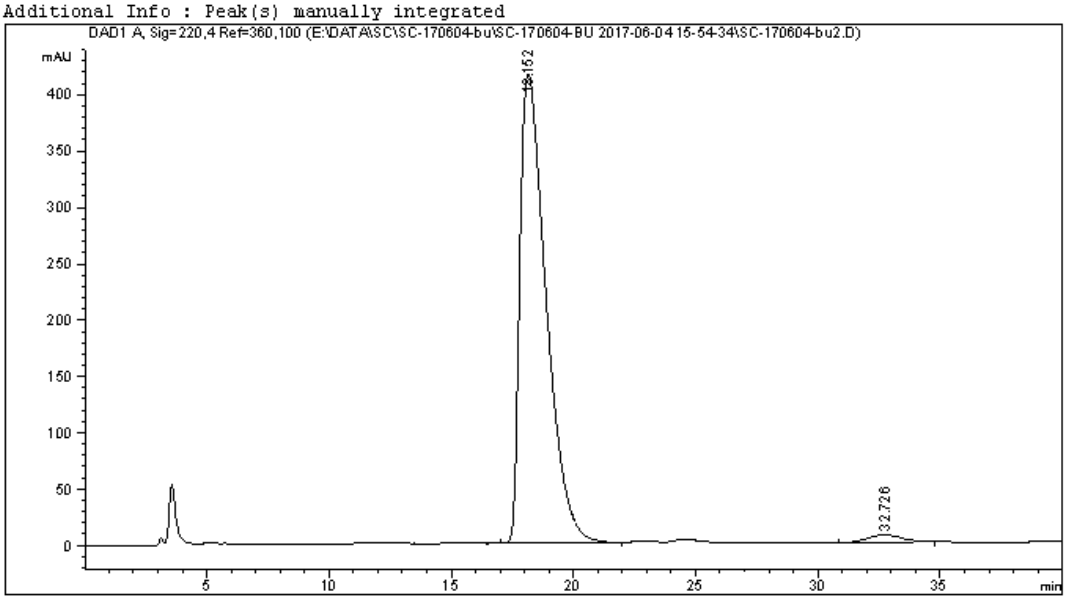
                  220NM-35MIN.M
Last changed    : 6/4/2017 4:44:06 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-1-ASH-95-5-
                  220NM-35MIN.M (Sequence Method)
Last changed    : 6/4/2017 5:37:53 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  18.152 BB    1.0897 3.09856e4   417.08008  98.0133
   2  32.726 BB    1.1150  628.07062    6.59519   1.9867

Totals :                  3.16137e4   423.67527
```


Figure S12. HPLC spectrum of **5d**, related to **Table 2**.

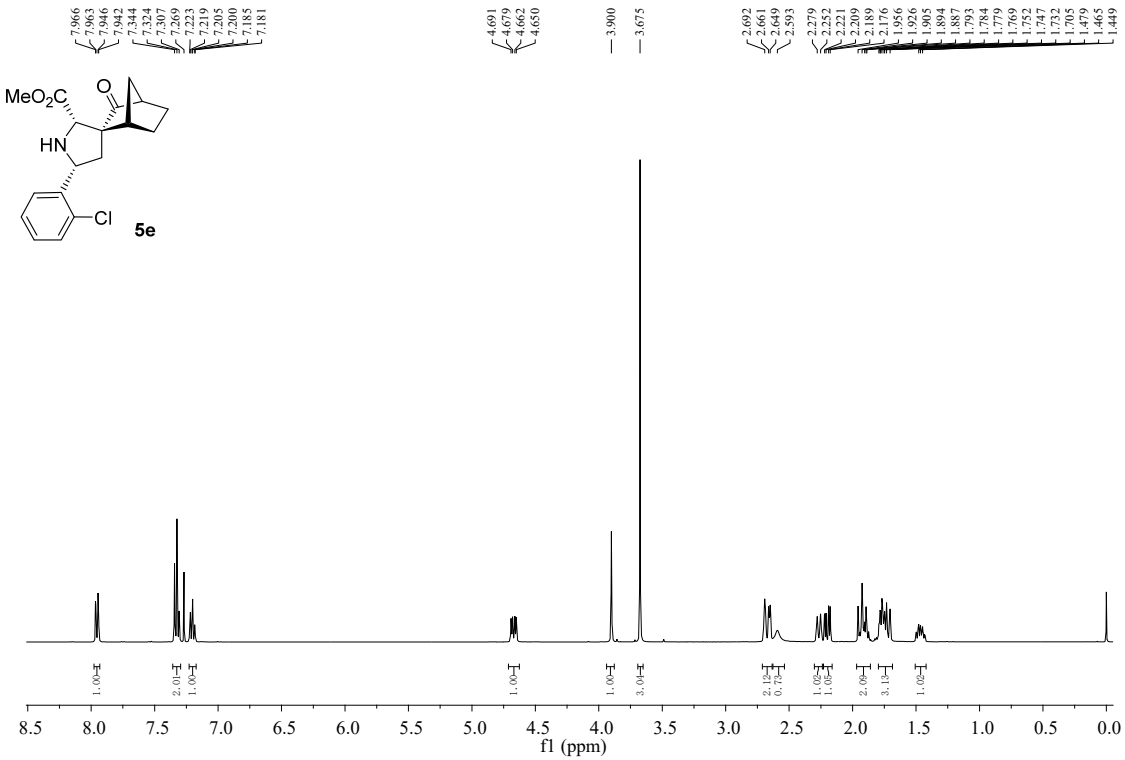


Figure S13. ^{1}H NMR spectrum of **5e**, related to **Table 2**.

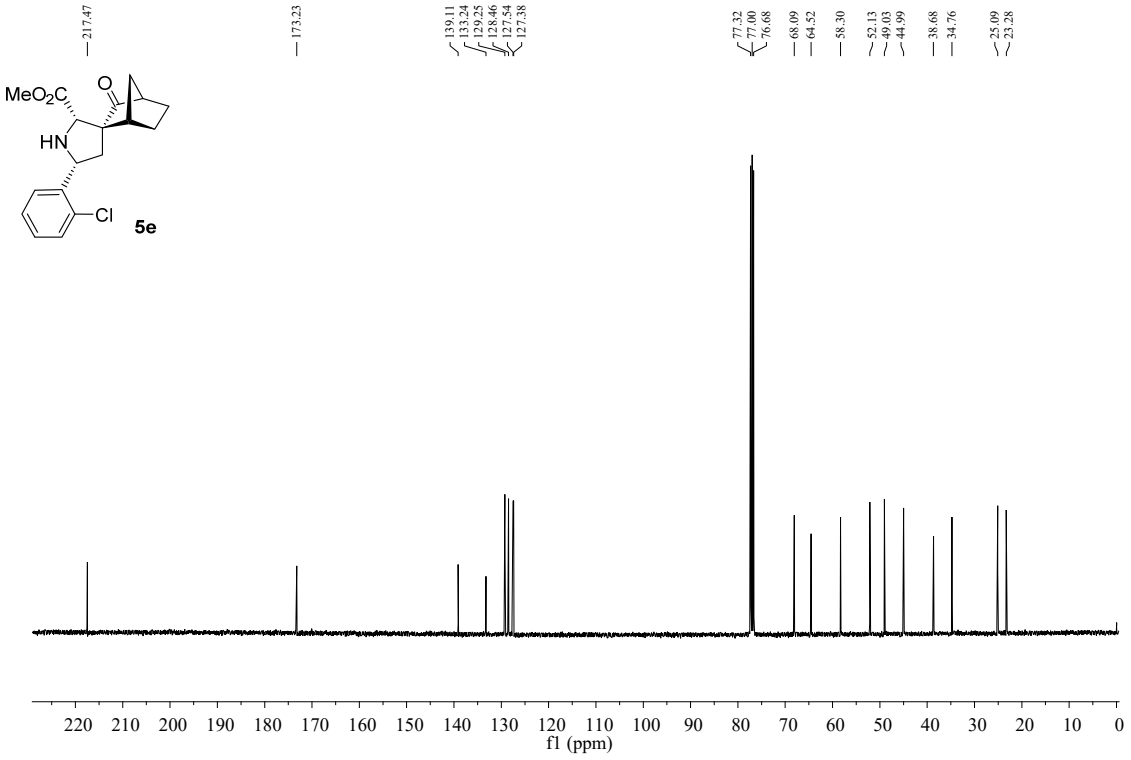
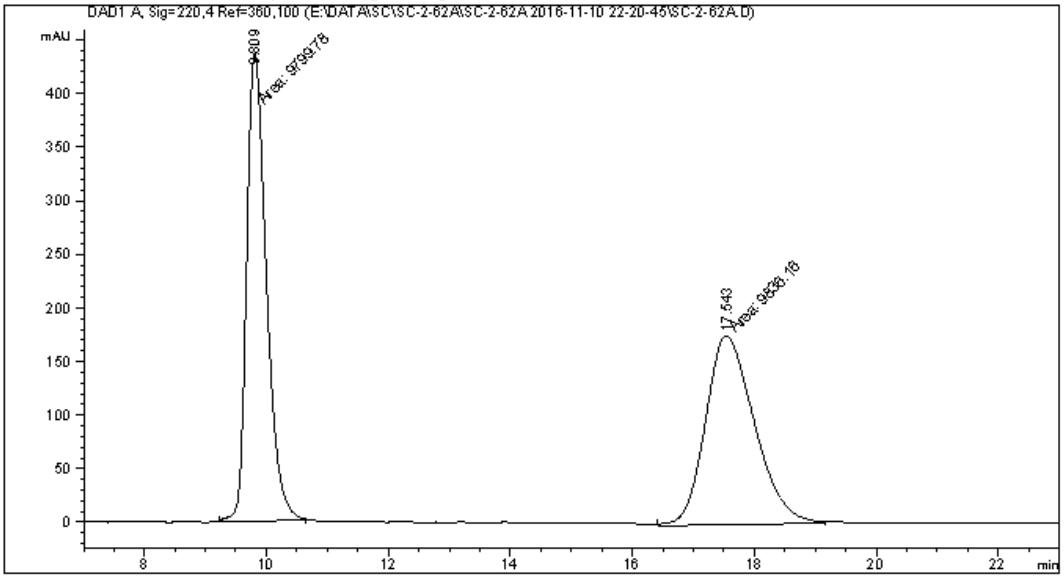


Figure S14. ^{13}C NMR spectrum of **5e**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-62A\SC-2-62A 2016-11-10 22-20-45\SC-2-62A.D
Sample Name: SC-2-62A

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   67
    Injection Date  : 11/11/2016 2:22:09 PM                Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-62A\SC-2-62A 2016-11-10 22-20-45\SC-1-ASH-90-10-DAD-1ML.M
    Last changed    : 11/11/2016 2:20:45 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-62A\SC-2-62A 2016-11-10 22-20-45\SC-1-ASH-90-10-DAD-1ML.M (
                      Sequence Method)
    Last changed    : 6/3/2017 8:38:19 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

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    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

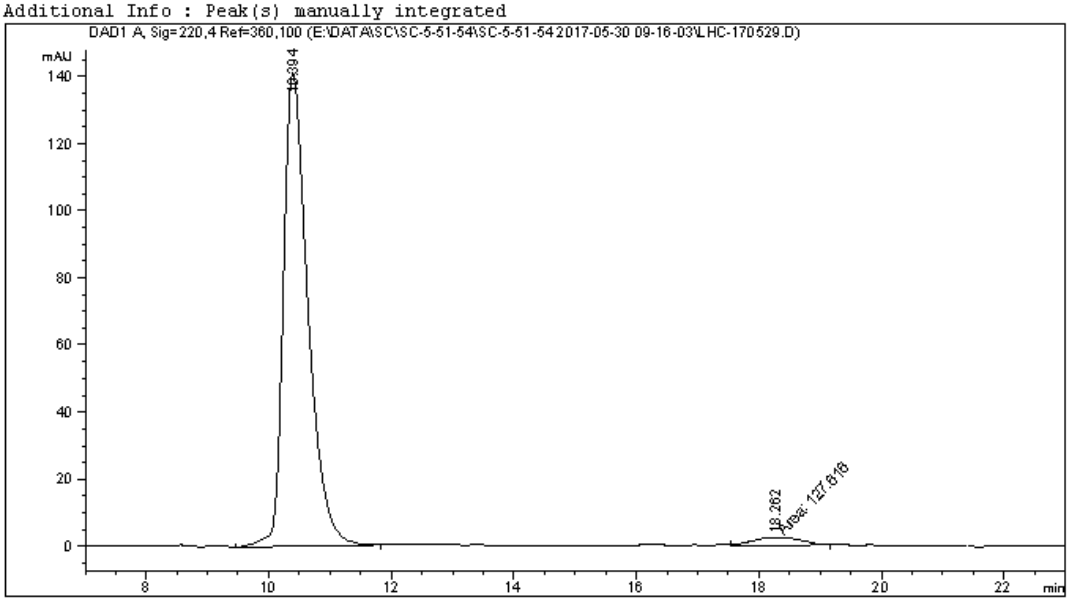

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1   9.809 MM    0.3740 9799.78125  436.71069  49.9074
       2  17.543 MM    0.9290 9836.15918  176.46739  50.0926

    Totals :                  1.96359e4   613.17809
```

Data File E:\DATA\SC\SC-5-51-54\SC-5-51-54 2017-05-30 09-16-03\LHC-170529.D
Sample Name: SC-5-51

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                            Location :   13
Injection Date  : 5/30/2017 9:17:32 AM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-51-54\SC-5-51-54 2017-05-30 09-16-03\SC-1-ASH-90-10-220NM-
                  30MIN.M
Last changed    : 5/30/2017 9:16:03 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-51-54\SC-5-51-54 2017-05-30 09-16-03\SC-1-ASH-90-10-220NM-
                  30MIN.M (Sequence Method)
Last changed    : 6/3/2017 9:05:01 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.394 BB    0.4210 3927.09277  140.99124  96.8526
   2  18.262 MM    0.9076  127.61635    2.34348   3.1474

Totals :                  4054.70912  143.33472
```


Figure S15. HPLC spectrum of **5e**, related to **Table 2**.

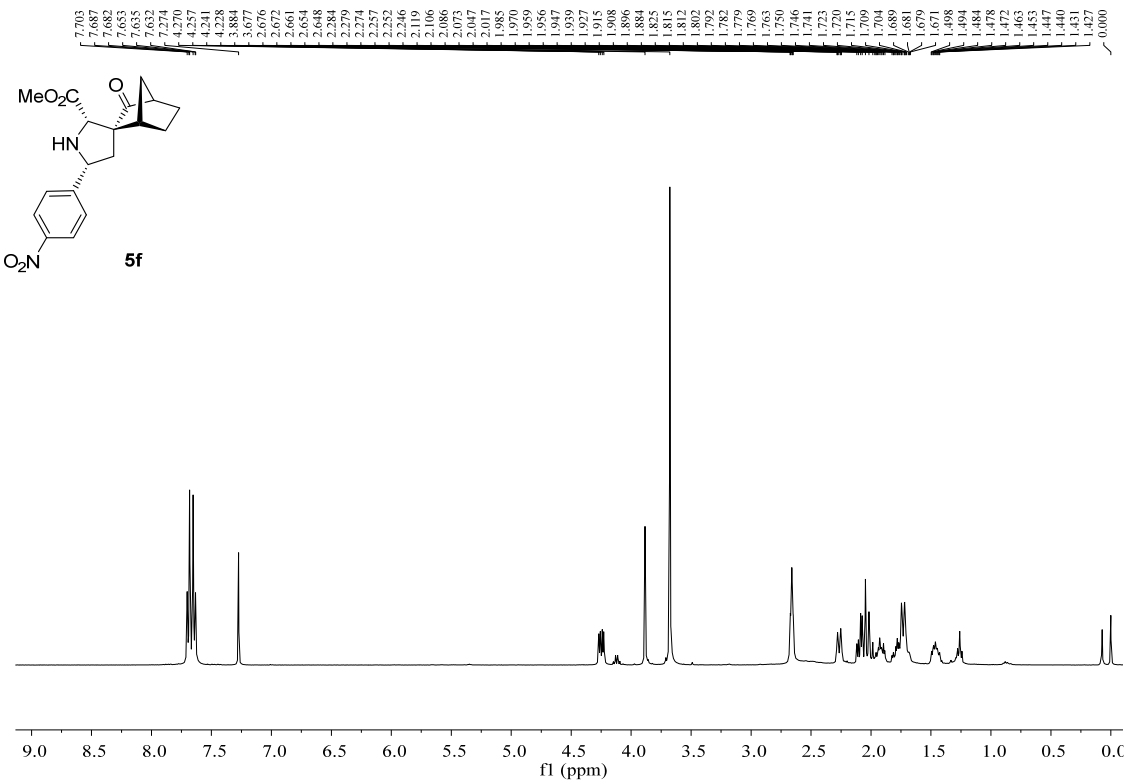


Figure S16. ^{1}H NMR spectrum of **5f**, related to **Table 2.**

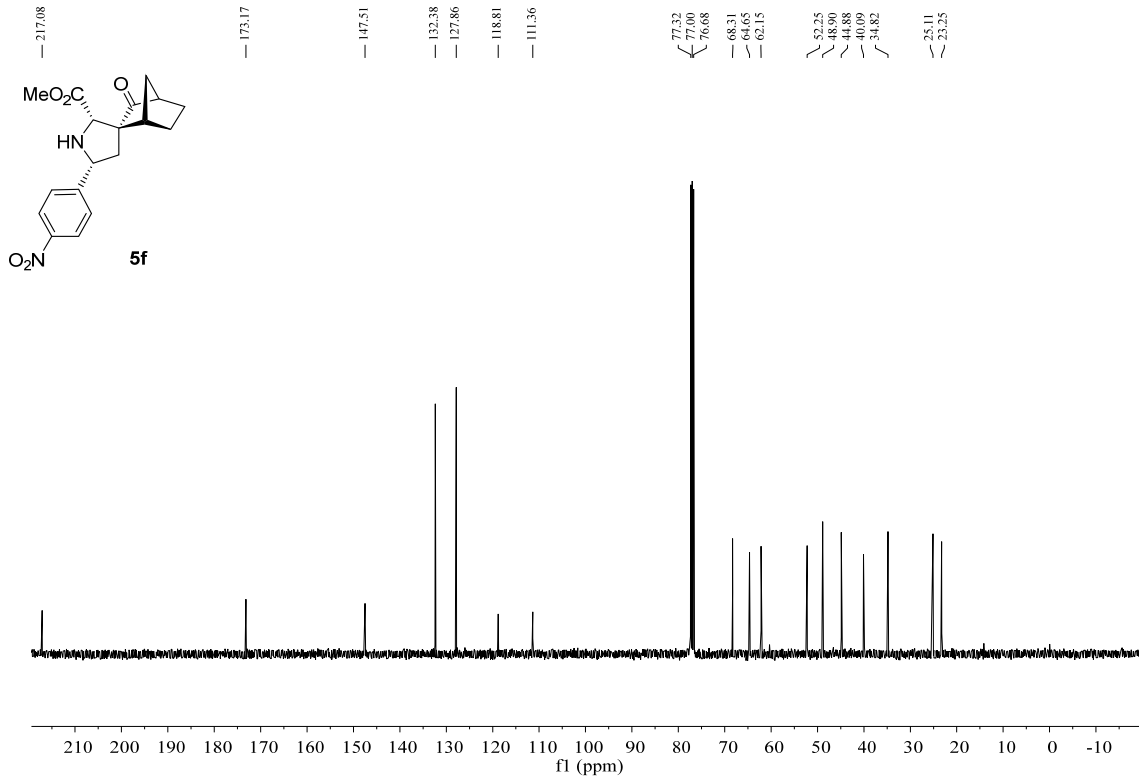
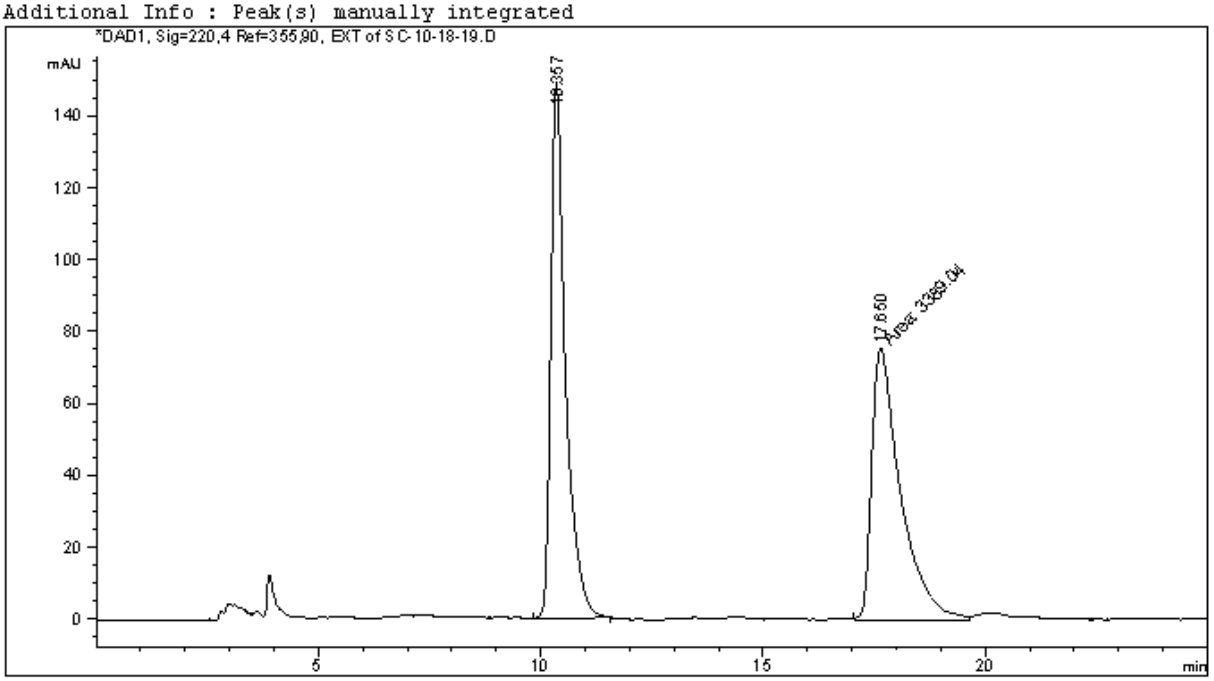


Figure S17. ^{13}C NMR spectrum of **5f**, related to **Table 2**.

Data File E:\DATA\SC\SC-10-18-19\SC-10-18-19 2018-10-12 17-25-57\SC-10-18-19.D
Sample Name: SC-10-18A

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   83
    Injection Date  : 10/12/2018 5:27:21 PM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-10-18-19\SC-10-18-19 2018-10-12 17-25-57\SC-2-ADH-70-30-DAD-
                      204NM-25MIN-1ML.M
    Last changed    : 10/12/2018 5:25:57 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-10-18-19\SC-10-18-19 2018-10-12 17-25-57\SC-2-ADH-70-30-DAD-
                      204NM-25MIN-1ML.M (Sequence Method)
    Last changed    : 10/30/2018 10:09:17 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

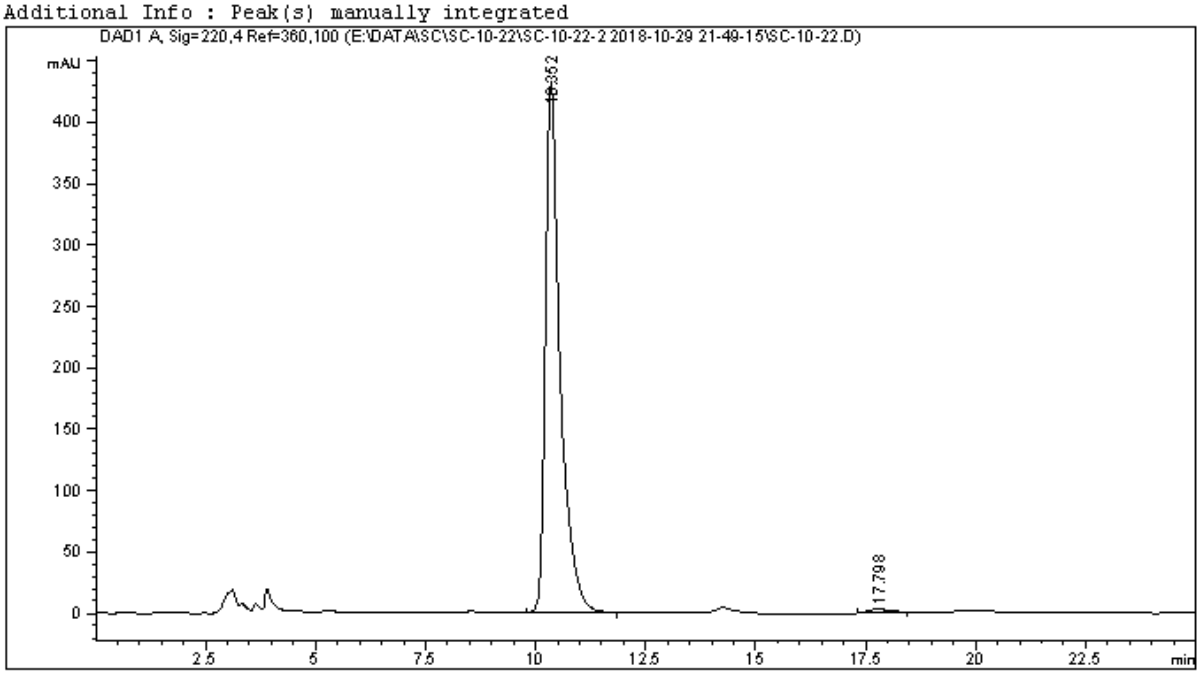

    Signal 1: DAD1, Sig=220,4 Ref=355,90, EXT
     Signal has been modified after loading from rawdata file!

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  10.357 BB    0.3339 3406.08594  148.89496  50.1254
       2  17.650 MM    0.7481 3389.04370   75.50265  49.8746

    Totals :                  6795.12964  224.39761
```

Data File E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-10-22.D
Sample Name: SC-10-22A-2

```
======================================================================
Acq. Operator    : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                              Location :   87
Injection Date  : 10/29/2018 9:50:46 PM                 Inj :   1
                                                  Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-2-ADH-70-30-220NM-
                  25MIN-1ML.M
Last changed    : 10/29/2018 9:49:15 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-2-ADH-70-30-220NM-
                  25MIN-1ML.M (Sequence Method)
Last changed    : 10/30/2018 10:13:33 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.352 BB    0.3377 1.00233e4   431.92621  98.9833
   2  17.798 BB    0.3699  102.95480    3.27403   1.0167

Totals :                  1.01263e4   435.20023

1260 10/30/2018 10:13:36 PM SYSTEM                    Page 1 of 2
```

Figure S18. HPLC spectrum of **5f**, related to **Table 2**.

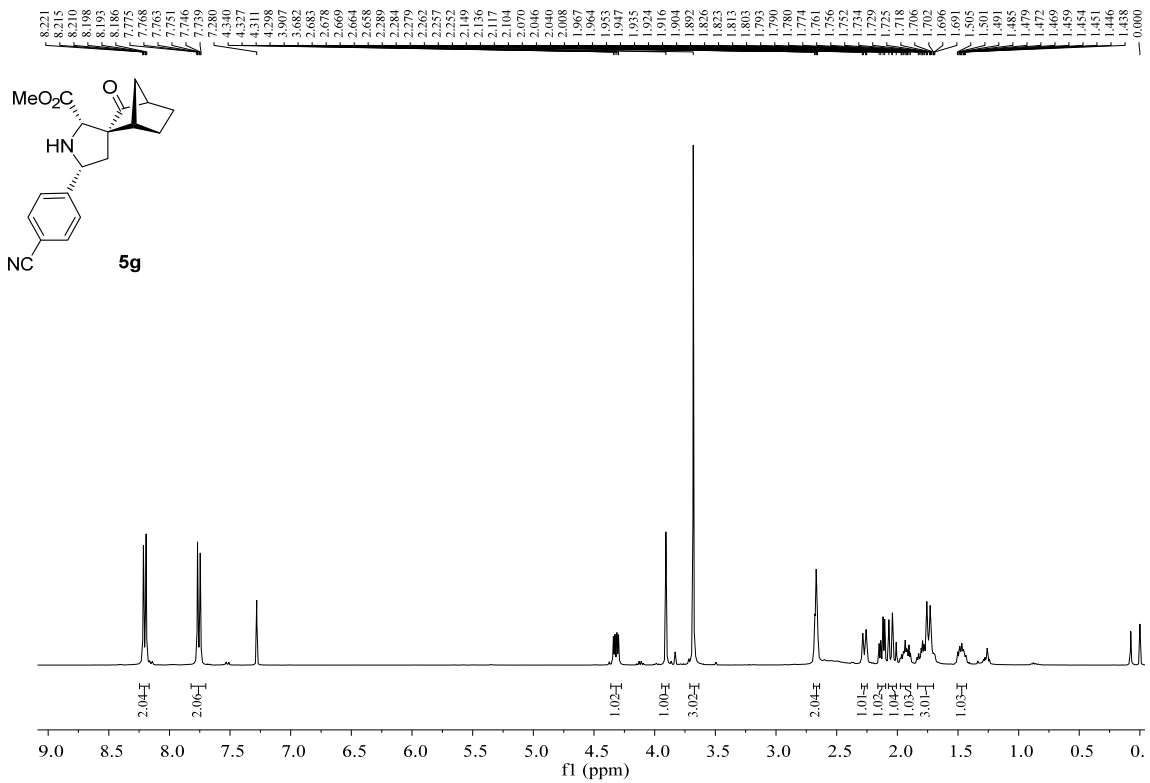


Figure S19. ^{1}H NMR spectrum of **5g**, related to **Table 2**.

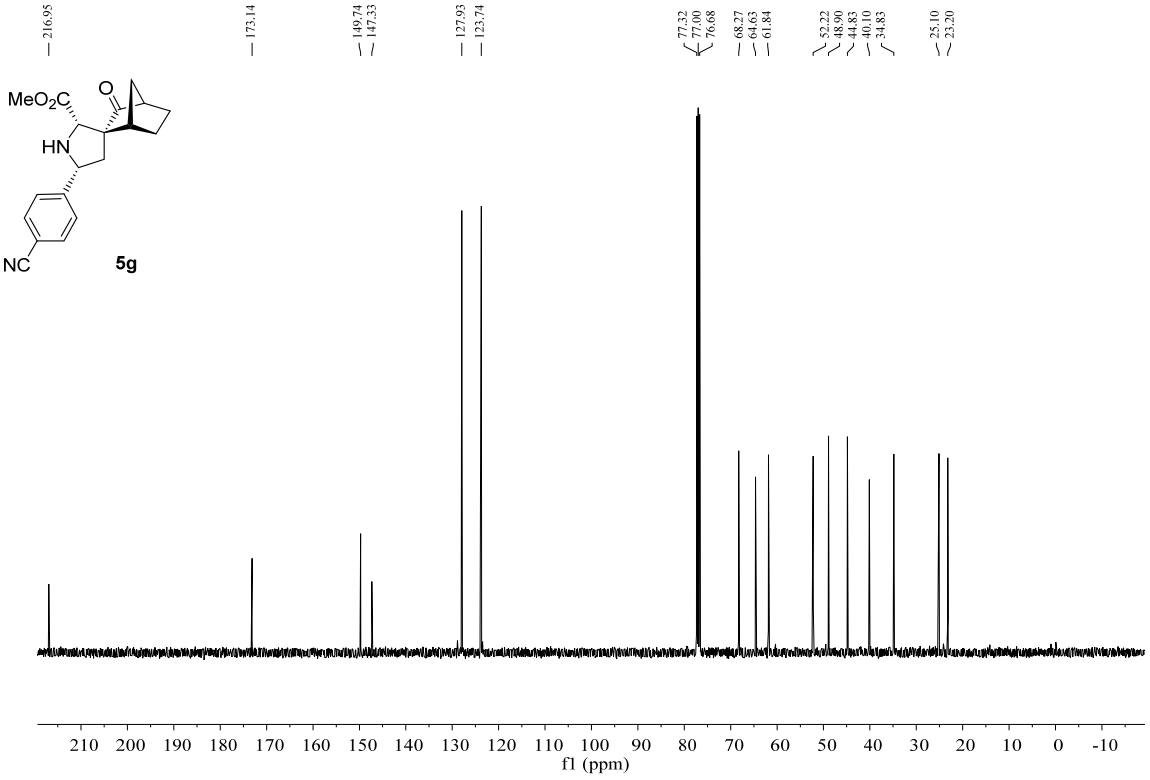
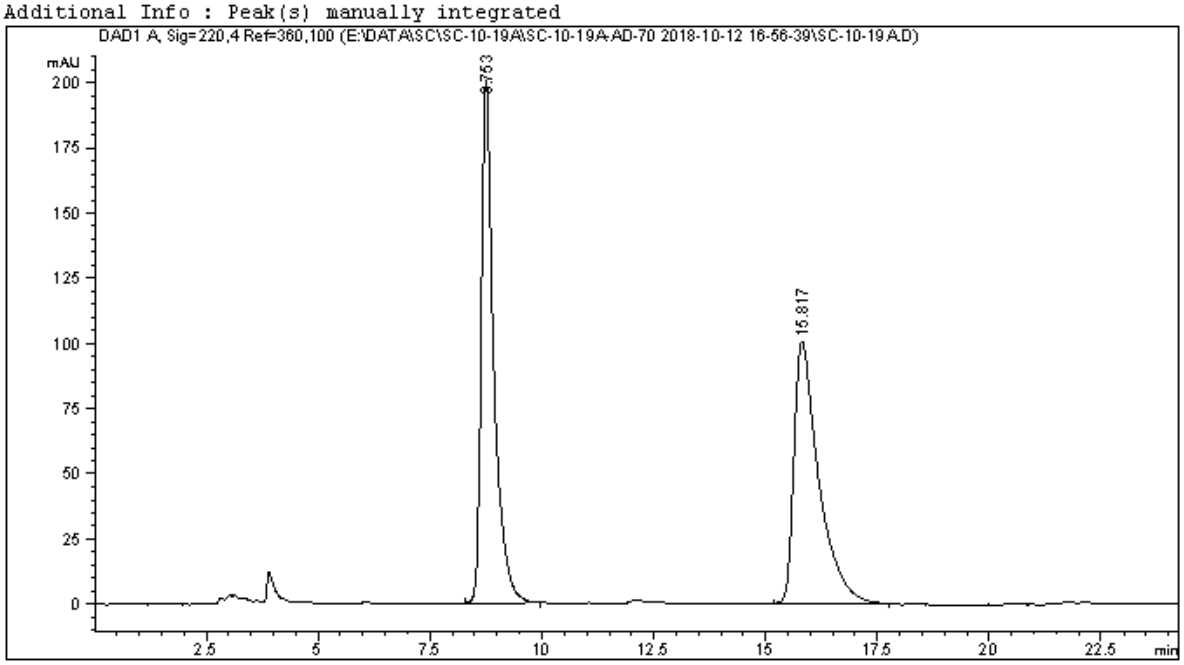


Figure S20. ^{13}C NMR spectrum of **5g**, related to **Table 2**.

Data File E:\DATA\SC\SC-10-19A\SC-10-19A-AD-70 2018-10-12 16-56-39\SC-10-19A.D
Sample Name: SC-10-19A

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   85
    Injection Date  : 10/12/2018 4:58:05 PM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-10-19A\SC-10-19A-AD-70 2018-10-12 16-56-39\SC-2-ADH-70-30-DAD
                      -1ML.M
    Last changed    : 10/12/2018 4:56:39 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-10-19A\SC-10-19A-AD-70 2018-10-12 16-56-39\SC-2-ADH-70-30-DAD
                      -1ML.M (Sequence Method)
    Last changed    : 10/30/2018 10:15:12 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

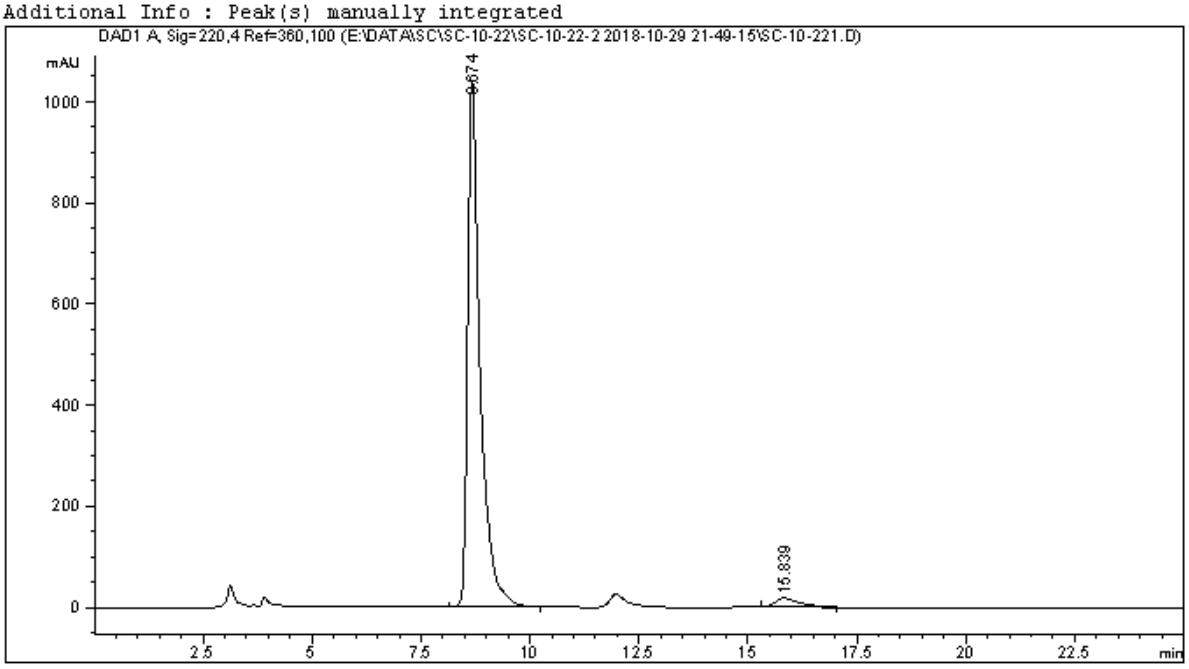

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.753 BB    0.2834 3888.39844  200.38562  50.1301
       2  15.817 BB    0.5381 3868.21045  100.48194  49.8699

    Totals :                  7756.60889  300.86756
```

Data File E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-10-221.D
Sample Name: SC-10-22B-2

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : 1260                           Location :   88
Injection Date  : 10/29/2018 10:17:15 PM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-2-ADH-70-30-220NM-
                  25MIN-1ML.M
Last changed    : 10/29/2018 9:49:15 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-10-22\SC-10-22-2 2018-10-29 21-49-15\SC-2-ADH-70-30-220NM-
                  25MIN-1ML.M (Sequence Method)
Last changed    : 10/30/2018 10:16:38 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.674 BB    0.2939 2.08546e4  1040.20422  97.0665
   2  15.839 BB    0.4449  630.25385   16.75473   2.9335

Totals :                  2.14849e4  1056.95895

1260 10/30/2018 10:16:40 PM SYSTEM                          Page 1 of 2
```

Figure S21. HPLC spectrum of **5g**, related to **Table 2**.

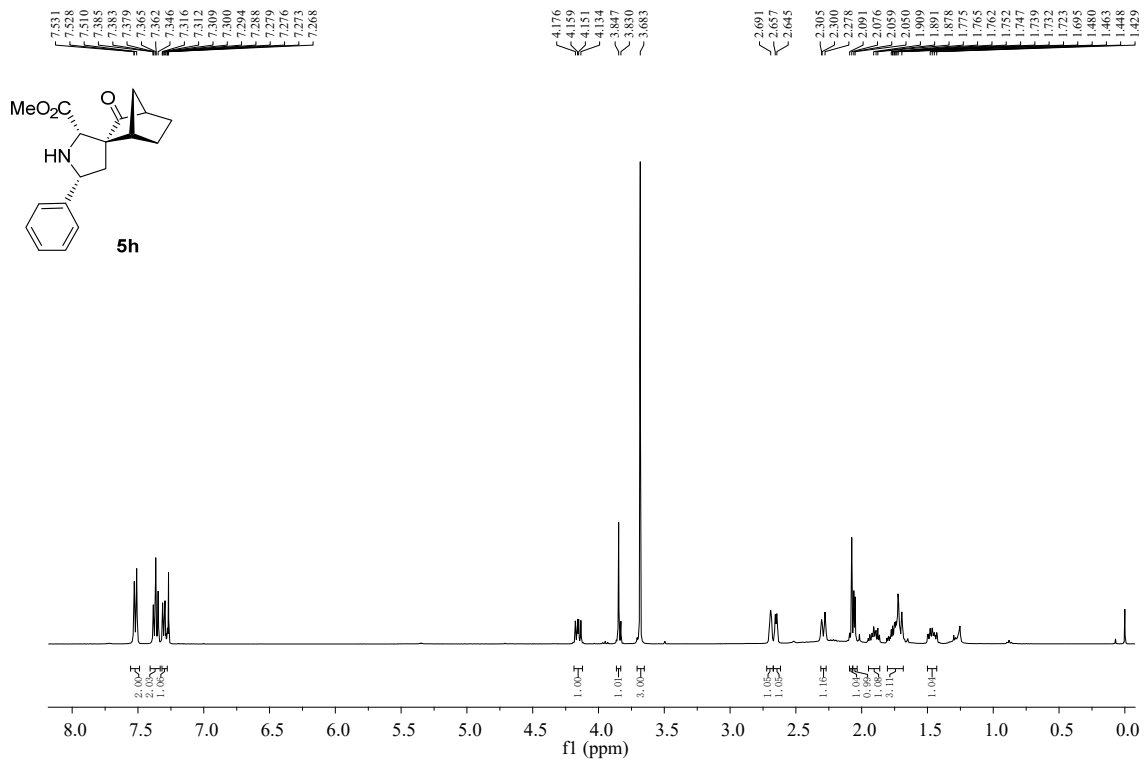


Figure S22. ^{1}H NMR spectrum of **5h**, related to **Table 2**.

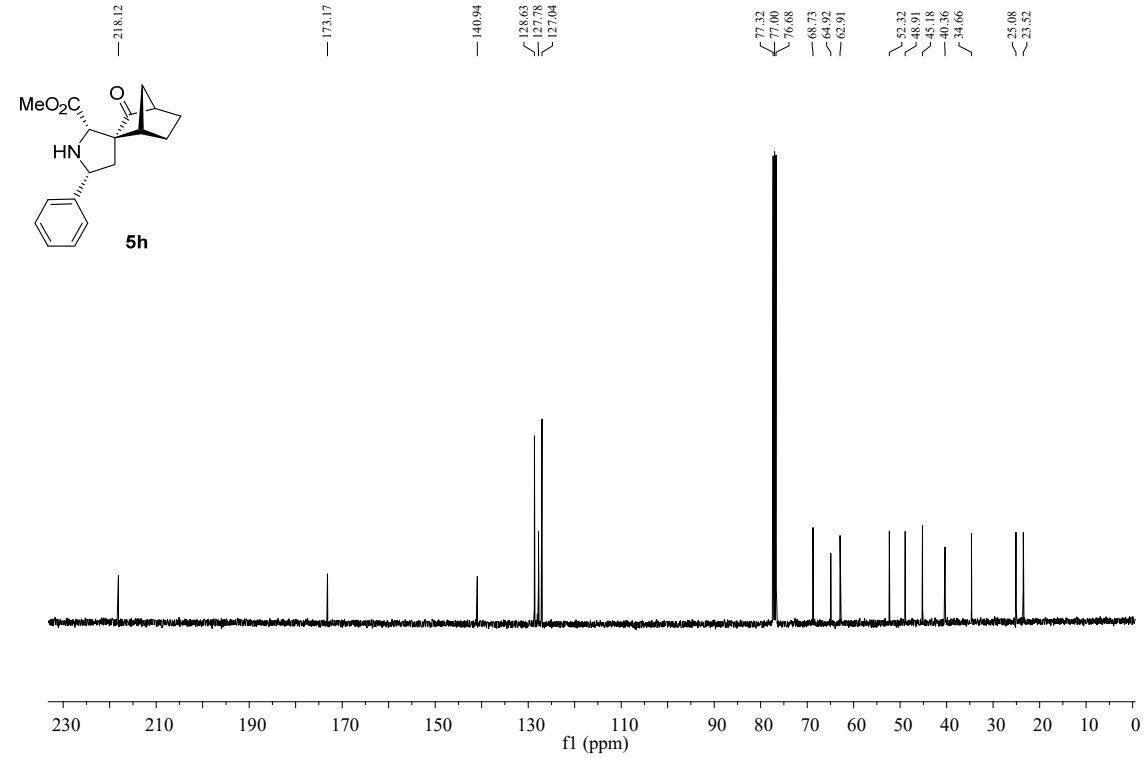
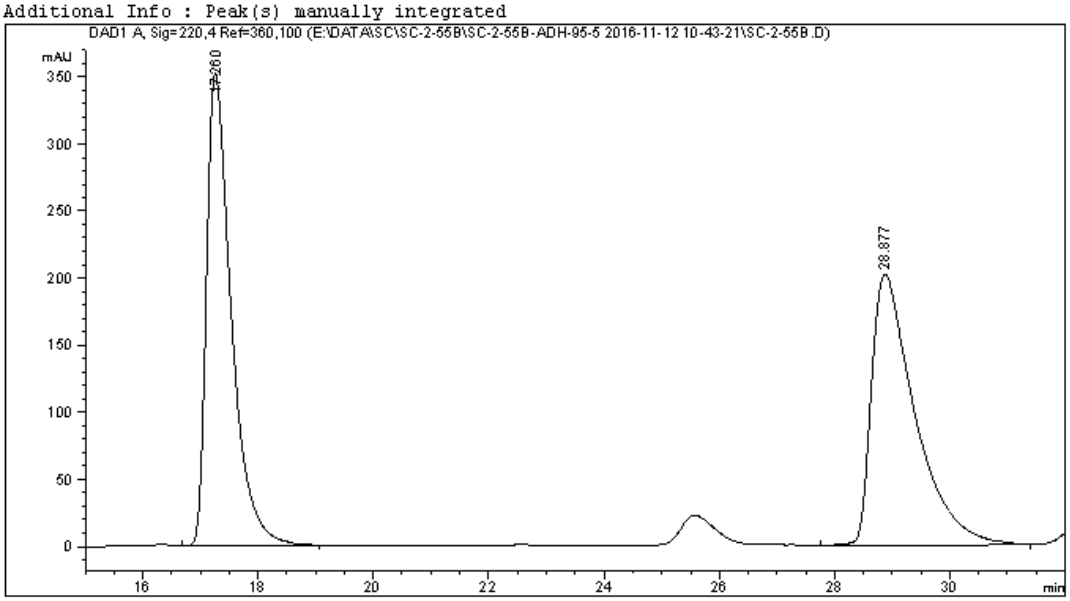


Figure S23. ^{13}C NMR spectrum of **5h**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-55B\SC-2-55B-ADH-95-5 2016-11-12 10-43-21\SC-2-55B.D
Sample Name: SC-2-55B-ADH-95-5

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   62
    Injection Date  : 11/13/2016 2:44:43 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-55B\SC-2-55B-ADH-95-5 2016-11-12 10-43-21\SC-2-ADH-95-5-
                      220NM-1ML.M
    Last changed    : 11/13/2016 2:43:22 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-55B\SC-2-55B-ADH-95-5 2016-11-12 10-43-21\SC-2-ADH-95-5-
                      220NM-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 8:47:52 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

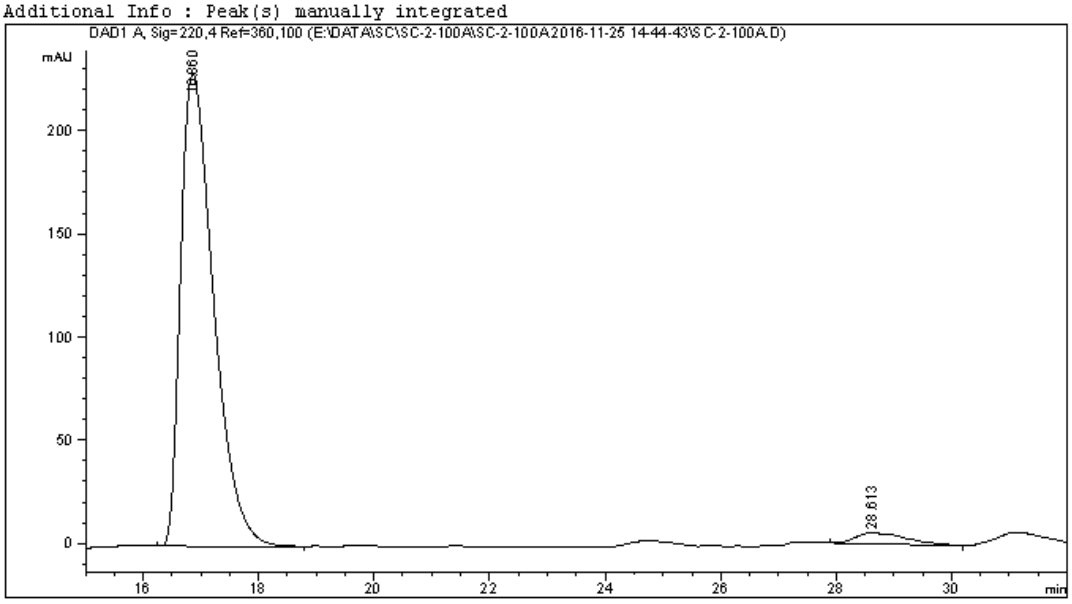

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  17.260 BB    0.4462 1.05059e4   351.96869  49.9229
       2  28.877 BB    0.7447 1.05383e4   201.66565  50.0771

    Totals :                  2.10442e4   553.63434
```

Data File E:\DATA\SC\SC-2-100A\SC-2-100A 2016-11-25 14-44-43\SC-2-100A.D
Sample Name: SC-2-100A

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   64
    Injection Date  : 11/26/2016 6:46:08 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-100A\SC-2-100A 2016-11-25 14-44-43\SC-2-ADH-95-5-220NM-
                      40MIN.M
    Last changed    : 11/26/2016 6:44:43 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-100A\SC-2-100A 2016-11-25 14-44-43\SC-2-ADH-95-5-220NM-
                      40MIN.M (Sequence Method)
    Last changed    : 6/3/2017 8:52:57 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  16.860 BB    0.6081 9089.69336  228.97258  96.4986
       2  28.613 BB    0.7308  329.81909    5.29420   3.5014

    Totals :                  9419.51245  234.26678
```


Figure S24. HPLC spectrum of **5h**, related to **Table 2**.

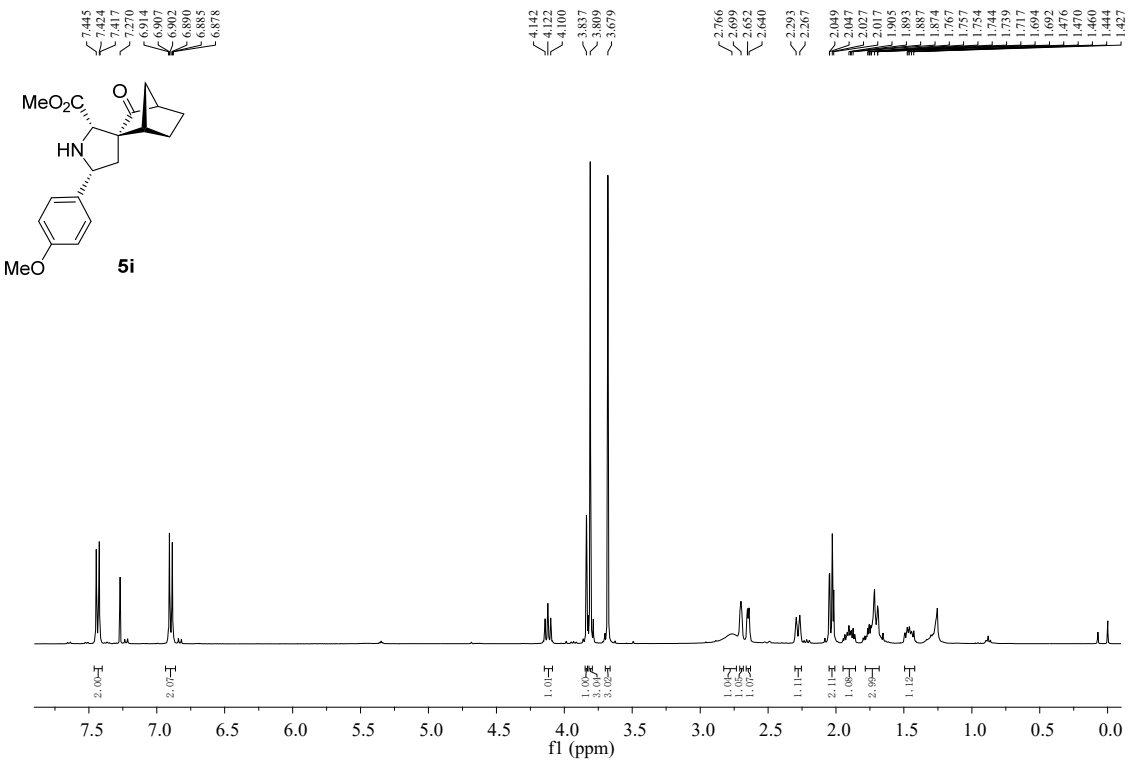


Figure S25. ^{1}H NMR spectrum of **5i**, related to **Table 2**.

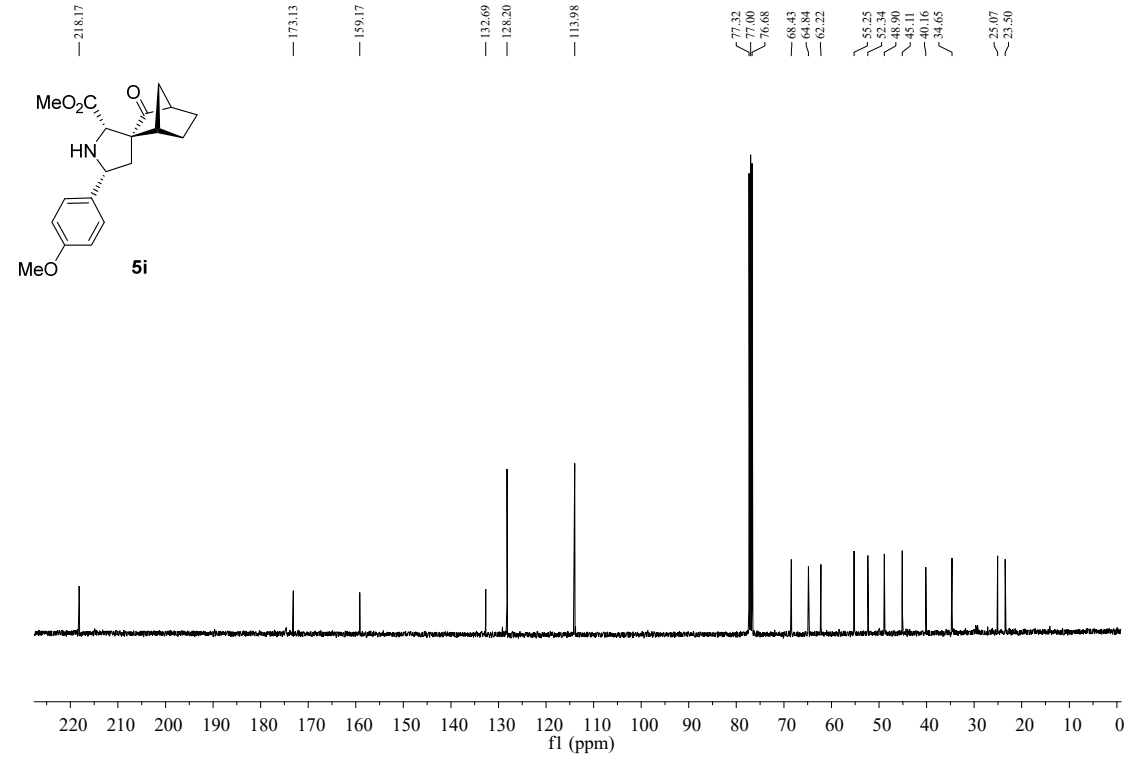
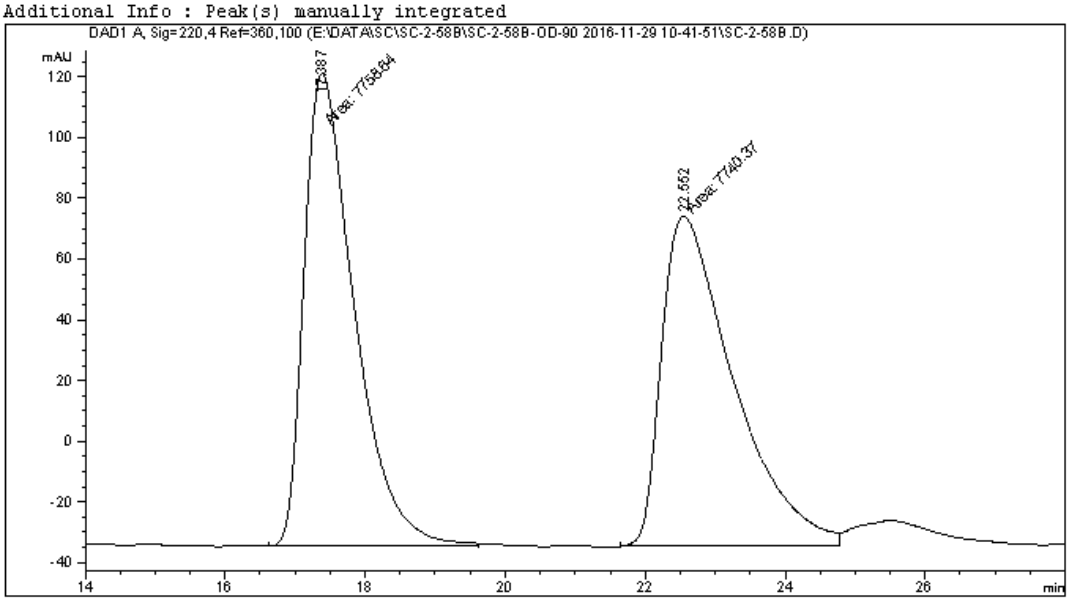


Figure S26. ^{13}C NMR spectrum of **5i**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-58B\SC-2-58B-OD-90 2016-11-29 10-41-51\SC-2-58B.D
Sample Name: SC-2-58B-OD-90

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   63
    Injection Date  : 11/30/2016 2:43:15 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-58B\SC-2-58B-OD-90 2016-11-29 10-41-51\SC-6-ODH-90-10-DAD-
                      1ML.M
    Last changed    : 11/30/2016 2:41:51 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-58B\SC-2-58B-OD-90 2016-11-29 10-41-51\SC-6-ODH-90-10-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/3/2017 8:56:01 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  17.387 MM    0.8313 7758.63818  155.54788  50.0589
       2  22.552 MM    1.1893 7740.37256  108.47194  49.9411

    Totals :                  1.54990e4   264.01982
```

Data File E:\DATA\SC\SC-2-105B\SC-2-105B-OD-90 2016-11-29 11-18-34\SC-2-105B.D
Sample Name: SC-2-105B-OD-90

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   65
Injection Date  : 11/30/2016 3:20:00 AM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-105B\SC-2-105B-OD-90 2016-11-29 11-18-34\SC-6-ODH-90-10-DAD
                  -1ML.M
Last changed    : 11/30/2016 3:18:34 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-105B\SC-2-105B-OD-90 2016-11-29 11-18-34\SC-6-ODH-90-10-DAD
                  -1ML.M (Sequence Method)
Last changed    : 6/4/2017 11:14:07 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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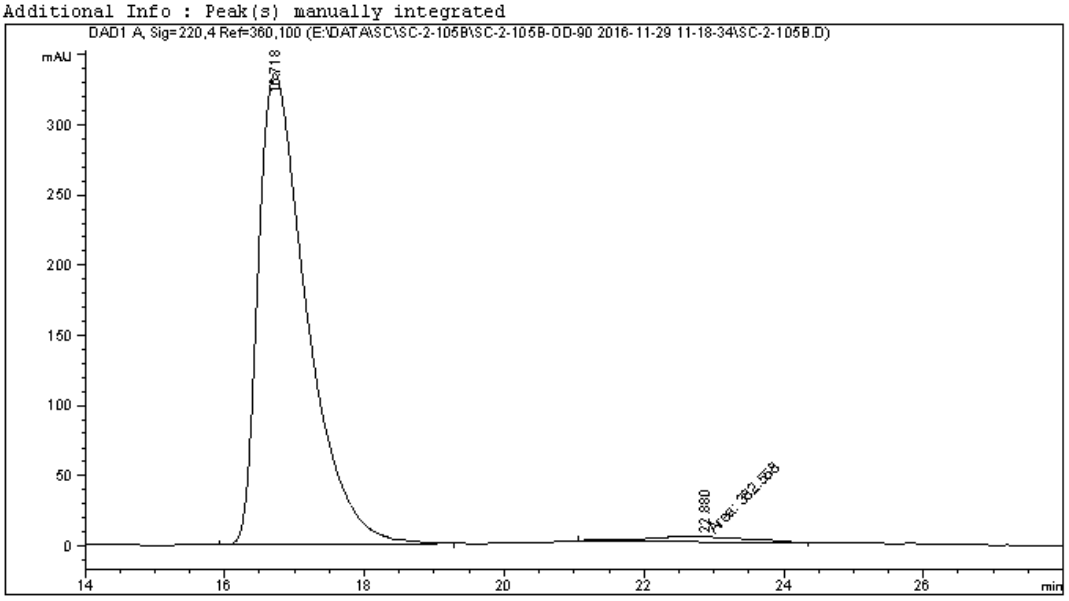



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  16.718 BB    0.7235 1.61356e4   335.85165  97.6840
   2  22.880 MM    1.6828  382.55798    3.78891   2.3160

Totals :                  1.65181e4   339.64057
```


Figure S27. HPLC spectrum of **5i**, related to **Table 2**.

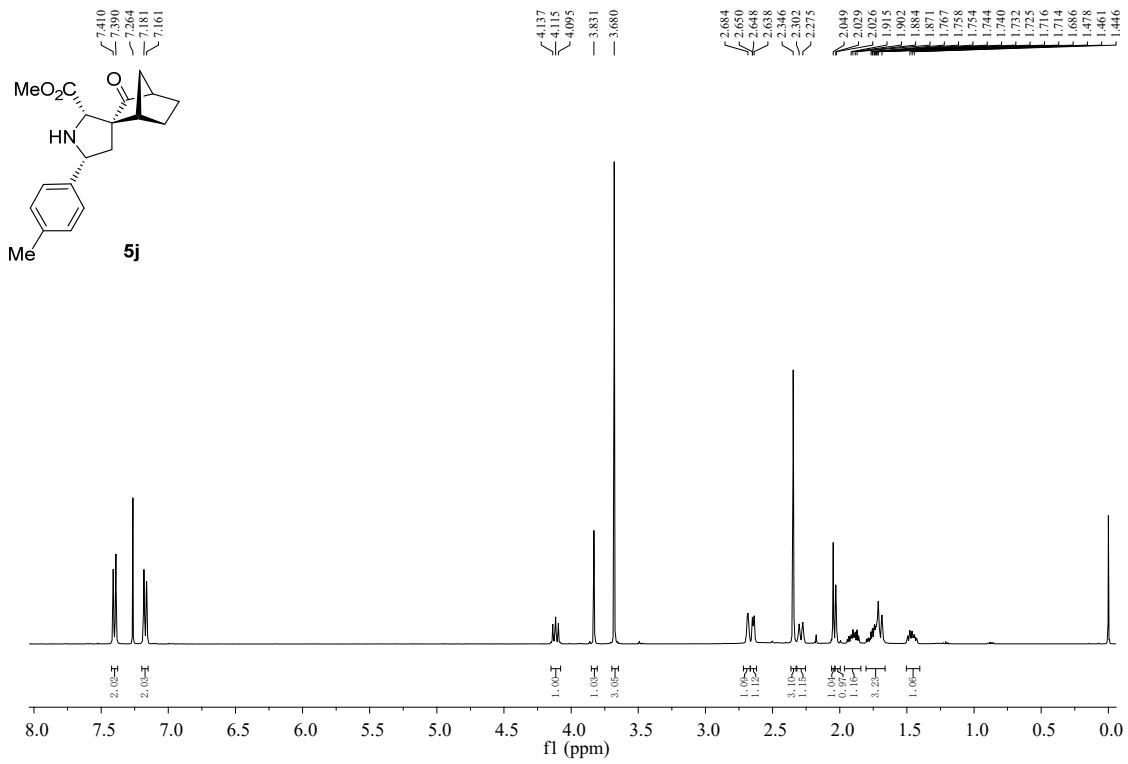


Figure S28. ^{1}H NMR spectrum of **5j**, related to **Table 2**.

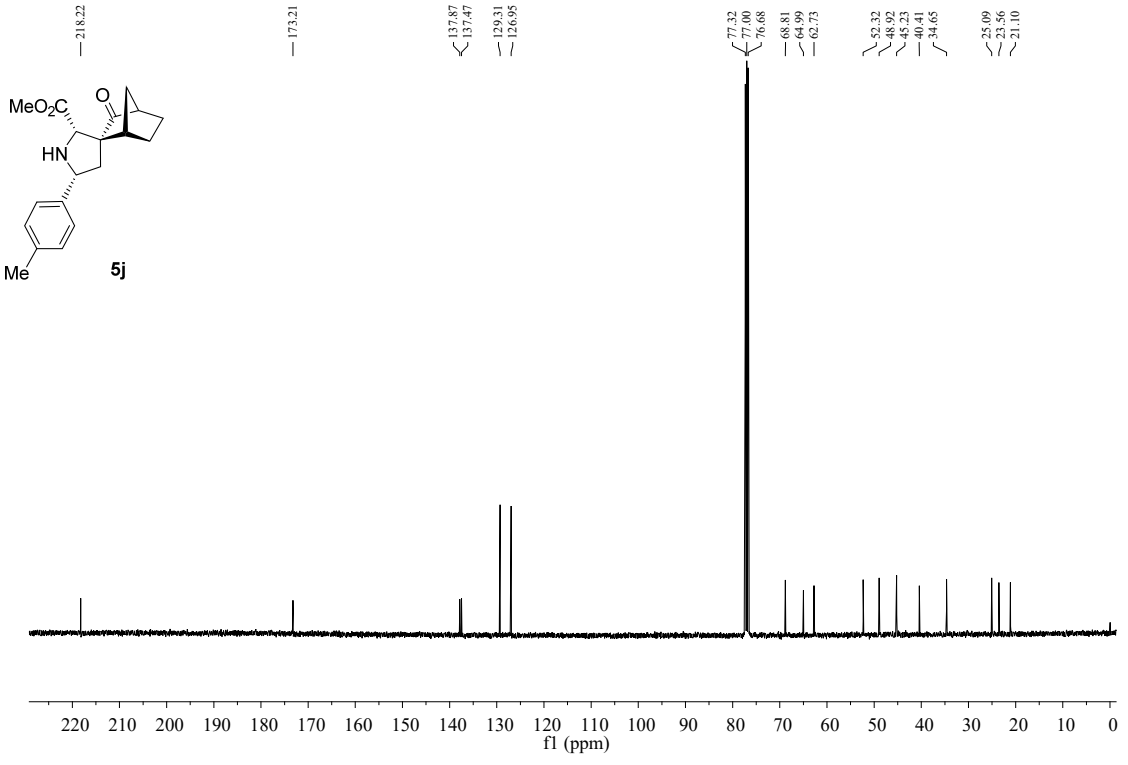
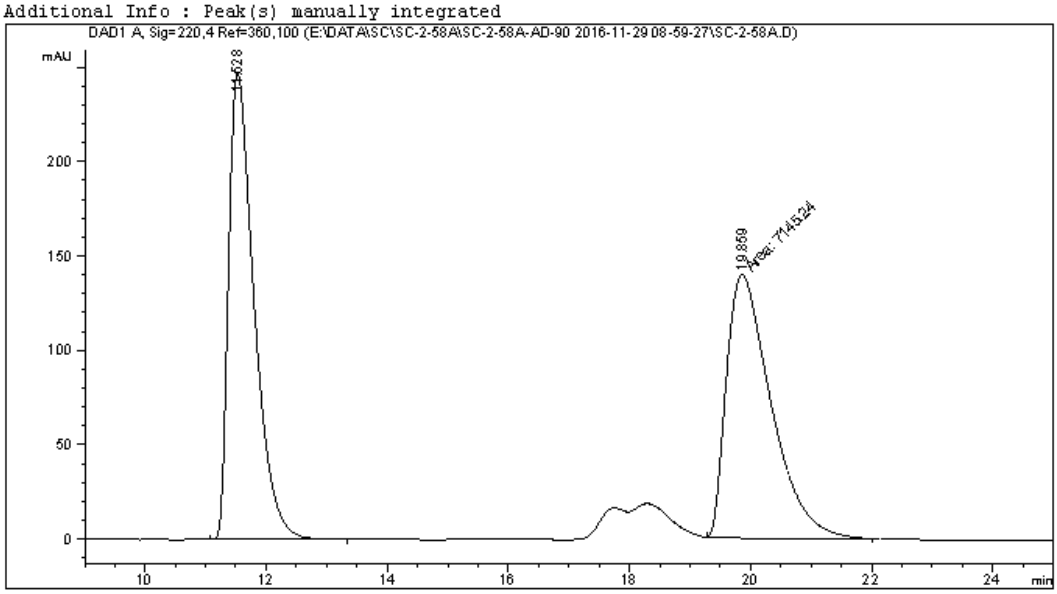


Figure S29. ^{13}C NMR spectrum of **5j**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-58A\SC-2-58A-AD-90 2016-11-29 08-59-27\SC-2-58A.D
Sample Name: SC-2-58A-AD-90

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   62
    Injection Date  : 11/30/2016 1:00:52 AM              Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-58A\SC-2-58A-AD-90 2016-11-29 08-59-27\SC-1-ADH-90-10-DAD-
                      1ML.M
    Last changed    : 11/30/2016 12:59:27 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-58A\SC-2-58A-AD-90 2016-11-29 08-59-27\SC-1-ADH-90-10-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/3/2017 9:09:36 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

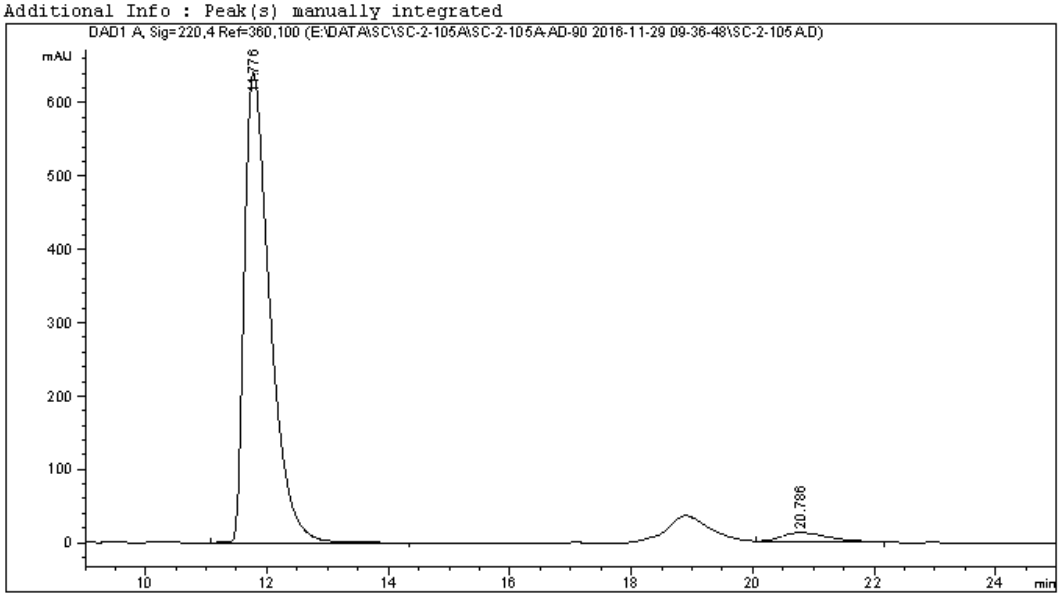

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.528 BB    0.4417 7197.94727  247.20734  50.1838
       2  19.859 MM    0.8527 7145.23584  139.65518  49.8162

    Totals :                  1.43432e4   386.86252
```

Data File E:\DATA\SC\SC-2-105A\SC-2-105A-AD-90 2016-11-29 09-36-48\SC-2-105A.D
Sample Name: SC-2-105A-AD-90

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   64
Injection Date  : 11/30/2016 1:38:14 AM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-105A\SC-2-105A-AD-90 2016-11-29 09-36-48\SC-2-ADH-90-10-
                  220NM-35MIN-1ML.M
Last changed    : 11/30/2016 1:36:48 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-105A\SC-2-105A-AD-90 2016-11-29 09-36-48\SC-2-ADH-90-10-
                  220NM-35MIN-1ML.M (Sequence Method)
Last changed    : 6/3/2017 9:11:31 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.776 BB    0.4358 1.86037e4   640.57727  96.6226
   2  20.786 BB    0.6269  650.27484   12.17872   3.3774

Totals :                  1.92540e4   652.75599
```


Figure S30. HPLC spectrum of **5j**, related to **Table 2**.

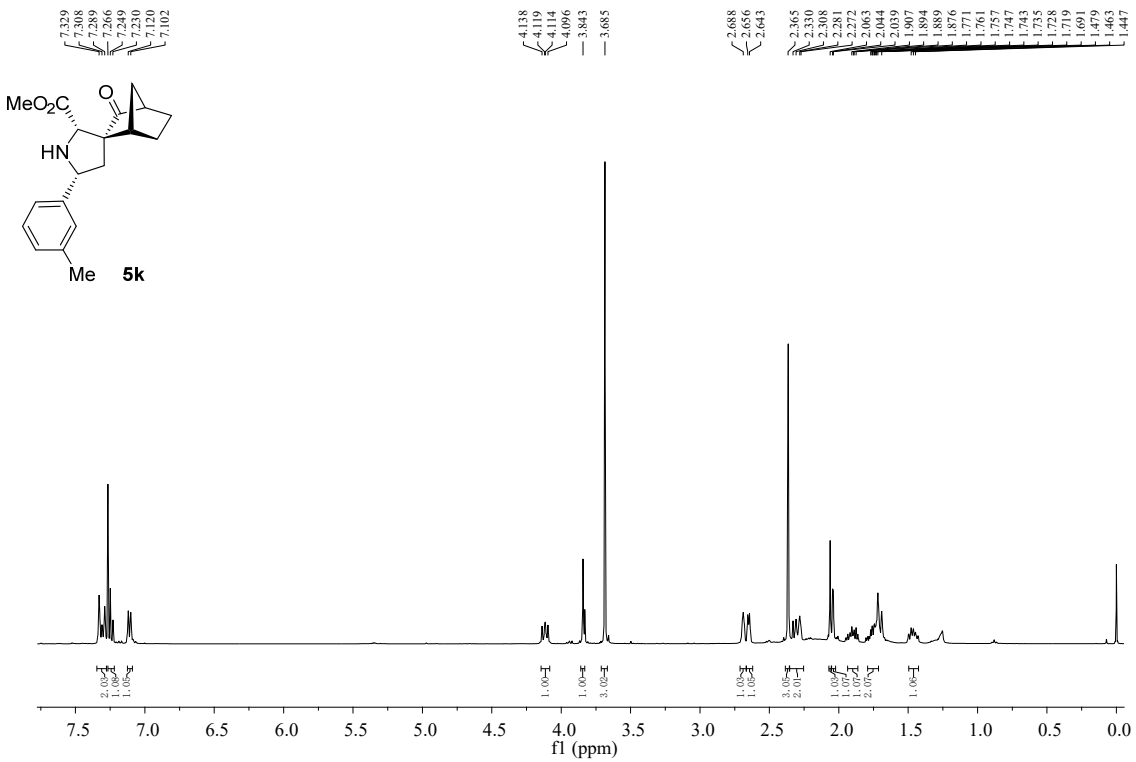


Figure S31. ^{1}H NMR spectrum of **5k**, related to **Table 2**.

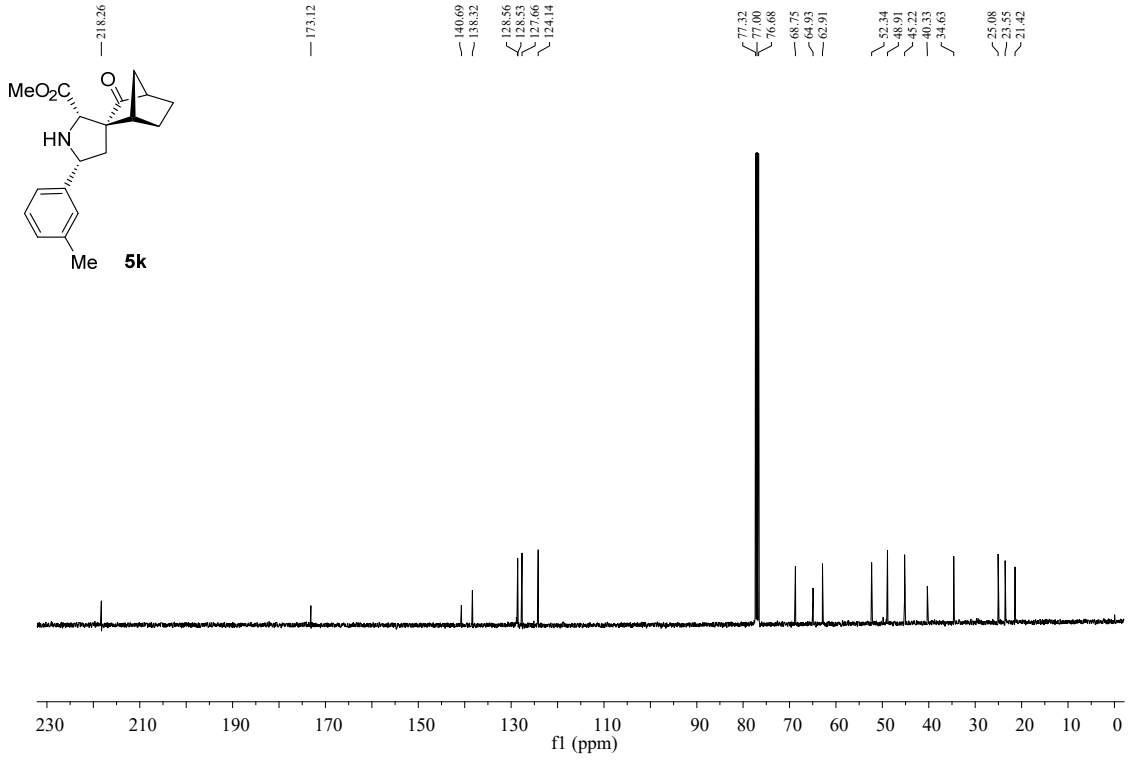
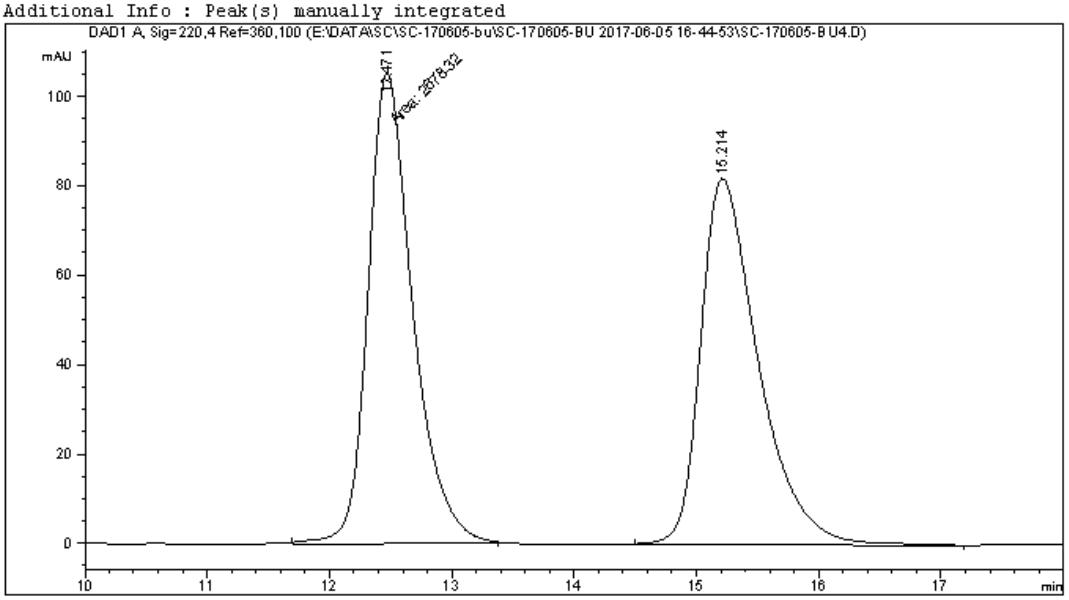


Figure S32. ^{13}C NMR spectrum of **5k**, related to **Table 2**.

Data File E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-170605-BU4.D
Sample Name: SC-2-68A

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   5
    Acq. Instrument : 1260                           Location :   73
    Injection Date  : 6/5/2017 6:26:01 PM                 Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-
                      220NM-30MIN-1ML.M
    Last changed    : 6/5/2017 4:44:53 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-
                      220NM-30MIN-1ML.M (Sequence Method)
    Last changed    : 6/5/2017 8:36:55 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

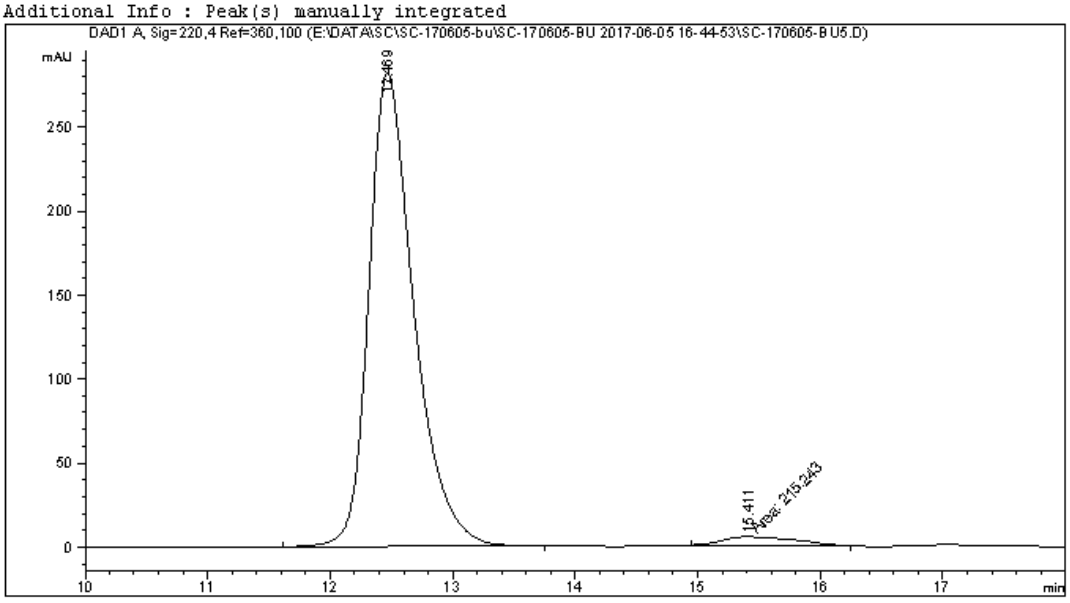

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.471 MM    0.4238 2678.32300  105.33327  49.9513
       2  15.214 BB    0.4838 2683.54980   81.79721  50.0487

    Totals :                  5361.87280  187.13048
```

Data File E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-170605-BU5.D
Sample Name: SC-2-109A

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   6
    Acq. Instrument : 1260                             Location :   74
    Injection Date  : 6/5/2017 6:57:27 PM                  Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-
                      220NM-30MIN-1ML.M
    Last changed    : 6/5/2017 4:44:53 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-
                      220NM-30MIN-1ML.M (Sequence Method)
    Last changed    : 6/5/2017 8:38:27 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.469 BB    0.3854 7205.32129  281.66907  97.0994
       2  15.411 MM    0.6841  215.24338    5.24432   2.9006

    Totals :                  7420.56467  286.91338
```


Figure S33. HPLC spectrum of **5k**, related to **Table 2**.

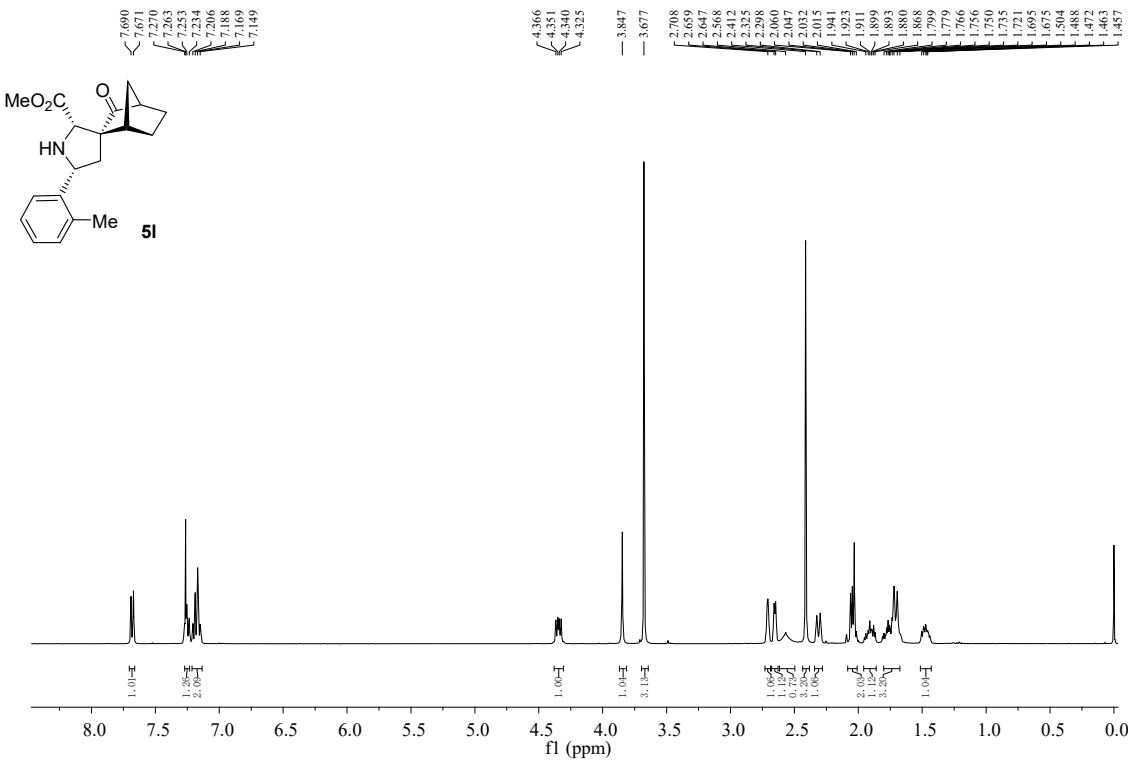


Figure S34. ^{1}H NMR spectrum of **5l**, related to **Table 2**.

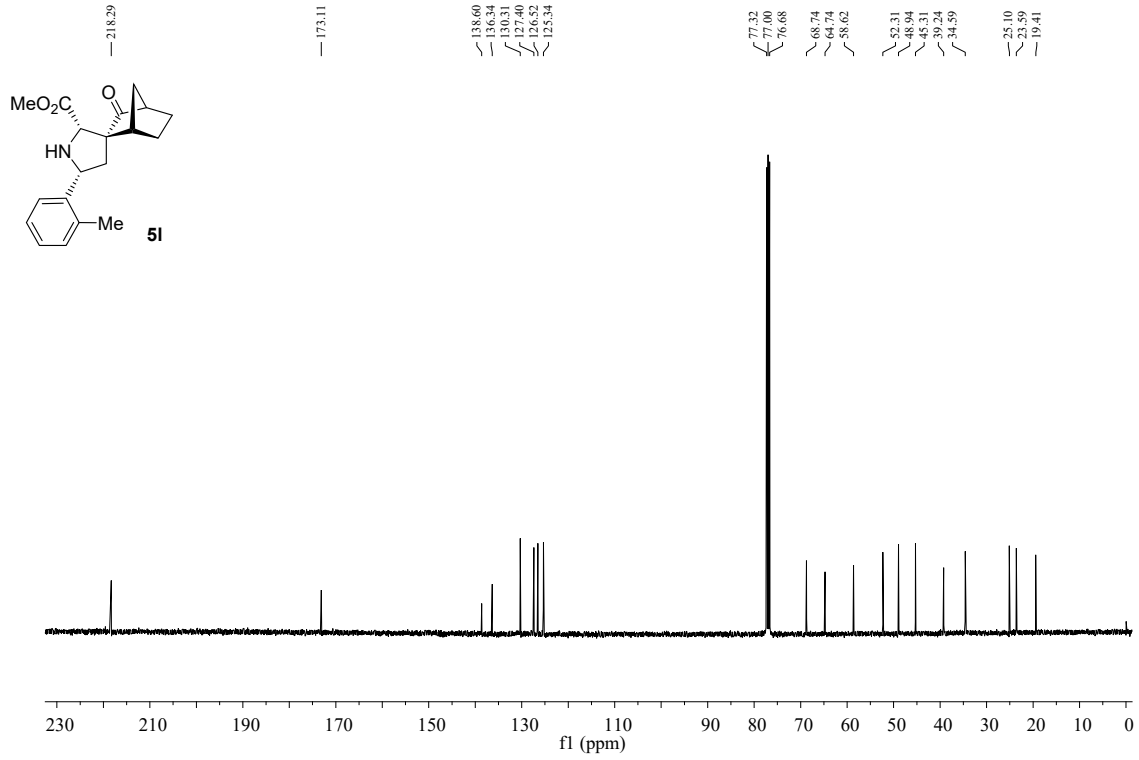
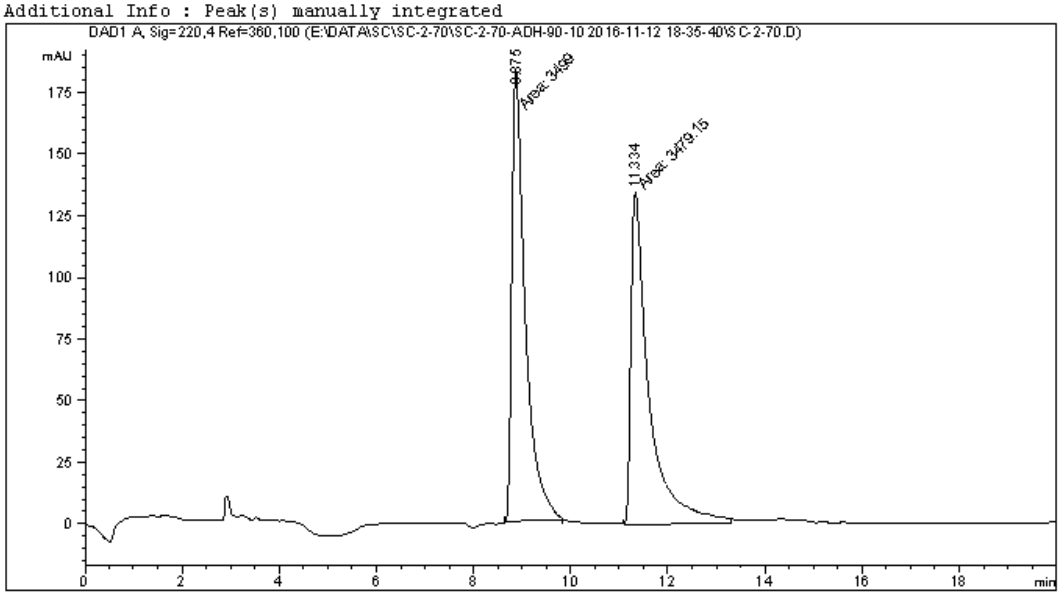


Figure S35. ^{13}C NMR spectrum of **5l**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-70\SC-2-70-ADH-90-10 2016-11-12 18-35-40\SC-2-70.D
Sample Name: SC-2-70-ADH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   65
    Injection Date  : 11/13/2016 10:37:04 AM             Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-70\SC-2-70-ADH-90-10 2016-11-12 18-35-40\SC-2-ADH-90-10-DAD
                      -1ML.M
    Last changed    : 11/13/2016 10:35:40 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-70\SC-2-70-ADH-90-10 2016-11-12 18-35-40\SC-2-ADH-90-10-DAD
                      -1ML.M (Sequence Method)
    Last changed    : 6/3/2017 11:43:56 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

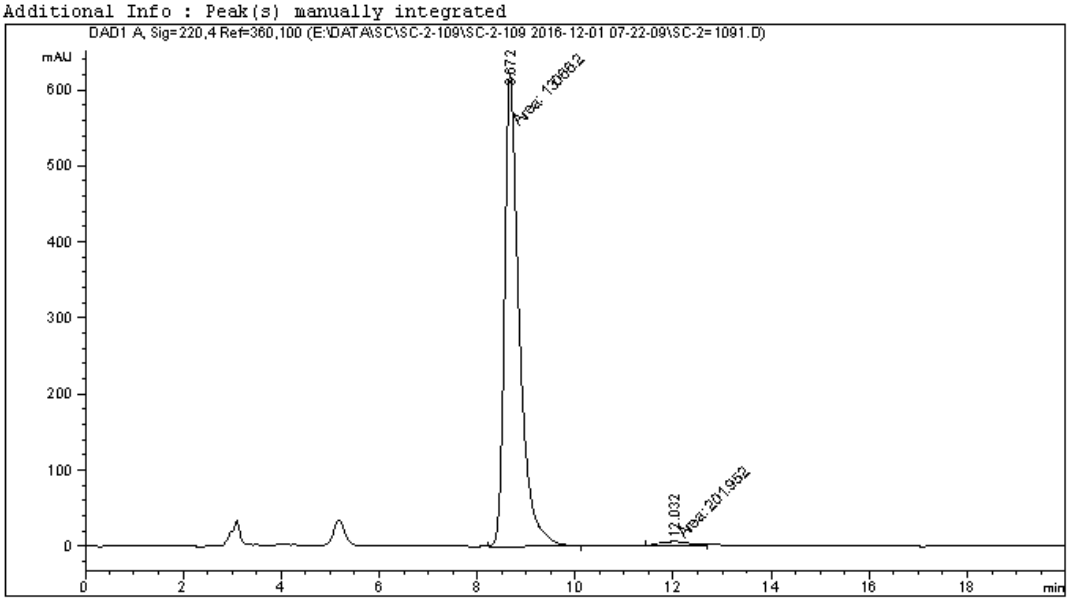

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.875 MM    0.3205 3499.00317  181.92896  50.1422
       2  11.334 MM    0.4306 3479.15088  134.67351  49.8578

    Totals :                  6978.15405  316.60246
```

Data File E:\DATA\SC\SC-2-109\SC-2-109 2016-12-01 07-22-09\SC-2=1091.D
Sample Name: SC-2=109B

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                           Location :   63
Injection Date  : 12/1/2016 7:59:57 AM                Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-114\SC-2-109 2016-12-01 07-22-09\SC-2-ADH-90-10-220NM-35MIN
                  -1ML.M
Last changed    : 12/1/2016 7:22:09 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-109\SC-2-109 2016-12-01 07-22-09\SC-2-ADH-90-10-220NM-35MIN
                  -1ML.M (Sequence Method)
Last changed    : 6/3/2017 11:46:16 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.672 MM    0.3502 1.30662e4   621.78638  98.4779
   2  12.032 MM    0.7140  201.95180    4.71421   1.5221

Totals :                  1.32681e4   626.50059
```


Figure S36. HPLC spectrum of **5l**, related to **Table 2**.

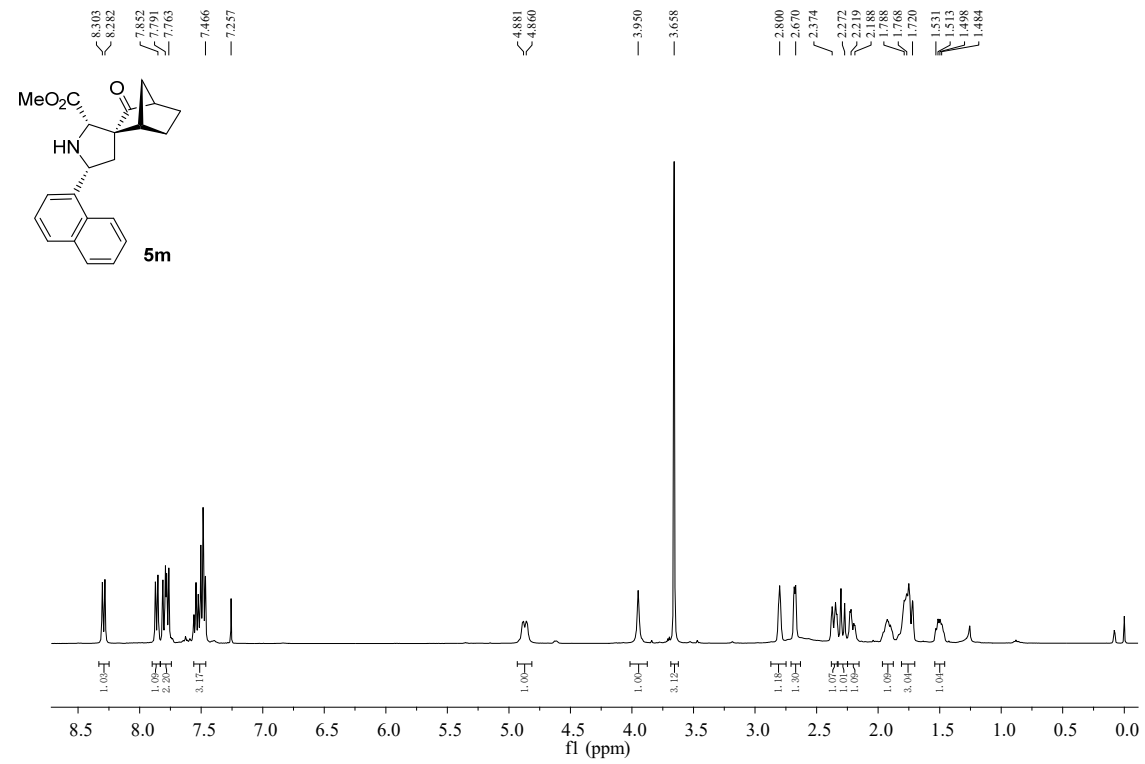


Figure S37. [1]H NMR spectrum of **5m**, related to **Table 2**.

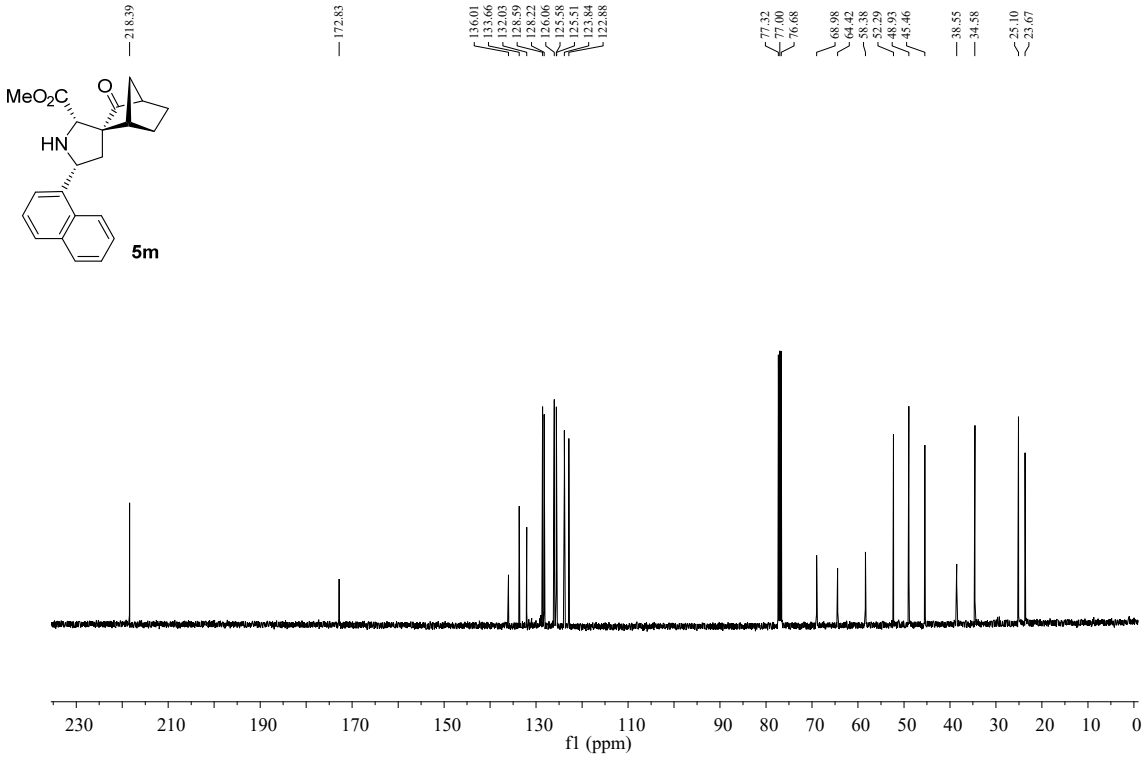
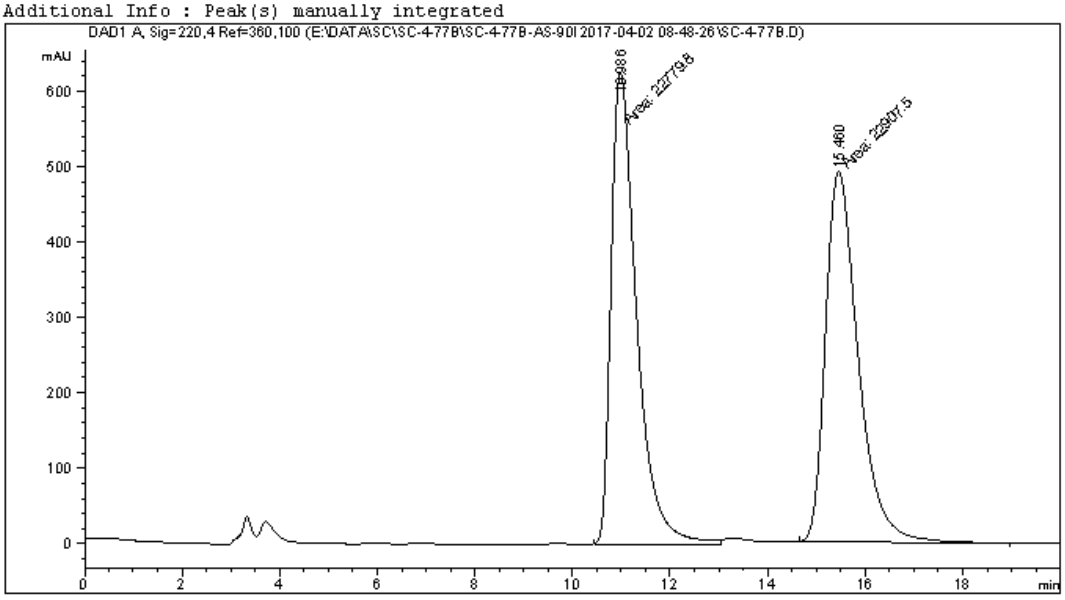


Figure S38. [13]C NMR spectrum of **5m**, related to **Table 2**.

Data File E:\DATA\SC\SC-4-77B\SC-4-77B-AS-901 2017-04-02 08-48-26\SC-4-77B.D
Sample Name: SC-4-77B-AS-90

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   17
    Injection Date  : 4/2/2017 8:49:50 AM                  Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-4-77B\SC-4-77B-AS-901 2017-04-02 08-48-26\SC-1-ASH-90-10-DAD-
                      1ML.M
    Last changed    : 4/2/2017 8:48:26 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-4-77B\SC-4-77B-AS-901 2017-04-02 08-48-26\SC-1-ASH-90-10-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 3:13:24 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

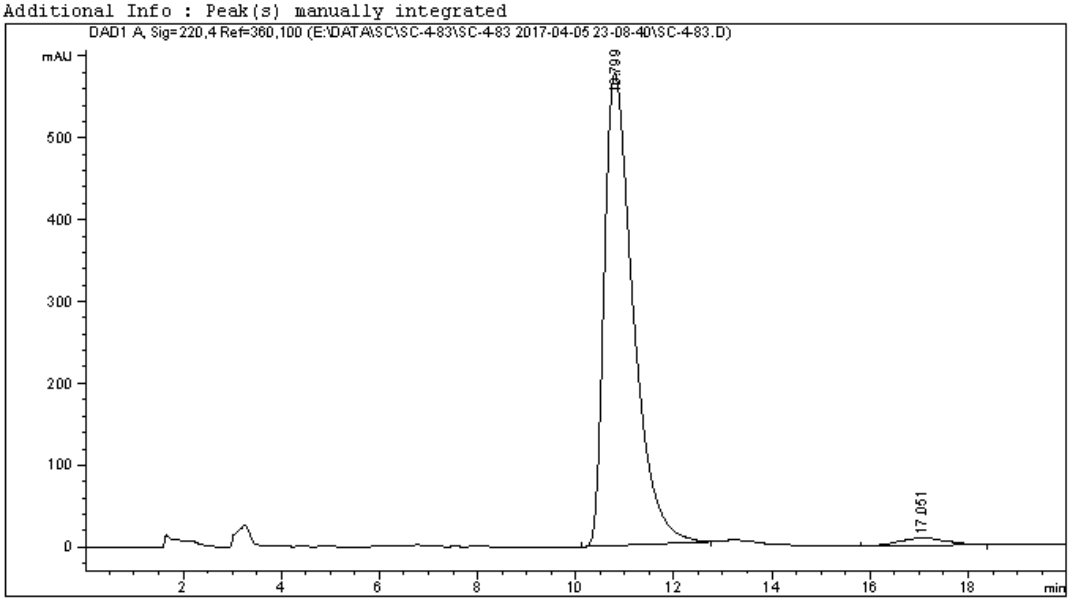

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1  10.986 MM    0.6069 2.27798e4   625.56281  49.8603
       2  15.460 MM    0.7776 2.29075e4   490.98962  50.1397

    Totals :                  4.56873e4  1116.55243
```

Data File E:\DATA\SC\SC-4-83\SC-4-83 2017-04-05 23-08-40\SC-4-83.D
Sample Name: SC-4-83B

```
=====================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                             Location :   14
Injection Date  : 4/5/2017 11:10:04 PM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-83\SC-4-83 2017-04-05 23-08-40\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 4/5/2017 11:08:40 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-83\SC-4-83 2017-04-05 23-08-40\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 3:04:07 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.799 BB    0.6191 2.35686e4   577.55780  97.6028
   2  17.051 BB    0.7913  578.85376    8.58831   2.3972

Totals :                  2.41474e4   586.14611
```


Figure S39. HPLC spectrum of **5m**, related to **Table 2**.

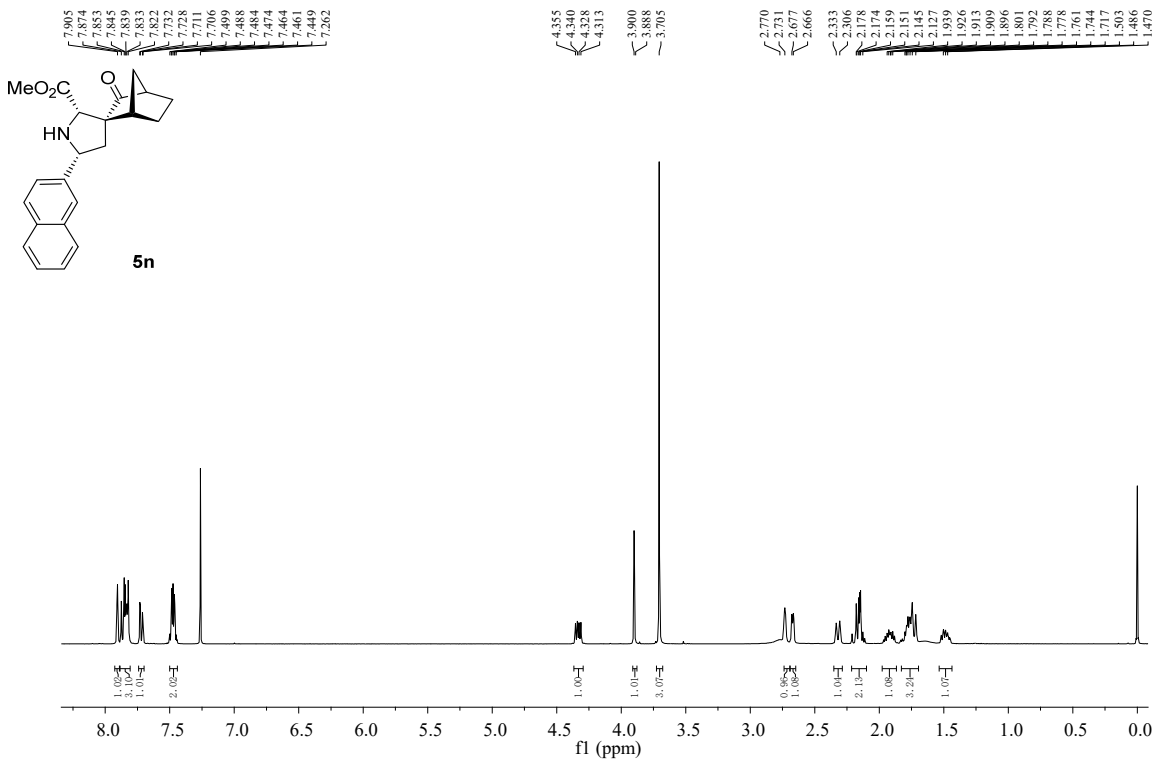


Figure S40. ^{1}H NMR spectrum of **5n**, related to **Table 2**.

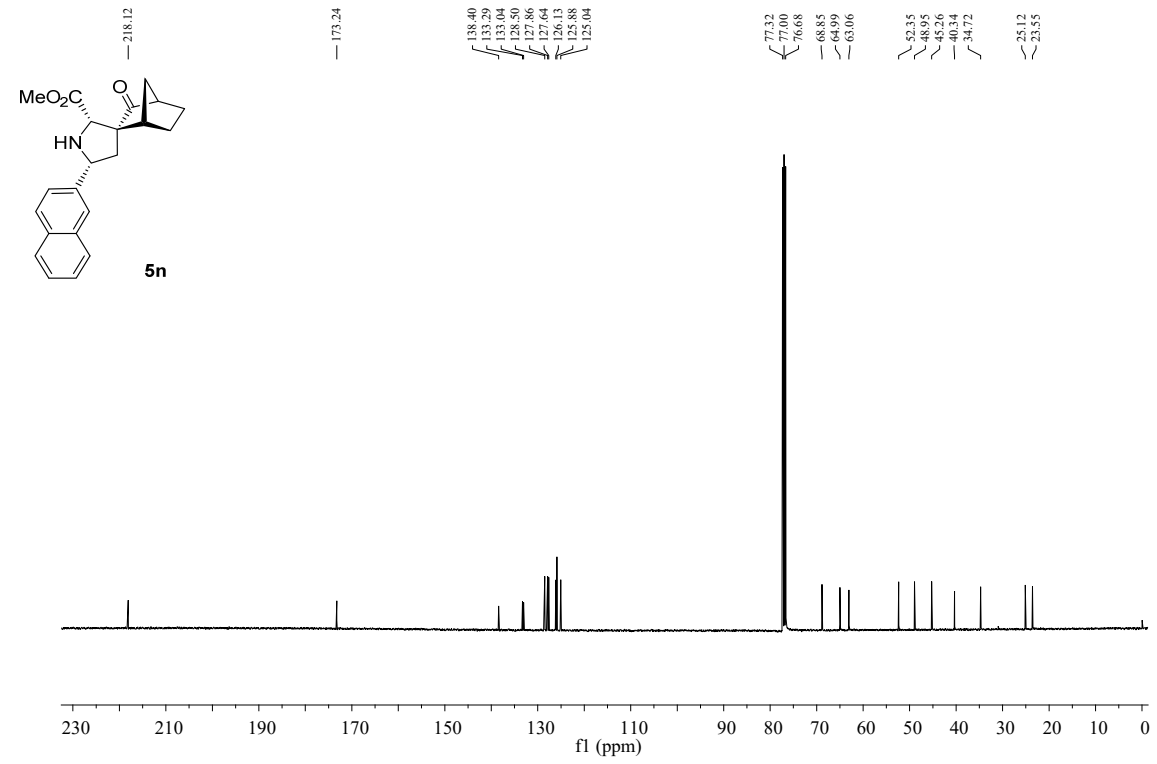
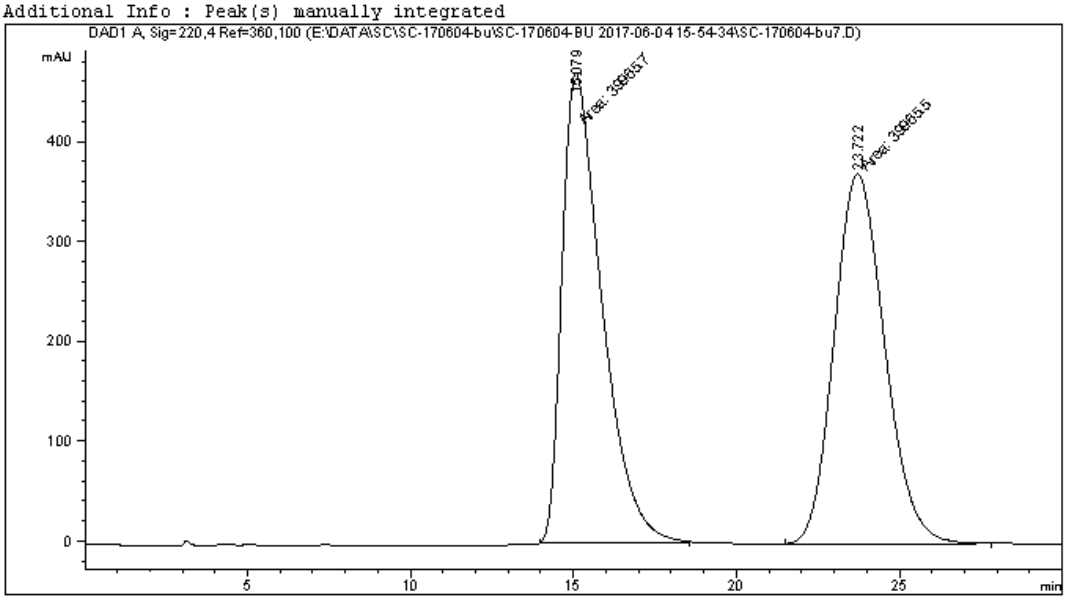


Figure S41. ^{13}C NMR spectrum of **5n**, related to **Table 2**.

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu7.D
Sample Name: SC-2-62B

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   8
Acq. Instrument : 1260                          Location :   75
Injection Date  : 6/4/2017 7:14:34 PM                Inj :   1
                                               Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-1-ASH-90-10-
                  220NM-30MIN.M
Last changed    : 6/4/2017 3:54:36 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-1-ASH-90-10-
                  220NM-30MIN.M (Sequence Method)
Last changed    : 6/5/2017 8:42:41 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

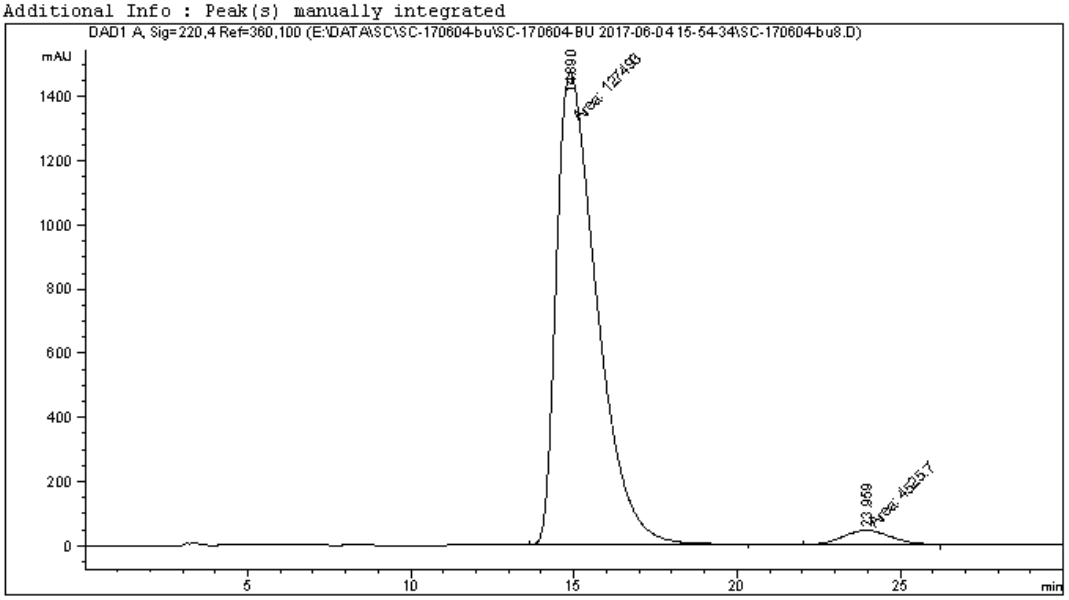

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  15.079 MM    1.4168 3.99657e4   470.13986  50.0001
   2  23.722 MM    1.7954 3.99655e4   371.00281  49.9999

Totals :                  7.99312e4   841.14267
```

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu8.D
Sample Name: SC-2-100B

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   9
Acq. Instrument : 1260                           Location :   76
Injection Date  : 6/4/2017 7:46:02 PM                Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-1-ASH-90-10-
                  220NM-30MIN.M
Last changed    : 6/4/2017 3:54:36 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-1-ASH-90-10-
                  220NM-30MIN.M (Sequence Method)
Last changed    : 6/5/2017 8:42:41 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.890 MM    1.4420 1.27493e5  1473.53821  96.5719
   2  23.959 MM    1.7100 4525.70068   44.11012   3.4281

Totals :                  1.32019e5  1517.64833
```


Figure S42. HPLC spectrum of **5n**, related to **Table 2**.

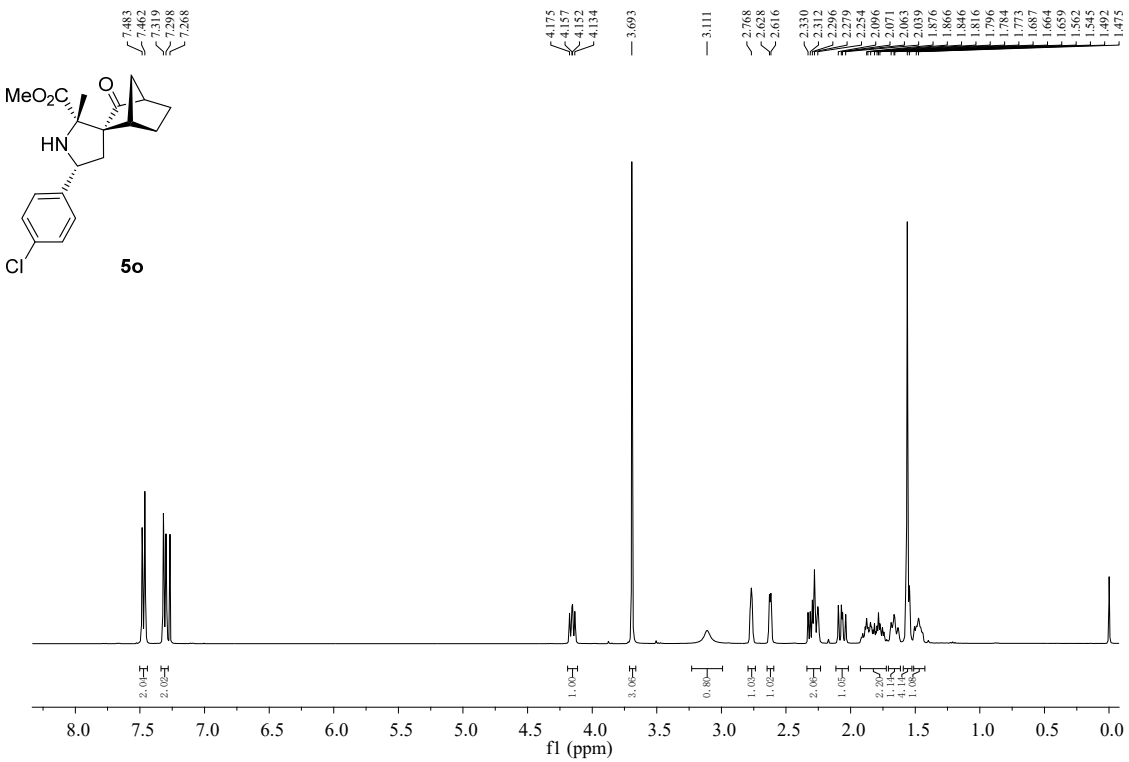


Figure S43. ^{1}H NMR spectrum of **5o**, related to **Table 2**.

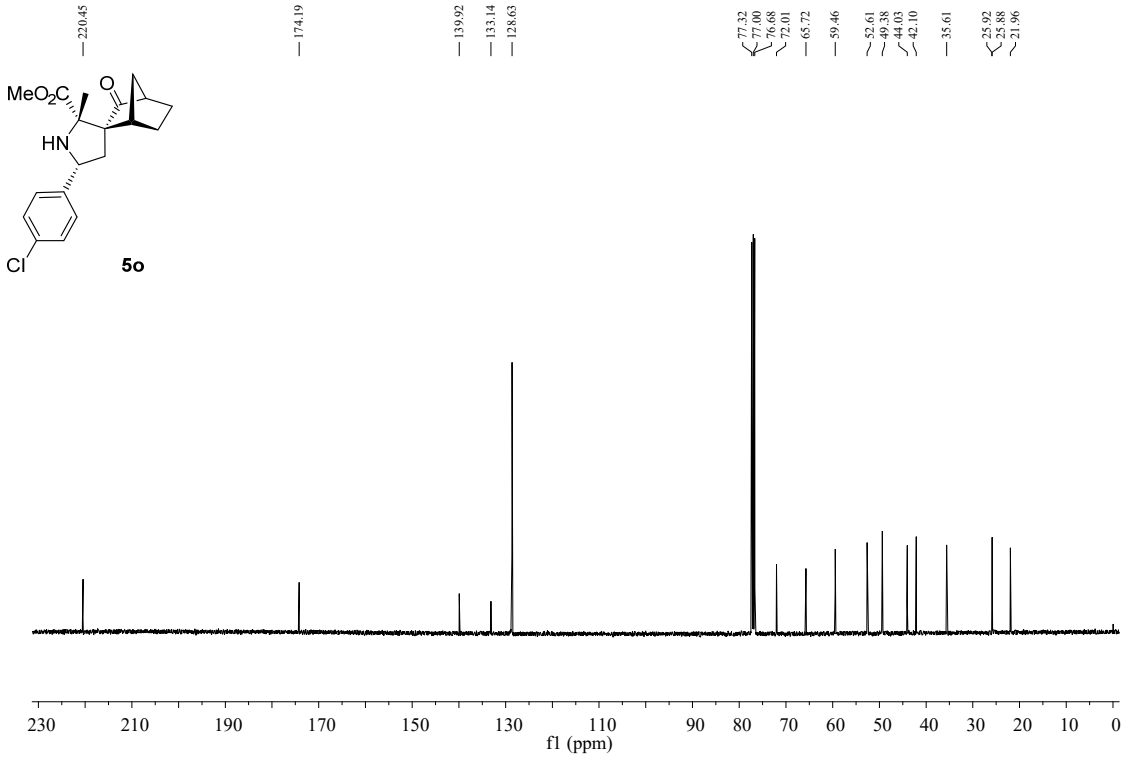
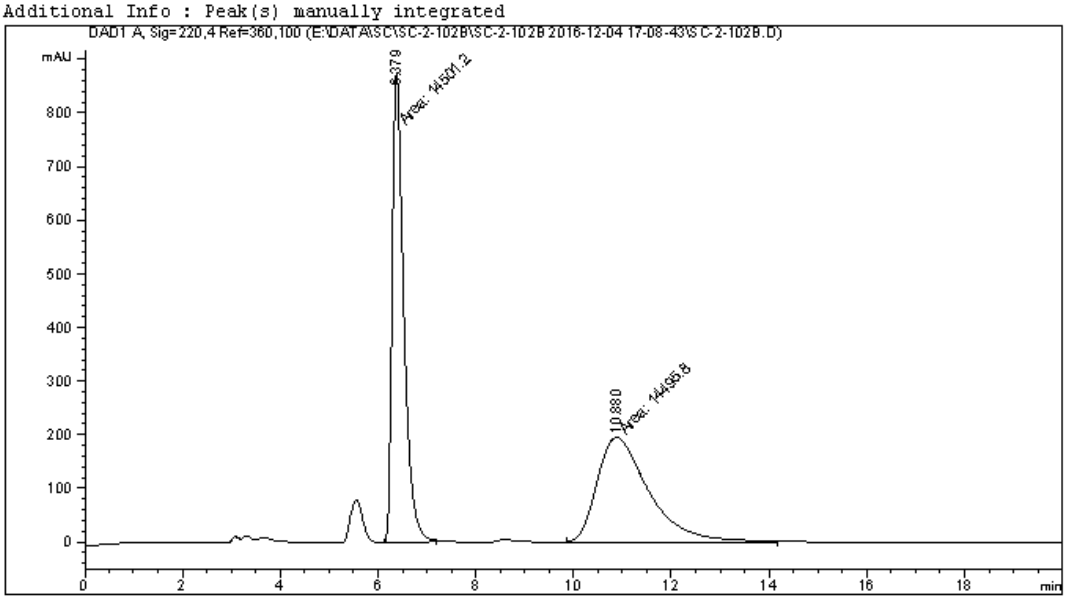


Figure S44. ^{13}C NMR spectrum of **5o**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-102B\SC-2-102B 2016-12-04 17-08-43\SC-2-102B.D
Sample Name: SC-2-102B

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                              Location :   31
Injection Date  : 12/4/2016 5:10:04 PM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-102B\SC-2-102B 2016-12-04 17-08-43\SC-1-ASH-90-10-DAD-1ML.M
Last changed    : 12/4/2016 5:08:43 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-102B\SC-2-102B 2016-12-04 17-08-43\SC-1-ASH-90-10-DAD-1ML.M
                  (Sequence Method)
Last changed    : 6/4/2017 3:28:32 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

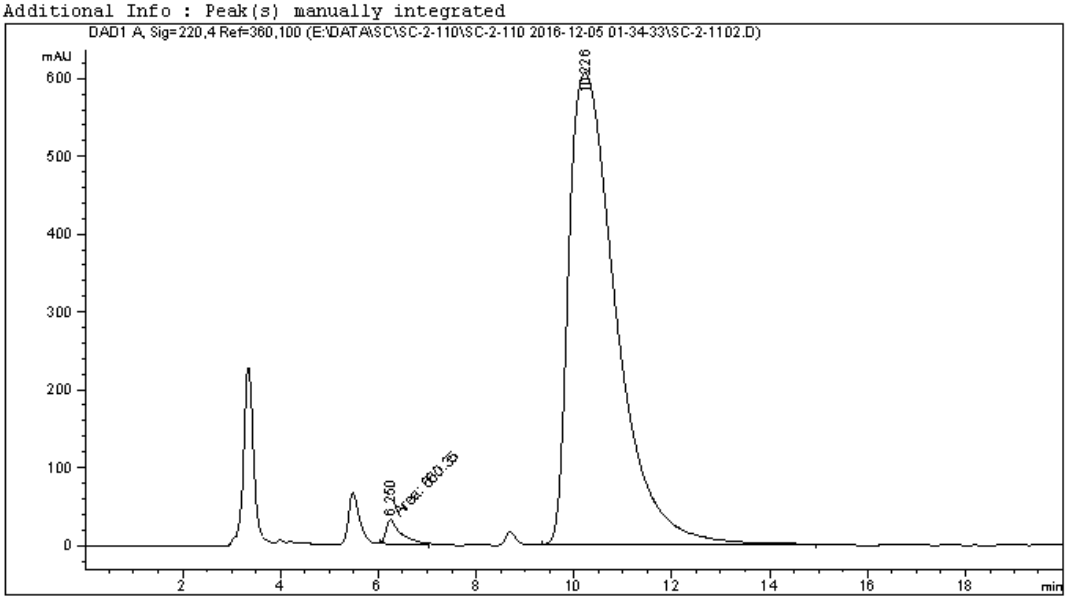

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.379 MM    0.2763 1.45012e4   874.86603  50.0093
   2  10.880 MM    1.2352 1.44958e4   195.59187  49.9907

Totals :                  2.89970e4  1070.45790
```

Data File E:\DATA\SC\SC-2-110\SC-2-110 2016-12-05 01-34-33\SC-2-1102.D
Sample Name: SC-2-110A

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   73
Injection Date  : 12/5/2016 2:23:10 AM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-110\SC-2-110 2016-12-05 01-34-33\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 12/5/2016 1:34:33 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-110\SC-2-110 2016-12-05 01-34-33\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 3:31:18 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.250 MM    0.3521  660.35010   31.25616   1.6042
   2  10.226 BB    1.0170 4.05026e4   605.81183  98.3958

Totals :                  4.11630e4   637.06799
```


Figure S45. HPLC spectrum of **5o**, related to **Table 2**.

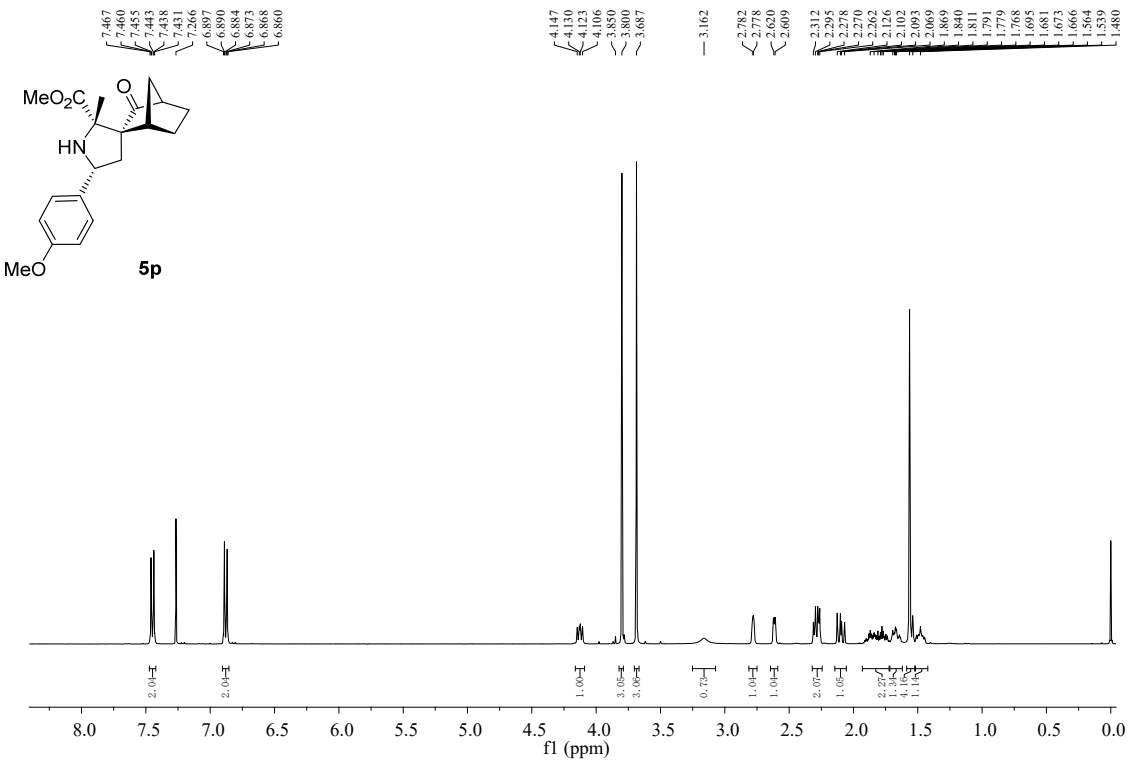


Figure S46. ^{1}H NMR spectrum of **5p**, related to **Table 2**.

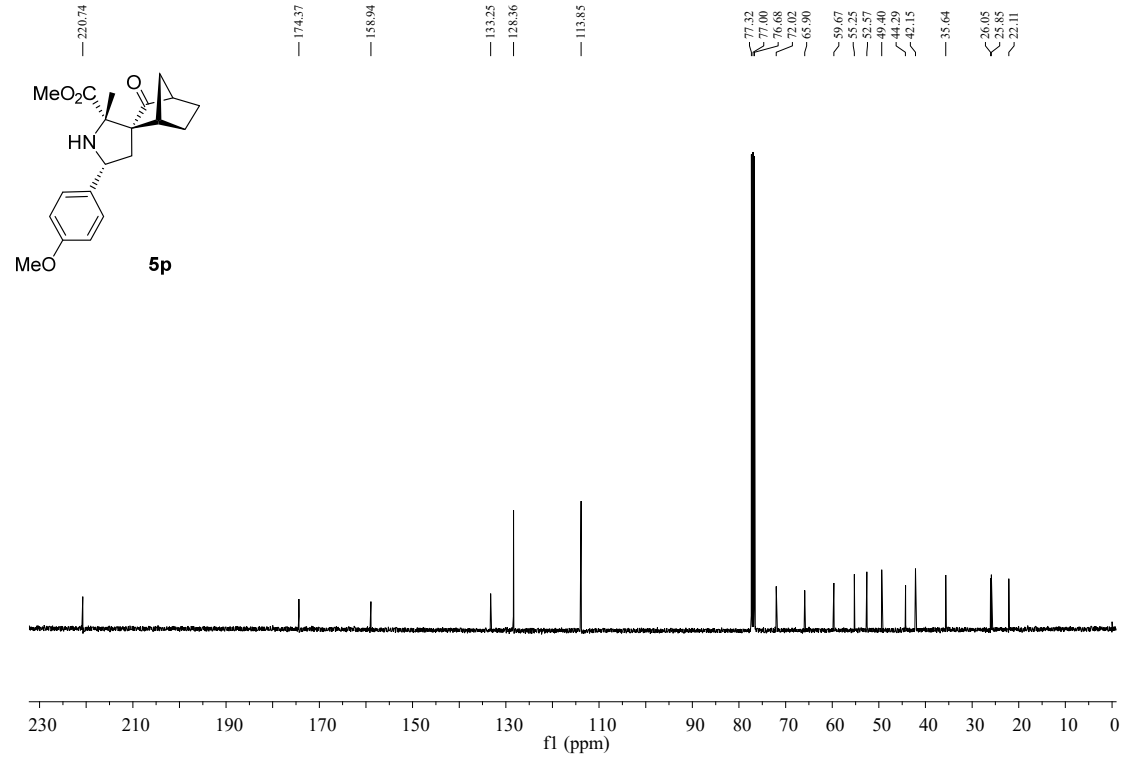
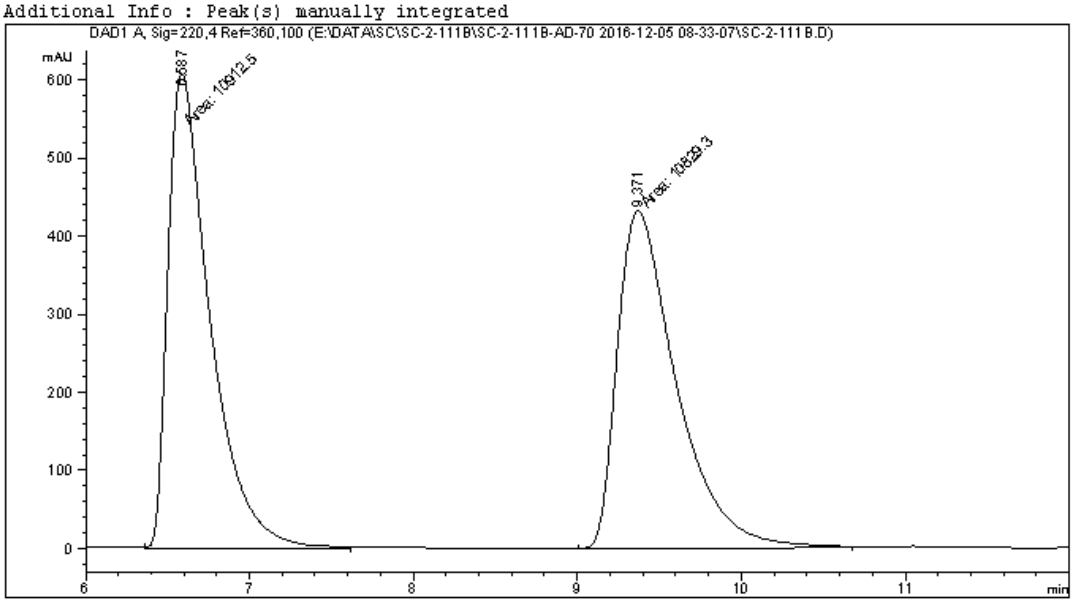


Figure S47. ^{13}C NMR spectrum of **5p**, related to **Table 2**.

Data File E:\DATA\SC\SC-2-111B\SC-2-111B-AD-70 2016-12-05 08-33-07\SC-2-111B.D
Sample Name: SC-2-111B-AD-70

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   74
    Injection Date  : 12/5/2016 8:34:34 AM                  Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-111B\SC-2-111B-AD-70 2016-12-05 08-33-07\SC-2-ADH-70-30-DAD
                      -1ML.M
    Last changed    : 12/5/2016 8:33:07 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-111B\SC-2-111B-AD-70 2016-12-05 08-33-07\SC-2-ADH-70-30-DAD
                      -1ML.M (Sequence Method)
    Last changed    : 6/4/2017 3:34:18 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

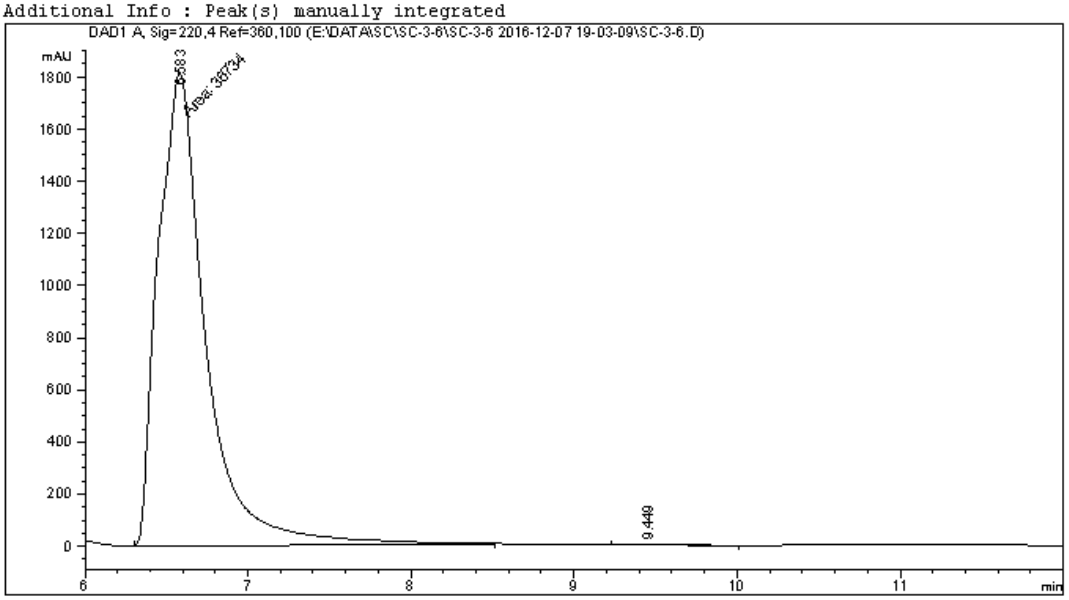

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   6.587 MM    0.2991 1.09125e4   608.11237  50.1914
       2   9.371 MM    0.4181 1.08293e4   431.73206  49.8086

    Totals :                   2.17418e4  1039.84442
```

Data File E:\DATA\SC\SC-3-6\SC-3-6 2016-12-07 19-03-09\SC-3-6.D
Sample Name: SC-3-6A

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   13
Injection Date  : 12/7/2016 7:04:31 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-6\SC-3-6 2016-12-07 19-03-09\SC-2-ADH-70-30-220NM-25MIN-1ML
                  .M
Last changed    : 12/7/2016 7:03:09 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-6\SC-3-6 2016-12-07 19-03-09\SC-2-ADH-70-30-220NM-25MIN-1ML
                  .M (Sequence Method)
Last changed    : 6/4/2017 3:36:42 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.583 MM    0.3376 3.67340e4  1813.29407  99.8808
   2   9.449 BB    0.2971   43.83621    1.89315   0.1192

Totals :                  3.67778e4  1815.18721
```


Figure S48. HPLC spectrum of **5p**, related to **Table 2**.

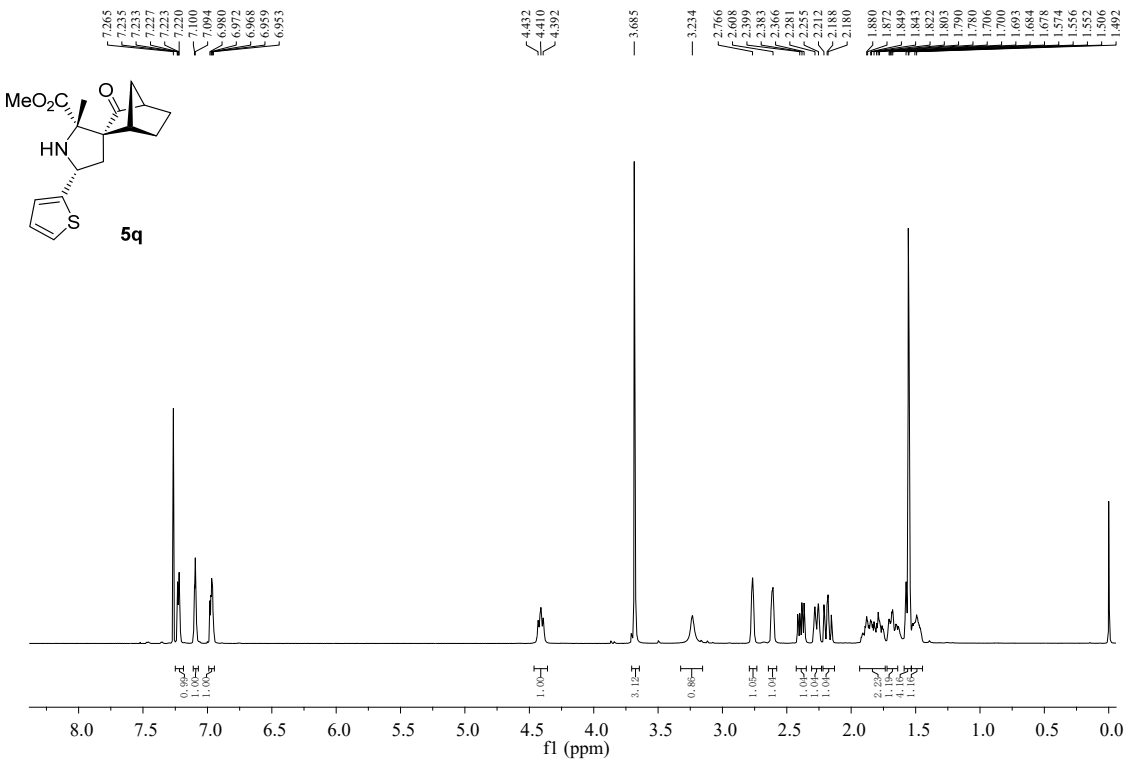


Figure S49. ^{1}H NMR spectrum of **5q**, related to **Table 2**.

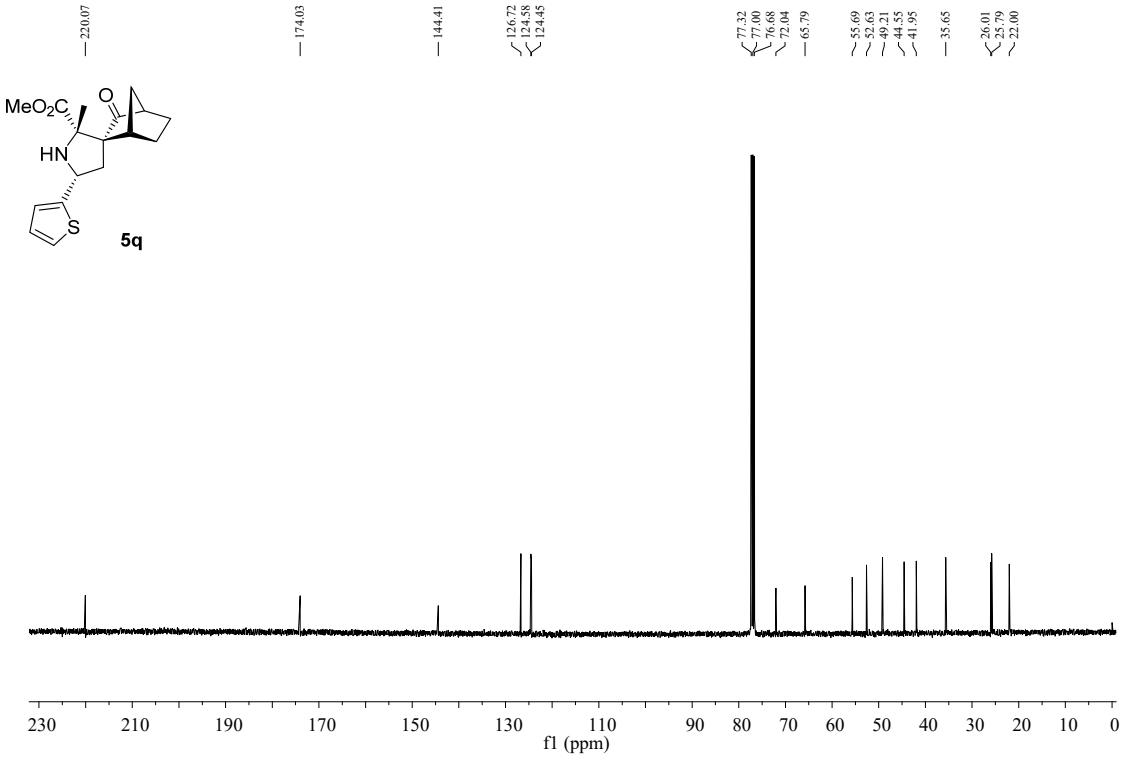
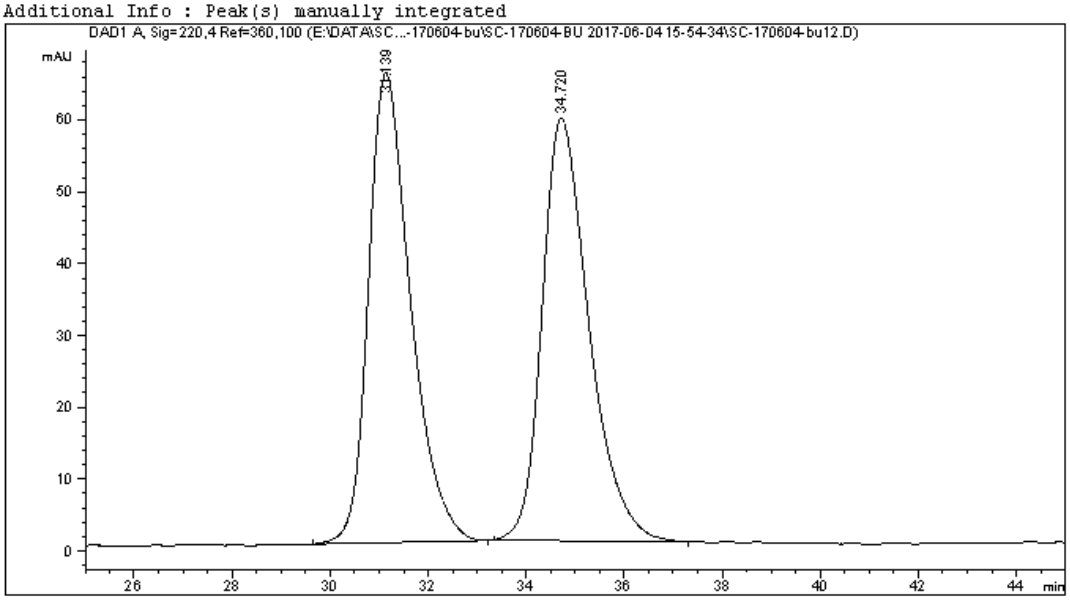


Figure S50. ^{13}C NMR spectrum of **5q**, related to **Table 2**.

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu12.D
Sample Name: SC-2-112A

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :  13
    Acq. Instrument : 1260                           Location :   77
    Injection Date  : 6/4/2017 10:03:37 PM               Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-2-ADH-97-3-
                      220NM-40MIN.M
    Last changed    : 6/4/2017 10:37:50 PM by SYSTEM
                      (modified after loading)
    Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-2-ADH-97-3-
                      220NM-40MIN.M (Sequence Method)
    Last changed    : 6/5/2017 8:49:45 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

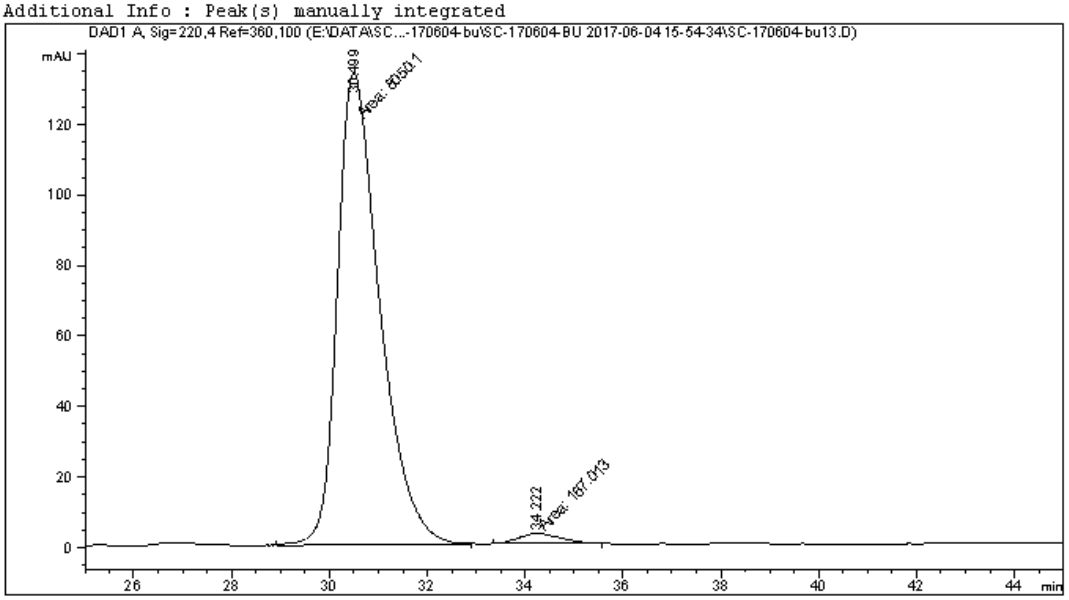

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  31.139 BB    0.8509 3906.25781   65.39045  50.0133
       2  34.720 BB    0.9147 3904.18262   58.79784  49.9867

    Totals :                  7810.44043  124.18829
```

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu13.D
Sample Name: SC-3-6B

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :  14
Acq. Instrument : 1260                           Location :  78
Injection Date  : 6/4/2017 10:50:05 PM               Inj :  1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-2-ADH-97-3-
                  220NM-40MIN.M
Last changed    : 6/4/2017 10:37:50 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-2-ADH-97-3-
                  220NM-40MIN.M (Sequence Method)
Last changed    : 6/5/2017 8:49:45 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.499 MM    1.0024 8050.09863  133.84961  97.9675
   2  34.222 MM    0.9854  167.01291    2.82470   2.0325

Totals :                  8217.11154  136.67431
```


Figure S51. HPLC spectrum of **5q**, related to **Table 2**.

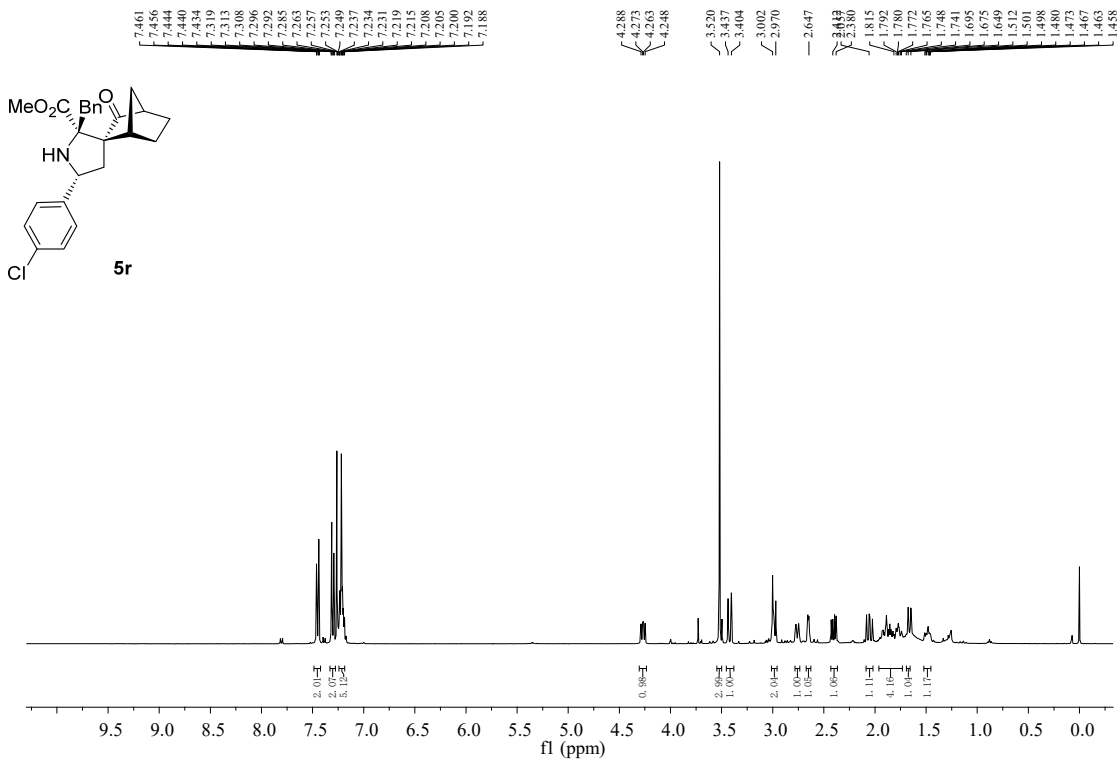


Figure S52. ^{1}H NMR spectrum of **5r**, related to **Table 2**.

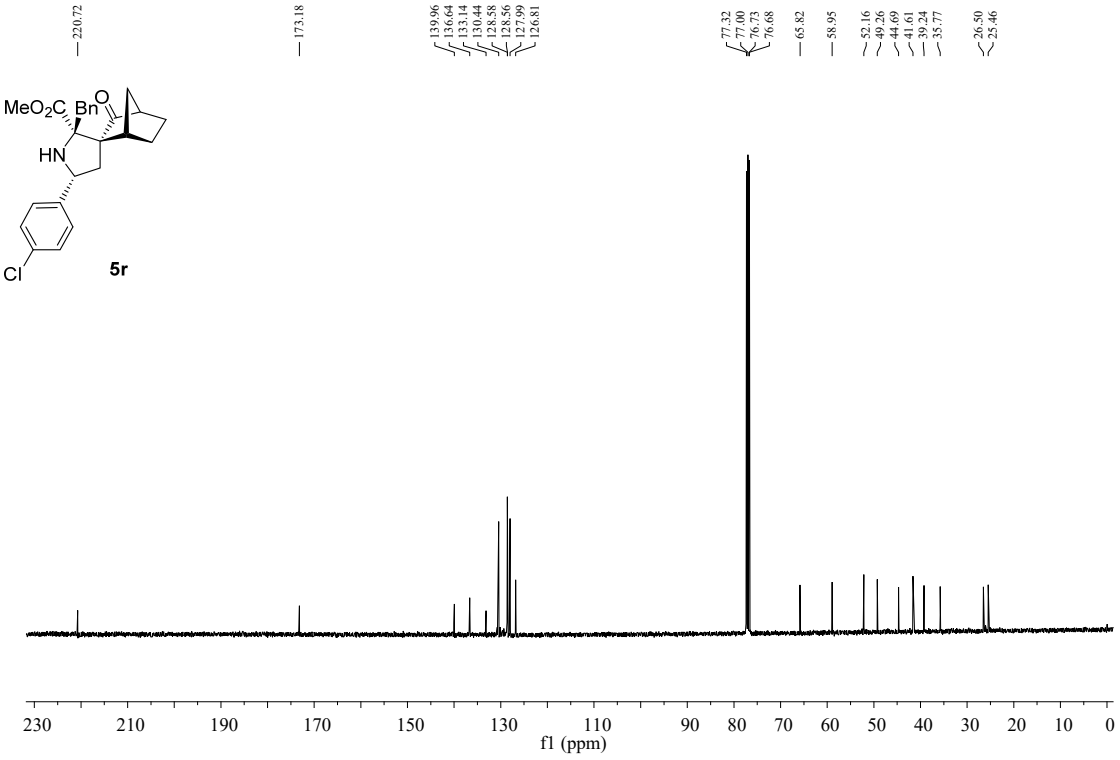
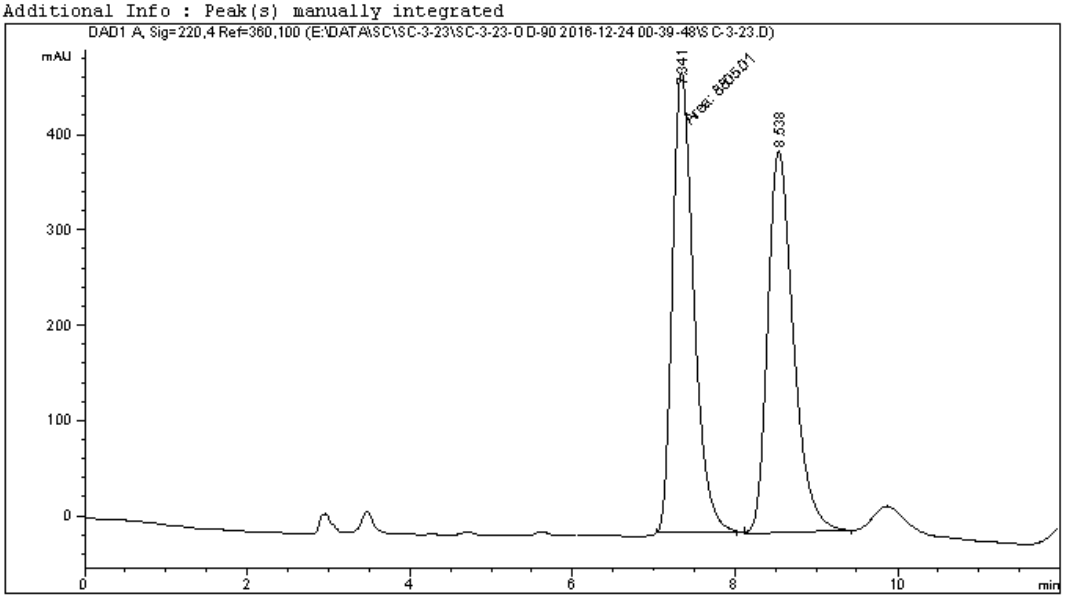


Figure S53. ^{13}C NMR spectrum of **5r**, related to **Table 2**.

Data File E:\DATA\SC\SC-3-23\SC-3-23-OD-90 2016-12-24 00-39-48\SC-3-23.D
Sample Name: SC-3-23-OD-90

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                            Location :   11
Injection Date  : 12/24/2016 12:41:09 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-23\SC-3-23-OD-90 2016-12-24 00-39-48\SC-6-ODH-90-10-DAD-1ML
                  .M
Last changed    : 12/24/2016 12:39:49 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-23\SC-3-23-OD-90 2016-12-24 00-39-48\SC-6-ODH-90-10-DAD-1ML
                  .M (Sequence Method)
Last changed    : 6/4/2017 3:48:46 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

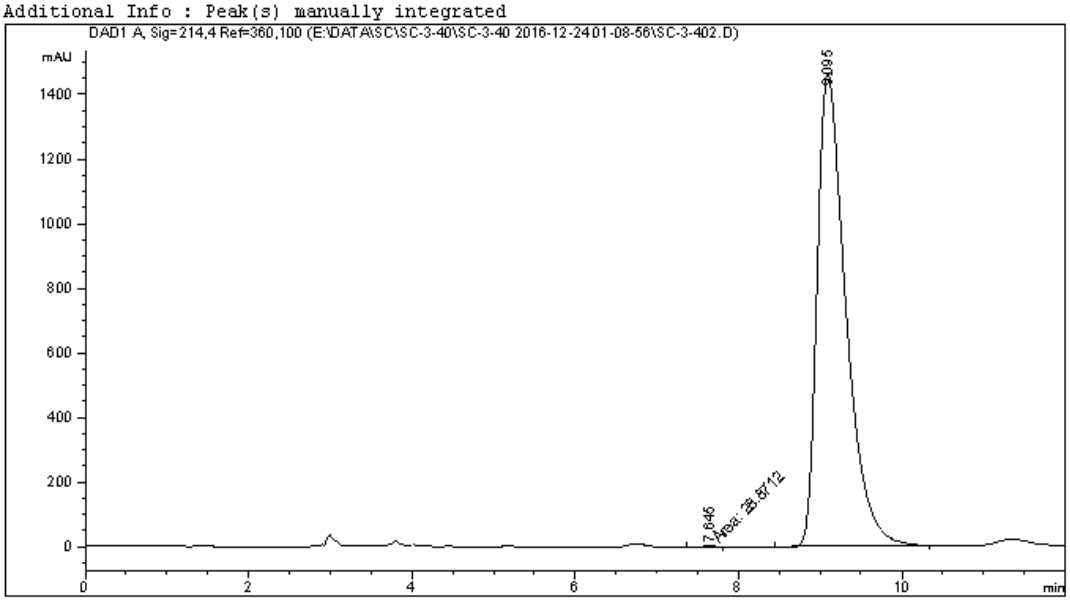

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.341 MM    0.3040 8805.00684  482.73367  50.0162
   2   8.538 VB    0.3355 8799.30664  400.28638  49.9838

Totals :                  1.76043e4   883.02005
```

Data File E:\DATA\SC\SC-3-40\SC-3-40 2016-12-24 01-08-56\SC-3-402.D
Sample Name: SC-3-40

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                            Location :   12
Injection Date  : 12/24/2016 1:52:28 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-40\SC-3-40 2016-12-24 01-08-56\SC-6-ODH-95-5-214NM-1ML-
                  20MIN.M
Last changed    : 12/24/2016 1:08:56 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-40\SC-3-40 2016-12-24 01-08-56\SC-6-ODH-95-5-214NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 3:51:58 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=214,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.645 MM    0.2381   28.87121    2.02056   0.0809
   2   9.095 BB    0.3670 3.56509e4  1464.29285  99.9191

Totals :                  3.56798e4  1466.31341
```


Figure S54. HPLC spectrum of **5r**, related to **Table 2**.

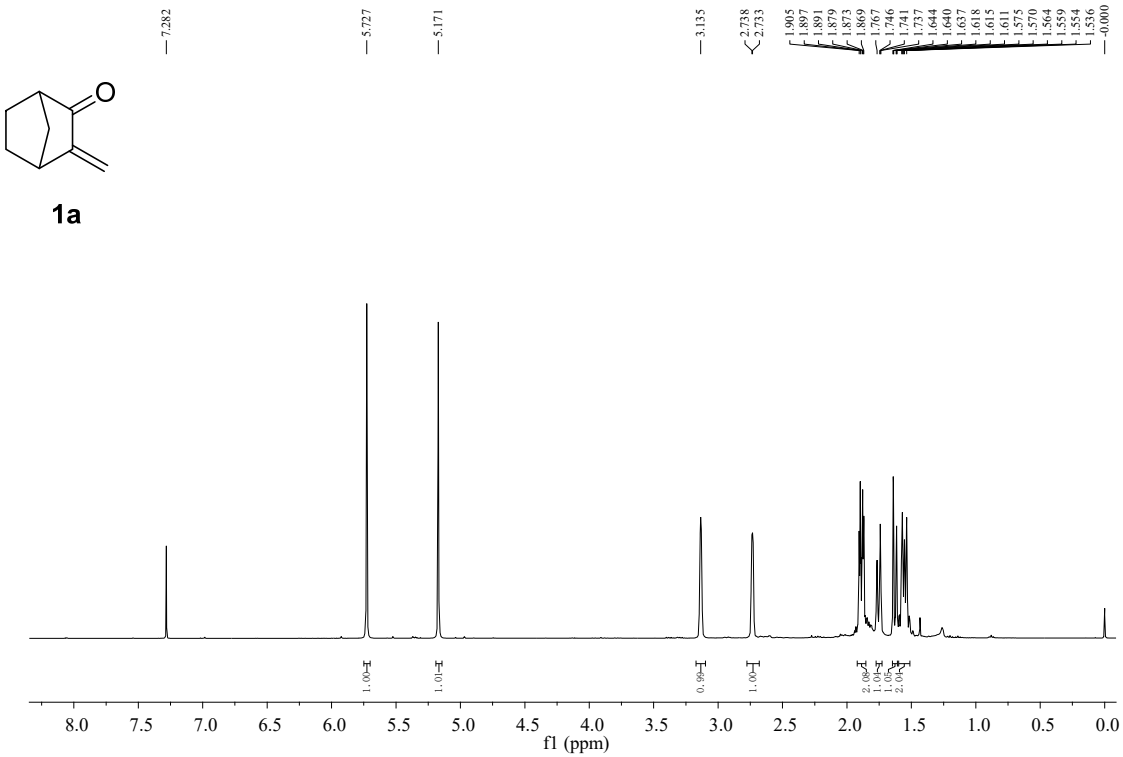


Figure S55. [1]H NMR spectrum of **1a**, related to **Table 3**.

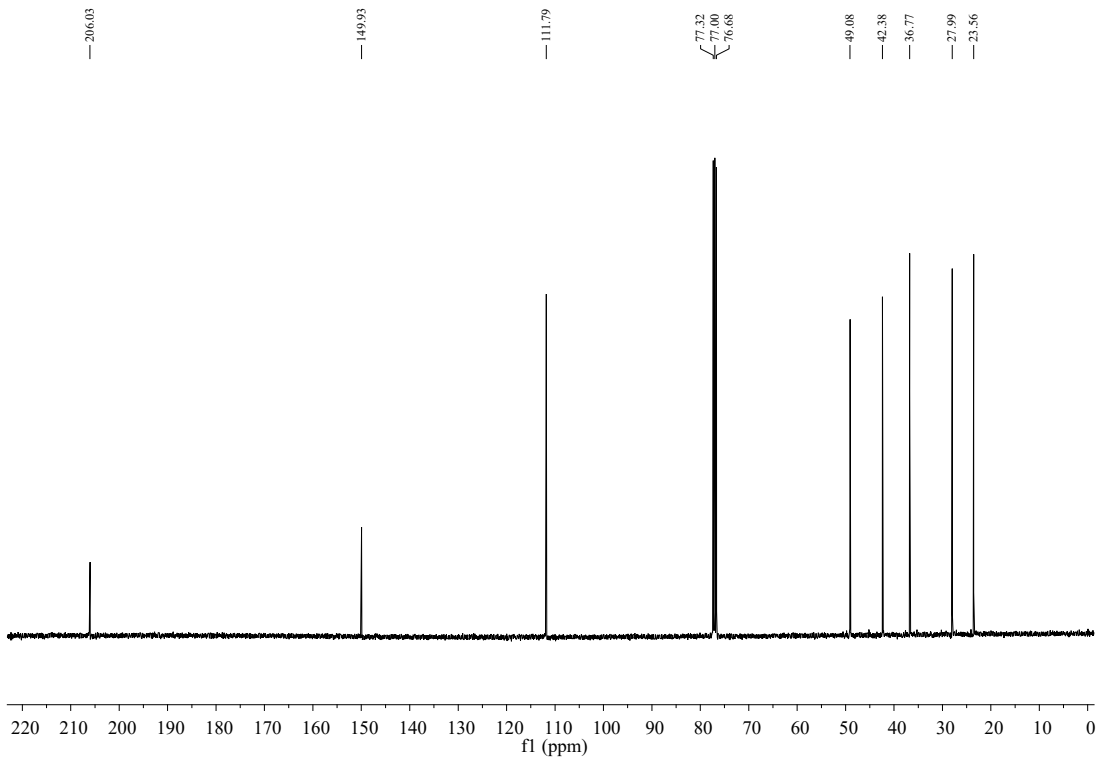
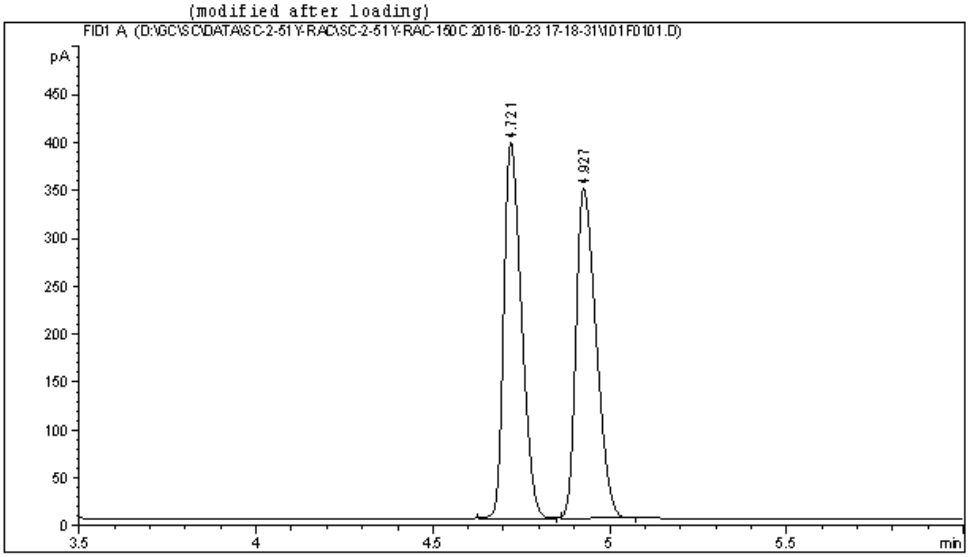


Figure S56. [13]C NMR spectrum of **1a**, related to **Table 3**.

Data File D:\GC\SC\DATA\SC-2-51Y-RAC\SC-2-51Y-RAC-150C 2016-10-23 17-18-31\101F0101.D
Sample Name: SC-2-51Y-RAC

```
    ====================================================================
    Acq. Operator   : LHC                          Seq. Line :   1
    Acq. Instrument : Instrument 2                  Location : Vial 101
    Injection Date  : 23-Oct-16, 17:19:49                Inj :   1
                                                   Inj Volume : 1 µl
    Acq. Method     : D:\GC\SC\Data\SC-2-51Y-RAC\SC-2-51Y-RAC-150C 2016-10-23 17-18-31\CS-1000-
                      150C-1ML.M
    Last changed    : 10/23/2016 5:17:22 PM by LHC
    Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
    Last changed    : 6/22/2017 9:56:59 AM by DWW
                      (modified after loading)
```




```
    ====================================================================
                              Area Percent Report
    ====================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

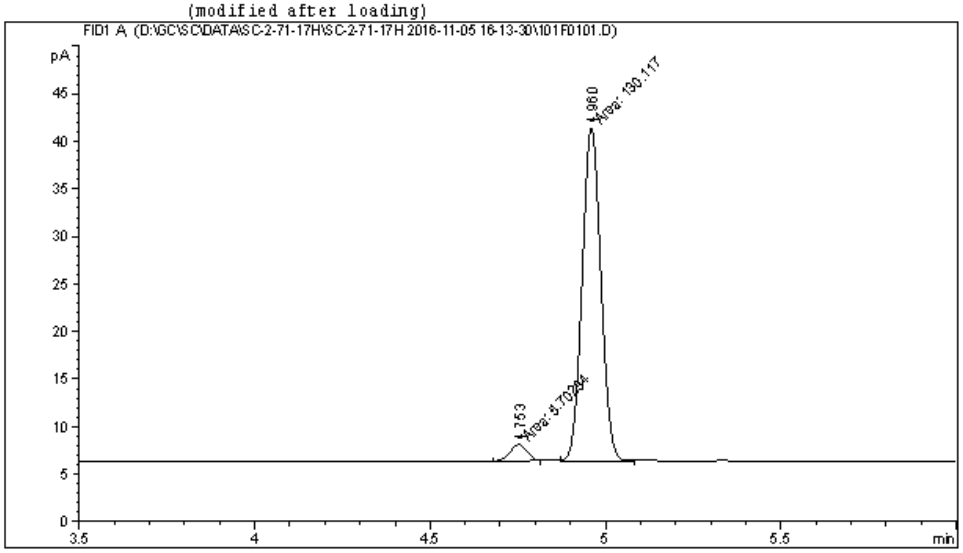
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1   4.721 BB    0.0536 1361.50562  391.70834 50.07118
       2   4.927 BB    0.0601 1357.63477  343.88904 49.92882

    Totals :                   2719.14038  735.59738


    ====================================================================
                              *** End of Report ***
```

Data File D:\GC\SC\DATA\SC-2-71-17H\SC-2-71-17H 2016-11-05 16-13-30\101F0101.D
Sample Name: SC-2-71-17H

Acq. Operator	: LHC	Seq. Line	: 1
Acq. Instrument	: Instrument 2	Location	: Vial 101
Injection Date	: 05-Nov-16, 16:14:28	Inj	: 1
		Inj Volume	: 1 µl
Acq. Method	: D:\GC\SC\Data\SC-2-71-17H\SC-2-71-17H 2016-11-05 16-13-30\CS-1000-150C-1ML-10MIN.M		
Last changed	: 10/23/2016 5:31:45 PM by LHC		
Analysis Method	: D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M		
Last changed	: 7/19/2017 11:28:02 AM by DWW (modified after loading)		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

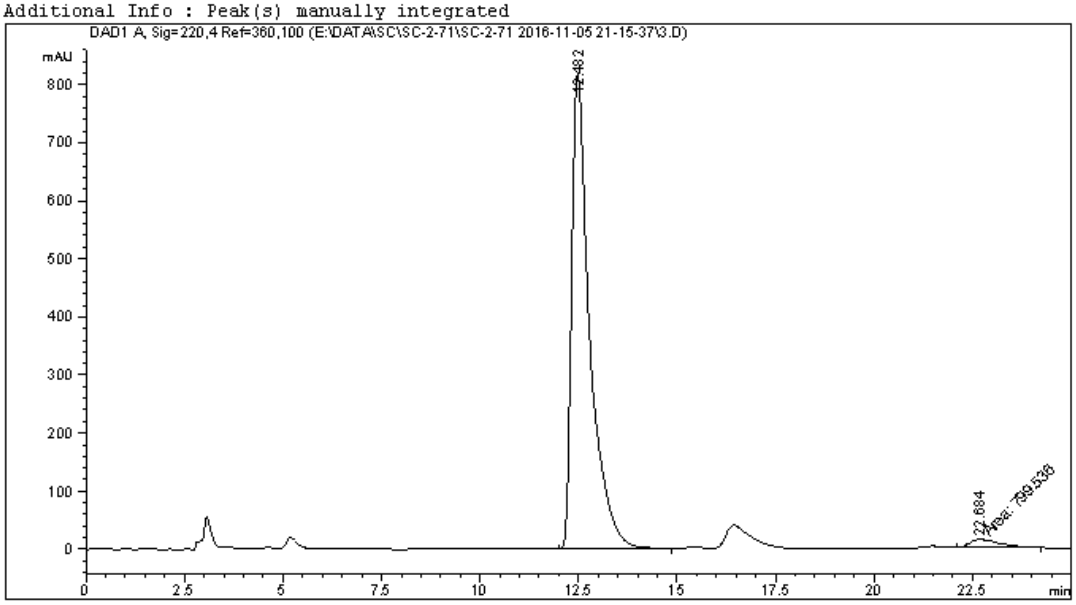
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	4.753	MM	0.0563	5.70234	1.68784	4.19847
2	4.960	MM	0.0619	130.11713	35.04598	95.80153
Totals :				135.81947	36.73382	

*** End of Report ***

Figure S57. HPLC spectrum of **1a**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-71\SC-2-71 2016-11-05 21-15-37\3.D
Sample Name: SC-2-71

```
=====================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : 1260                              Location :   63
Injection Date  : 11/6/2016 2:05:38 PM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-71\SC-2-71 2016-11-05 21-15-37\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M
Last changed    : 11/6/2016 12:15:37 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-71\SC-2-71 2016-11-05 21-15-37\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M (Sequence Method)
Last changed    : 7/18/2017 11:24:55 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

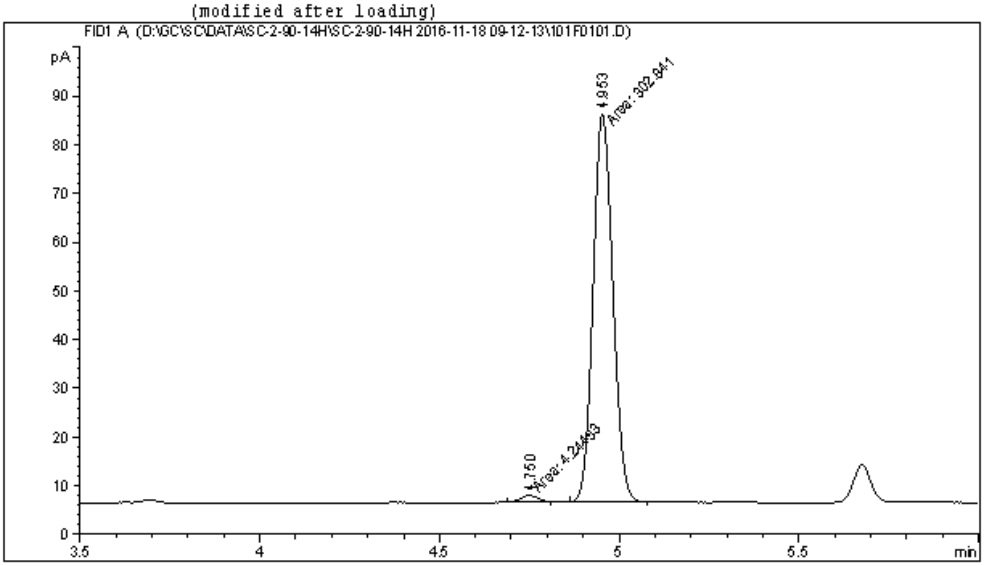
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.482 BB    0.4626 2.60106e4   818.85400  97.0178
   2  22.684 MM    0.9236  799.53644   14.42819   2.9822

Totals :                  2.68102e4   833.28219
```


Figure S58. HPLC spectrum of **5a**, related to **Table 3**.

Data File D:\GC\SC\DATA\SC-2-90-14H\SC-2-90-14H 2016-11-18 09-12-13\101F0101.D
Sample Name: SC-2-90A-14H

```
==================================================================
Acq. Operator   : LHC                          Seq. Line :   1
Acq. Instrument : Instrument 2                  Location : Vial 101
Injection Date  : 18-Nov-16, 09:13:35                Inj :   1
                                               Inj Volume : 1 µl
Acq. Method     : D:\GC\SC\Data\SC-2-90-14H\SC-2-90-14H 2016-11-18 09-12-13\CS-1000-150C-
                  1ML-10MIN.M
Last changed    : 11/9/2016 10:01:13 PM by LHC
Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
Last changed    : 6/22/2017 10:02:49 AM by DWW
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   4.750 MM    0.0545    4.24453    1.29729  1.38220
   2   4.953 MM    0.0634  302.84061   79.56886 98.61780

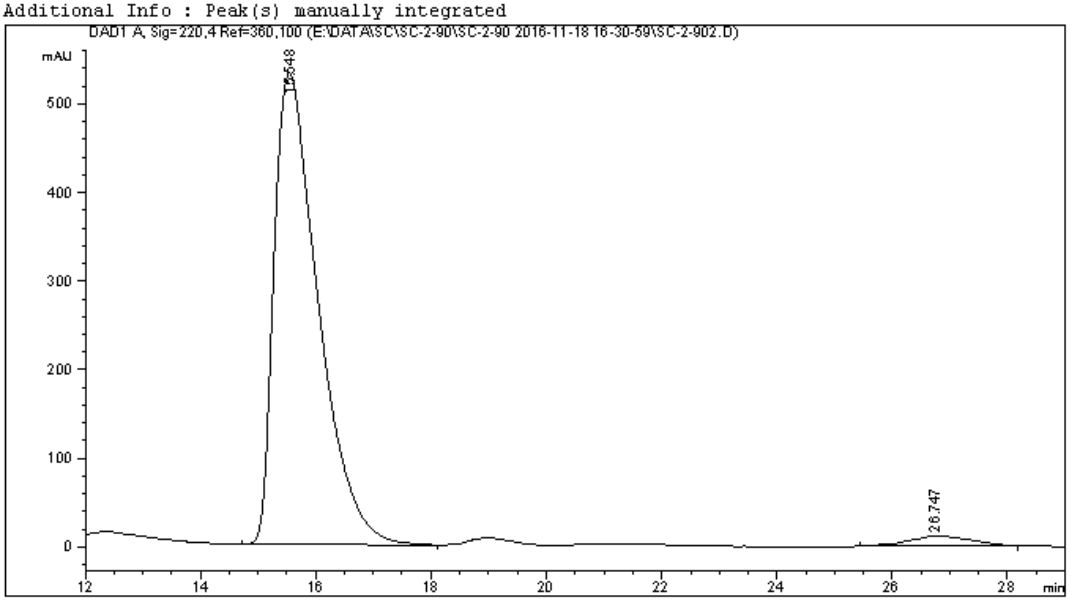
Totals :                   307.08514   80.86615


==================================================================
                          *** End of Report ***
```


Figure S59. HPLC spectrum of **1a**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-90\SC-2-90 2016-11-18 16-30-59\SC-2-902.D
Sample Name: SC-2-90A

```
=====================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                             Location :   64
Injection Date  : 11/19/2016 9:45:12 AM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-90\SC-2-90 2016-11-18 16-30-59\SC-1-ASH-95-5-220NM-35MIN.M
Last changed    : 11/19/2016 8:30:59 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-90\SC-2-90 2016-11-18 16-30-59\SC-1-ASH-95-5-220NM-35MIN.M
                  (Sequence Method)
Last changed    : 6/4/2017 4:00:25 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  15.548 BB    0.7806 2.82635e4   532.19116  97.0411
   2  26.747 BB    0.8960  861.79474   11.46468   2.9589

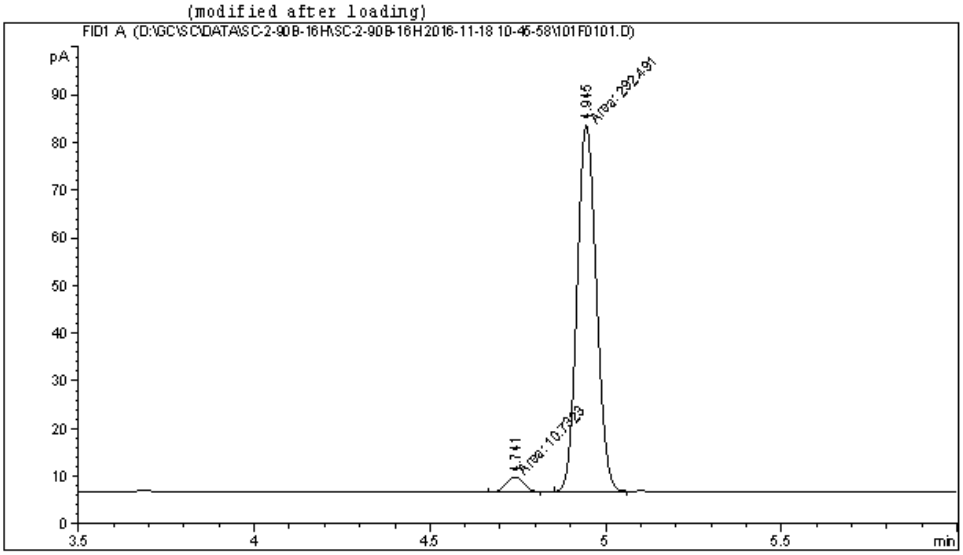
Totals :                  2.91253e4   543.65584


1260 6/4/2017 4:00:35 AM SYSTEM                          Page 1 of 2
```

Figure S60. HPLC spectrum of **5b**, related to **Table 3**.

Data File D:\GC\SC\DATA\SC-2-90B-16H\SC-2-90B-16H 2016-11-18 10-45-58\101F0101.D
Sample Name: SC-2-90B-16H

```
==================================================================
Acq. Operator   : LHC                          Seq. Line :   1
Acq. Instrument : Instrument 2                  Location : Vial 101
Injection Date  : 18-Nov-16, 10:46:56                Inj :   1
                                               Inj Volume : 1 µl
Acq. Method     : D:\GC\SC\Data\SC-2-90B-16H\SC-2-90B-16H 2016-11-18 10-45-58\CS-1000-150C-
                  1ML-10MIN.M
Last changed    : 11/9/2016 10:01:13 PM by LHC
Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
Last changed    : 6/22/2017 10:07:56 AM by DWW
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1   4.741 MM    0.0580   10.73233    3.08488  3.53942
   2   4.945 MM    0.0634  292.49060   76.84565 96.46058

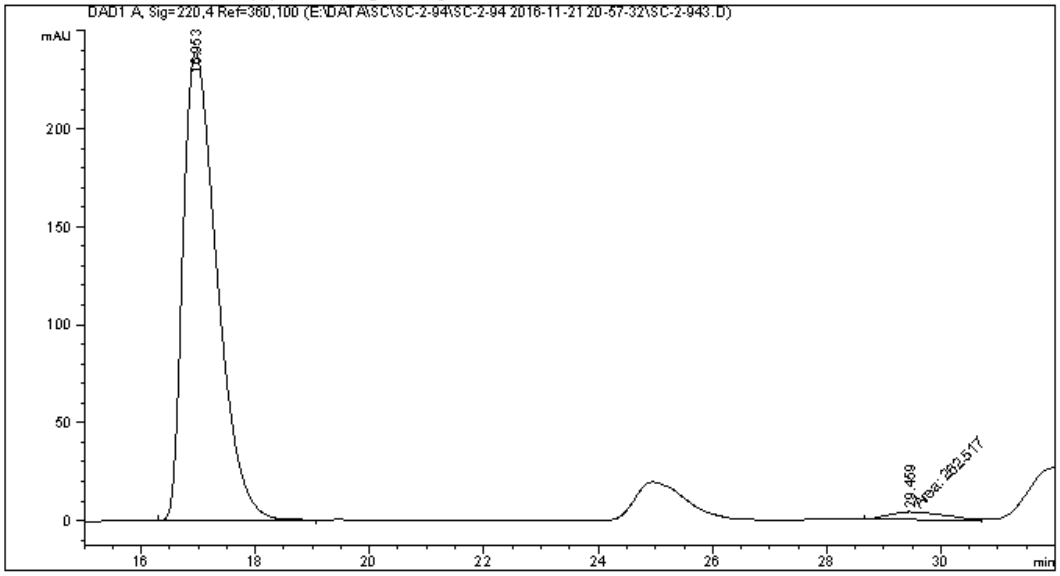
Totals :                   303.22293   79.93053


==================================================================
                          *** End of Report ***
```


Figure S61. HPLC spectrum of **1a**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-94\SC-2-94 2016-11-21 20-57-32\SC-2-943.D
Sample Name: SC-2-91A

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   4
Acq. Instrument : 1260                           Location :   64
Injection Date  : 11/22/2016 2:52:35 PM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-94\SC-2-94 2016-11-21 20-57-32\SC-2-ADH-95-5-220NM-40MIN.M
Last changed    : 11/22/2016 12:57:33 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-94\SC-2-94 2016-11-21 20-57-32\SC-2-ADH-95-5-220NM-40MIN.M
                  (Sequence Method)
Last changed    : 6/4/2017 4:04:52 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  16.953 BB    0.6425 9873.51660  238.74211  97.4101
   2  29.459 MM    1.1078  262.51691    3.94956   2.5899

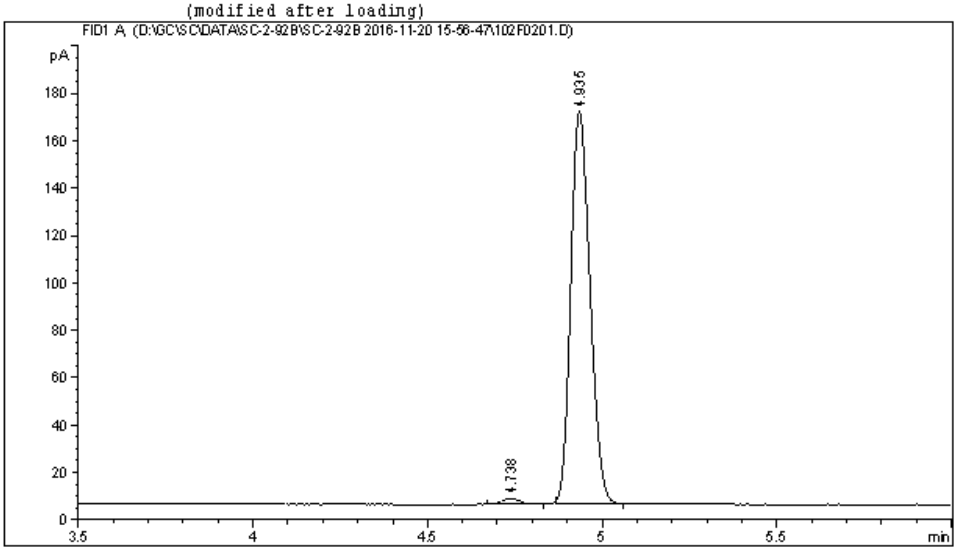
Totals :                  1.01360e4   242.69167


1260 6/4/2017 4:05:21 AM SYSTEM                          Page 1 of 2
```

Figure S62. HPLC spectrum of **5h**, related to **Table 3.**

Data File D:\GC\SC\DATA\SC-2-92B\SC-2-92B 2016-11-20 15-56-47\102F0201.D
Sample Name: SC-2-93B

```
==================================================================
Acq. Operator   : LHC                          Seq. Line :   2
Acq. Instrument : Instrument 2                  Location : Vial 102
Injection Date  : 20-Nov-16, 16:08:38                Inj :   1
                                               Inj Volume : 1 µl
Acq. Method     : D:\GC\SC\Data\SC-2-92B\SC-2-92B 2016-11-20 15-56-47\CS-1000-150C-1ML-
                  10MIN.M
Last changed    : 11/9/2016 10:01:13 PM by LHC
Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
Last changed    : 6/22/2017 10:11:12 AM by DWW
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   4.738 BB    0.0543    8.69957    2.51797  1.35116
   2   4.935 BB    0.0598  635.15985  165.54564 98.64884

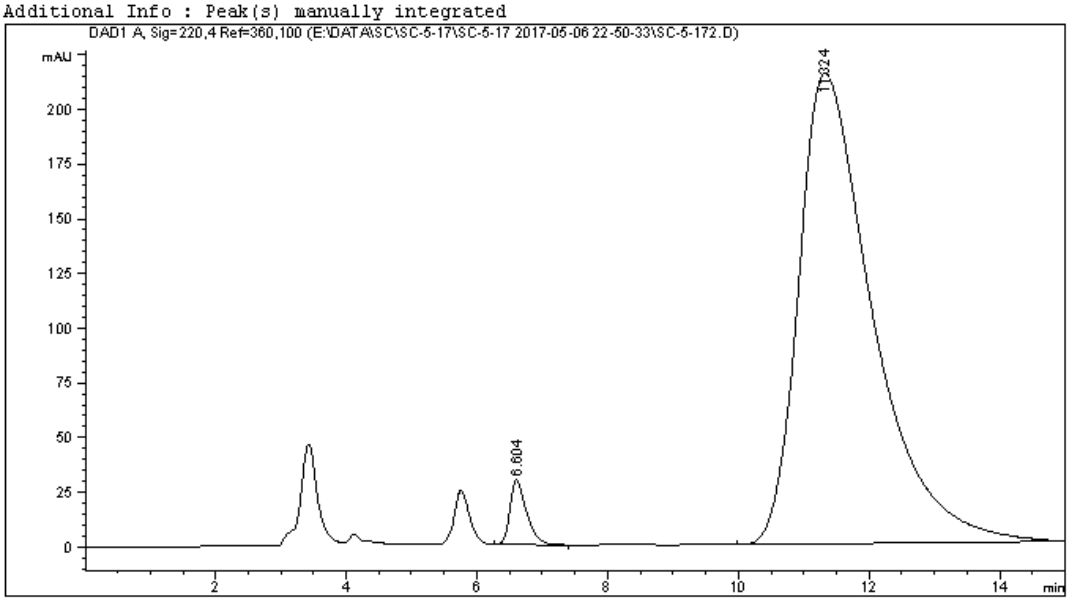
Totals :                    643.85942  168.06360


==================================================================
                        *** End of Report ***
```


Figure S63. HPLC spectrum of **1a**, related to **Table 3**.

Data File E:\DATA\SC\SC-5-17\SC-5-17 2017-05-06 22-50-33\SC-5-172.D
Sample Name: SC-5-17B-18H

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   16
Injection Date  : 5/6/2017 11:49:23 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-17\SC-5-17 2017-05-06 22-50-33\SC-1-ASH-90-10-220NM-1ML-
                  15MIN.M
Last changed    : 5/6/2017 10:50:33 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-17\SC-5-17 2017-05-06 22-50-33\SC-1-ASH-90-10-220NM-1ML-
                  15MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:11:03 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.604 BB    0.2612  521.08728   29.48012   2.9931
   2  11.324 BBA   1.1293 1.68887e4   215.03746  97.0069

Totals :                  1.74098e4   244.51758
```


Figure S64. HPLC spectrum of **5o**, related to **Table 3**.

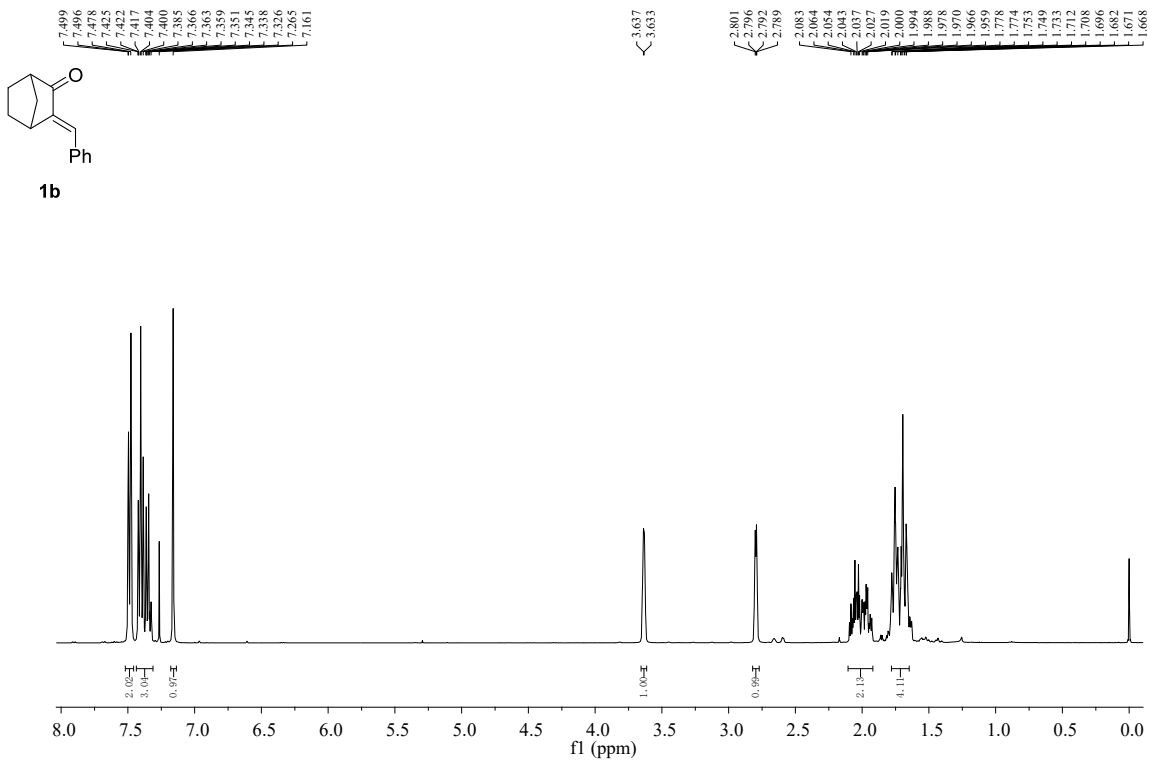


Figure S65. ^{1}H NMR spectrum of **1b**, related to **Table 3**.

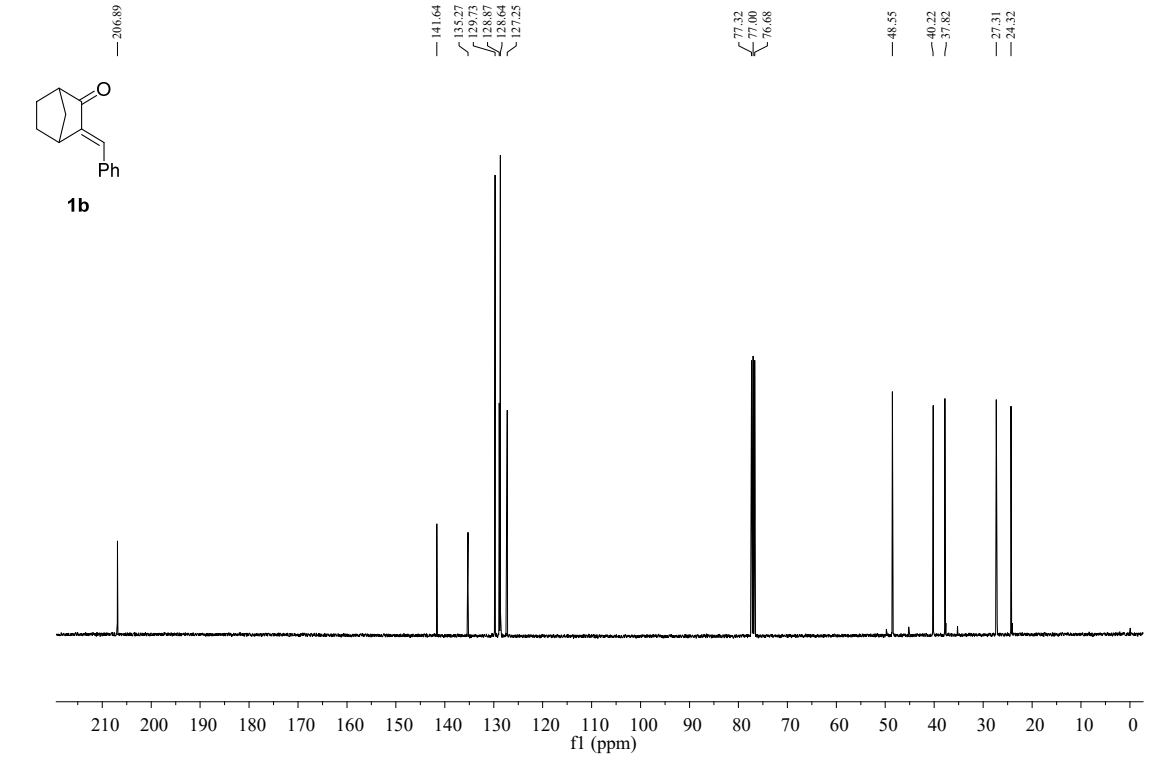
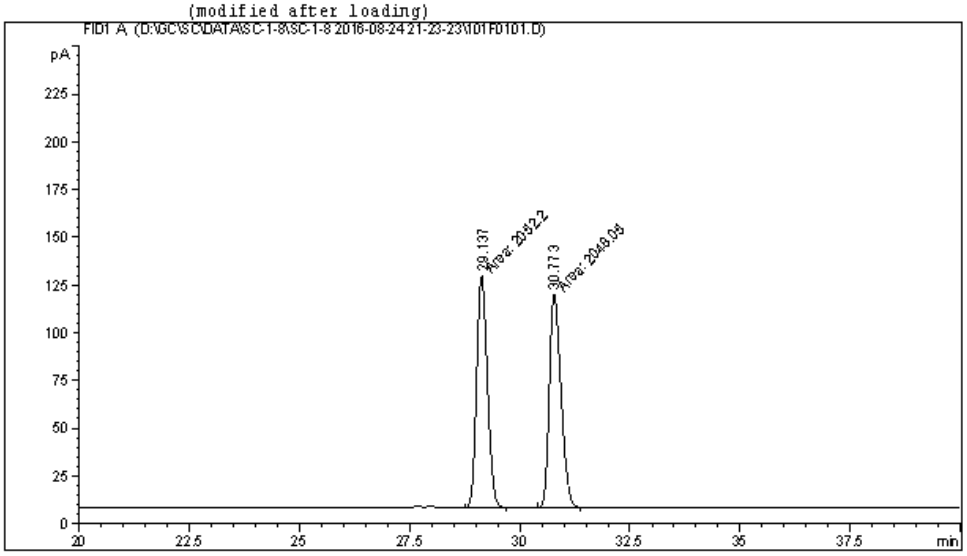


Figure S66. ^{13}C NMR spectrum of **1b**, related to **Table 3**.

Data File D:\GC\SC\DATA\SC-1-8\SC-1-8 2016-08-24 21-23-23\101F0101.D
Sample Name: SC-1-8-Rac

```
    ======================================================================
    Acq. Operator   : LHC                          Seq. Line :   1
    Acq. Instrument : Instrument 2                  Location : Vial 101
    Injection Date  : 24-Aug-16, 21:24:31                Inj :   1
                                                   Inj Volume : 1 µl
    Acq. Method     : D:\GC\SC\Data\SC-1-8\SC-1-8 2016-08-24 21-23-23\CS-1000-180C-1ML.M
    Last changed    : 8/24/2016 8:58:35 PM by LHC
    Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
    Last changed    : 6/22/2017 9:48:41 AM by DWW
                      (modified after loading)
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

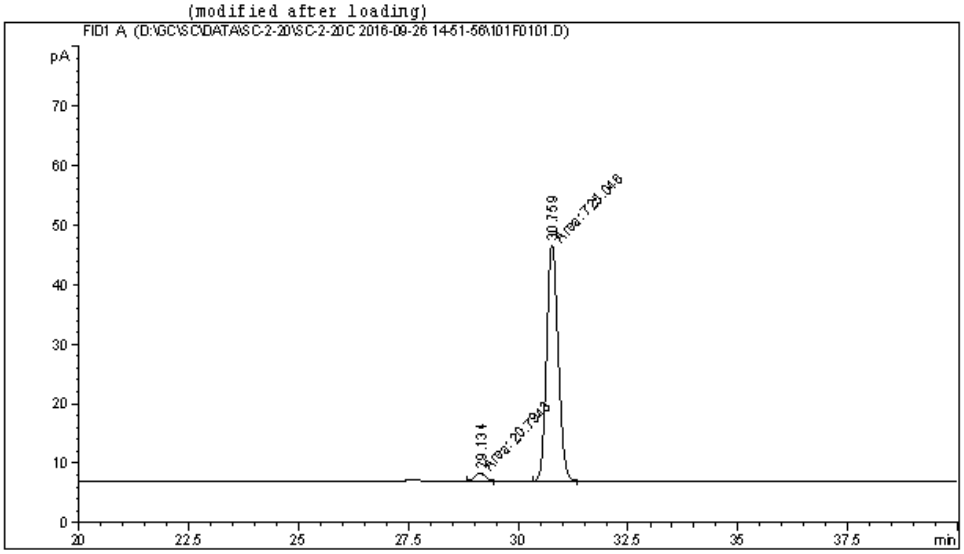
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|------|----|-------|----------|----------|--------|
       1  29.137 MM    0.2820 2052.20386  121.26871 50.05061
       2  30.773 MM    0.3062 2048.05322  111.49104 49.94939

    Totals :                  4100.25708  232.75975


    ======================================================================
                              *** End of Report ***
```

Data File D:\GC\SC\DATA\SC-2-20\SC-2-20C 2016-09-26 14-51-56\101F0101.D
Sample Name: SC-2-20C

Acq. Operator	: LHC	Seq. Line	: 1
Acq. Instrument	: Instrument 2	Location	: Vial 101
Injection Date	: 26-Sep-16, 14:52:52	Inj	: 1
		Inj Volume	: 1 µl
Acq. Method	: D:\GC\SC\Data\SC-2-20\SC-2-20C 2016-09-26 14-51-56\CS-1000-180C-1ML-45MIN.M		
Last changed	: 9/15/2016 11:39:41 AM by LHC		
Analysis Method	: D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M		
Last changed	: 6/22/2017 9:52:21 AM by DWW (modified after loading)		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.134	MM	0.2691	20.79435	1.28800	2.78804
2	30.759	MM	0.3049	725.04578	39.63926	97.21196
Totals :				745.84012	40.92726	

*** End of Report ***

Figure S67. HPLC spectrum of **2b**, related to **Table 3**.

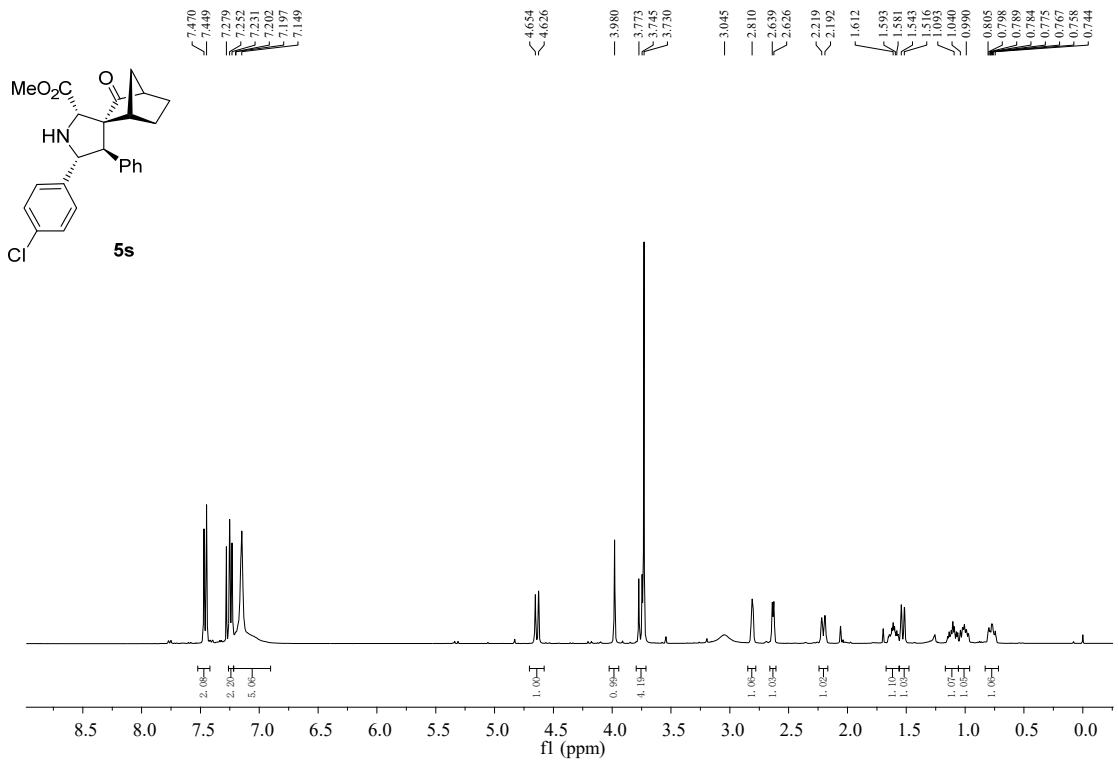


Figure S68. ^{1}H NMR spectrum of **5s**, related to **Table 3**.

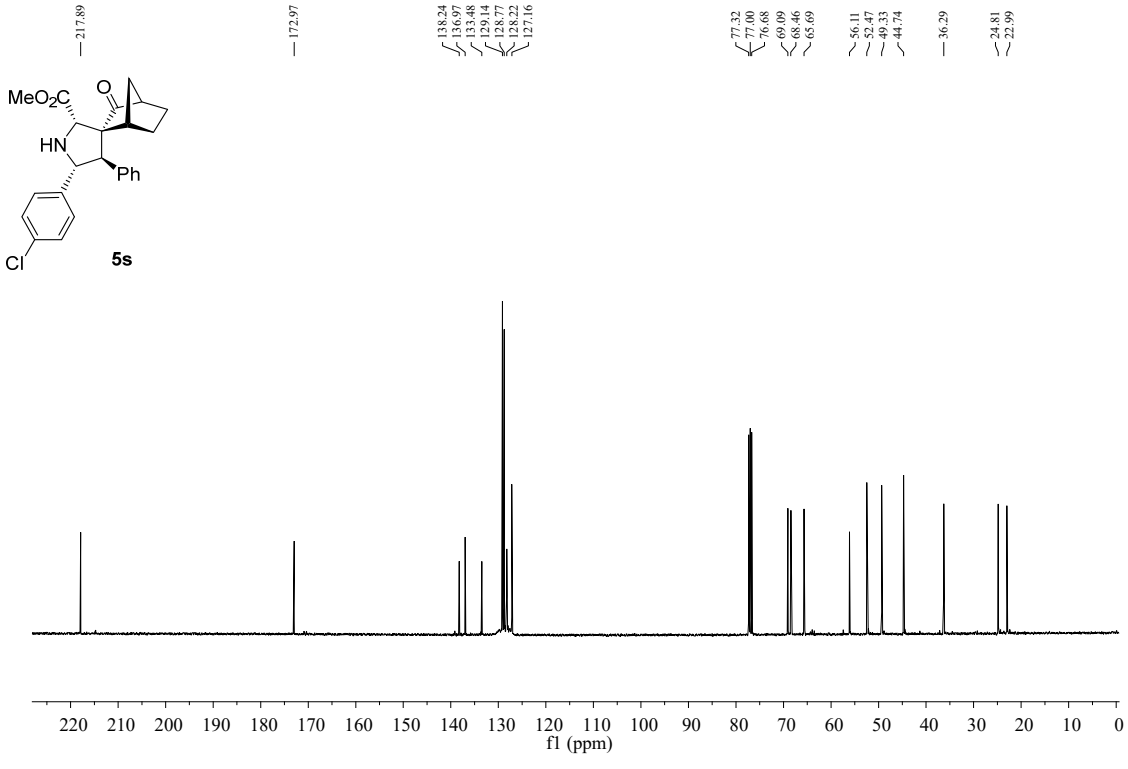
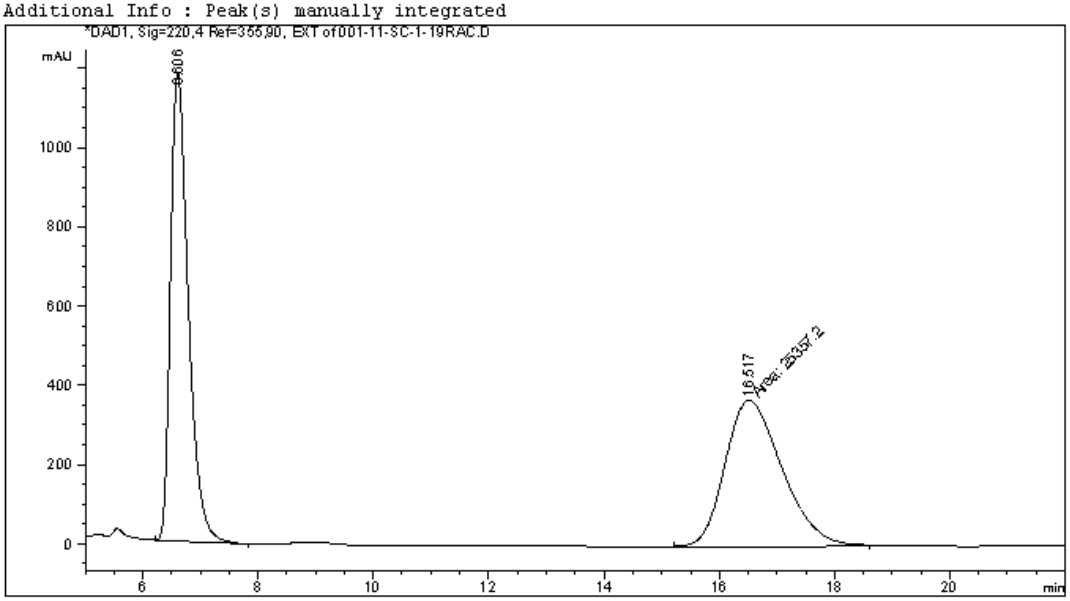


Figure S69. ^{13}C NMR spectrum of **5s**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-23\SC-2-23 2016-09-29 20-42-11\001-11-SC-1-19RAC.D
Sample Name: SC-1-19RAC

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   11
    Injection Date  : 9/30/2016 11:43:34 AM                 Inj :   1
                                                     Inj Volume : 10.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-23\SC-2-23 2016-09-29 20-42-11\SC-ASH-90-10-25MIN.M
    Last changed    : 9/30/2016 11:42:11 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-23\SC-2-23 2016-09-29 20-42-11\SC-ASH-90-10-25MIN.M (
                      Sequence Method)
    Last changed    : 6/3/2017 9:21:00 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

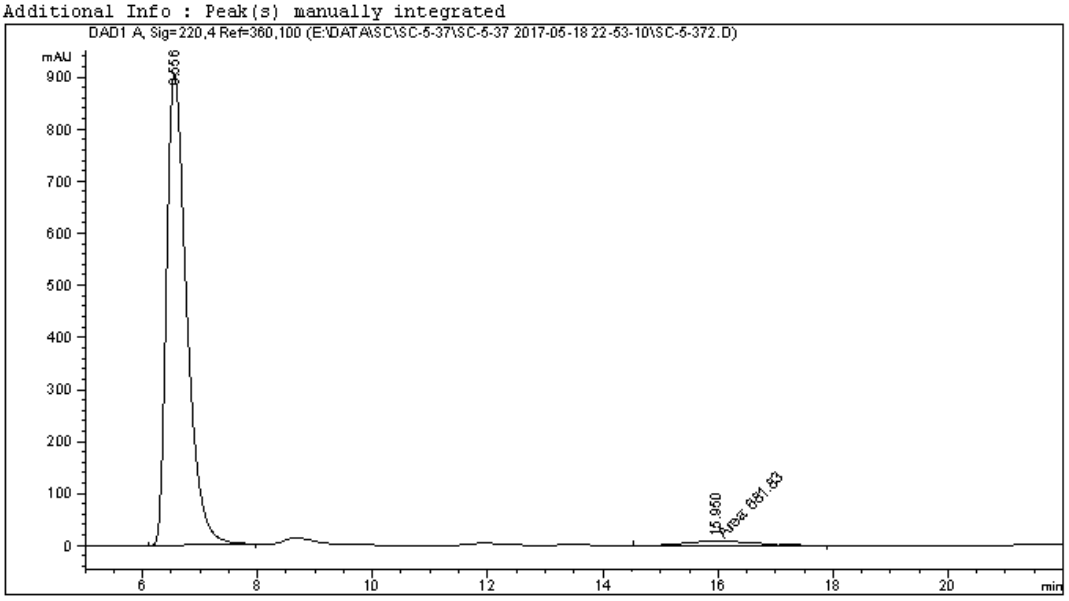

    Signal 1: DAD1, Sig=220,4 Ref=355,90, EXT
     Signal has been modified after loading from rawdata file!

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   6.606 BB    0.3291 2.53283e4  1181.33020  49.9714
       2  16.517 MM    1.1469 2.53572e4   368.49432  50.0286

    Totals :                  5.06855e4  1549.82452
```

Data File E:\DATA\SC\SC-5-37\SC-5-37 2017-05-18 22-53-10\SC-5-372.D
Sample Name: SC-5-37B

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                              Location :   12
Injection Date  : 5/18/2017 11:56:51 PM                 Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-37\SC-5-37 2017-05-18 22-53-10\SC-2-ASH-90-10-220NM-25MIN-
                  1ML.M
Last changed    : 5/18/2017 10:53:10 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-37\SC-5-37 2017-05-18 22-53-10\SC-2-ASH-90-10-220NM-25MIN-
                  1ML.M (Sequence Method)
Last changed    : 6/3/2017 9:24:20 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   6.556 BB    0.3687 2.19733e4   906.67065  96.9904
   2  15.950 MM    1.3227  681.82983    8.59143   3.0096

Totals :                  2.26552e4   915.26208
```


Figure S70. HPLC spectrum of **5s**, related to **Table 3**.

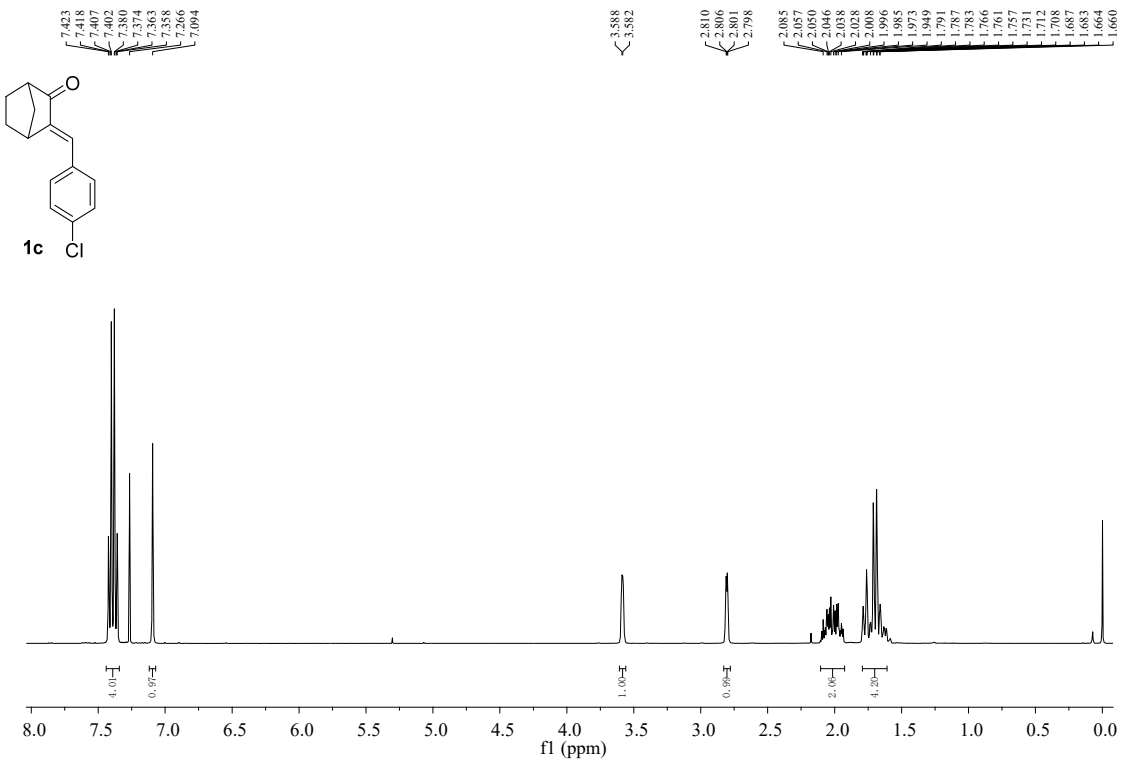


Figure S71. [1]H NMR spectrum of **1c**, related to **Table 3**.

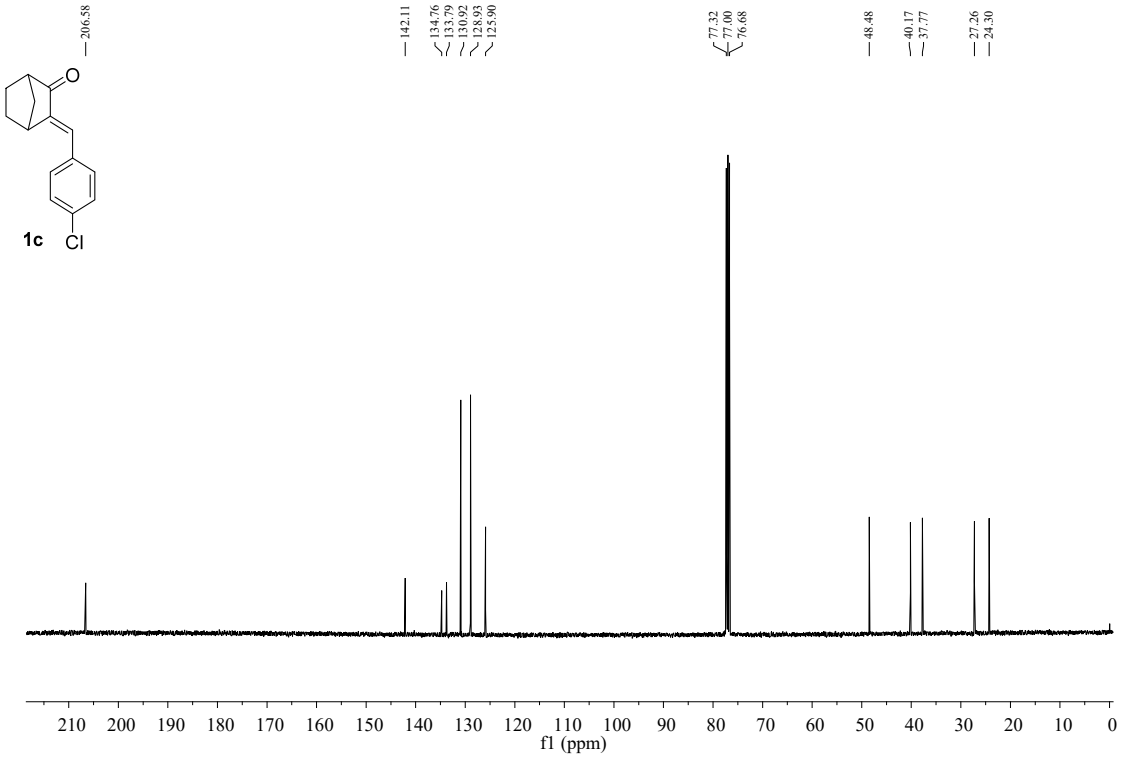
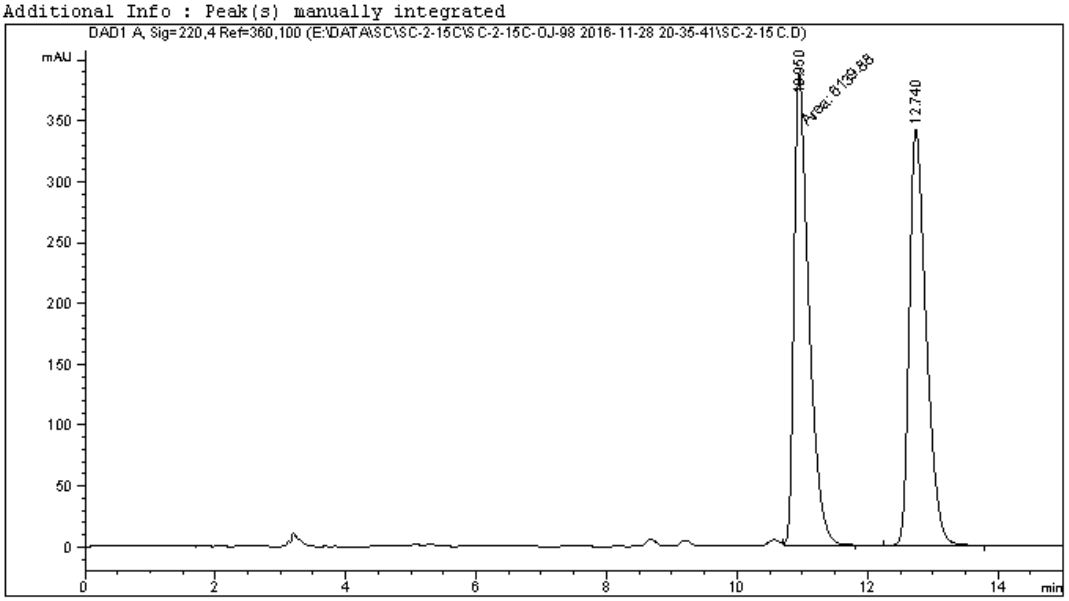


Figure S72. [13]C NMR spectrum of **1c**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-15C\SC-2-15C-0J-98 2016-11-28 20-35-41\SC-2-15C.D
Sample Name: SC-2-15C-0J-98

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   63
    Injection Date  : 11/29/2016 12:37:06 PM              Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-15C\SC-2-15C-0J-98 2016-11-28 20-35-41\SC-5-0JH-98-2-DAD-
                      1ML.M
    Last changed    : 11/29/2016 12:35:42 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-15C\SC-2-15C-0J-98 2016-11-28 20-35-41\SC-5-0JH-98-2-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 4:15:53 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

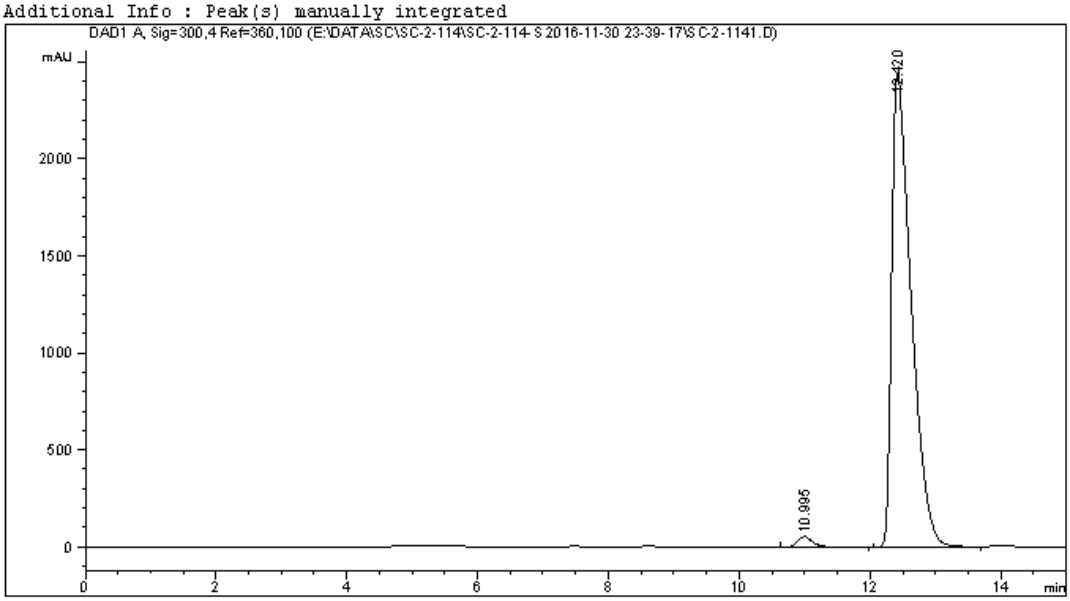

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  10.950 MM    0.2637 6139.87939  388.00522  49.9601
       2  12.740 BB    0.2714 6149.68896  342.69366  50.0399

    Totals :                  1.22896e4   730.69888
```

Data File E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-2-1141.D
Sample Name: SC-2-114B-S

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : 1260                           Location :   65
Injection Date  : 12/1/2016 12:02:08 AM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M
Last changed    : 11/30/2016 11:39:17 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:17:56 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=300,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.995 BB    0.2319  795.39307   51.88279   1.5593
   2  12.420 BB    0.3061 5.02152e4  2440.30078  98.4407

Totals :                  5.10105e4  2492.18357
```


Figure S73. HPLC spectrum of **1c**, related to **Table 3**.

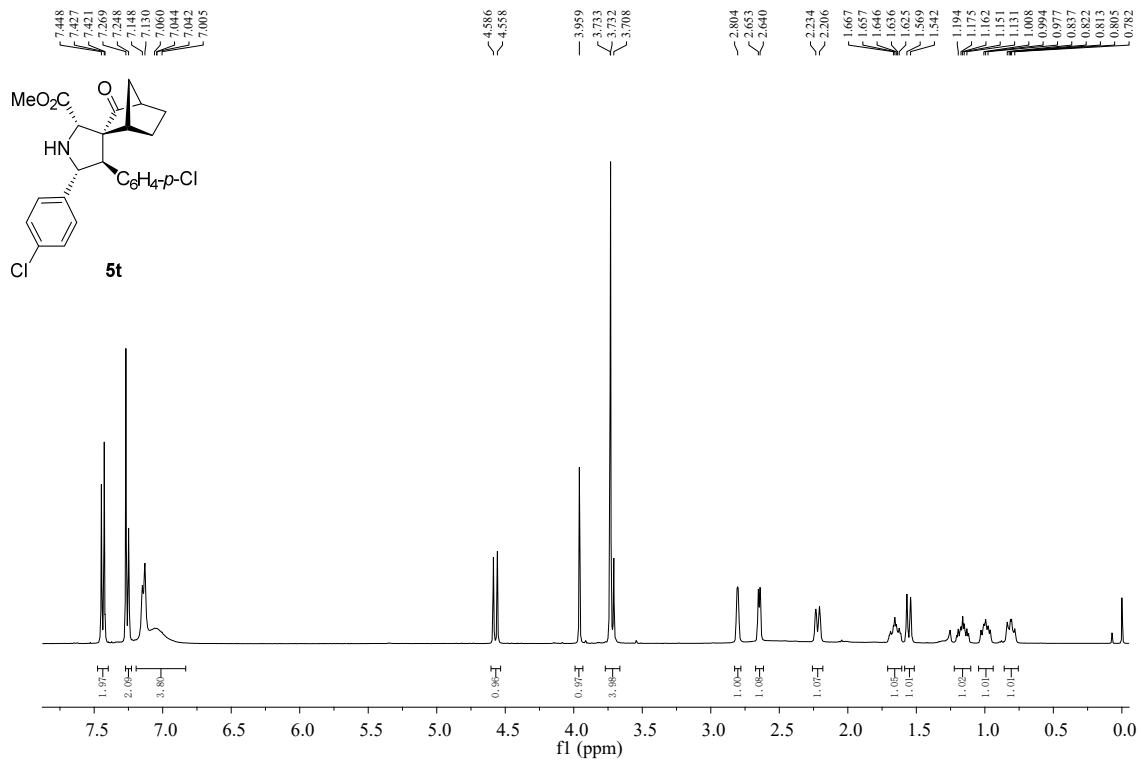


Figure S74. [1]H NMR spectrum of **5t**, related to **Table 3**.

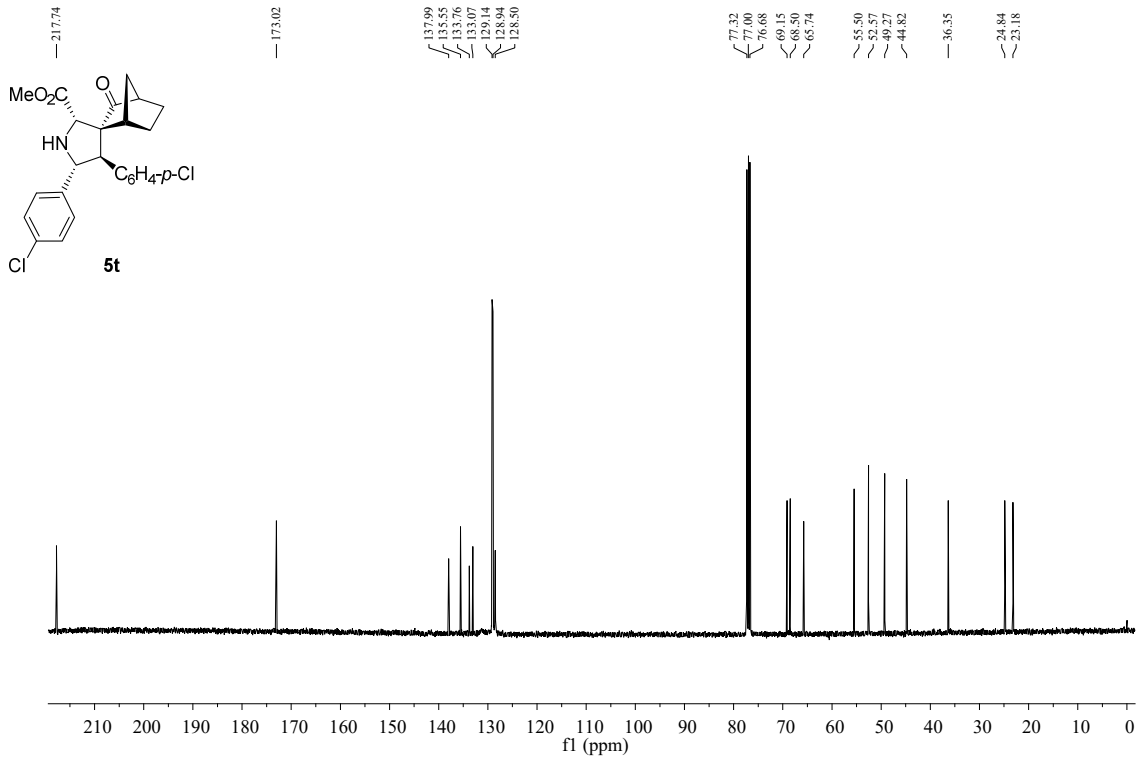
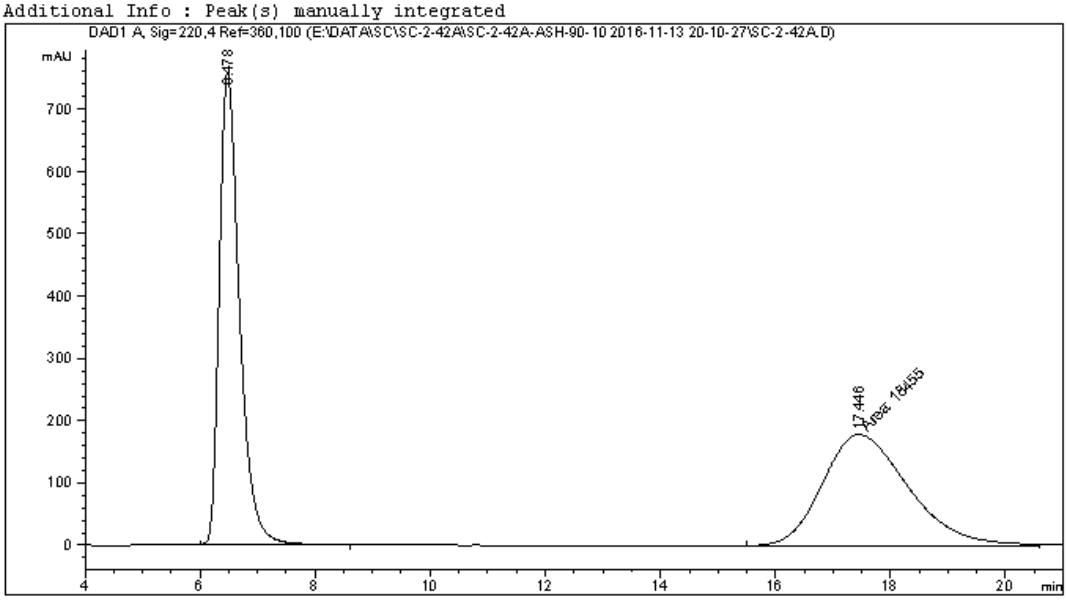


Figure S75. [13]C NMR spectrum of **5t**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-42A\SC-2-42A-ASH-90-10 2016-11-13 20-10-27\SC-2-42A.D
Sample Name: SC-2-42A-ASH-90-10

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   62
Injection Date  : 11/14/2016 12:11:47 PM             Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-42A\SC-2-42A-ASH-90-10 2016-11-13 20-10-27\SC-1-ASH-90-10-
                  DAD-1ML.M
Last changed    : 11/14/2016 12:10:27 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-42A\SC-2-42A-ASH-90-10 2016-11-13 20-10-27\SC-1-ASH-90-10-
                  DAD-1ML.M (Sequence Method)
Last changed    : 6/3/2017 9:38:50 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

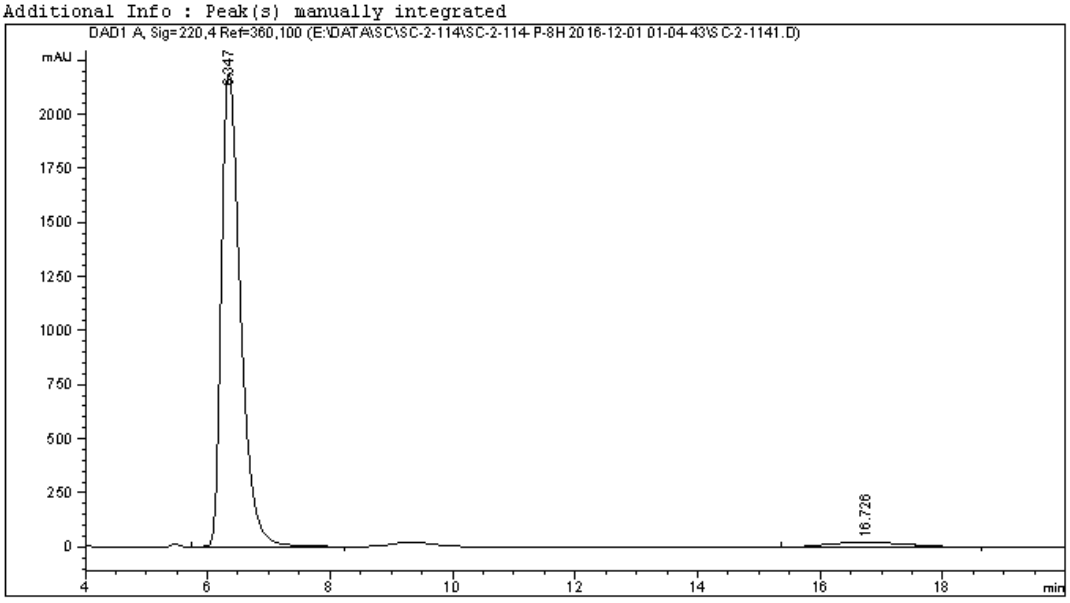

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.478 BB    0.3717 1.84074e4   756.95520  49.9355
   2  17.446 MM    1.7170 1.84550e4   179.13693  50.0645

Totals :                  3.68624e4   936.09213
```

Data File E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-2-1141.D
Sample Name: SC-2-114B-P

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : 1260                          Location :   67
Injection Date  : 12/1/2016 1:27:31 AM               Inj :   1
                                               Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-1-ASH-90-10-220NM-
                  1ML-20MIN.M
Last changed    : 12/1/2016 1:04:43 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-1-ASH-90-10-220NM-
                  1ML-20MIN.M (Sequence Method)
Last changed    : 7/12/2017 10:17:31 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.347 BB    0.3316 4.74010e4  2188.93872  96.4888
   2  16.726 BB    0.9415 1724.90381   21.81492   3.5112

Totals :                  4.91259e4  2210.75364
```


Figure S76. HPLC spectrum of **5t**, related to **Table 3**.

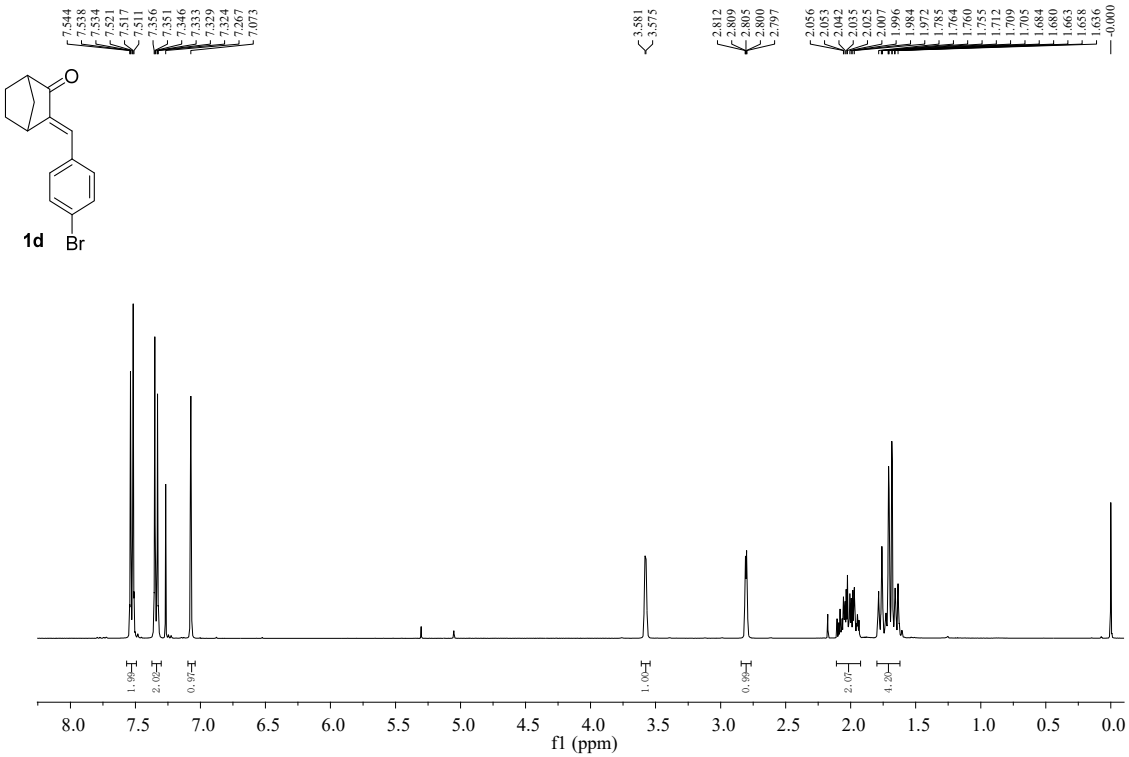


Figure S77. ^{1}H NMR spectrum of **1d**, related to **Table 3**.

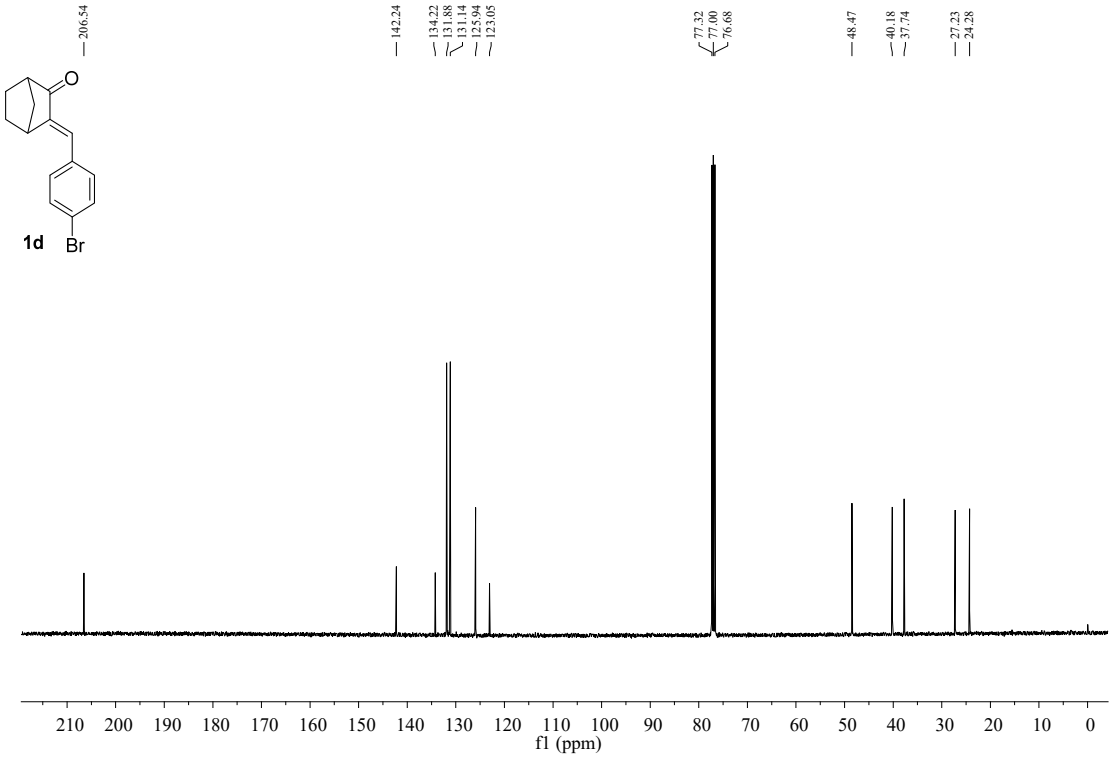
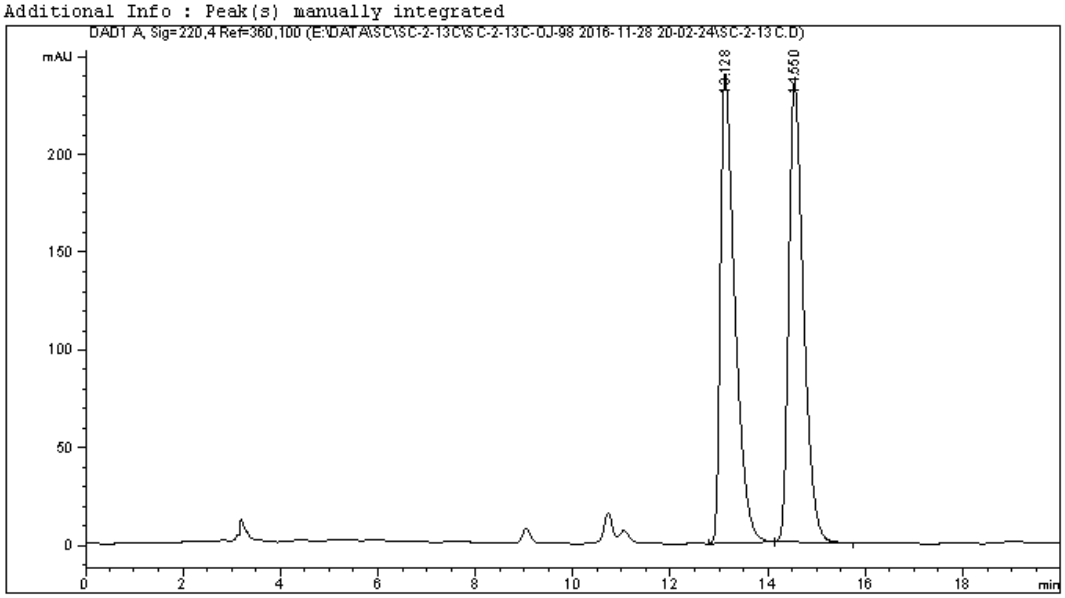


Figure S78. ^{13}C NMR spectrum of **1d**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-13C\SC-2-13C-0J-98 2016-11-28 20-02-24\SC-2-13C.D
Sample Name: SC-2-13C-0J-98

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   62
    Injection Date  : 11/29/2016 12:03:47 PM               Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC-2-13C\SC-2-13C-0J-98 2016-11-28 20-02-24\SC-5-0JH-98-2-DAD-1ML.M
    Last changed    : 11/29/2016 12:02:24 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-13C\SC-2-13C-0J-98 2016-11-28 20-02-24\SC-5-0JH-98-2-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 4:22:41 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

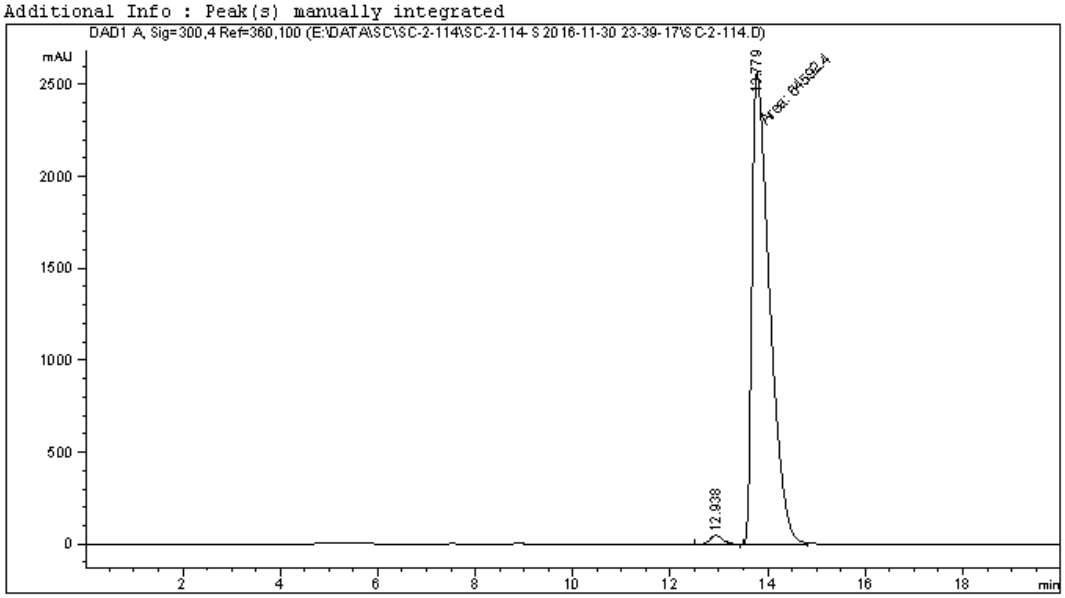

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  13.128 BB    0.3062 4947.04688  240.25314  49.9844
       2  14.550 BB    0.3186 4950.12793  234.16545  50.0156

    Totals :                  9897.17480  474.41859
```

Data File E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-2-114.D
Sample Name: SC-2-114A-S

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   64
Injection Date  : 11/30/2016 11:40:43 PM             Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M
Last changed    : 11/30/2016 11:39:17 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-114\SC-2-114-S 2016-11-30 23-39-17\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:22:01 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=300,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.938 BV    0.2823  844.58960   45.97598   1.2907
   2  13.779 MM    0.4188 6.45924e4  2570.39966  98.7093

Totals :                  6.54370e4  2616.37564
```


Figure S79. HPLC spectrum of **1d**, related to **Table 3**.

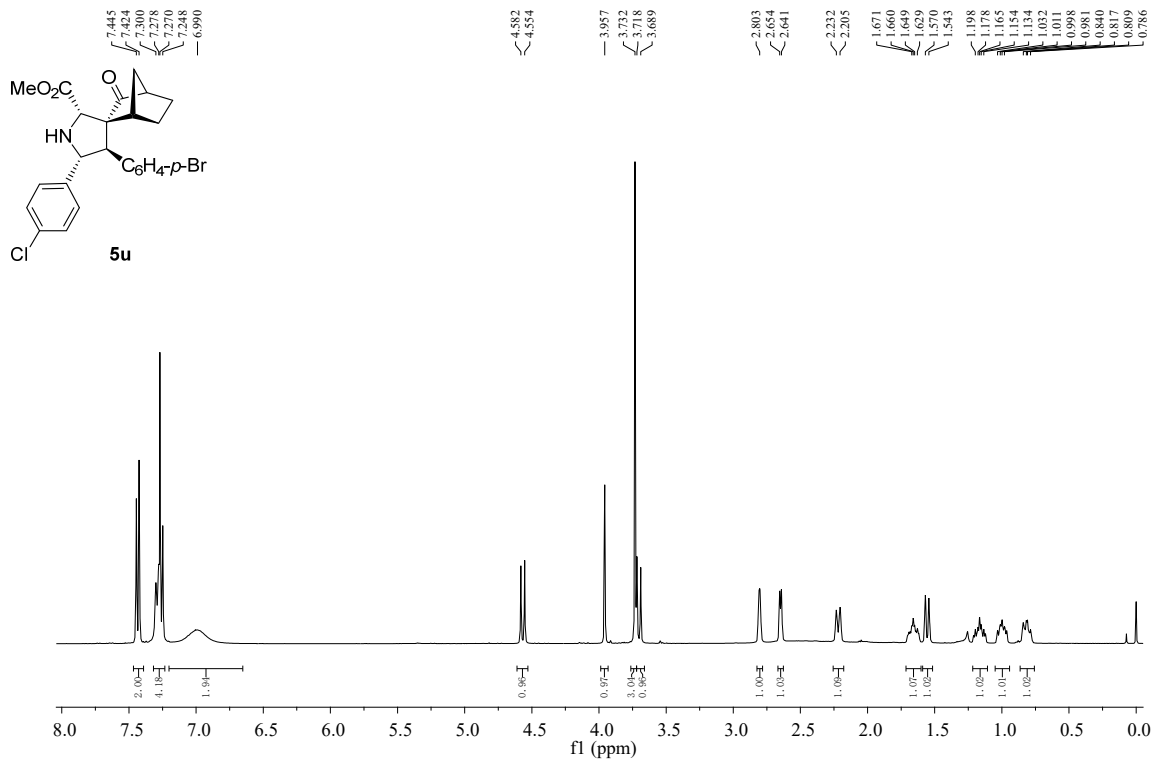


Figure S80. ^{1}H NMR spectrum of **5u**, related to **Table 3**.

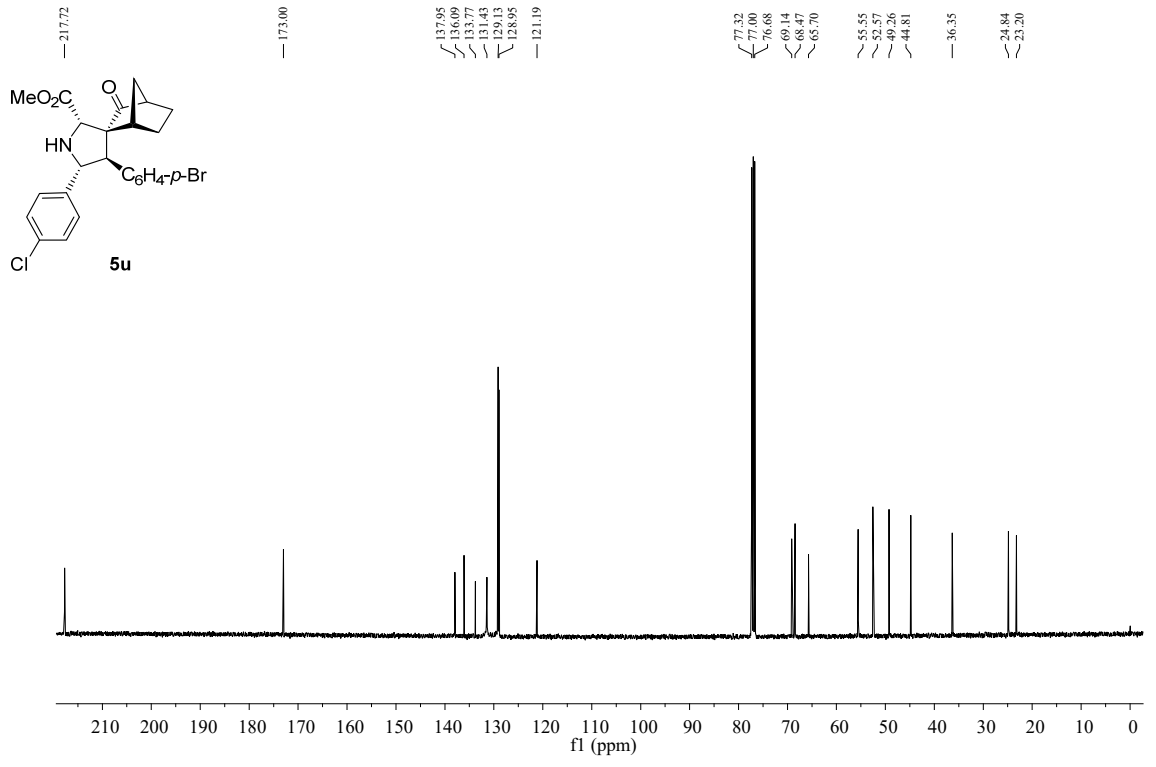
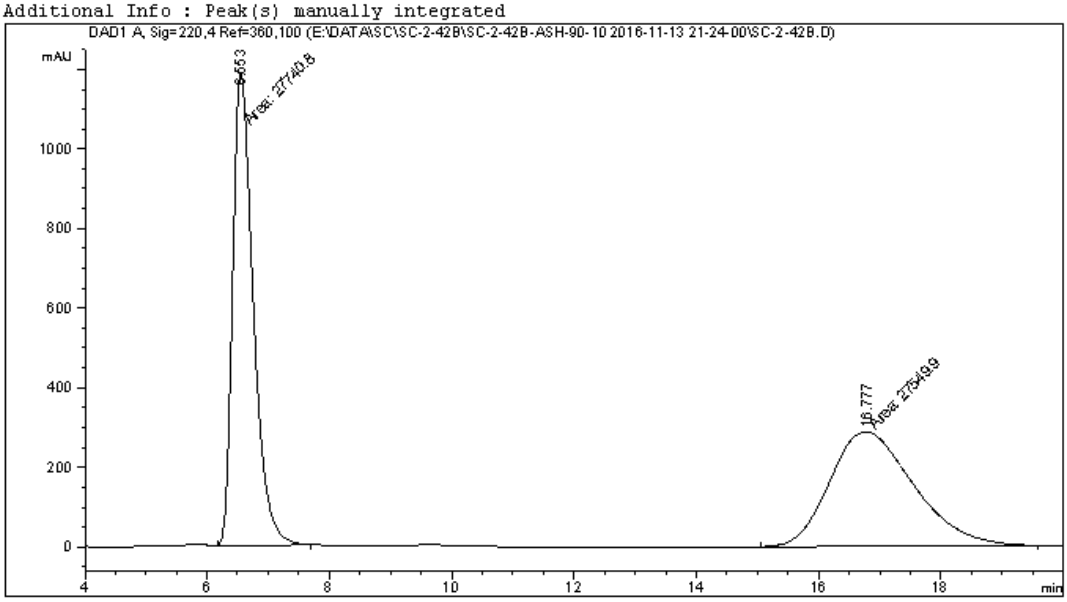


Figure S81. ^{13}C NMR spectrum of **5u**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-2-42B.D
Sample Name: SC-2-42B-ASH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   63
    Injection Date  : 11/14/2016 1:25:23 PM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-1-ASH-90-10-
                      DAD-1ML.M
    Last changed    : 11/14/2016 1:24:00 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-1-ASH-90-10-
                      DAD-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 9:47:50 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

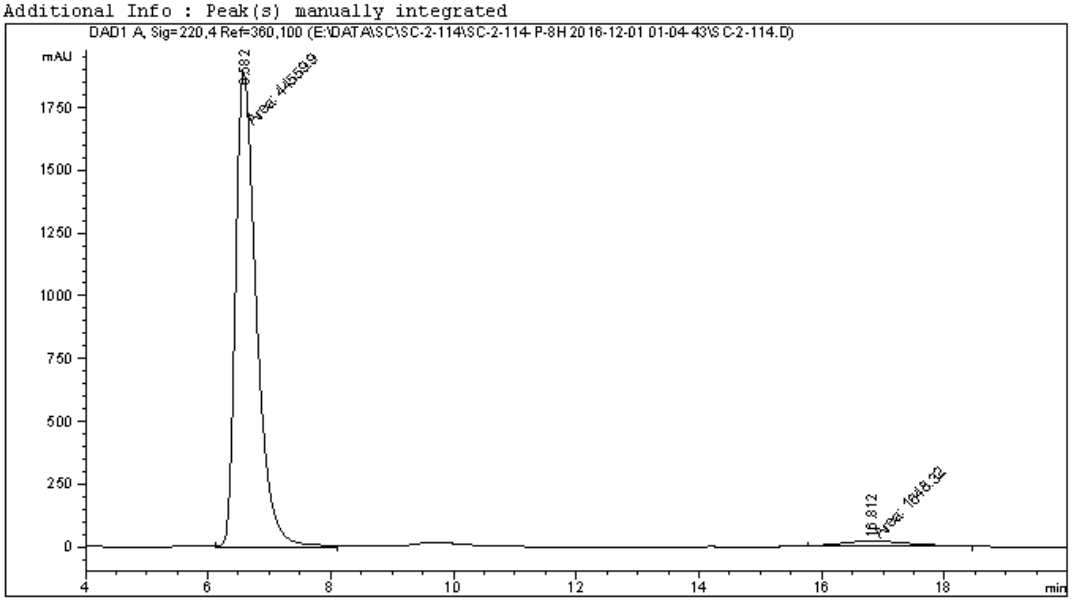

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   6.553 MM    0.3897 2.77408e4  1186.50159  50.1726
       2  16.777 MM    1.5977 2.75499e4   287.39413  49.8274

    Totals :                  5.52907e4  1473.89572
```

Data File E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-2-114.D
Sample Name: SC-2-114A-P

Acq. Operator	: SYSTEM	Seq. Line	: 1
Acq. Instrument	: 1260	Location	: 66
Injection Date	: 12/1/2016 1:06:07 AM	Inj	: 1
		Inj Volume	: 5.000 µl
Acq. Method	: E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-1-ASH-90-10-220NM-1ML-20MIN.M		
Last changed	: 12/1/2016 1:04:43 AM by SYSTEM		
Analysis Method	: E:\DATA\SC\SC-2-114\SC-2-114-P-8H 2016-12-01 01-04-43\SC-1-ASH-90-10-220NM-1ML-20MIN.M (Sequence Method)		
Last changed	: 6/3/2017 9:52:26 AM by SYSTEM (modified after loading)		
Additional Info	: Peak(s) manually integrated		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.582	MM	0.3934	4.45599e4	1888.04858	96.4328
2	16.812	MM	1.3210	1648.31824	20.79683	3.5672
Totals :				4.62082e4	1908.84541	

Figure S82. HPLC spectrum of **5u**, related to **Table 3**.

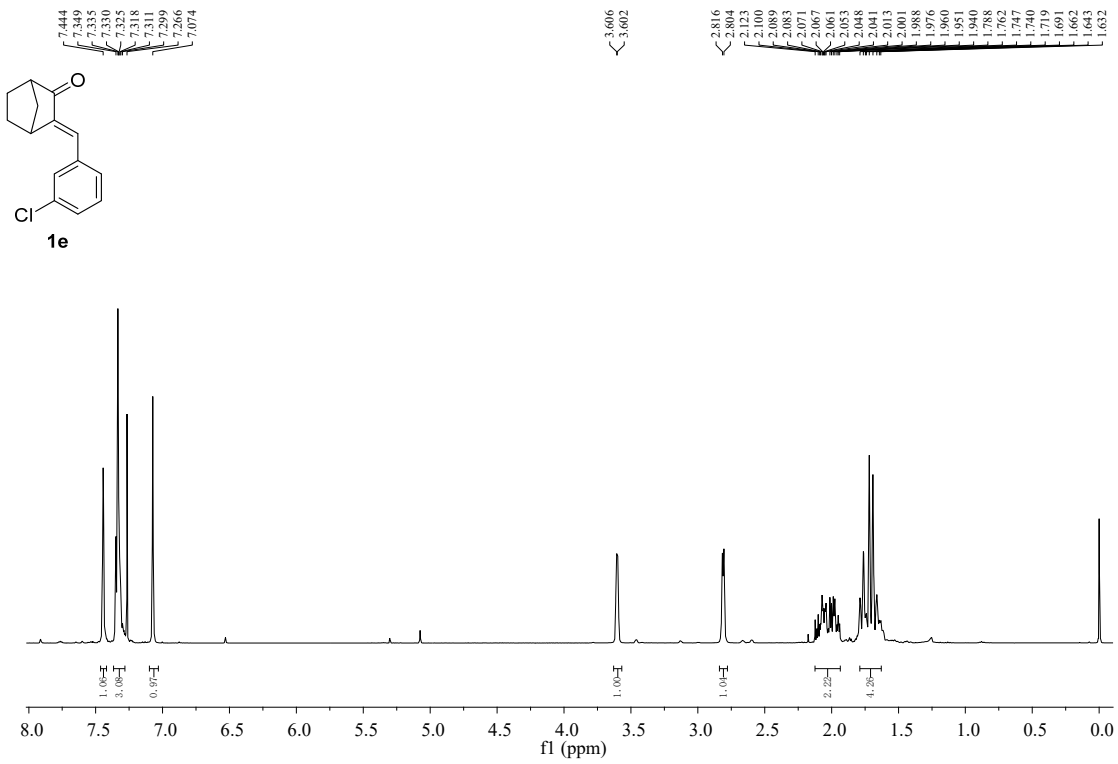


Figure S83. ^{1}H NMR spectrum of **1e**, related to **Table 3**.

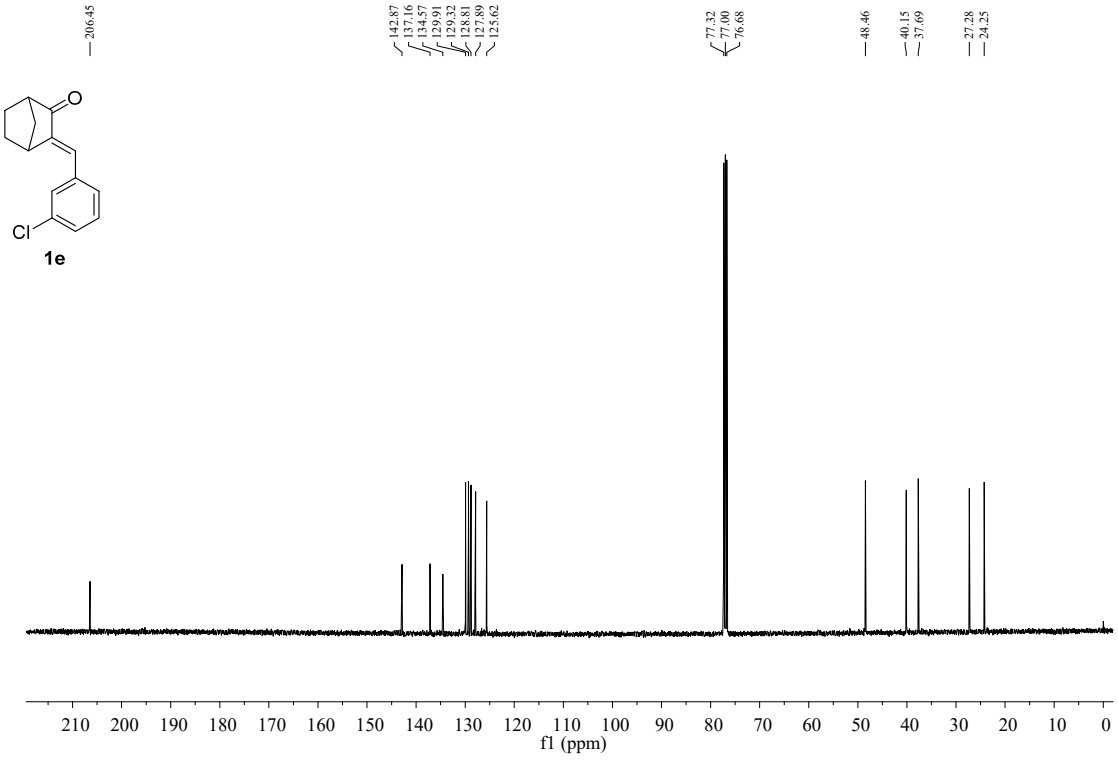


Figure S84. ^{13}C NMR spectrum of **1e**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-15B\SC-2-15B-0J-98 2016-11-27 16-53-53\SC-2-15B.D
Sample Name: SC-2-15B-0J-98

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   68
    Injection Date  : 11/28/2016 8:55:19 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-15B\SC-2-15B-0J-98 2016-11-27 16-53-53\SC-5-0JH-98-2-DAD-
                      1ML.M
    Last changed    : 11/28/2016 8:53:53 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-15B\SC-2-15B-0J-98 2016-11-27 16-53-53\SC-5-0JH-98-2-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 4:26:12 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
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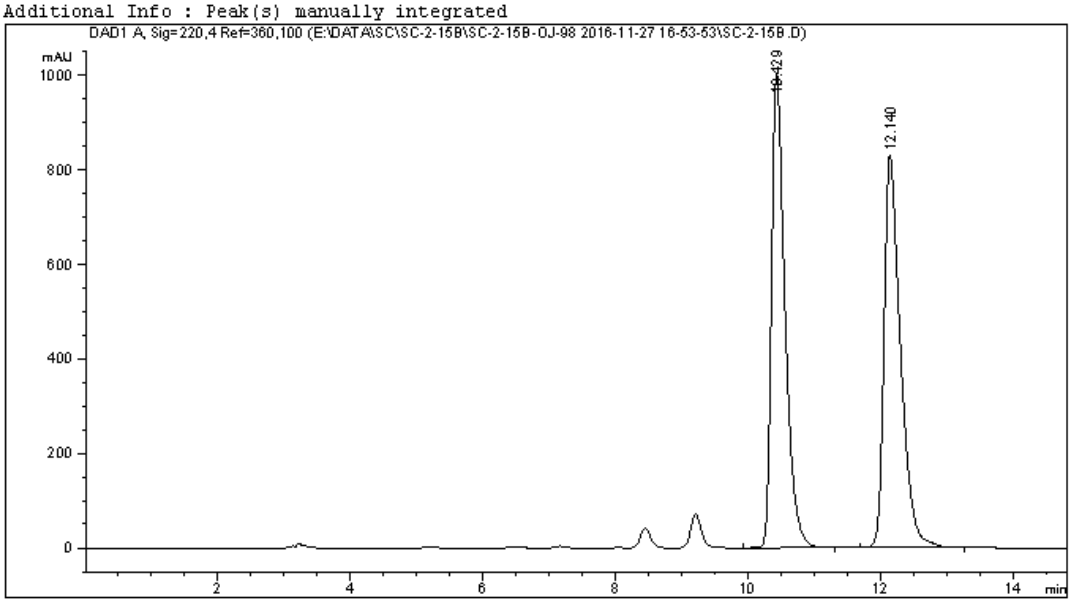


```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1  10.429 BB    0.2122 1.42060e4  1003.01691  49.7720
       2  12.140 BB    0.2574 1.43361e4   830.58258  50.2280

    Totals :                  2.85421e4  1833.59949
```

Data File E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-3-131.D
Sample Name: SC-3-15-S

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                             Location :   12
Injection Date  : 12/10/2016 10:39:54 PM               Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M
Last changed    : 12/10/2016 10:17:11 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:30:49 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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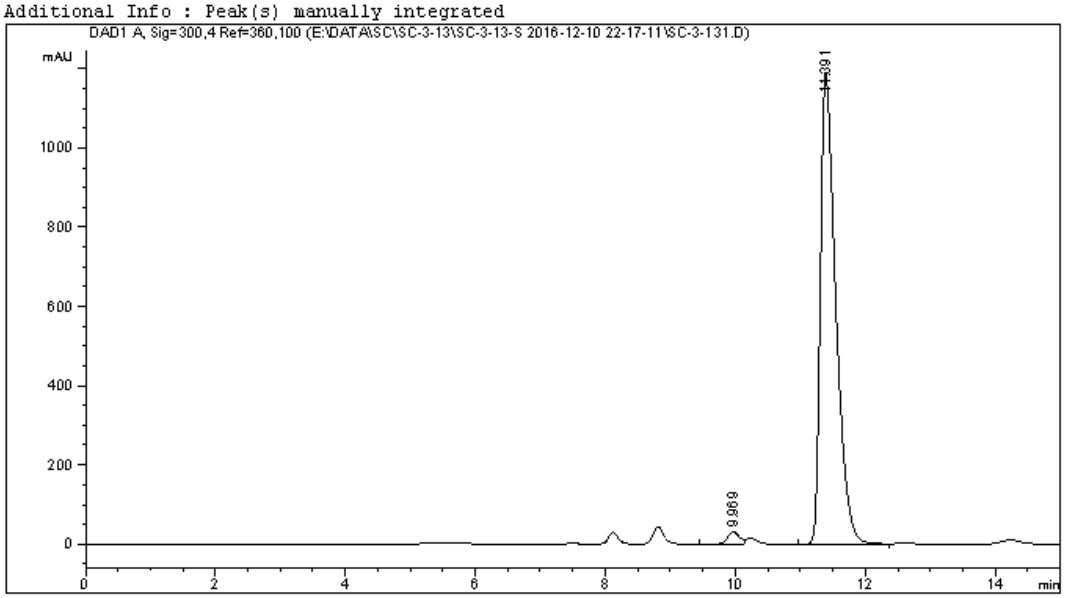


```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=300,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   9.969 BV    0.1925  387.10367   30.62425   1.9481
   2  11.391 BB    0.2471 1.94840e4  1189.20984  98.0519

Totals :                  1.98711e4  1219.83409
```


Figure S85. HPLC spectrum of **1e**, related to **Table 3**.

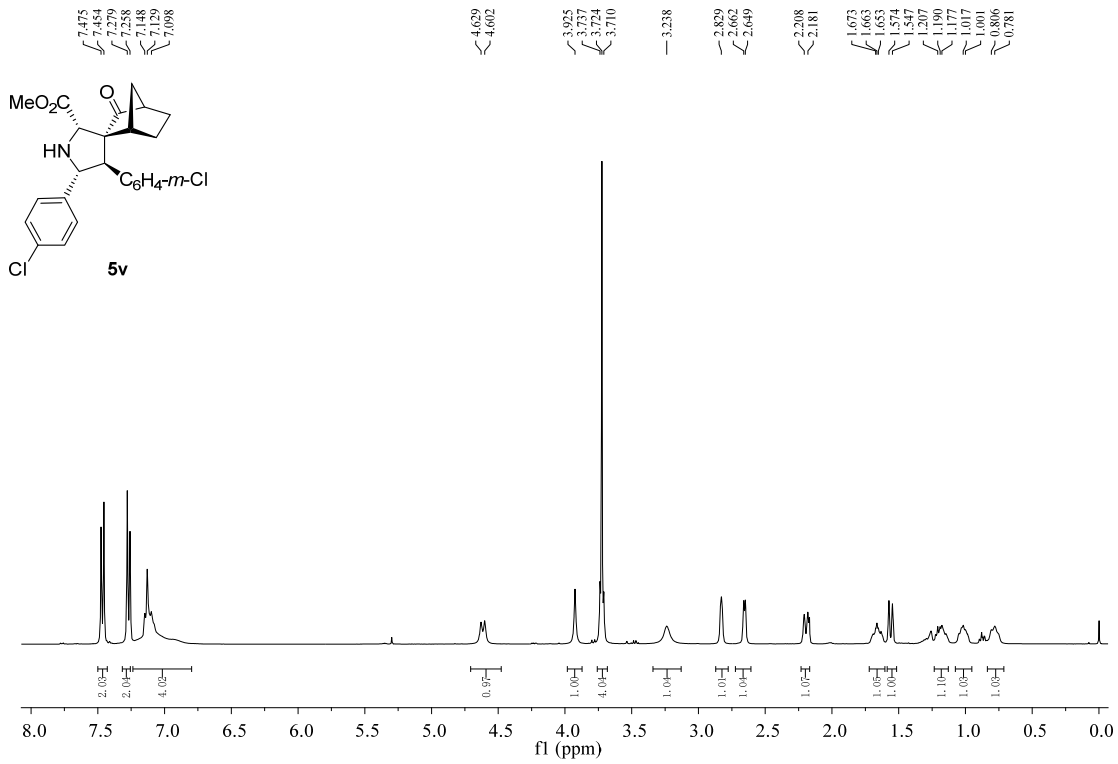

Figure S86. ^{1}H NMR spectrum of **5v**, related to **Table 3**.

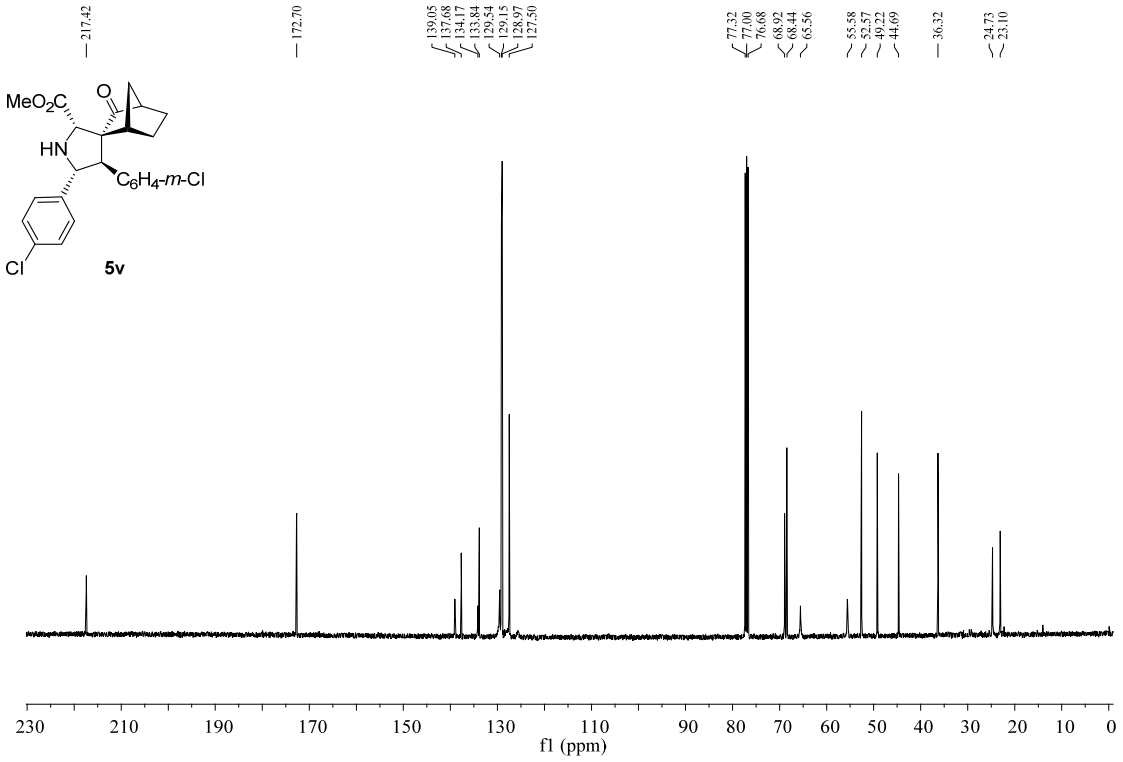

Figure S87. ^{13}C NMR spectrum of **5v**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-47A\SC-2-47A-ASH-90-10 2016-11-13 23-07-52\SC-2-47A.D
Sample Name: SC-2-47A-ASH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   66
    Injection Date  : 11/14/2016 3:09:16 PM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-47A\SC-2-47A-ASH-90-10 2016-11-13 23-07-52\SC-1-ASH-90-10-
                      DAD-1ML.M
    Last changed    : 11/14/2016 3:07:52 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-47A\SC-2-47A-ASH-90-10 2016-11-13 23-07-52\SC-1-ASH-90-10-
                      DAD-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 10:00:47 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
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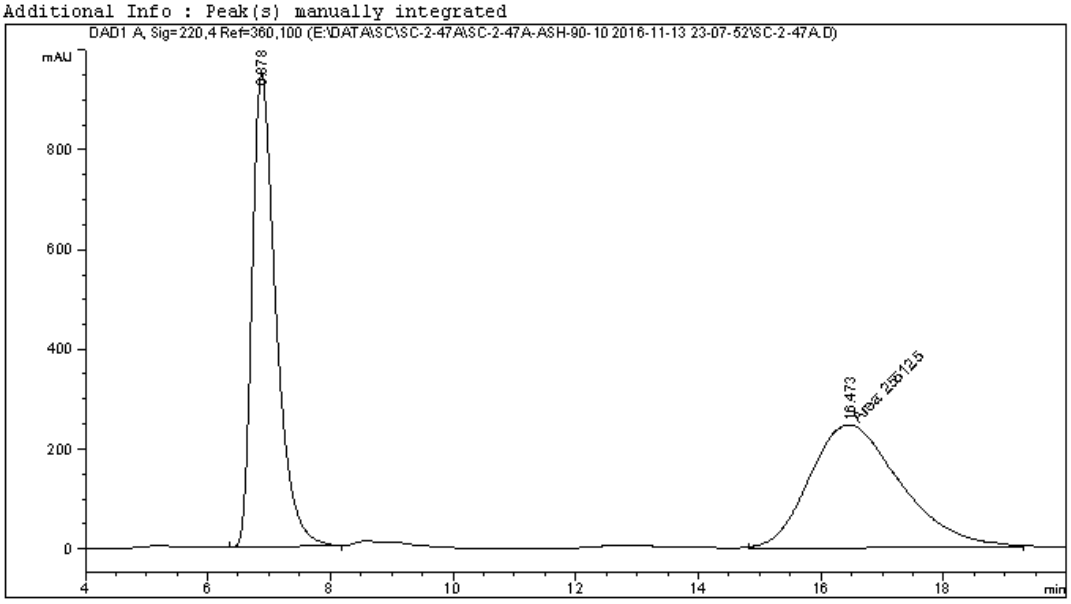



```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

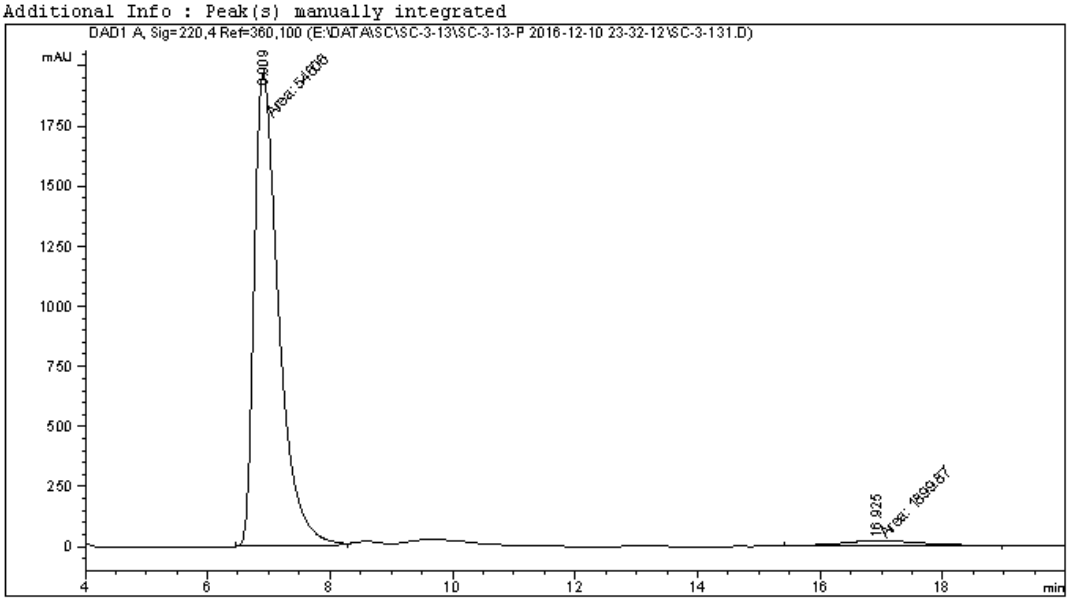

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   6.878 BB    0.4075 2.55858e4   949.24866  50.0718
       2  16.473 MM    1.7289 2.55125e4   245.93962  49.9282

    Totals :                  5.10983e4  1195.18828
```

Data File E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-3-131.D
Sample Name: SC-3-15-P

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : 1260                           Location :   16
Injection Date  : 12/10/2016 11:54:58 PM             Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 12/10/2016 11:32:12 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/3/2017 9:57:23 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.909 MM    0.4632 5.46060e4  1964.88562  96.6377
   2  16.925 MM    1.5842 1899.86963   19.98772   3.3623

Totals :                  5.65059e4  1984.87334
```


Figure S88. HPLC spectrum of **5v**, related to **Table 3**.

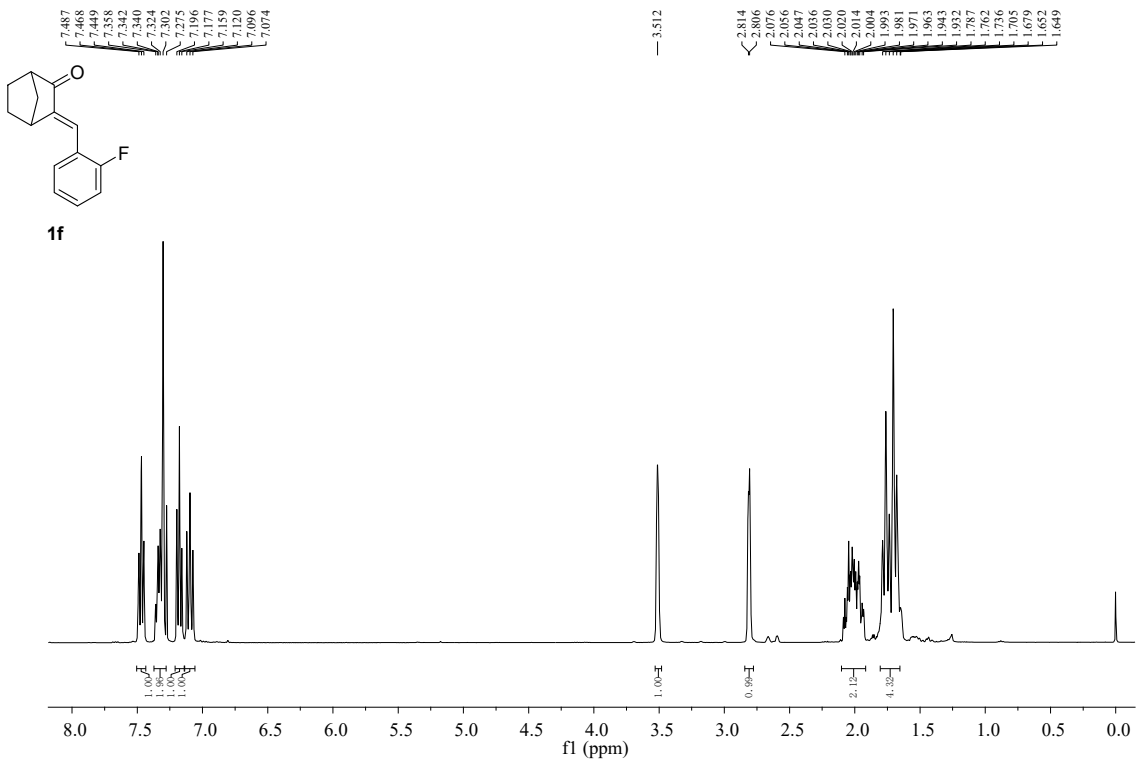


Figure S89. ^{1}H NMR spectrum of **1f**, related to **Table 3**.

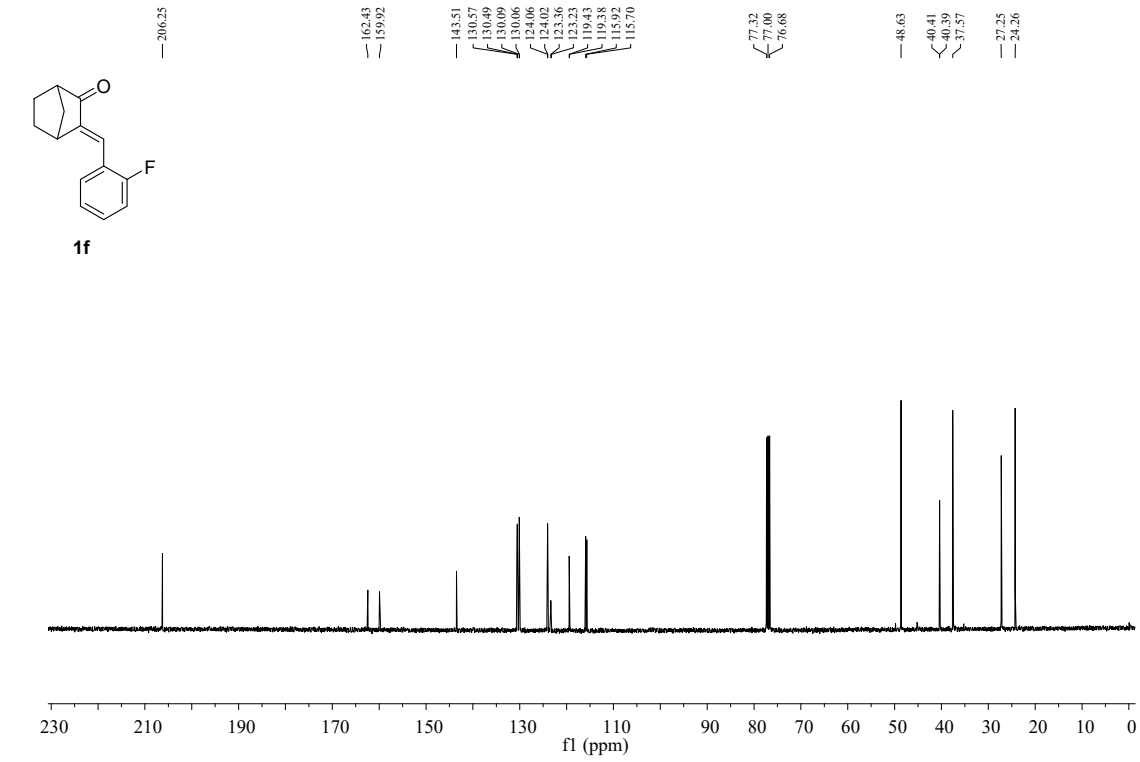
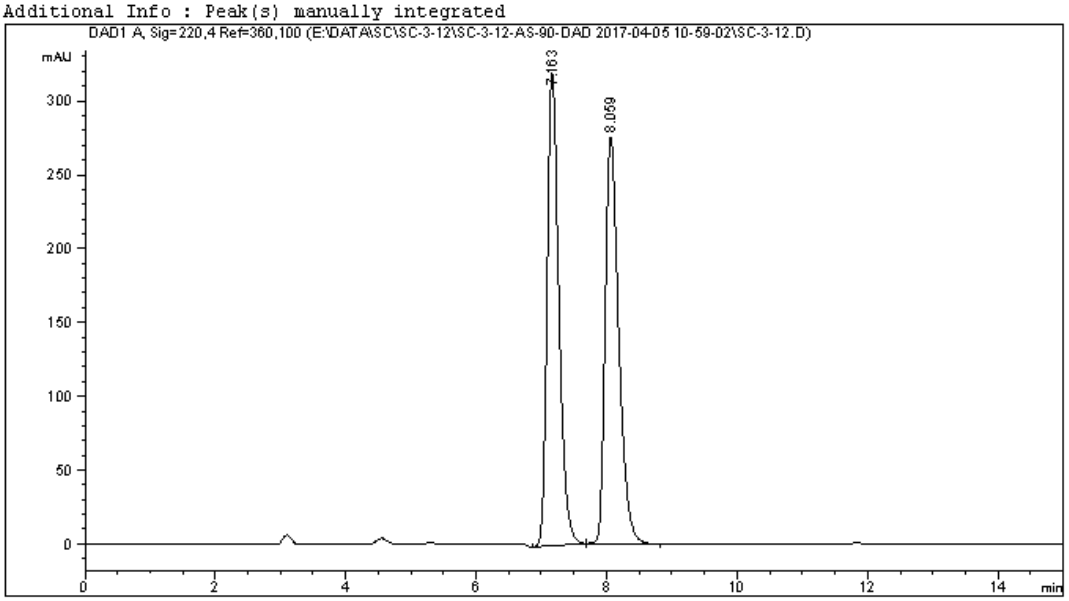


Figure S90. ^{13}C NMR spectrum of **1f**, related to **Table 3**.

Data File E:\DATA\SC\SC-3-12\SC-3-12-AS-90-DAD 2017-04-05 10-59-02\SC-3-12.D
Sample Name: SC-3-12

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                              Location :   11
Injection Date  : 4/5/2017 11:00:25 AM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-12\SC-3-12-AS-90-DAD 2017-04-05 10-59-02\SC-1-ASH-90-10-DAD
                  -1ML.M
Last changed    : 4/5/2017 10:59:02 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-12\SC-3-12-AS-90-DAD 2017-04-05 10-59-02\SC-1-ASH-90-10-DAD
                  -1ML.M (Sequence Method)
Last changed    : 6/4/2017 4:33:24 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

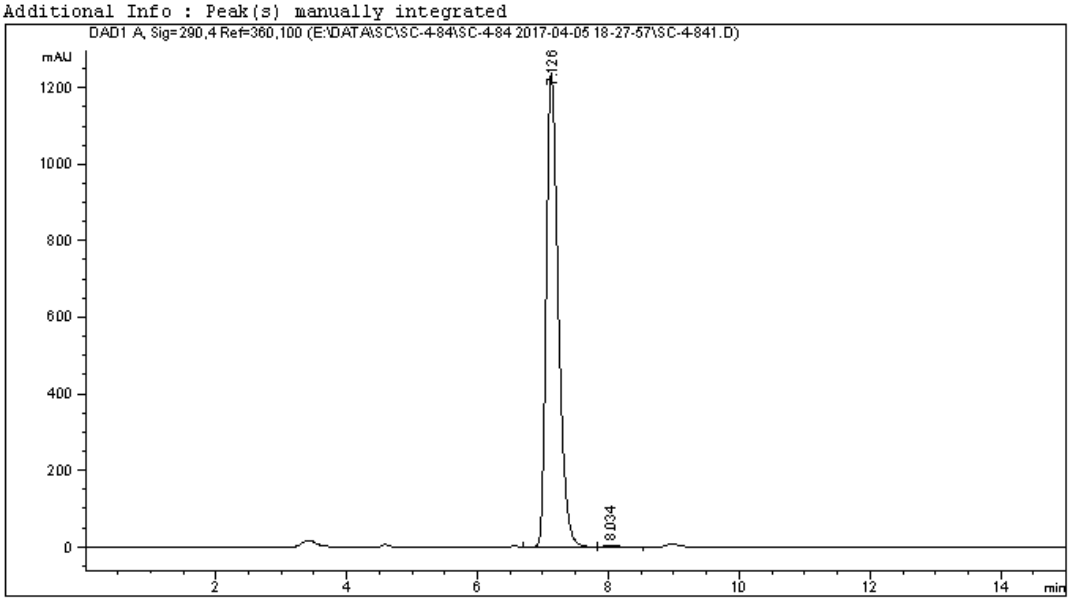

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.163 BB    0.1910 4004.91187  320.04797  50.1550
   2   8.059 BB    0.2193 3980.16113  275.93500  49.8450

Totals :                   7985.07300  595.98297
```

Data File E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-4-841.D
Sample Name: SC-4-84-S

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                              Location :   11
Injection Date  : 4/5/2017 6:45:12 PM                    Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-1-ASH-90-10-290NM-15MIN-
                  1ML.M
Last changed    : 4/5/2017 6:27:57 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-1-ASH-90-10-290NM-15MIN-
                  1ML.M (Sequence Method)
Last changed    : 6/4/2017 4:36:00 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=290,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.126 BB    0.1944 1.57274e4  1236.70776  99.7928
   2   8.034 BB    0.1934   32.65266    2.51566   0.2072

Totals :                  1.5760le4  1239.22343
```


Figure S91. HPLC spectrum of **1f**, related to **Table 3**.

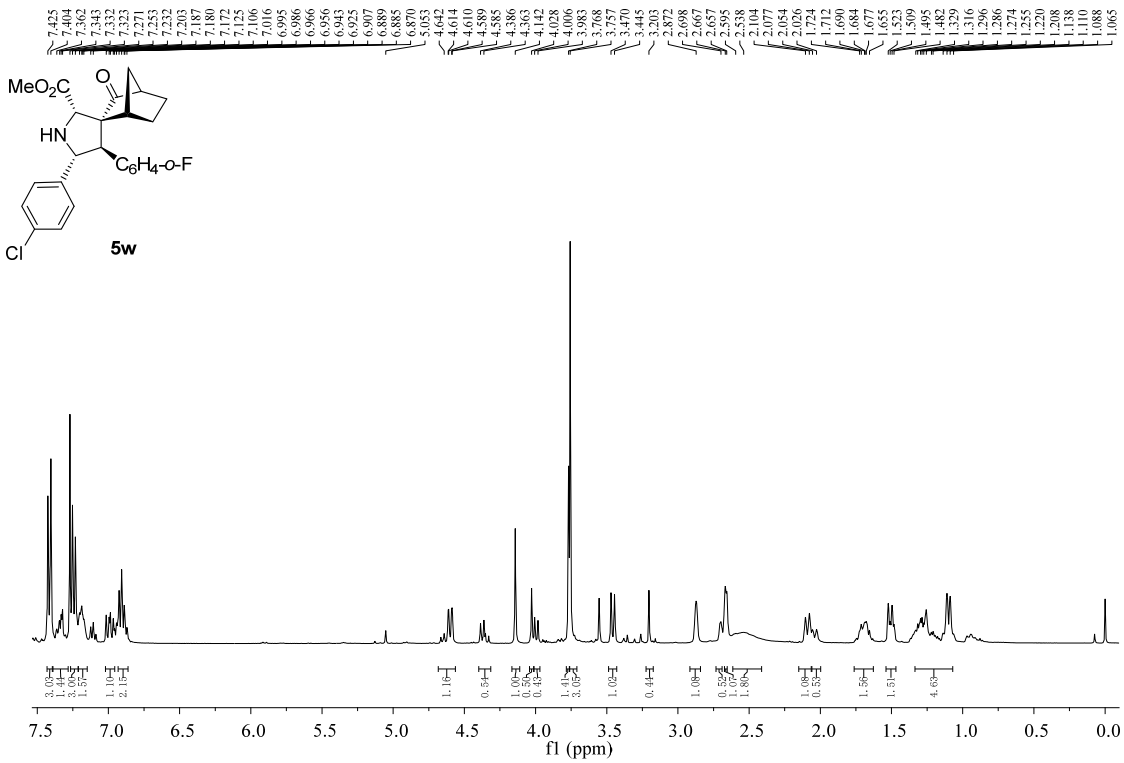


Figure S92. ^{1}H NMR spectrum of **5w**, related to **Table 3**.

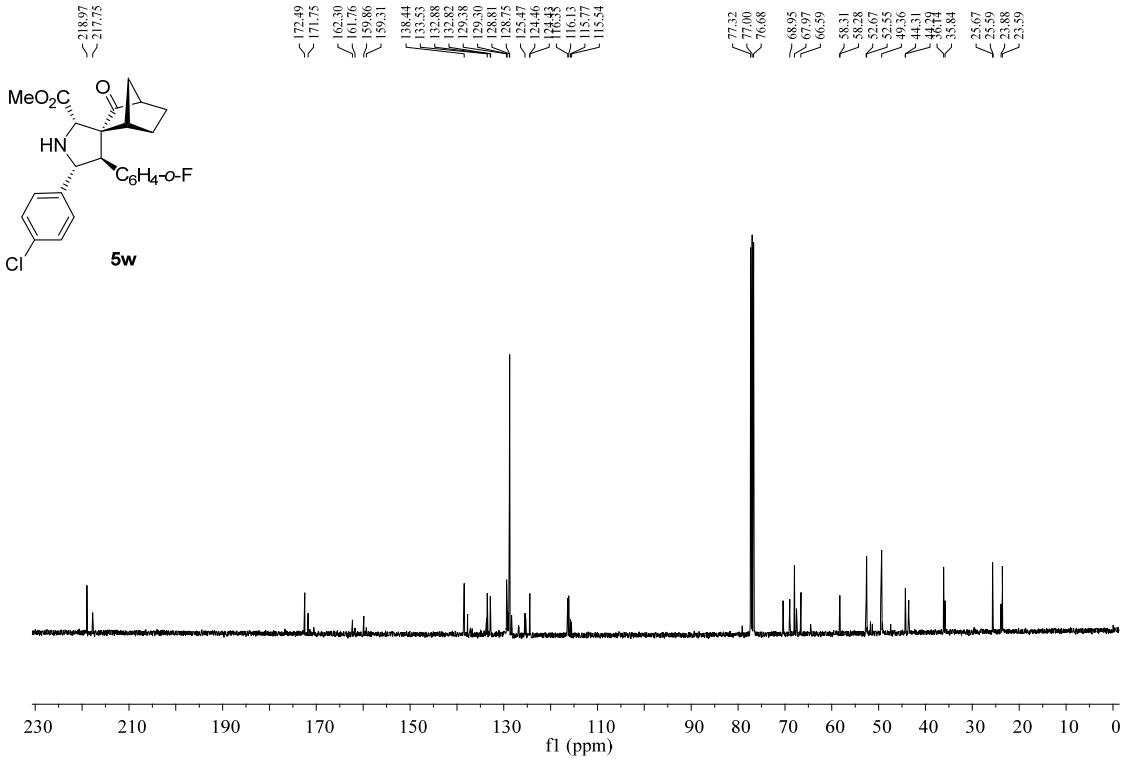
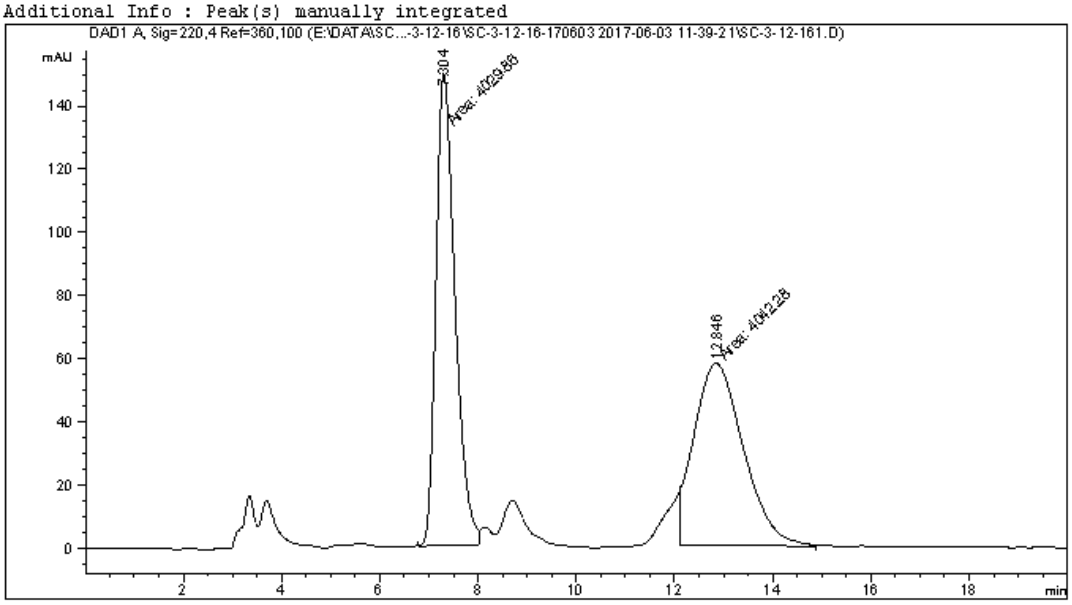


Figure S93. ^{13}C NMR spectrum of **5w**, related to **Table 3**.

Data File E:\DATA\SC\SC-3-12-16\SC-3-12-16-170603 2017-06-03 11-39-21\SC-3-12-161.D
Sample Name: SC-3-16

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                           Location :   16
Injection Date  : 6/3/2017 11:57:20 AM                Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-12-16\SC-3-12-16-170603 2017-06-03 11-39-21\SC-1-ASH-90-10-
                  220NM-1ML-20MIN.M
Last changed    : 6/3/2017 11:39:21 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-12-16\SC-3-12-16-170603 2017-06-03 11-39-21\SC-1-ASH-90-10-
                  220NM-1ML-20MIN.M (Sequence Method)
Last changed    : 6/16/2017 2:49:00 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

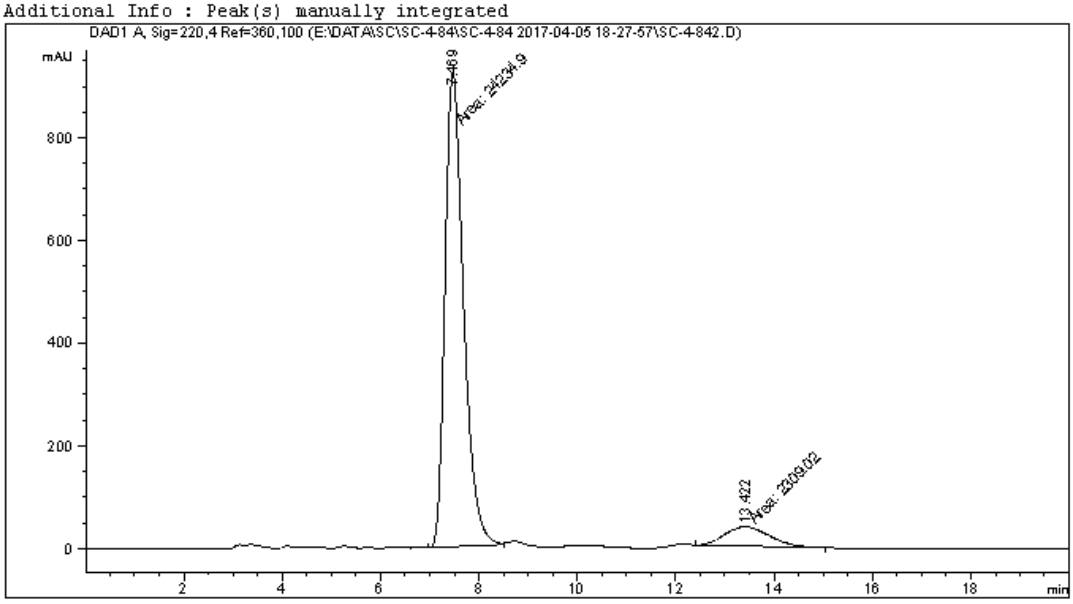

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.304 MM    0.4495 4029.85547  149.41939  49.9231
   2  12.846 MM    1.1670 4042.27661   57.72923  50.0769

Totals :                  8072.13208  207.14862
```

Data File E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-4-842.D
Sample Name: SC-4-84-P

```
=====================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                             Location :   12
Injection Date  : 4/5/2017 7:01:37 PM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 4/5/2017 6:27:57 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-84\SC-4-84 2017-04-05 18-27-57\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/16/2017 2:44:56 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.469 MM    0.4376 2.42349e4   922.97101  91.3012
   2  13.422 MM    1.0329 2309.01538   37.25814   8.6988

Totals :                  2.65439e4   960.22915
```


Figure S94. HPLC spectrum of **5w**, related to **Table 3**.

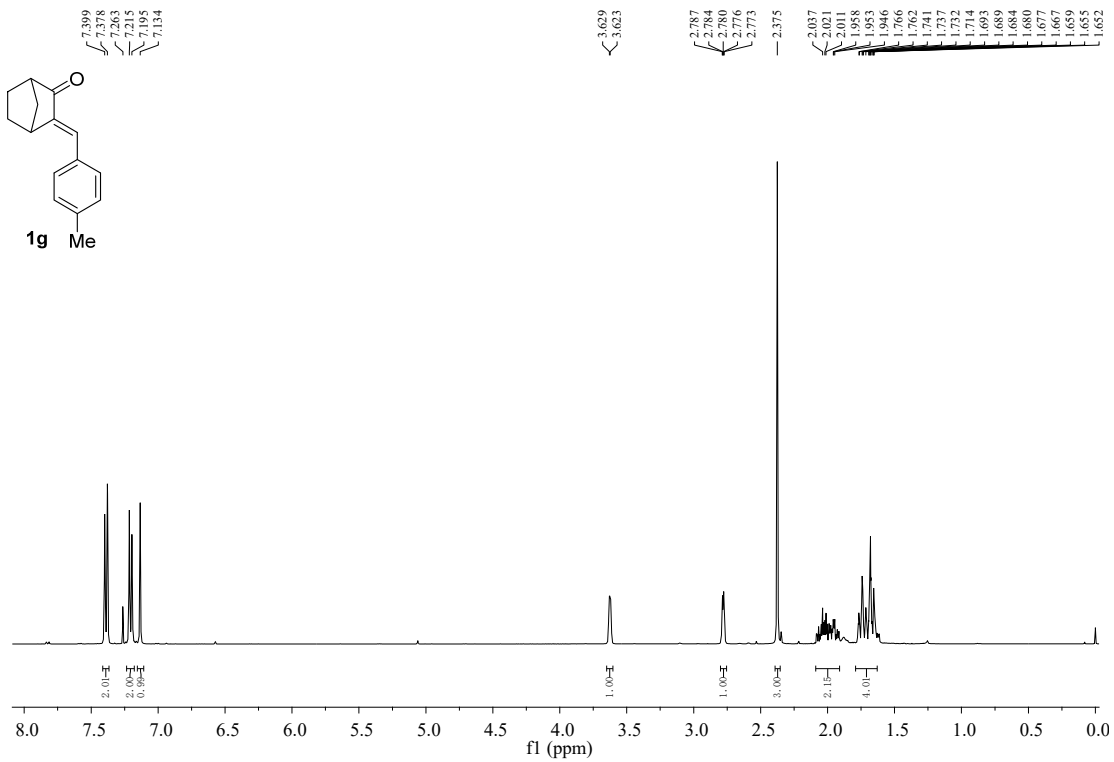


Figure S95. ^{1}H NMR spectrum of **1g**, related to **Table 3**.

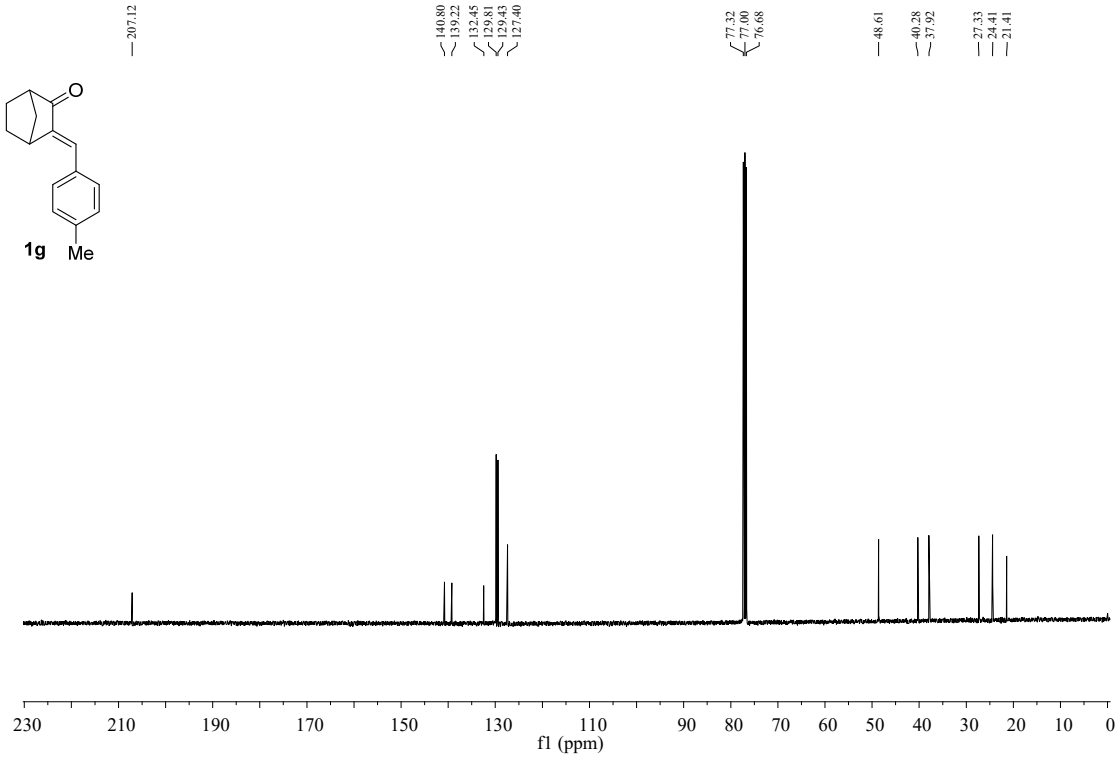
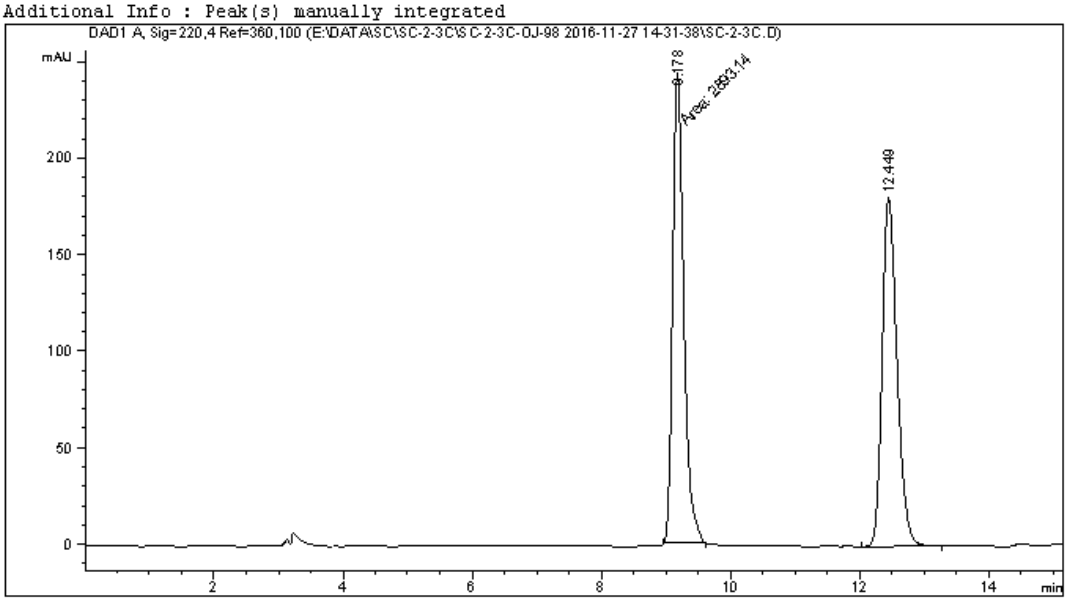


Figure S96. ^{13}C NMR spectrum of **1g**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-3C\SC-2-3C-OJ-98 2016-11-27 14-31-38\SC-2-3C.D
Sample Name: SC-2-3C-OJ-98

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   64
    Injection Date  : 11/28/2016 6:33:02 AM              Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-3C\SC-2-3C-OJ-98 2016-11-27 14-31-38\SC-5-OJH-98-2-DAD-1ML.
                      M
    Last changed    : 11/28/2016 6:31:38 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-3C\SC-2-3C-OJ-98 2016-11-27 14-31-38\SC-5-OJH-98-2-DAD-1ML.
                      M (Sequence Method)
    Last changed    : 6/4/2017 4:39:42 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

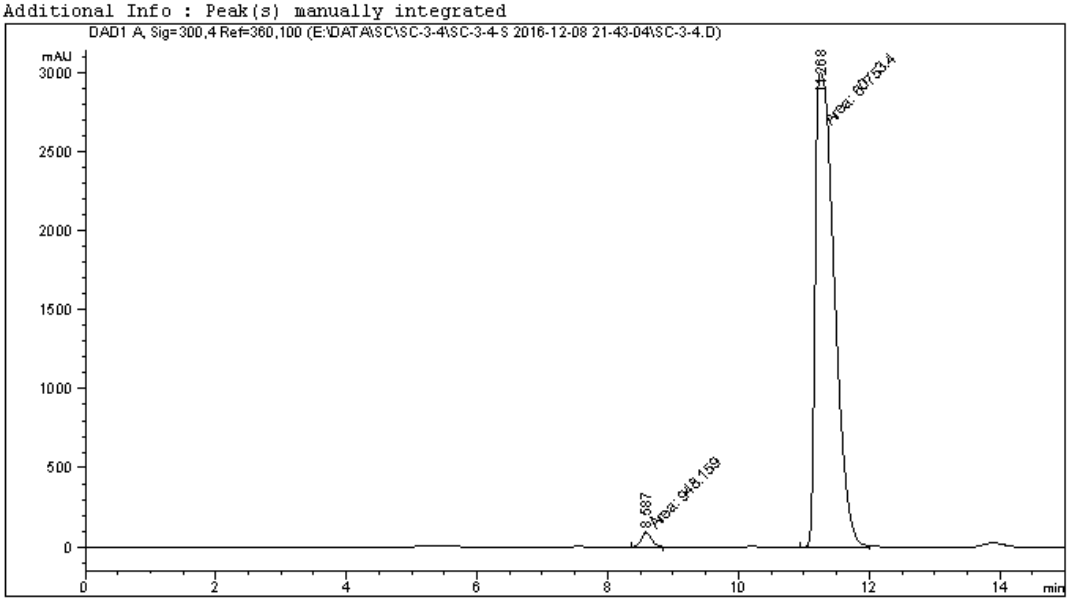

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   9.178 MM    0.1983 2893.13599  243.19118  50.0472
       2  12.449 BB    0.2435 2887.68091  180.65796  49.9528

    Totals :                  5780.81689  423.84914
```

Data File E:\DATA\SC\SC-3-4\SC-3-4-S 2016-12-08 21-43-04\SC-3-4.D
Sample Name: SC-3-4A-S

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   11
Injection Date  : 12/8/2016 9:44:23 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-4\SC-3-4-S 2016-12-08 21-43-04\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M
Last changed    : 12/8/2016 9:43:04 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-4\SC-3-4-S 2016-12-08 21-43-04\SC-5-0JH-98-2-300NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:42:40 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=300,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.587 MM    0.1758  948.15851   89.89142   1.5367
   2  11.268 MM    0.3380 6.07534e4  2995.76514  98.4633

Totals :                  6.17016e4  3085.65656
```


Figure S97. HPLC spectrum of **1g**, related to **Table 3**.

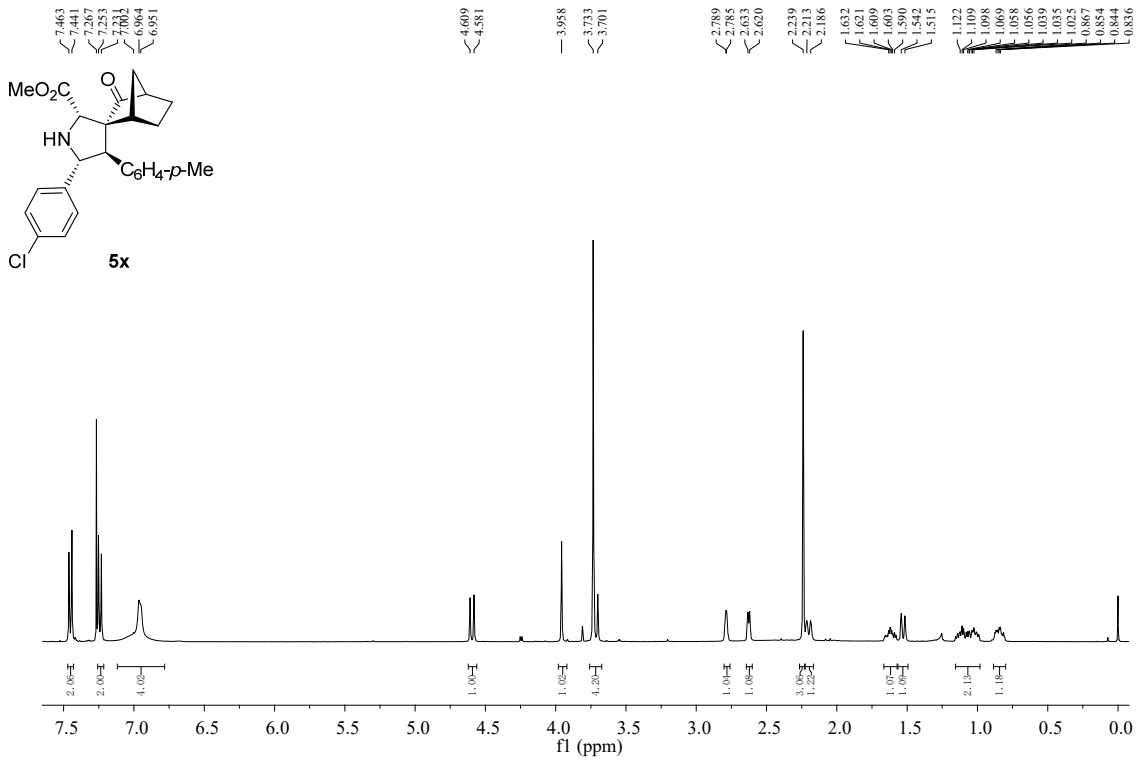


Figure S98. ^{1}H NMR spectrum of **5x**, related to **Table 3**.

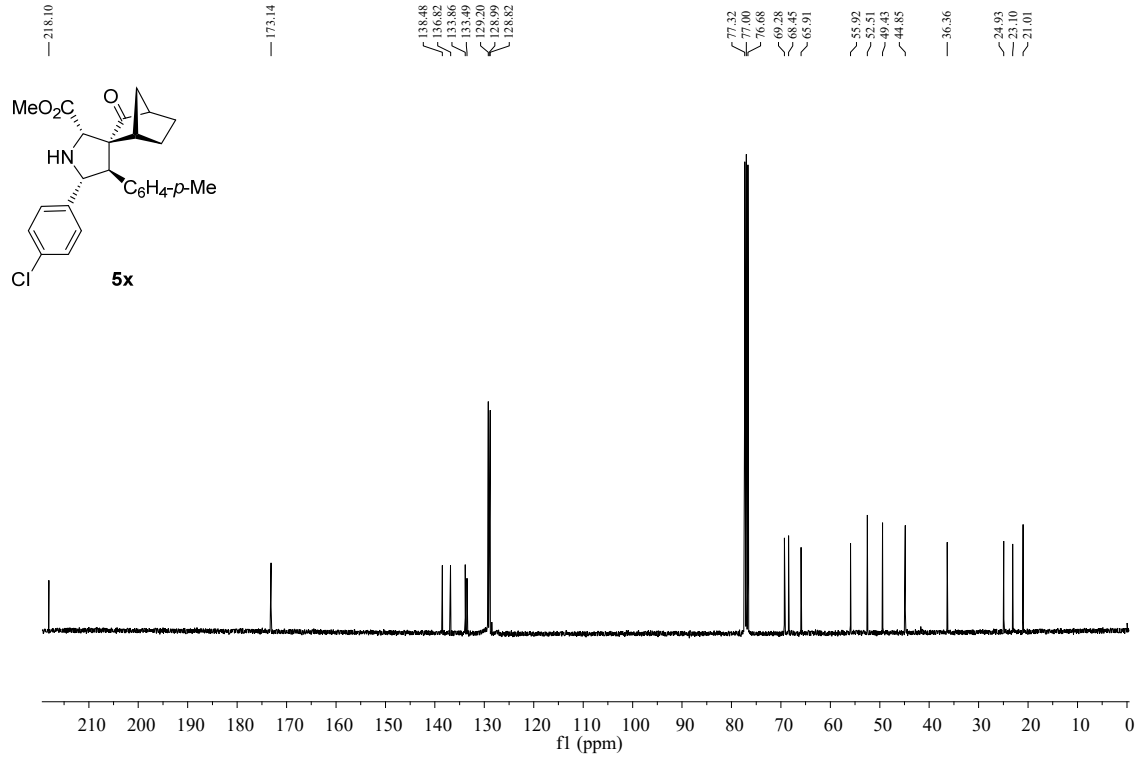


Figure S99. ^{13}C NMR spectrum of **5x**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-45A\SC-2-45A-ASH-90-10 2016-11-13 21-55-49\SC-2-45A.D
Sample Name: SC-2-45A-ASH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   64
    Injection Date  : 11/14/2016 1:57:12 PM              Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-45A\SC-2-45A-ASH-90-10 2016-11-13 21-55-49\SC-1-ASH-90-10-
                      DAD-1ML.M
    Last changed    : 11/14/2016 1:55:49 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-45A\SC-2-45A-ASH-90-10 2016-11-13 21-55-49\SC-1-ASH-90-10-
                      DAD-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 10:56:38 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
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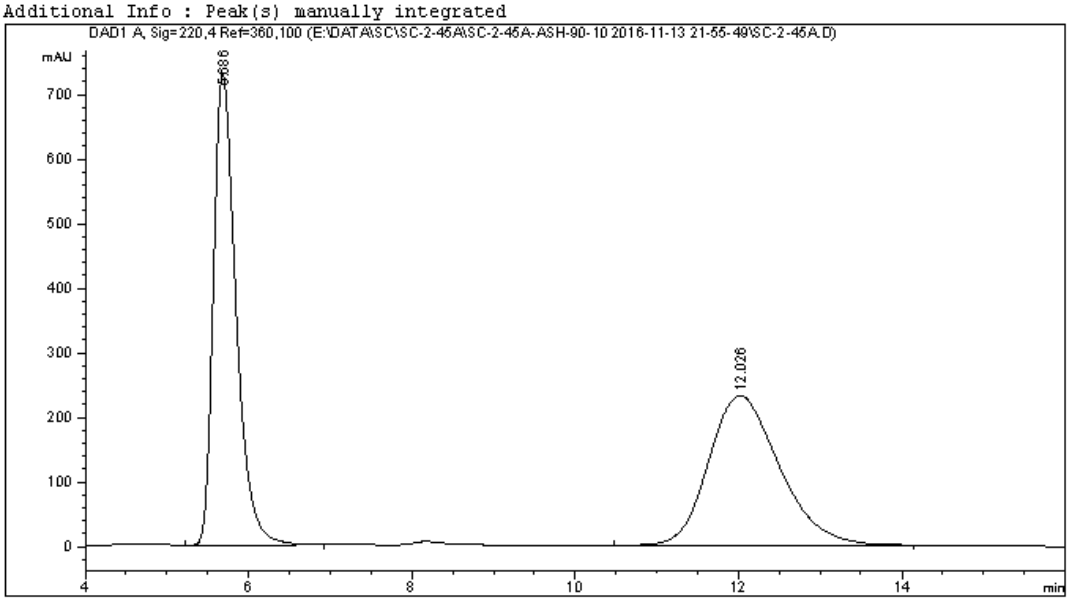


```
    ======================================================================
                          Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   5.686 BB    0.2916 1.40093e4   731.02673  50.0029
       2  12.026 BB    0.9290 1.40077e4   232.14807  49.9971

    Totals :                  2.80170e4   963.17480
```

Data File E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-3-42.D
Sample Name: SC-3-4A-P

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   14
Injection Date  : 12/8/2016 11:57:05 PM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 12/8/2016 11:13:25 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/3/2017 11:02:58 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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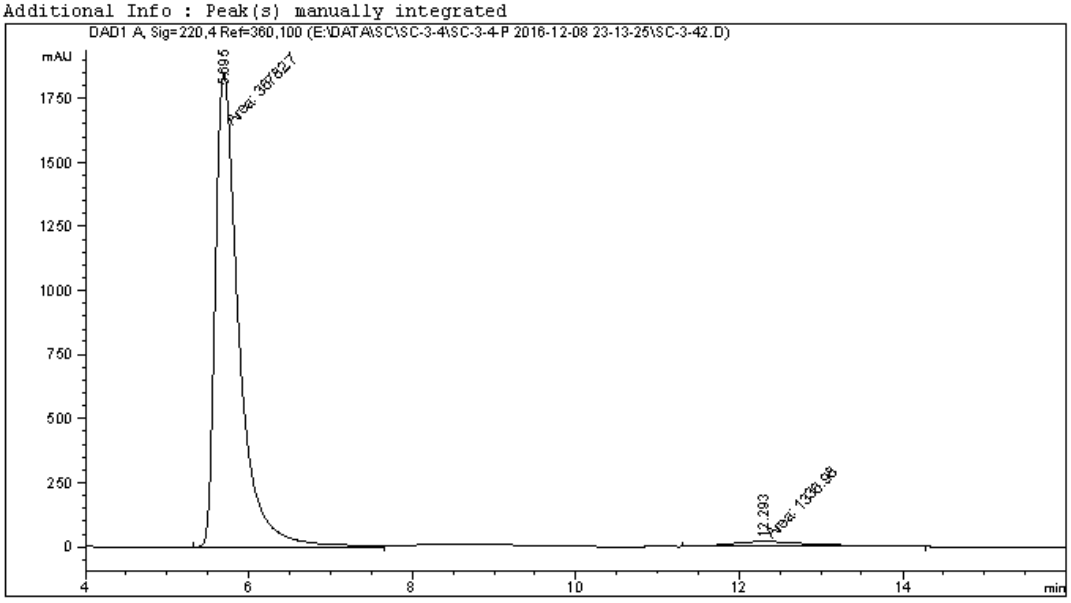


```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.695 MM    0.3316 3.67827e4  1848.61414  96.4927
   2  12.293 MM    1.2042 1336.98352   18.50492   3.5073

Totals :                  3.81197e4  1867.11906
```


Figure S100. HPLC spectrum of **5x**, related to **Table 3**.

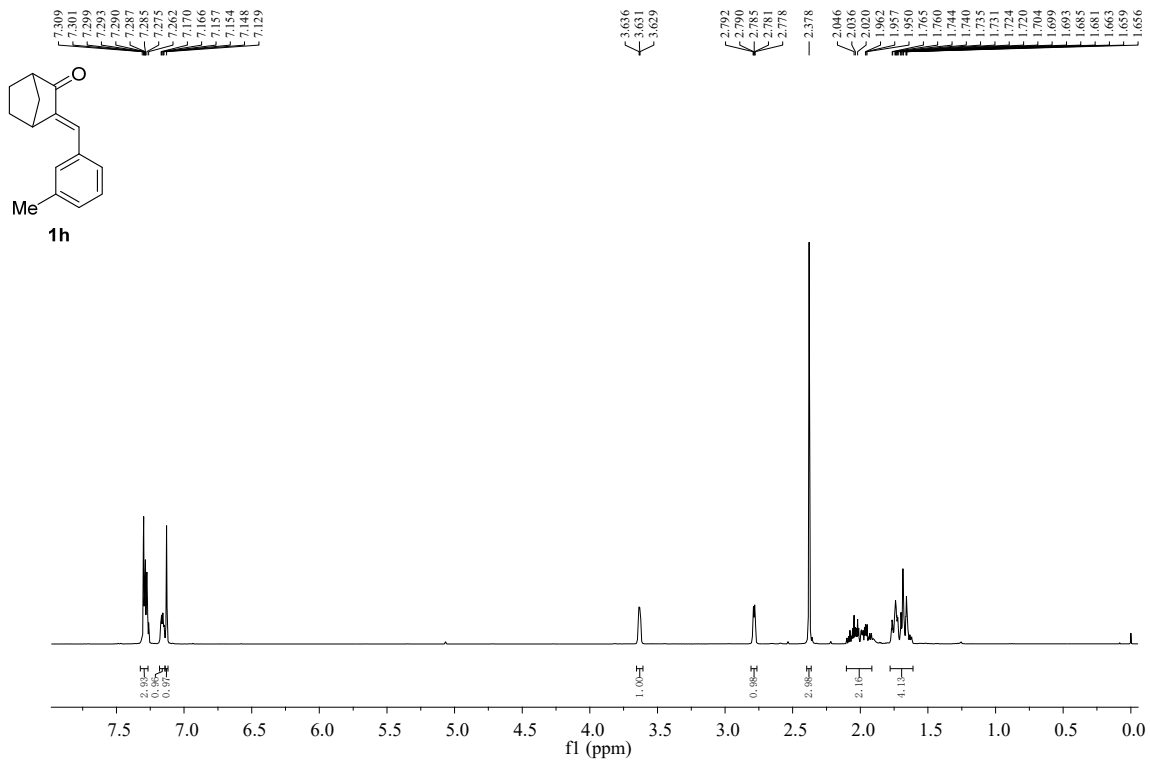

Figure S101. ^{1}H NMR spectrum of **1h**, related to **Table 3**.

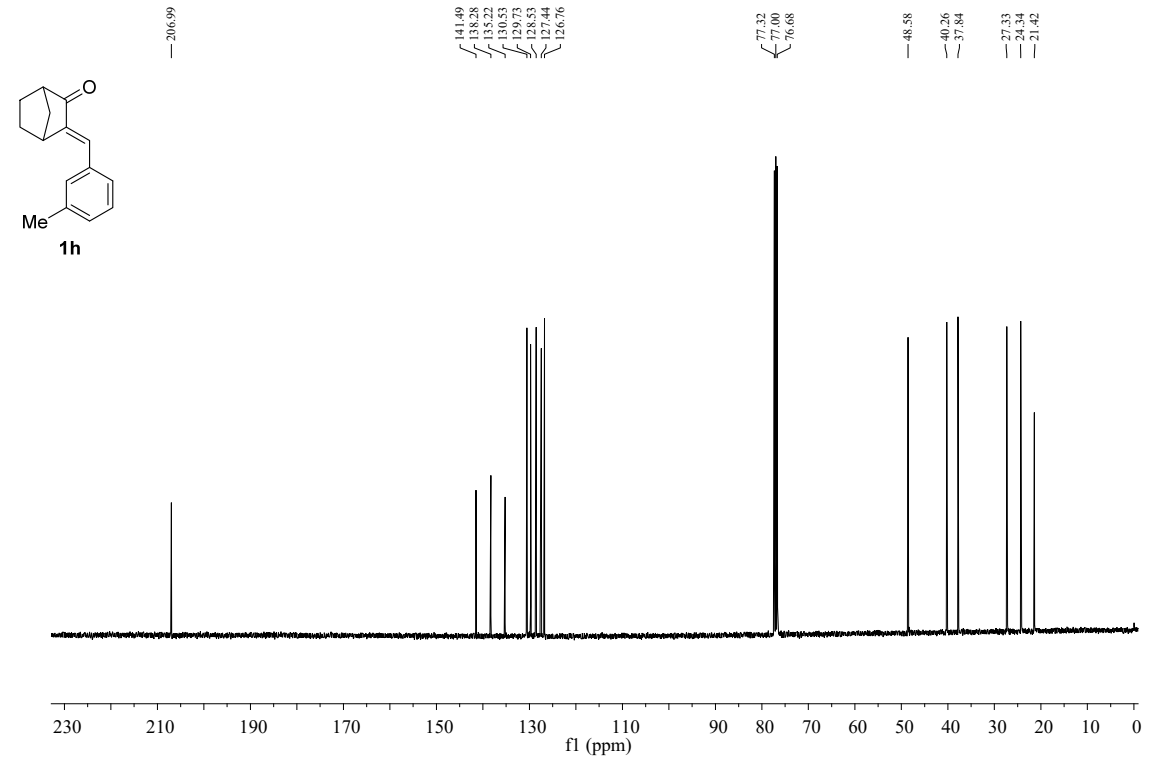

Figure S102. ^{13}C NMR spectrum of **1h**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-3B\SC-2-3B-0J-98 2016-11-27 15-06-24\SC-2-3B.D
Sample Name: SC-2-3B-0J-98

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    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   63
    Injection Date  : 11/28/2016 7:07:47 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-3B\SC-2-3B-0J-98 2016-11-27 15-06-24\SC-5-0JH-98-2-DAD-1ML.
                      M
    Last changed    : 11/28/2016 7:06:24 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-3B\SC-2-3B-0J-98 2016-11-27 15-06-24\SC-5-0JH-98-2-DAD-1ML.
                      M (Sequence Method)
    Last changed    : 6/4/2017 4:44:23 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
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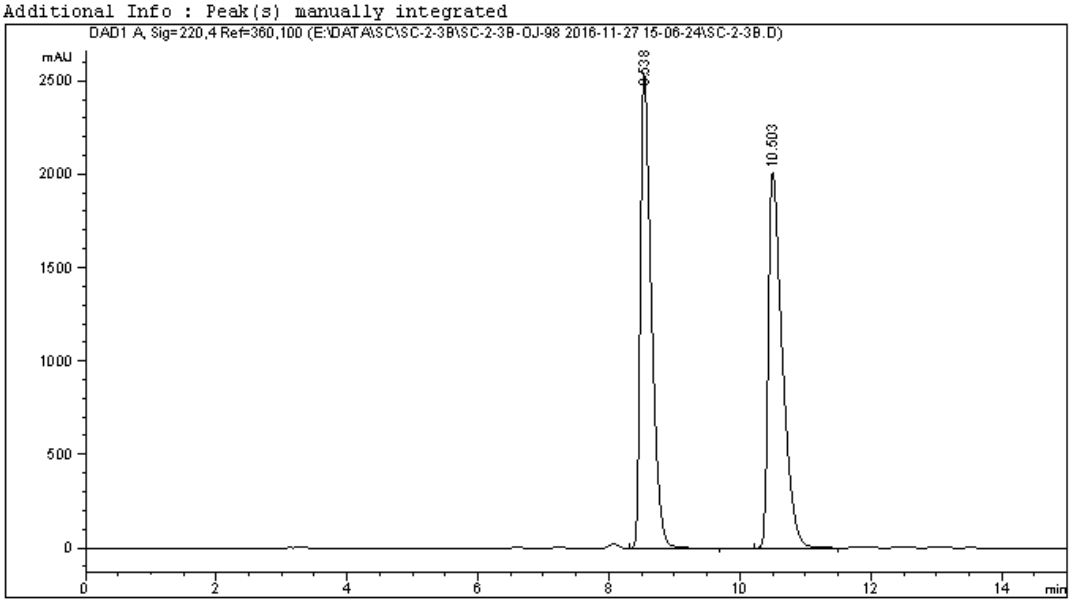


```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.538 VB    0.1775 2.97270e4  2540.16943  49.9502
       2  10.503 BB    0.2196 2.97862e4  2013.80249  50.0498

    Totals :                  5.95132e4  4553.97192
```

Data File E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-3-13.D
Sample Name: SC-3-13-S

```
==========================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                          Location :   11
Injection Date  : 12/10/2016 10:18:33 PM             Inj :   1
                                               Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-5-OJH-98-2-300NM-1ML-
                  20MIN.M
Last changed    : 12/10/2016 10:17:11 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-13\SC-3-13-S 2016-12-10 22-17-11\SC-5-OJH-98-2-300NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/4/2017 4:46:06 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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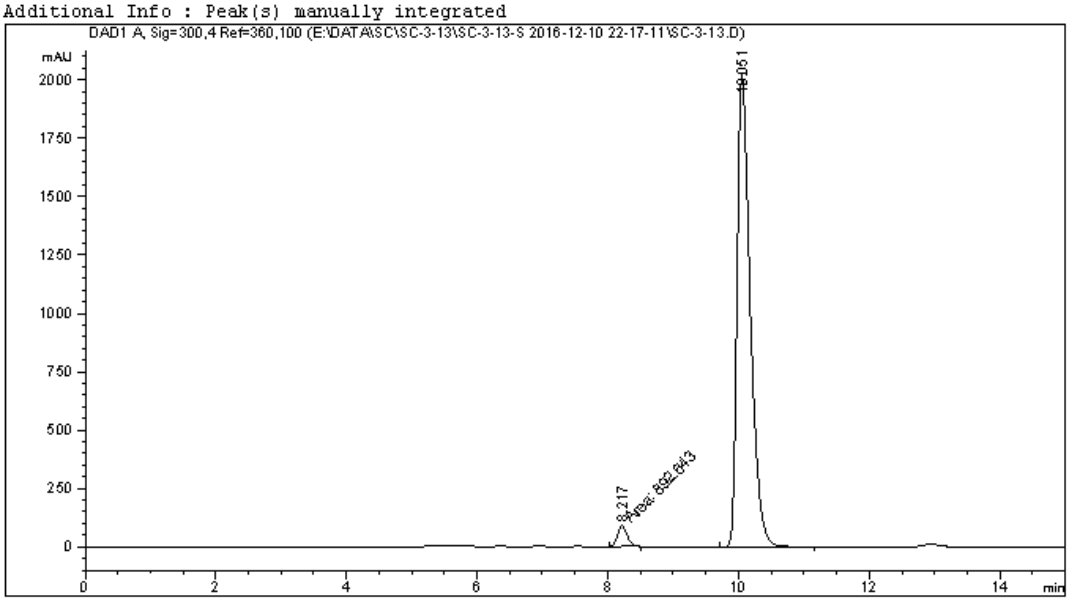



```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=300,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.217 MM    0.1686  892.64343   88.22587   3.0682
   2  10.051 BB    0.2082 2.82012e4  2027.93701  96.9318

Totals :                  2.90938e4  2116.16288
```


Figure S103. HPLC spectrum of **1h**, related to **Table 3**.

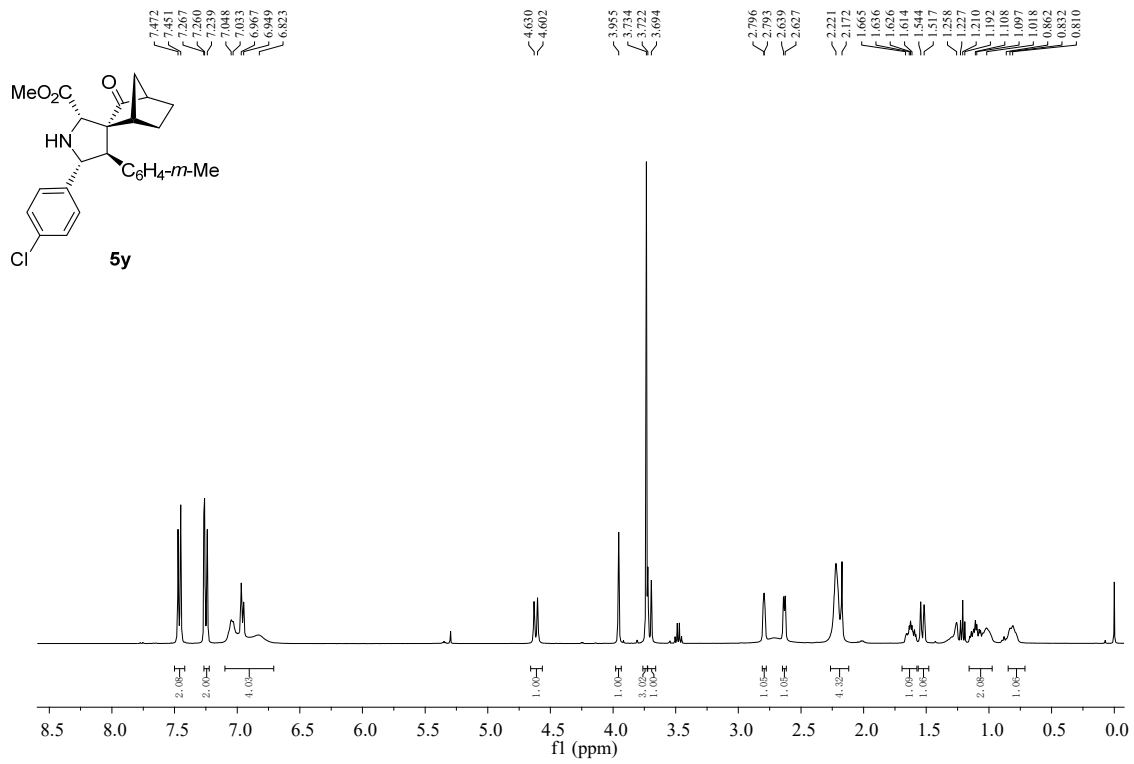


Figure S104. ^{1}H NMR spectrum of **5y**, related to **Table 3**.

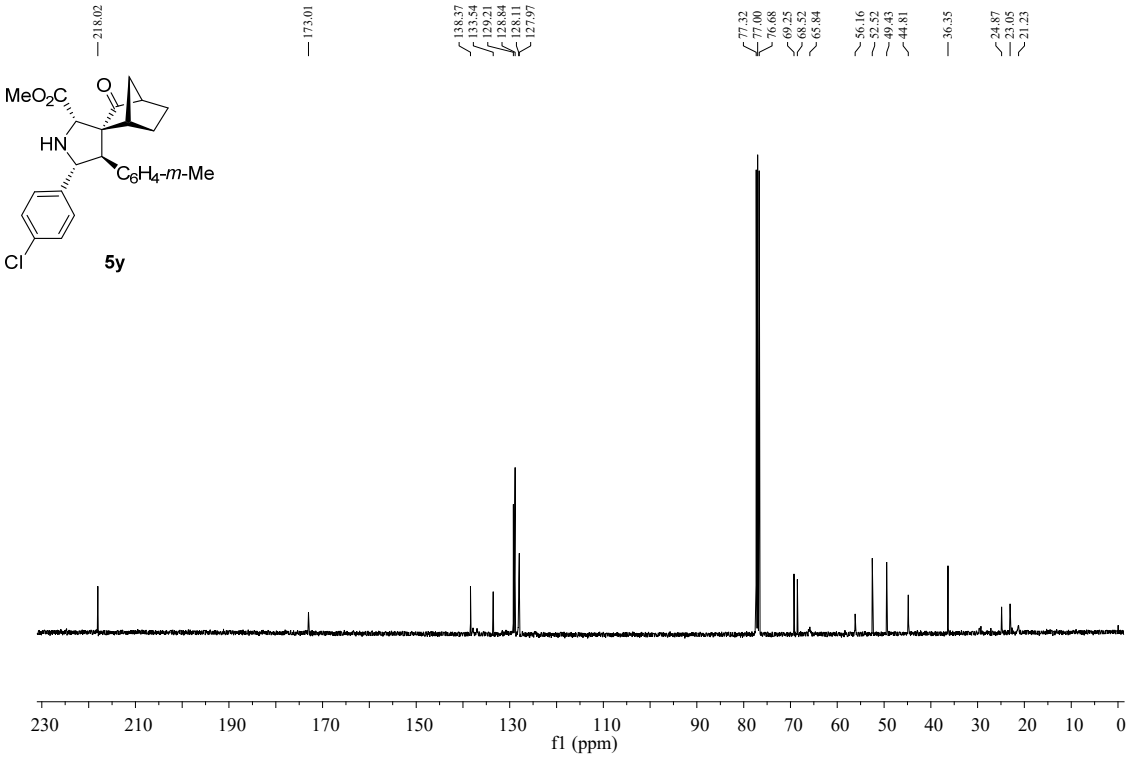
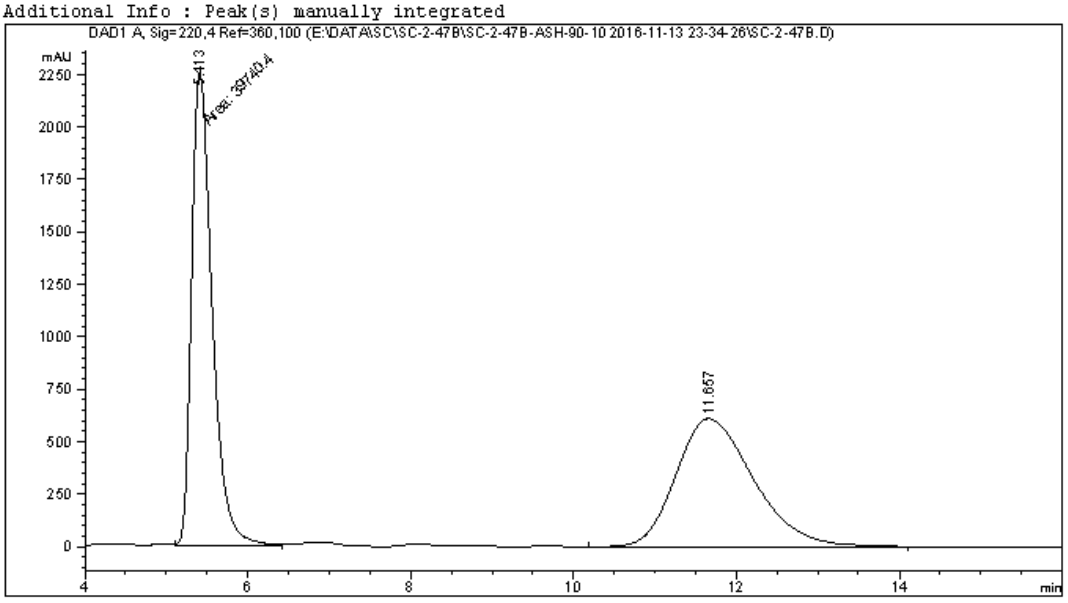


Figure S105. ^{13}C NMR spectrum of **5y**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-47B\SC-2-47B-ASH-90-10 2016-11-13 23-34-26\SC-2-47B.D
Sample Name: SC-2-47B-ASH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   67
    Injection Date  : 11/14/2016 3:35:49 PM              Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-47B\SC-2-47B-ASH-90-10 2016-11-13 23-34-26\SC-1-ASH-90-10-
                      DAD-1ML.M
    Last changed    : 11/14/2016 3:34:26 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-47B\SC-2-47B-ASH-90-10 2016-11-13 23-34-26\SC-1-ASH-90-10-
                      DAD-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 11:06:28 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

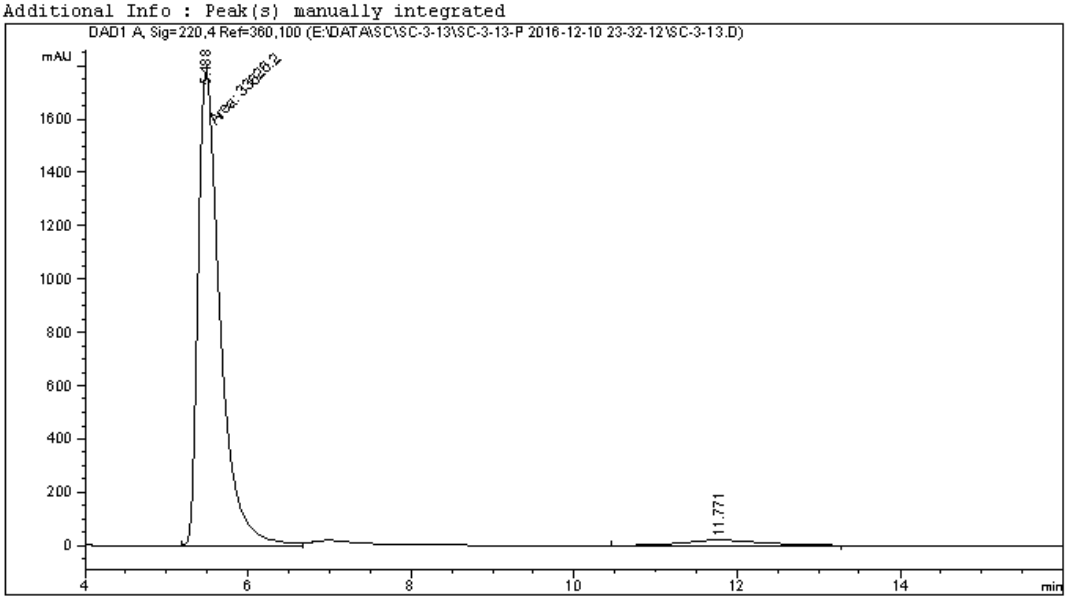

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   5.413 MM    0.2941 3.97404e4  2251.75903  49.7197
       2  11.657 BB    1.0093 4.01886e4   608.70270  50.2803

    Totals :                  7.99290e4  2860.46173
```

Data File E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-3-13.D
Sample Name: SC-3-13-P

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                              Location :   15
Injection Date  : 12/10/2016 11:33:34 PM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 12/10/2016 11:32:12 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-13\SC-3-13-P 2016-12-10 23-32-12\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/3/2017 11:08:38 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.488 MM    0.3157 3.36262e4  1775.29590  96.4275
   2  11.771 BB    0.7996 1245.80261   19.01017   3.5725

Totals :                  3.48720e4  1794.30607
```


Figure S106. HPLC spectrum of **5y**, related to **Table 3**.

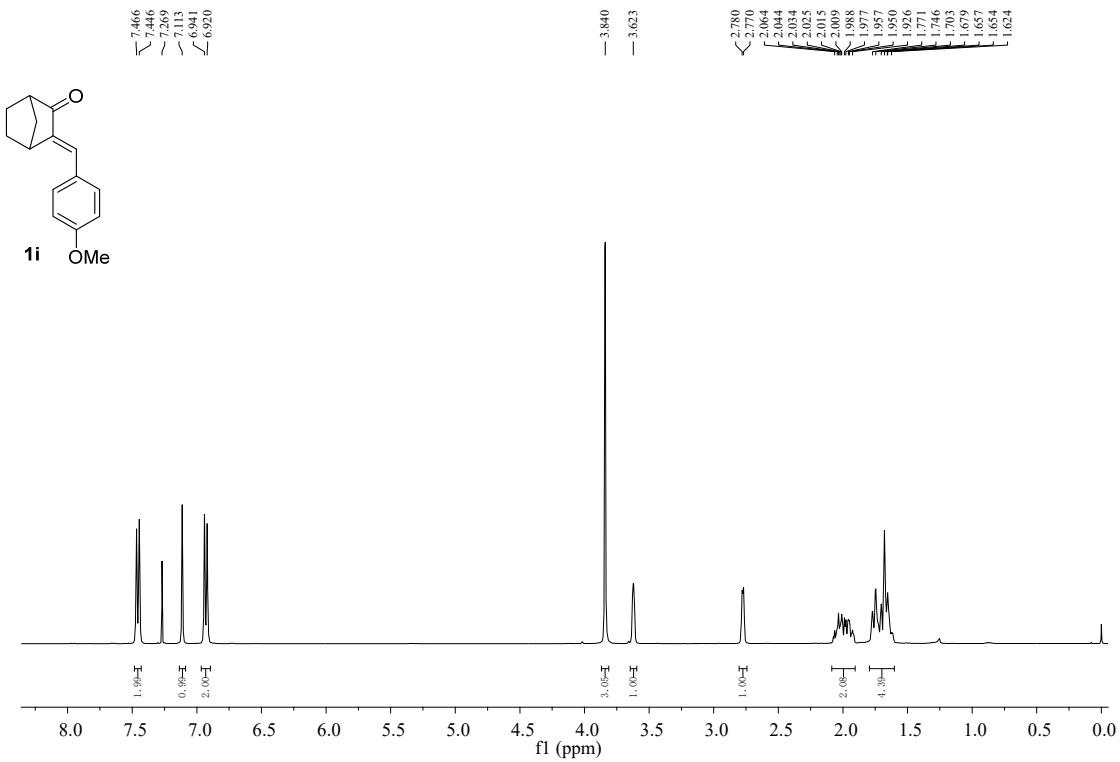


Figure S107. [1]H NMR spectrum of **1i**, related to **Table 3**.

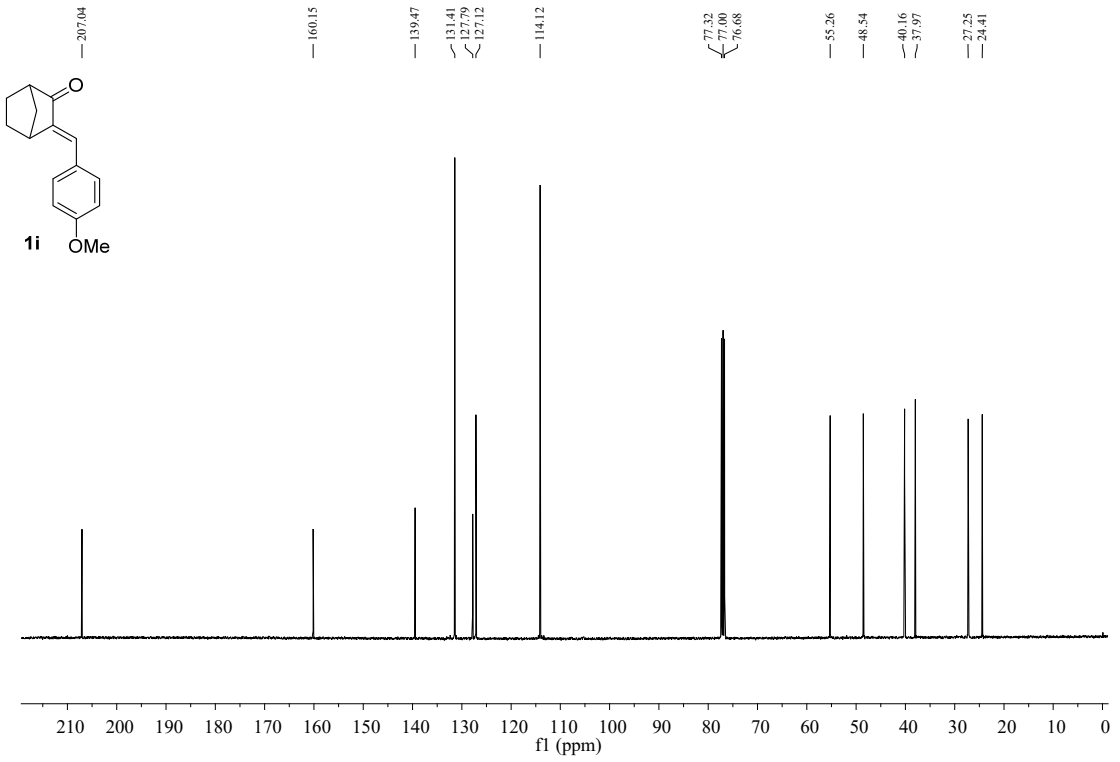


Figure S108. [13]C NMR spectrum of **1i**, related to **Table 3**.

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu17.D
Sample Name: SC-2-18

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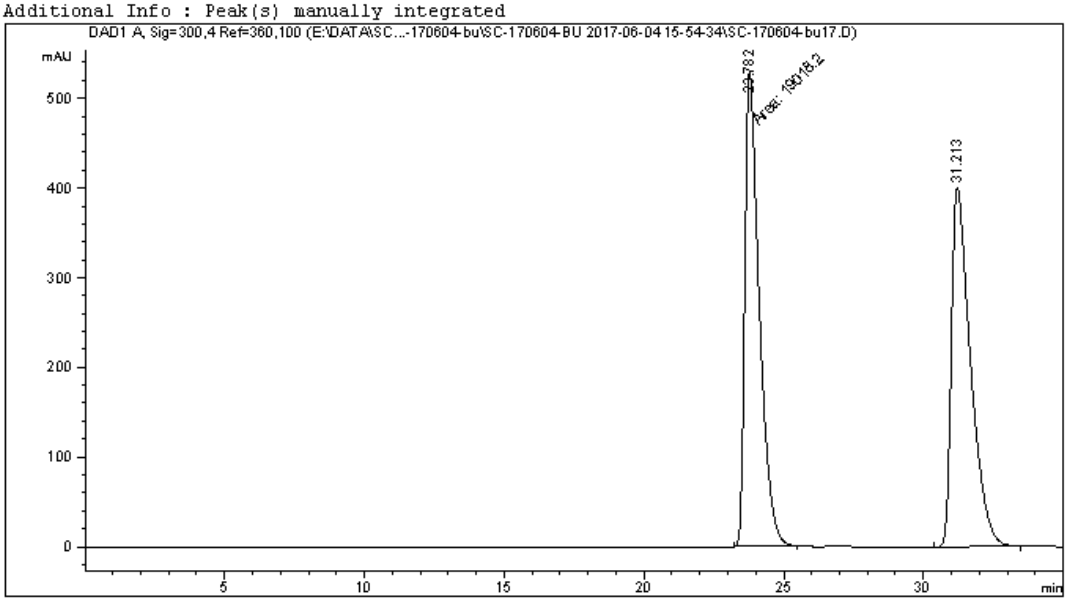
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :  18
    Acq. Instrument : 1260                             Location :  80
    Injection Date  : 6/5/2017 12:50:07 AM                 Inj :  1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-5-OJH-98-2-
                      300NM-1ML-35MIN.M
    Last changed    : 6/4/2017 3:54:36 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-5-OJH-98-2-
                      300NM-1ML-35MIN.M (Sequence Method)
    Last changed    : 6/5/2017 8:56:33 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

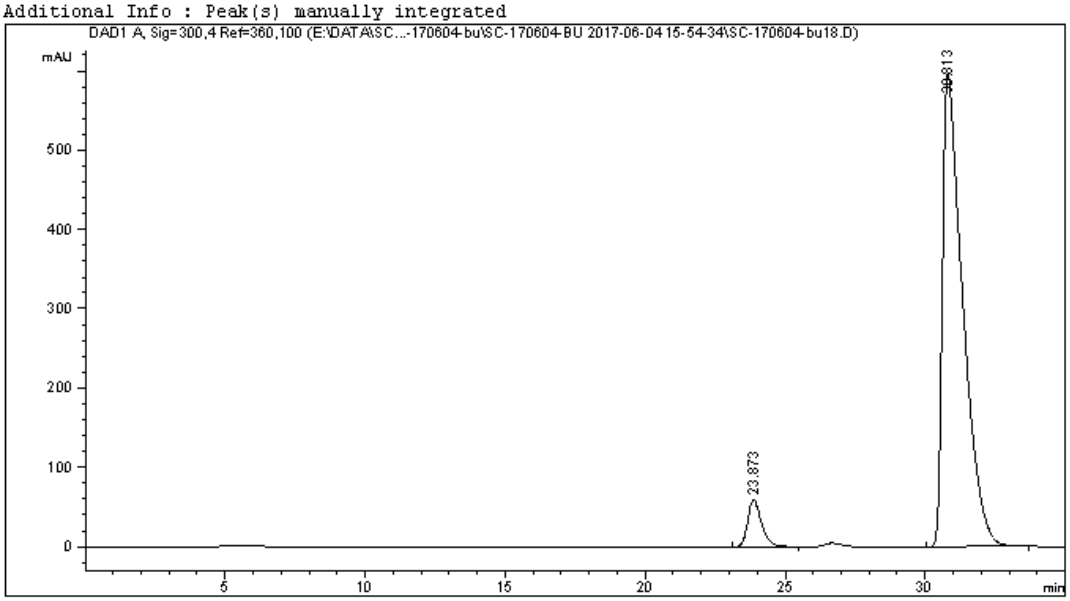

    Signal 1: DAD1 A, Sig=300,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.782 MM    0.6005 1.90182e4   527.81378  50.0455
       2  31.213 BB    0.6980 1.89837e4   400.51453  49.9545

    Totals :                  3.80019e4   928.32831
```

Data File E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-170604-bu18.D
Sample Name: SC-3-4B

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :  19
    Acq. Instrument : 1260                             Location :  81
    Injection Date  : 6/5/2017 1:26:30 AM                  Inj :  1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-5-OJH-98-2-
                      300NM-1ML-35MIN.M
    Last changed    : 6/4/2017 3:54:36 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-170604-bu\SC-170604-BU 2017-06-04 15-54-34\SC-5-OJH-98-2-
                      300NM-1ML-35MIN.M (Sequence Method)
    Last changed    : 6/5/2017 8:56:33 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=300,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.873 BB    0.5135 2009.01843   59.26756   6.2881
       2  30.813 BB    0.7163 2.99405e4   596.83704  93.7119

    Totals :                  3.19495e4   656.10460
```


Figure S109. HPLC spectrum of **1i**, related to **Table 3**.

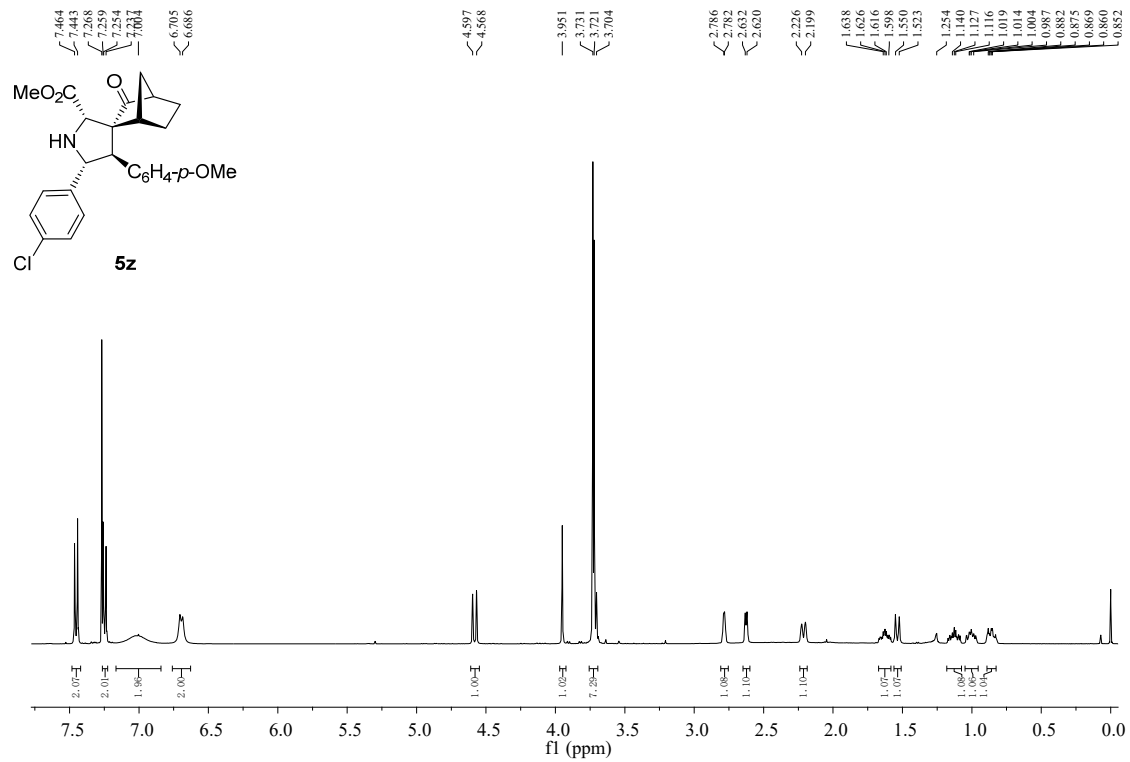


Figure S110. ^{1}H NMR spectrum of **5z**, related to **Table 3**.

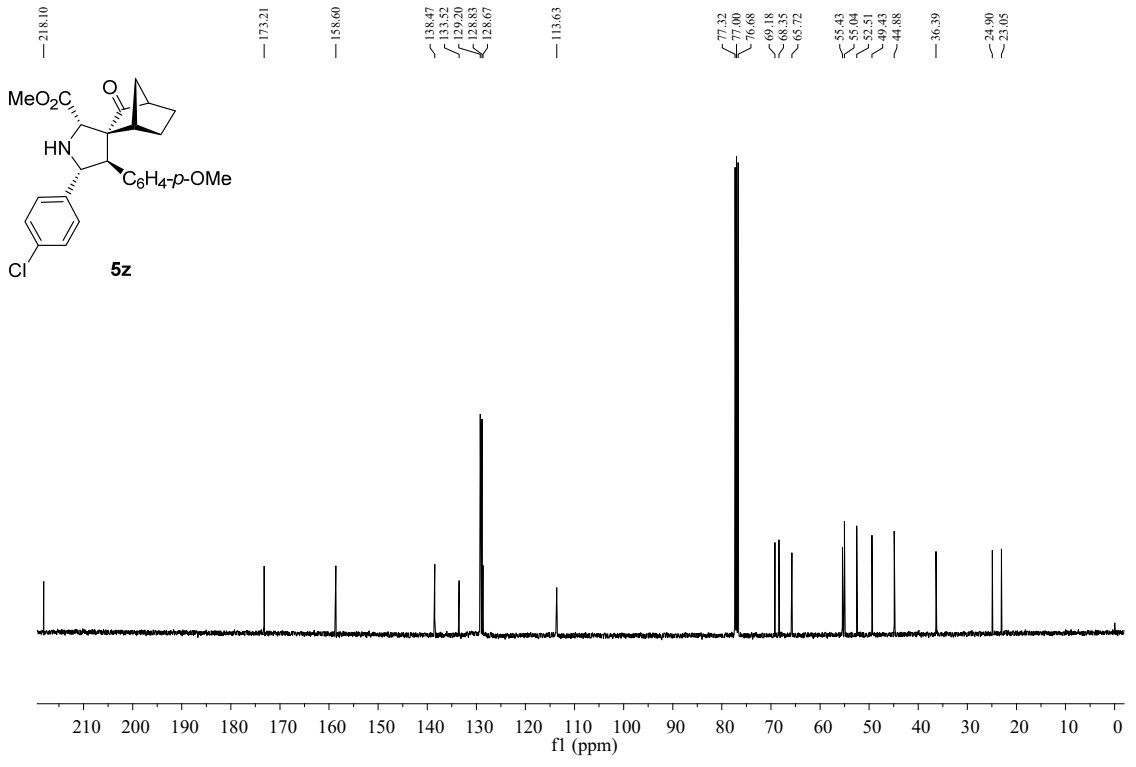
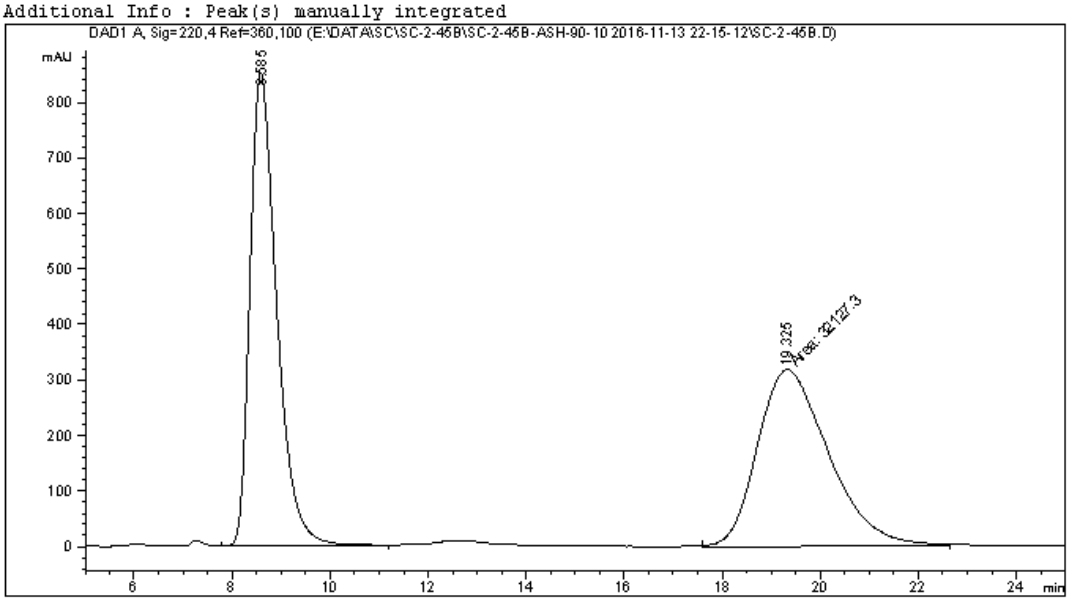


Figure S111. ^{13}C NMR spectrum of **5z**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-45B\SC-2-45B-ASH-90-10 2016-11-13 22-15-12\SC-2-45B.D
Sample Name: SC-2-45B-ASH-90-10

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   65
    Injection Date  : 11/14/2016 2:16:37 PM               Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-45B\SC-2-45B-ASH-90-10 2016-11-13 22-15-12\SC-1-ASH-90-10-
                      DAD-1ML.M
    Last changed    : 11/14/2016 2:15:12 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-45B\SC-2-45B-ASH-90-10 2016-11-13 22-15-12\SC-1-ASH-90-10-
                      DAD-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 11:11:28 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

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                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

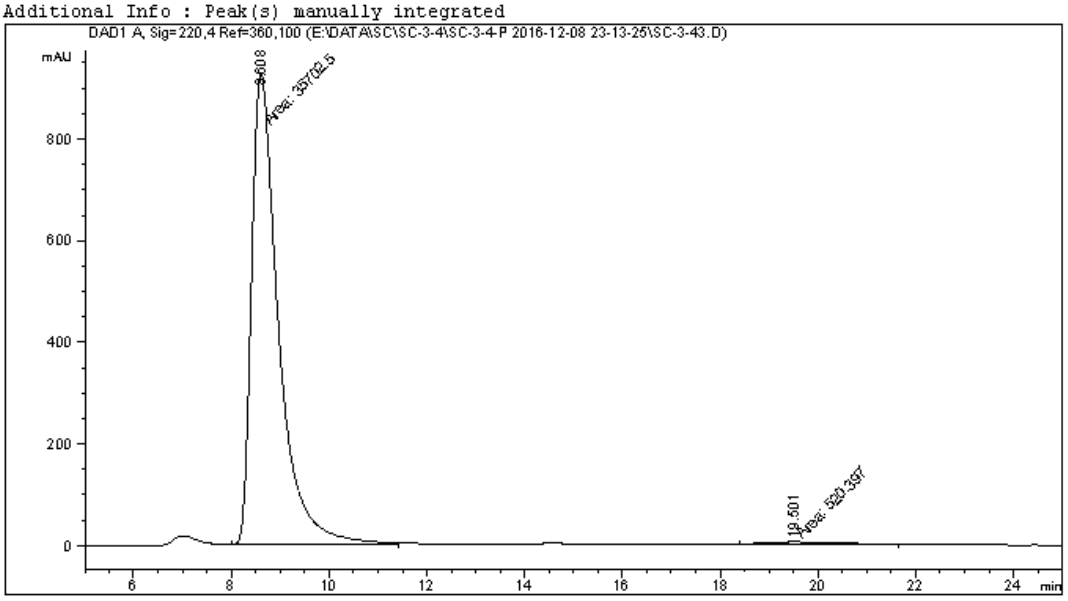

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.585 BB    0.5769 3.22033e4   850.27032  50.0591
       2  19.325 MM    1.6814 3.21273e4   318.46292  49.9409

    Totals :                  6.43305e4  1168.73325
```

Data File E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-3-43.D
Sample Name: SC-3-4B-P

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : 1260                            Location :   15
Injection Date  : 12/9/2016 12:18:31 AM               Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-2-ASH-90-10-220NM-25MIN-
                  1ML.M
Last changed    : 12/8/2016 11:13:25 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-4\SC-3-4-P 2016-12-08 23-13-25\SC-2-ASH-90-10-220NM-25MIN-
                  1ML.M (Sequence Method)
Last changed    : 6/3/2017 11:14:19 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.608 MM    0.6409 3.57025e4   928.50531  98.5633
   2  19.501 MM    1.6818  520.39667    5.15701   1.4367

Totals :                  3.62229e4   933.66232
```


Figure S112. HPLC spectrum of **5z**, related to **Table 3**.

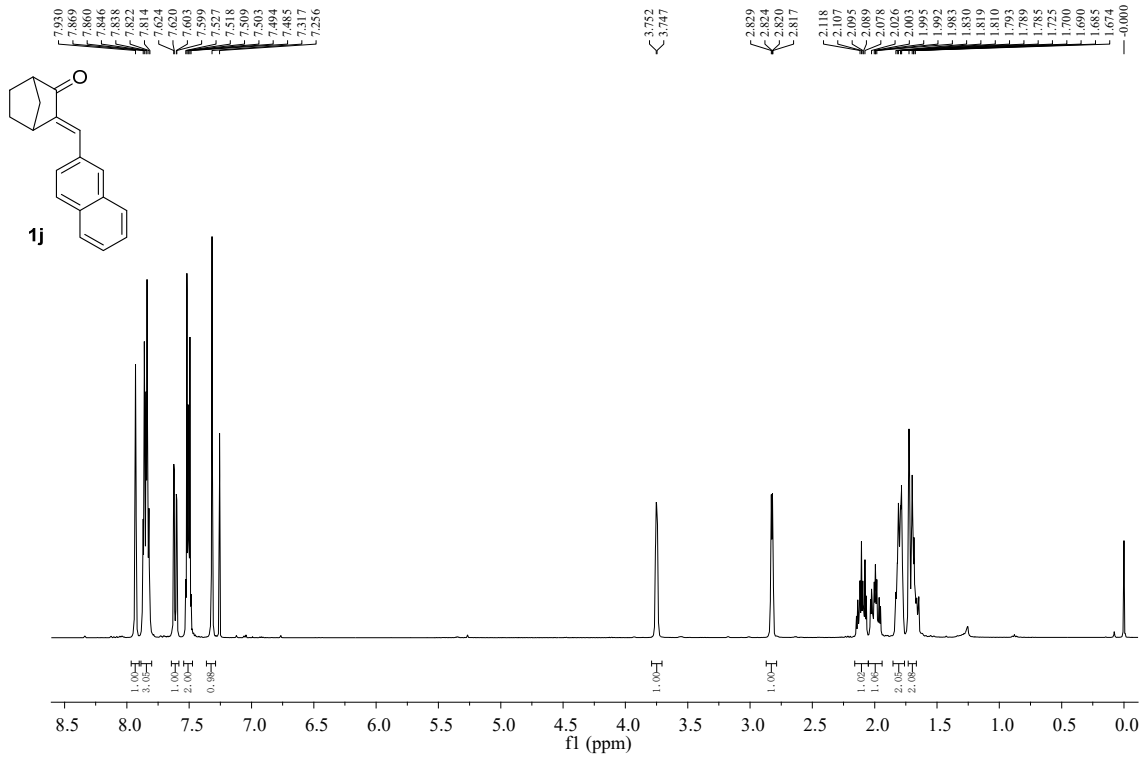


Figure S113. [1]H NMR spectrum of **1j**, related to **Table 3**.

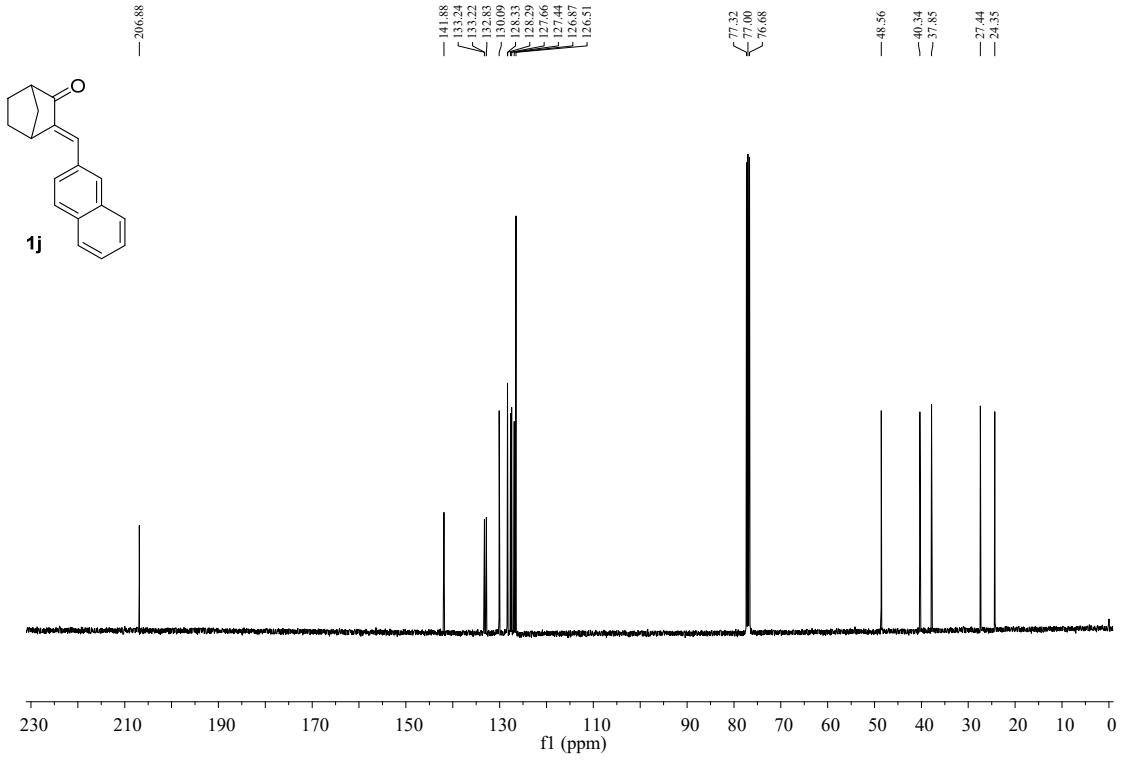
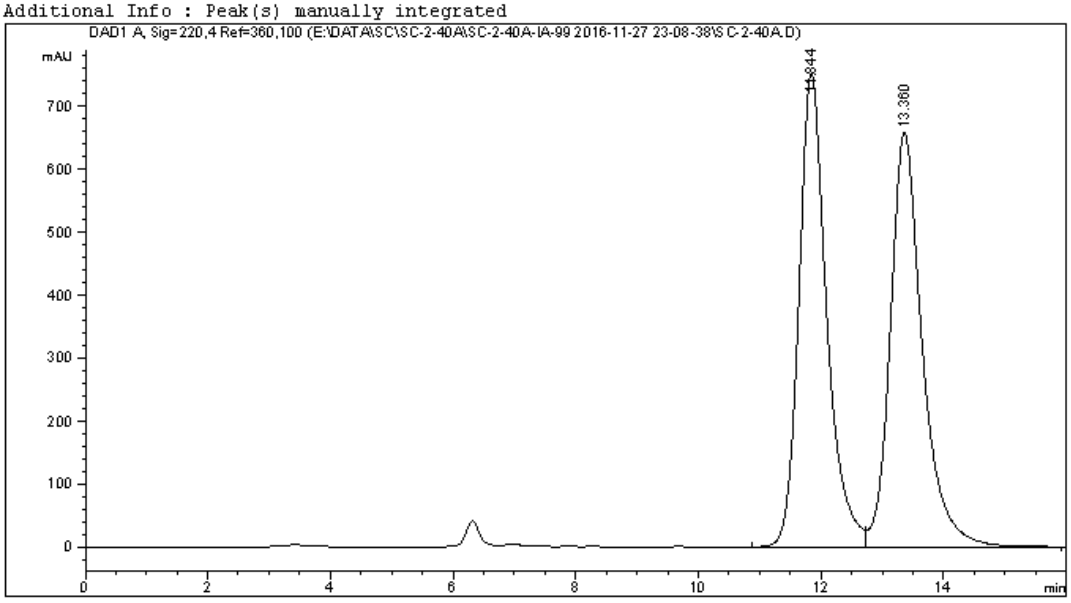


Figure S114. [1]H NMR spectrum of **1j**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-40A\SC-2-40A-IA-99 2016-11-27 23-08-38\SC-2-40A.D
Sample Name: SC-2-40A-IA-99

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   93
    Injection Date  : 11/28/2016 3:09:57 PM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-40A\SC-2-40A-IA-99 2016-11-27 23-08-38\SC-3-IA-99-1-DAD-1ML
                      .M
    Last changed    : 11/28/2016 3:08:38 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-40A\SC-2-40A-IA-99 2016-11-27 23-08-38\SC-3-IA-99-1-DAD-1ML
                      .M (Sequence Method)
    Last changed    : 6/4/2017 4:57:47 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

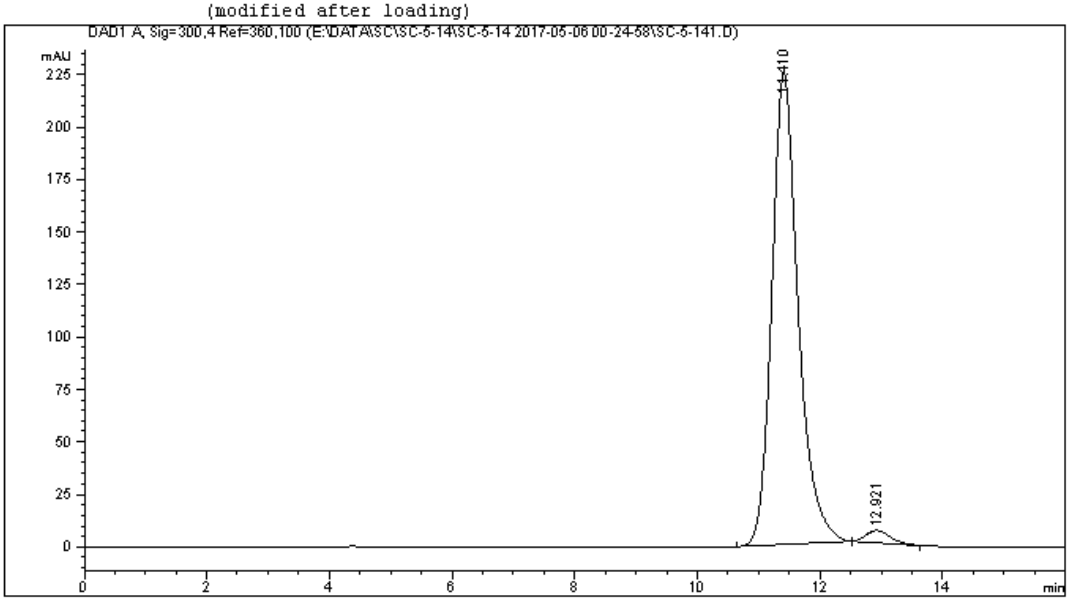

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.844 BV    0.4690 2.36626e4   752.19580  49.8919
       2  13.360 VB    0.5331 2.37652e4   658.41266  50.1081

    Totals :                  4.74278e4  1410.60846
```

Data File E:\DATA\SC\SC-5-14\SC-5-14 2017-05-06 00-24-58\SC-5-141.D
Sample Name: SC-5-14A-S

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   2
    Acq. Instrument : 1260                             Location :   11
    Injection Date  : 5/6/2017 12:47:14 AM                 Inj :   1
                                                     Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-5-14\SC-5-14 2017-05-06 00-24-58\SC-3-IA-99-1-300NM-1ML-20MIN
                      .M
    Last changed    : 5/6/2017 12:24:58 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-5-14\SC-5-14 2017-05-06 00-24-58\SC-3-IA-99-1-300NM-1ML-20MIN
                      .M (Sequence Method)
    Last changed    : 6/4/2017 4:58:25 AM by SYSTEM
                      (modified after loading)
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=300,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1  11.410 BB    0.4459 6702.06592  224.73598  97.6798
       2  12.921 BB    0.3487  159.19275    5.88305   2.3202

    Totals :                  6861.25867  230.61903
```


Figure S115. HPLC spectrum of **1j**, related to **Table 3**.

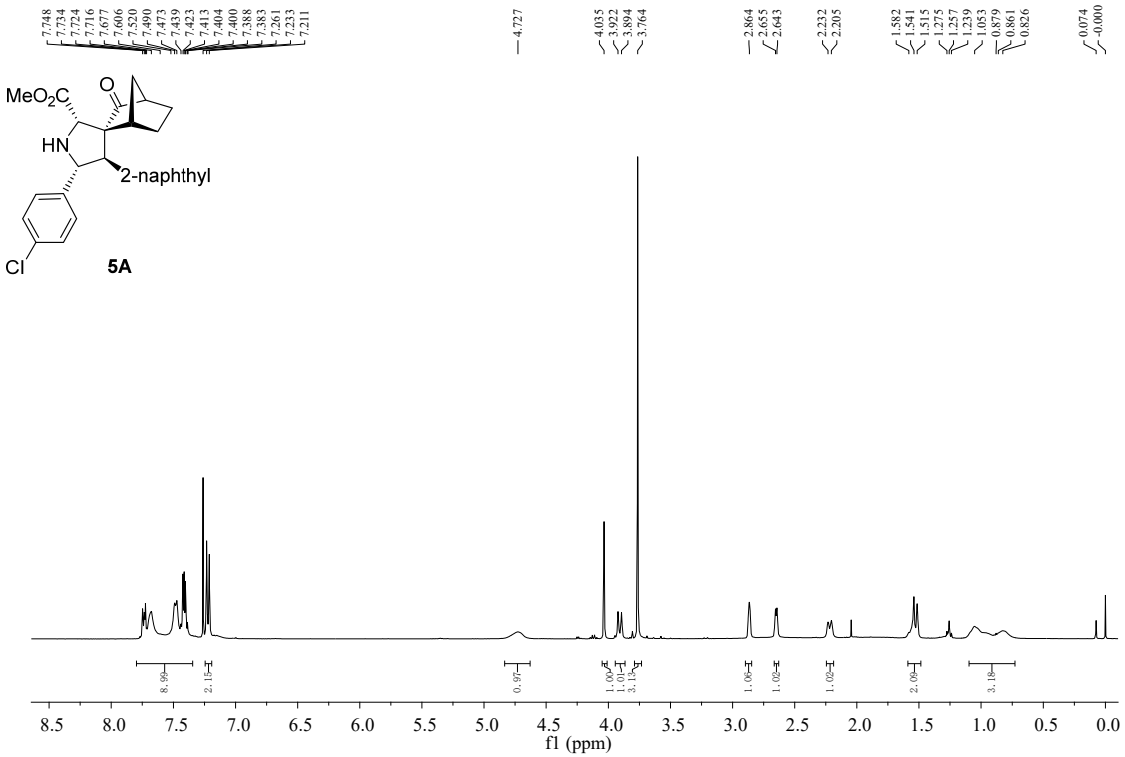


Figure S116. ^{1}H spectrum of **5A**, related to **Table 3**.

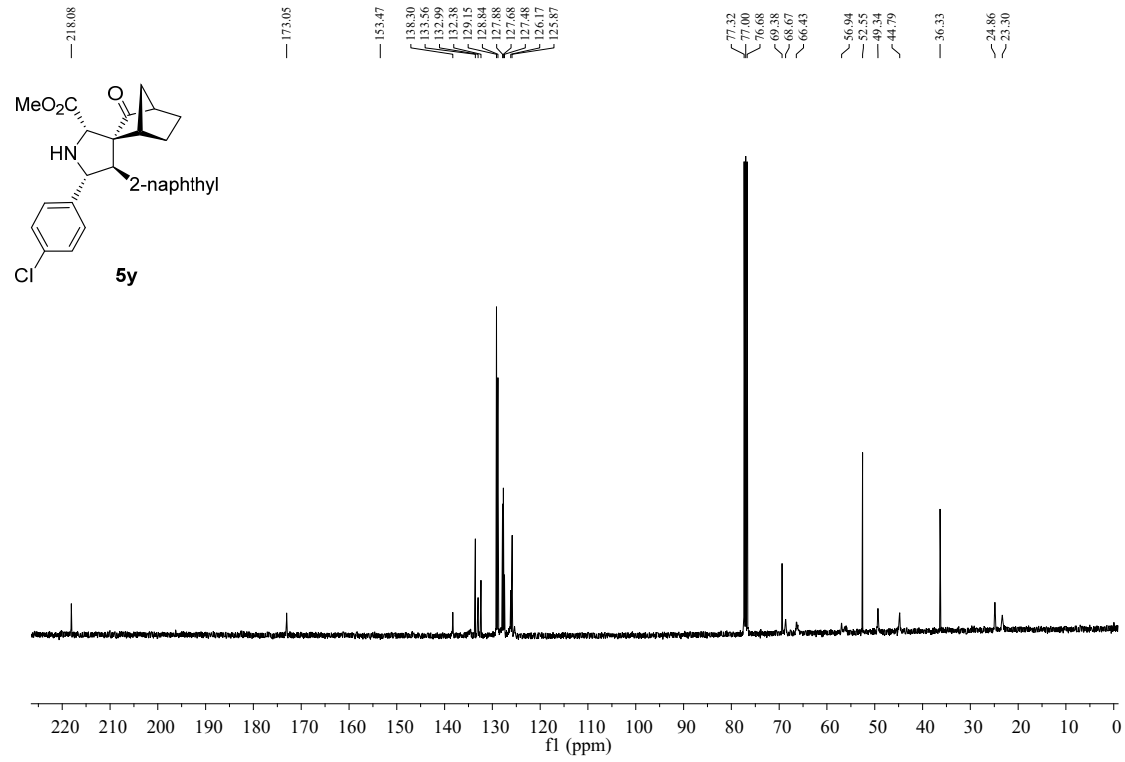
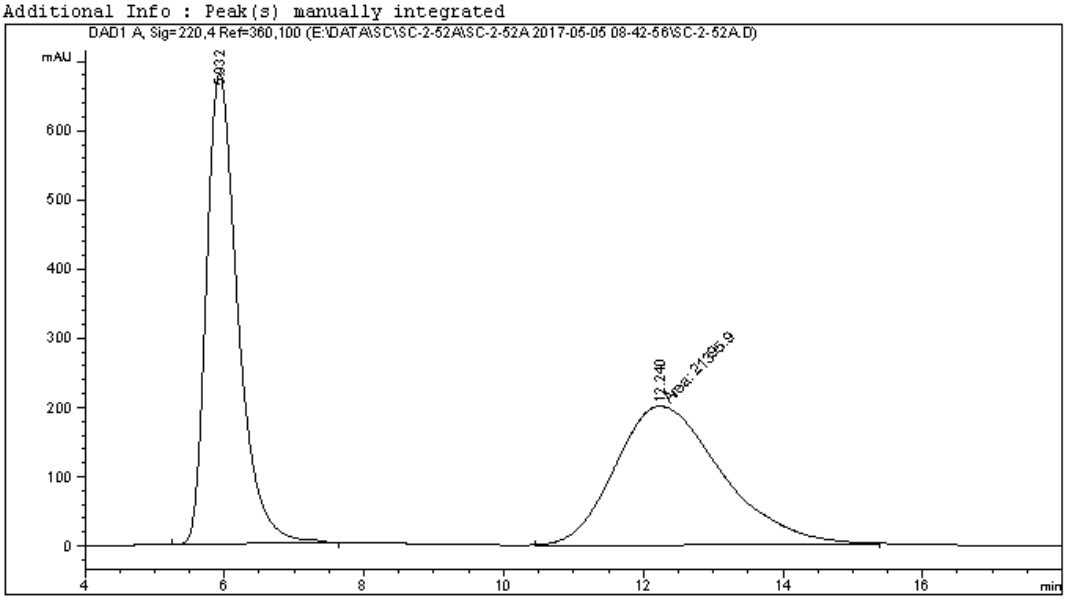


Figure S117. ^{13}C NMR spectrum of **5A**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-52A\SC-2-52A 2017-05-05 08-42-56\SC-2-52A.D
Sample Name: SC-2-52A

```
=====================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                             Location :   38
Injection Date  : 5/5/2017 8:44:20 AM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-52A\SC-2-52A 2017-05-05 08-42-56\SC-1-ASH-80-20-220NM-1ML-
                  40MIN.M
Last changed    : 5/5/2017 8:42:56 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-52A\SC-2-52A 2017-05-05 08-42-56\SC-1-ASH-80-20-220NM-1ML-
                  40MIN.M (Sequence Method)
Last changed    : 6/3/2017 11:20:37 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

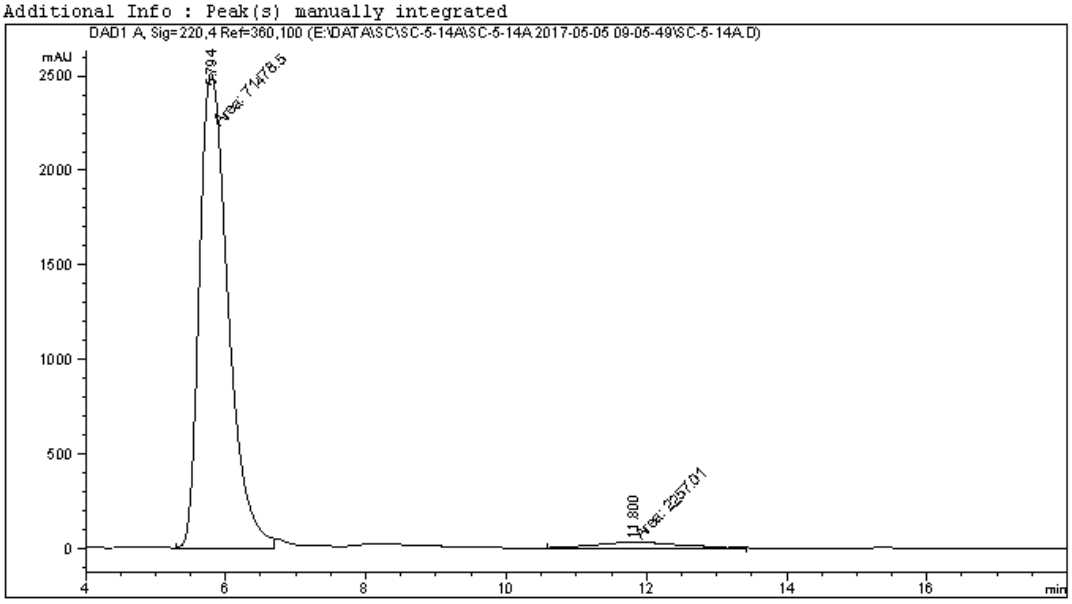

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.932 BB    0.4722 2.12265e4   679.97308  49.8013
   2  12.240 MM    1.7772 2.13959e4   200.65399  50.1987

Totals :                  4.26223e4   880.62708
```

Data File E:\DATA\SC\SC-5-14A\SC-5-14A 2017-05-05 09-05-49\SC-5-14A.D
Sample Name: SC-5-14A-1lH-P

Acq. Operator	: SYSTEM	Seq. Line	: 1
Acq. Instrument	: 1260	Location	: 32
Injection Date	: 5/5/2017 9:07:11 AM	Inj	: 1
		Inj Volume	: 5.000 µl
Acq. Method	: E:\DATA\SC\SC-5-14A\SC-5-14A 2017-05-05 09-05-49\SC-1-ASH-80-20-220NM-1ML-25MIN.M		
Last changed	: 5/5/2017 9:05:49 AM by SYSTEM		
Analysis Method	: E:\DATA\SC\SC-5-14A\SC-5-14A 2017-05-05 09-05-49\SC-1-ASH-80-20-220NM-1ML-25MIN.M (Sequence Method)		
Last changed	: 6/3/2017 11:24:53 AM by SYSTEM (modified after loading)		
Additional Info	: Peak(s) manually integrated		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.794	MM	0.4744	7.14785e4	2511.26685	96.9390
2	11.800	MM	1.3900	2257.01074	27.06268	3.0610
Totals :				7.37355e4	2538.32952	

Figure S118. HPLC spectrum of **5A**, related to **Table 3**.

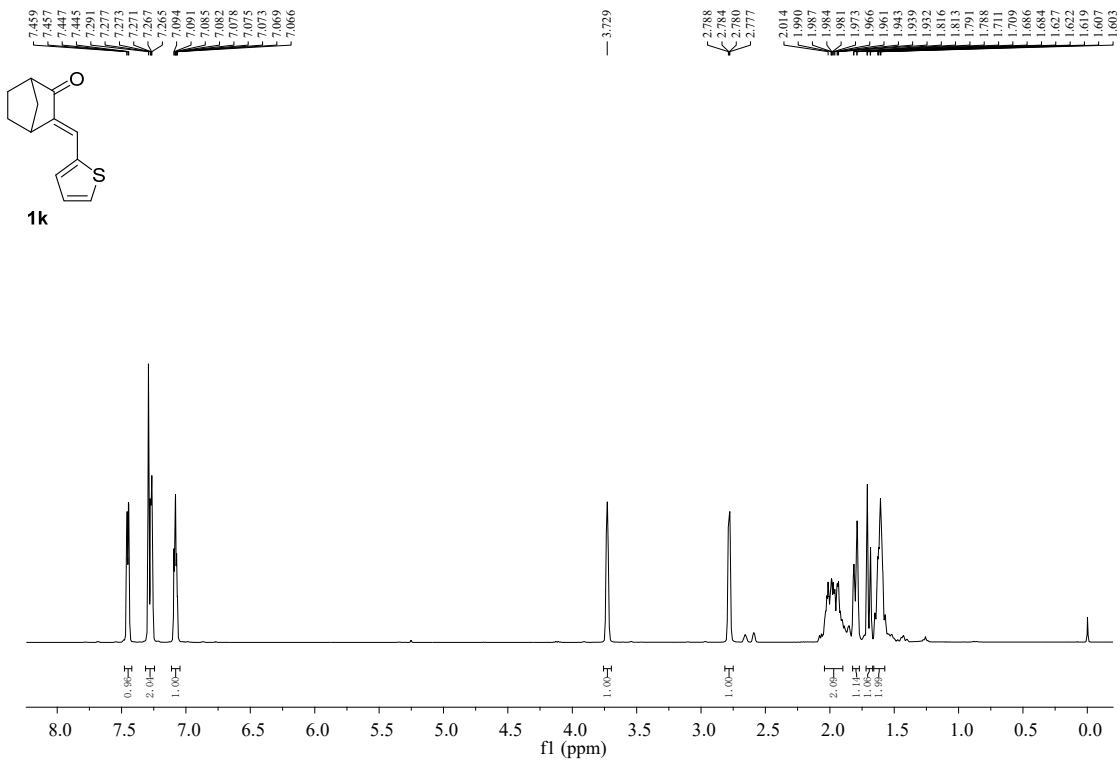


Figure S119. ^{1}H NMR spectrum of **1k**, related to **Table 3**.

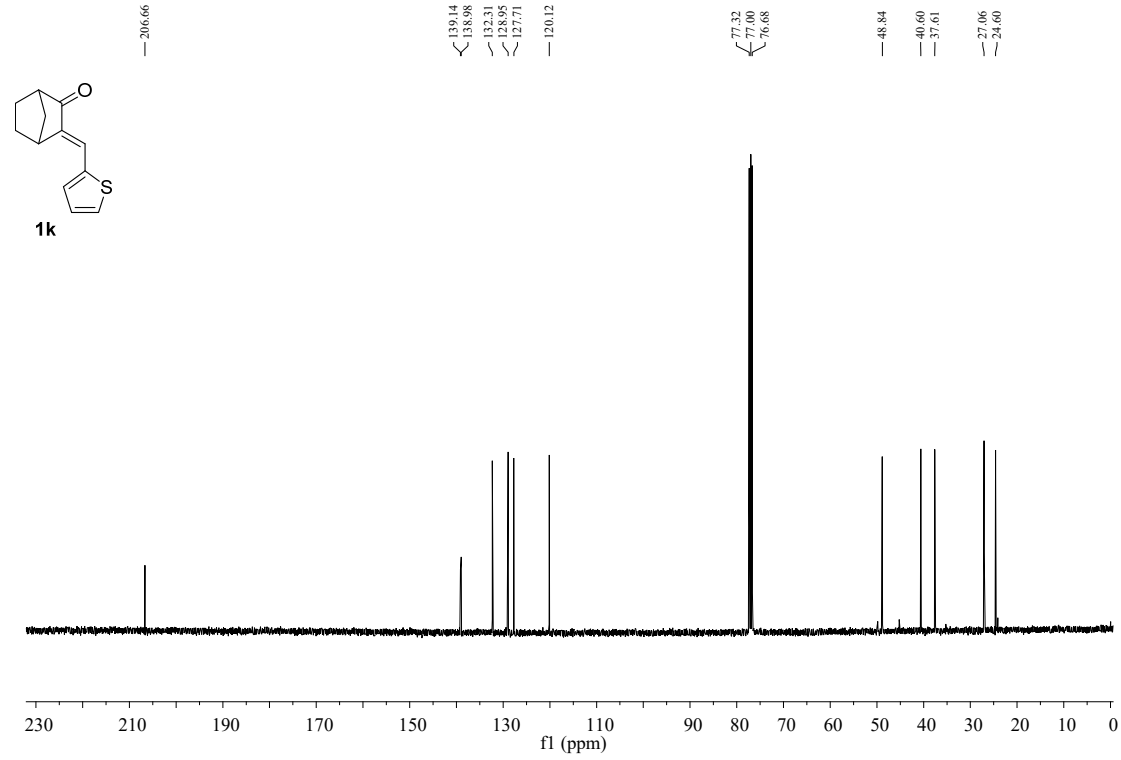
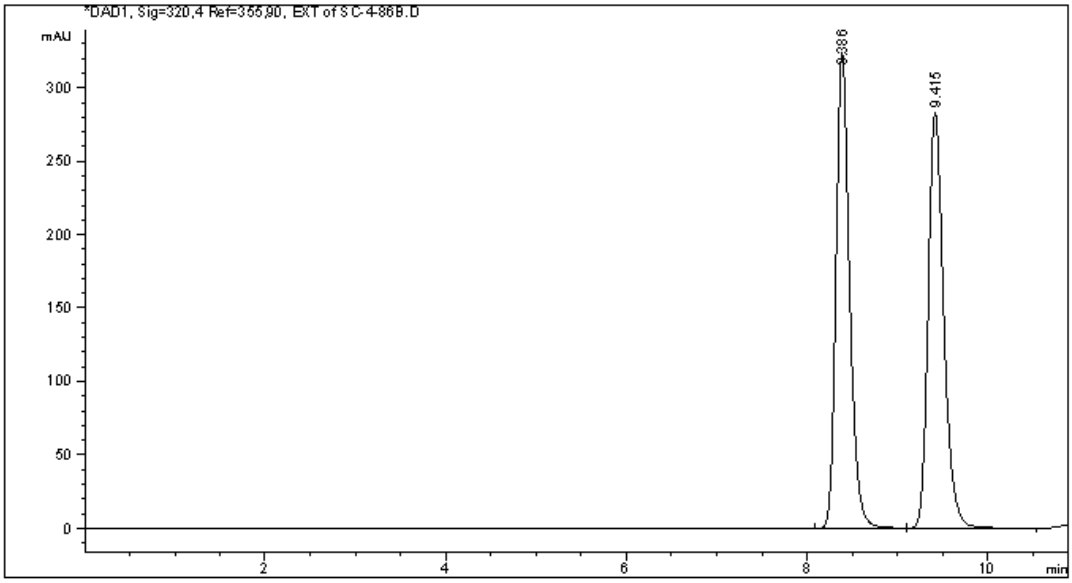


Figure S120. ^{13}C NMR spectrum of **1k**, related to **Table 3**.

Data File E:\DATA\SC\SC-4-86B\SC-4-86B-0J-90 2017-04-09 16-20-56\SC-4-86B.D
Sample Name: SC-4-86B-0J-90

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   17
    Injection Date  : 4/9/2017 4:22:22 PM                  Inj :   1
                                                     Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-4-86B\SC-4-86B-0J-90 2017-04-09 16-20-56\SC-5-0JH-90-10-DAD-
                      1ML.M
    Last changed    : 4/9/2017 4:20:56 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-4-86B\SC-4-86B-0J-90 2017-04-09 16-20-56\SC-5-0JH-90-10-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 5:07:59 AM by SYSTEM
                      (modified after loading)
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

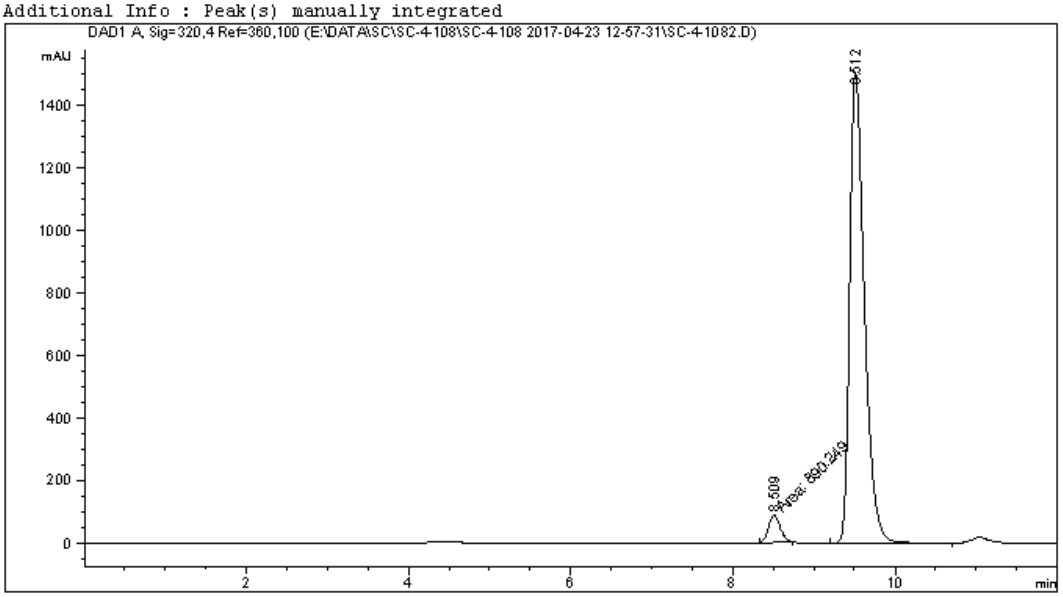

    Signal 1: DAD1, Sig=320,4 Ref=355,90, EXT
     Signal has been modified after loading from rawdata file!

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.386 BB    0.1587 3378.11938  323.76913  50.0061
       2   9.415 BB    0.1820 3377.29370  283.40698  49.9939

    Totals :                   6755.41309  607.17612
```

Data File E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-4-1082.D
Sample Name: SC-4-108B-S

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                              Location :   32
Injection Date  : 4/23/2017 1:25:12 PM                  Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-5-OJH-90-10-320NM-1ML-
                  12MIN.M
Last changed    : 4/23/2017 12:57:32 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-5-OJH-90-10-320NM-1ML-
                  12MIN.M (Sequence Method)
Last changed    : 6/4/2017 5:10:21 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=320,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   8.509 MM    0.1707  890.24921   86.93507   4.5118
   2   9.512 BB    0.1899 1.88415e4  1506.41113  95.4882

Totals :                  1.97317e4  1593.34620
```


Figure S121. HPLC spectrum of **1k**, related to **Table 3**.

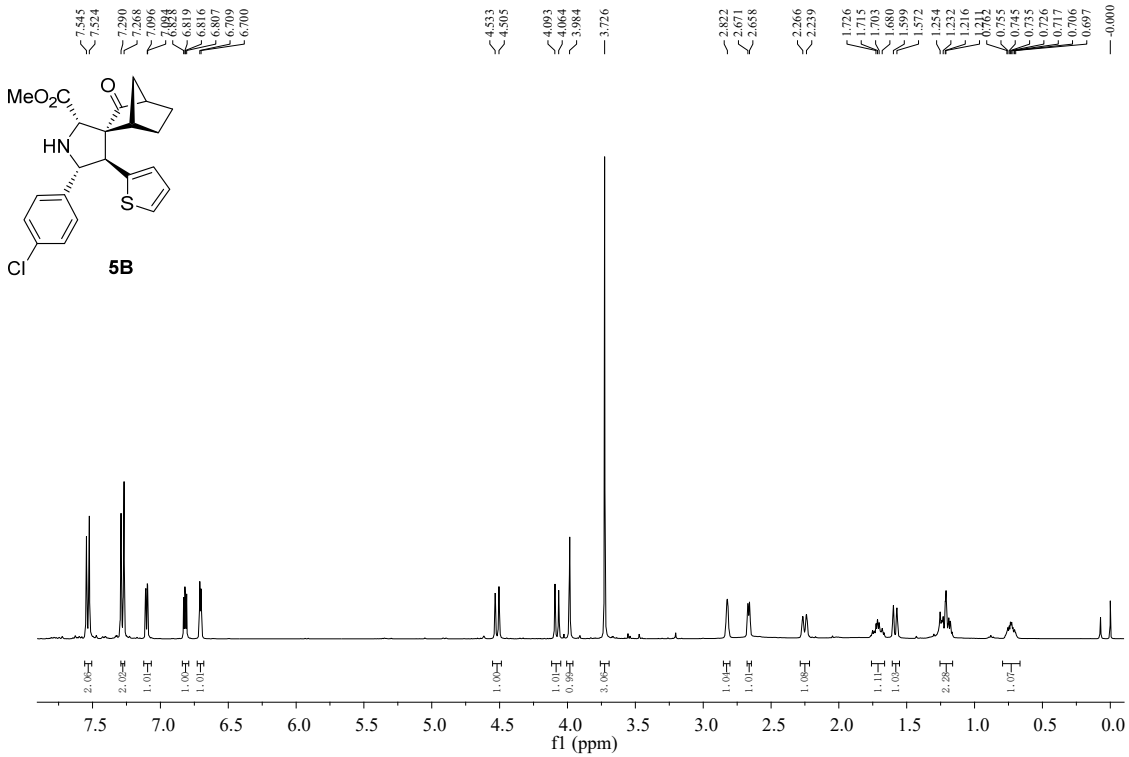


Figure S122. ^{1}H NMR spectrum of **5B**, related to **Table 3**.

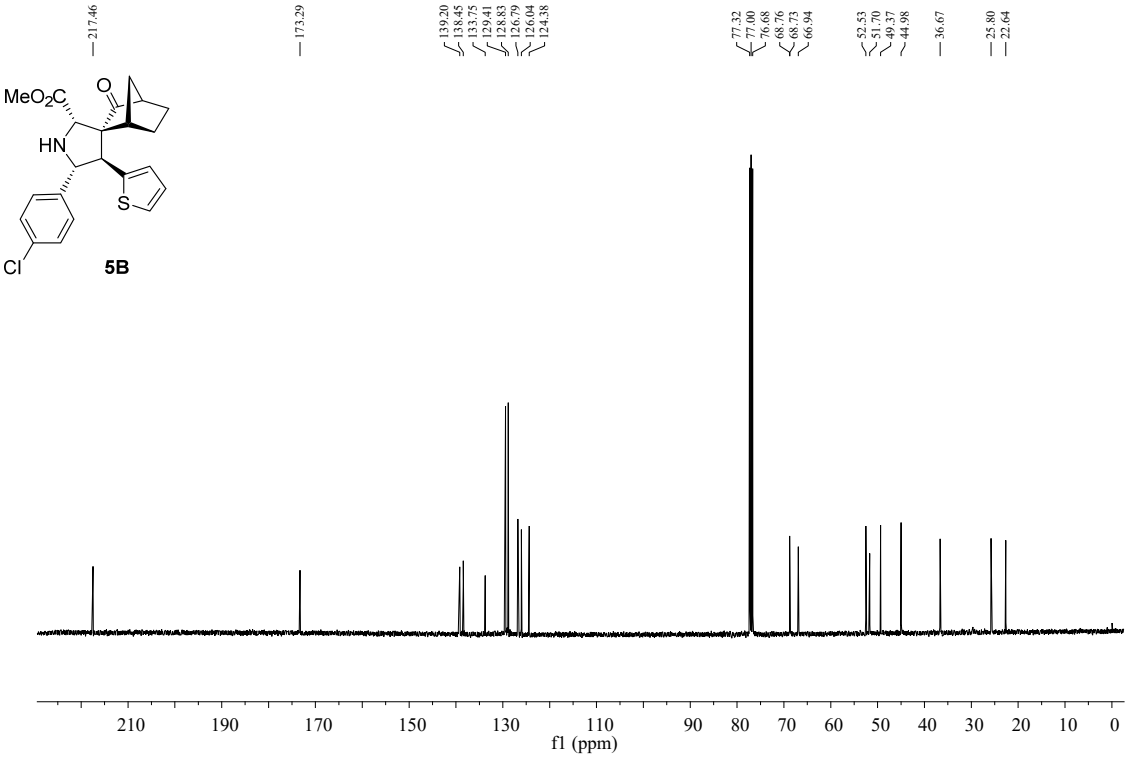
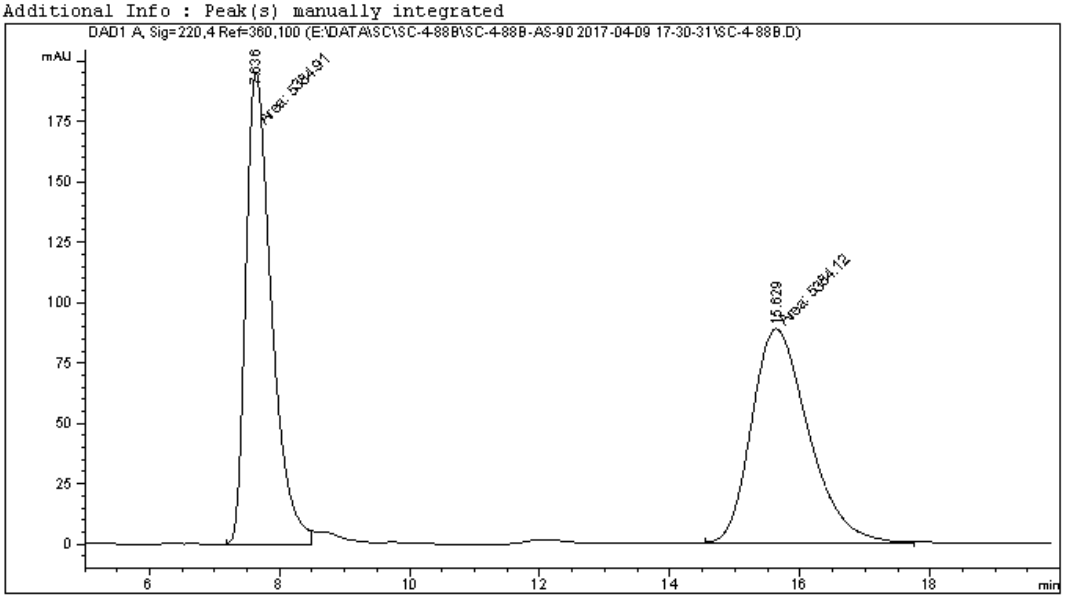


Figure S123. ^{13}C NMR spectrum of **5B**, related to **Table 3**.

Data File E:\DATA\SC\SC-4-88B\SC-4-88B-AS-90 2017-04-09 17-30-31\SC-4-88B.D
Sample Name: SC-4-88B-AS-90

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   19
    Injection Date  : 4/9/2017 5:31:57 PM                  Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-4-88B\SC-4-88B-AS-90 2017-04-09 17-30-31\SC-1-ASH-90-10-DAD-
                      1ML.M
    Last changed    : 4/9/2017 5:30:31 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-4-88B\SC-4-88B-AS-90 2017-04-09 17-30-31\SC-1-ASH-90-10-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/3/2017 11:41:05 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

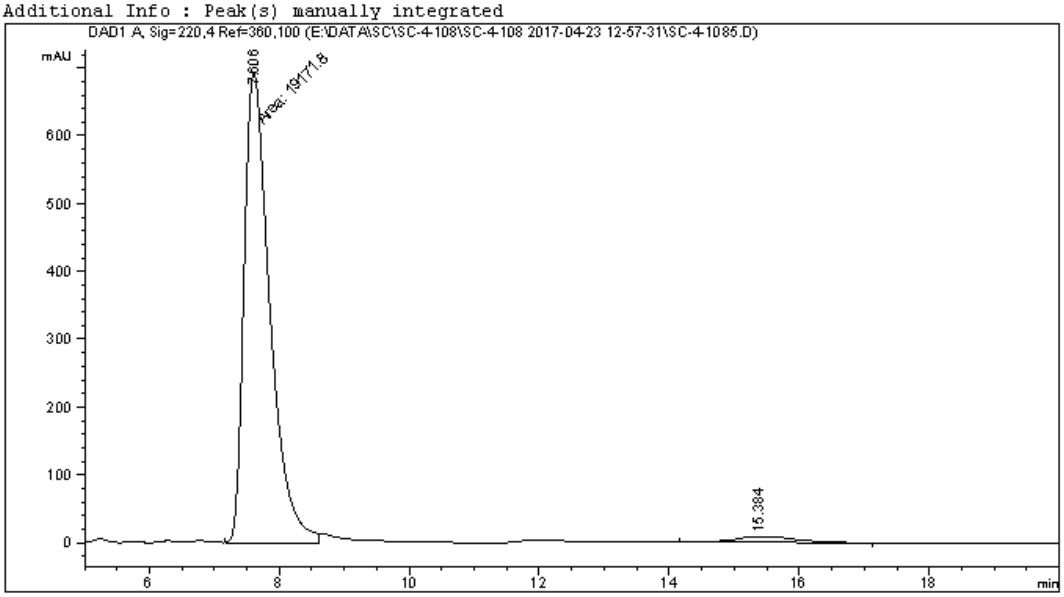

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1   7.636 MM    0.4587 5384.91455  195.66675  50.0037
       2  15.629 MM    1.0129 5384.12256   88.59551  49.9963

    Totals :                  1.07690e4   284.26226
```

Data File E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-4-1085.D
Sample Name: SC-4-108B-P

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   6
Acq. Instrument : 1260                             Location :   34
Injection Date  : 4/23/2017 2:20:52 PM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 4/23/2017 12:57:32 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-108\SC-4-108 2017-04-23 12-57-31\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/3/2017 11:43:14 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.606 MM    0.4606 1.91718e4   693.72382  97.1851
   2  15.384 BB    0.7498  555.30835    8.79283   2.8149

Totals :                  1.97271e4   702.51664
```


Figure S124. HPLC spectrum of **5B**, related to **Table 3**.

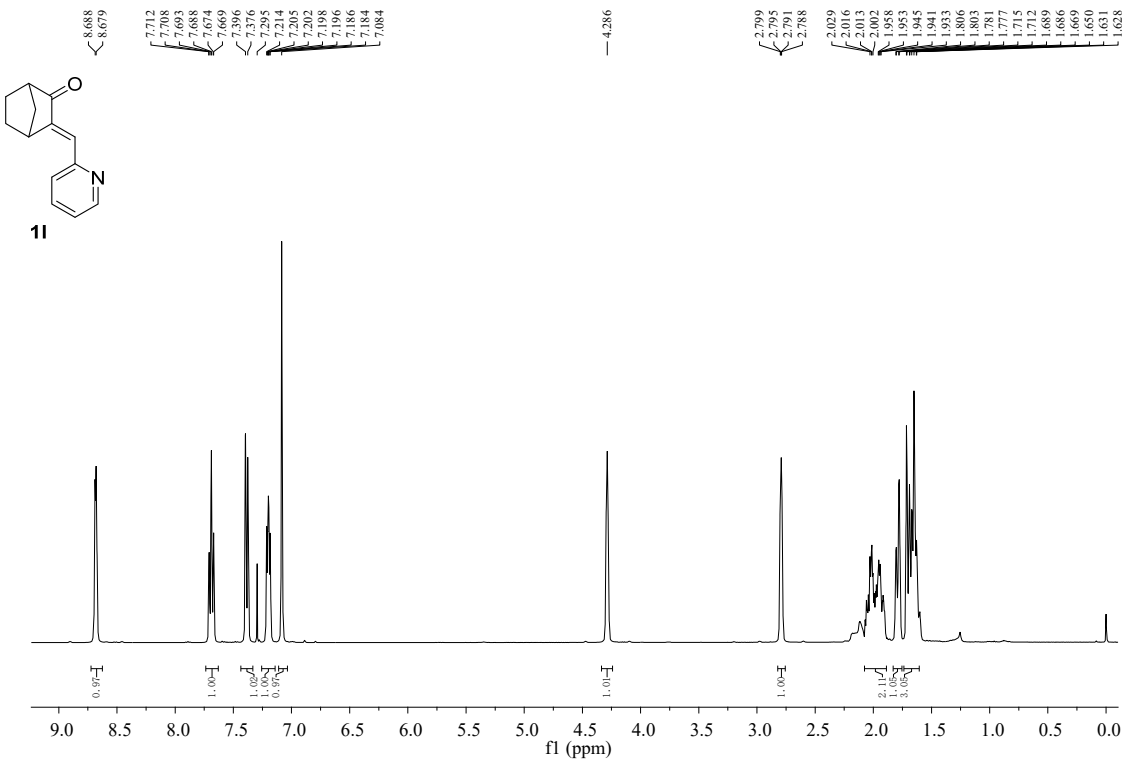


Figure S125. ^{1}H NMR spectrum of **1l**, related to **Table 3**.

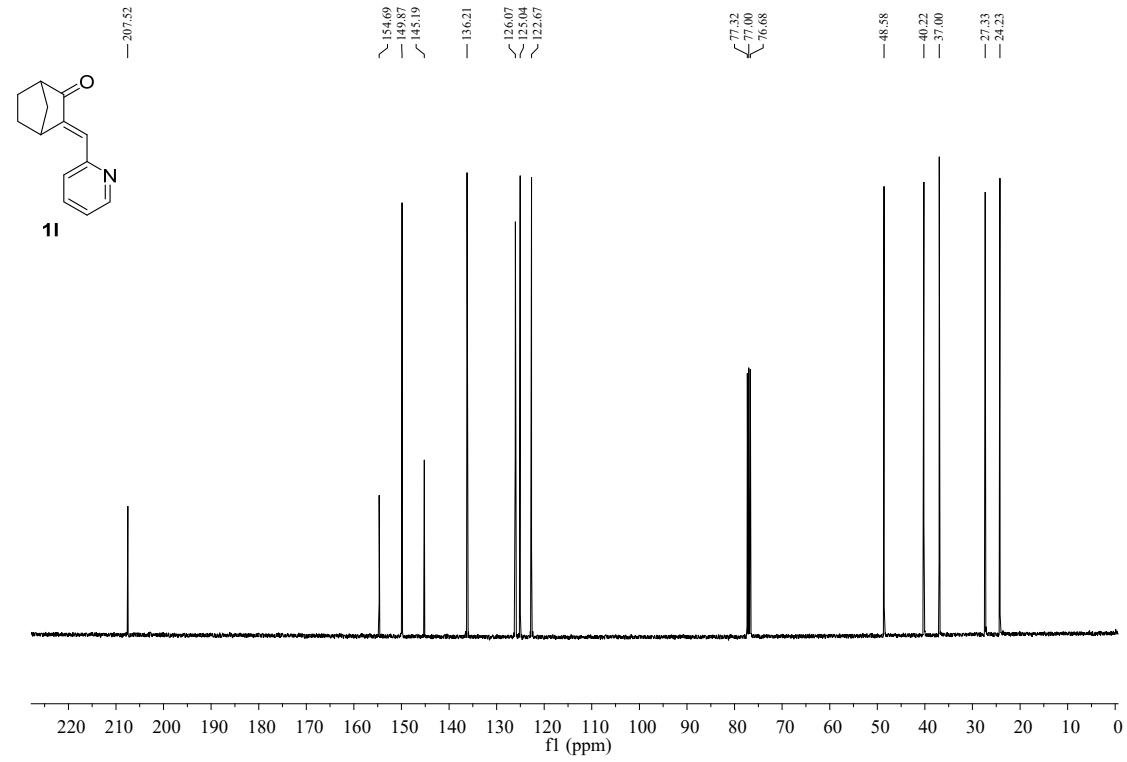
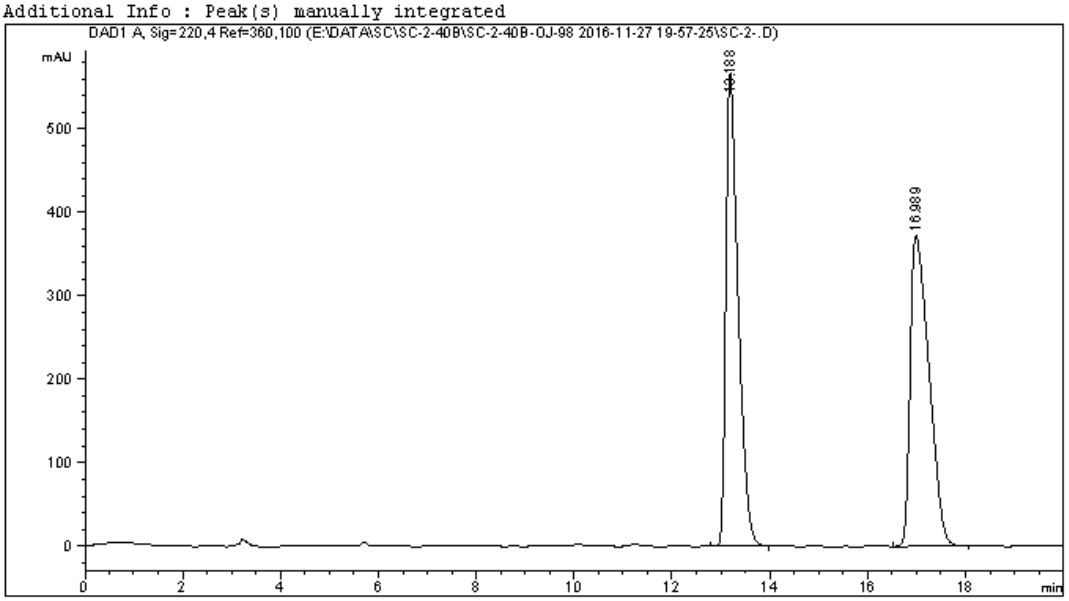


Figure S126. ^{13}C NMR spectrum of **1l**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-40B\SC-2-40B-0J-98 2016-11-27 19-57-25\SC-2-.D
Sample Name: SC-2-40B-0J-98

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   94
    Injection Date  : 11/28/2016 11:58:46 AM              Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-2-40B\SC-2-40B-0J-98 2016-11-27 19-57-25\SC-5-0JH-98-2-DAD-
                      1ML.M
    Last changed    : 11/28/2016 11:57:25 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-2-40B\SC-2-40B-0J-98 2016-11-27 19-57-25\SC-5-0JH-98-2-DAD-
                      1ML.M (Sequence Method)
    Last changed    : 6/4/2017 5:14:34 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

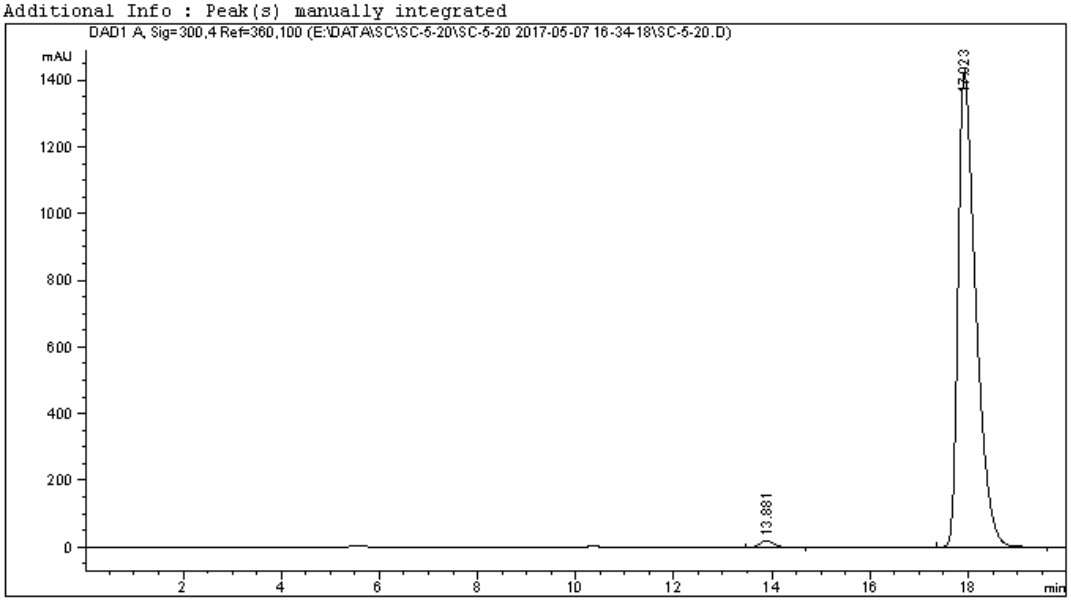

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  13.188 BB    0.2590 9856.99023  566.47467  49.8885
       2  16.989 BB    0.4243 9901.04590  372.22961  50.1115

    Totals :                  1.97580e4   938.70428
```

Data File E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-5-20.D
Sample Name: SC-5-20-S

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   35
    Injection Date  : 5/7/2017 4:35:49 PM                  Inj :   1
                                                     Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-5-0JH-98-2-300NM-1ML-
                      20MIN.M
    Last changed    : 5/7/2017 4:34:18 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-5-0JH-98-2-300NM-1ML-
                      20MIN.M (Sequence Method)
    Last changed    : 6/4/2017 5:12:09 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=300,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  13.881 BB    0.2684  359.14682   20.10318   0.9957
       2  17.923 BB    0.3761 3.57117e4  1421.27563  99.0043

    Totals :                  3.60708e4  1441.37881
```


Figure S127. HPLC spectrum of **1l**, related to **Table 3**.

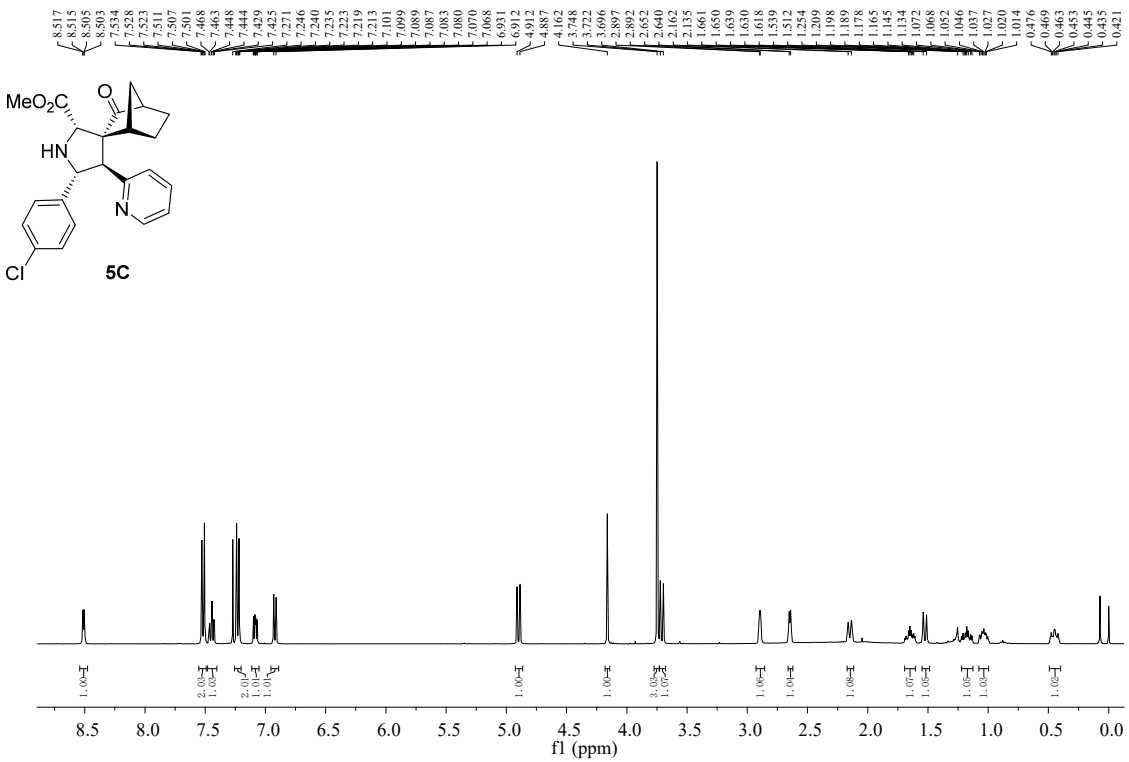


Figure S128. ^{1}H NMR spectrum of **5C**, related to **Table 3**.

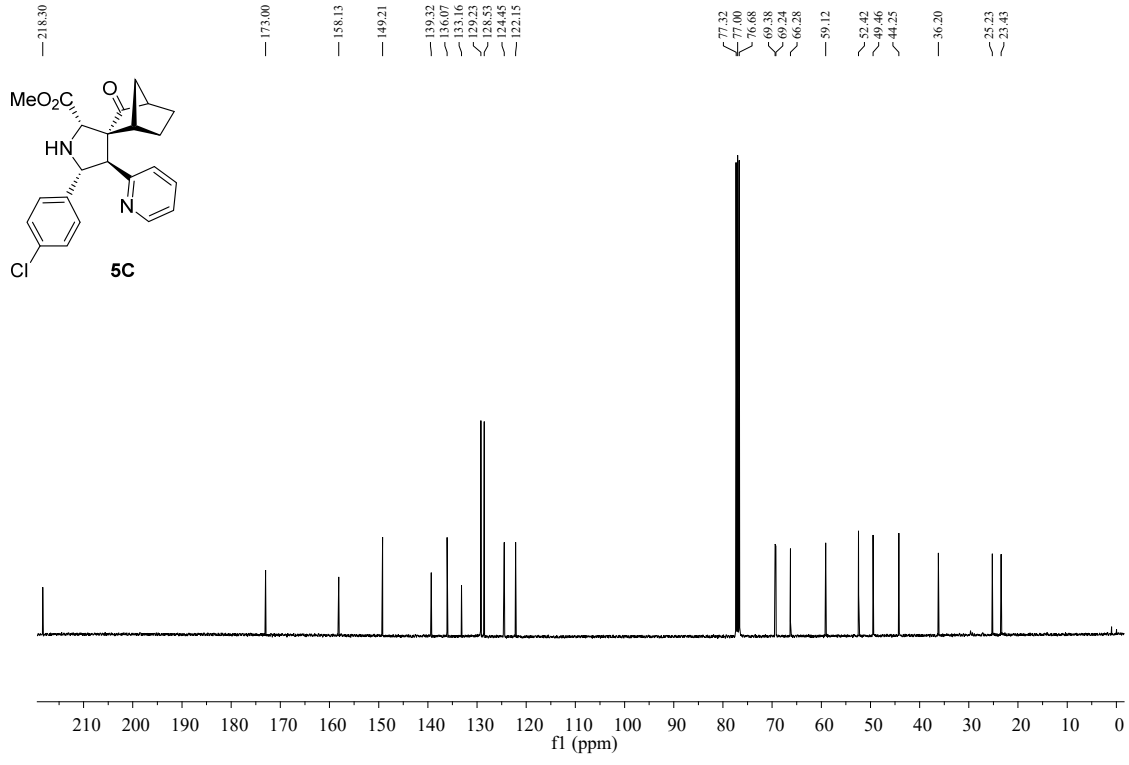
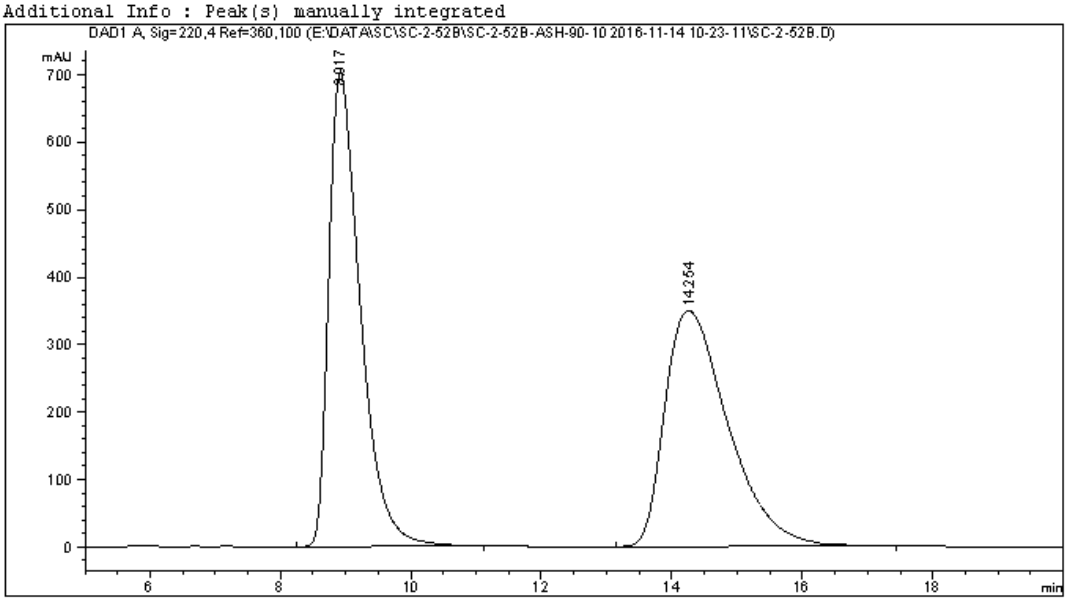


Figure S129. ^{13}C NMR spectrum of **5C**, related to **Table 3**.

Data File E:\DATA\SC\SC-2-52B\SC-2-52B-ASH-90-10 2016-11-14 10-23-11\SC-2-52B.D
Sample Name: SC-2-52B-ASH-90-10

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                             Location :   92
Injection Date  : 11/15/2016 2:24:27 AM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-2-52B\SC-2-52B-ASH-90-10 2016-11-14 10-23-11\SC-1-ASH-90-10-
                  DAD-1ML.M
Last changed    : 11/15/2016 2:23:11 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-52B\SC-2-52B-ASH-90-10 2016-11-14 10-23-11\SC-1-ASH-90-10-
                  DAD-1ML.M (Sequence Method)
Last changed    : 6/3/2017 11:45:29 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

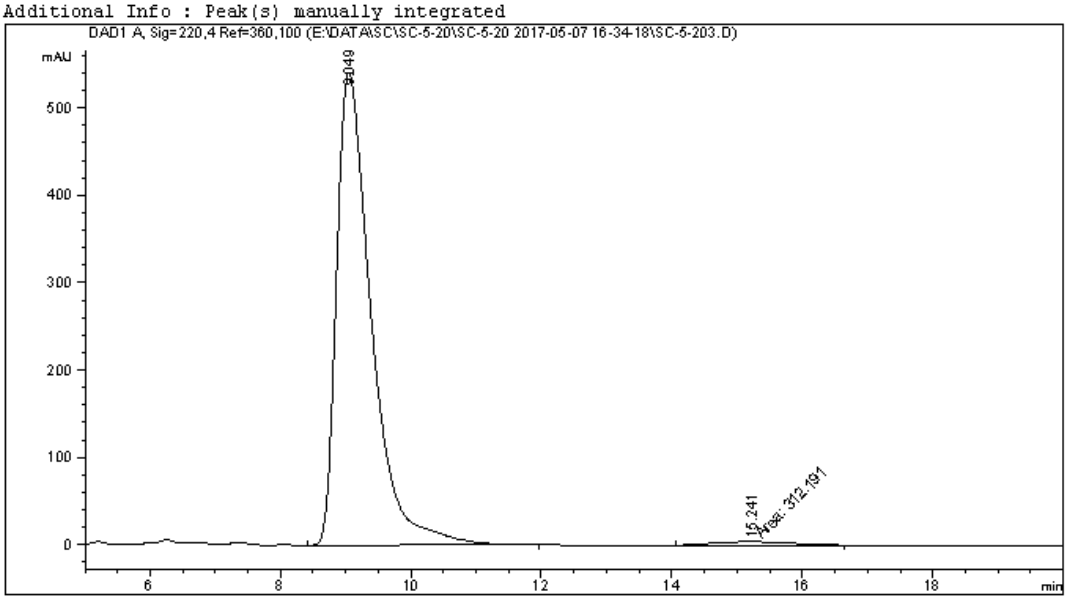

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.917 BB    0.5172 2.35650e4   700.90344  50.0115
   2  14.254 BB    1.0250 2.35542e4   349.17953  49.9885

Totals :                  4.71192e4  1050.08298
```

Data File E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-5-203.D
Sample Name: SC-5-20-P

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : 1260                              Location :   37
Injection Date  : 5/7/2017 5:29:36 PM                   Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M
Last changed    : 5/7/2017 4:34:18 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-20\SC-5-20 2017-05-07 16-34-18\SC-1-ASH-90-10-220NM-1ML-
                  20MIN.M (Sequence Method)
Last changed    : 6/3/2017 11:48:08 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   9.049 BB    0.5513 1.99574e4   539.90472  98.4598
   2  15.241 MM    1.3013  312.19092    3.99833   1.5402

Totals :                  2.02695e4   543.90305
```


Figure S130. HPLC spectrum of **5C**, related to **Table 3**.

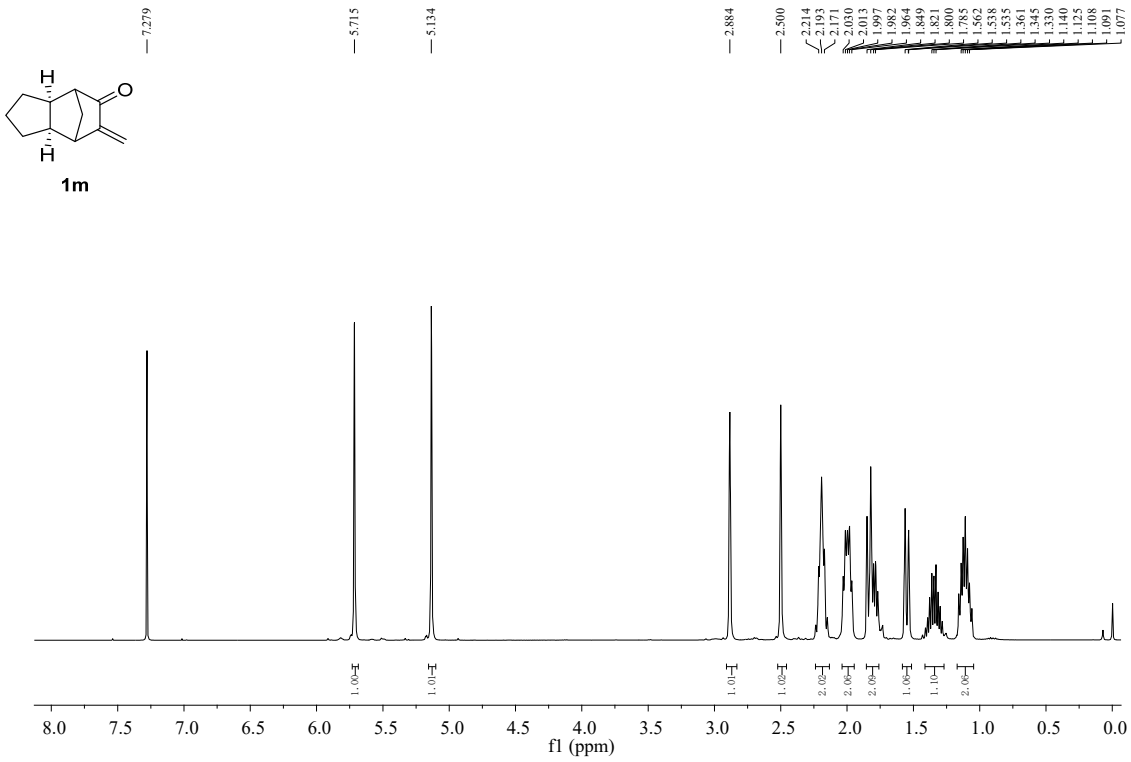


Figure S131. ^{1}H NMR spectrum of **1m**, related to **Table 3**.

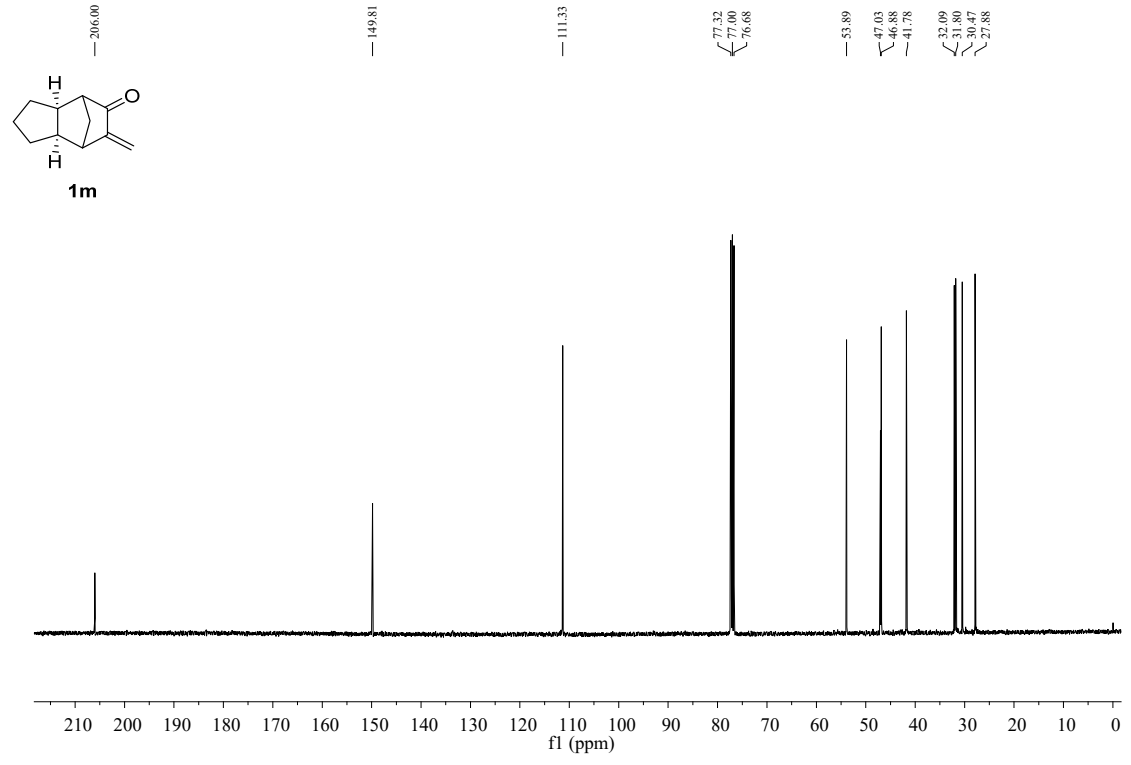
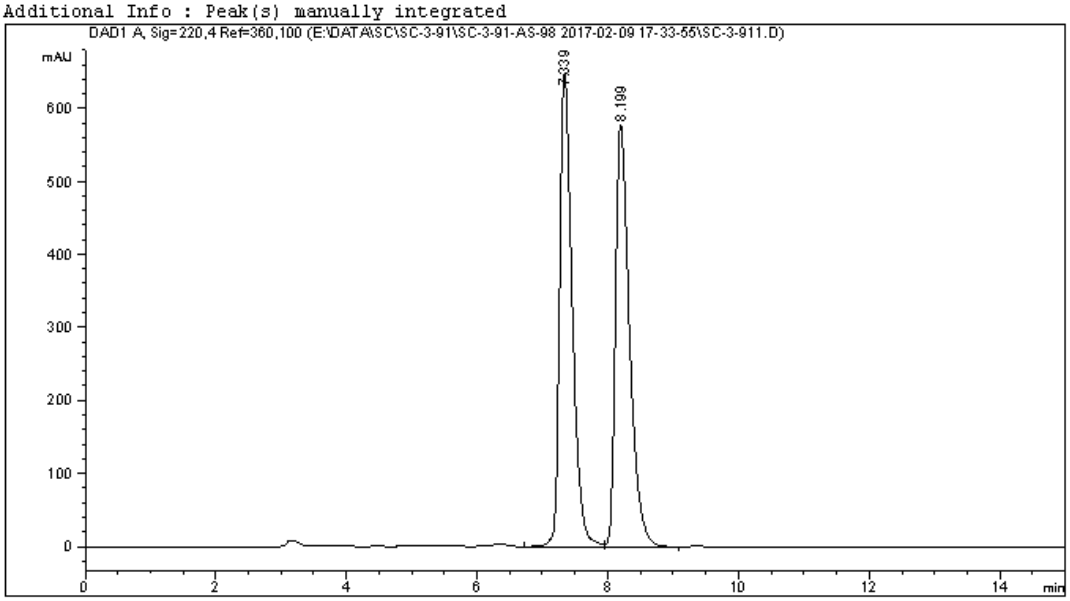


Figure S132. ^{13}C NMR spectrum of **1m**, related to **Table 3.**

Data File E:\DATA\SC\SC-3-91\SC-3-91-AS-98 2017-02-09 17-33-55\SC-3-911.D
Sample Name: SC-3-91

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                             Location :   11
Injection Date  : 2/9/2017 5:56:12 PM                   Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-91\SC-3-91-AS-98 2017-02-09 17-33-55\SC-2-ASH-98-2-DAD-1ML.
                  M
Last changed    : 2/9/2017 5:33:55 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-91\SC-3-91-AS-98 2017-02-09 17-33-55\SC-2-ASH-98-2-DAD-1ML.
                  M (Sequence Method)
Last changed    : 6/4/2017 5:18:34 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

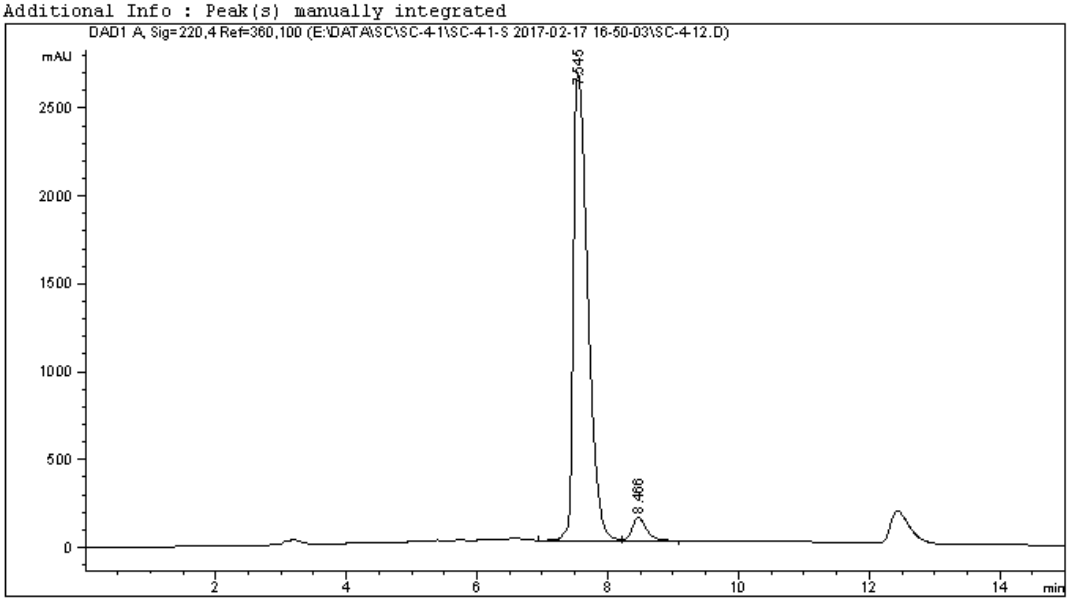

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.339 BV    0.2036 8708.80078  648.61542  50.2459
   2   8.199 VB    0.2263 8623.55371  577.35950  49.7541

Totals :                  1.73324e4  1225.97491
```

Data File E:\DATA\SC\SC-4-1\SC-4-1-S 2017-02-17 16-50-03\SC-4-12.D
Sample Name: SC-4-1B-S

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   12
Injection Date  : 2/17/2017 5:33:43 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-1\SC-4-1-S 2017-02-17 16-50-03\SC-1-ASH-98-2-220NM-1ML-
                  15MIN.M
Last changed    : 2/17/2017 4:50:03 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-1\SC-4-1-S 2017-02-17 16-50-03\SC-1-ASH-98-2-220NM-1ML-
                  15MIN.M (Sequence Method)
Last changed    : 6/4/2017 5:16:59 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.545 BV    0.2359 4.08279e4  2662.42480  95.4632
   2   8.466 VB    0.2244 1940.30542  130.51927   4.5368

Totals :                  4.27682e4  2792.94408
```


Figure S133. HPLC spectrum of **1m**, related to **Table 3**.

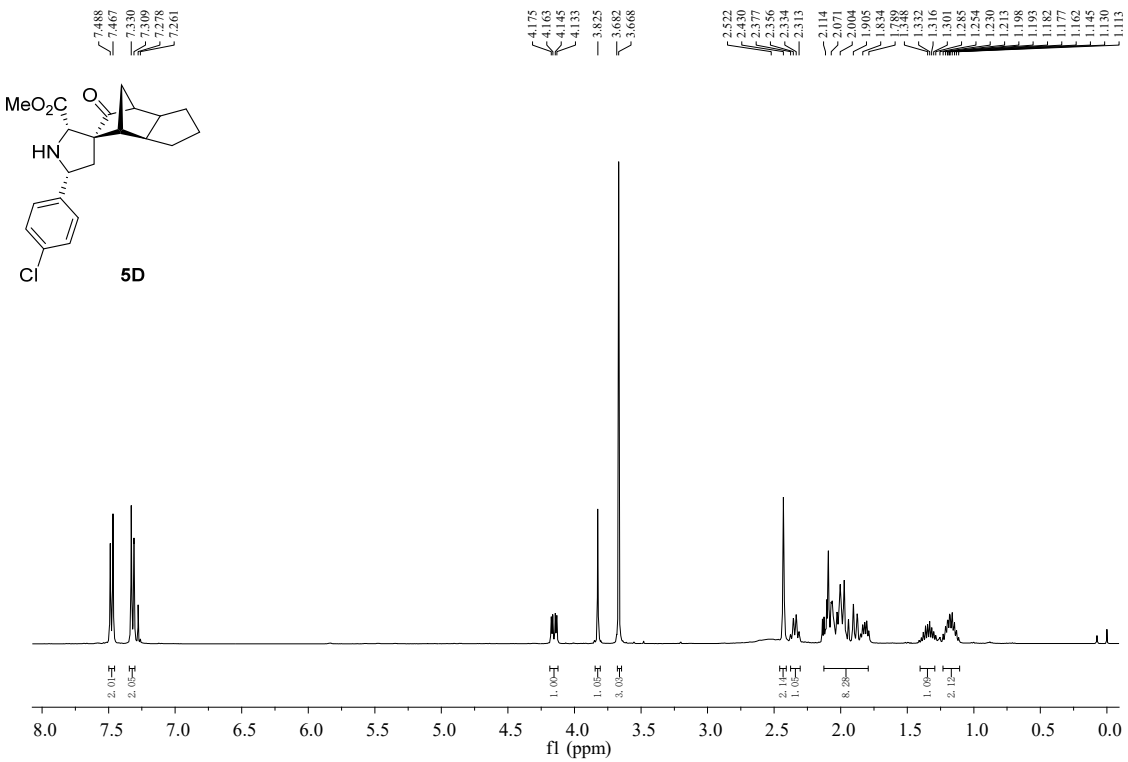


Figure S134. ^{1}H NMR spectrum of **5D**, related to **Table 3**.

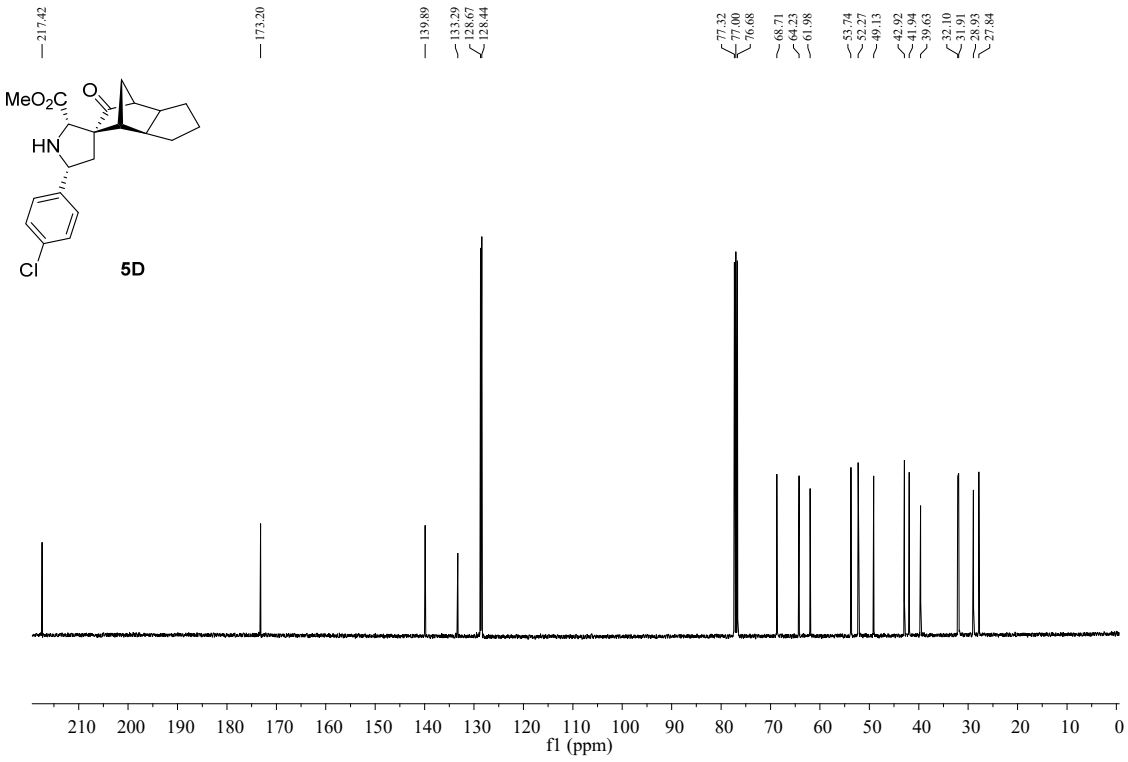
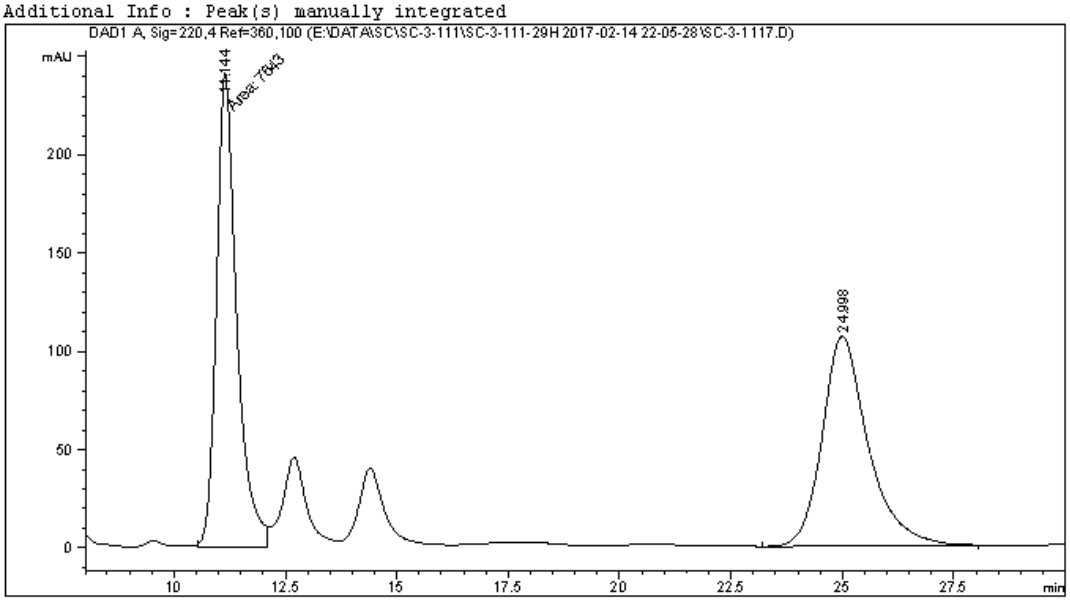


Figure S135. ^{13}C NMR spectrum of **5D**, related to **Table 3**.

Data File E:\DATA\SC\SC-3-111\SC-3-111-29H 2017-02-14 22-05-28\SC-3-1117.D
Sample Name: SC-3-100

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   8
    Acq. Instrument : 1260                             Location :   14
    Injection Date  : 2/15/2017 12:30:27 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-3-111\SC-3-111-29H 2017-02-14 22-05-28\SC-3-IA-90-10-220NM-
                      60MIN-1ML.M
    Last changed    : 2/14/2017 10:05:28 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-3-111\SC-3-111-29H 2017-02-14 22-05-28\SC-3-IA-90-10-220NM-
                      60MIN-1ML.M (Sequence Method)
    Last changed    : 6/3/2017 7:42:10 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

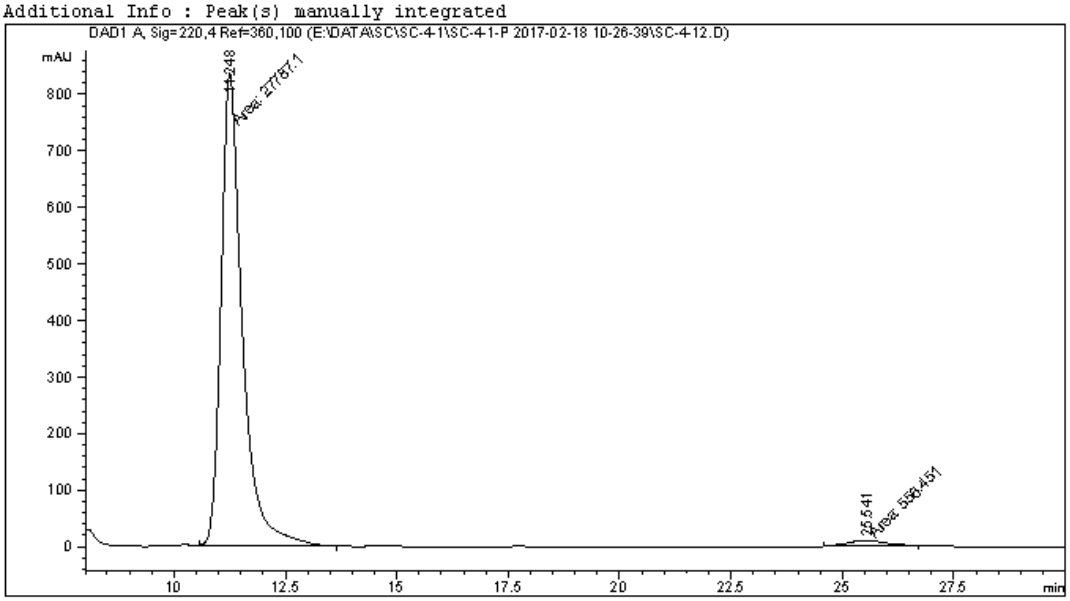

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.144 MM    0.5275 7642.99609  241.49182  49.9295
       2  24.998 BB    1.0049 7664.58838  106.72145  50.0705

    Totals :                  1.53076e4   348.21327
```

Data File E:\DATA\SC\SC-4-1\SC-4-1-P 2017-02-18 10-26-39\SC-4-12.D
Sample Name: SC-4-1B-P

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   14
Injection Date  : 2/18/2017 11:10:20 AM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-1\SC-4-1-P 2017-02-18 10-26-39\SC-3-IA-90-10-220NM-35MIN-
                  1ML.M
Last changed    : 2/18/2017 10:26:40 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-1\SC-4-1-P 2017-02-18 10-26-39\SC-3-IA-90-10-220NM-35MIN-
                  1ML.M (Sequence Method)
Last changed    : 6/3/2017 7:45:14 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.248 MM    0.5536 2.77871e4   836.48492  98.0368
   2  25.541 MM    0.9801  556.45062    9.46207   1.9632

Totals :                  2.83435e4   845.94700
```


Figure S136. HPLC spectrum of **5D**, related to **Table 3**.

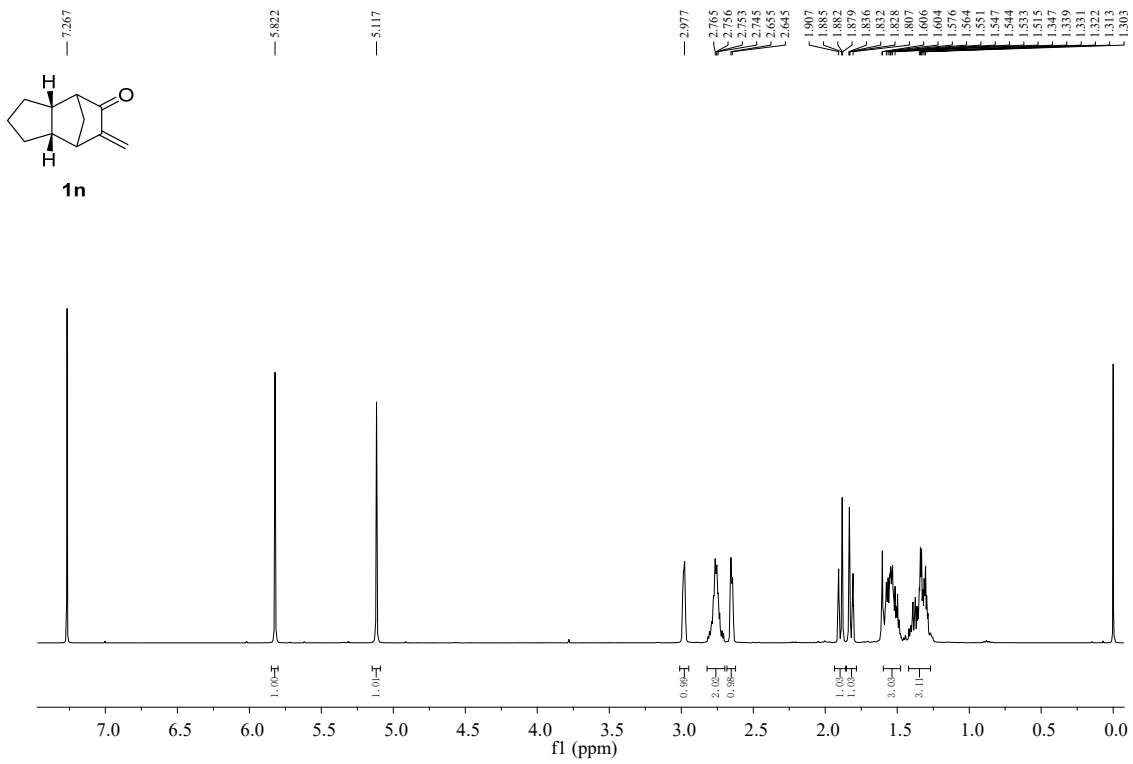


Figure S137. ^{1}H NMR spectrum of **1n**, related to **Table 3**.

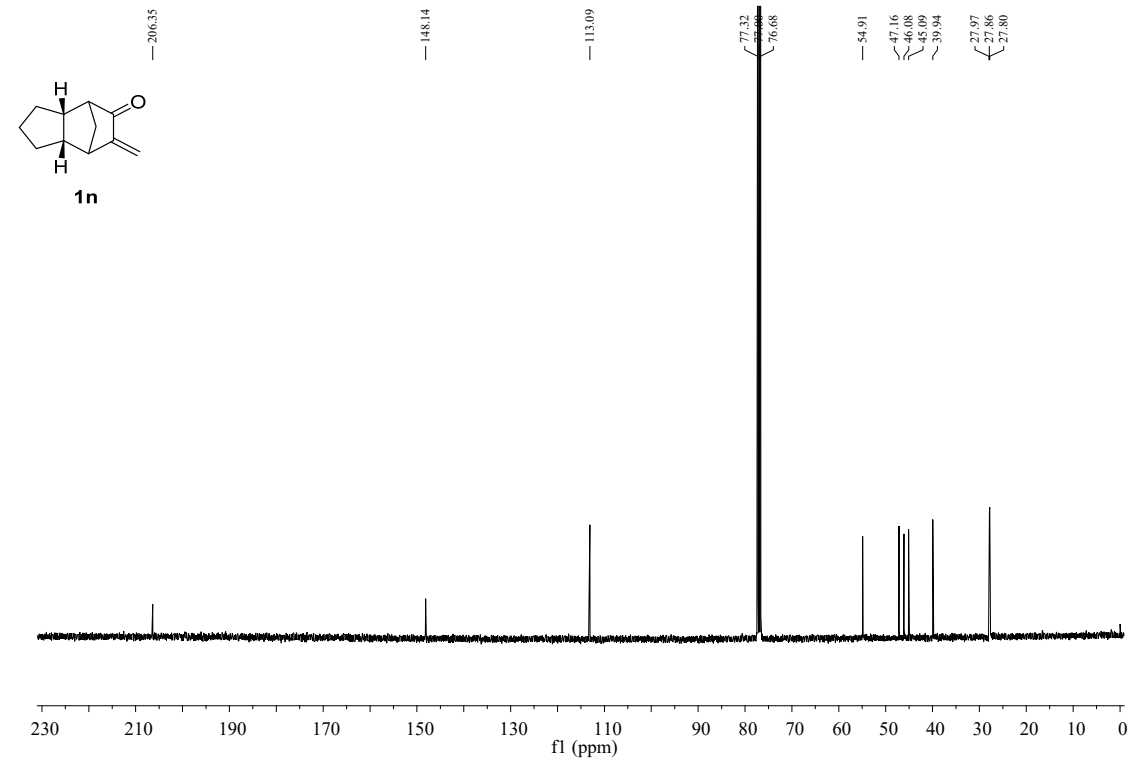
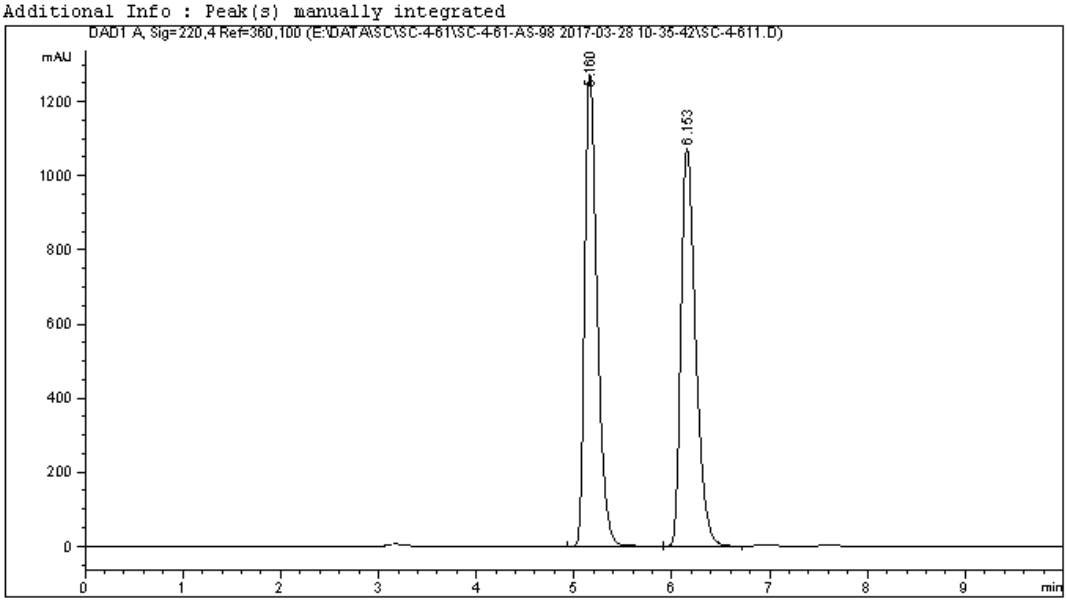


Figure S138. ^{13}C NMR spectrum of **1n**, related to **Table 3**.

Data File E:\DATA\SC\SC-4-61\SC-4-61-AS-98 2017-03-28 10-35-42\SC-4-611.D
Sample Name: SC-4-61

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
                                                 Location :   14
Injection Date  : 3/28/2017 10:53:10 AM               Inj :   1
Acq. Method     : SC-2-ASH-98-2-DAD-1ML.M
Analysis Method : E:\DATA\SC\SC-4-61\SC-4-61-AS-98 2017-03-28 10-35-42\SC-2-ASH-98-2-DAD-1ML.
                  M (Sequence Method)
Last changed    : 6/4/2017 5:22:35 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

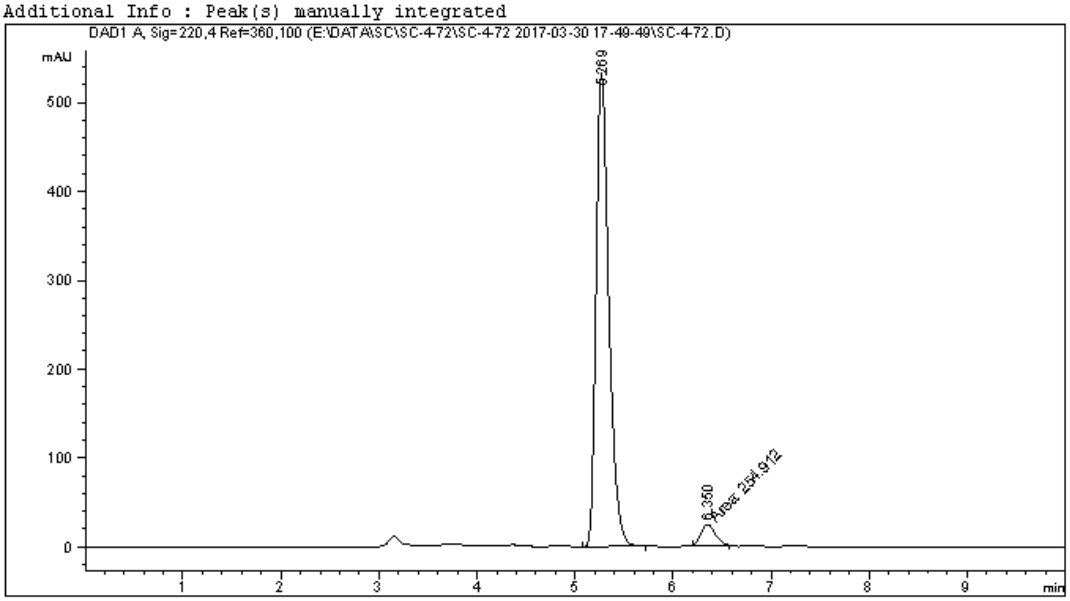
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.160 BB    0.1345 1.12148e4  1275.88586  49.9971
   2   6.153 BB    0.1600 1.12161e4  1072.96985  50.0029

Totals :                  2.24309e4  2348.85571


======================================================================
                        *** End of Report ***
```

Data File E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-4-72.D
Sample Name: SC-4-72-36H-S

```
=====================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   17
Injection Date  : 3/30/2017 5:51:21 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-1-ASH-98-2-220NM-1ML-
                  10MIN.M
Last changed    : 3/30/2017 5:49:49 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-1-ASH-98-2-220NM-1ML-
                  10MIN.M (Sequence Method)
Last changed    : 6/4/2017 5:20:50 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.269 BB    0.1385 4812.08447  532.27582  94.9692
   2   6.350 MM    0.1743  254.91188   24.37050   5.0308

Totals :                  5066.99635  556.64632
```


Figure S139. HPLC spectrum of **1n**, related to **Table 3**.

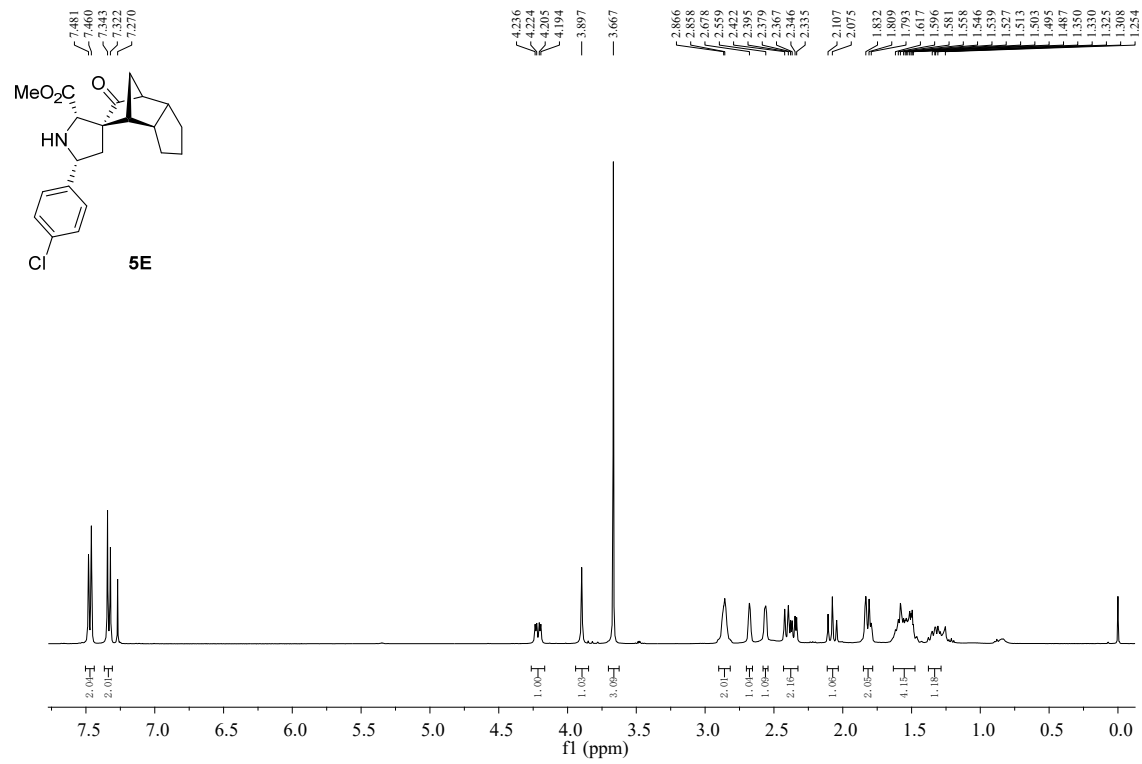


Figure S140. ^{1}H NMR spectrum of **5E**, related to **Table 3**.

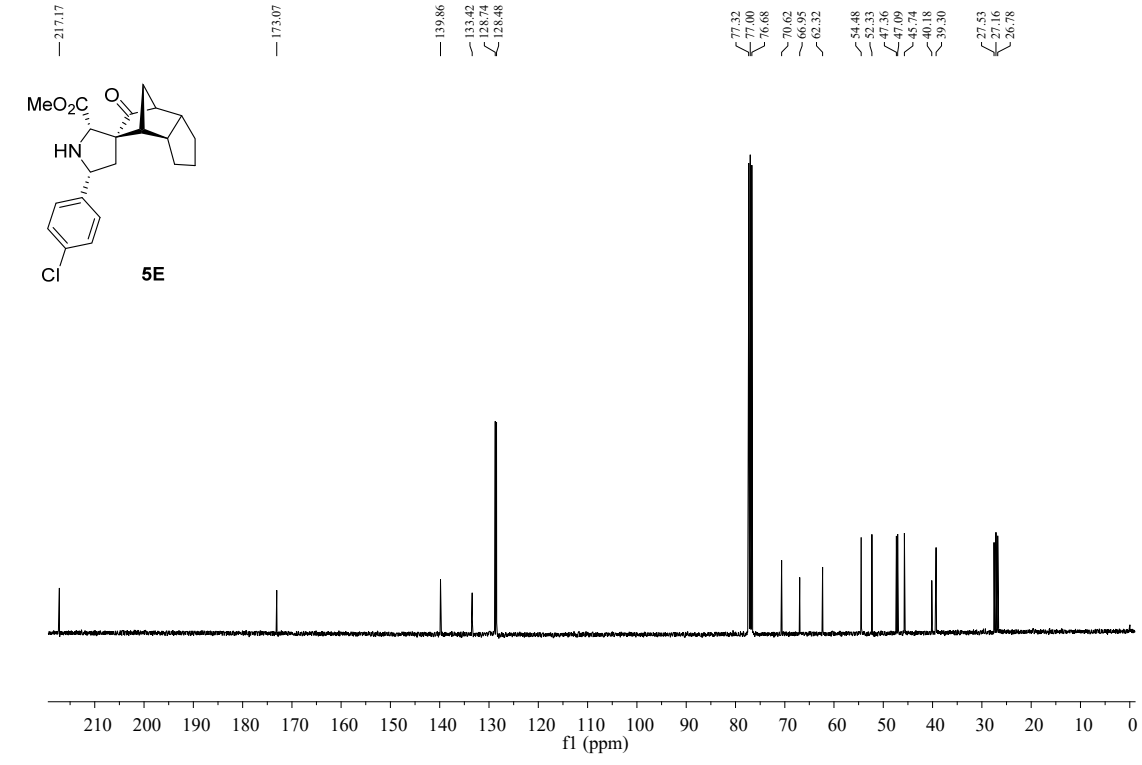
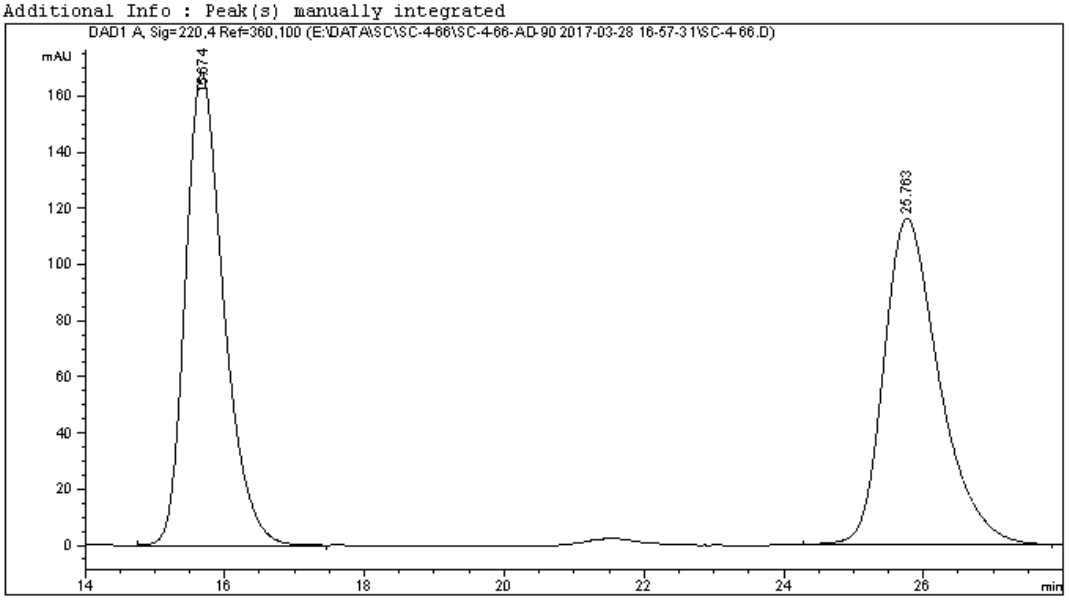


Figure S141. ^{13}C NMR spectrum of **5E**, related to **Table 3**.

Data File E:\DATA\SC\SC-4-66\SC-4-66-AD-90 2017-03-28 16-57-31\SC-4-66.D
Sample Name: SC-4-66

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   1
    Acq. Instrument : 1260                           Location :   15
    Injection Date  : 3/28/2017 4:59:01 PM               Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-4-66\SC-4-66-AD-90 2017-03-28 16-57-31\SC-2-ADH-90-10-DAD-1ML
                      .M
    Last changed    : 3/28/2017 4:57:31 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-4-66\SC-4-66-AD-90 2017-03-28 16-57-31\SC-2-ADH-90-10-DAD-1ML
                      .M (Sequence Method)
    Last changed    : 6/3/2017 7:53:52 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                          Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

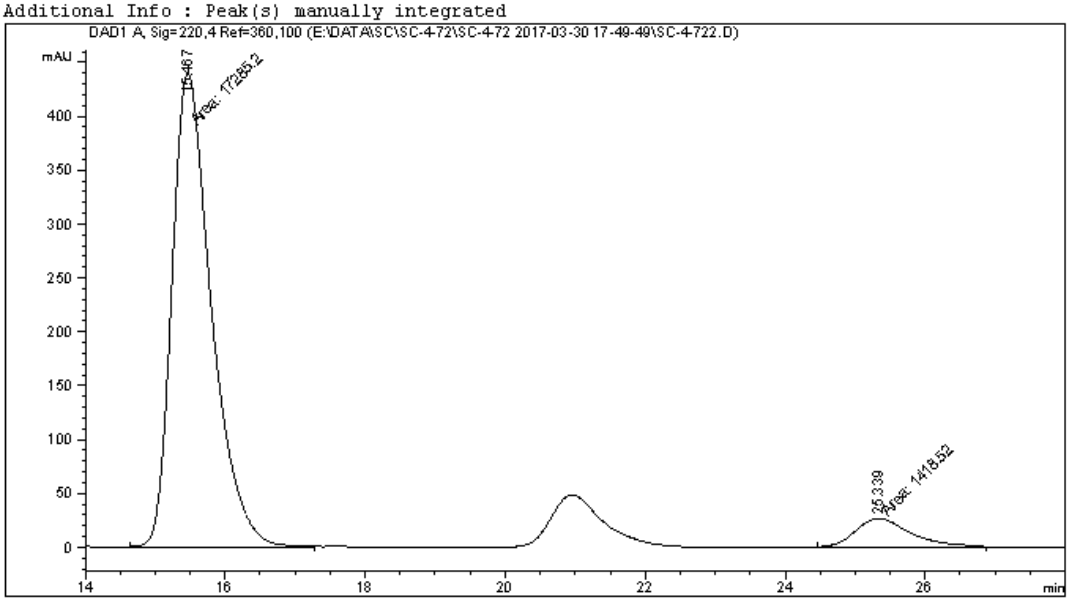

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  15.674 BB    0.5771 6402.79102  168.19650  50.0528
       2  25.763 BB    0.8068 6389.29053  116.13609  49.9472

    Totals :                  1.2792le4   284.33259
```

Data File E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-4-722.D
Sample Name: SC-4-72-36H-P

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   18
Injection Date  : 3/30/2017 6:23:47 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-2-ADH-90-10-220NM-30MIN-
                  1ML.M
Last changed    : 3/30/2017 5:49:49 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-4-72\SC-4-72 2017-03-30 17-49-49\SC-2-ADH-90-10-220NM-30MIN-
                  1ML.M (Sequence Method)
Last changed    : 6/3/2017 7:52:16 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.467 MM    0.6539 1.72852e4   440.56662  92.4158
   2  25.339 MM    0.9111 1418.52429   25.95018   7.5842

Totals :                  1.87037e4   466.51680
```


Figure S142. HPLC spectrum of **5E**, related to **Table 3**.

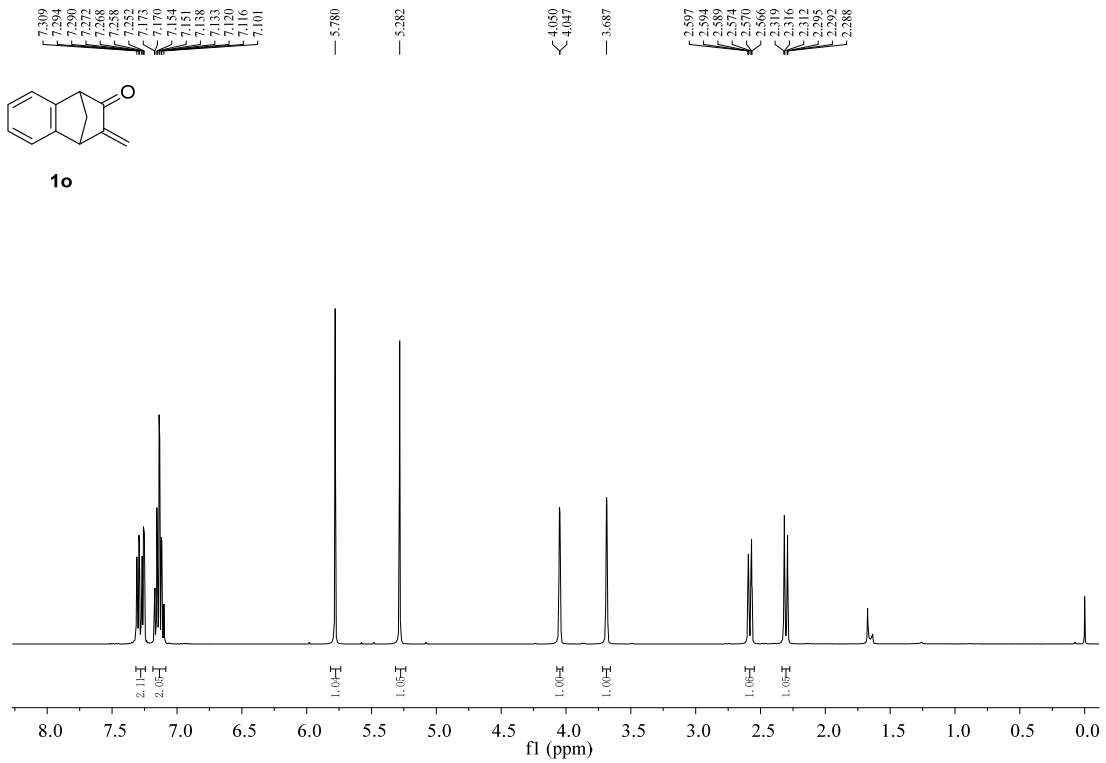


Figure S143. ^{1}H NMR spectrum of **1o**, related to **Table 3**.

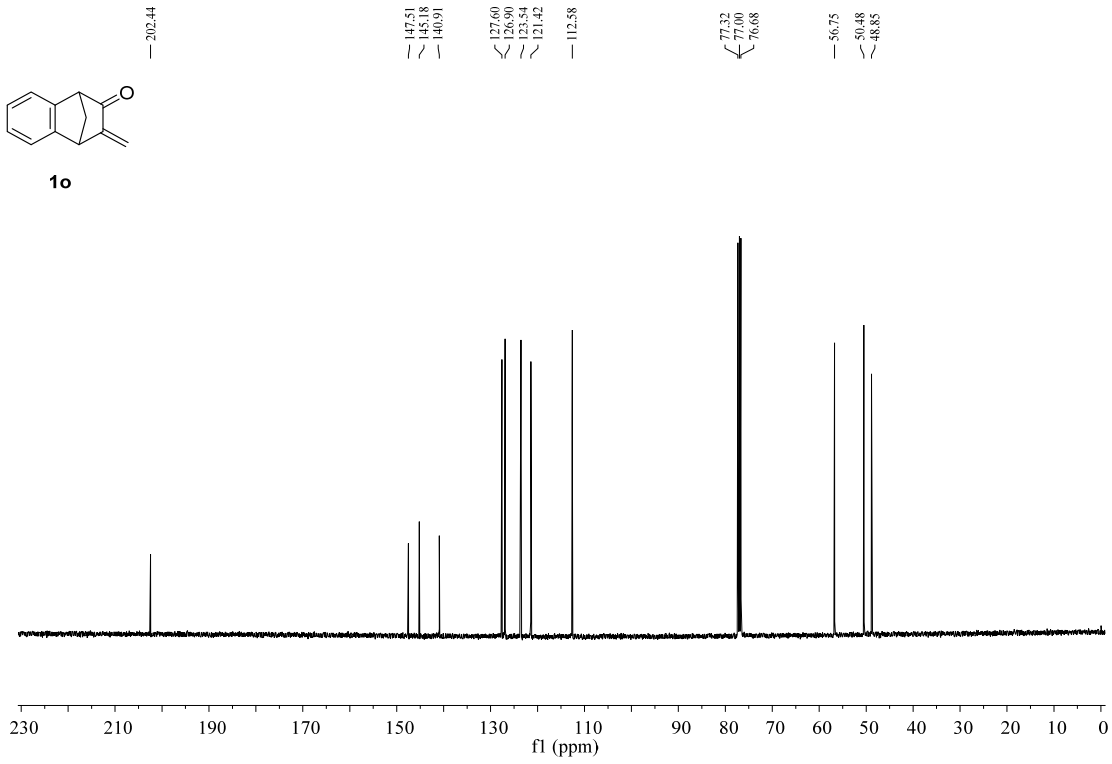
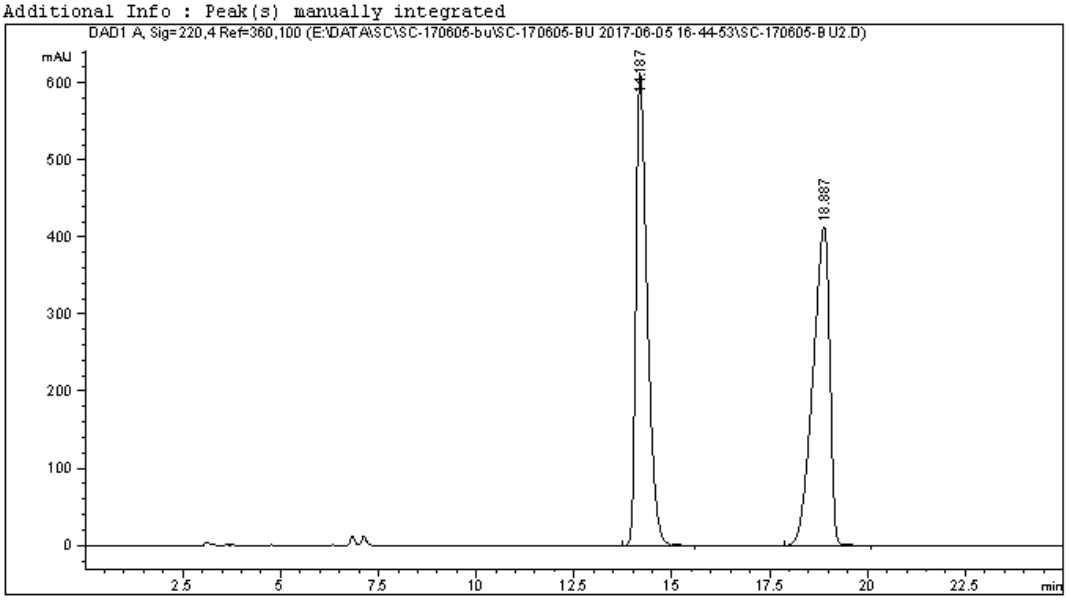


Figure S144. ^{13}C NMR spectrum of **1o**, related to **Table 3**.

Data File E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-170605-BU2.D
Sample Name: SC-3-94-1

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : 1260                           Location :   82
Injection Date  : 6/5/2017 5:38:38 PM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-5-0JH-90-10-
                  220NM-25MIN-1ML.M
Last changed    : 6/5/2017 5:32:34 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170605-bu\SC-170605-BU 2017-06-05 16-44-53\SC-5-0JH-90-10-
                  220NM-25MIN-1ML.M (Sequence Method)
Last changed    : 6/5/2017 8:33:34 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

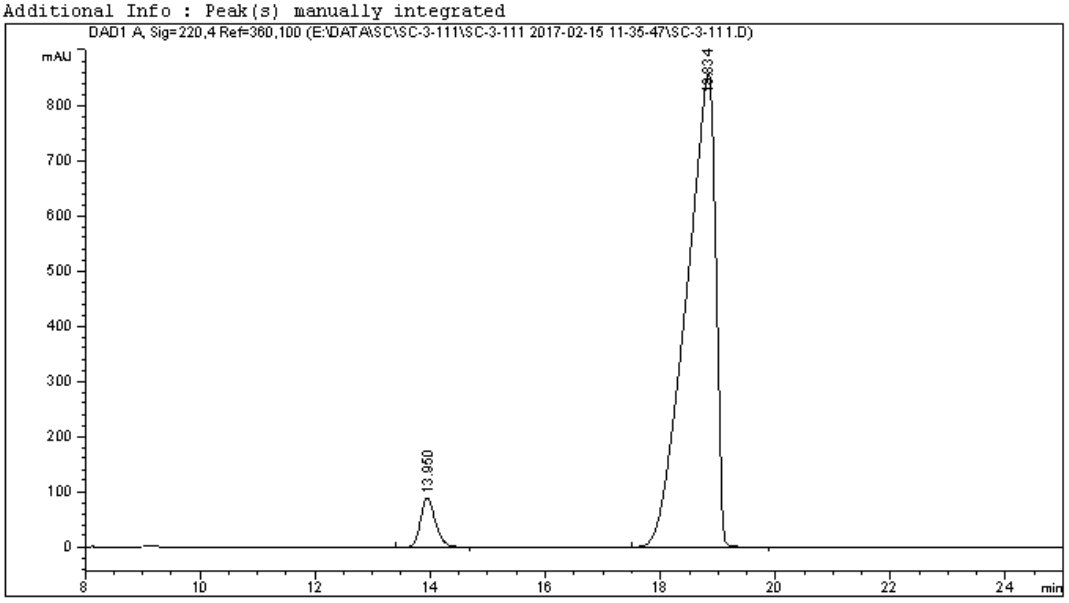

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  14.187 BB    0.3021 1.22925e4   612.48792  50.0043
   2  18.887 BB    0.4516 1.22904e4   413.70169  49.9957

Totals :                  2.45829e4  1026.18961
```

Data File E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-3-111.D
Sample Name: SC-3-111A-S

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : 1260                           Location :   35
Injection Date  : 2/15/2017 11:37:17 AM              Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-5-OJH-90-10-220NM-25MIN
                  -1ML.M
Last changed    : 2/15/2017 11:35:47 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-5-OJH-90-10-220NM-25MIN
                  -1ML.M (Sequence Method)
Last changed    : 6/4/2017 5:25:01 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.950 BB    0.2716 1571.54919   88.74484   4.9405
   2  18.834 BB    0.5058 3.02377e4   858.80731  95.0595

Totals :                  3.18092e4   947.55215
```


Figure S145. HPLC spectrum of **1o**, related to **Table 3**.

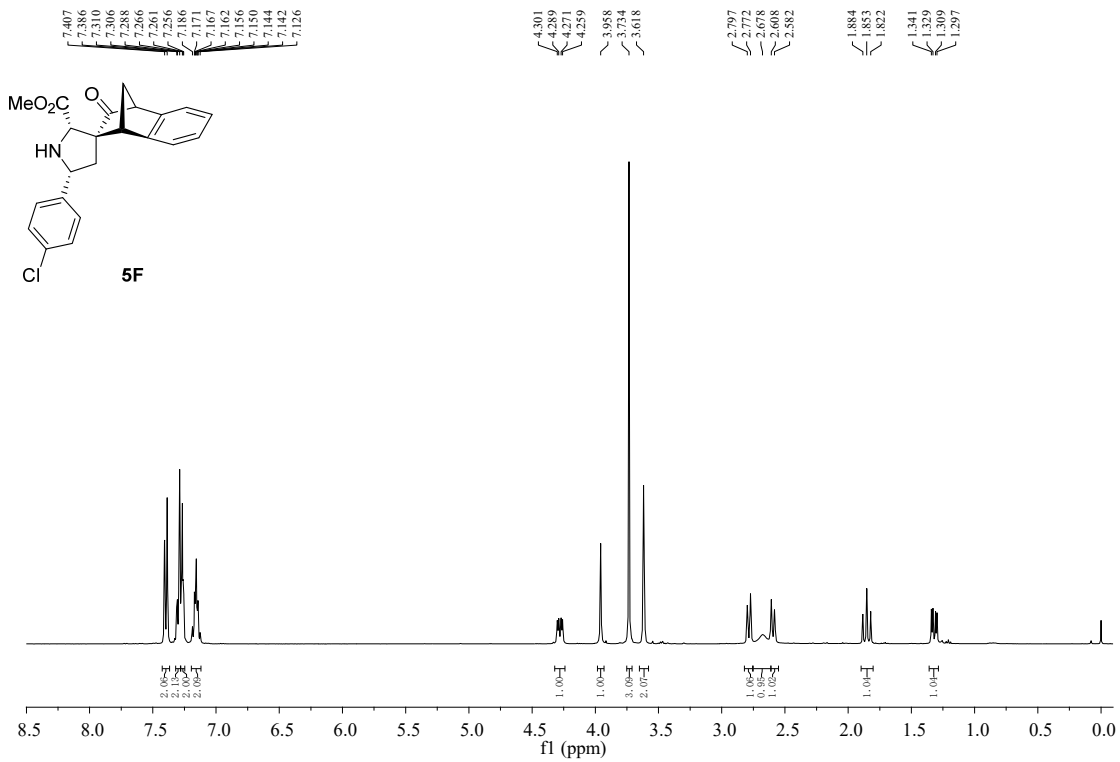


Figure S146. ^{1}H NMR spectrum of **5F**, related to **Table 3**.

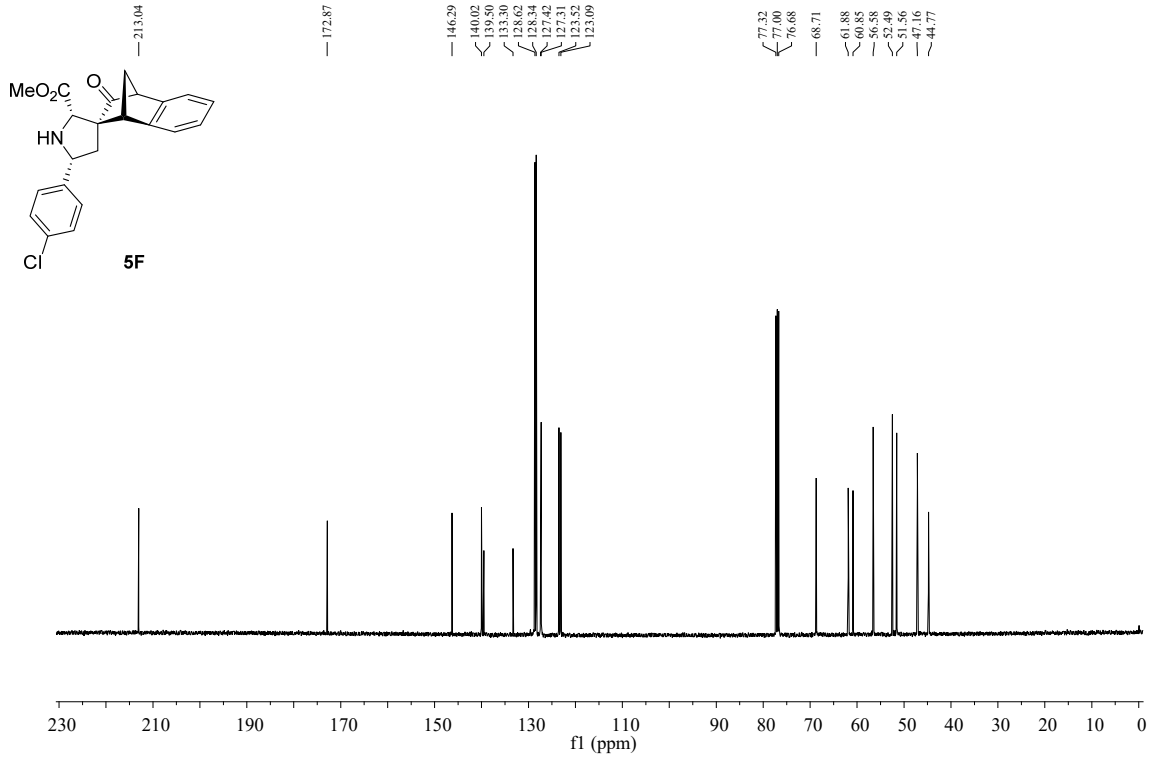
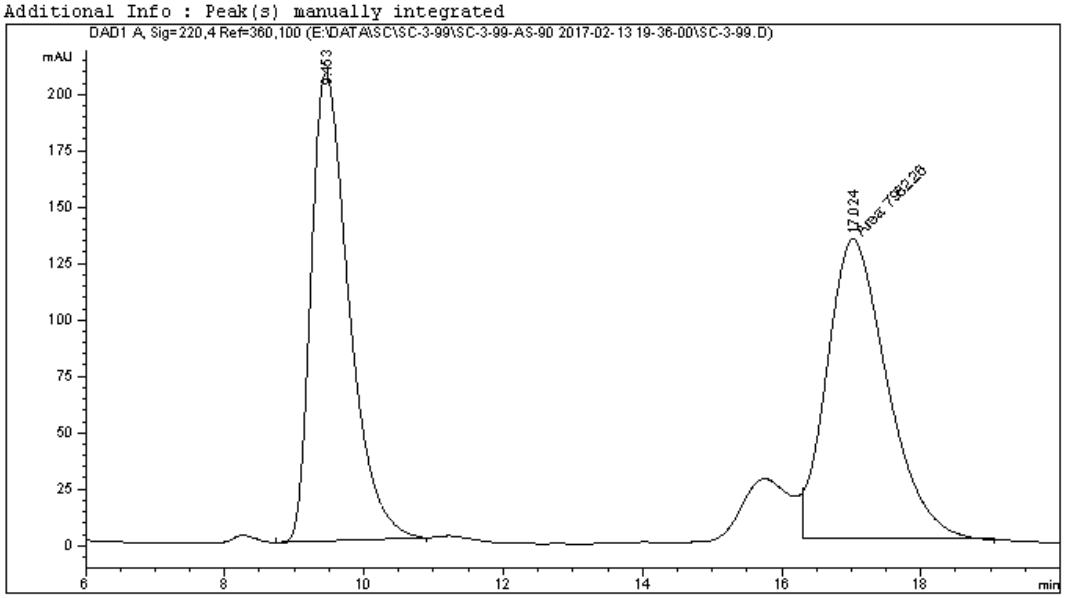


Figure S147. ^{13}C NMR spectrum of **5F**, related to **Table 3**.

Data File E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-3-99.D
Sample Name: SC-3-99

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   13
    Injection Date  : 2/13/2017 7:37:23 PM                 Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-1-ASH-90-10-DAD-1ML
                      .M
    Last changed    : 2/13/2017 7:36:00 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-1-ASH-90-10-DAD-1ML
                      .M (Sequence Method)
    Last changed    : 6/3/2017 8:10:42 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

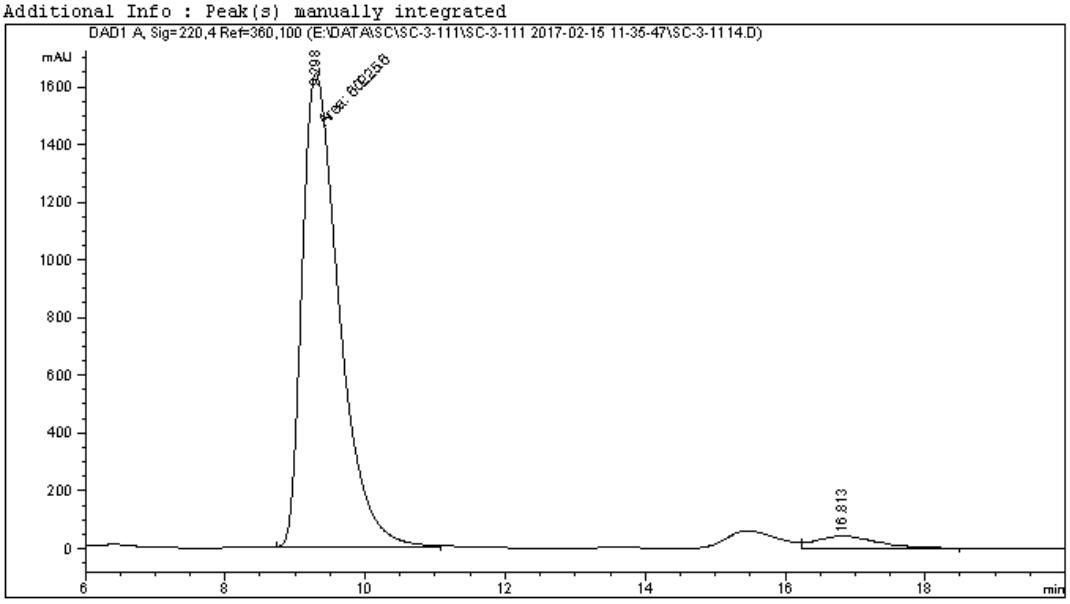

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1   9.453 BB    0.5783 7806.53467  207.34389  49.4435
       2  17.024 MM    1.0002 7982.25781  133.01588  50.5565

    Totals :                  1.57888e4   340.35977
```

Data File E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-3-1114.D
Sample Name: SC-3-111A-P

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   5
    Acq. Instrument : 1260                             Location :   37
    Injection Date  : 2/15/2017 12:57:05 PM                Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-2-ASH-90-10-220NM-25MIN
                      -1ML.M
    Last changed    : 2/15/2017 11:35:47 AM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-3-111\SC-3-111 2017-02-15 11-35-47\SC-2-ASH-90-10-220NM-25MIN
                      -1ML.M (Sequence Method)
    Last changed    : 6/3/2017 8:09:57 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

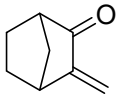
    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1   9.298 MM    0.6114 6.02256e4  1641.77576  96.0791
       2  16.813 VB    0.8640 2457.76025   40.84505   3.9209

    Totals :                  6.26833e4  1682.62081
```

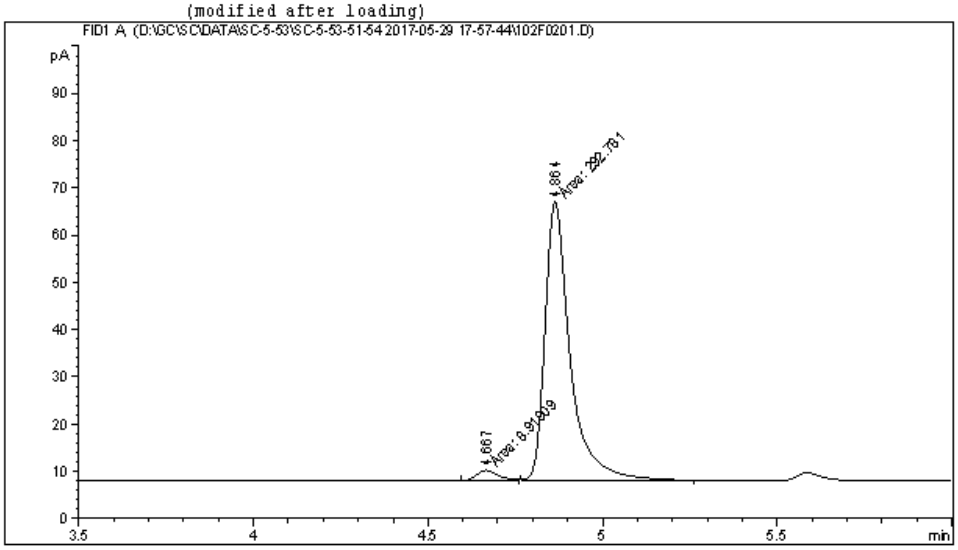

Figure S148. HPLC spectrum of **5F**, related to **Table 3**.



1a

Data File D:\GC\SC\DATA\SC-5-53\SC-5-53-51-54 2017-05-29 17-57-44\102F0201.D
Sample Name: SC-5-51

```
    ====================================================================
    Acq. Operator   : LHC                          Seq. Line :   2
    Acq. Instrument : Instrument 2                  Location : Vial 102
    Injection Date  : 29-May-17, 18:24:29              Inj :   1
                                                   Inj Volume : 1 µl
    Acq. Method     : D:\GC\SC\Data\SC-5-53\SC-5-53-51-54 2017-05-29 17-57-44\CS-1000-150C-1ML-
                      10MIN.M
    Last changed    : 5/22/2017 8:58:06 PM by dww
    Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
    Last changed    : 6/22/2017 10:33:36 AM by DWW
                      (modified after loading)
```




```
    ====================================================================
                            Area Percent Report
    ====================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1   4.667 MM    0.0698    8.91909    2.12853  2.95628
       2   4.864 MM    0.0830  292.78098   58.82206 97.04372

    Totals :                    301.70006   60.95059


    ====================================================================
                            *** End of Report ***
```


Figure S149. HPLC spectrum of **1a**, related to **Table 1**.

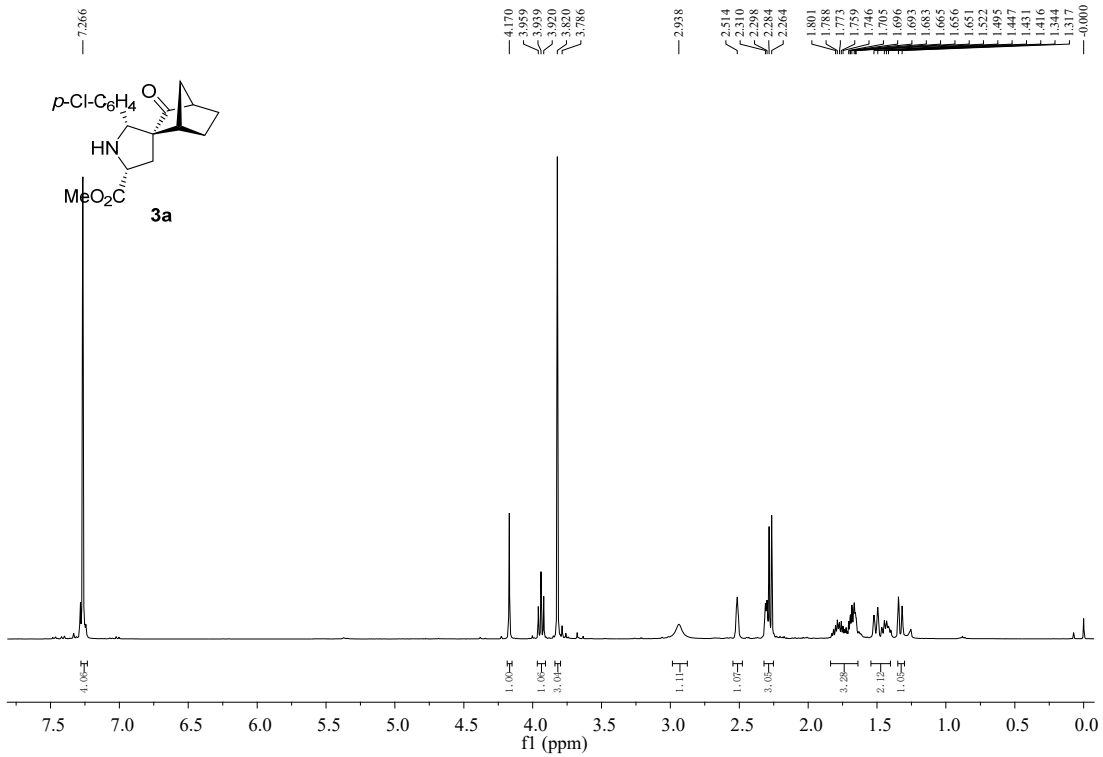


Figure S150. [1]H NMR spectrum of **3a,** related to **Table 1.**

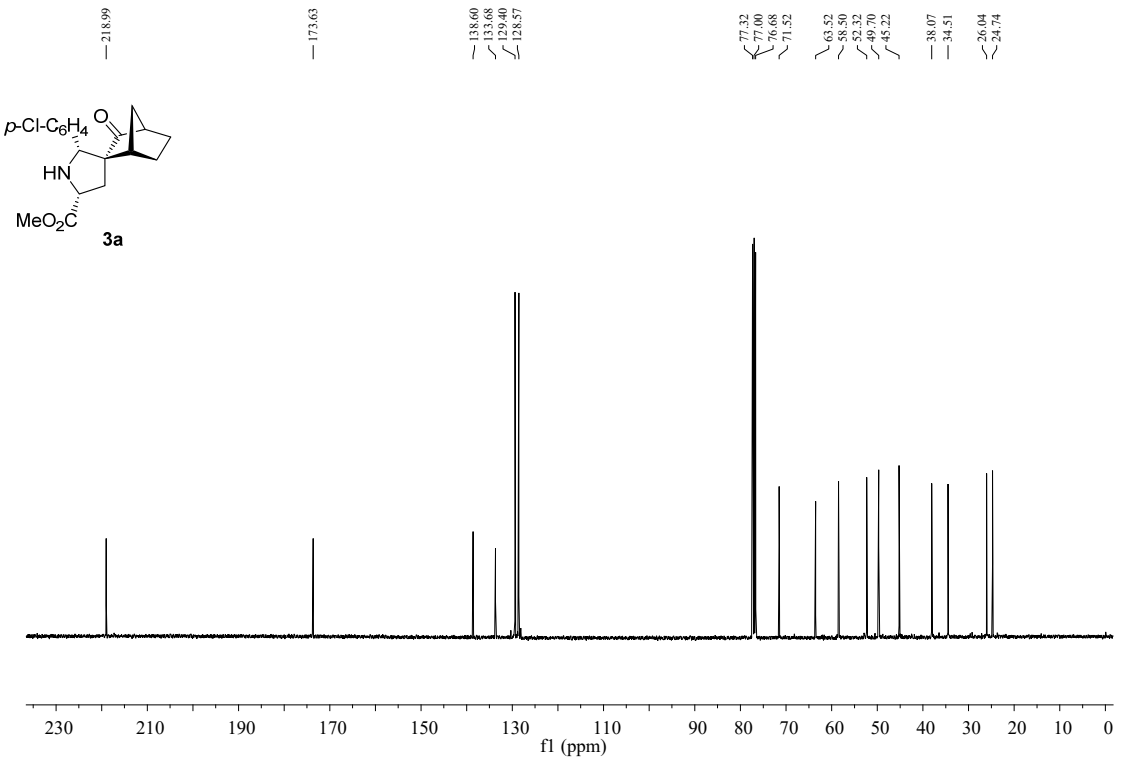
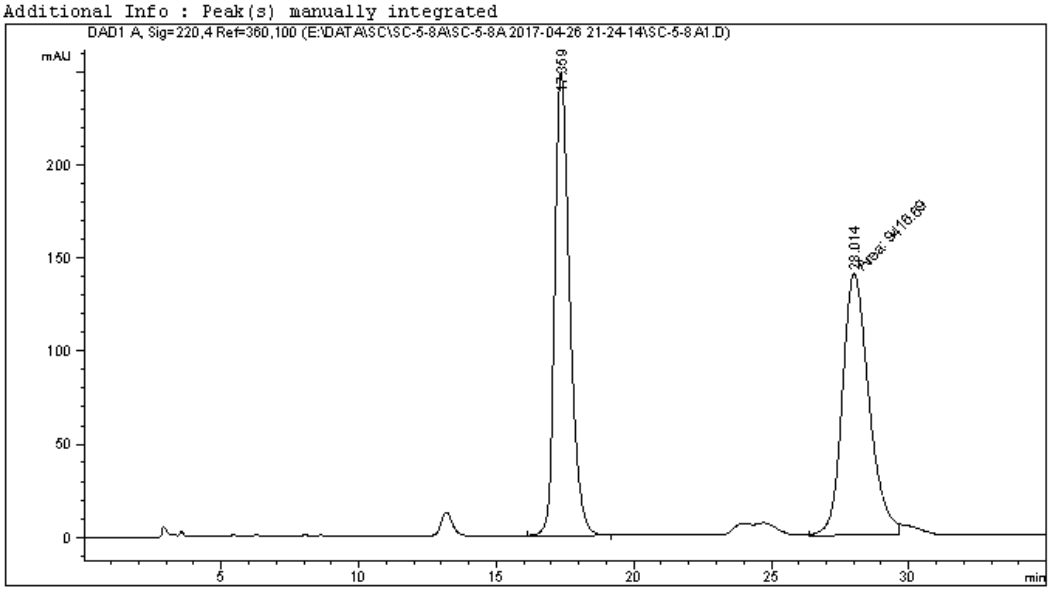


Figure S151. [13]C NMR spectrum of **3a,** related to **Table 1.**

Data File E:\DATA\SC\SC-5-8A\SC-5-8A 2017-04-26 21-24-14\SC-5-8A1.D
Sample Name: SC-5-8A

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                             Location :   31
Injection Date  : 4/26/2017 9:46:37 PM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-8A\SC-5-8A 2017-04-26 21-24-14\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M
Last changed    : 4/26/2017 9:24:14 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-8A\SC-5-8A 2017-04-26 21-24-14\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M (Sequence Method)
Last changed    : 7/18/2017 11:17:15 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

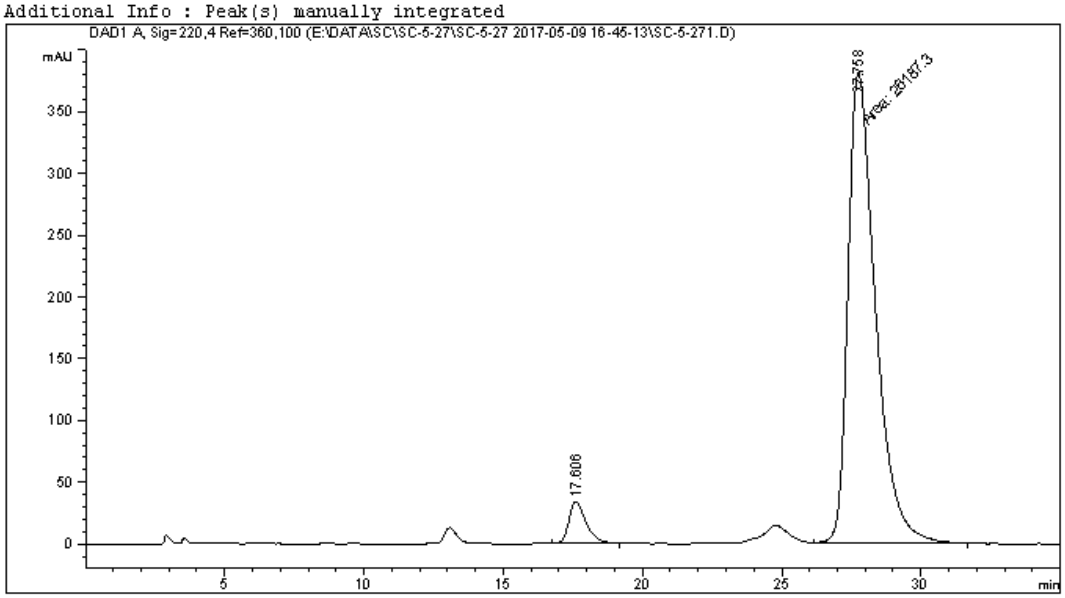

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  17.359 BB    0.5769 9443.14355  248.73465  50.0701
   2  28.014 MM    1.1189 9416.68848  140.26993  49.9299

Totals :                  1.88598e4   389.00458
```

Data File E:\DATA\SC\SC-5-27\SC-5-27 2017-05-09 16-45-13\SC-5-271.D
Sample Name: SC-5-27-1H

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : 1260                              Location :   14
Injection Date  : 5/9/2017 5:23:07 PM                   Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-27\SC-5-27 2017-05-09 16-45-13\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M
Last changed    : 5/9/2017 4:45:13 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-27\SC-5-27 2017-05-09 16-45-13\SC-2-ADH-90-10-220NM-35MIN-
                  1ML.M (Sequence Method)
Last changed    : 7/18/2017 11:18:05 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  17.606 BB    0.6115 1421.97327   33.54998   5.1503
   2  27.758 MM    1.1461 2.61873e4   380.80704  94.8497

Totals :                  2.76093e4   414.35702
```


Figure S152. HPLC spectrum of **3a**, related to **Table 1**.

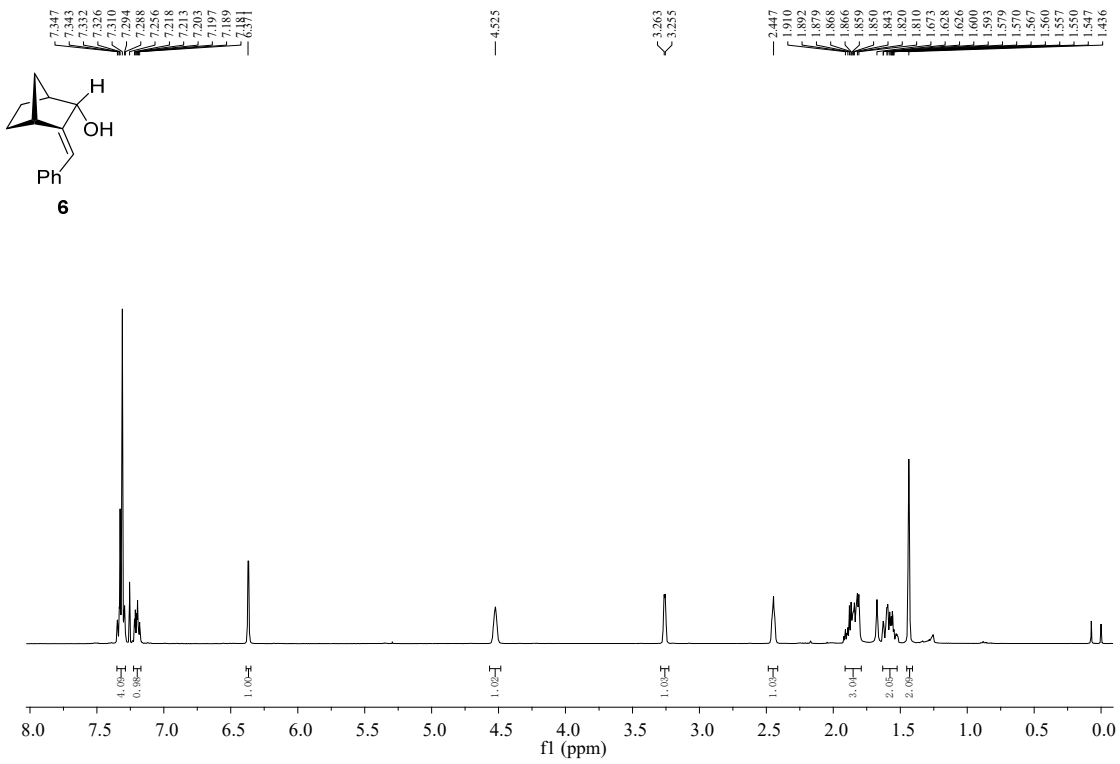


Figure S153. ^{1}H NMR spectrum of **6**, related to **Scheme 4**.

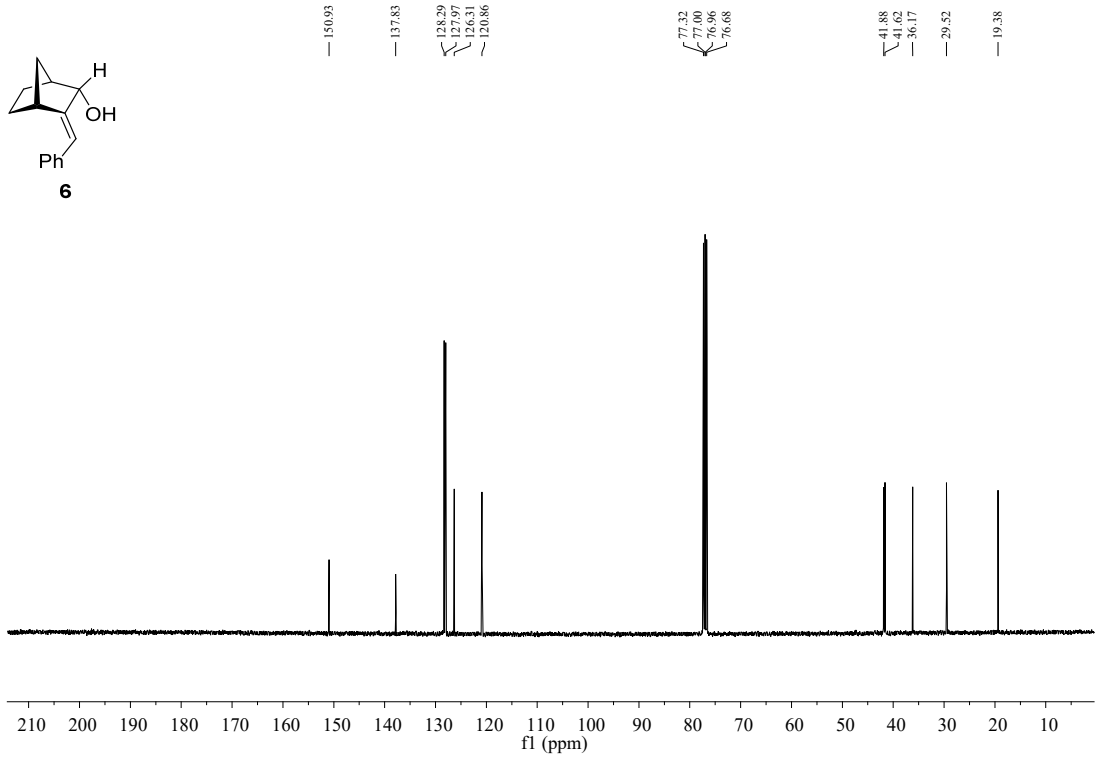
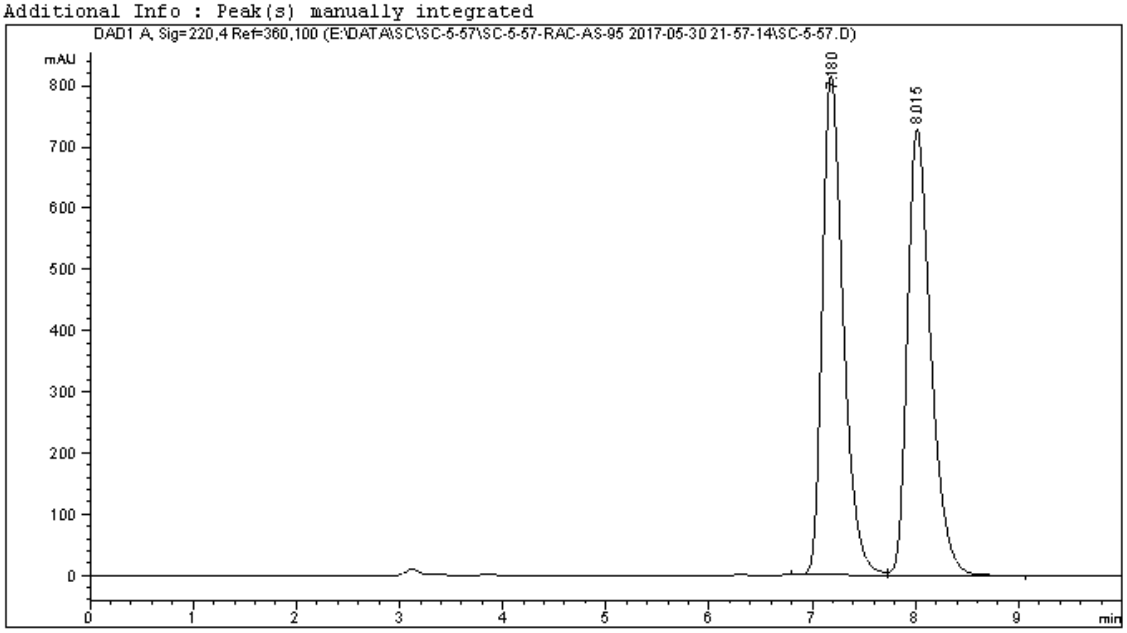


Figure S154. ^{13}C NMR spectrum of **6**, related to **Scheme 4**.

Data File E:\DATA\SC\SC-5-57\SC-5-57-RAC-AS-95 2017-05-30 21-57-14\SC-5-57.D
Sample Name: SC-5-57-RAC-AS-95

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : 1260                           Location :   11
Injection Date  : 5/30/2017 9:58:36 PM                Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-57\SC-5-57-RAC-AS-95 2017-05-30 21-57-14\SC-1-ASH-95-5-DAD-
                  1ML.M
Last changed    : 5/30/2017 9:57:14 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-57\SC-5-57-RAC-AS-95 2017-05-30 21-57-14\SC-1-ASH-95-5-DAD-
                  1ML.M (Sequence Method)
Last changed    : 6/22/2017 3:36:03 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

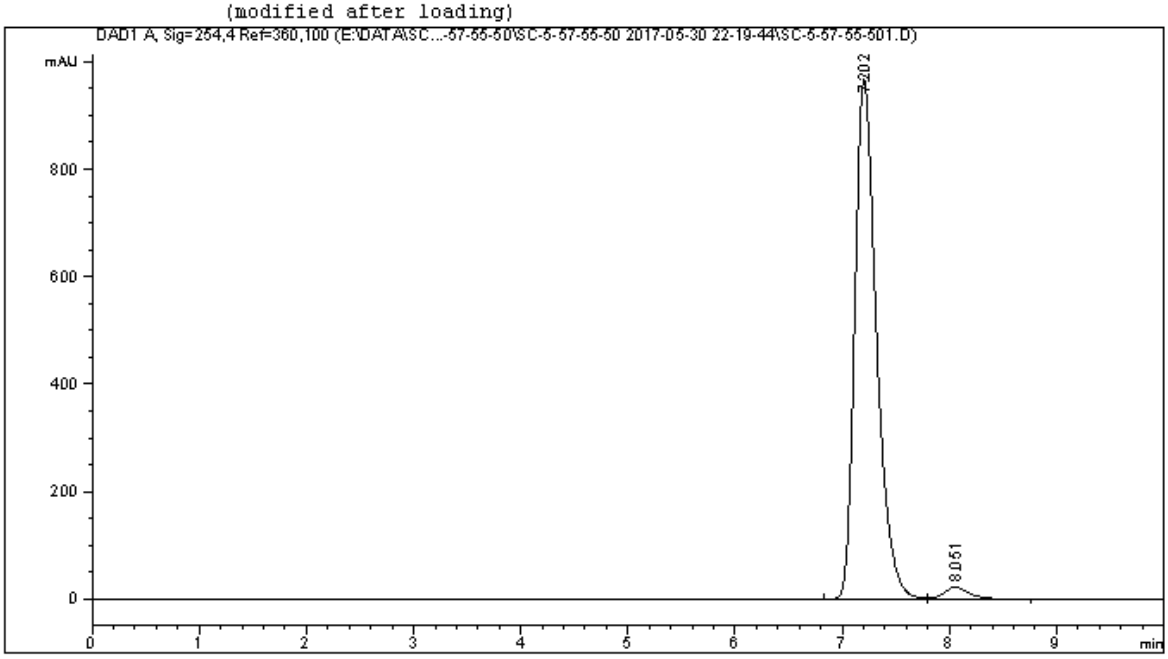

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.180 BV    0.2158 1.15081e4   814.45087  50.2217
   2   8.015 VB    0.2388 1.14065e4   728.02155  49.7783

Totals :                  2.29146e4  1542.47241
```

Data File E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-5-57-55-501.D
Sample Name: SC-5-57

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : 1260                          Location :   12
Injection Date  : 5/30/2017 10:37:03 PM              Inj :   1
                                               Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-1-ASH-95-5-
                  254NM-15MIN.M
Last changed    : 5/30/2017 10:19:44 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-1-ASH-95-5-
                  254NM-15MIN.M (Sequence Method)
Last changed    : 6/22/2017 3:37:49 PM by SYSTEM
                  (modified after loading)
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.202 BV    0.2123 1.35220e4   966.21387  97.5301
   2   8.051 VB    0.2349  342.43372   22.08290   2.4699

Totals :                  1.38644e4   988.29677
```


Figure S155. HPLC spectrum of **6,** related to **Scheme 4.**

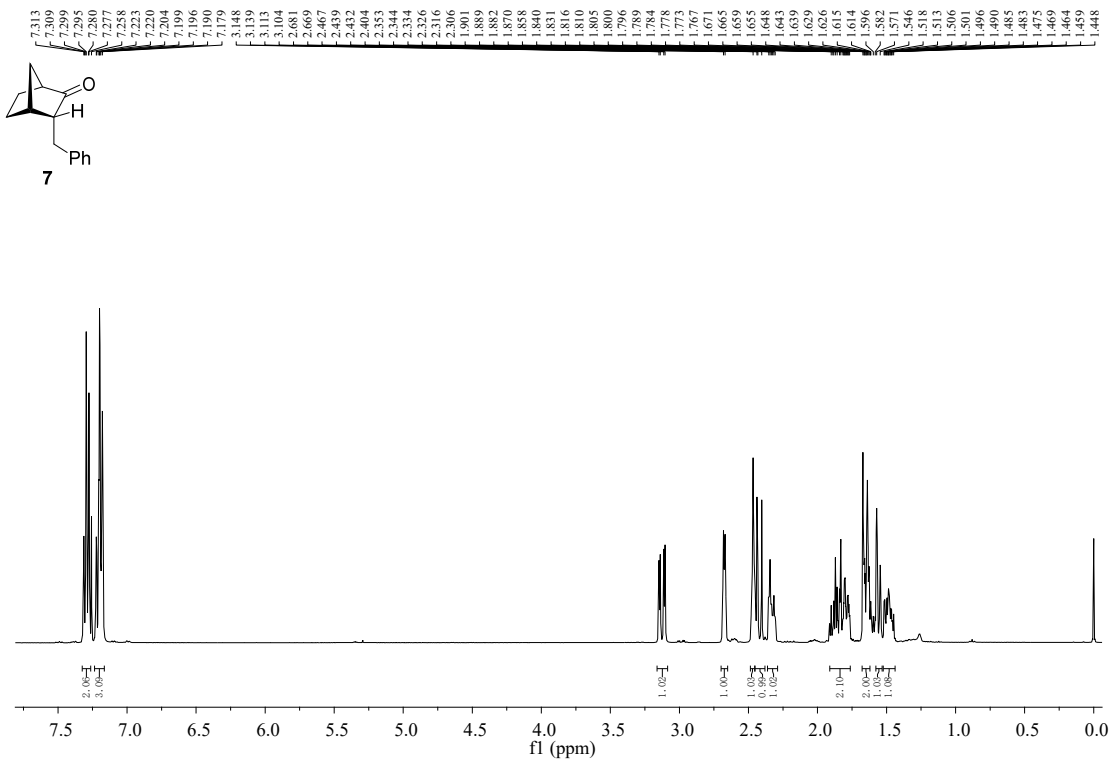


Figure S156. [1]H NMR spectrum of **7**, related to **Scheme 4**.

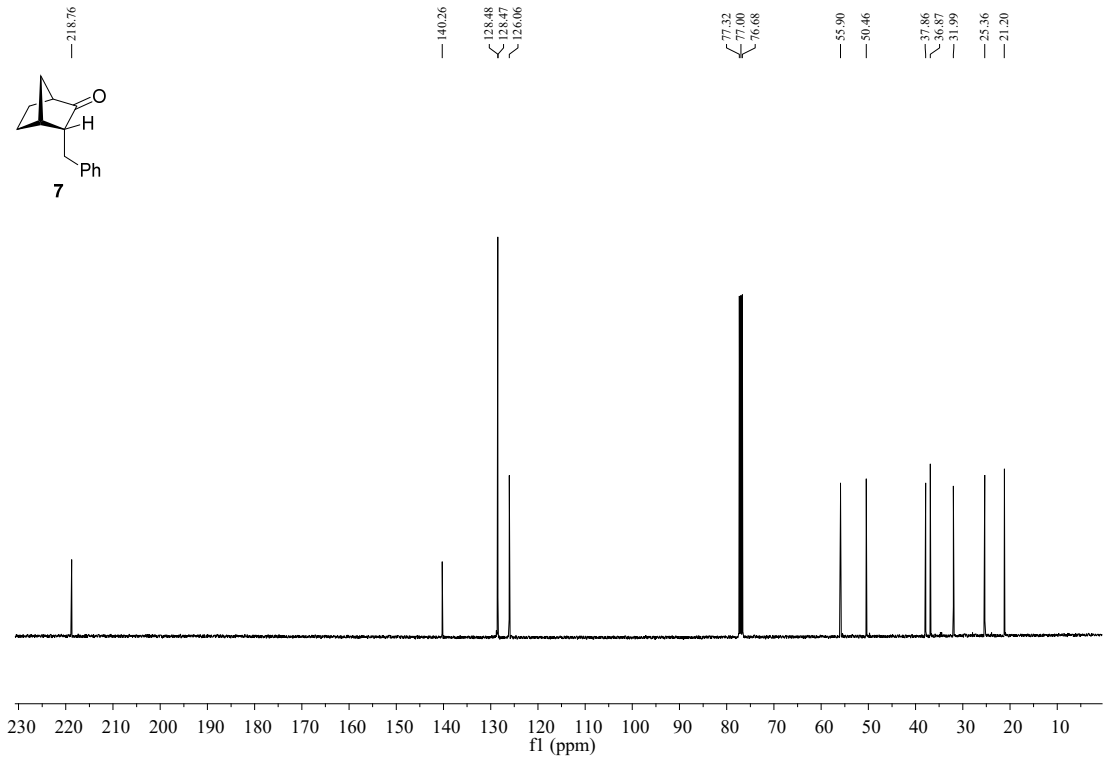
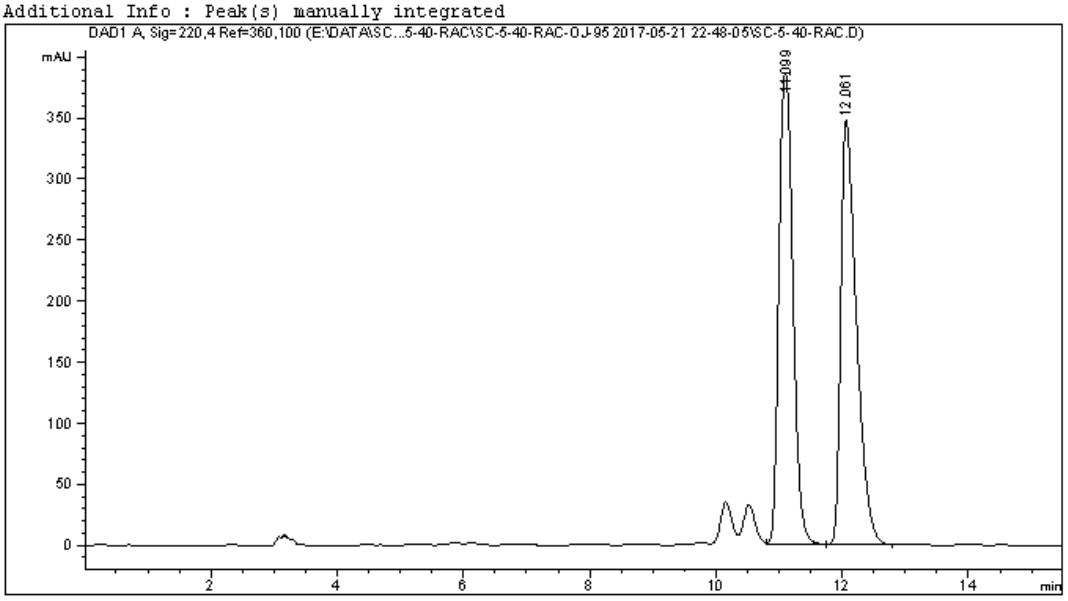


Figure S157. [13]C NMR spectrum of **7**, related to **Scheme 4**.

Data File E:\DATA\SC\SC-5-40-RAC\SC-5-40-RAC-0J-95 2017-05-21 22-48-05\SC-5-40-RAC.D
Sample Name: SC-5-40-RAC-0J-95

```
    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : 1260                             Location :   1
    Injection Date  : 5/21/2017 10:49:30 PM                 Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-5-40-RAC\SC-5-40-RAC-0J-95 2017-05-21 22-48-05\SC-5-0JH-95-5-
                      DAD-1ML-30MIN.M
    Last changed    : 5/21/2017 10:48:05 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-5-40-RAC\SC-5-40-RAC-0J-95 2017-05-21 22-48-05\SC-5-0JH-95-5-
                      DAD-1ML-30MIN.M (Sequence Method)
    Last changed    : 6/22/2017 3:32:17 PM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

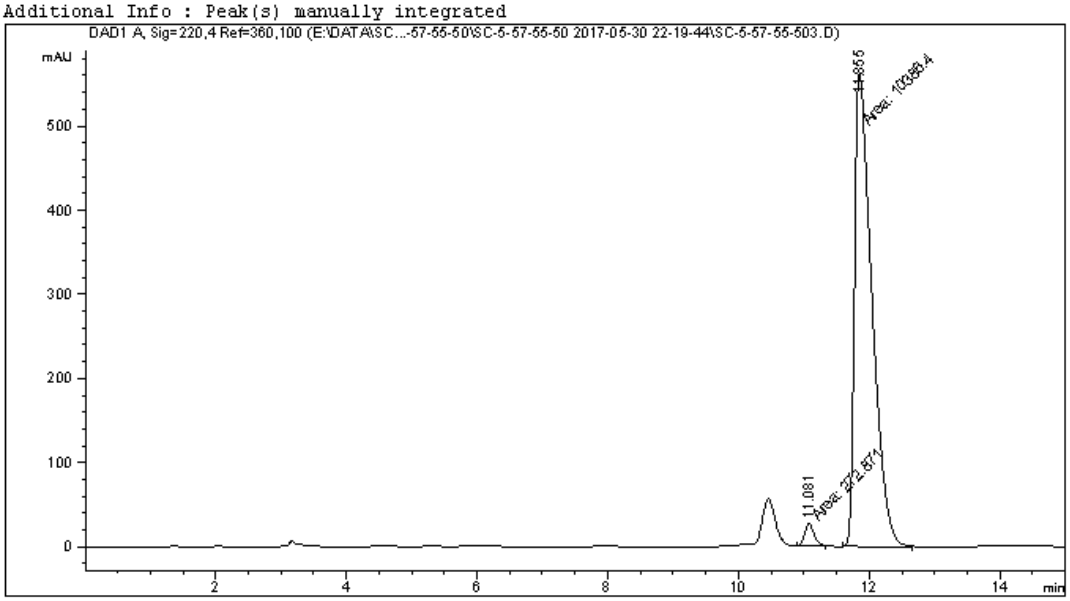

    Signal 1: DAD1 A, Sig=220,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.099 VB    0.2462 5968.00098  386.33896  49.9076
       2  12.061 BB    0.2611 5990.10400  347.58603  50.0924

    Totals :                  1.1958le4   733.92499
```

Data File E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-5-57-55-503.D
Sample Name: SC-5-55

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   4
Acq. Instrument : 1260                          Location :   13
Injection Date  : 5/30/2017 11:09:29 PM              Inj :   1
                                               Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-5-OJH-95-5-
                  220NM-1ML-15MIN.M
Last changed    : 5/30/2017 10:19:44 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-57-55-50\SC-5-57-55-50 2017-05-30 22-19-44\SC-5-OJH-95-5-
                  220NM-1ML-15MIN.M (Sequence Method)
Last changed    : 6/22/2017 3:33:11 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.081 MM    0.1702  272.87115   26.72730   2.5599
   2  11.855 MM    0.3079 1.03864e4   562.25043  97.4401

Totals :                  1.06593e4   588.97773
```


Figure S158. HPLC spectrum of **7**, related to **Scheme 4**.

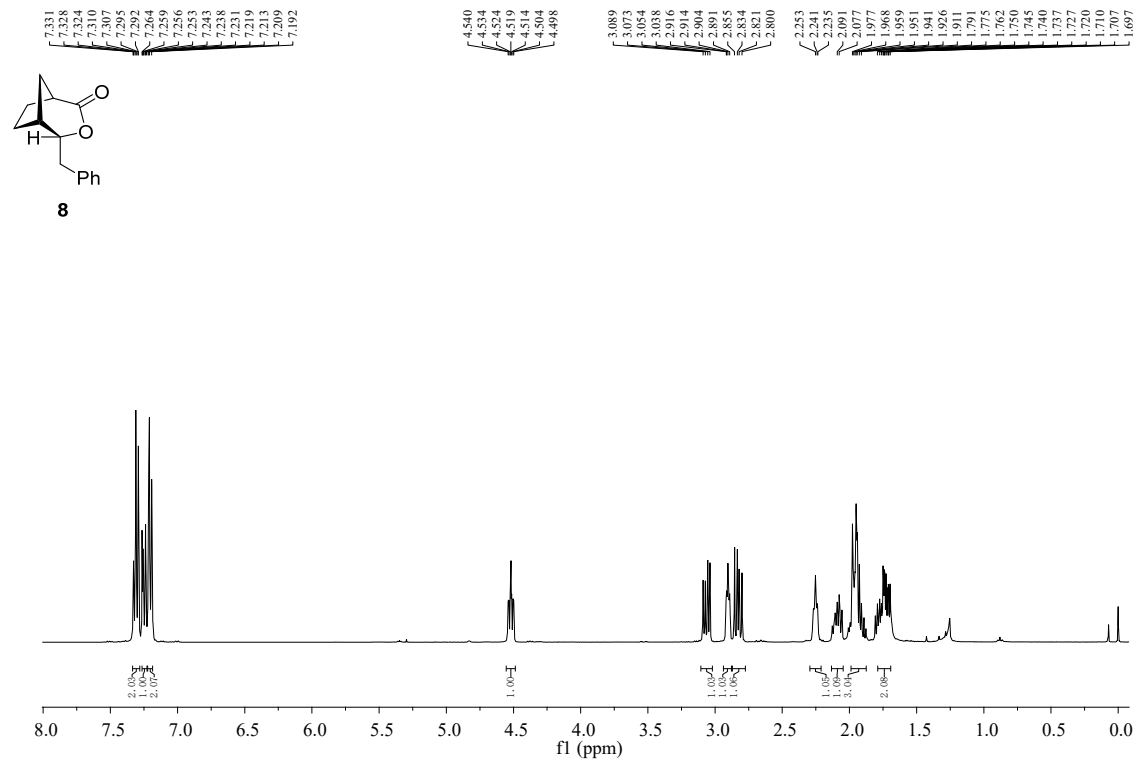


Figure S159. [1]H NMR spectrum of **8**, related to **Scheme 4**.

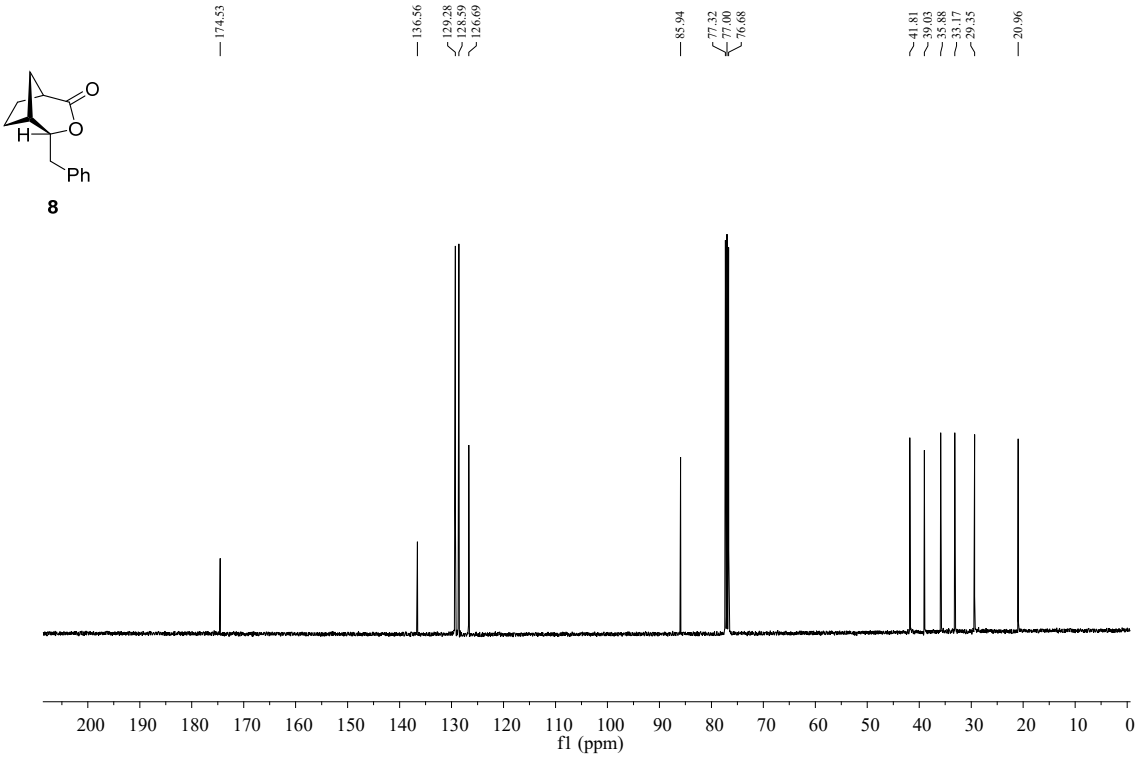


Figure S160. [1]H NMR spectrum of **8**, related to **Scheme 4**.

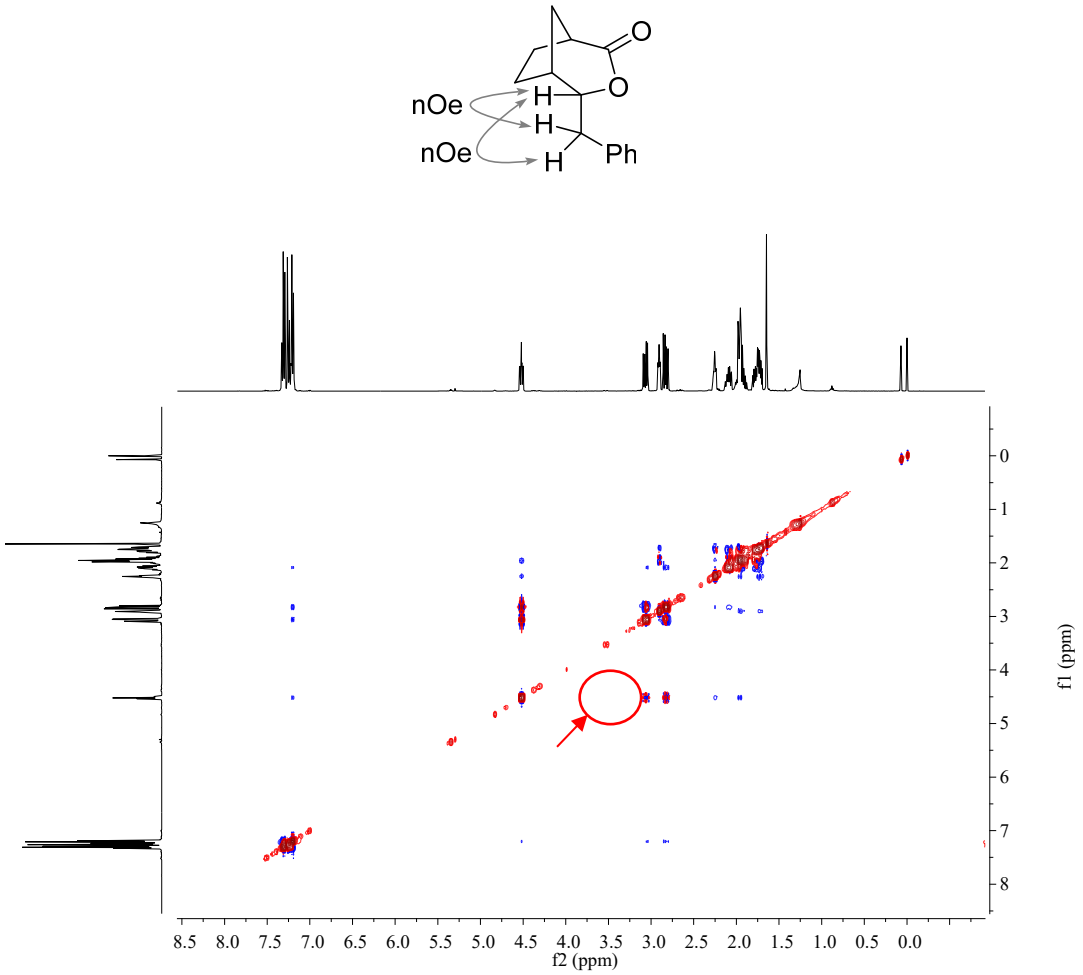
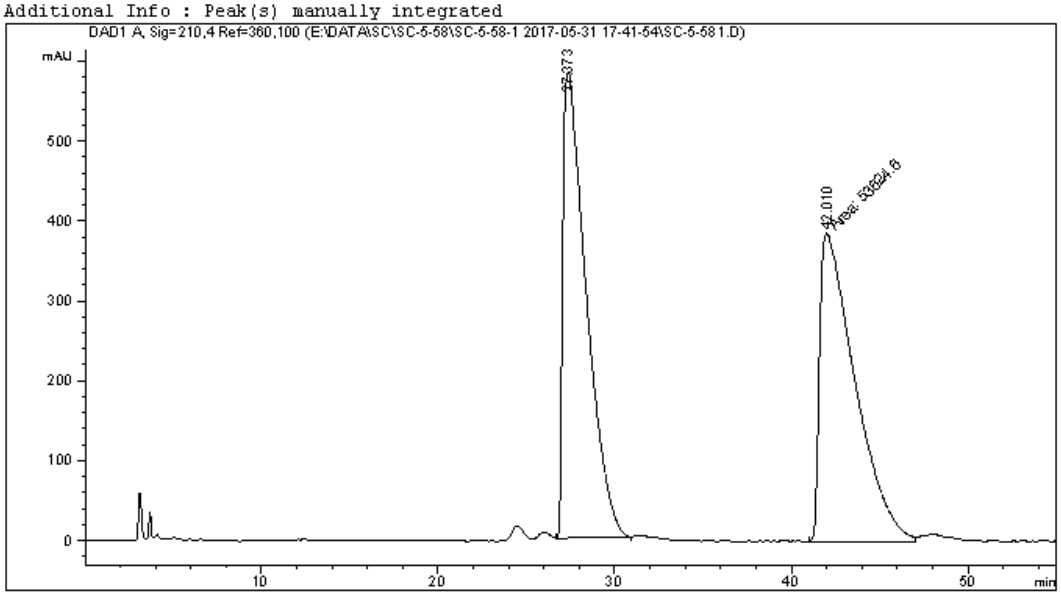


Figure S161. NOESY NMR spectrum of **8**, related to **Scheme 4**.

Data File E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-5-581.D
Sample Name: SC-5-58-RAC

```
    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :   2
    Acq. Instrument : 1260                           Location :   13
    Injection Date  : 5/31/2017 5:59:15 PM               Inj :   1
                                                  Inj Volume : 5.000 µl
    Acq. Method     : E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-1-ASH-90-10-210NM-55MIN
                      -1ML.M
    Last changed    : 5/31/2017 5:41:54 PM by SYSTEM
    Analysis Method : E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-1-ASH-90-10-210NM-55MIN
                      -1ML.M (Sequence Method)
    Last changed    : 6/22/2017 11:45:58 AM by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Do not use Multiplier & Dilution Factor with ISTDs

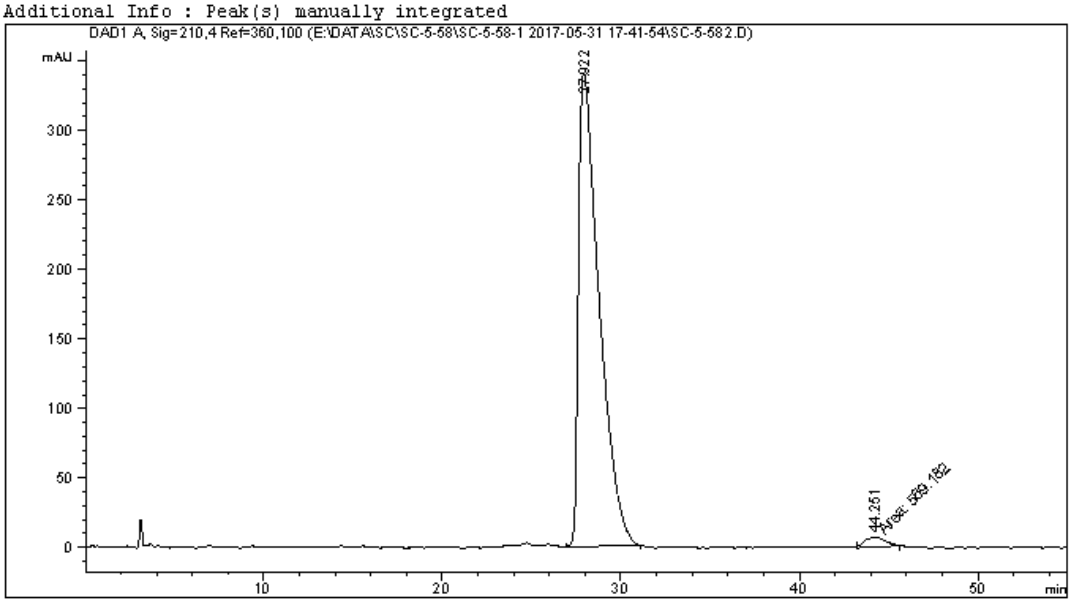

    Signal 1: DAD1 A, Sig=210,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  27.373 VB    1.2168 5.34075e4   583.53680  49.8986
       2  42.010 MM    2.3166 5.36246e4   385.80280  50.1014

    Totals :                  1.07032e5   969.33960
```

Data File E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-5-582.D
Sample Name: SC-5-58

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : 1260                           Location :   14
Injection Date  : 5/31/2017 6:55:38 PM               Inj :   1
                                                Inj Volume : 5.000 µl
Acq. Method     : E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-1-ASH-90-10-210NM-55MIN
                  -1ML.M
Last changed    : 5/31/2017 5:41:54 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-58\SC-5-58-1 2017-05-31 17-41-54\SC-1-ASH-90-10-210NM-55MIN
                  -1ML.M (Sequence Method)
Last changed    : 6/22/2017 11:45:58 AM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.922 BB    1.0707 2.74461e4   340.02341  97.9683
   2  44.251 MM    1.3646  569.18195    6.95169   2.0317

Totals :                  2.80152e4   346.97510
```


Figure S162. HPLC spectrum of **8**, related to **Scheme 4**.

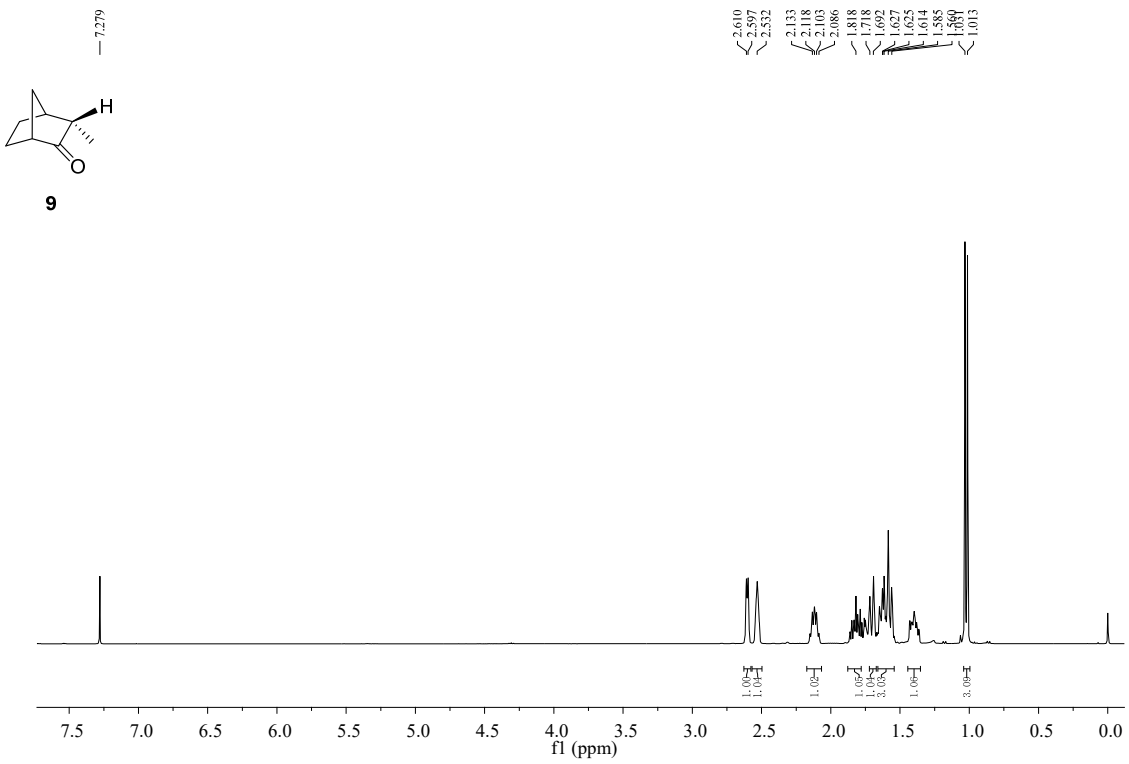


Figure S163. [1]H NMR spectrum of **9**, related to **Scheme 4**.

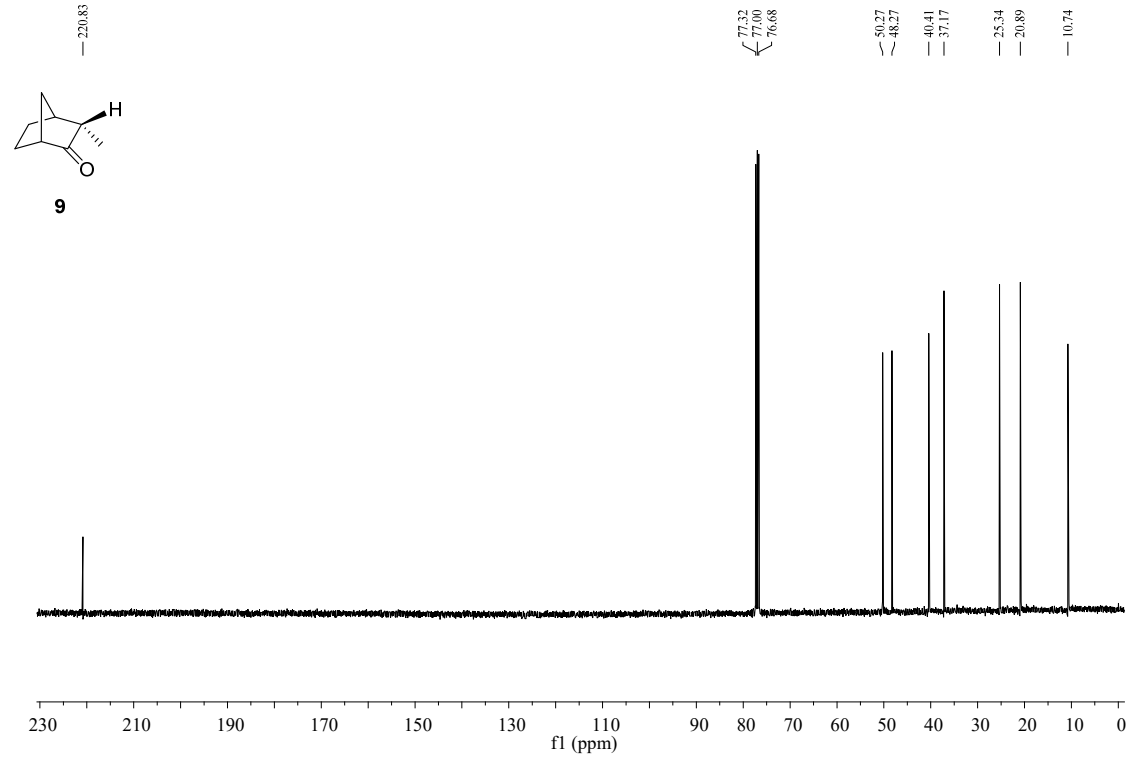
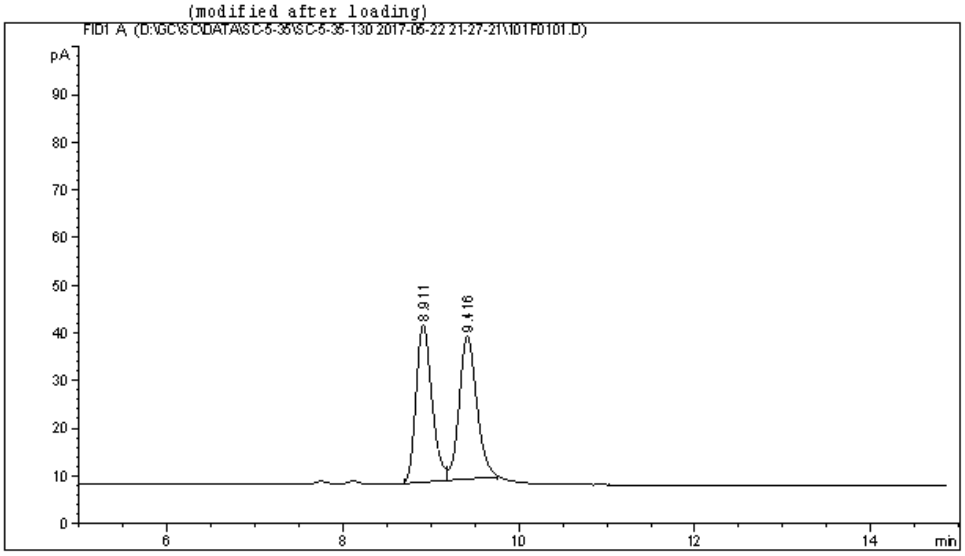


Figure S164. [13]C NMR spectrum of **9**, related to **Scheme 4**.

Data File D:\GC\SC\DATA\SC-5-35\SC-5-35-130 2017-05-22 21-27-21\101F0101.D
Sample Name: SC-5-35

```
======================================================================
Acq. Operator   : dww                          Seq. Line :   1
Acq. Instrument : Instrument 2                  Location : Vial 101
Injection Date  : 22-May-17, 21:28:10                Inj :   1
                                               Inj Volume : 1 µl
Acq. Method     : D:\GC\SC\Data\SC-5-35\SC-5-35-130 2017-05-22 21-27-21\CS-1000-130C-1ML.M
Last changed    : 5/22/2017 9:24:18 PM by dww
Analysis Method : D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M
Last changed    : 6/22/2017 10:14:52 AM by DWW
                  (modified after loading)
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

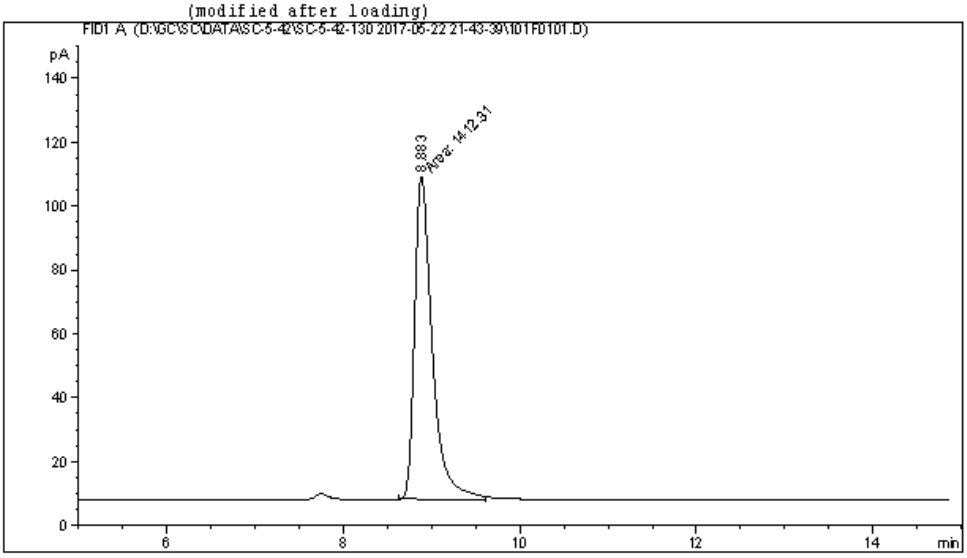
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   8.911 BV    0.1681  415.17255   32.92714 50.00257
   2   9.416 VB    0.1926  415.12982   29.97781 49.99743

Totals :                   830.30237   62.90495


======================================================================
                          *** End of Report ***
```

Data File D:\GC\SC\DATA\SC-5-42\SC-5-42-130 2017-05-22 21-43-39\101F0101.D
Sample Name: SC-5-42

Acq. Operator	: dww	Seq. Line	: 1
Acq. Instrument	: Instrument 2	Location	: Vial 101
Injection Date	: 22-May-17, 21:44:29	Inj	: 1
		Inj Volume	: 1 µl
Acq. Method	: D:\GC\SC\Data\SC-5-42\SC-5-42-130 2017-05-22 21-43-39\CS-1000-130C-1ML.M		
Last changed	: 5/22/2017 9:24:18 PM by dww		
Analysis Method	: D:\GC\CX\METHOD\CS-1000-180C-1ML-1.M		
Last changed	: 6/22/2017 10:16:52 AM by DWW (modified after loading)		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	8.883	MM	0.2328	1412.30896	101.12673	1.000e2
Totals :				1412.30896	101.12673	

*** End of Report ***

Figure S165. HPLC spectrum of **9**, related to **Scheme 4**.

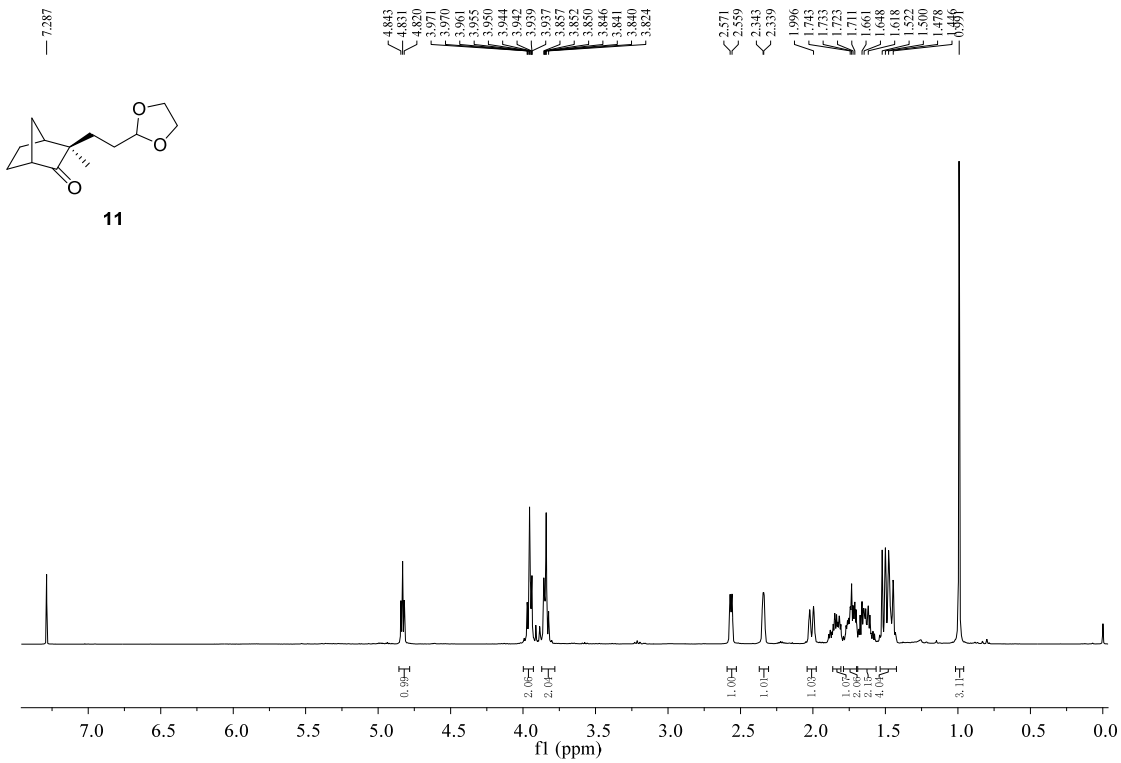


Figure S166. [1]H NMR spectrum of **11**, related to **Scheme 4**.

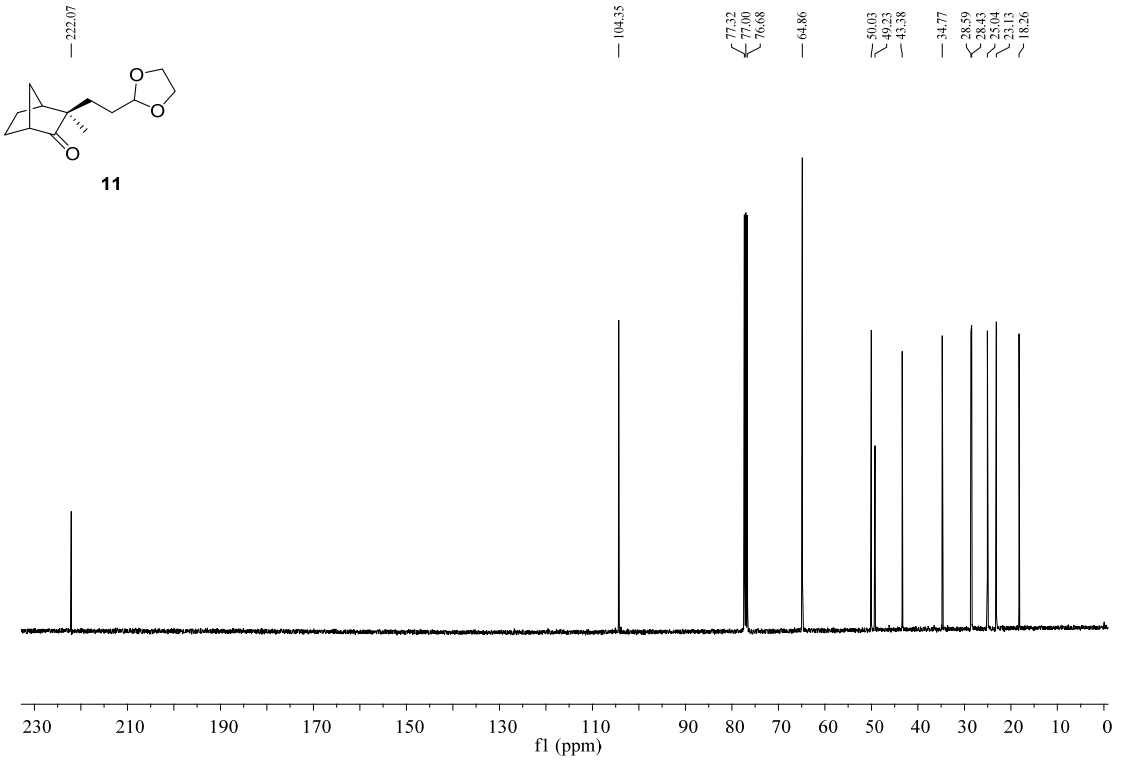
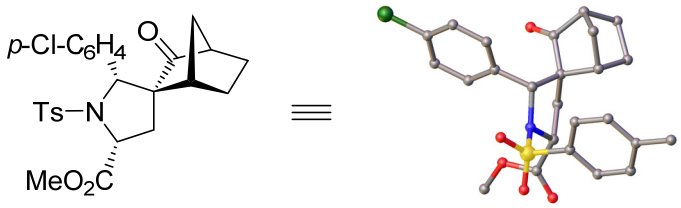


Figure S167. [13]C NMR spectrum of **11**, related to **Scheme 4**.

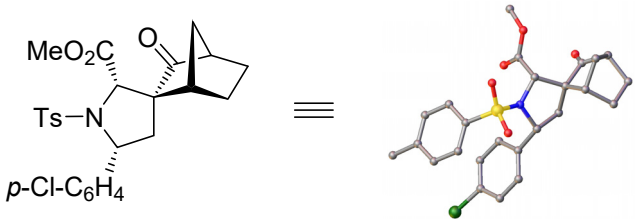
Supplemental Figures for X-ray Structures of the Tosylated Cycloadduct (±)-3a, Tosylated Cycloadduct (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5a, Cycloadduct (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5b, Tosylated (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*)-5s, Cycloadduct (±)-5u and Alkylidene Norcamphor (±)-1d



tosylated (±)-*endo*-**3a** (CCDC 1562399)

Figure S168. X-ray structure of tosylated (±)-**3a**
(Hydrogen atoms were deleted for clarity), related to **Scheme 1.**

Crystal data for tosylated (±)-**3a**: $C_{25}H_{26}ClNO_5S$, $M_r = 487.98$, $T = 296$ K, Monoclinic, space group $P2(1)/n$, $a = 10.1095(14)$, $b = 13.7964(19)$, $c = 17.127(2)$ Å, $V = 2338.0(6)$ Å^3, $Z = 4$, 4613 unique reflections, final $R_1 = 0.0390$ and $wR_2 = 0.1074$ for 5863 observed [$I>2\sigma(I)$] reflections. CCDC 1562399 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

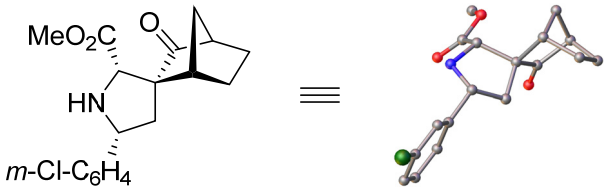


tosylated *endo'*-**5a** (CCDC 1562400)

Figure S169. X-ray structure of tosylated (1*S*,2*S*,2'*S*,4*R*,5'*R*)-**5a**
(Hydrogen atoms were deleted for clarity), related to **Scheme 1.**

Crystal data for tosylated (1*S*,2*S*,2'*S*,4*R*,5'*R*)-**5a**: $2(C_{25}H_{26}ClNO_5S)$, $M_r = 975.95$, $T = 293$ K, Triclinic, space group $P1$, $a = 7.2009(8)$, $b = 7.6006(9)$, $c = 22.280(3)$ Å, $V = 1212.4(3)$ Å^3, $Z = 1$, 6117 unique reflections, final $R_1 = 0.0428$ and $wR_2 = 0.1041$ for 7406 observed [$I>2\sigma(I)$] reflections, Flack $\chi = 0.04(3)$. CCDC 1562400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union

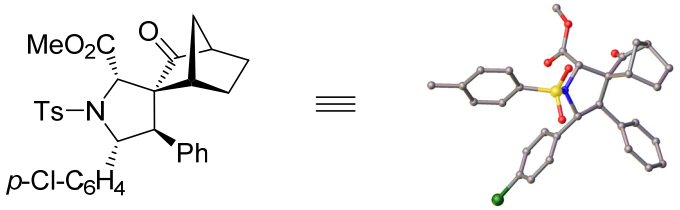
Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



(1*S*,2*S*,2'*S*,4*R*,5'*R*)-**5b** (CCDC 1562402)

Figure S170. X-ray structure of (1*S*,2*S*,2'*S*,4*R*,5'*R*)-**5b**
(Hydrogen atoms were deleted for clarity), related to **Table 2.**

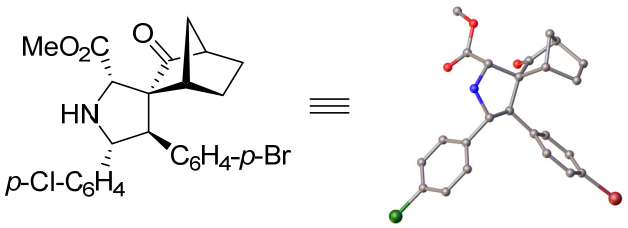
Crystal data for (1*S*,2*S*,2'*S*,4*R*,5'*R*)-**5b**: $C_{18}H_{20}ClNO_3$, M_r = 333.80, T = 296 K, Orthorhombic, space group $P2(1)2(1)2(1)$, a = 6.7241(16), b = 6.8383(16), c = 35.075(8) Å, V = 1612.8(7) Å^3, Z = 4, 3043 unique reflections, final R_1 = 0.0430 and wR_2 = 0.1098 for 4003 observed [I>2σ(I)] reflections, Flack χ = -0.01(4). CCDC 1562402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



(1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*)-**5s** (CCDC 1562404)

Figure S171. X-ray structure of tosylated (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*)-**5s**
(Hydrogen atoms were deleted for clarity), related to **Table 3.**

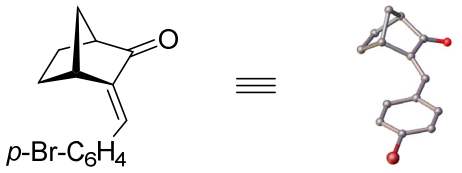
Crystal data for tosylated (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*)-**5s**: $C_{31}H_{30}ClNO_5S$, M_r = 564.07, T = 296 K, Orthorhombic, space group $P2(1)2(1)2(1)$, a = 9.509(3), b = 10.371(3), c = 27.390(7) Å, V = 2701.0(12) Å^3, Z = 4, 6637 unique reflections, final R_1 = 0.0317 and wR_2 = 0.0855 for 6911 observed [I>2σ(I)] reflections, Flack χ = 0.004(11). CCDC 1562404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



(±)-**5u** (CCDC 1562405)

Figure S172. X-ray structure of (±)-**5u**
(Hydrogen atoms were deleted for clarity), related to **Table 3.**

Crystal data for (±)-**5u**: $C_{24}H_{23}BrClNO_3$, M_r = 488.79, T = 293 K, Hexagonal, space group R-3, a = 19.3385(9), b = 19.3385(9), c = 30.7638(12) Å, V = 9963.6(8) Å^3, Z = 18, 2697 unique reflections, final R_1 = 0.0484 and wR_2 = 0.1373 for 5510 observed [I>2σ(I)] reflections. CCDC 1562405 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



(±)-**1d** (CCDC 1562406)

Figure S173. X-ray structure of (±)-**1d**
(Hydrogen atoms were deleted for clarity)**,** related to **Table 3.**

Crystal data for (±)-**1d**: $C_{14}H_{13}BrO$, M_r = 277.15, T = 293 K, Triclinic, space group P-1, a = 6.4885(14), b = 9.451(2), c = 10.440(2) Å, V = 600.7(2) Å^3, Z = 2, 1874 unique reflections, final R_1 = 0.0376 and wR_2 = 0.0904 for 2960 observed [I>2σ(I)] reflections. CCDC 1562406 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Computational Details

Density functional theory (DFT) calculations were carried out to understand the regioselectivity and key kinetic resolution of the ligand-controlled umpolung-type 1,3-dipolar cycloaddition. B3LYP (Becke, 1993; Lee et al., 1988; Stephens et al., 1994) method combined with a mixed basis set of SDD (Dolg et al., 1987) for Cu and 6-31G(d) (Ditchfield et al., 1971; Hehre et al., 1972; Hariharan and Pople, 1973) for the other atoms were used to optimize all the structures in gas phase. Such method was used to study the related Cu-catalyzed 1,3-dipolar cycloaddition (Wang et al., 2012). The effect of the solvent in DCM was then included by single-point calculation with the polarizable continuum model (PCM) (Tomasi et al., 2005; Scalmani and Frisch, 2010) using UAKS radii and including effects of solute-solvent dispersion interaction energy, solute-solvent repulsion interaction energy and solute cavitation energy. The electron distribution, in terms of natural population analysis (NPA) charges, for the two reacting carbon atoms of the complexes with $\mathbf{L1_D}$, $\mathbf{L5_D}$, $\mathbf{L1_U}$ and $\mathbf{L5_U}$ were calculated. All calculations were carried out by Gaussian 09 package (Gaussian 09, Revision D.01, 2009). All 3D images of the optimized structures were illustrated by CYLview (CYL View, version 1.0 b, 2009).

Table S1. The overall free-energy barrier (in kcal/mol) for the formation of several possible products from the reaction with **1a**-(1*R*,4*S*) and **1a**-(1*S*,4*R*) catalyzed by Cu(I)-**LI** in DCM solution by the PCM-B3LYP//B3LYP method, related to **Scheme 2** and **Scheme 3**.

Product[a]	ΔG_{soln}
$L1_D$[a]	
(1S,2S,2'R,4R,5'R)-3a	**16.4**
(1R,2R,2'S,4S,5'S)-3a'	**18.5**
(1S,2S,2'S,4R,5'S)-4a	25.6
(1R,2R,2'R,4S,5'R)-4a'	27.0
(1S,2S,2'S,4R,5'R)-5a	**19.4**
(1R,2R,2'R,4S,5'S)-5a'	20.4
(1S,2S,2'R,4R,5'S)-6a	28.9
(1R,2R,2'S,4S,5'R)-6a'	28.9
(1S,2R,2'S,4R,5'S)-7a	20.0
(1R,2S,2'R,4S,5'R)-7a'	19.5
(1S,2R,2'R,4R,5'R)-8a	28.0
(1R,2S,2'S,4S,5'S)-8a'	28.6
(1S,2R,2'R,4R,5'S)-9a	23.2
(1R,2S,2'S,4S,5'R)-9a'	21.6
(1S,2R,2'S,4R,5'R)-10a	30.4
(1R,2S,2'R,4S,5'S)-10a'	29.0
$L1_U$[a]	
(1S,2S,2'R,4R,5'R)-3a	22.7
(1R,2R,2'S,4S,5'S)-3a'	22.8
(1S,2S,2'S,4R,5'R)-5a	19.7
(1R,2R,2'R,4S,5'S)-5a'	28.9
(1S,2R,2'S,4R,5'S)-7a	23.3
(1R,2S,2'R,4S,5'R)-7a'	28.5

a. The two coordination modes of Ar in the Cu-azomethine ylide intermediates (**$L1_D$** and **$L1_U$**) were considered (D: Ar downward; U: Ar upward).

Table S2. The overall free-energy barrier (in kcal/mol) for the formation of the most important products from the reaction with **1a**-(1R,4S) and **1a**-(1S,4R) catalyzed by Cu(I)-**L5$_D$** in DCM solution by the PCM-B3LYP//B3LYP method, related to **Scheme 3**.

Product	ΔG_{soln}
L5$_D$[a]	
(1S,2S,2'R,4R,5'R)-3a	**18.9**
(1S,2S,2'S,4R,5'R)-5a	**18.0**
(1R,2R,2'R,4S,5'S)-5a′	**19.2**
L5$_U$[a]	
(1S,2S,2'R,4R,5'R)-3a	29.3
(1S,2S,2'S,4R,5'R)-5a	22.3
(1R,2R,2'R,4S,5'S)-5a′	25.9

a. The two coordination modes of Ar in the Cu-azomethine ylide intermediates (**L1$_D$** and **L1$_U$**) were considered (D: Ar downward; U: Ar upward).

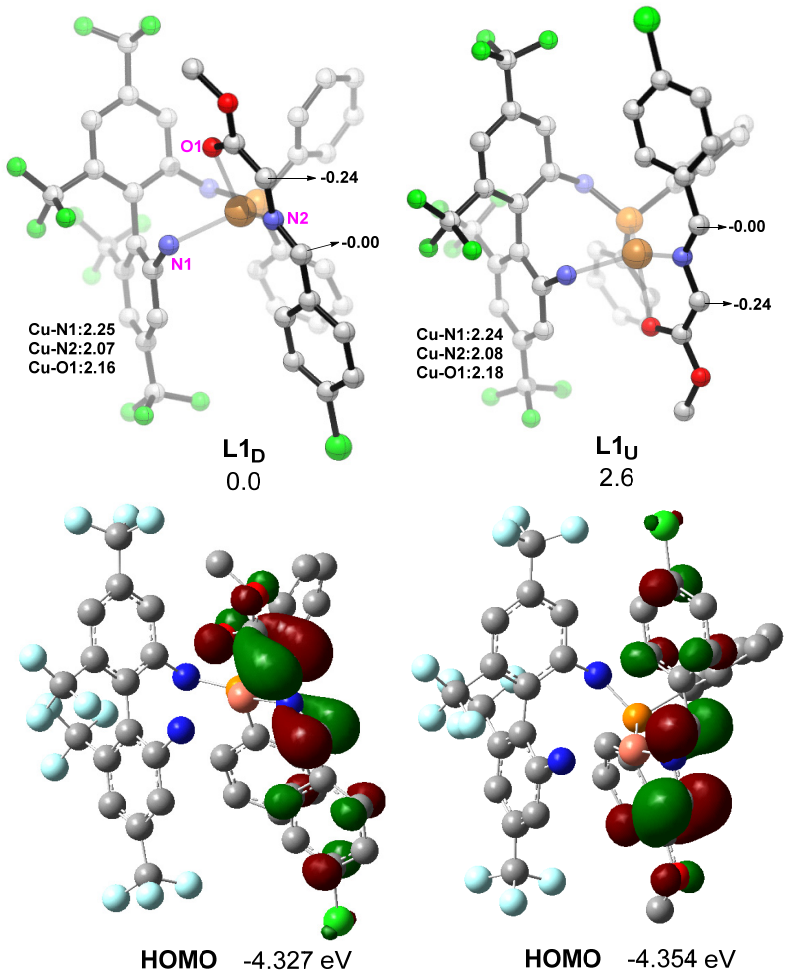


Figure S174. Optimized structures of Cu(I)-**LI** intermediates (**L1$_D$** and **L1$_U$**) with the key bond lengths (in angstrom), the NPA charge of the two reacting carbons and HOMO energies by the B3LYP method. Their relative free energies (in kcal/mol) in DCM solution are given. All hydrogen atoms were omitted for clarification, related to **Scheme 2** and **Figure 2**.

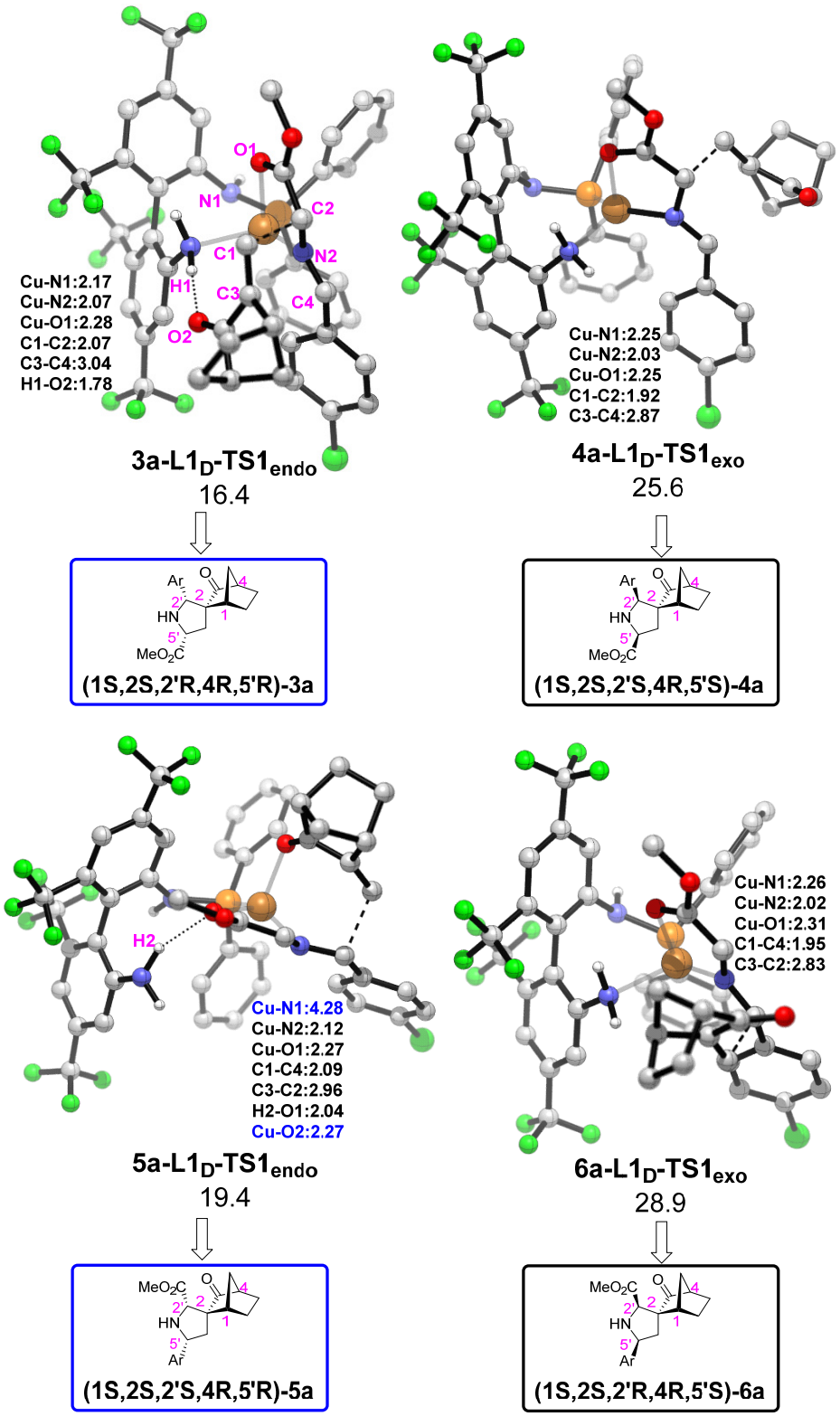


Figure S175. Optimized transition states for the reaction with **1a**-(1R,4S) catalyzed by $\mathbf{L1_D}$ in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 2**.

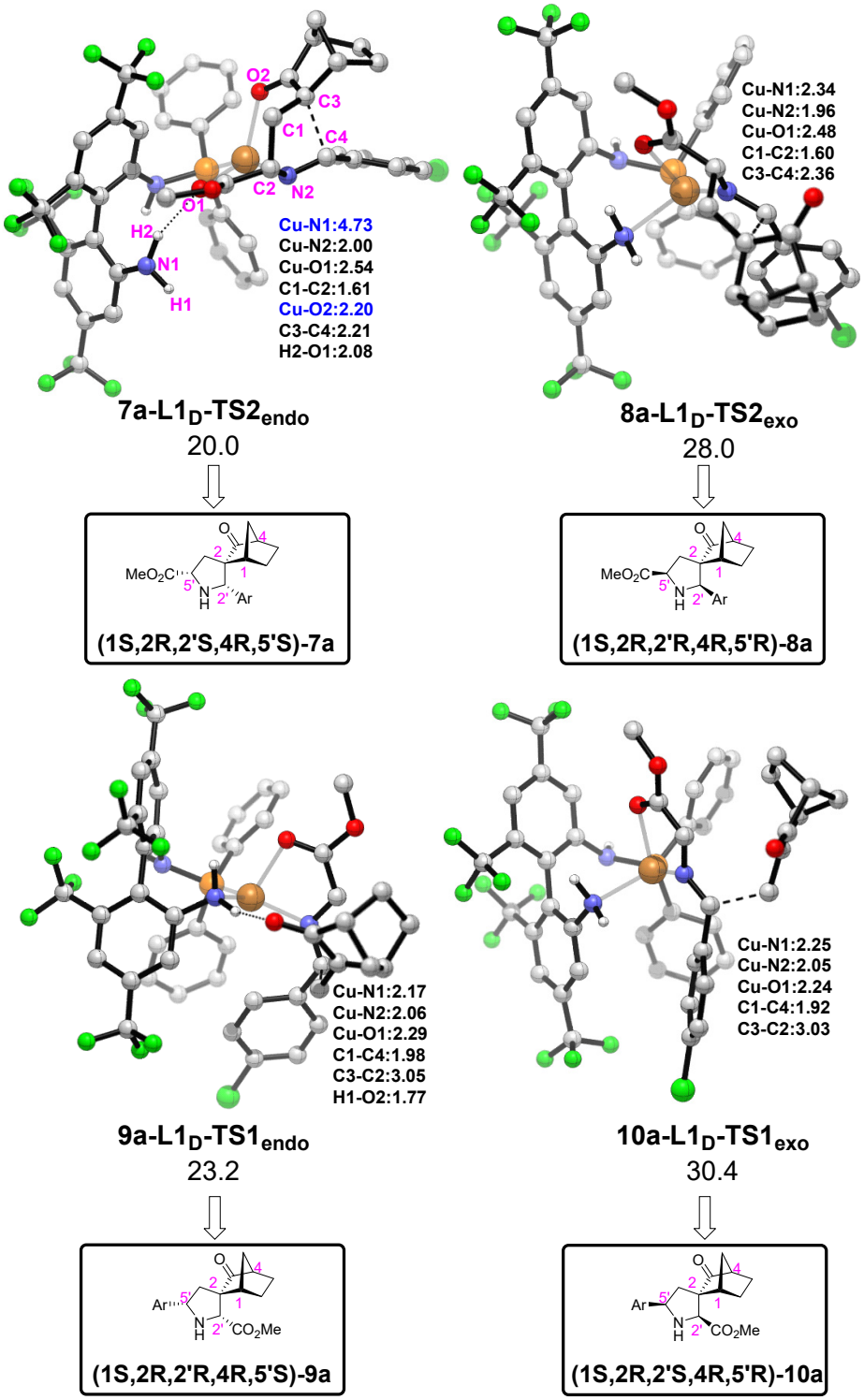


Figure S176. Optimized transition states for the reaction with **1a**-(1R,4S) catalyzed by $\mathbf{L1_D}$ in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 2**.

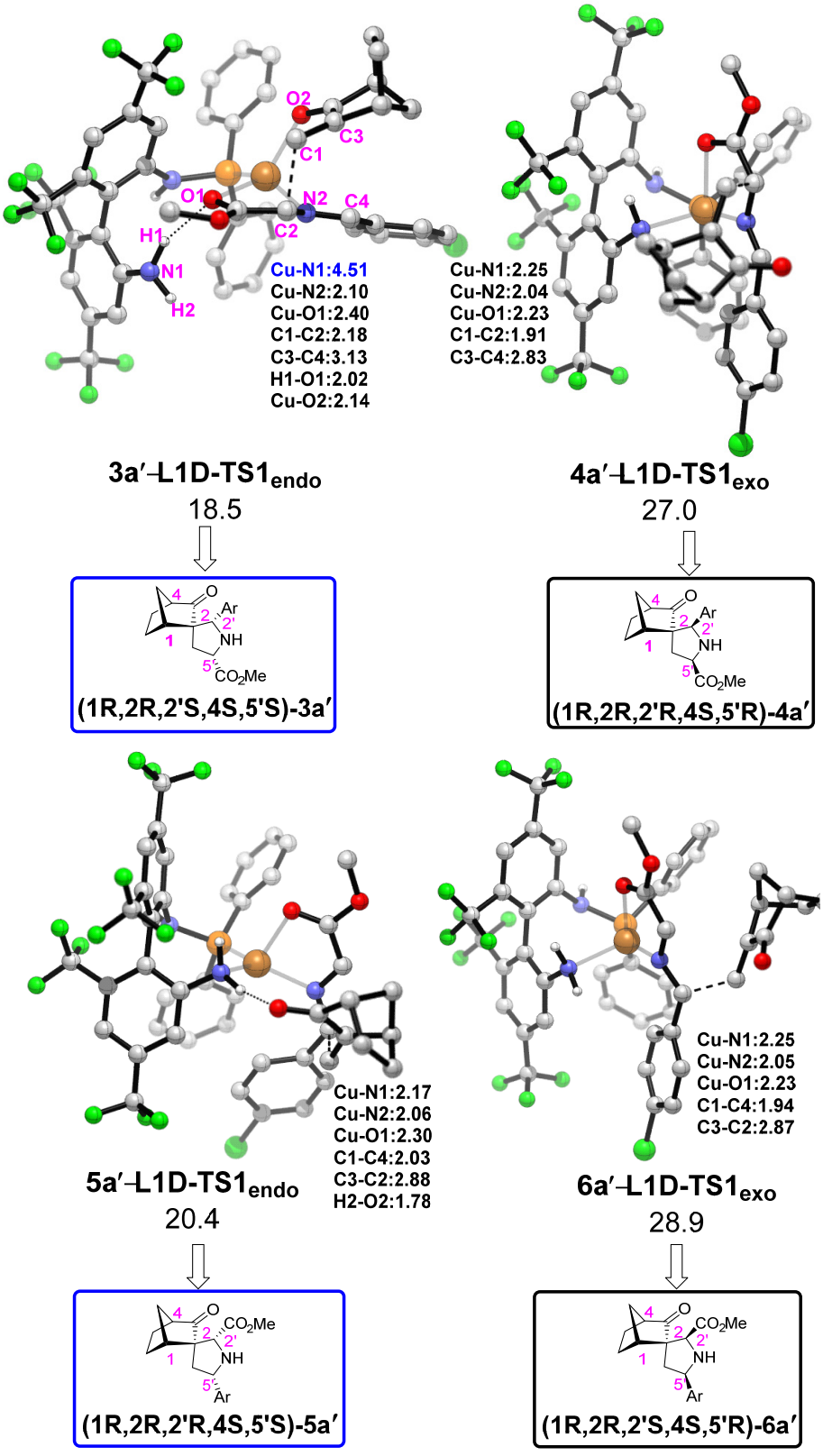


Figure S177. Optimized transition states for the reaction with **1a**-(1S,4R) catalyzed by $\mathbf{L1_D}$ in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 3**.

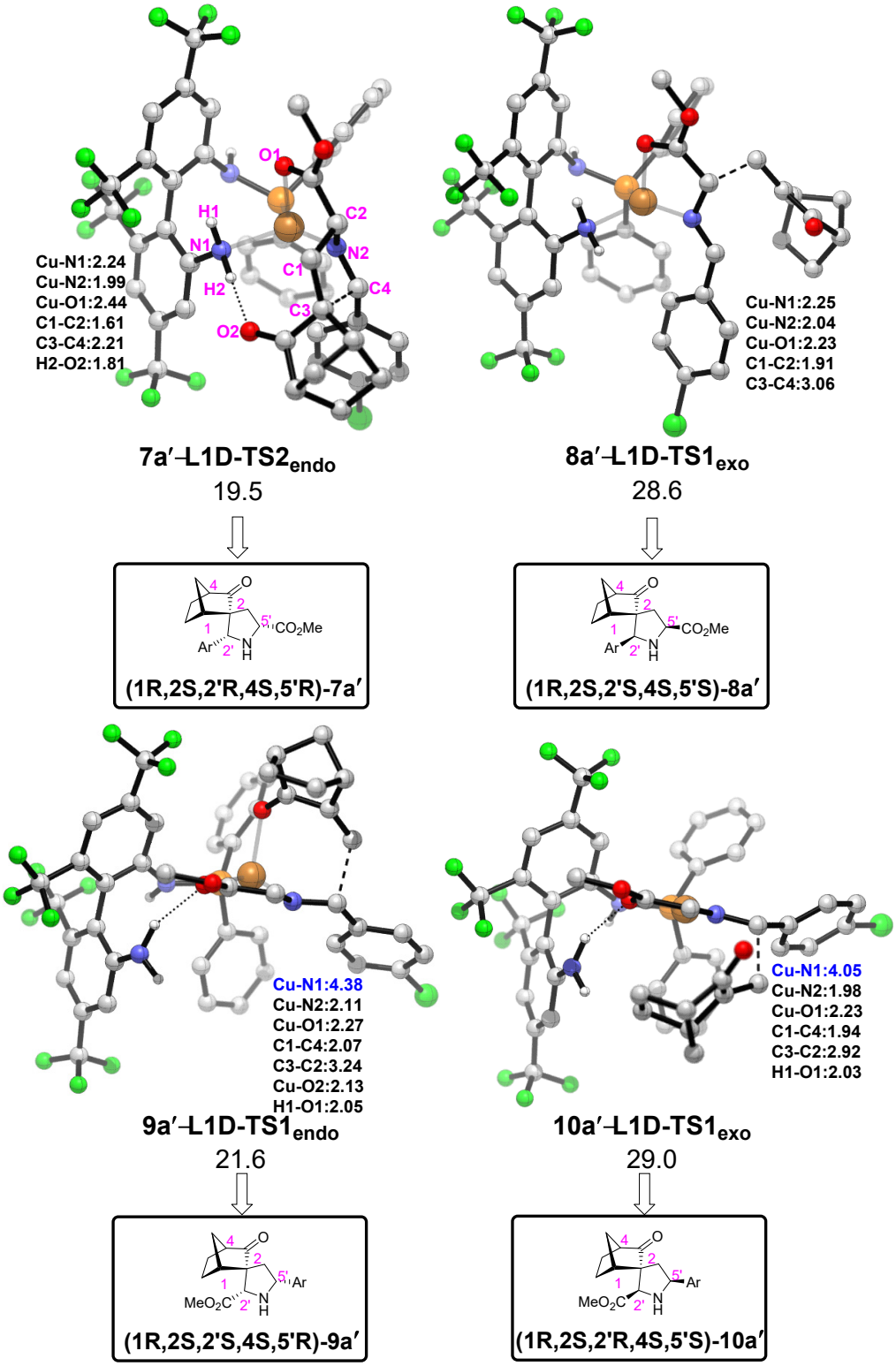


Figure S178. Optimized transition states for the reaction with **1a**-(1S,4R) catalyzed by $\mathbf{L1_D}$ in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 3**.

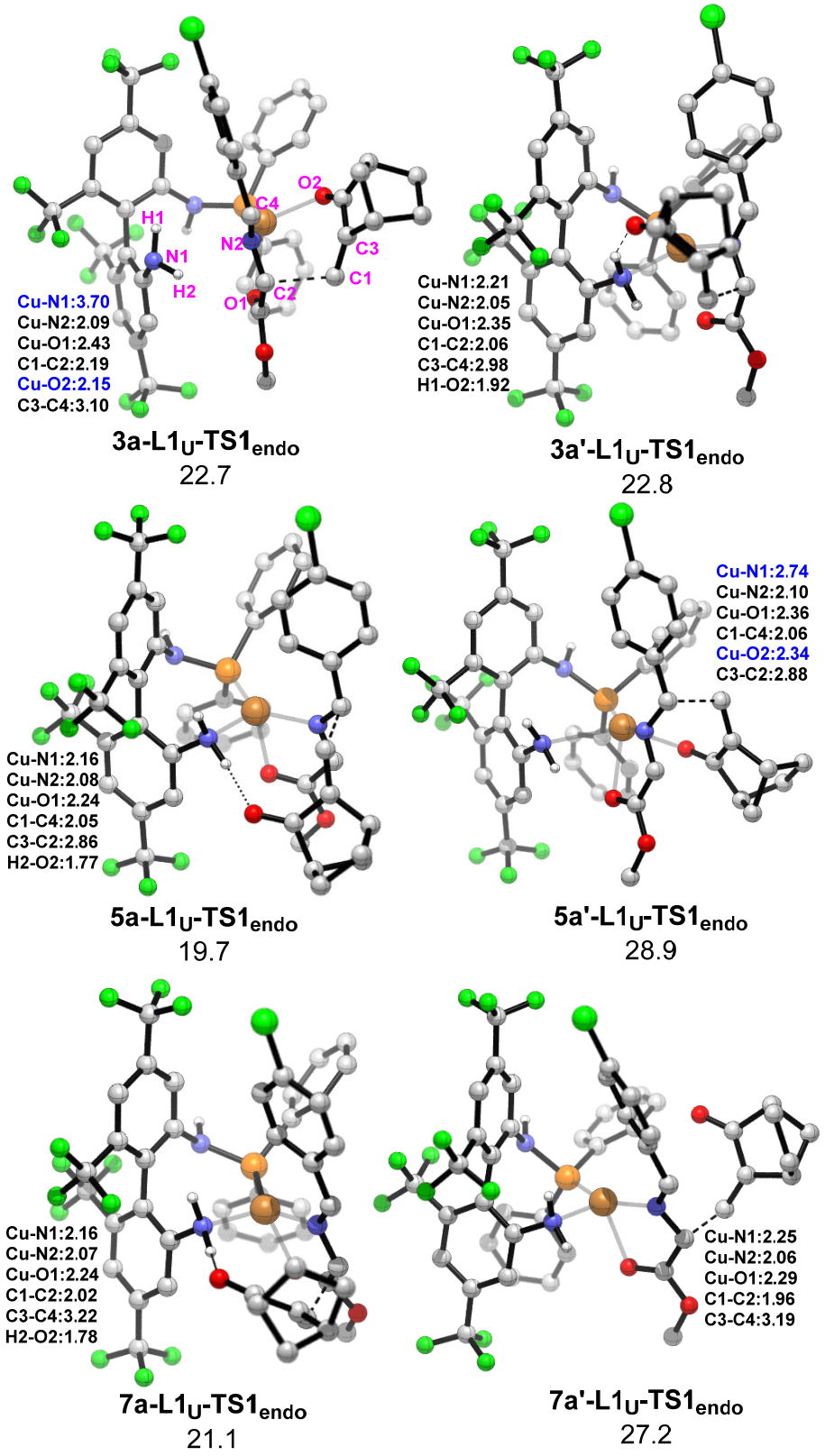


Figure S179. Optimized key transition states for the reaction with **1a**-(1R,4S) and **1a**-(1S,4R) catalyzed by $\mathbf{L1_U}$ in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 2** and **Scheme 3**.

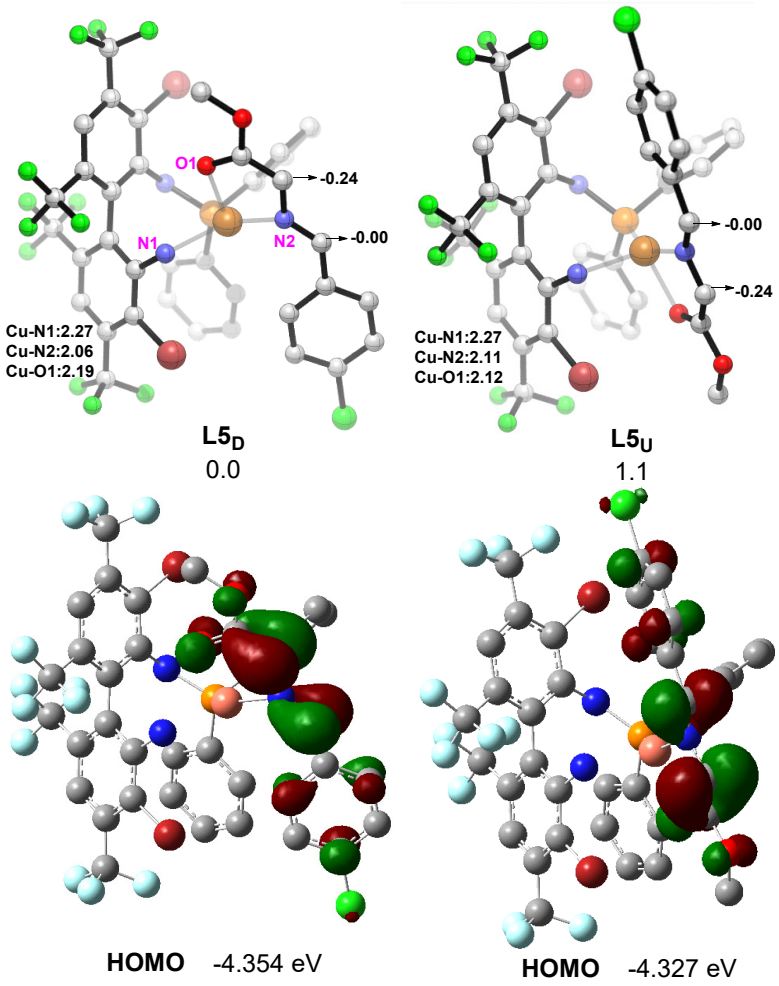


Figure S180. Optimized structures of Cu(I)-**L5** intermediates (**L5**$_{D}$ and **L5**$_{U}$) with the key bond lengths (in angstrom), the NPA charge of the two reacting carbons and HOMO energies by the B3LYP method. Their relative free energy (in kcal/mol) in DCM solution are given. All hydrogen atoms were omitted for clarification, related to **Figure 2** and **Scheme 3**.

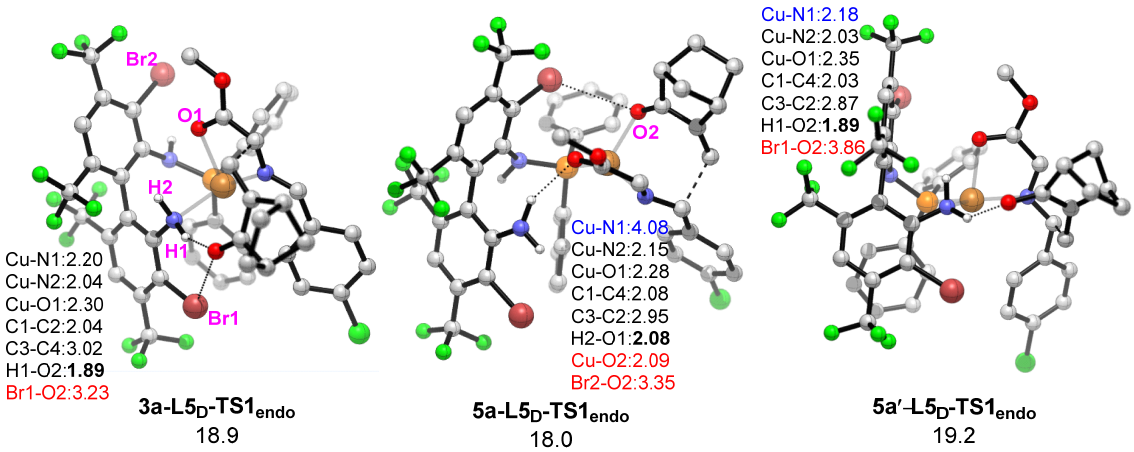


Figure S181. Optimized key transition states for the reaction with **1a**-(1R,4S) and **1a**-(1S,4R) catalyzed by **L5$_D$** in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 3**.

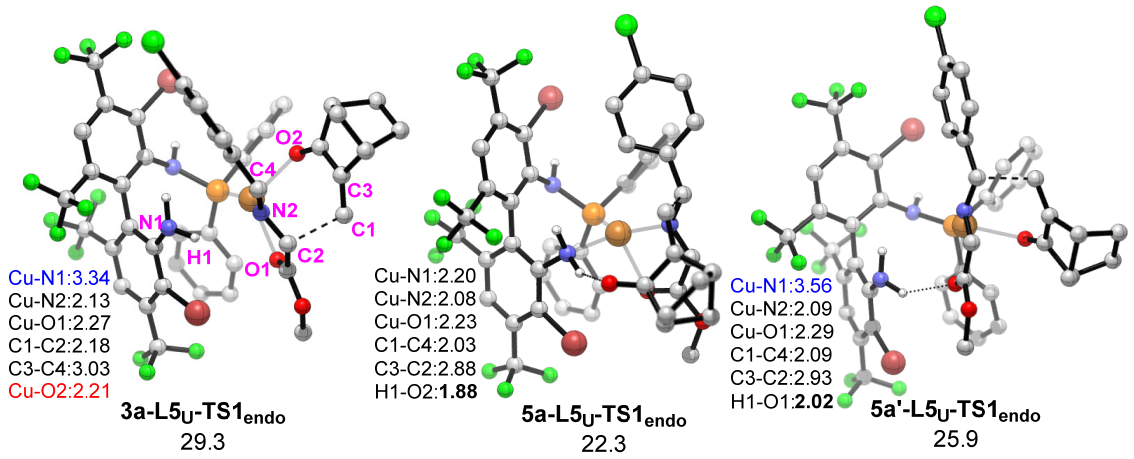


Figure S183. Optimized key transition states for the reaction with **1a**-(1R,4S) and **1a**-(1S,4R) catalyzed by **L5$_U$** in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to **Scheme 3**.

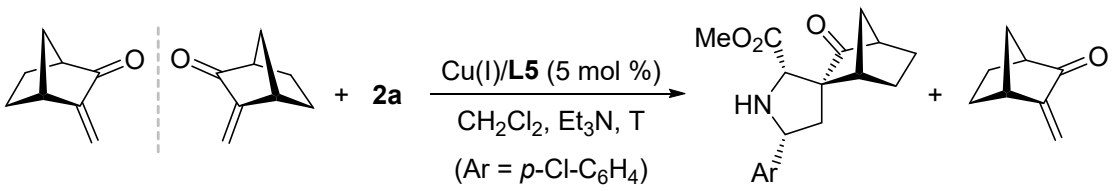
Table S3. The absolute (in Hartree) energies in gas phase and single point energies in DCM solution for the reaction catalyzed by Cu(I)-**L1** by the B3LYP method, related to **Scheme 2** and **Scheme 3**.

	E_{gas}	$(E+ZPE)_{gas}$	G_{gas}	E_{soln}
L1				
$L1_D$	-3975.508919	-3974.926423	-3975.023118	-3975.52314
$L1_U$	-3975.506122	-3974.923461	-3975.018880	-3975.520437
1a-(1R,4S)				
1a-(1R,4S)	-386.066275	-385.903069	-385.934594	-386.071059
3a-$L1_D$-$TS1_{endo}$	-4361.582085	-4360.833287	-4360.937046	-4361.595674
3a-$L1_D$-$TS2_{endo}$	-4361.586368	-4360.835435	-4360.937814	-4361.600515
4a-$L1_D$-$TS1_{exo}$	-4361.555589	-4360.807283	-4360.913976	-4361.577559
5a-$L1_D$-$TS1_{endo}$	-4361.577078	-4360.829568	-4360.933208	-4361.589614
5a-$L1_D$-$TS2_{endo}$	-4361.582363	-4360.832560	-4360.936949	-4361.596926
6a-$L1_D$-$TS1_{exo}$	-4361.552071	-4360.804264	-4360.911095	-4361.571714
7a-$L1_D$-$TS1_{endo}$	-4361.575110	-4360.828142	-4360.933877	-4361.587674
7a-$L1_D$-$TS2_{endo}$	-4361.573629	-4360.824295	-4360.930177	-4361.588277
8a-$L1_D$-$TS1_{exo}$	-4361.554115	-4360.806019	-4360.912416	-4361.574074
8a-$L1_D$-$TS2_{exo}$	-4361.554124	-4360.804736	-4360.911517	-4361.574689
9a-$L1_D$-$TS1_{endo}$	-4361.569399	-4360.821073	-4360.925575	-4361.583639
9a-$L1_D$-$TS2_{endo}$	-4361.572217	-4360.822106	-4360.927193	-4361.586313
10a-$L1_D$-$TS1_{exo}$	-4361.549101	-4360.801350	-4360.908659	-4361.568782
3a-$L1_U$-$TS1_{endo}$	-4361.569396	-4360.822588	-4360.928303	-4361.581683
5a-$L1_U$-$TS1_{endo}$	-4361.575519	-4360.826951	-4360.931116	-4361.589744
7a-$L1_U$-$TS1_{endo}$	-4361.570523	-4360.822318	-4360.927340	-4361.586281
7a-$L1_U$-$TS2_{endo}$	-4361.572054	-4360.82152	-4360.924792	-4361.586839
1a-(1S,4R)				
1a-(1S,4R)	-386.066275	-385.903069	-385.934594	-386.071059
3a'-$L1_D$-$TS1_{endo}$	-4361.577085	-4360.829957	-4360.934672	-4361.589709
3a'-$L1_D$-$TS2_{endo}$	-4361.582370	-4360.832672	-4360.937282	-4361.597447
4a'-$L1_D$-$TS1_{exo}$	-4361.556294	-4360.807835	-4360.913993	-4361.57606
5a'-$L1_D$-$TS1_{endo}$	-4361.573865	-4360.825507	-4360.929962	-4361.588062
5a'-$L1_D$-$TS2_{endo}$	-4361.581261	-4360.830795	-4360.934205	-4361.595991
6a'-$L1_D$-$TS1_{exo}$	-4361.552208	-4360.804294	-4360.910853	-4361.572065
7a'-$L1_D$-$TS1_{endo}$	-4361.579153	-4360.830461	-4360.934283	-4361.592828
7a'-$L1_D$-$TS2_{endo}$	-4361.578478	-4360.828152	-4360.932141	-4361.592043
8a'-$L1_D$-$TS1_{exo}$	-4361.553392	-4360.805264	-4360.909320	-4361.575257
9a'-$L1_D$-$TS1_{endo}$	-4361.574283	-4360.826857	-4360.930033	-4361.586508
9a'-$L1_D$-$TS2_{endo}$	-4361.574809	-4360.825215	-4360.928952	-4361.589161
10a'-$L1_D$-$TS1_{exo}$	-4361.553465	-4360.806179	-4360.913208	-4361.570703
3a'-$L1_U$-$TS1_{endo}$	-4361.569348	-4360.821439	-4360.925671	-4361.583984
5a'-$L1_U$-$TS1_{endo}$	-4361.559387	-4360.812157	-4360.916755	-4361.573373
7a'-$L1_U$-$TS1_{endo}$	-4361.559361	-4360.811209	-4360.915814	-4361.576873
7a'-$L1_U$-$TS2_{endo}$	-4361.562077	-4360.811858	-4360.914417	-4361.579022

Table S4. The absolute (in Hartree) energies in gas phase and single point energies in DCM solution for the reaction catalyzed by Cu(I)-**L5** by the B3LYP method, related to **Scheme 3**.

	E_{gas}	$(E+ZPE)_{gas}$	G_{gas}	E_{soln}
L5				
$L5_D$	-9117.713339	-9117.150688	-9117.248328	-9117.725244
$L5_U$	-9117.709710	-9117.147019	-9117.245311	-9117.722830
1a-(1R,4S)				
3a-$L5_D$-$TS1_{endo}$	-9503.779903	-9503.051551	-9503.156845	-9503.792486
3a-$L5_D$-$TS2_{endo}$	-9503.785237	-9503.054985	-9503.159414	-9503.798144
5a-$L5_D$-$TS1_{endo}$	-9503.776854	-9503.049918	-9503.158711	-9503.789010
5a-$L5_D$-$TS2_{endo}$	-9503.782951	-9503.053872	-9503.161882	-9503.795381
3a-$L5_U$-$TS1_{endo}$	-9503.763335	-9503.035774	-9503.141595	-9503.774688
5a-$L5_U$-$TS1_{endo}$	-9503.772176	-9503.044009	-9503.150394	-9503.785862
1a-(1S,4R)				
5a'-$L5_D$-$TS1_{endo}$	-9503.777596	-9503.049268	-9503.156014	-9503.790568
5a'-$L5_U$-$TS1_{endo}$	-9503.764974	-9503.037612	-9503.144511	-9503.778813

Table S5. Re-optimization Studies for Kinetic Resolution of Alkylidene Norcamphors related to **Table 3.**[a]



rac-**1a** **5a** (dr >20:1) (1*S*,4*R*)-**1a**

entry	T (^{o}C)	t (h)	ratio **1a**:**2a**	**1a** yield (ee) (%)[b]	**5a** yield (ee) (%)[b]	*S*[c]
1	-20	2	1:1.5	39(98)	47(87)	65
2	-20	3	1:1	38(99)	48(88)	82
3	-20	5	1:0.75	38(99)	47(89)	90
4	-40	4	1:1	41(97)	46(90)	90
5	-40	8	1:0.75	43(95)	46(90)	70
6	-60	35	1:1	40(95)	46(92)	89
7	-60	56	1:0.75	42(91)	45(93)	88
8	-60	21	1:1.5	44(92)	46(94)	106

[a] All reactions were carried out with 0.40 mmol of *rac*-**1a** in 2 mL of CH_2Cl_2. [b] Isolated yields based on *rac*-**1a**, >20:1 dr was determined by crude ^{1}H NMR, and *ee* value of **5a** and the recovered **1a** were determined by HPLC and GC analysis, respectively. [c] $S = \ln[(1 - Conv.)(1 - ee_1)]/\ln[(1 - Conv.)(1 + ee_1)]$, $Conv. = ee_1/(ee_1 + ee_5)$.

Supplemental Item Legends

Table S6. Cartesian Coordinates for Optimized Structures of reactants, related to **Scheme 2 and Figure 2**.

Table S7. Cartesian Coordinates for Optimized Structures of **L1**-1a-(1R,4S), related to **Scheme 2**.

Table S8. Cartesian Coordinates for Optimized Structures of **L1**-1a-(1S,4R), related to **Scheme 2 and Scheme 3**.

Table S9. Cartesian Coordinates for Optimized Structures of **L5**-1a-(1R,4S), related to **Figure 2 and Scheme 3**.

Table S10. Cartesian Coordinates for Optimized Structures of **L5**-1a-(1S,4R), related to **Scheme 3**.

Data S1. Crystal Data and Structure Refinement for tosylated (±)-endo-**3a**, related to **Scheme 1**.

Data S2. Crystal Data and Structure Refinement for tosylated (±)-endo-**5a**, related to **Scheme 1**.

Data S3. Crystal Data and Structure Refinement for **5b**, related to **Table 3**.

Data S4. Crystal Data and Structure Refinement for **5s**, related to **Table 3**.

Data S5. Crystal Data and Structure Refinement for (±)-**5u**, related to **Table 3**.

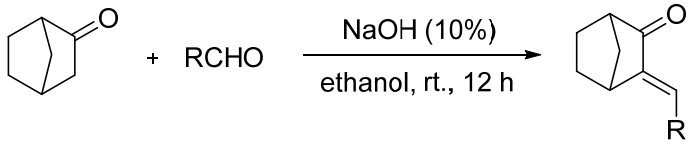
Data S6. Crystal Data and Structure Refinement for (±)-**1d**, related to **Table 3**.

Transparent Methods

^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quarter, m = multiple or unresolved, br s = broad single, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a Bruker 100 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. Solvents were purified prior to use according to the standard methods. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. Enantiomeric ratios were determined by chiral-phase HPLC and GC analysis in comparison with authentic racemic materials. 3-Methylene-2-norcamphor **1a** is commercially-available or prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Fehr et al., 2009). Racemic substituted methylene norcamphors **1b-1l** were synthesized by aldol condensation reaction (Satam et al., 2011). Racemic substituted methylene norcamphors **1m** and **1n** were prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Ghebreghiorgiset al., 2012), **1o**, **1p** and **1q** was prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Coe et al., 2004; Berthelette et al., 1997; Chuiko et al., 2002). Chiral ligands **L1-L5** were prepared according our previous procedure (Wang et al., 2008).

General Procedure for the Preparation of Alkylidene Norcamphors

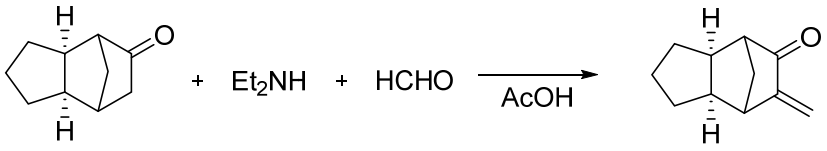
Procedure A: Preparation of Racemic Alkylidene Norcamphors 1b-1l:



In a 100 mL round-bottom flask, norcamphor (5.0 mmol, 1.0 equiv.) and aryl aldehyde (5.0 mmol, 1.0 equiv.) were dissolved with 20 mL ethanol, and then sodium hydroxide solution (10% in ethanol, 2.0 mL) was added dropwise to the solution. The reaction mixture was stirred at room temperature until TLC revealed complete conversion of norcamphor. After reaction completed, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 20 mL of CH_2Cl_2 and washed with 20 mL of sat. NaCl solution. Organic phase was separated and the aqueous phase was extracted with additional CH_2Cl_2 (2 × 20 mL).

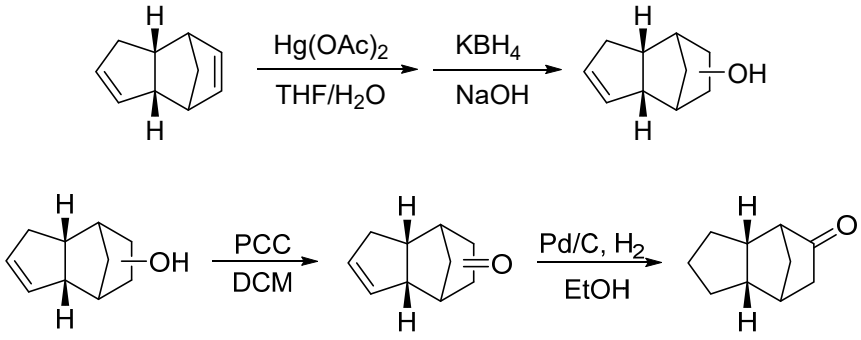
Combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, the crude mixture was purified by silica-gel flash column chromatography to obtain the racemic compounds **1b-1l** in moderate to good yields.

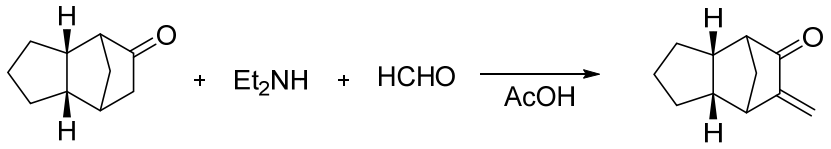
Procedure B: Preparation of Racemic 1m:



Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 min. period to formaldehyde (36% in H_2O, 40.0 mmol, 4.0 equiv.) at 0°C. The resultant mixture was treated over a 33 minutes' period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes' period to *exo*-octahydro-5H-4,7-methanoinden-5-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous 5% HCl and ice (pH = l). The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with H_2O, aqueous 5% NaOH and twice with brine, dried over Na_2SO_4 and filtered off. Et_2O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography to obtain the racemic compound **1m** in 55% yield.

Procedure C: Preparation of Racemic 1n:





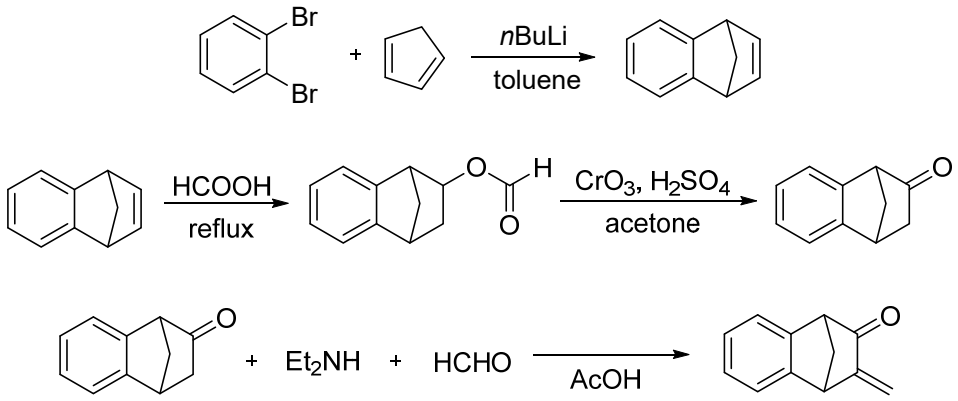
A solution of dicyclopentadiene (40 mmol, 1.0 equiv.) in THF (3.5 mL) was added over 2 minutes at room temperature to a yellow suspension of mercury(II) acetate (40 mmol, 1.0 equiv.) in THF/H_2O (35 mL/35 mL). After 5 minutes, the reaction mixture became colorless and was stirred at the same temperature for 20 minutes. The reaction was carefully quenched with slow addition of 3 M NaOH (44 mL of an aqueous solution) followed by dropwise addition of 0.5 M $NaBH_4$ (44 mL of a 3M NaOH aqueous solution) at 0°C. Liquid mercury (0) was filtered over celite and rinsed with diethyl ether (70 mL). The organic layer was separated, dried over $MgSO_4$, reduced under vacuum and the colorless oil obtained was used in the next step without further purification. PCC (80 mmol, 2.0 equiv.) was added over 5 minutes at room temperature to a crude material (40 mmol, 1.0 equiv.) in DCM (80 mL). The mixture was refluxed for 10 hours and cooled down to room temperature. The reaction mixture was filtered through a short plug of silica (eluted with DCM) and the organic layer was washed with 5% KOH, 5% HCl, saturated $NaHCO_3$, saturated NaCl, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:10) to give *endo*-3,3a,4,6,7,7a-hexahydro-5H-4,7-methanoinden-5-one and 1,3a,4,6,7,7a-hexahydro-5H-4,7-methanoinden-5-one in 50% yield for three steps.

A solution of ketones (20 mmol, 2.96 g) in 20 mL EtOH was added 100 mg Pd/C (10%). The reaction mixture was stirred at 50 °C under hydrogen atmosphere (80 bar) for 48 h. The reaction mixture was filtered through a short plug of silica (eluted with EtOAc) and The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:10) to give octahydro-5H-4,7-methanoinden-5-one in 60% yield.

Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 minutes' period to formaldehyde (36% in H_2O, 40.0 mmol, 4.0 equiv.) at 0 °C. The resultant mixture was treated over a 33 minutes' period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes' period to *endo*-octahydro-5H-4,7- methanoinden-5-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous 5% HCl and ice (pH = l). The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with H_2O,

aqueous 5% NaOH and twice with brine, dried over Na_2SO_4 and filtered off. Et_2O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography (EtOAc:hexane = 1:20) to obtain the racemic compound **1n** in 40% yield.

Procedure D: Preparation of Racemic 1o:



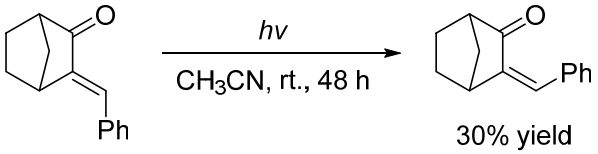
1,2-Dibromobenzene (40 mmol, 1 equiv.) and cyclopentadiene (40 mmol, 1 equiv.) were stirred in toluene (40 mL) at 0 ºC under N_2. To this solution was added *n*-BuLi (16 mL, 2.5M in hexane, 40 mmol) dropwise over 30 min during which the reaction solution became first yellow then cloudy white. After an additional 10 min at 0 ºC the mixture was allowed to warm to room temperature, stirred overnight and treated with H_2O (20 mL) and extracted with hexane (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to obtain a yellow oil. The product was purified by chromatography on silica gel eluting with hexane to provide 1,4-dihydro-1,4-methano-naphthalene as a clear, colorless oil (5.49 g, 97%).

Approximately 7 g (152 mmol, 4 equiv.) of 98–100% formic acid is added to 5.49 g (38 mmol, 1 equiv.) of 1,4-dihydro-1,4-methano-naphthalene in a 100 mL round-bottomed flask equipped with a condenser, and the mixture is boiled under reflux for 4 hours. The dark solution is cooled and formic acid was removed by rotary evaporation. The crude product was purified by column chromatography to give 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl formate in 58% yield. A solution of 4.14 g (22 mmol, 1 equiv.) of 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl formate in 10 mL of reagent grade acetone is contained in a 100 mL three-necked flask equipped with a thermometer, stirrer, and dropping funnel containing 8 N chromic acid solution. The flask is cooled with an ice bath and the oxidant is added at a rate such that the reaction temperature is maintained at 20–30 °C. Approximately 11 mL of oxidant solution is required; completion of the

reaction being shown by the persistence of the brownish orange color. A slight excess of oxidant is added, and the solution is stirred overnight at room temperature. Solid sodium bisulfite is added in portions to reduce the excess oxidant. The reaction mixture is poured into a large separatory funnel. The dark green chromic sulfate sludge, which has formed during the course of the reaction, is separated either by decantation and washing or by drawing it off from the bottom of the funnel. The acetone solution is washed three times with 10–15 mL portions of an aqueous saturated potassium carbonate solution and finally is dried over anhydrous Na_2SO_4 and concentrated. The product was purified by silica-gel flash column chromatography to provide 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one as a clear, colorless oil (2.78 g, 80%).

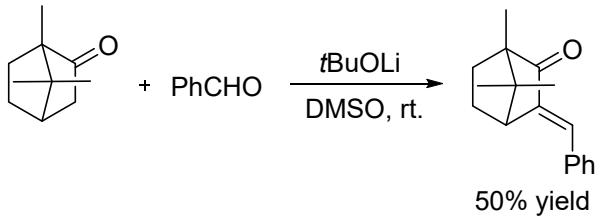
Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 minutes' period to formaldehyde (36% in H_2O, 40.0 mmol, 4.0 equiv.) at 0°C. The resultant mixture was treated over a 33 minutes' period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes' period to 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous HCl 5% and ice (pH = l). The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with H_2O, aqueous NaOH 5% and twice with brine, dried over Na_2SO_4 and filtered off. Et_2O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography to obtain the racemic compound **1o** in 45% yield.

Procedure E: Preparation of Racemic 1p:



(*E*)-3-benzylidenebicyclo[2.2.1]heptan-2-one **1b** (0.500 g, 2.5 mmol) was dissolved in CH_3CN (60 mL) and irradiated with a UV mercury lamp for 48 h while stirring at room temperature. The solvent was removed under reduced pressure, and the product was purified by silica-gel flash column chromatography to provide **1p** in 30% yield.

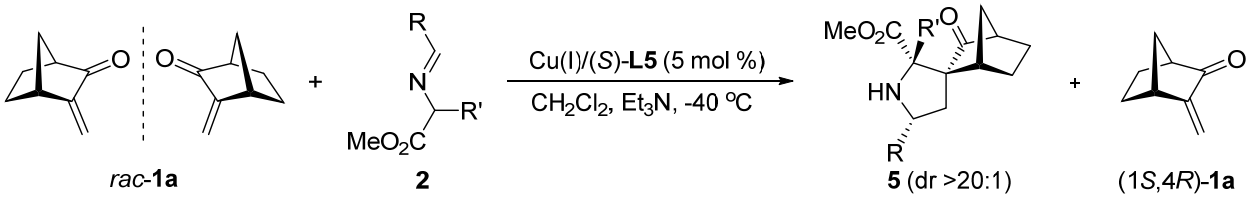
Procedure F: Preparation of Racemic 1q:



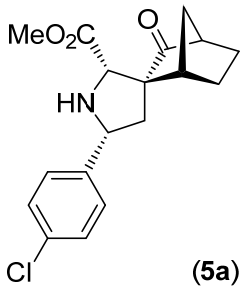
50% yield

In 10 ml of anhydrous DMSO were dissolved 1.52 g (10 mmol) of camphor and 11 mmol of bezaldehyde. To a mixture of 0.96 g (12 mmol) of *t*-BuOLi and 10 ml of anhydrous DMSO was added dropwise the solution of reagents controlling the rate of addition so as the temperature of the reaction mixture did not exceed 20 ºC; the reaction mixture was cooled with water bath. The stirring was continued till complete consumption of the camphor. Then the reaction mixture was poured into 150 ml of ice water containing 5 ml of acetic acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

General Procedure for the Umpolung-Type 1,3-Dipolar Cycloaddition of 3-Methylene-2-Norcamphor with Azomethine Ylides

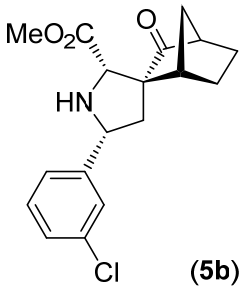


(*S*)-TF-BiphamPhos **L5** (17.6 mg, 0.022 mmol) and $Cu(CH_3CN)_4BF_4$ (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL CH_2Cl_2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -40 ºC (unless otherwise noted) and the imino ester **2** (0.20 mmol), Et_3N (0.060 mmol) were added sequentially. Then 3-methylene-2-norcamphor **1a** (0.40 mmol) was added. After the reaction completed, the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the products, which was then directly analyzed by chiral-phase HPLC to determine the enantiomeric excess.



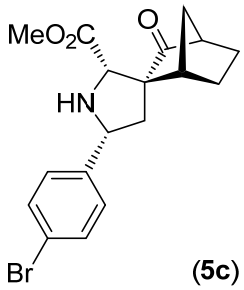
(**5a**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine] -2'-carboxylate (5a): Yield (91%); yellow solid; m.p. 109-111 °C; $[\alpha]^{30}_D$ = +21.5 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.14 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.70 – 2.62 (m, 2H), 2.30 – 2.24 (m, 1H), 2.06 – 1.86 (m, 3H), 1.80 – 1.68 (m, 3H), 1.53 – 1.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.8, 173.2, 139.8, 133.4, 128.7, 128.5, 68.6, 64.8, 62.2, 52.3, 48.9, 45.1, 40.3, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For $C_{18}H_{20}ClNNaO_3$ ($[M+Na]^+$): 356.1024, found: 356.1022. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 12.94 and 23.80 min.



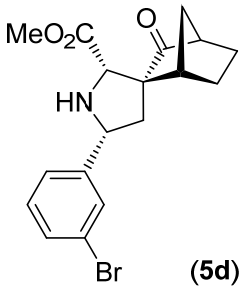
(**5b**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(3-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5b): Yield (88%); white solid; m.p. 130-132 °C; $[\alpha]^{30}_D$ = +42.1 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.43 (d, *J* = 6.8 Hz, 1H), 7.32 – 7.24 (m, 2H), 4.14 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.85 (s, 1H), 3.68 (s, 3H), 2.68 – 2.63 (m, 2H), 2.60 (brs, 1H), 2.31 – 2.24 (m, 1H), 2.11 – 1.97 (m, 2H), 1.96 – 1.86 (m, 1H), 1.83 – 1.65 (m, 3H), 1.51 – 1.41 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 173.1, 143.5, 134.3, 129.9, 127.8, 127.3, 125.1, 68.6, 64.7, 62.3, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For $C_{18}H_{21}ClNO_3$ ($[M+H]^+$): 334.1204, found: 334.1207. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak ASH, *i*-propanol /hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 14.72 and 24.80 min.



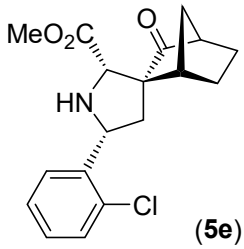
(**5c**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(4-bromophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5c): Yield (84%); white solid; m.p. 108-110 ºC; $[\alpha]^{30}_{D}$ = +12.3 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.44 – 7.38 (m, 2H), 4.13 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.68 – 2.64 (m, 2H), 2.31 – 2.24 (m, 1H), 2.09 – 1.97 (m, 2H), 1.95 – 1.86 (m, 1H), 1.79 – 1.66 (m, 3H), 1.51 – 1.41 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 173.2, 140.4, 131.7, 128.8, 121.5, 68.6, 64.8, 62.2, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For $C_{18}H_{20}BrNNaO_3$ ($[M+Na]^+$): 400.0519, found: 400.0520. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AD-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 13.83 and 25.28 min.



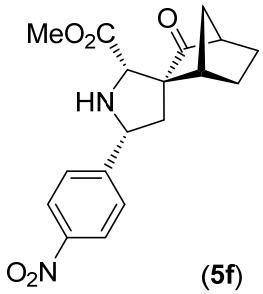
(**5d**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(3-bromophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5d): Yield (85%); white solid; m.p. 117-118 ºC; $[\alpha]^{30}_{D}$ = +36.2 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 7.6, 2.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.67 – 2.63 (m, 2H), 2.59 (brs, 1H), 2.32 – 2.24 (m, 1H), 2.11 – 1.96 (m, 2H), 1.96 – 1.85 (m, 1H), 1.81 – 1.65 (m, 3H), 1.50 – 1.41 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 173.1, 143.8, 130.8, 130.3, 130.2, 125.6, 122.6, 68.6, 64.7, 62.2, 52.3, 48.9, 45.0, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For $C_{18}H_{20}BrNNaO_3$ ($[M+Na]^+$): 400.0519, found: 400.0521. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 18.15 and 32.73 min.



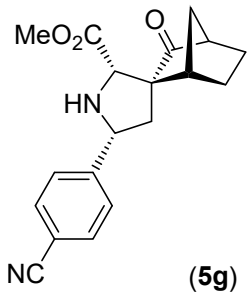
(**5e**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(2-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5e): Yield (94%); white solid; m.p. 128-130 ºC; $[\alpha]^{30}_D$ = +53.5 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.32 (m, 2H), 7.20 (m, 1H), 4.67 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.90 (s, 1H), 3.67 (s, 3H), 2.71 – 2.63 (m, 2H), 2.59 (brs, 1H), 2.30 – 2.24 (m, 1H), 2.23 – 2.16 (m, 1H), 1.97 – 1.86 (m, 2H), 1.80 – 1.69 (m, 3H), 1.51 – 1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5, 173.2, 139.1, 133.2, 129.3, 128.5, 127.5, 127.4, 68.1, 64.5, 58.3, 52.1, 49.0, 45.0, 38.7, 34.8, 25.1, 23.3.; HRMS (ESI+) Calcd. For $C_{18}H_{21}ClNO_3$ ($[M+H]^+$): 334.1204, found: 334.1204. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 10.39 and 18.26 min.



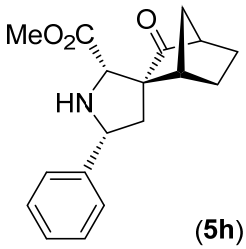
(**5f**)

methyl (1S,2S,2'S,4R,5'R)-5'-(4-nitrophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5f): Yield (72%); yellow solid; m.p. 102 – 103 ºC; $[\alpha]^{15}_D$ = +7.4 (*c* 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 2H), 7.82 – 7.70 (m, 2H), 4.32 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.91 (s, 1H), 3.68 (s, 3H), 2.69 – 2.64 (m, 2H), 2.30 – 2.25 (m, 1H), 2.16 – 2.10 (m, 1H), 2.07 – 2.01 (m, 1H), 1.97 – 1.89 (m, 1H), 1.83 – 1.70 (m, 3H), 1.51 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 173.1, 149.7, 147.3, 127.9, 123.7, 68.3, 64.6, 61.8, 52.2, 48.9, 44.8, 40.1, 34.8, 25.1, 23.2.; HRMS (ESI+) Calcd. For $C_{18}H_{21}N_2O_5$ ($[M+H]^+$): 345.1445, found: 345.1443. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AD-H, *i*-propanol /hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 10.35 and 17.80 min.



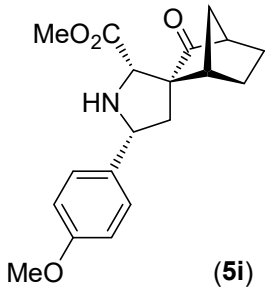
(**5g**)

methyl (1S,2S,2'S,4R,5'R)-5'-(4-cyanophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5g): Yield (83%); white solid; m.p. 107 – 108 °C; $[\alpha]^{15}_{D}$ = +20.0 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.61 (m, 4H), 4.25 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.88 (s, 1H), 3.68 (s, 3H), 2.70 – 2.62 (m, 2H), 2.31 – 2.22 (m, 1H), 2.14 – 2.05 (m, 1H), 2.07 – 1.99 (m, 1H), 2.01 – 1.86 (m, 1H), 1.85 – 1.65 (m, 3H), 1.52 – 1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1, 173.2, 147.5, 132.4, 127.9, 118.8, 111.4, 68.3, 64.7, 62.2, 52.3, 48.9, 44.9, 40.1, 34.8, 25.1, 23.3.; HRMS (ESI+) Calcd. For $C_{19}H_{21}N_2O_3$ ($[M+H]^+$): 325.1547, found: 325.1549. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.67 and 15.84 min.



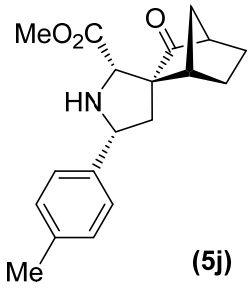
(**5h**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-3-oxo-5'-phenylspiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'- carboxylate (5h): Yield (86%); white thick liquid; $[\alpha]^{30}_{D}$ = +44.7 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.41 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 4.15 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.85 (s, 1H), 3.68 (s, 3H), 2.72 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.31 – 2.27 (m, 1H), 2.09 – 2.07 (m, 1H), 2.07 – 2.03 (m, 1H), 1.95 – 1.86 (m, 1H), 1.80 – 1.68 (m, 3H), 1.50 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 173.2, 140.9, 128.6, 127.8, 127.0, 68.7, 64.9, 62.9, 52.3, 48.9, 45.2, 40.4, 34.7, 25.1, 23.5.; HRMS (ESI+) Calcd. For $C_{18}H_{22}NO_3$ ($[M+H]^+$): 300.1594, found: 300.1597. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AD-H, *i*-propanol /hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 16.86 and 28.61 min.



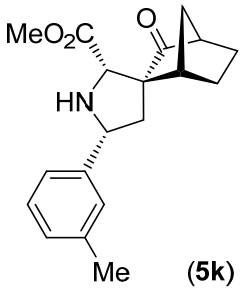
(**5i**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(4-methoxyphenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine] -2'-carboxylate (5i): Yield (59%); yellow thick liquid; $[\alpha]^{30}_{D}$ = +36.2 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 6.94 – 6.86 (m, 2H), 4.12 (dd, *J* = 9.0, 8.4 Hz, 1H), 3.84 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.77 (s, 1H), 2.71 – 2.68 (m, 1H), 2.66 – 2.63 (m, 1H), 2.30 – 2.26 (m, 1H), 2.05 – 2.01 (m, 2H), 1.95 – 1.86 (m, 1H), 1.78 – 1.68 (m, 3H), 1.50 – 1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 173.1, 159.2, 132.7, 128.2, 114.0, 68.4, 64.8, 62.2, 55.3, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.5.; HRMS (ESI+) Calcd. For $C_{18}H_{22}NO_3$ ($[M+H]^+$): 330.1700, found: 330.1700. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak OD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 16.72 and 22.88 min.



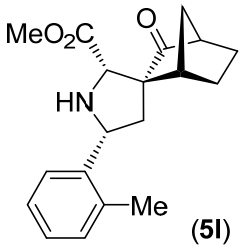
(5j)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-3-oxo-5'-(p-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'- carboxylate (5j): Yield (74%); yellow solid; m.p. 76-78 ºC; $[\alpha]^{30}_{D}$ = +49.4 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.15 – 4.08 (m, 1H), 3.83 (s, 1H), 3.68 (s, 3H), 2.72 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.35 (s, 3H), 2.32 – 2.26 (m, 1H), 2.06 – 2.04 (m, 1H), 2.03 – 2.00 (m, 1H), 1.97 – 1.84 (m, 1H), 1.80 – 1.66 (m, 3H), 1.50 – 1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 173.2, 137.9, 137.5, 129.3, 127.0, 68.8, 65.0, 62.7, 52.3, 48.9, 45.2, 40.4, 34.7, 25.1, 23.6, 21.1.; HRMS (ESI+) Calcd. For $C_{19}H_{23}NO_3$ ($[M+H]^+$): 314.1751, found: 314.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AD-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.78 and 20.79 min.



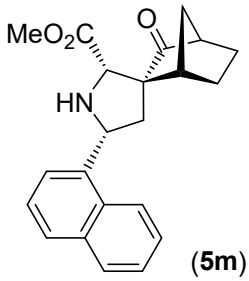
(**5k**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-3-oxo-5'-(m-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'- carboxylate (5k): Yield (66%); yellow thick liquid; $[\alpha]^{30}_{D}$ = +40.6 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 4.12 (dd, *J* = 9.6, 7.6 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.71 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.36 (s, 3H), 2.35 – 2.25 (m, 2H), 2.07 – 2.05 (m, 1H), 2.05 – 2.02 (m, 1H), 1.94 – 1.86 (m, 1H), 1.79 – 1.71 (m, 2H), 1.50 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 173.1, 140.7, 138.3, 128.6, 128.5, 127.7, 124.1, 68.8, 64.9, 62.9, 52.3, 48.9, 45.2, 40.3, 34.6, 25.1, 23.6, 21.4.; HRMS (ESI+) Calcd. For $C_{19}H_{23}NO_3$ ($[M+H]^+$): 314.1751, found: 314.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 12.47 and 15.41 min.



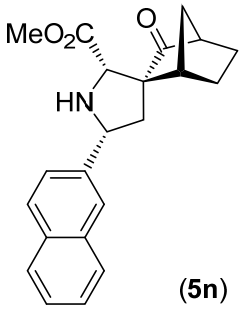
(**5l**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-3-oxo-5'-(o-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'- carboxylate (5l): Yield (64%); white solid; m.p. 126-128 ºC; $[\alpha]^{30}_{D}$ = +58.7 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.18 (m, 2H), 4.35 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.85 (s, 1H), 3.68 (s, 3H), 2.73 – 2.69 (m, 1H), 2.68 – 2.63 (m, 1H), 2.57 (brs, 1H), 2.41 (s, 3H), 2.34 – 2.28 (m, 1H), 2.08 – 2.01 (m, 2H), 1.96 – 1.86 (m, 1H), 1.80 – 1.67 (m, 3H), 1.51 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 173.1, 138.6, 136.3, 130.3, 127.4, 126.5, 125.3, 68.7, 64.7, 58.6, 52.3, 48.9, 45.3, 39.2, 34.6, 25.1, 23.6, 19.4.; HRMS (ESI+) Calcd. For $C_{19}H_{23}NO_3$ ($[M+H]^+$): 314.1751, found: 314.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.67 and 12.03 min.



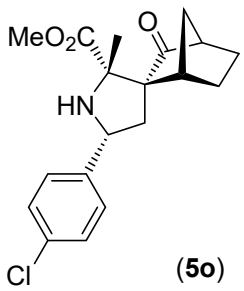
(**5m**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(naphthalen-1-yl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5m): Yield (73%); yellow solid; m.p. 123-125 °C; $[\alpha]^{30}_{D}$ = +77.0 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (m, 2H), 7.56 – 7.46 (m, 3H), 4.87 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 1H), 3.66 (s, 3H), 2.87 – 2.75 (m, 1H), 2.71 – 2.63 (m, 1H), 2.38 – 2.33 (m, 1H), 2.32 – 2.25 (m, 1H), 2.25 – 2.16 (m, 1H), 1.97 – 1.88 (m, 1H), 1.81 – 1.70 (m, 3H), 1.54 – 1.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4, 172.8, 136.0, 133.7, 132.0, 128.6, 128.2, 126.1, 125.6, 125.5, 123.8, 122.9, 69.0, 64.4, 58.4, 52.3, 48.9, 45.5, 38.6, 34.6, 25.1, 23.7.; HRMS (ESI+) Calcd. For $C_{22}H_{24}NO_3$ ($[M+H]^+$): 350.1751, found: 350.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 10.80 and 17.05 min.



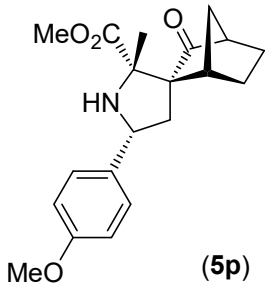
(**5n**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(naphthalen-2-yl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5n): Yield (88%); white solid; m.p. 138-140 °C; $[\alpha]^{30}_{D}$ = +34.4 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.88 – 7.81 (m, 3H), 7.72 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 4.33 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.89 (s, 1H), 3.71 (s, 3H), 2.74 – 2.69 (m, 1H), 2.69 – 2.65 (m, 1H), 2.35 – 2.29 (m, 1H), 2.21 – 2.10 (m, 2H), 1.98 – 1.87 (m, 1H), 1.83 – 1.70 (m, 3H), 1.54 – 1.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 173.2, 138.4, 133.3, 133.0, 128.5, 127.9, 127.6, 126.1, 125.9, 125.0, 68.9, 65.0, 63.1, 52.4, 49.0, 45.3, 40.3, 34.7, 25.1, 23.6.; HRMS (ESI+) Calcd. For $C_{22}H_{24}NO_3$ ($[M+H]^+$): 350.1751, found: 350.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 14.89 and 23.96 min.



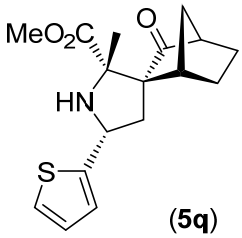
(**5o**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(4-chlorophenyl)-2'-methyl-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5o): Yield (70%); white solid; m.p. 116-118 ºC; $[\alpha]^{30}_{D}$ = +14.1 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.15 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.69 (s, 3H), 3.11 (brs, 1H), 2.79 – 2.74 (m, 1H), 2.65 – 2.59 (m, 1H), 2.34 – 2.23 (m, 2H), 2.11 – 2.02 (m, 1H), 1.92 – 1.72 (m, 2H), 1.71 – 1.61 (m, 1H), 1.59 – 1.53 (m, 1H), 1.56 (s, 3H), 1.51 – 1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.5, 174.2, 139.9, 133.1, 128.6, 72.0, 65.7, 59.5, 52.6, 49.4, 44.0, 42.1, 35.6, 25.9, 25.9, 22.0.; HRMS (ESI+) Calcd. For $C_{19}H_{23}ClNO_3$ ($[M+H]^+$): 348.1361, found: 348.1361. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.25 and 10.23 min.



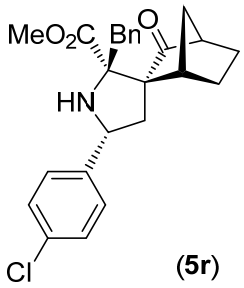
(**5p**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-5'-(4-methoxyphenyl)-2'-methyl-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5p): Yield (57%); white solid; m.p. 106-109 ºC; $[\alpha]^{30}_{D}$ = +7.6 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 6.90 – 6.85 (m, 2H), 4.13 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.16 (brs, 1H), 2.81 – 2.75 (m, 1H), 2.64 – 2.59 (m, 1H), 2.32 – 2.24 (m, 2H), 2.14 – 2.06 (m, 1H), 1.93 – 1.72 (m, 2H), 1.72 – 1.62 (m, 1H), 1.56 (s, 3H), 1.55 – 1.52 (m, 1H), 1.52 – 1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 174.4, 158.9, 133.3, 128.4, 113.9, 72.0, 65.9, 59.7, 55.3, 52.6, 49.4, 44.3, 42.2, 35.6, 26.1, 25.9, 22.1.; HRMS (ESI+) Calcd. For $C_{20}H_{26}NO_4$ ($[M+H]^+$): 344.1856, found: 344.1856. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.58 and 9.45 min.



(**5q**)

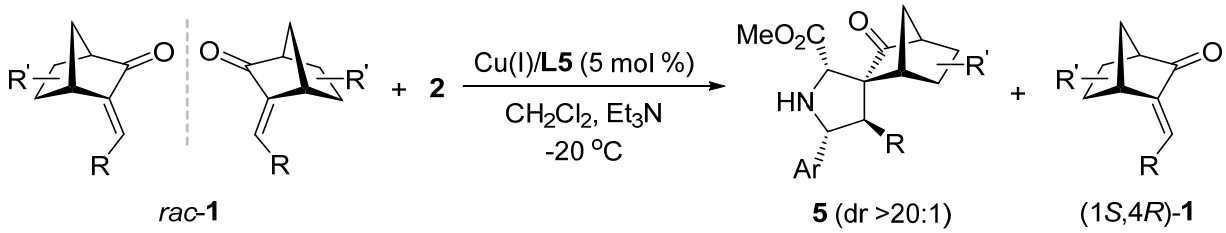
Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-2'-methyl-3-oxo-5'-(thiophen-2-yl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5q): Yield (64%); yellow solid; m.p. 94-96 °C; $[\alpha]^{30}_{D}$ = +3.1 (*c* 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.97 (m, 1H), 4.46 – 4.36 (m, 1H), 3.69 (s, 3H), 3.23 (brs, 1H), 2.79 – 2.73 (m, 1H), 2.64 – 2.58 (m, 1H), 2.43 – 2.35 (m, 1H), 2.31 – 2.23 (m, 1H), 2.22 – 2.13 (m, 1H), 1.94 – 1.74 (m, 2H), 1.72 – 1.64 (m, 1H), 1.59 – 1.56 (m, 1H), 1.56 (s, 3H), 1.53 – 1.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 174.0, 144.4, 126.7, 124.6, 124.5, 72.0, 65.8, 55.7, 52.6, 49.2, 44.6, 42.0, 35.7, 26.0, 25.8, 22.0.; HRMS (ESI+) Calcd. For $C_{17}H_{21}NNaO_3S^+$ ($[M+Na]^+$): 342.1134, found: 342.1137. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 3/97, flow rate 1.0 mL/min, λ = 220 nm); t_r = 30.50 and 34.22 min.



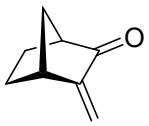
(**5r**)

Methyl (1*S*,2*S*,2'*S*,4*R*,5'*R*)-2'-benzyl-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5r): Yield (68%); colorless thick liquid; $[\alpha]^{30}_{D}$ = −16.3 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 5H), 4.27 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.52 (s, 3H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.00 (brs, 1H), 2.99 (d, *J* = 13.2 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.67 – 2.63 (m, 1H), 2.43 – 2.37 (m, 1H), 2.09 – 2.02 (m, 1H), 1.96 – 1.73 (m, 4H), 1.69 – 1.66 (m, 1H), 1.52 – 1.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 173.2, 140.0, 136.6, 133.1, 130.4, 128.58, 128.56, 128.0, 126.8, 76.7, 65.8, 59.0, 52.2, 49.3, 44.7, 41.6, 39.2, 35.8, 26.5, 25.5.; HRMS (ESI+) Calcd. For $C_{25}H_{26}ClNNaO_3^+$ ($[M+Na]^+$): 446.1493, found: 446.1493. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak OD-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.65 and 9.10 min.

General Procedure for the Efficient Kinetic Resolution of Alkylidene Norcamphors with Azomethine Ylides

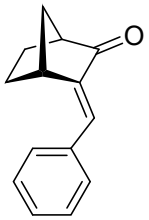


(*S*)-TF-BiphamPhos **L5** (17.6 mg, 0.022 mmol) and $Cu(CH_3CN)_4BF_4$ (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL CH_2Cl_2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -20 °C (unless otherwise noted) and the imino ester **2** (0.60 mmol), Et_3N (0.060 mmol) were added sequentially. Then 3-alkylidene-2-norcamphor **1** (0.40 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the recovered **1** and the cycloadduct **5**, which were then directly analyzed by chiral-phase GC or HPLC to determine the enantiomeric excess.



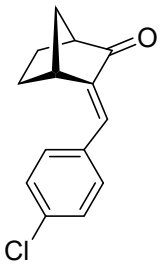
(1a)

(1*S*,4*R*)-3-methylenebicyclo[2.2.1]heptan-2-one (**1a**): 44% yield; yellow liquid; $[\alpha]^{30}_D = -3.0$ (*c* 0.29, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.17 (s, 1H), 3.17 – 3.10 (m, 1H), 2.78 – 2.68 (m, 1H), 1.92 – 1.85 (m, 2H), 1.77 – 1.73 (m, 1H), 1.65 – 1.61 (m, 1H), 1.60 – 1.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 149.9, 111.8, 49.1, 42.4, 36.8, 28.0, 23.6.; The product was analyzed by GC to determine the enantiomeric excess: 92% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 150 °C, carrier gas: N_2, 1.0 mL/min); t_r = 4.75 and 4.95 min.



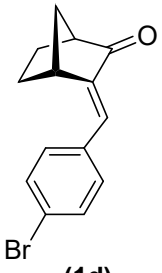
(1b)

(1*S*,4*R*)-3-((*E*)-benzylidene)bicyclo[2.2.1]heptan-2-one: 46% yield; yellow solid; $[\alpha]^{30}_D$ = −552.1 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.44 – 7.31 (m, 3H), 7.16 (s, 1H), 3.66 – 3.61 (m, 1H), 2.82 – 2.77 (m, 1H), 2.11 – 1.92 (m, 2H), 1.78 – 1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 141.6, 135.3, 129.7, 128.9, 128.6, 127.3, 48.6, 40.2, 37.8, 27.3, 24.3.; The product was analyzed by GC to determine the enantiomeric excess: 94% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 180 °C, carrier gas: N_2, 1.0 mL/min); t_r = 29.13 and 30.76 min.



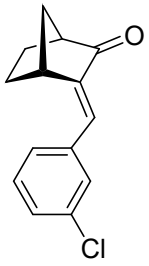
(1c)

(1*S*,4*R*)-3-((*E*)-4-chlorobenzylidene)bicyclo[2.2.1]heptan-2-one (**1c**): 45% yield; yellow solid; $[\alpha]^{30}_D$ = −415.9 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H), 7.09 (s, 1H), 3.63 – 3.55 (m, 1H), 2.84 – 2.76 (m, 1H), 2.10 – 1.93 (m, 2H), 1.79 – 1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 142.1, 134.8, 133.8, 130.9, 128.9, 125.9, 48.5, 40.2, 37.8, 27.3, 24.3.; The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 11.00 and 12.42 min.



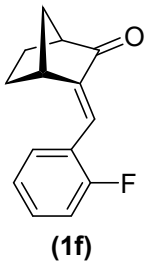
(1d)

(1*S*,4*R*)-3-((*E*)-4-bromobenzylidene)bicyclo[2.2.1]heptan-2-one (**1d**): 45% yield; white solid; m.p. 85-86 ºC; $[\alpha]^{30}_D$ = −331.4 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.37 – 7.30 (m, 2H), 7.07 (s, 1H), 3.61 – 3.55 (m, 1H), 2.84 – 2.77 (m, 1H), 2.11 – 1.92 (m, 2H), 1.80 – 1.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 142.2, 134.2, 131.9, 131.1, 125.9, 123.1, 48.5, 40.2, 37.7, 27.2, 24.3.; HRMS (ESI+) Calcd. For $C_{14}H_{13}BrNaO^+$ ($[M+Na]^+$): 299.0042, found: 299.1110. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 12.94 and 13.78 min.



(1e)

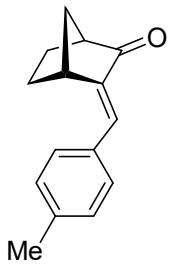
(1*S*,4*R*)-3-((*E*)-3-chlorobenzylidene)bicyclo[2.2.1]heptan-2-one (**1e**): 45% yield; yellow liquid; $[\alpha]^{30}_D$ = −313.1 (*c* 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.37 – 7.28 (m, 3H), 7.07 (s, 1H), 3.64 – 3.57 (m, 1H), 2.85 – 2.77 (m, 1H), 2.12 – 1.93 (m, 2H), 1.79 – 1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 142.9, 137.2, 134.6, 129.9, 129.3, 128.8, 127.9, 125.6, 48.5, 40.2, 37.7, 27.3, 24.3.; HRMS (ESI+) Calcd. For $C_{14}H_{13}ClNaO^+$ ($[M+Na]^+$): 255.0547, found: 255.0551. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak OJ-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 9.97 and 11.39 min.



(1f)

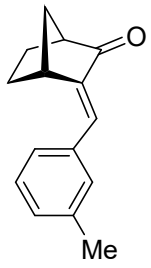
(1*S*,4*R*)-3-((*E*)-2-fluorobenzylidene)bicyclo[2.2.1]heptan-2-one (**1f**): 43% yield; yellow liquid; $[\alpha]^{25}_D$ = −261.1 (*c* 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.6 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.14 – 7.06 (m, 1H), 3.54 – 3.48 (m, 1H), 2.85 – 2.77 (m, 1H), 2.10 – 1.92 (m, 2H), 1.81 – 1.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 161.2 (d, *J* = 251.0 Hz), 143.5, 130.5 (d, *J* = 8.0 Hz), 130.1 (d, *J*

= 3.0 Hz), 124.0 (d, J = 4.0 Hz), 123.3 (d, J = 13.0 Hz), 119.4 (d, J = 5.0 Hz), 115.8 (d, J = 22.0 Hz), 48.6, 40.4 (d, J = 2.0 Hz), 37.6, 27.3, 24.3.; HRMS (ESI+) Calcd. For $C_{14}H_{13}FNaO^+$ ([M+Na]$^+$): 239.0843, found: 239.0845. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 290 nm); t_r = 7.13 and 8.03 min.



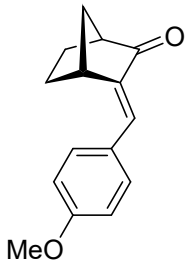
(1g)

(1*S*,4*R*)-3-((*E*)-4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (**1g**): 46% yield; $[\alpha]^{30}_D$ = −529.1 (*c* 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.13 (s, 1H), 3.65 – 3.61 (m, 1H), 2.80 – 2.75 (m, 1H), 2.38 (s, 3H), 2.09 – 1.91 (m, 2H), 1.79 – 1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 140.8, 139.2, 132.5, 129.8, 129.4, 127.4, 48.6, 40.3, 37.9, 27.3, 24.4, 21.4.; The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 8.59 and 11.27 min.



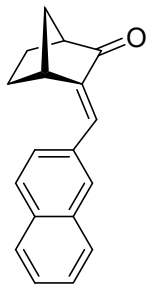
(1h)

(1*S*,4*R*)-3-((*E*)-3-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (**1h**): 47% yield; yellow liquid; $[\alpha]^{30}_D$ = −293.9 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 3H), 7.18 – 7.14 (m, 1H), 7.13 (s, 1H), 3.66 – 3.61 (m, 1H), 2.81 – 2.76 (m, 1H), 2.38 (s, 3H), 2.10 – 1.91 (m, 2H), 1.78 – 1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 141.5, 138.3, 135.2, 130.5, 129.7, 128.5, 127.4, 126.8, 48.6, 40.3, 37.8, 27.3, 24.3, 21.4.; HRMS (ESI+) Calcd. For $C_{15}H_{16}NaO^+$ ([M+Na]$^+$): 235.1093, found: 235.1104. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak OJH, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 8.22 and 10.05 min.



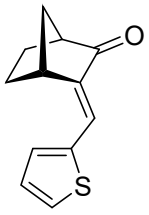
(1i)

(1*S*,4*R*)-3-((*E*)-4-methoxybenzylidene)bicyclo[2.2.1]heptan-2-one (**1i**): 50% yield; $[\alpha]^{30}_{D}$ = −416.0 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 3.66 – 3.58 (m, 1H), 2.80 – 2.74 (m, 1H), 2.09 – 1.91 (m, 2H), 1.79 – 1.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 160.2, 139.5, 131.4, 127.8, 127.1, 114.1, 55.3, 48.5, 40.2, 38.0, 27.3, 24.4.; The product was analyzed by HPLC to determine the enantiomeric excess: 87% ee (Chiralpak OJ-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 23.87 and 30.81 min.



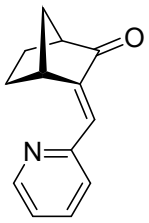
(1j)

(1*S*,4*R*,*E*)-3-(naphthalen-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (**1j**): 46% yield; yellow solid; m.p. 91-93 °C; $[\alpha]^{30}_{D}$ = −504.2 (*c* 0.28 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.89 – 7.80 (m, 3H), 7.61 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.32 (s, 1H), 3.78 – 3.71 (m, 1H), 2.86 – 2.79 (m, 1H), 2.15 – 2.05 (m, 1H), 2.04 – 1.94 (m, 1H), 1.85 – 1.76 (m, 2H), 1.73 – 1.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 141.9, 133.24, 133.22, 132.8, 130.1, 128.33, 128.29, 127.7, 127.4, 126.9, 126.5, 48.6, 40.3, 37.9, 27.4, 24.4.; HRMS (ESI+) Calcd. For $C_{18}H_{16}NaO^+$ ($[M+Na]^+$): 271.1093, found: 271.1100. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak IA, *i*-propanol /hexane = 1/99, flow rate 1.0 mL/min, λ = 300 nm); t_r = 11.41 and 12.92 min.



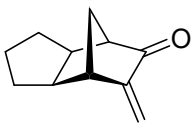
(1k)

(1*S*,4*R*,*E*)-3-(thiophen-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (**1k**): 46% yield; sepia liquid; $[\alpha]^{30}_{D}$ = −513.5 (*c* 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.11 – 7.05 (m, 1H), 3.76 – 3.70 (m, 1H), 2.81 – 2.75 (m, 1H), 2.04 – 1.90 (m, 2H), 1.82 – 1.77 (m, 1H), 1.72 – 1.67 (m, 1H), 1.66 – 1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 139.1, 139.0, 132.3, 129.0, 127.7, 120.1, 48.8, 40.6, 37.6, 27.1, 24.6.; HRMS (ESI+) Calcd. For $C_{12}H_{12}NaOS^+$ ($[M+Na]^+$): 227.0501, found: 227.0486. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralpak OJ-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 320 nm); t_r = 8.51 and 9.51 min.



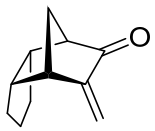
(1l)

(1*S*,4*R*,*E*)-3-(pyridin-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (**1l**): 45% yield; yellow liquid; $[\alpha]^{30}_{D}$ = −219.2 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 3.6 Hz, 1H), 7.74 – 7.63 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.14 (m, 1H), 7.08 (s, 1H), 4.34 – 4.26 (m, 1H), 2.83 – 2.75 (m, 1H), 2.08 – 1.89 (m, 2H), 1.83 – 1.75 (m, 1H), 1.74 – 1.61 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 154.7, 149.9, 145.2, 136.2, 126.1, 125.0, 122.7, 48.6, 40.2, 37.0, 27.3, 24.2.; HRMS (ESI+) Calcd. For $C_{13}H_{14}NO^+$ ($[M+Na]^+$): 200.1070, found: 200.1068. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak OJ-H, *i*-propanol /hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); t_r = 13.88 and 17.92 min.



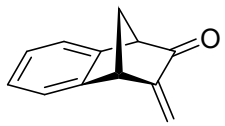
(1m)

(3a*R*,4*R*,7*S*,7a*S*)-6-methyleneoctahydro-5H-4,7-methanoinden-5-one (**1m**): 45% yield; $[\alpha]^{30}_{D} = -0.7$ (*c* 0.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 5.13 (s, 1H), 2.91 – 2.85 (m, 1H), 2.54 – 2.47 (m, 1H), 2.24 – 2.13 (m, 2H), 2.04 – 1.95 (m, 2H), 1.85 – 1.76 (m, 2H), 1.58 – 1.51 (m, 1H), 1.34 (m, 1H), 1.17 – 1.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 149.8, 111.3, 53.9, 47.0, 46.9, 41.8, 32.1, 31.8, 30.5, 27.9.; The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralpak AS-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.55 and 8.47 min.



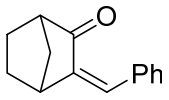
(1n)

(3a*S*,4*R*,7*S*,7a*R*)-6-methyleneoctahydro-5H-4,7-methanoinden-5-one (**1n**): 44% yield; $[\alpha]^{30}_{D} = +25.0$ (*c* 0.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.12 (s, 1H), 3.01 – 2.95 (m, 1H), 2.82 – 2.70 (m, 2H), 2.68 – 2.62 (m, 1H), 1.94 – 1.86 (m, 1H), 1.85 – 1.78 (m, 1H), 1.60 – 1.48 (m, 3H), 1.42 – 1.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 148.1, 113.1, 54.9, 47.2, 46.1, 45.1, 39.9, 28.0, 27.9, 27.8.; The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak AS-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.27 and 6.35 min.



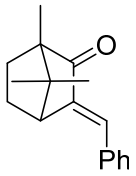
(1o)

(1*R*,4*S*)-3-methylene-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one (**1o**): 46% yield; $[\alpha]^{30}_{D} = +36.3$ (*c* 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.19 – 7.09 (m, 2H), 5.78 (s, 1H), 5.28 (s, 1H), 4.07 – 4.02 (m, 1H), 3.72 – 3.66 (m, 1H), 2.62 – 2.55 (m, 1H), 2.33 – 2.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 147.5, 145.2, 140.9, 127.6, 126.9, 123.5, 121.4, 112.6, 56.8, 50.5, 48.9.; The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak OJ-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 13.95 and 18.83 min.



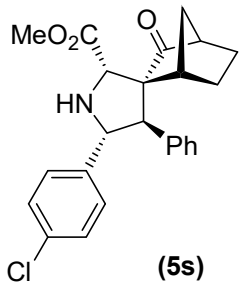
(1p)

(*Z*)-3-benzylidenebicyclo[2.2.1]heptan-2-one (**1p**): 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.85 (m, 2H), 7.39 – 7.28 (m, 3H), 6.60 (s, 1H), 3.17 – 3.08 (m, 1H), 2.81 – 2.71 (m, 1H), 1.97 – 1.82 (m, 3H), 1.67 – 1.56 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 141.8, 134.7, 133.1, 130.4, 129.1, 128.0, 51.8, 46.8, 37.1, 28.5, 23.7.



(1q)

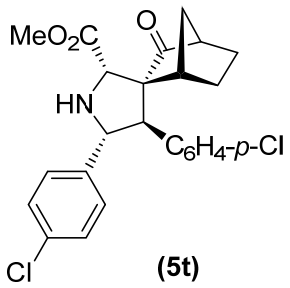
(*E*)-3-benzylidene-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1q**): 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.44 – 7.31 (m, 3H), 7.24 (s, 1H), 3.11 (d, *J* = 4.2 Hz, 1H), 2.23 – 2.14 (m, 1H), 1.83 – 1.74 (m, 1H), 1.65 – 1.48 (m, 2H), 1.03 (s, 3H), 1.00 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 142.0, 135.6, 129.7, 128.7, 128.6, 127.5, 57.1, 49.1, 46.7, 30.6, 25.9, 20.6, 18.3, 9.3.



(5s)

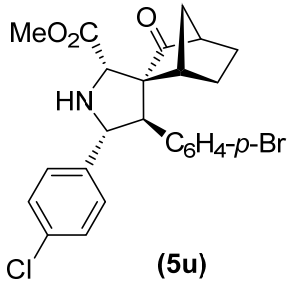
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*)-5'-(4-chlorophenyl)-3-oxo-4'-phenylspiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (**5s**)**:** Yield (48%); yellow liquid; $[\alpha]^{30}_{D}$ = +57.5 (*c* 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.03 (m, 7H), 4.64 (d, *J* = 11.2 Hz, 1H), 3.98 (s, 1H), 3.76 (d, *J* = 11.2 Hz, 1H), 3.73 (s, 3H), 2.85 – 2.78 (m, 1H), 2.66 – 2.61 (m, 1H), 2.24 – 2.17 (m, 1H), 1.67 – 1.56 (m, 1H), 1.56 – 1.48 (m, 1H), 1.17 – 1.06 (m, 1H), 1.06 – 0.96 (m, 1H), 0.83 – 0.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 173.0, 138.2, 137.0, 133.5, 129.1, 128.8, 128.2, 127.2, 69.1, 68.5, 65.7, 56.1, 52.5, 49.3, 44.7, 36.3, 24.8, 23.0.; HRMS (ESI+) Calcd. $C_{24}H_{24}ClNNaO_3^+$ ($[M+Na]^+$): 432.1337, found: 432.1337. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H,

i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.56 and 15.95 min.



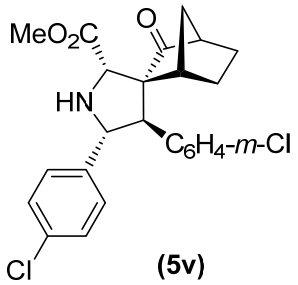
(5t)

Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -4',5'-bis(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5t): Yield (49%); yellow solid; m.p. 145-147 °C; $[\alpha]^{30}_D$ = +21.5 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.19 – 6.83 (m, 4H), 4.57 (d, *J* = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.72 (d, *J* = 11.2 Hz, 1H), 2.83 – 2.78 (m, 1H), 2.67 – 2.62 (m, 1H), 2.26 – 2.18 (m, 1H), 1.71 – 1.61 (m, 1H), 1.59 – 1.52 (m, 1H), 1.22 – 1.10 (m, 1H), 1.05 – 0.94 (m, 1H), 0.86 – 0.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 173.0, 138.0, 135.6, 133.8, 133.1, 129.1, 128.9, 128.5, 69.2, 68.5, 65.7, 55.5, 52.6, 49.3, 44.8, 36.4, 24.8, 23.2.; HRMS (ESI+) Calcd. For $C_{24}H_{23}Cl_2NNaO_3^+$ ($[M+Na]^+$): 466.0947, found: 466.0949. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.35 and 16.73 min.



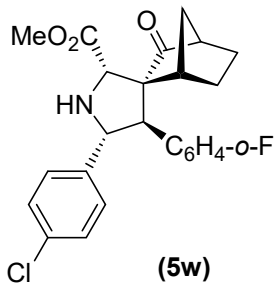
(5u)

Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -4'-(4-bromophenyl)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5u): Yield (50%); yellow solid; m.p. 148-150 °C; $[\alpha]^{30}_D$ = +15.3 (*c* 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.27 (m, 4H), 6.99 (s, 2H), 4.57 (d, *J* = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.70 (d, *J* = 11.2 Hz, 1H), 2.82 – 2.78 (m, 1H), 2.67 – 2.63 (m, 1H), 2.26 – 2.18 (m, 1H), 1.71 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.22 – 1.11 (m, 1H), 1.05 – 0.94 (m, 1H), 0.86 – 0.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 173.0, 138.0, 136.1, 133.8, 131.4, 129.1, 129.0, 121.2, 69.1, 68.5, 65.8, 55.6, 52.6, 49.3, 44.8, 36.4, 24.8, 23.2.; HRMS (ESI+) Calcd. For $C_{24}H_{23}BrClNNaO_3^+$ ($[M+Na]^+$): 510.0442, found: 510.0446. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.58 and 16.81 min.



(5v)

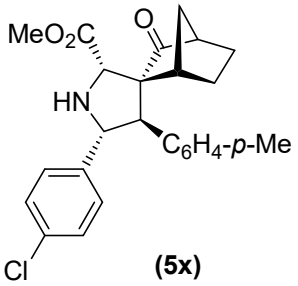
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -4'-(3-chlorophenyl)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5v): Yield (48%); white solid; m.p. 123-125 °C; $[\alpha]^{30}_{D}$ = +39.0 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.21 – 6.85 (m, 4H), 4.62 (d, *J* = 10.8 Hz, 1H), 3.93 (s, 1H), 3.724 (s, 3H), 3.723 (d, *J* = 10.8 Hz, 1H), 3.24 (s, 1H), 2.87 – 2.78 (m, 1H), 2.72 – 2.61 (m, 1H), 2.23 – 2.17 (m, 1H), 1.72 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.23 – 1.13 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 1H), 0.79 (d, *J* = 10.0Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 172.7, 139.1, 137.7, 134.2, 133.8, 129.5, 129.2, 129.0, 127.5, 68.9, 68.4, 65.6, 55.6, 52.6, 49.2, 44.7, 36.3, 24.7, 23.1.; HRMS (ESI+) Calcd. For $C_{24}H_{23}Cl_2NNaO_3^+$ ($[M+Na]^+$): 466.0947, found: 466.0953. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.91 and 16.93 min.



(5w)

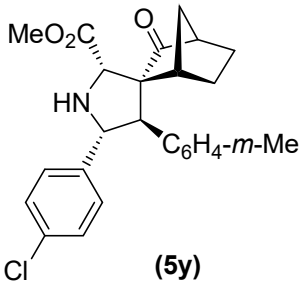
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-4'-(2-fluorophenyl)-3-oxospiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5w): Yield (51%); yellow liquid; $[\alpha]^{30}_{D}$ = +48.6 (*c* 0.66, CH_2Cl_2); Major (**5w**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 3H), 7.27 – 7.21 (m, 3H), 6.93 – 6.86 (m, 2H), 4.60 (d, *J* = 10.0 Hz, 1H), 4.14 (s, 1H), 3.76 (s, 3H), 3.46 (d, *J* = 10.0 Hz, 1H), 2.91– 2.84 (m, 1H), 2.68– 2.64 (m, 1H), 2.54 (brs, 1H), 2.14– 2.06 (m, 1H), 1.76 – 1.63 (m, 1H), 1.54– 1.48 (m, 1H), 1.33 – 1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 172.5, 161.1 (d, *J* = 244 Hz), 138.4, 133.5, 132.9, 128.81, 128.75, 125.4 (d, *J* = 14 Hz), 124.5 (d, *J* = 4 Hz), 116.2 (d, *J* = 22 Hz), 70.4, 68.0, 66.7, 58.3, 52.6, 49.4, 44.3 (d, *J* = 2 Hz), 36.1, 25.7, 23.6. Minor (**3w**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 3H), 7.21 – 7.15 (m, 3H), 7.02 – 6.96 (m, 2H), 4.35 (d, *J* = 9.2 Hz, 1H), 4.03 (s, 1H), 3.99 (d, *J* = 9.2 Hz, 1H),3.77 (s, 3H), 2.74 – 2.67 (m, 1H), 2.65 – 2.55 (m, 1H), 2.09 – 2.00 (m, 1H), 1.76 – 1.63 (m, 1H), 1.52 – 1.47 (m, 1H), 1.33 – 1.07 (m, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 217.75, 171.75, 161.1 (d, J = 246 Hz), 137.7, 133.7, 132.8, 129.4, 129.3, 126.8 (d, J = 15 Hz), 124.3 (d, J = 3 Hz), 115.7 (d, J = 23 Hz), 69.0 (d, J = 4 Hz), 67.52, 66.6, 58.3, 52.7, 49.6, 43.57, 35.8, 25.6, 23.9.; HRMS (ESI+) Calcd. For $C_{24}H_{23}ClFNNaO_3^+$ ([M+Na]$^+$): 450.1243, found: 450.1243. The product was analyzed by HPLC to determine the enantiomeric excess: 83% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.47 and 13.42 min.



(5x)

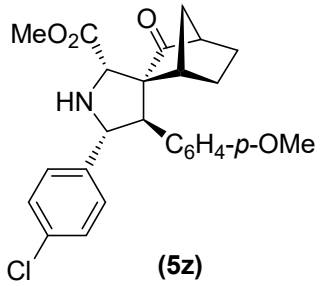
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-3-oxo-4'-(p-tolyl)spiro[bicyclo[2.2.1]heptane -2,3'-pyrrolidine]-2'-carboxylate (5x): Yield (47%); yellow solid; m.p. 124-126 °C; $[\alpha]^{30}_D$ = +40.8 (*c* 0.66, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.24 (m, 2H), 6.97 (m, 4H), 4.59 (d, J = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.72 (d, J = 11.2 Hz, 1H), 2.80 – 2.76 (m, 1H), 2.64 – 2.60 (m, 1H), 2.24 (s, 3H), 2.22 – 2.17 (m, 1H), 1.67 – 1.57 (m, 1H), 1.57 – 1.49 (m, 1H), 1.16 – 0.98 (m, 2H), 0.89 – 0.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 173.1, 138.5, 136.8, 133.9, 133.5, 129.2, 129.0, 128.8, 69.3, 68.5, 65.9, 55.9, 52.5, 49.4, 44.9, 36.4, 24.9, 23.1, 21.0.; HRMS (ESI+) Calcd. For $C_{25}H_{26}ClNNaO_3^+$ ([M+Na]$^+$): 446.1493, found: 446.1497. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.70 and 12.29 min.



(5y)

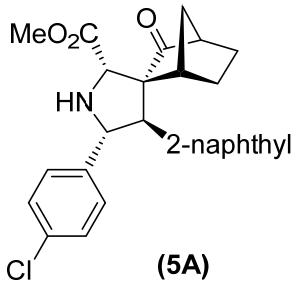
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-3-oxo-4'-(m-tolyl)spiro[bicyclo[2.2.1]heptane -2,3'-pyrrolidine]-2'-carboxylate (5y): Yield (46%); white to yellow solid; m.p. 118-120 °C; $[\alpha]^{30}_D$ = +45.1 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.10 – 6.71 (m, 4H), 4.62 (d, J = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.71 (d, J = 11.2 Hz, 1H), 2.81 – 2.78 (m, 1H), 2.65 – 2.62 (m, 1H), 2.22 (s, 3H), 2.21 – 2.12 (m, 1H), 1.69 – 1.57 (m, 1H), 1.56 – 1.48 (m, 1H), 1.16 – 0.97 (m, 2H),

0.85 – 0.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.0, 173.0, 138.4, 133.5, 129.2, 128.8, 128.1, 128.0, 69.3, 68.5, 65.8, 56.2, 52.5, 49.4, 44.8, 36.4, 24.9, 23.1, 21.2.; HRMS (ESI+) Calcd. For $C_{25}H_{26}ClNNaO_3^+$ ($[M+Na]^+$): 446.1493, found: 446.1493. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.49 and 11.77 min.



(5z)

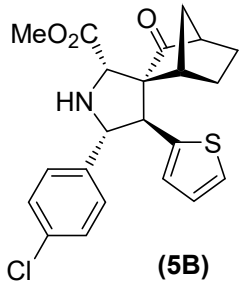
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-4'-(4-methoxyphenyl)-3-oxospiro[bicycle [2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5z): Yield (42%); yellow solid; m.p. 140-141 °C; $[\alpha]^{30}_D$ = +36.0 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.26 – 7.22 (m, 2H), 7.00 (s, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 3.95 (s, 1H), 3.73 (s, 3H), 3.721 (s, 3H), 3.719 (d, *J* = 11.6 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.65 – 2.60 (m, 1H), 2.24 – 2.19 (m, 1H), 1.67 – 1.58 (m, 1H), 1.56 – 1.51 (m, 1H), 1.18 – 1.07 (m, 1H), 1.05 – 0.96 (m, 1H), 0.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 173.2, 158.6, 138.5, 133.5, 129.2, 128.8, 128.7, 113.6, 69.2, 68.4, 65.7, 55.4, 55.0, 52.5, 49.4, 44.9, 36.4, 24.9, 23.1.; HRMS (ESI+) Calcd. For $C_{25}H_{26}ClNNaO_4^+$ ($[M+Na]^+$): 462.1443, found: 462.1443. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.61 and 19.50 min.



(5A)

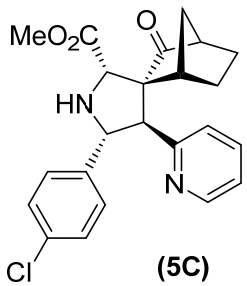
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-4'-(naphthalen-2-yl)-3-oxospiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5A): Yield (46%); white solid; m.p. 140-142 °C; $[\alpha]^{30}_D$ = +10.5 (*c* 0.75, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.34 (m, 9H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.03 (s, 1H), 3.91 (d, *J* = 11.2 Hz, 1H), 3.76 (s, 3H), 2.90 – 2.85 (m, 1H), 2.66 – 2.63 (m, 1H), 2.24 –

2.19 (m, 1H), 1.59 – 1.48 (m, 2H), 1.10 – 0.73 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 173.1, 153.5, 138.3, 133.6, 133.0, 132.4, 129.2, 128.8, 127.9, 127.7, 127.5, 126.2, 125.9, 69.4, 68.7, 66.4, 56.9, 52.6, 49.3, 44.8, 36.3, 24.9, 23.3.; HRMS (ESI+) Calcd. For $C_{28}H_{26}ClNNaO_3^+$ ($[M+Na]^+$): 482.1493, found: 482.1493. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, *i*-propanol /hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.79 and 11.80 min.



(5B)

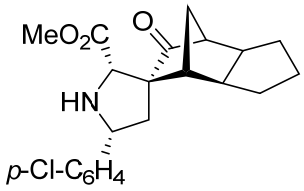
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-3-oxo-4'-(thiophen-2-yl)spiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5B): Yield (45%); yellow solid; m.p. 157-159 ºC; $[\alpha]^{30}_D$ = +82.6 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.10 (dd, *J* = 4.8, 0.8 Hz, 1H), 6.82 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.70 (d, *J* = 3.6 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.08 (d, *J* = 11.2 Hz, 1H), 3.98 (s, 1H), 3.73 (s, 3H), 2.85 – 2.80 (m, 1H), 2.68 – 2.64 (m, 1H), 2.28 – 2.22 (m, 1H), 1.76 – 1.66 (m, 1H), 1.61 – 1.55 (m, 1H), 1.25 – 1.16 (m, 2H), 0.79 – 0.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5, 173.3, 139.2, 138.5, 133.8, 129.4, 128.8, 126.8, 126.0, 124.4, 68.8, 68.7, 66.9, 52.5, 51.7, 49.4, 45.0, 36.7, 25.8, 22.6.; HRMS (ESI+) Calcd. For $C_{22}H_{22}ClNNaO_3S^+$ ($[M+Na]^+$): 416.1082, found: 416.1085. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.61 and 15.38 min.



(5C)

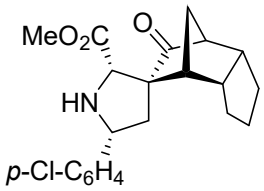
Methyl (1*S*,2*R*,2'*S*,4*R*,4'*R*,5'*R*) -5'-(4-chlorophenyl)-3-oxo-4'-(pyridin-2-yl)spiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5C): Yield (46%); yellow solid; m.p. 162-164 ºC; $[\alpha]^{30}_D$ = +15.0 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (td, *J* = 8.0, 2.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.08 (ddd, *J* = 7.2, 4.8, 0.8 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.90 (d, *J* =

10.0 Hz, 1H), 4.16 (s, 1H), 3.75 (s, 3H), 3.71 (d, *J* = 10.0 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.66 – 2.62 (m, 1H), 2.17 – 2.12 (m, 1H), 1.69 – 1.60 (m, 1H), 1.55 – 1.49 (m, 1H), 1.22 – 1.13 (m, 1H), 1.08 – 1.00 (m, 1H), 0.49 – 0.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 173.0, 158.1, 149.2, 139.3, 136.1, 133.2, 129.2, 128.5, 124.5, 122.2, 69.4, 69.2, 66.3, 59.1, 52.4, 49.5, 44.3, 36.2, 25.2, 23.4.; HRMS (ESI+) Calcd. For $C_{23}H_{23}ClN_2NaO_3^+$ ($[M+Na]^+$): 433.1289, found: 433.1287. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 9.05 and 15.24 min.



(5D)

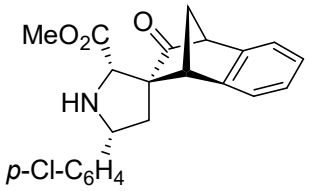
Methyl (2*S*,3*S*,3a'*R*,4'*R*,5*R*,7'*S*,7a'*S*)-5-(4-chlorophenyl)-6'-oxooctahydrospiro[pyrrolidine-3,5'-[4,7] methanoindene]-2-carboxylate (5D): Yield (48%); yellow liquid; $[\alpha]^{30}_D$ = −37.8 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.15 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.82 (s, 1H), 3.67 (s, 3H), 2.52 (brs, 1H), 2.46 – 2.41 (m, 2H), 2.38 – 2.30 (m, 1H), 2.13 – 1.79 (m, 8H), 1.40 – 1.29 (m, 1H), 1.23 – 1.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 173.2, 139.9, 133.3, 128.7, 128.4, 68.7, 64.2, 62.0, 53.7, 52.3, 49.1, 42.9, 41.9, 39.6, 32.1, 31.9, 28.9, 27.8.; HRMS (ESI+) Calcd. For $C_{21}H_{25}ClNO_3^+$ ($[M+H]^+$): 374.1517, found: 374.1517. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak IA, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.25 and 25.54 min.



(5E)

Methyl (2*S*,3*S*,3a'*R*,4'*R*,5*R*,7'*S*,7a'*R*)-5-(4-chlorophenyl)-6'-oxooctahydrospiro[pyrrolidine-3,5'-[4,7] methanoindene]-2-carboxylate (5E): Yield (45%); white liquid; $[\alpha]^{30}_D$ = +2.1 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.21 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.90 (s, 1H), 3.67 (s, 3H), 2.90 – 2.82 (m, 2H), 2.70 – 2.66 (m, 1H), 2.58 – 2.54 (m, 1H), 2.43 – 2.33 (m, 2H), 2.11 – 2.03 (m,

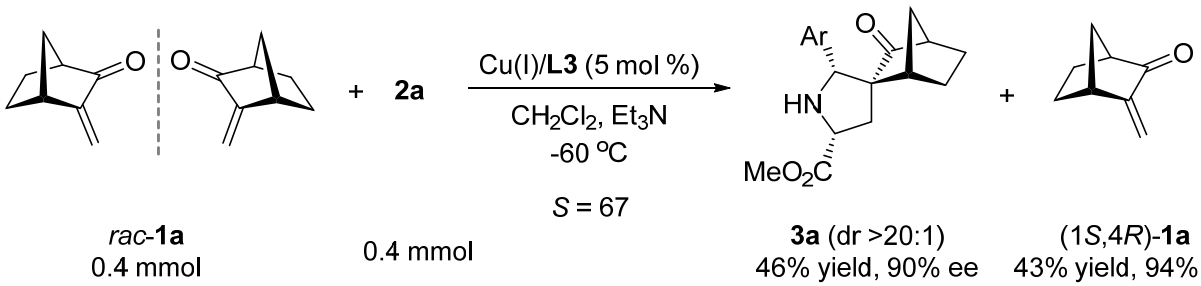
1H), 1.85 – 1.78 (m, 2H), 1.63 – 1.47 (m, 4H), 1.38 – 1.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.2, 173.1, 139.9, 133.4, 128.7, 128.5, 70.6, 67.0, 62.3, 54.5, 52.3, 47.4, 47.1, 45.7, 40.2, 39.3, 27.5, 27.2, 26.8.; HRMS (ESI+) Calcd. For $C_{21}H_{24}ClNNaO_3^+$ ([M+Na]$^+$): 396.1337, found: 396.1337. The product was analyzed by HPLC to determine the enantiomeric excess: 85% ee (Chiralpak AD-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 15.47 and 25.34 min.



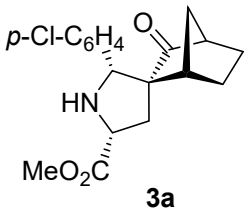
(5F)

Methyl (1'*R*,2*S*,3*S*,4'*S*,5*R*)-5-(4-chlorophenyl)-3'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-[1,4] methanonaphthalene]-2-carboxylate (5F): Yield (47%); yellow solid; m.p. 166-167 ºC; $[\alpha]^{30}_D$ = −183.8 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.27 – 7.25 (m, 2H), 7.19 – 7.12 (m, 2H), 4.28 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.65 – 3.58 (m, 2H), 2.82 – 2.76 (m, 1H), 2.68 (brs, 1H), 2.61 – 2.55 (m, 1H), 1.90 – 1.80 (m, 1H), 1.36 – 1.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 172.9, 146.3, 140.0, 139.5, 133.3, 128.6, 128.3, 127.4, 127.3, 123.5, 123.1, 68.7, 61.9, 60.9, 56.6, 52.5, 51.6, 47.2, 44.8.; HRMS (ESI+) Calcd. For $C_{22}H_{20}ClNNaO_3^+$ ([M+H]$^+$): 404.1024, found: 404.1024. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AS-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 9.30 and 16.81 min.

Cu(I)/L3-Catalyzed Kinetic Resolution of 3-Methylene-2-Norcamphor



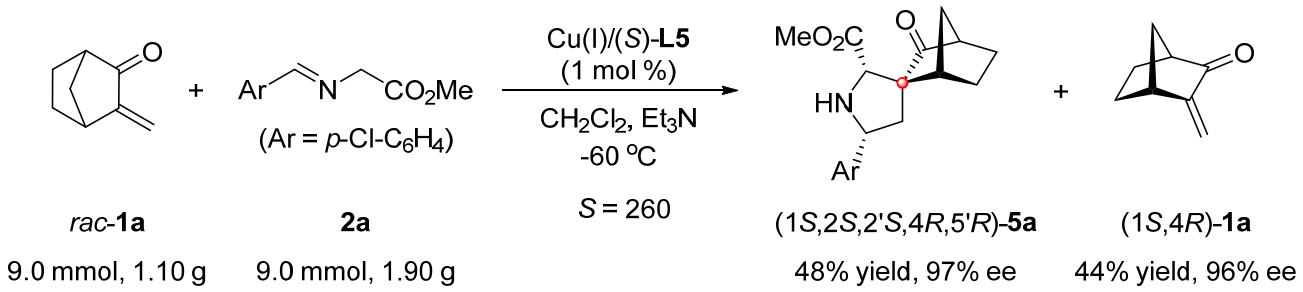
(*S*)-TF-BiphamPhos **L3** (20.1 mg, 0.022 mmol) and $Cu(CH_3CN)_4BF_4$ (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL CH_2Cl_2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -60 °C and the imino ester **2a** (0.40 mmol), Et_3N (0.060 mmol) were added sequentially. Then 3-methylene-2-norcamphor **1a** (0.40 mmol) was added. After the reaction completed in 1 h (monitored by chiral-phase GC and HPLC), the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the recovered **1a** and the cycloadduct **3a**, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively.



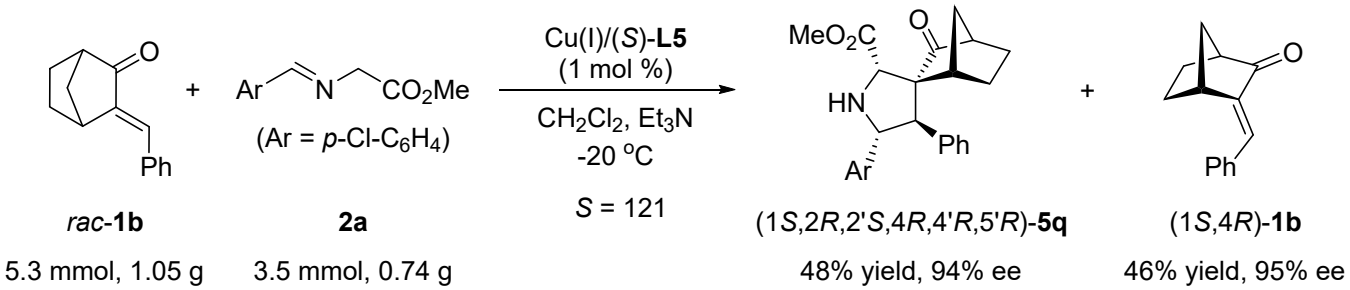
3a

Methyl (1S,2S,2'R,4R,5'R)-2'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine] -5'-carboxylate (3a): Yield (46%); yellow liquid; $[\alpha]^{24}_D$ = +3.5 (*c* 0.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H), 4.17 (s, 1H), 3.94 (t, *J* = 8.0 Hz, 1H), 3.82 (s, 3H), 2.94 (s, 1H), 2.55 – 2.48 (m, 1H), 2.32 – 2.25 (m, 3H), 1.84 – 1.64 (m, 3H), 1.54 – 1.40 (m, 2H), 1.35 – 1.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 173.6, 138.6, 133.7, 129.4, 128.6, 71.5, 63.5, 58.5, 52.3, 49.7, 45.2, 38.1, 34.5, 26.0, 24.7.; HRMS (ESI+) Calcd. For $C_{18}H_{20}ClNNaO_3$ ($[M+Na]^+$): 356.1024, found: 356.1022. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak AD-H, *i*-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 17.61 and 27.76 min.

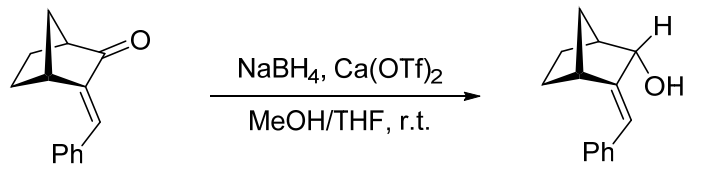
Gram Scales and Synthetic Transformations



(*S*)-TF-BiphamPhos **L5** (79.0 mg, 0.099 mmol) and $Cu(CH_3CN)_4BF_4$ (28.3 mg, 0.090 mmol) were dissolved in 9.0 mL CH_2Cl_2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -60 °C and the imino ester **2a** (1.90 g, 9.00 mmol), Et_3N (0.14 g, 1.35 mmol) were added sequentially. Then 3-methylene-2-norcamphor **1a** (1.10 g, 9.00 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture without quenched and the residue was purified by column chromatography rapidly to give the recovered **1a** and the cycloadduct **5a**, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively. Meanwhile, nearly 80% yield of chiral ligand **L5** could be recovered, which can be reused in the model reaction in Table 1 under standard reaction condition without loss of yield and enantioselectivity control.



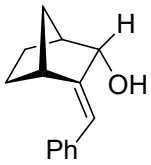
(*S*)-TF-BiphamPhos **L5** (46.3 mg, 0.058 mmol) and $Cu(CH_3CN)_4BF_4$ (16.7 mg, 0.053 mmol) were dissolved in 5.0 mL CH_2Cl_2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -20 °C and the imino ester **2a** (0.74 g, 3.50 mmol), Et_3N (0.08 g, 0.80 mmol) were added sequentially. Then 3-benzylidene-2-norcamphor **1b** (1.05 g, 5.30 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture without quenched and the residue was purified by column chromatography rapidly to give the recovered **1a** and the cycloadduct **5q**, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively. Meanwhile, nearly 80% yield of chiral ligand **L5** could be recovered, which can be reused in the model reaction in Table 1 under standard reaction condition without loss of yield and enantioselectivity control.



(1*S*,4*R*)-**1b**
95% ee

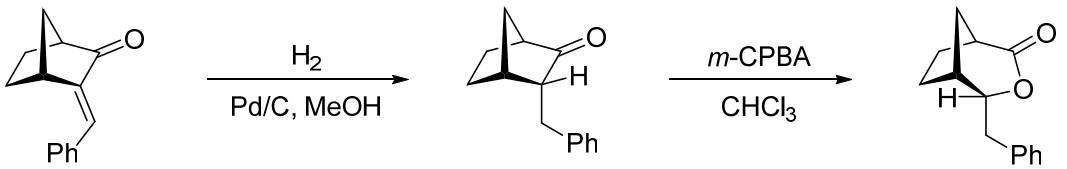
6, 88% yield
95% ee, >20:1 dr

To a suspension of $NaBH_4$ (2.0 mmol, 75.7 mg) in THF (6 mL) was added in one portion $Ca(OTf)_2$ (0.5 mmol, 169.1 mg) and (1*S*,4*R*)-**1b** (0.80 mmol, 158.6 mg, 95% ee) in MeOH (0.5 mL). The reaction mixture was stirred for 30 min at rt until consumption of the starting material (monitored by TLC). The reaction mixture was quenched with H_2O (3 mL) and the aqueous phase was extracted with Et_2O (3 × 4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (EtOAc:hexane = 1:10 to 1:5) to give **6** in 88% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.



6

(1*S*,2*S*,4*R*)-3-((*E*)-benzylidene)bicyclo[2.2.1]heptan-2-ol (6): Yield (88%); white solid; m.p. 108-110 °C; $[\alpha]^{30}_D = -300.8$ (*c* 0.41, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.23 – 7.17 (m, 1H), 6.37 (s, 1H), 4.52 (brs, 1H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.49 – 2.41 (m, 1H), 1.91 – 1.79 (m, 3H), 1.63 – 1.52 (m, 2H), 1.45 – 1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 137.8, 128.3, 128.0, 126.3, 120.9, 77.0, 41.9, 41.6, 36.2, 29.5, 19.4. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.20 and 8.05 min.



(1*S*,4*R*)-**1b**
95% ee

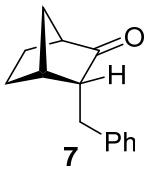
7, 81% yield
95% ee, >20:1 dr

8, 98% yield
96% ee

A solution of (1*S*,4*R*)-**1b** (0.80 mmol, 158.6 mg, 95% ee) in 4 mL MeOH was added 16 mg Pd/C (10%).

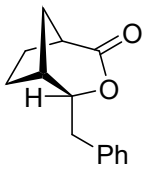
The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 bar) for 4 h. The reaction mixture was filtered through a short plug of silica (eluted with EtOAc) and the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:20) to give (1*S*,3*R*,4*R*)-3-benzylbicyclo[2.2.1]heptan-2-one **7** in 81% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.

To a solution of *m*-CPBA (0.22 mmol) and $NaHCO_3$ (0.22 mmol) in DCM (6 mL) at 0-5 °C, was added **7** (0.2 mmol) in DCM (1 mL) dropwise over 10 min, the reaction was allowed to warm to rt. After 6 h the reaction was filtrated, the residue was washed with DCM. The organic filtrate was washed with sat. $NaHCO_3$, sat. NaCl, dried over Na_2SO_4 and concentrated in vacuum. The concentrate was directly purified by column chromatography (EtOAc:hexane = 1:10 to 1:3) to give **8** in 98% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.



7

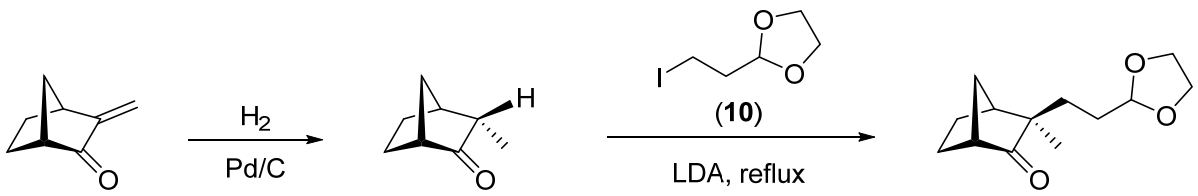
(1*S*,3*R*,4*R*)-3-benzylbicyclo[2.2.1]heptan-2-one (7): Yield (81%); colorless liquid; $[\alpha]^{30}_D$ = −35.3 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 3.13 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.49 – 2.46 (m, 1H), 2.42 (dd, *J* = 14.0, 2.4 Hz, 1H), 2.36 – 2.29 (m, 1H), 1.91 – 1.76 (m, 2H), 1.68 – 1.62 (m, 2H), 1.58 – 1.53 (m, 1H), 1.52 – 1.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8, 140.3, 128.48, 128.47, 126.1, 55.9, 50.5, 37.9, 36.9, 32.0, 25.4, 21.2.; HRMS (ESI+) Calcd. For $C_{14}H_{16}NaO^+$ ($[M+Na]^+$): 223.1093, found: 223.1093. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak OJ-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.08 and 11.86 min.



8

(1*S*,4*R*,5*R*)-4-benzyl-3-oxabicyclo[3.2.1]octan-2-one (8): Yield (98%); white solid; m.p. 70-72 °C; $[\alpha]^{30}_D$ = +20.7 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.22 – 7.19 (m,

2H), 4.52 (ddd, *J* = 8.4, 6.4, 2.4 Hz, 1H), 3.06 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.83 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.13 – 2.05 (m, 1H), 1.99 – 1.87 (m, 3H), 1.79 – 1.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 136.6, 129.3, 128.6, 126.7, 85.9, 41.8, 39.0, 35.9, 33.2, 29.4, 21.0.; HRMS (ESI+) Calcd. For $C_{14}H_{16}NaO_2^+$ ($[M+Na]^+$): 239.1043, found: 239.1043. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 210 nm); t_r = 27.92 and 44.25 min.



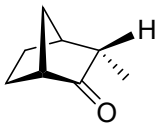
(1*R*,4*S*)-**1a**
>99% ee

9, 99% yield
>20:1 dr, >99% ee

11, 70% yield
>20:1 dr, >99% ee

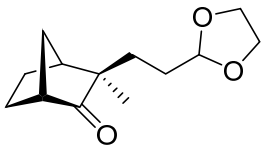
A solution of (1*R*,4*S*)-**1a** (2.50 mmol, 305 mg, >99% ee) in 5 mL MeOH was added 50 mg 10% Pd/C. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 bar) for 2 h. The reaction mixture was filtered through a short plug of silica (eluted with Et_2O) and The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (Et_2O:hexane = 1:20) to give (1*R*,3*S*,4*S*)-3-methylbicyclo[2.2.1]heptan-2-one **9** in 99% yield which was then directly analyzed by GC to determine the enantiomeric excess.

A 2.5 M solution of *n*-butyllithium in hexane (0.60 mL, 1.50 mmol) was added dropwise to a solution of THF (2 mL) and diisopropylamine (161.9 mg, 1.60 mmol) at 0 ºC and let stir under argon for 10 min. And (1*R*,3*S*,4*S*)-3-methylbicyclo[2.2.1] heptan-2-one **9** (124.2 mg, 1.00 mmol) was added. After 30 min, 2-(2-iodoethyl)-l,3-dioxolane **10** (342 mg, 1.50 mmol) was added dropwise. The mixture was refluxed for 20 hours and cooled down to room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc then the organic was dried over Na_2SO_4 and concentrated to give an oil. The crude product was purified by column chromatography (Et_2O:hexane = 1:20) to give (1*R*,3*R*,4*S*)-3-(2-(1,3-dioxolan-2-yl) ethyl)-3-methylbicyclo[2.2.1]heptan-2-one **11** in 70% yield.



9

(1*R*,3*S*,4*S*)-3-methylbicyclo[2.2.1]heptan-2-one (9): Yield (99%); colorless liquid; $[\alpha]^{30}_D$ = −46.1 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 – 2.58 (m, 1H), 2.57 – 2.50 (m, 1H), 2.17 – 2.07 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 (m, 1H), 1.66 – 1.54 (m, 3H), 1.44 – 1.35 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8, 50.3, 48.3, 40.4, 37.2, 25.3, 20.9, 10.7.; HRMS (ESI+) Calcd. For $C_8H_{12}NaO^+$ ($[M+Na]^+$): 147.0780, found: 147.0780. The product was analyzed by GC to determine the enantiomeric excess: >99% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 150 ºC, carrier gas: N_2, 1.0 mL/min); t_r = 8.88 and 9.42 min.



11

(1*R*,3*R*,4*S*)-3-(2-(1,3-dioxolan-2-yl)ethyl)-3-methylbicyclo[2.2.1]heptan-2-one (11): Yield (70%); $[\alpha]^{22}_D$ = −79.3 (*c* 3.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (t, *J* = 4.4 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.87 – 3.78 (m, 2H), 2.59 – 2.54 (m, 1H), 2.37 – 2.30 (m, 1H), 2.01 (d, *J* = 10.4 Hz, 1H), 1.86 – 1.81 (m, 1H), 1.79 – 1.70 (m, 2H), 1.69 – 1.56 (m, 2H), 1.54 – 1.42 (m, 4H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.1, 104.4, 64.9, 50.0, 49.2, 43.4, 34.8, 28.6, 28.4, 25.0, 23.1, 18.3.;

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