TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2020) 44: 1445-1462

doi:10.3906/kim-2004-81

Effective synthesis of bicyclodienes via palladium-catalyzed asymmetric allylic alkylation and ruthenium-catalyzed cycloisomerization

Nizam HAVARE*
Department of Chemistry, School of Humanities & Sciences, Stanford University, Stanford, California 94305-5580, United States

Received: 30.04.2020 • **Accepted/Published Online:** 18.07.2020 • **Final Version:** 16.12.2020

Abstract: [n.3.0]Bicycles (n = 3–6) can be synthesized using palladium-catalyzed asymmetric allylic alkylation followed by ruthenium-catalyzed cycloisomerization. New types of triarylphosphino-1,2-diaminooxazoline ligands show the same high levels of enantioselectivity observed with Trost ligand when employed in Pd-catalyzed allylic alkylation reactions. The enyne products of these allylic alkylation reactions were further elaborated using a Ru-catalyzed redox isomerization process, for which a mechanism is proposed.

Key words: Synthetic method development, asymmetric catalysis, *Tsuji-Trost*-reaction, palladium-catalyzed asymmetric allylic alkylation, ruthenium-catalyzed cycloisomerization

1. Introduction

The development of novel and effective cyclization methods constitutes a continuing challenge in organic synthesis, as five- and six-membered cycles are essential structural units in pharmaceuticals, agrochemicals, and other biologically active molecules [1]. Transition-metal carbenes play a fundamental role as reactive intermediates in the synthesis of these pharmaceuticals and/or agrochemicals [2,3]. Since the initial report by Trost et. al., metal-catalyzed enyne cycloisomerization [4] has become an important tool for synthesizing complex molecules [5–8] from simple building blocks while maintaining good selectivity [9] and perfect atom economy [10]. Several inter- and intramolecular reaction types have been developed including: alkyne addition to allylic alcohols [11–14], intramolecular addition of alkyne to alcohol [15,16], Alder-ene reaction [17–19] and its application to natural product synthesis [20–29], and allene-alkene addition [30,31] using common Ru-complexes: $[CpRu(CH_3CN)_3]$ PF_6, $[CpRu(PPh_3)_2Cl]$, $[IndRu(PPh_3)_2Cl]$, [CpRu(cod)Cl], and chiral $[C_{19}H_{23}N_2O_2RuS]$ [32–35]. The utility of ruthenium catalysis has been studied in intramolecular cycloisomerizations, providing an efficient, atom-economical method to access an array of 1,3- or 1,4-dienes [31] and other types of bicyclic compounds [36,37]. The synthesis of *cis* and/or *trans* 2-alkylbicyclo[n.3.0]-diene compounds starting from the derivatives of allene-2-yl, cycloalk-2-enyl dimethyl malonate has also been reported in good to excellent yield using palladium [38–45].

Palladium-catalyzed asymmetric allylic alkylation (AAA), also known as the Tsuji-Trost reaction, is one of the most efficient methods for forming allylic C-C, C-O, C-N, C-S, and C-P bonds. It tolerates a broad range of olefins that contain a leaving group in the allylic position, employs mild reaction conditions, and forms the desired products in very high enantioselectivities and yields [6,46,47]. The Trost-Group has had a long-standing interest in this area, as well as in the area of TM-catalyzed AAA, and the aim was to combine these two general methods into a unified approach to synthesize bicyclodienes.

A useful new application of these two general methods is reported here for the synthesis of 2-alkyl-bicyclo[n.3.0]-diene compounds. Here n = 3–6. Starting from malonate protected by trityl group and cycloalk-2-enyl carbonyl derivatives, enyne compounds can be synthesized with high enantioselectivities and yields. These compounds were then deprotected using $BiCl_3$ and treated with $[IndRu(PPh_3)_2Cl]$ **1** [48] for cyclized end products (Figure 1).

2. Results

Malonate 2a [49] was tested as a nucleophile with cyclopent-2-enyl benzoate 3a as an electrophile under different reaction conditions to obtain high enantioselectivity and yield of allylated malonate 4 (Table 1). $Pd_2(dba)_3{\cdot}CHCl_3$ catalyzed the asymmetric allylic reaction in the presence of (*S*,*S*)-Trost-ligand (L_{std}) in THF in very good yield and very low enantioselectivity (entry 1, Table 1).

* Correspondence: nizamhavare@yahoo.de

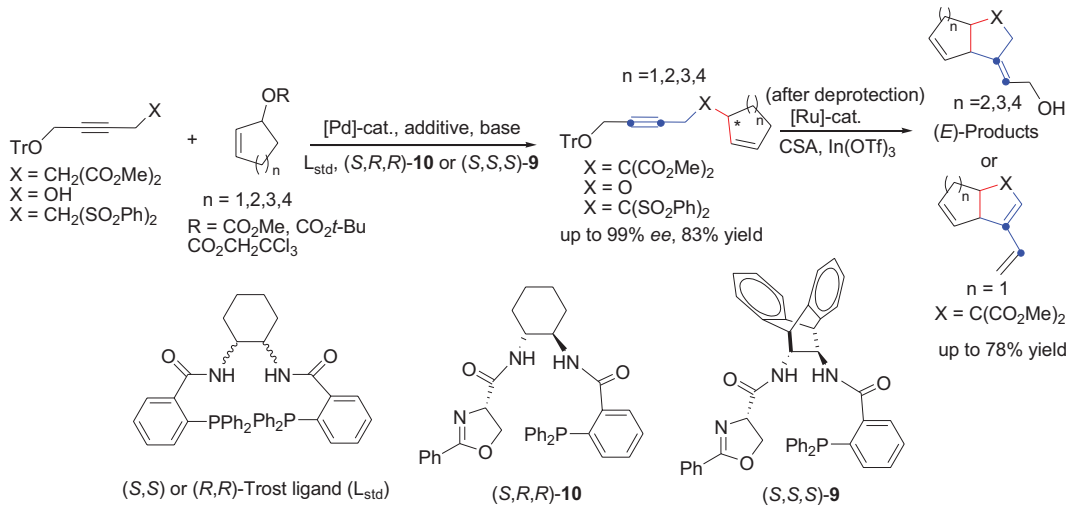
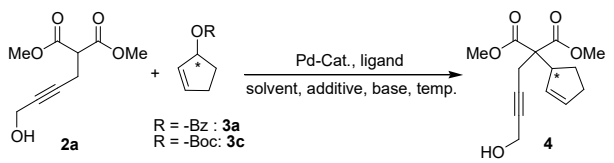


Figure 1. New synthetic method using Pd-catalyzed AAA and Ru-catalyzed cycloisomerization.

Table 1. Optimization of palladium-catalyzed asymmetric allylic alkylation (Pd-catalyzed AAA).

Entry	Cat.	-R	L	Base	Additive	Solvent	Temp.	Yield (%)	*ee* (%)
1	$Pd_2(dba)_3CHCl_3$	-Boc	L_{std} (*S*,*S*)	NaH	-	THF	r.t.	70	16
2	$[\eta^3\text{-}C_3H_5PdCl]_2$	-Bz	L_{std} (*R*,*R*)	NaH	THAB	CH_2Cl_2	r.t.	71	-49
3	$[\eta^3\text{-}C_3H_5PdCl]_2$	-Bz	L_{std} (*R*,*R*)	NaH/DBU	-	CH_2Cl_2	-20 → r.t.	70	-55
4	$Pd_2(dba)_3CHCl_3$	-Boc	L_{std} (*S*,*S*)	DBU	-	THF	r.t.	50	40
5	$[\eta^3\text{-}C_3H_5PdCl]_2$	-Bz	L_{std} (*R*,*R*)	NaH/DBU	-	CH_2Cl_2	-78 → r.t.	82	-67



When the reaction was carried out in dichloromethane (DCM) with tetrahexylammonium bromide (THAB) as an additive, the enantioselectivity increased to 49% *ee* (entry 2, Table 1). It is assumed that THAB plays a role as a phase transfer catalyst to increase the solubility of sodium malonate salt [46,47,49]. When the reaction was carried out in DCM in the presence of sodium hydride (60% in mineral oil) and 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) starting at –20 °C and slowly warming to r.t. overnight, the enantioselectivity increased again to 55% *ee* (entry 3, Table 1). Using only DBU as a base in THF without any additive decreased the enantioselectivity of the reaction to 40% *ee* (entry 4, Table 1). Switching the solvent from DCM to THF and/or the higher temperature compared to entry 3 may be reasons for the lower enantioselectivity. The highest enantioselectivity was obtained in DCM by addition of the sodium hydride and DBU at –78 °C and allowing the reaction mixture to slowly warm to r.t. (entry 5, Table 1).

It is well known that the three dimensional direction and/or steric hindrance of the Trost-ligand in situ play distinct roles in determining the enantioselectivity of asymmetric allylic alkylation, but the angle (Θ) between π-allylpalladium intermediate and the bonding post of the coordinated ligand is also significant [50]. Therefore, the design of Trost-ligand with different bonding will help to understand the asymmetric allylic alkylation for a broad range of substrate [50]. After low *ee* using standard Trost-ligand (L_{std}) in Table 1 was obtained, it was decided to synthesize new ligands with a different bonding post.

These novel ligands are synthesized according to the established synthetic strategy starting from the fragment **6** [51] (1 eq.),which can be synthesized from commercially available2-(diphenylphosphino)benzoic acid and *N*-hydroxysuccinimide

(NHS) in the presence of *N*, *N*′-Diisopropylcarbodiimide (DIC) in DCM (Figure 2). (*S*)-**5**was synthesized according to established protocols by Pfaltz et. al. starting from benzamide and L-serine methyl ester in three steps in 63% overall yield. Fragment 6 was then reacted with either commercially available (*R*,*R*)-1,2-diamino-cyclohexane (2 eq.), or (*S*,*S*)-**7**(2 eq.) to form (*R*,*R*)-11, or (*S*,*S*)-8[52,53] and then coupled with (*S*)-5 using the TBTU and HOBT in the presence of Hünig's base to form (*S*,*R*,*R*)-10 and (*S*,*S*,*S*)-9 in good yields (Figure 2) [54,55].

It is assumed that the free hydroxyl group in 2a may have been partially responsible for the moderate *ee* observed for 4, so going forward, it was decided to protect the hydroxyl group with it's trityl ether [56,57]. The yields of the protected alcohols are moderate to excellent depending on the propargylic alcohol derivatives (Figure 3). The protected substrates were then reexamined using the optimized conditions from Table 1. Substrates in Figure 3 were then tested in the conditions of Table 1 (Table 2).

After the protection of the alcohol with a trityl group, very high enantioselectivities using the reaction conditions in Table 2 and Table 3 could be obtained. Two types of reactions were tested with ligands L_{std}, (*S*,*S*,*S*)-9 and (*S*,*R*,*R*)-10. First, the formation of C-C bond quarter centers of carbon atom (Table 2), then the formation of C-O bond by the use of 4-(trityloxy) but-2-yn-1-ol as nucleophilic source (Table 3) has been tested. The new ligands (*S*,*S*,*S*)-9 and (*S*,*R*,*R*)-10 also

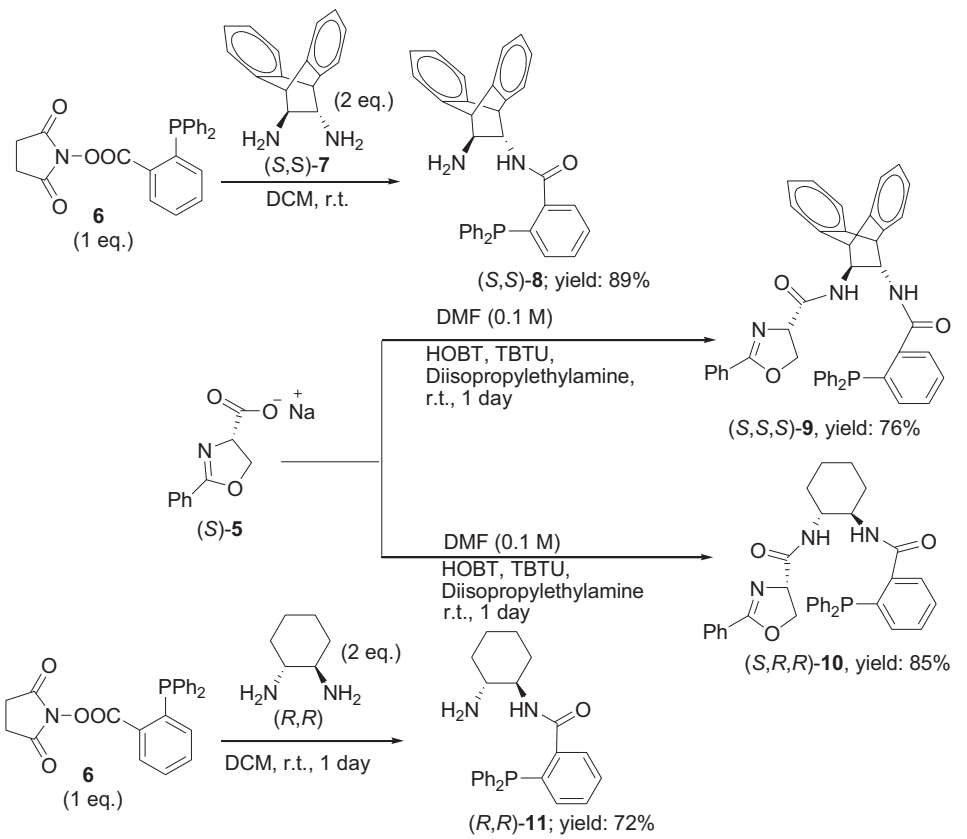


Figure 2. Synthesis of new ligands (*S*,*S*,*S*)-9 and (*S*,*R*,*R*)-10.

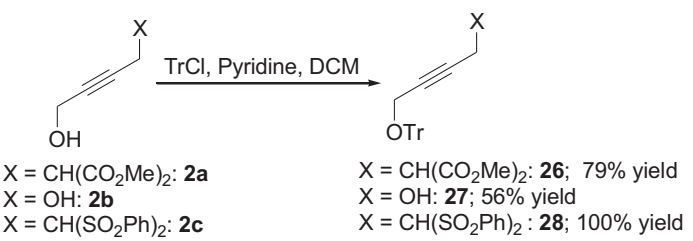
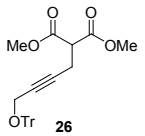
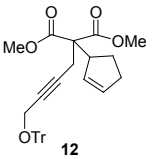
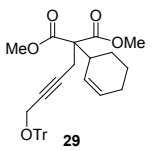
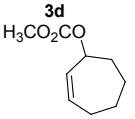
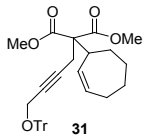
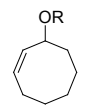
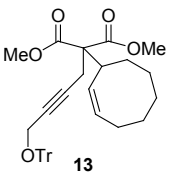
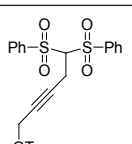
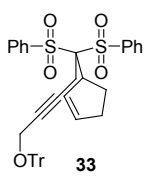


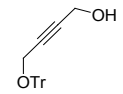
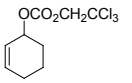
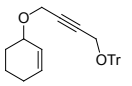
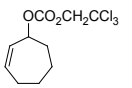
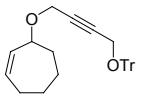
Figure 3. Protection of the hydroxyl group.

Table 2. Substrate scope with trityl protected propargylic alcohol derivatives.

Entry	Substrate (nucleophile)	Substrate (electrophile)	Product	Reaction condition	Yield (%)[a]	ee (%)[b]
1	 **26**	 **3a**	 **12**	$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), PPh_3 (30%), NaH (1.3 eq.), THF (0.2 M)	70	-
2				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), (*S,R,R*)-**10**(7.5%),NaH/DBU (2/2 eq.),THAB (1 eq.),DCM (0.25 M), r.t., 1 day	82	99
3				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), L_{std} (*R,R*) (7.5%), NaH/DBU (2/2 eq.),THAB (1 eq.),DCM (0.25 M), -78°C → r.t., 1 day	73	98
4				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%) (*S,S,S*)-**9**(7.5%), NaH/DBU (2/2 eq.), THAB (1 eq.), DCM (0.25 M), r.t., 1 day	81	99
5			 **29**	$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), PPh_3 (30%), NaH (2 eq.) DCM (0.1 M), r.t., 1 day	90	-
6				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), L_{std} (*R,R*), (7.5%), NaH/DBU (2/2 eq.), THAB, DCM (0.21 M), r.t., 1 day	60	91
7		**3d**  **3e**	 **31**	$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), PPh_3 (30%), DCM, Δ, 1 day.	66	-
8				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), L_{std} (R,R), NaH/DBU, THAB, DCM (0.25 M), -78°C → r.t., 1 day	51	99[c]
9		 R = CO_2CH_3: **3f** R = $CO_2CH_2CCl_3$: **3i**	 **13**	R = CO_2CH_3;$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), PPh_3 (30%), DBU (3 eq.), THF (0.25 M), Δ, 3 days.	37	-
10				R = $CO_2CH_2CCl_3$;$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%) (*S,R,R*)-**8** (7.5%), NaH/DBU (2/2 eq.), THAB, DCM (**0.1 M**), r.t., 1 day	75	93
11				R = CO_2CH_3; $Pd_2(dba)_3CHCl_3$ (2.5%), L_{std} (*S,S*) (7.5%), DBU (2 eq.), THF (0.25 M), r.t., 1day	37	71
12				R = CO_2CH_3; $[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5 %), L_{std}(*R,R*) (7.5%), NaH/DBU (2/2 eq.), THAB, DCM (0.25 M), r.t., 1 day	40	99
13	 **28**	 R = COPh: **3a** R = CO_2CH_3: **3b**	 **33**	R = CO_2Me; $Pd_2(dba)_3CHCl_3$, PPh_3 (30%), NaH (1.3 eq.), THF (0.3 M), r.t., 1 day.	66	-
14				R = COPh; $[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), (*S,R,R*)-**10** (7.5%), NaH (1.3 eq.), THF (0.25 M), r.t., 1 day	74	70

[a]Isolated yield. [b]The *ee* was determined by chiral HPLC except for entry 8. [c]The *ee* was determined by chiral GC after deprotection.

Table 3. The formation of C-O bonds with the use of (*S,R,R*)-10 ligands.

1	 **27**	 **3g**	 **34**	$Pd_2(dba)_3CHCl_3$ (2.5%); dppp (7.5 %), NaH (1.3 eq.), THF (0.3 M), r.t., 1 day.	86	-
2				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), (*S,R,R*)-**10**(7.5%), NaH/ DBU (2/2 eq.), THAB, DCM (0.25 M), r.t., 1 day.	82	0
3		 **3h**	 **35**	$Pd_2(dba)_3CHCl_3$ (2.5%), dppp (7.5 %), NaH (1.3 eq.), THF (0.3 M), 1 day.	49	-
4				$[\eta^3\text{-}C_3H_5PdCl]_2$ (2.5%), (*S,R,R*)-**10**(7.5%), NaH/ DBU (2/2 eq.), THAB, DCM (0.25 M), r.t., 1 day.	67	57

showed very high enantioselectivities and yields in the optimized reaction conditions (see entries 2,4,10, and 14,Table 2 and entry 4, Table 3). However, the enantioselectivities of the allylic alkylation decreased, if different types of nucleophiles were used under the same reaction conditions (entries 5–8, Table 2). It is assumed that the malonate carbonyl group (entries 1–4, Table 2) or sulfonyl group (entries 13–14, Table 2) may coordinate to the active catalyst in situ, giving rise to higher enantioselectivities.

Unfortunately, the novel synthesized ligand has brought low enantioselectivity in the formation of C-O bonds (Table 3). However, the yields varied from moderate to very good. One side trityl-protected but-2-yne-1,4-ol was tested as a nucleophilic source in the presence of (*S,R,R*)-10. Probably the nucleophilic source also plays a crucial role in maintaining a high enantioselectivity. Why the product is obtained as a racemic mixture in the presence of chial(*S,R,R*)-10 ligand, when 2,2,2-trichloroethyl cyclohex-2-enyl carbonate is used as the electrophile source, is not clear (entry 2, Table 3). When the seven-membered ring is inserted, the *ee* increases up to 57% under the same reaction condition (entry 4, Table 3).

However, the steric effect of the substrates was not studied in detail in the literature. Only the steric effect of the ligands on the substrates is studied in detail. The reasons for the high *ee* in Table 2 have been previously calculated theoretically in detail for the Trost-ligand L_{std} in the transition state of the Pd-catalyst [58–61]. The crystal structure, a 3D calculated model of the active catalyst of π-allyl palladium complex in situ, is shown in Figure 4 [58–61]. The ligand L consists mainly of three important parts: a linker (red), a chiral scaffold (black), and a binding post (green). According to Trost et. al., the linkers play a crucial role in nucleophile attacking the π-cyclohexenyl palladium complex. This step occurs in palladium catalytic cycles asymmetrically (Structure C, Figure 4). To demonstrate that the linkers (red) are very important in the enantioselectivity of the products, Trost et. al. synthesized a new chiral ligand without any additional group on binding post and tested it in the Pd-catalyzed AAA [58].

Based on the theoretical calculations of ligand L_{std} (Structure B) and other similar bisoxazoline ligands [62], the structures in Figure 5 were proposed that suggest transition states of the two catalysts Pd-(*S,S,S*)-9 and Pd-(*S,R,R*)-10. It is assumed that the phenyl group of the amide group and the phenyl group of the oxaziline group sterically hinder the nucleophilic attack from one side and this leads to high enantioselectivity in the reaction. Here, symmetrical electrophilic (R-CHCHCH-R^+) was only used to understand better the steric hindrance of the ligands (*S,S,S*)-9 and (*S,R,R*)-10 to nucleophiles (Figure 5). It is still unclear whether the trityl group will act as an additional steric hindrance in substrates to increase the *ees* of the products. To determine whether the trityl group plays a special role, one has to test with another protective group for the same substrates in the same reaction conditions. Further detailed DFT calculations using complicated electrophile and nucleophile for the transition states of ligands (*S,S,S*)-9 and (*S,R,R*)-10 will be published in a separate manuscript.

Because a free hydroxyl group is required for the subsequent ruthenium-catalyzed redox cycloisomerization, a series of the *ee*-pure products 12 to 13 were deprotected with catalytic $BiCl_3$ in DCM [63,64]. The corresponding deprotected malonates were isolated in good yield. Those compounds (Table 4) were then tested in cycloisomerization reactions using two types of Ru-catalysts.

Different types of substrates for redox cycloisomerisation were tested as well. With 6-((*E*)-penta-2,4-dienyloxy)hexa-2,4-diyn-1-ol 14 using $[IndRu(PPh_3)_2Cl]$, CSA, and $In(OTf)_3$ in THF, which was synthesized starting from commercially available compounds 15 and 16 (Figure 6). Compound 17 was obtained as a cyclization product in 75% yield. Here, $[IndRu(PPh_3)_2Cl]$ 1 catalyzes a Diels-Alder type reaction (Figure 6).

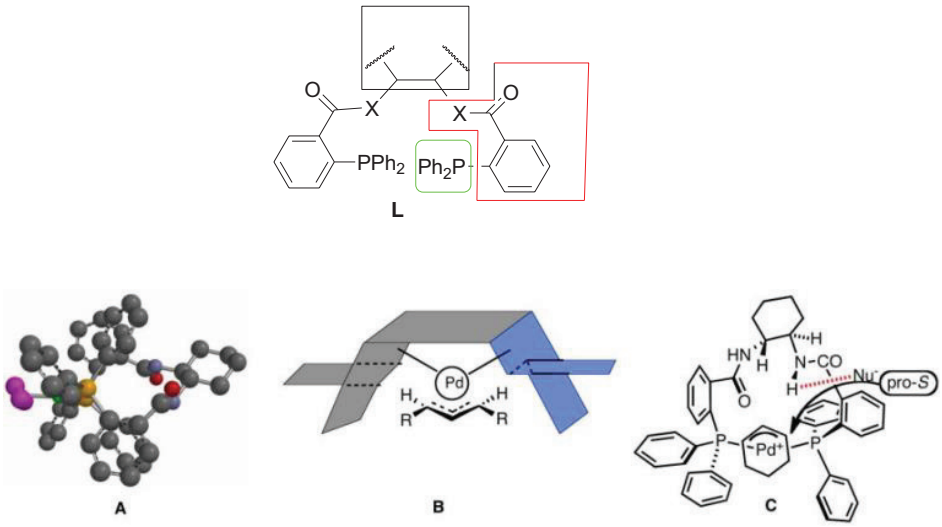


Figure 4. L: General representation of the Trost-ligand(s). A: Crystal structure of ligand L_{std}. B: 3D proposed model for active catalyst π-allylpalladium complex in situ. C: 3D proposed model for π-cyclohexenyl palladium complex in situ.

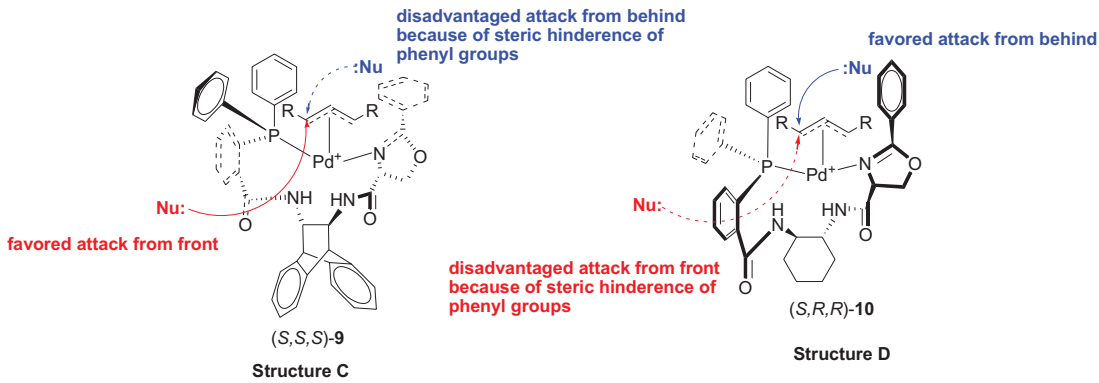


Figure 5. Proposed attacks of nucleophile (Nu:) in transition states of the catalysts using (*S,S,S*)-9 (Structure C) and using (*S,R,R*)-10 (Structure D) for the symmetrical π-allyl electrophile (R-CHCHCH-R^+).

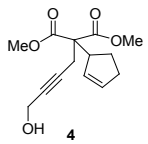
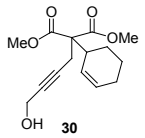
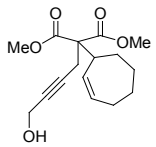
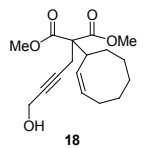
In Table 5, enantiomerically pure and racematic substrates were used. The yield of the products in Table 5 were compared using racemic substrate and enantiomerically pure substrates. The same yields were obtained for all used substrates. The products, where the enantiomerically pure substrates were used, were not checked for enantiomeric purity.

Two different catalysts in Table 5 were tested for cycloisomerization. $[CpRu(CH_3CN)_3]PF_6$ showed no chemoselectivity, and resulted in the formation of 6 different unidentified products by LC-MS! However, $[IndRu(PPh_3)_2Cl]$ 1 catalyzed the reaction in the presence of camphorsulfonic acid (CSA) and $In(OTf)_3$ in THF (n = 2,3,4) or acetone (n = 1). The elimination of water if n=1 (entry 1, Table 5) was obtained. It is assumed that acetone, which is used as a solvent only for entry 1 (Table 5) may play a role as a solvent in the elimination of water. However, in the reactions carried out in THF, the corresponding alcohols were obtained (entries 2–4, Table 5). A series of racemic compounds *rac*-4, 18, 30, and 32 were first tested and the results were compared with the series of the enantiomerically enriched compounds 4, 18, 30, and 32. All of the compounds gave the same products with the same yields (Table 5).

It is proposed that the catalytic cycle occurs by H-migration followed by cycloaddition to form the bicycle products shown in Table 5 (Figure 7). The first step in the catalytic cycle is to form the active catalyst 19 from the catalyst 1 in situ using $In(OTf)_3$, which abstracts chloride ion.

It is assumed that the reaction mechanism proceeds as follows; first, $In(OTf)_3$ reacts with chlorine to form the active catalyst 19. The coordination of the enyne starting material results in the elimination of triphenyl phosphine and a proton to form 20. The triple bond reacts afterwards to double bond to form Intermediate 21, which has resonance with 22 (Figure 7).

Table 4. Removing the trityl group using $BiCl_3$.

Entry	Substrate	Product (*ee*-pure)	Time	Yield (%)
1	**12**	 **4**	15 min	77
2	**29**	 **30**	1 h	75
3	**31**	 **32**	1 h	70
4	**13**	 **18**	1 h	69

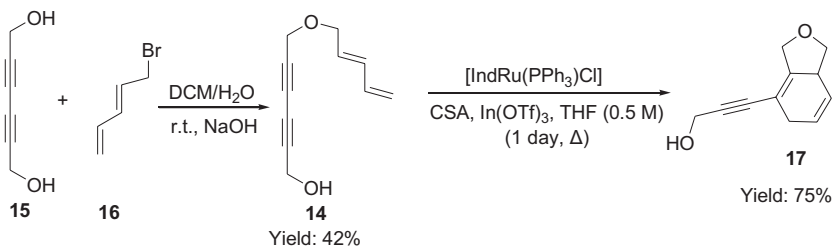
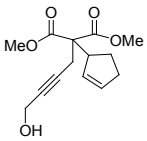
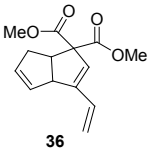
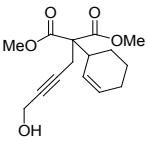
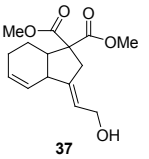
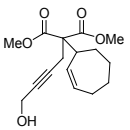
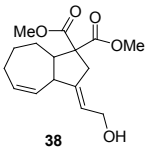
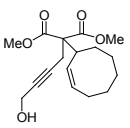
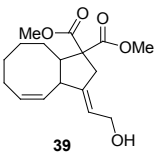


Figure 6. Testing for cycloisomerization with different type of substrates.

The Intermediates 21 and 22 should be armchair shape conformation and prefer the formation of metalacyclohexane 23. Through β-hydrogen elimination and cycloisomerization, intermediate 23 reacts to form intermediate 24. After that, the hydrogen migration between intermediates 24 and 25 occurs. It is assumed that the Ru-H bond is one of the key intermediates to different types of bicycle compounds. Intermediate 24 can be formed by a second H-migration to carbon atom. The intermediates 24 and 25 can be formed by H-migration. In the following step, the catalyst detaches from the intermediate 25 by reductive elimination to form the corresponding products (entries 2–4, Table5) and regenerate the active catalyst 19. The mechanism was proposed using another Ru-catalyzed cycloisomerization reaction, which is published in ref. [18,19,21,22,34,35, and 48]. No additional experiments were carried out to detect the intermediates.

Table 5. Redox cycloisomerization using [IndRu(PPh_3)$_2$Cl] to form bicycles.

Entry	Substrates	Product	Yield (%)
1	 *ee*-pure4 or *rac*-4	 **36**	78
2	 *ee*-pure30 or *rac*-30	 **37**	63
3	 *ee*-pure32 or *rac*-32	 **38**	70
4	 *ee*-pure18 or *rac*-18	 **39**	50

3. Conclusion

In summary, a novel method was developed successfully to synthesize asymmetrically a series of [n.3.0] bicyclic molecules (n = 3–6) bicyclodienes of various ring sizes in three steps starting from dimethyl 2-(4-(trityloxy)but-2-ynyl) malonate **3a**[65] or symmetrically in two steps starting from dimethyl 2-(4-hydroxybut-2-ynyl)malonate 2a via palladium-catalyzed allylic alkylation and Ru-catalyzed cycloisomerization. For that, two new ligands (*S,S,S*)-9 and (*S,R,R*)-10 were developed and tested for the palladium-catalyzed asymmetric allylic alkylation (Figure 6). These ligands were used in the asymmetric cycloalkylation of trityl protected propargylic alcohols and resulted in excellent *ee* and up to very good yields (Table 2). [n.3.0] bicyclic molecules (n = 3–6) in Table 5 were then synthesized from the synthesized *ee*-pure or racemic propargylic compounds in Table 4 using the catalyst [IndRu(PPh_3)$_2$Cl]. The supplementary material is available free of charge on the website of Turkish Journal of Chemistry[1].

4. Experimental section

4.1. General Information

NMR spectra were obtained using a 400 spectrometer (^{1}H at 300, 400, or 500 MHz, and ^{13}C at 101 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). IR spectra were obtained as liquid films with a spectrometer. GC–MS was obtained using electron ionization. HRMS was obtained with an LCMS-IT-TOF mass

[1] Turkish Journal of Chemistry (2020). Effective Synthesis of Bicyclodienes Via Palladium-Catalyzed Asymmetric Allylic Alkylation and Ruthenium-Catalyzed Cycloisomerization [online]. Website: https://journals.tubitak.gov.tr/chem/accepted.htm [accessed 10th october 2020]

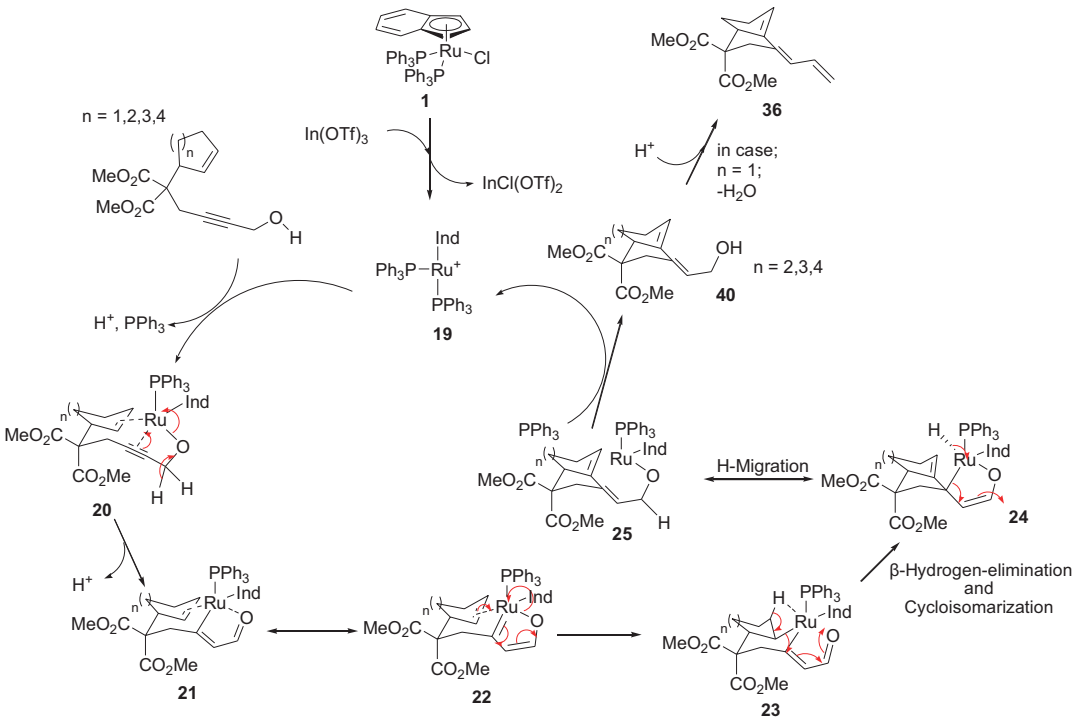


Figure 7. Proposed reaction mechanism for redox cycloisomerization.

spectrometer. Unless stated otherwise, commercial reagents were used without further purification. All reagents were weighed and handled in air at room temperature.

Dimethyl 2-(4-hydroxybut-2-ynyl)malonate; compound 2a, Table 1):

K_2CO_3 anhydrous (5.56 g, 40.26 mmol, 3 eq.) was charged in a dried flask, and dried with a flame in a high vacuum for 2 min. Then 60 ml dry acetone was added under argon atmosphere. Dimethylmalonate (1.77 g, 13.42 mmol, 1 eq.) were dissolved in 20 mL dry acetone and added to a suspension of potassium carbonate under argon. The suspension was stirred for 20 min. under argon at room temperature. 1,4-Dihydroxy-2-butyne (2 g, 13.42 mmol, 1 eq.) and 20 mL acetone were added to the mixture slowly. The reaction mixture was stirred vigorously under argon atmosphere at room temperature for 2 days. After 2 days, the reaction mixture was filtered off and the solvent was removed under reduced pressure. The product was isolated by column chromatography (eluent: PE:EA = 2:1 and then pure EA). A 68% yield of colorless oil (1.826 g) was isolated. ^{1}H-NMR (300 MHz, CHLOROFORM-*d*) d ppm 2.84 (dt, J = 7.69, 2.14 Hz, 2 H) 3.60 (t, J = 7.69 Hz, 1 H) 3.77 (bs, 6 H) 4.23 (t, J = 1.95 Hz, 2 H). The NMR-data correspond to the published data (see supporting info of ref.[49]).

4.2. General procedure 1 for the synthesis of cycloalkyl-2-enyl benzoate compound: 3a [66–69] Cycloalkene (2.5 eq.) was placed in an oven dry flask with reflux condenser. CuBr (0.18 % eq.) was added to cycloalkene. Mixture was washed with argon. Mixture was heated neat under argon and reflux condenser (in the case of cyclopentene to 45–50 °C, in the case of cyclohexene to 80 °C, in the case of cycloheptene to 90 °C, and in the case of cis-cyclooctene to 95 °C). BzOO*t*-Bu (1 eq.) was added neat over 24 h using a syringe pump via syringe to the mixture drop by drop at those temperatures. After a while, the reaction has the color of ocean blue. The product was isolated by silica gel chromatography by directly adding the neat reaction mixture to silica gel. (Eluent for all: PE/EtOAc: 10/1). The isolated products correspond to the published NMR-data [66–69].

4.3. General procedure 2 for the synthesis of racemic compounds:*rac*-12, *rac*-29, *rac*-31, *rac*-13, *rac*-33, *rac*-34 and *rac*-35 (entries 1,5,7,9, and 13, Table 2 and **entries 1, 3 Table 3):** Flask A: An oven dried microwave flask was charged with Pd-cat. ($Pd_2(dba)_3CHCl_3$ or $[\eta^3\text{-}C_3H_5PdCl]_2$; for the use of Pd-cat.; see Table 2, reaction conditions) (2.5 mol% eq.) and ligand: triphenyl phosphine (30 mol % eq.) or dppp (7.5 mol% eq.). These were washed with argon. The mixture was dissolved in one third mL of THF or DCM (for the solvents see the table). The reaction mixture was stirred for 30 min. in room temperature. Substrate (electrophile) (1 eq.) was added in one third / mL of THF or DCM to the reaction mixture. This reaction mixture was stirred for 30 min. at room temperature under argon. Flask B: In a dry microwave flask charged with NaH (for the required equivalent see table; 60% in oil). This was washed immediately with argon. Substrate

(nucleophile) (1 eq.) was added in one third / mL of THF or DCM (for the solvent see table) to sodium hydride, slowly under argon flow to reach the concentration in table. The reaction mixture was stirred for 10 min. more at room temperature. The contents of flask A were injected via syringe to the reaction mixture. The whole reaction mixture was heated or stirred at room temperature for one day (for the conditions see Table 2). The reaction mixture was washed with water, extracted three times with DCM and dried over magnesium sulfate. The solvent was evaporated under reduced vacuum. The product was isolated by silica gel chromatography.

4.4. General procedure 3 for the synthesis of *ee*-pure compounds 12, 29, 31, 13, 31, 33, 34, 35 (entries 2,3,4,6,8,10,11,12, and 14, Table 2 and **entries 2,4, Table 3):** Flask A: Pd-cat. $Pd_2(dba)_3CHCl_3$ or $[\eta^3\text{-}C_3H_5PdCl]_2$; for the used Pd-cat.; see Table 2; 2.5 % eq. and the corresponding ligand (7.5 mol% eq.) was dissolved in one third / mL of solvent. The reaction mixture was stirred for 30 min. at room temperature. Electrophile (1 eq., see table 2) in one third / mL of solvent was added to the reaction mixture. This reaction mixture was stirred for 20 min. at room temperature under argon. Flask B: Flame dried flask was charged with NaH (for eq. see table; 60% in mineral oil) and with THAB (1 eq., in table if necessary). The flask was washed under argon flow. Nucleophile substrate (1 eq.) in one third of solvent was added to NaH slowly under an open flow of argon gas, where the generation of hydrogen gas was observed. After addition, the reaction was stirred for a further 5 min. DBU (2 eq.) was added to this mixture (if necessary, see Table 2). The reaction mixture was stirred for 10 min. at room temperature. The contents of flask A were injected via syringe to the reaction mixture. The whole reaction mixture was stirred under the described conditions (see table) for one day. The reaction mixture was washed with water, extracted three times with DCM and dried over magnesium sulfate. The solvent was evaporated under reduced vacuum. The product was isolated by column chromatography (eluent: Hexane: EtOAc = 4:1).

4.5. General procedure 4 for the synthesis of 26–28 (Figure 3): An oven dried flask was charged with propargyl alcohol (2a, 2b, or 2c) (1 eq.), in case of but-2-yne-1,4-diol (**2b**) was charged with 3 eq.), 4-Dimethylaminopyridine (DMAP) (20% eq.) and trityl chloride (2 eq.). Those were washed under argon. The required amount of a half ml of DCM, was added to the mixture, and subsequently pyridine (2 eq.) in the other half ml of DCM, was added to reaction mixture. The reaction mixture was stirred for a day at room temperature (Eluent: Hexane: EA: 100:30). The rest was filtered. The liquid was evaporated. The products were isolated by silica gel chromatography (eluents: hexane: EtOAc = 100:30). The isolated products correspond to the published NMR-data in ref.[56,57,63].

4.6. General procedure 5 for the deprotection of alcohol group from trityl group (Table 4): Starting material (1 eq.) was dissolved in acetonitrile, so that the solution concentration could be 1 M. The solution was washed under argon. $BiCl_3$ (5 mol%) was subsequently added in one portion to the solution. The solution was stirred as much as necessary (for stirring time see table). More stirring in r.t or addition of more than 5 mol% $BiCl_3$ showed the decomposition of the products under this condition. The products were directly purified and isolated by silica gel chromatography (eluent for all: PE/EtOAc: 100:30). For yield of the products see Table 2. For the procedure with other compounds see ref. [64].

4.7. General procedure 6 for Ru-catalyzed cycloisomerization: synthesis of 36-39 (Table 5): $[IndRu(PPh_3)_2Cl]$ **1** (0.01172 mmol, 3 mol% eq.) and camphorsulfonic acid (CSA) (0.01955, 5 mol%) were added to an oven dried flask. The flask was washed under argon. Starting material (4, 18, 30 and 32) (0.391 mmol, 1 eq.) in 0.5 mL THF (in case n = 1, 0.5 mL acetone was used as solvent) was added to the solid mixture. The reaction mixture was stirred for 5 min. $In(OTf)_3$ (0.01172 mmol, 3 mol) in 0.5 mL was subsequently added to the reaction mixture. The reaction mixture was heated in the case of THF at 63 °C and in the case of acetone at 54 °C for one day. The product was directly isolated by silica gel chromatography (eluent for all: PE/EtOAc: 10:4).

4.8. General procedure 7 synthesis of the new ligands (*S*,*S*,*S*)-9 and (*S*,*R*,*R*)-10: An oven dried microwave flask was charged with (*S*)-5 (1 eq.), one of the compounds: (*R*,*R*)-11 (1.04 eq.) or (*S*,*S*)-7 (1.04 eq.) and the coupling reagents: 1-Hydroxybenzotriazol (HOBT, 1.12 eq.) and *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-tetrafluoroborate (TBTU, 1.04 eq.). The flask was washed with argon. Diisopropylethylamine (3 eq.) was added to the reaction mixture, subsequently DMF was added under argon, until the concentration of the solution was 0.1 M. The reaction mixture was stirred for a day at room temperature. The reaction was washed with 20 mL saturated NH_4Cl solution and extracted three times with DCM. The organic phase was dried over Mg_2SO_4. The solvent was evaporated. The products were isolated by silica gel chromatography (eluent: EtOAc/Hexane: 2/1). The rest of the viscous oil after the chromatography was recrystallized over Et_2O and then pentane was added drop by drop until observation of full precipitation (recrystallization at room temperature) to obtain the white solid (*S*,*R*,*R*)-10 in 85% yield or pale yellow solid (*S*,*S*,*S*)-9in 76% yield.

4.9. General procedure 8 for the synthesis of the fragments (*S*,*S*)-8 and (*R*,*R*)-11: An oven dry flask was charged with compound **6** (879 mg, 2.179 mmol, 1 eq.). The flask was washed under argon. DCM (25 mL) is added to the mixture. Then, (*R*,*R*)-1,2-diaminocyclohexane or (*S*,*S*)-1,2-*trans*-antracene diamine ((*S*,*S*)-**7**) (1.03 g, 4.359 mmol, 2 eq.), which are dissolved in 10 mL DCM, were added drop wise using syringe pump over 5 h. The reaction mixture was stirred under argon

for a day. A total of 25 milliliters of water was added to the solution. The organic phase was extracted three times with each 10 mL DCM. The solvent was evaporated. The product was isolated by silica gel chromatography (eluent: CH_2Cl_2/MeOH: 5/1).

4.10. General procedure 9: for the racemate of the products: (4-(cycloalkyl-2-enyloxy)but-2-ynyloxy)-triphenyl methane: Compounds *rac*-34 and *rac*-35 (entries 1,3, table 3): Flask A: $Pd_2(dba)_3CHCl_3$ (0.05 mmol, 2.5 mol% eq.) and 1,3-bis(diphenylphosphino)propane (dppp) (0.0375 mmol, 7.5 mol%) were charged in an oven dry microwave flask. The flask was washed with argon, 0.7 ml THF was added and stirred for 30 min at room temperature. 2,2,2-trichloroethyl cycloalk-2-enyl carbonate (0.5 mmol, 1 eq.) was added in 0.5 ml to the reaction mixture. The reaction mixture was stirred for 30 min. Flask B: An oven dry microwave flask was charged with NaH (0.65 mmol, 1.3 eq.) and 4-(trityloxy)but-2-yn-1-ol (0.5 mmol, 1 eq.). The flask was washed subsequently with argon and 0.5 mmol THF was added to the mixture (hydrogen gas generation). The mixture was stirred for 10 min. in r.t. The contents of flask A were injected into the flask B via syringe. The whole reaction mixture was stirred for a day in r.t. Five milliliters of water were added to the reaction mixture. The organic phase was extracted three times with DCM. The solvent was dried over Mg_2SO_4 and filtered. The solvent was evaporated. The product was isolated by silica gel chromatography (Eluent: PE/EtOAc = 10/3).

4.11. General procedure 10 for the enantioselective synthesis of the products: Compounds 34 and 35 (entries 2,4, Table 3): (4-(cycloalkyl-2-enyloxy)-but-2-ynyloxy)-triphenyl methane: Flask A: $[\eta^3\text{-}C_3H_5PdCl]_2$ (0.006225 mmol, 2.5 mol% eq.) and ligands (*S*,*S*,*S*)-9 or (*S*,*R*,*R*)-10 (0.01867, 7.5 mol%). The flask was washed with argon and 0.25 ml DCM was added and stirred for 30 min at room temperature. 2,2,2-trichloroethyl cycloalkyl-2-enyl carbonate (0.25 mmol, 1 eq.) was added in 0.25 ml to the reaction mixture. The reaction mixture was stirred for 30 min. Flask B: An oven dry microwave flask was charged with NaH (0.50 mmol, 2 eq.), 4-(trityloxy)but-2-yn-1-ol[57] (0.25 mmol, 1 eq.) and THAB (0.25 mmol, 1 eq.) was added. The flask was washed subsequently with argon and 0.25 mmol DCM was added to the mixture. DBU (0.50 mmol, 150 µL, 2 eq.) was added (hydrogen gas generation!). The mixture was stirred for 10 min in r.t. The contents of flask A were injected into flask B via syringe. The whole Five milliliters of water were added to the reaction mixture. The organic phase was extracted three times with DCM. The solvent was dried over Mg_2SO_4 and filtered. The solvent was evaporated. The product was isolated by silica gel chromatography. (Eluent: PE/EtOAc = 10/3).

4.12 General procedure 11 for the synthesis of 2,2,2-trichloroethyl cycloalkyl-2-enyl carbonate: compounds 3g, 3h

Cycloalk-2-enol (1 eq.) and 2,2,2-trichloroethyl chloroformate (1.1 eq.) were dissolved in two of thirds ml in DCM, which is needed for the 0.5 M concentration. The solution was washed with argon. The solution was cooled to 0 °C using an ice bath. Pyridine (6 eq.) was dissolved in one third of ml of DCM. The solution was slowly added via syringe. The reaction was left under stirring, warming to room temperature for one day. The reaction was quenched using saturated $CuSO_4$. The organic phase was extracted three times with DCM and one time with Et_2O. The organic phase was dried over Mg_2SO_4 and filtered. The solvent was evaporated. The product was isolated using silica gel chromatography (eluent: PE/EtOAc = 10/1).

4.13. General procedure 12 for the synthesis of cyclopent-2-enyl methyl carbonate (3b), cyclohept-2-enyl methyl carbonate (3e), cyclooct-2-enyl methyl carbonate (3f) (Table 2):

Cycloalk-2-enol (1 eq.) was added to an oven dry flask. Dry DCM was added, so that the whole solution could be concentrated to 0.33 M. The whole solution was washed with argon. Dry pyridine (6 eq.) was added to the solution via syringe. The solution was cooled to 0 °C with an ice bath. Methyl chloroformate (2.5 eq.) was added slowly to the solution via syringe. The reaction mixture was allowed, under stirring, to warm to room temperature over 1 day. The reaction mixture was washed twice with HCl (1 M, 2.5 eq.). The organic phase was washed with saturated $NaHCO_3$. The organic phase was dried over Mg_2SO_4 and filtered. The solvent was evaporated. The isolated products correspond to the published NMR-data.

cyclopent-2-enyl benzoate: compound 3a: colorless liquid. Yield: 70%: It was synthesized according to the published procedure [66–69]: the spectroscopy data correspond to the data in ref. [66–69].

cyclopent-2-enyl methyl carbonate (3b), (Z)-cyclohept-2-enyl methyl carbonate (3e), (Z)-cyclooct-2-enyl methyl carbonate (3f): colorless liquids. It was synthesized in three steps starting from cycloheptene to form cyclohept-2enyl benzoate (see: general procedure 6), hydrolysis with KOH/MeOH [70] (heating for 1 day at 63 °C) concentration of the solution, and protection of alcohol using methyl chloroformate according to the general procedure 11.

tert-butyl cyclohex-2-enyl carbonate: compound 3d: colorless liquid. It was synthesized in three steps starting from cyclohexene to form cyclohex-2enyl benzoate (see: general procedure 6), hydrolysis with KOH/MeOH[70] (heating 1 day at 63°C) and protection of alcohol using Boc_2 according to the published procedure in ref. [70].

2,2,2-trichloroethyl cyclohex-2-enyl carbonate (3g) (2,2,2-trichloroethyl (Z)-cyclohept-2-enyl carbonate (3h): colorless liquids. It was synthesized in three steps starting from cyclohexene and *cis*-cycloheptene to form cyclohex-2-enyl benzoate and (*Z*)-cyclohept-2-enyl benzoate (see: general procedure 6), hydrolysis with KOH/MeOH [70] and protection of alcohol using 2,2,2-trichloroethyl chloroformate according to the general procedure 11.

2,2,2-trichloroethyl cycloalkyl-2-enyl carbonate: compounds 3g, 3h:

It was synthesized in three steps starting from cyclohexene or cycloheptene to form cyclohex-2-enyl benzoate or cyclohept-2-enyl benzoate (see: general procedure 6), hydrolysis with KOH/MeOH [70] (heating overnight at 63 °C) and protection of alcohol using 2,2,2-trichloroethyl chloroformate according to the general procedure 11.

2,2,2-trichloroethyl cyclohexyl-2-enyl carbonate: compound 3g: colorless liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.58 - 1.71 (m, 1 H) 1.72 - 1.95 (m, 3 H) 1.95 - 2.19 (m, 3 H) 4.77 (s, 2 H) 5.19 (br. s., 1 H) 5.63 - 6.14 (m, 2 H).

FT-IR (thin film, cm^{-1}) = 3397, 3035, 2949, 2871, 2835, 1753, 1652, 1437, 1379, 1246, 1169, 1098, 1049, 1003, 966, 912, 811, 784, 726, 570.

*2,2,2-trichloroethyl cycloheptyl-2-enyl carbonate: compound 3h:*colorless liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.30 - 1.52 (m, 1 H) 1.61 - 1.87 (m, 3 H) 1.91 - 2.37 (m, 4 H) 4.70 - 4.84 (m, 2 H) 5.15 - 5.48 (m, 1 H) 5.63 - 6.14 (m, 2 H).

FT-IR (thin film, cm^{-1}) = 3506, 3031, 3000, 2858, 1748, 1655, 1568, 1446, 1380, 1323, 1128, 1095, 1065, 923, 895, 821, 785, 730, 570.

Dimethyl 2-(cyclopent-2-enyl)-2-(4-hydroxybut-2-ynyl) malonate: compound 4: colorless liquid.^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.66 - 1.81 (m, 2 H) 1.96 - 2.16 (m, 2 H) 2.29 (br. s., 2 H) 2.85 (br. s., 2 H) 3.61 (m, 1 H) 3.71 (s, 3 H) 3.74 (s, 3 H) 4.21 (br. s., 2 H) 5.68 - 5.86 (m, 2 H).^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 23.76, 25.45, 29.96, 31.97, 49.15, 51.48, 52.68, 52.87, 60.53, 81.56, 131.13, 133.06, 170.62, 170.82. FT-IR (thin film, cm^{-1}) = 3442, 2954, 1732, 1436, 1267, 1079, 916, 731. LRMS (ESI) *m*/*z*: calcd for $C_{14}H_{18}NaO_5$ [M+Na]$^+$ 289.1053; found 289.10.

(*S*)-5 (Figure 2): white solid: yield: 63% (over three steps): the spectroscopy data correspond to the established data in ref. [54,55].

6 (Figure 2): pale yellow solid: yield: 98%; the spectroscopy data correspond to the published data in ref.[51–53].

(S,S)-8: pale yellow solid; yield: 89%; M.P. 195-197 °C. $[\alpha]_D^{25}$ = +61.67 (*c* = 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.57 - 3.86 (m, 1 H) 4.04 - 4.27 (m, 2 H) 5.74 (d, *J*=5.87 Hz, 1 H) 6.87 (dd, *J*=6.94, 4.40 Hz, 1 H) 7.01 - 7.42 (m, 23 H) 7.47 (dd, *J*=6.85, 3.13 Hz, 1 H). ^{13}C NMR (101 MHz, CHLOROFORM-d_6) δ ppm 48.69, 51.32, 60.43, 6056, 124.76, 124.89, 125.64, 126.50, 126.63, 126.89, 127.02, 128.18, 128.21, 128.88, 128.94, 129.00, 129.06, 129.24, 129.30, 130.56, 133.96, 134.15, 134.31, 135.91, 136.07, 136.91, 136.99, 138.68, 139.31, 140.49, 140.86, 141.06, 142.45, 169.54. ^{31}P NMR (162 MHz, CHLOROFORM-*d*) δ ppm -10.29. FT-IR (thin film, cm^{-1}): 3409, 3284, 3050, 2950, 1652, 1583, 1502, 1484, 1371, 1293, 1265, 1138, 1090, 1026, 997, 908, 635, 560. HRMS (ESI) m/z: calcd for $C_{35}H_{29}N_2NaOP$ [M+Na]$^+$ 547.1915; found 547.1939.

*(S,S,S)-9 (*Figure 2*):* pale yellow solid; Yield: 76%; M.P.: 95-96°C, $[\alpha]_D^{25}$ = +137.49 (*c* = 0.355, $CHCl_3$). ^{1}H NMR (400 MHz, BENZENE-d_6) δ ppm 3.77 (t, *J*=9.29 Hz, 1 H) 3.88 - 4.02 (m, 1 H) 4.10 (br. s., 1 H) 4.21 - 4.39 (m, 1 H) 4.61 - 4.74 (m, 1 H) 4.88 (br. s., 1 H) 6.63 (d, *J*=9.00 Hz, 1 H) 6.74 (q, *J*=6.97 Hz, 2 H) 6.85 (d, *J*=4.11 Hz, 3 H) 6.89 - 6.94 (m, 1 H) 6.95 - 7.20 (m, 13 H) 7.29 - 7.48 (m, 6 H) 7.51 (br. s., 2 H) 7.91 (d, *J*=6.65 Hz, 2 H). ^{13}C NMR (101 MHz, BENZENE-d_6) δ ppm 34.98, 38.09, 48.98, 49.80, 54.41, 58.41, 68.46, 68.54, 124.34, 124.98, 125.38, 126.11, 126.27, 126.55, 126.70, 127.38, 127.44, 127.68, 127.93, 128.09, 128.16, 128.22, 128.28, 128.38, 128.44, 128.48, 129.60, 131.65, 133.57, 133.77, 133.86, 134.07, 134.56, 137.01, 137.23, 138.23, 138.34, 138.90, 139.18, 139.31, 140.00, 140.96, 141.38, 142.21, 142.49, 161.58, 164.76, 168.47, 170.98. ^{31}P NMR (162 MHz, BENZENE-d_6) δ ppm -10.13. FT-IR (thin film, cm^{-1}) 3297, 3051, 2951, 1654, 1581, 1520, 1465, 1454, 1360, 1291, 1265, 1155, 1091, 1026, 746, 697, 638, 559. HRMS (ESI) *m*/*z*: calcd for $C_{45}H_{36}N_3NaO_3P$ [M+Na]$^+$ 720.2392; found 720.2384.

(S,R,R)-10 (Figure 2): white solid: yield: 85%; M.P. 80-81°C; $[\alpha]_D^{25}$ = -45.05 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, BENZENE-d_6) δ ppm 0.84 - 1.04 (m, 3 H) 1.11 (t, *J*=6.94 Hz, 1 H) 1.32 (br. s., 2 H) 1.79 (d, *J*=11.15 Hz, 1 H) 1.99 (d, *J*=9.98 Hz, 1 H) 3.63 - 3.95 (m, 2 H) 4.05 - 4.19 (m, 1 H) 4.58 - 4.68 (m, 2 H) 6.46 (d, *J*=7.83 Hz, 1 H) 6.79 - 6.92 (m, 2 H) 7.05 (d, *J*=2.35 Hz, 10 H) 7.28 (d, *J*=5.28 Hz, 2 H) 7.36 (t, *J*=6.94 Hz, 2 H) 7.44 (d, *J*=7.43 Hz, 1 H) 7.54 - 7.63 (m, 1 H) 8.08 - 8.19 (m, 2 H). ^{13}C NMR (101 MHz, BENZENE-d_6) δ ppm 15.24, 24.65, 24.80, 30.48, 31.89, 35.12, 38.11, 53.42, 53.52, 65.49, 69.58, 69.91, 127.44, 127.54, 127.68, 127.93, 128.05, 128.24, 128.31, 128.63, 129.44, 131.23, 133.76, 133.88, 133.96, 134.08, 136.77, 137.00, 138.58, 138.71, 141.51, 141.76, 162.12 165.28, 168.50, 171.62. ^{31}P NMR (162 MHz, BENZENE-d_6) δ ppm -9.44. FT-IR (thin film, cm^{-1}) = 3298, 3054, 2934, 2857, 1643, 1526, 1478, 1450, 1324, 1264, 1207, 1146, 1088, 1026, 967, 929, 854, 853, 779, 741, 696. HRMS (ESI) *m*/*z*: calcd for $C_{35}H_{34}N_3NaO_3P$ [M+Na]$^+$ 598.2236; found 598.2258.

(R,R)-11 (Figure 2): white solid: yield: 72% the spectroscopy and $[\alpha]_D^{25}$ -rotation data correspond to the published data in ref. [51–53].

Dimethyl 2-(cyclopent-2-enyl)-2-(4-(trityloxy)but-2-ynyl)malonate: compound ***12****:* white viscous liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.67 - 1.86 (m, 1 H) 1.98 - 2.19 (m, 1 H) 2.31 (t, *J*=7.04 Hz, 1 H) 2.87 (s, 2 H) 3.67 (t, 2 H) 3.71 (s, 3 H) 3.74 (s, 3 H) 5.64 - 5.92 (t, *J* = 7 Hz, 2 H) 6.93 - 7.63 (m, 15 H). ^{13}C NMR (101 MHz,

CHLOROFORM-*d*) δ ppm 23.51, 25.24, 29.71, 31.74, 48.95, 52.39, 52.56, 60.32, 79.55, 80.97, 87.42, 127.11-128.55 (15C), 131.10, 132.67, 143.58 (3 C) 170.43, 170.58. IR (thin film, cm^{-1}) = 3473, 3058, 3000, 2958, 2952, 2854, 2245, 1960, 1734, 1596, 1491, 1447, 1368, 1261, 1223, 1156, 1055, 911,802, 764, 706, 632, 583. HRMS (ESI) *m*/*z*: calcd for $C_{33}H_{32}NaO_5$ $[M+Na]^+$ 531.2147; found 531.2161.

Dimethyl 2-((Z)-cyclooct-2-enyl)-2-(4-(trityloxy)but-2-ynyl) malonate: compound ***13****:* colorless viscous liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.33 - 1.74 (m, 8 H) 1.84 - 2.40 (m, 2 H) 2.53 (s, 2 H) 3.69 (s, 3 H) 3.71 (br. s, 1 H) 3.77 (s, 3 H) 5.39 - 5.88 (m, 2 H) 7.13 - 7.54 (m, 15 H).

^{13}C-NMR (101 MHz, CHLOROFORM-*d*) δ ppm 15.06, 23.46, 26.01, 26.57, 29.02, 33.52, 35.20, 52.05, 53.61, 54.84, 84.07, 87.59, 127.34, 127.50, 128.14, 128.83, 130.31, 143.77, 172.67. FT-IR (thin film, cm^{-1}) 3485, 3025, 2930, 2859, 1747, 1653, 1619, 1437, 1380, 1261, 1154, 1097, 1022, 937, 849, 809, 757, 718, 568.

6-((E)-penta-2,4-dienyloxy)hexa-2,4-diyn-1-ol: compound ***14****:* yellow liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) *δ* ppm 4.11 (d, *J*=6.35 Hz, 2 H) 4.24 (s, 2 H) 4.36 (d, *J*=5.86 Hz, 2 H) 5.03 - 5.34 (m, 2 H) 5.64 - 5.83 (m, 1 H) 6.13 - 6.50 (m, 2 H). FT-IR (thin film, cm^{-1}) = 3405, 2920, 2851, 1723, 1688, 1462, 1364, 1263, 1048, 903, 782, 731.

3-(1,3,3a,6-tetrahydroisobenzofuran-7-yl)prop-2-yn-1-ol: compound ***17****:*pale yellow solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.78 (br. s., 1 H) 2.71 - 2.96 (m, 2 H) 3.21 (br. s., 1 H) 3.27 - 3.35 (m, 1 H) 4.24 (t, *J*=7.24 Hz, 1 H) 4.41 (br. s., 2 H) 4.50 (br. s., 2 H) 5.53 - 5.97 (m, 2 H). ^{13}C (101 MHz, CHLOROFORM-*d*) δ ppm 31.41, 40.96, 51.84, 69.85, 72.32, 83.92, 90.75, 108.71, 122.53, 126.79, 146.57.

FT-IR (thin film, cm^{-1}) = 3399, 3031, 2924, 2857, 1721, 1425, 1362, 1319, 1269, 1238, 1157, 1098, 1070, 1023, 977, 939, 785, 748, 699, 610.

Dimethyl 2-((Z)-cyclooct-2-enyl)-2-(4-hydroxybut-2-ynyl)-malonate: compound ***18****:* pale yellow liquid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.28 - 1.74 (m, 8H) 1.86 - 2.35 (m, 2H) 2.80 (d, *J*=7.81 Hz, 2 H) 3.58 (t, *J*=7.57 Hz, 1 H) 3.73 (br. s., 1 H) 3.74 (s, 6 H) 4.64 (br. s., 2 H) 5.41 - 5.73 (m, 2 H).

^{13}C-NMR (101 MHz, CHLOROFORM-*d*) δ ppm 14.39, 19.00, 23.41, 26.54, 28.96, 35.13, 50.89, 53.14, 55.76, 60.76, 82.18, 83.67, 130.05, 130.46, 154.34, 168.51. IR (thin film, cm^{-1}) 3485, 3025, 2930, 2859, 1747, 1658, 1619, 1437, 1380, 1261, 1154, 1097, 1022, 937, 809, 718, 757, 568.

(5,5-bis(phenylsulfonyl)pent-2-ynyloxy)triphenylmethane: compound ***28****:* white solid.

It was synthesized in three steps starting from commercially available bis(phenylthio)methane first to form bis(phenylsulfonyl)methane using *m*-CPBA according to the published procedure in ref. [70]. The Bis(phenylthio) methane was treated with 4-bromobut-2-yn-1-ol [71] to form 5,5-bis(phenylsulfonyl)pent-2-yn-1-ol according to the same procedure: dimethyl 2-(4-hydroxybut-2-ynyl)malonate. Titel compound was then synthesized according to general procedure 2. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.14 (d, *J*=4.89 Hz, 2 H) 3.48 (br. s., 2 H) 4.27 - 4.78 (t, *J* = 6.01, 1 H) 7.18 - 7.35 (m, 10 H) 7.36 - 7.46 (m, 5 H) 7.53 (t, *J*=7.43 Hz, 4 H) 7.57 - 7.67 (m, 2 H) 8.00 (d, *J*=7.63 Hz, 4 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 17.48, 53.26, 77.23, 77.55, 77.87, 78.71, 81.01, 82.12, 87.67, 127.58, 128.29, 128.86, 129.43, 130.04, 135.15, 138.12, 143.61.

Dimethyl 2-(cyclohex-2-enyl)-2-(4-(trityloxy)but-2-ynyl)-malo-nate: compound ***29****:* white viscous liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.45 - 1.67 (m, 1 H) 1.82 (dd, *J*=10.01, 5.37 Hz, 3 H) 1.96 (br. s., 2 H) 2.77 - 2.99 (m, 2 H) 3.14 (m, 1 H) 3.72 (s, 3 H) 3.76 (s, 3 H) 4.21 (s, 2 H) 5.60 - 5.81 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 22.51, 23.08, 25.09, 24.50, 29.96, 39.17, 51.50, 52.64, 52.84, 60.77, 81.52, 81.64, 127.57, 129.40, 170.41, 170.65. FT-IR (thin film, cm^{-1}) = 3411, 2924, 1734, 1447, 1261, 1052, 706. HRMS (ESI) *m*/*z*: calcd for $C_{34}H_{34}NaO_5$ $[M+Na]^+$ 545.2304; found 545.2280.

Dimethyl 2-(cyclohex-2-enyl)-2-(4-hydroxybut-2-ynyl)malonate: compound ***30****:* colorless liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.45 - 1.65 (m, 4 H) 1.77-1.88 (m, 2 H) 1.96 (br. s., 1 H) 2.81 - 2.99 (m, 2 H) 3.08-3.16 (m, 1 H) 3.73 (s, 3 H), 3.76 (s, 3H) 4.21 (s, 2 H) 5.60 - 5.81 (m, 2 H).^{13}C NMR (101 MHz, CHLOROFORM-*d*) 22.51, 23.08, 25.09, 24.50, 29.96, 39.17, 51.50, 52.64, 52.84, 60.77, 81.52, 81.64, 127.57, 129.40, 170.41, 170.65. FT-IR (thin film, cm^{-1}) = 3411, 2924, 1734, 1447, 1261, 1052, 706. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1208; found 303.1209.

Dimethyl 2-((Z)-cyclohept-2-enyl)-2-(4-(trityloxy)but-2-ynyl)-malonate: compound ***31****:* pale yellow viscous liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.85 (br. s., 2 H) 1.49 - 2.24 (m, 4 H) 2.91 (br. s., 2 H) 3.25 (br. s., 1 H) 3.54 - 3.83 (m, 6 H) 5.55 - 6.09 (m, 2 H) 6.84 - 7.96 (m, 15 H).^{13}C-NMR (101 MHz, CHLOROFORM-*d*) δ ppm 24.04, 26.32, 28.22, 30.00, 31.77, 43.30, 53.75, 61.03, 79.90, 81.34, 87.59, 127.35, 128.15, 128.82, 133.00, 143.86, 170.73, 170.79. IR (thin film, cm^{-1}) = 3398, 3024, 2923, 2853, 1734, 1596, 1491, 1447, 1369, 1274, 1223, 1156, 1053, 975, 899, 802, 746, 706, 631. HRMS (ESI) *m*/*z*: calcd for $C_{35}H_{36}NaO_5$ $[M+Na]^+$ 559.2460; found 559.2486.

*Dimethyl 2-((Z)-cyclohept-2-enyl)-2-(4-hydroxybut-2-ynyl)-malonate: compound **32**:* colorless liquid.

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.48 - 1.87 (m, 4 H) 1.99 - 2.10 (m, 2 H) 2.11 - 2.22 (m, 2 H) 2.89 (s, 2 H) 3.18 (d, *J*=6.35 Hz, 1 H) 3.72 - 3.78 (br. s., 6 H) 4.22 (s, 2 H) 5.61 - 5.95 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 24.10, 26.21, 28.14, 31.65, 43.36, 51.25, 52.86, 61.05, 81.15, 81.81, 132.45, 132.77, 170.72, 170.79.FT-IR (thin film, cm^{-1}) = 3476, 3025, 2924, 2851, 1733, 1436, 1309, 1277, 1223, 1144, 1070, 1044, 1019. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{22}NaO_5$ $[M+Na]^+$ 317.1365; found 317.1372.

(5-(cyclopent-2-enyl)-5,5-bis(phenylsulfonyl)pent-2-ynyloxy)-triphenylmethane:compound 33: white solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.06 - 2.43 (m, 4 H) 3.23 (m, 2 H) 3.64 (br. s., 2 H) 3.94 - 4.27 (m, 1 H) 5.77 (d, *J*=13.30 Hz, 2 H) 7.19 - 7.36 (m, 10 H) 7.38 - 7.48 (m, 5 H) 7.52 (q, *J*=7.30 Hz, 4 H) 7.58 - 7.69 (m, 2 H) 8.09 - 8.24 (m, 4 H). ^{13}C-NMR (101 MHz, CHLOROFORM-*d*) δ ppm 23.64, 25.28, 32.09, 48.02, 53.68, 78.20, 83.05, 87.79, 92.30, 127.52, 128.25, 128.68, 128.83, 123.07, 123.14, 133.27, 134.84, 138.28, 138.38, 143.69. FT-IR (thin film, cm^{-1}) = 3385, 3061, 2924, 2854, 2254, 1718, 1583, 1447, 1383, 1368, 1145, 1075, 1056, 977, 909, 732, 730, 631, 591, 572.

*(4-(cyclohex-2-enyloxy)but-2-ynyloxy)triphenylmethane: compound **34**:* colorless liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.56 - 2.37 (m, 6 H) 3.74 - 3.94 (m, 2 H) 4.66 - 4.89 (m, 2 H) 5.18 (d, *J*=1.96 Hz, 1 H) 5.66 - 6.12 (m, 2 H) 7.08 - 7.44 (m, 15 H). ^{13}C (101 MHz, CHLOROFORM-*d*) δ ppm 18.49, 24.81, 28.16, 53.03, 55.49, 72.41, 78.86, 84.12, 87.52, 124.71, 127.19, 127.94, 128.59, 133.57, 143.34, 154.27.

*(4-((Z)-cyclohept-2-enyloxy)but-2-ynyloxy)triphenylmethane compound **35**:* white viscous liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.48 - 1.82 (m, 4 H) 1.85 - 2.31 (m, 4 H) 3.82 (br. s., 2 H) 4.75 (br. s., 2 H) 5.14 - 5.40 (m, 1 H) 5.57 - 5.96 (m, 2 H) 7.02 - 7.61 (m, 15 H).^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 26.31, 26.45, 28.40, 32.70, 53.02, 55.58, 78.77, 84.19, 87.52, 127.20, 127.94, 128.58, 132.05, 132.64, 143.32, 154.13. FT-IR (thin film, cm^{-1}) = 3414, 3058, 3031, 2927, 2859, 1746, 1597, 1490, 1447, 1377, 1322, 1258, 1156, 1057, 967, 964, 899, 789, 764, 705, 632.

*Dimethyl 6,6a-dihydro-3-vinylpentalene-1,1(3aH)-dicarboxylate: compound **36**:* colorless liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.93 - 2.12 (m, 1 H) 2.48-2.61 (m, 1 H) 3.72 (s, 3 H) 3.74 (s, 3H) 3.75 - 3.81 (m, 1 H) 4.03 (br. s., 1 H) 5.22 (d, *J*=10.76 Hz, 1 H) 5.35 (d, *J*=17.61 Hz, 1 H) 5.60 - 5.70 (m, 2 H) 5.89 (br. s., 1 H) 6.44 (dd, *J*=17.41, 10.76 Hz, 1 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 35.50, 45.91, 52.58, 53.16, 56.20, 69.14, 117.81, 125.81, 130.53, 130.69, 132.04, 147.93, 171.21. HRMS (ESI) *m*/*z*: calcd for $C_{14}H_{16}NaO_4$ $[M+Na]^+$ 271.0946; found 271.0938.

(3E)-dimethyl 3,3a,7,7a-tetrahydro-3-(2-hydroxyethylidene)-2H-indene-1,1(6H)-dicarboxylate: compound 37: colorless viscous liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.01 - 1.16 (m, 1 H) 1.21 - 1.37 (m, 2 H) 1.92 - 2.18 (m, 2 H) 2.73 - 3.01 (m, 2 H) 3.16 - 3.36 (m, 2 H) 3.70 - 3.76 (m, 7 H) 4.15 (d, *J*=6.41 Hz, 2 H) 5.35 - 5.46 (m, 1 H) 5.67 - 5.90 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 21.35, 24.83, 34.67, 42.76, 43.32, 52.89, 53.14, 60.90, 62.68, 122.25, 126.27, 145.36, 170.45, 172.36. FT-IR (thin film, cm^{-1}) = 3405, 2922, 1733, 1435, 1267, 1042. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1208; found 303.1206.

(3E,4Z)-dimethyl 3,3a,6,7,8,8a-hexahydro-3-(2-hydroxyethyl-idene)azulene-1,1(2H)-dicarboxylate: compound 38: colorless viscous liquid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.55 - 1.84 (m, 4 H) 1.98 - 2.07 (m, 2 H) 2.11 - 2.20 (m, 3 H) 2.88 (s, 2 H) 3.16 (d, *J*=6.56 Hz, 1 H) 3.74 (s, 6 H) 4.21 (br. s., 2 H) 5.57 - 5.99 (m, 2 H). ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 24.06, 26.25, 28.20, 30.01, 31.70, 43.41, 51.57, 52.80, 52.88, 61.05, 81.60, 81.73, 126.31, 132.50, 132.80, 151.93, 170.73. FT-IR (thin film, cm^{-1}) = 3443, 2924, 2851, 1732, 1436, 1276, 1222, 1070, 1046. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{22}NaO_5$ $[M+Na]^+$ 317.1365; found 317.1358.

*(3E,4Z)-dimethyl 3,3a,7,8,9,9a-hexahydro-3-(2-hydroxyethyl-idene)-2H-cyclopenta[8]annulene-1,1(6H)-dicarboxylate: compound **39**:* pale yellow viscous liquid.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.30 - 1.77 (m, 8 H) 1.89 - 2.37 (m, 3 H) 2.84 (d, *J*=7.57 Hz, 2 H) 3.26 (s, 1 H) 3.52 - 3.63 (m, 1 H) 3.70 - 3.88 (m, 5 H) 4.16 (d, *J*=7.57 Hz, 1 H) 4.68 (s, 2 H) 5.43 - 5.85 (m, 3 H). ^{13}C (101 MHz, CHLOROFORM-*d*) δ ppm 19.02, 23.42, 25.97, 26.55, 28.97, 35.14, 50.91, 53.14, 55.76, 75.95, 76.51, 77.17, 83.68, 130.08, 130.47, 154.32, 168.48. FT-IR (thin film, cm^{-1}) = 3404, 2930, 2858, 1742, 1437, 1340, 1279, 1262, 1154, 1023, 938. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{24}NaO_5$ $[M+Na]^+$ 331.1521 found: 331.1509.

Acknowledgments

I am most grateful to TÜBİTAK (The Scientific and Technological Research Council of Turkey) with "2219 research fellow program" for their generous financial support.

Supplementary Material

The supplementary material is available free of charge on the website of Turkish Journal of Chemistry.

The NMR, FT-IR, and HR-MS spectral data, as well as HPLC and GC separation conditions for all new compounds (PDF).

References

1. Weintraub PM, Sabol JS, Kane JM, Borcherding DR. Recent advances in the synthesis of piperidones and piperidines. Tetrahedron 2003; 59 (17): 2953-2989. doi: 10.1016/S0040-4020(03)00295-3.
2. Dörrwald ZF. Metal Carbenes in Organic Synthesis.Hoboken, NJ, USA: Wiley-VCH, 2008.
3. Barluenga J, Rodríguez F, Fañanás FJ, Flórez J. Cycloaddition Reactions of Group 6 Fischer Carbene Complexes. In: Metal Carbenes in Organic Synthesis. Topics in Organometallic Chemistry. Berlin, Heidelberg, Germany: Springer Berlin Heidelberg, 2004: pp. 59-121.
4. Trost BM, Lautens M. Cyclization via isomerization: a palladium(2+)-catalyzed carbocyclization of 1,6-enynes to 1,3- and 1,4-dienes. Journal of the American Chemical Society 1985; 107 (6): 1781-1783. doi: 10.1021/ja00292a065.
5. Trost BM, Verhoeven TR. Allylic alkylation. Palladium-catalyzed substitutions of allylic carboxylates.Stereo- and regiochemistry. Journal of the American Chemical Society 1980; 102 (14): 4730-4743. doi: 10.1021/ja00534a029.
6. Trost BM, Bunt RC. Asymmetric induction in allylicalkylations of 3-(acyloxy)cycloalkenes. Journal of the American Chemical Society 1994; 116 (9): 4089-4090. doi: 10.1021/ja00088a059.
7. Trost BM, Organ MG, O'Doherty GA. Asymmetric synthesis of allylicsulfones useful as asymmetric building blocks. Journal of the American Chemical Society 1995; 117 (38): 9662-9670. doi: 10.1021/ja00143a007.
8. Trost BM, Stenkamp D, Pulley SR. An Enantioselective Synthesis ofcis-4-tert-Butoxycarbamoyl-1-methoxycarbonyl-2-cyclopentene—A Useful, General Building Block. Chemistry - A European Journal 1995; 1 (8): 568-572. doi: 10.1002/chem.19950010812.
9. Trost BM. The atom economy--a search for synthetic efficiency. Science (New York, N.Y.) 1991; 254 (5037): 1471-1477. doi: 10.1126/science.1962206.
10. Trost BM. Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. Angewandte Chemie International Edition in English 1995; 34 (3): 259-281. doi: 10.1002/anie.199502591.
11. Trost BM, Dyker G, Kulawiec RJ. A ruthenium-catalyzed reconstitutive condensation of acetylenes and allyl alcohols. Journal of the American Chemical Society 1990; 112 (21): 7809-7811. doi: 10.1021/ja00177a059.
12. Trost BM, Kulawiec RJ. Mechanism of the ruthenium-catalyzed reconstitutive condensation of allylic alcohols and terminal alkynes. Journal of the American Chemical Society 1992; 114 (14): 5579-5584. doi: 10.1021/ja00040a015.
13. Trost BM, Kulawiec RJ, Hammes A. Ruthenium catalyzed reconstitutive condensation. Application to functionalized steroid side chains. Tetrahedron Letters 1993; 34 (4): 587-590. doi: 10.1016/S0040-4039(00)61626-X.
14. Trost BM, Flygare JA. A Practical Synthesis of Rosefuran.Furans from Acetylenes and Allyl Alcohols. The Journal of Organic Chemistry 1994; 59 (5): 1078-1082. doi: 10.1021/jo00084a026.
15. Trost BM, Rhee YH. Ruthenium-Catalyzed Cycloisomerization−Oxidation of Homopropargyl Alcohols. A New Access to γ-Butyrolactones. Journal of the American Chemical Society 1999; 121 (50): 11680-11683. doi: 10.1021/ja992013m.
16. Trost BM, Rhee YH. A Ru catalyzed divergence: oxidative cyclization vscycloisomerization of bis-homopropargylic alcohols. Journal of the American Chemical Society 2002; 124 (11): 2528-2533. doi: 10.1021/ja011840w.
17. Trost BM, Martinez JA, Kulawiec RJ, Indolese AF. Ruthenium-catalyzed addition of allyl alcohols and acetylenes. A simple synthesis of .gamma.,.delta.-unsaturated ketones. Journal of the American Chemical Society 1993; 115 (22): 10402-10403. doi: 10.1021/ja00075a083.
18. Trost BM, Indolese A. Ruthenium-catalyzed addition of alkenes to acetylenes. Journal of the American Chemical Society 1993; 115 (10): 4361-4362. doi: 10.1021/ja00063a064.
19. Trost BM, Imi K, Indolese AF. 1,5-Cyclooctadiene as a bis-homodiene partner in a metal-catalyzed [4 + 2]cycloaddition. Journal of the American Chemical Society 1993; 115 (19): 8831-8832. doi: 10.1021/ja00072a043.
20. Trost BM, Probst GD, Schoop A. Ruthenium-Catalyzed Alder Ene Type Reactions. A Formal Synthesis of Alternaric Acid. Journal of the American Chemical Society 1998; 120 (36): 9228-9236. doi: 10.1021/ja981540n.
21. Trost BM, Pinkerton AB, Toste FD, Sperrle M. Synthesis of 1,1-disubstituted alkenes via a Ru-catalyzed addition. Journal of the American Chemical Society 2001; 123 (50): 12504-12509. doi: 10.1021/ja012009m.
22. Trost BM, Shen HC, Pinkerton AB. A Synthesis of Trisubstituted Alkenes by a Ru-Catalyzed Addition. Chemistry - A European Journal 2002; 8 (10): 2341. doi: 10.1002/1521-3765(20020517)8:10<2341::AID-CHEM2341>3.0.CO;2-A.

23. Trost BM, Gunzner JL. Total synthesis of deschlorocallipeltoside A. Journal of the American Chemical Society 2001; 123 (38): 9449-9450. doi: 10.1021/ja011424b.

24. Trost BM, Gunzner JL, Dirat O, Rhee YH. Callipeltoside a: total synthesis, assignment of the absolute and relative configuration, and evaluation of synthetic analogues. Journal of the American Chemical Society 2002; 124 (35): 10396-10415. doi: 10.1021/ja0205232.

25. Trost BM, Chisholm JD, Wrobleski ST, Jung M. Ruthenium-catalyzed alkene-alkyne coupling: synthesis of the proposed structure of amphidinolide A. Journal of the American Chemical Society 2002; 124 (42): 12420-12421. doi: 10.1021/ja027883+.

26. Trost BM. Centenary Lecture. Cyclopentanoids: a challenge for new methodology. Chemical Society Reviews 1982; 11 (2): 141. doi: 10.1039/CS9821100141.

27. Trost BM, Machacek MR, Ball ZT. Ruthenium-catalyzed vinylsilane synthesis and cross-coupling as a selective approach to alkenes: benzyldimethylsilyl as a robustvinylmetal functionality. Organic letters 2003; 5 (11): 1895-1898. doi: 10.1021/ol034463w.

28. Trost BM, Machacek MR. An efficient one-pot enantio- and diastereoselective synthesis of heterocycles. Angewandte Chemie (International ed. in English) 2002; 41 (24): 4693-4697. doi: 10.1002/anie.200290019.

29. Trost BM, Yang H, Probst GD. A formal synthesis of (-)-mycalamide A. Journal of the American Chemical Society 2004; 126 (1): 48-49. doi: 10.1021/ja038787r.

30. Trost BM, Pinkerton AB. A Ruthenium-Catalyzed Two-Component Addition To Form 1,3-Dienes. Journal of the American Chemical Society 1999; 121 (16): 4068-4069. doi: 10.1021/ja990291f.

31. Trost BM, Pinkerton AB, Seidel M. Ruthenium-catalyzed two-component addition to form 1,3-dienes: optimization, scope, applications, and mechanism. Journal of the American Chemical Society 2001; 123 (50): 12466-12476. doi: 10.1021/ja011428g.

32. Clark JL, Duckett SB. Photochemical studies of (η5-C5H5)Ru(PPh3)2Cl and (η5-C5H5)Ru(PPh3)2Me: formation of Si-H and C-H bond activation products. Dalton transactions (Cambridge, England : 2003) 2014; 43 (3): 1162-1171. doi: 10.1039/C3DT52069B.

33. Trost BM, Older CM. A Convenient Synthetic Route to [CpRu(CH 3 CN) 3]PF 6. Organometallics 2002; 21 (12): 2544-2546. doi: 10.1021/om020143p.

34. Trost BM, Frederiksen MU, Rudd MT. Ruthenium-catalyzed reactions--a treasure trove of atom-economic transformations. AngewandteChemie (International ed. in English) 2005; 44 (41): 6630-6666. doi: 10.1002/anie.200500136.

35. Trost BM, Ryan MC, Rao M. Chiral cyclopentadienylrutheniumsulfoxide catalysts for asymmetric redox bicycloisomerization. Beilstein journal of organic chemistry 2016; 12: 1136-1152.doi: 10.3762/bjoc.12.110.

36. Trost BM, Toste FD. Mechanistic dichotomy in CpRu(CH(3)CN)(3)PF(6) catalyzed enynecycloisomerizations. Journal of the American Chemical Society 2002; 124 (18): 5025-5036. doi: 10.1021/ja012450c.

37. Trost BM, Ferreira EM, Gutierrez AC. Ruthenium- and palladium-catalyzed enynecycloisomerizations: differentially stereoselective syntheses of bicyclic structures. Journal of the American Chemical Society 2008; 130 (48): 16176-16177. doi: 10.1021/ja8078835.

38. Piera J, Persson A, Caldentey X, Bäckvall J-E. Water as nucleophile in palladium-catalyzed oxidative carbohydroxylation of allene-substituted conjugated dienes. Journal of the American Chemical Society 2007; 129 (46): 14120-14121. doi: 10.1021/ja075488j.

39. Franzén J, Bäckvall J-E. Carbon-carbon bond formation in palladium(II)-catalyzed allylic oxidation: a novel oxidative carbocyclization of allene-substituted olefins. Journal of the American Chemical Society 2003; 125 (20): 6056-6057. doi: 10.1021/ja029505a.

40. Löfstedt J, Närhi K, Dorange I, Bäckvall J-E. Palladium-catalyzed carbocyclization of allene-diene derivatives.Exploring different nucleophiles. The Journal of Organic Chemistry 2003; 68 (19): 7243-7248. doi: 10.1021/jo034412c.

41. Dorange I, Löfstedt J, Närhi K, Franzén J, Bäckvall J-E. Allenes as carbon nucleophiles in intramolecular attack on (pi-1,3-diene)palladium complexes: evidence for trans carbopalladation of the 1,3-diene. Chemistry - A European Journal 2003; 9 (14): 3445-3449. doi: 10.1002/chem.200305056.

42. Löfstedt J, Franzén J, Bäckvall JE. Carbon-carbon bond formation in regio- and stereoselective palladium-catalyzed cyclization of allene-substituted conjugated dienes. The Journal of Organic Chemistry 2001; 66 (24): 8015-8025. doi: 10.1021/jo0157324.

43. Piera J, Närhi K, Bäckvall J-E. PdII-catalyzed aerobic allylic oxidative carbocyclization of allene-substituted olefins: immobilization of an oxygen-activating catalyst. Angewandte Chemie (International ed. in English) 2006; 45 (41): 6914-6917. doi: 10.1002/anie.200602421.

44. Franzén J, Löfstedt J, Dorange I, Bäckvall J-E. Allenes as carbon nucleophiles in palladium-catalyzed reactions: observation of anti attack of allenes on (pi-allyl)palladium complexes. Journal of the American Chemical Society 2002; 124 (38): 11246-11247. doi: 10.1021/ja026150m.

45. Johnston EV, Karlsson EA, Lindberg SA, Akermark B, Bäckvall J-E. Efficient reoxidation of palladium by a hybrid catalyst in aerobic palladium-catalyzed carbocyclization of enallenes. Chemistry - A European Journal 2009; 15 (28): 6799-6801. doi: 10.1002/chem.200900980.

46. Trost BM. The 2014 Tetrahedron Prize for Creativity in Organic Chemistry. Palladium and Other Transition Metal-Catalyzed Reactions: Methods and Applications. Tetrahedron 2015; 71 (35): 5707. doi: 10.1016/j.tet.2015.06.043.

47. Trost BM, Fleming I. Comprehensive organic synthesis: Selectivity, strategy & efficiency in modern organic chemistry, Vol. 7. Oxford, UK: Pergamon Press, 1991.

48. Trost BM, Gutierrez AC, Ferreira EM. Differential reactivities of enyne substrates in ruthenium- and palladium-catalyzed cycloisomerizations. Journal of the American Chemical Society 2010; 132 (26): 9206-9218. doi: 10.1021/ja103663h.

49. Campbell MJ, Pohlhaus PD, Min G, Ohmatsu K, Johnson JS. An "anti-Baldwin" 3-exo-dig cyclization: preparation of vinylidenecyclopropanes from electron-poor alkenes. Journal of the American Chemical Society 2008; 130 (29): 9180-9181. doi: 10.1021/ja803553a.

50. Trost BM, Breit B, Peukert S, Zambrano J, Ziller JW. A New Platform for Designing Ligands for Asymmetric Induction in AllylicAlkylations. AngewandteChemie International Edition in English 1995; 34 (21): 2386-2388. doi: 10.1002/anie.199523861.

51. Huang D, Liu X, Li L, Cai Y, Liu W. et al. Enantioselectivebromoaminocyclization of allyl N-tosylcarbamates catalyzed by a chiral phosphine-Sc(OTf)3 complex. Journal of the American Chemical Society 2013; 135 (22): 8101-8104. doi: 10.1021/ja4010877.

52. Myers EL, Raines RT. Inside Cover: A Phosphine-Mediated Conversion of Azides into Diazo Compounds AngewandteChemie (International ed. in English) 2009; 48 (13): 2246. doi: 10.1002/anie.200990061.

53. Coffinier R, El Assal M, Peixoto PA, Bosset C, Miqueu K. et al. Total Synthesis of (-)-Bacchopetiolone via an Asymmetric Hydroxylative Phenol Dearomatization/4+2-Dimerization Cascade Promoted by a Novel Salen-Type Chiral Iodane. Organic letters 2016; 18 (5): 1120-1123. doi: 10.1021/acs.orglett.6b00224.

54. Glorius F, Neuburger M, Pfaltz A. Highly Enantio- and RegioselectiveAllylicAlkylations Catalyzed by Chiral [Bis(dihydrooxazole)] molybdenum Complexes. Helvetica ChimicaActa 2001; 84 (10): 3178-3196. doi: 10.1002/1522-2675(20011017)84:10<3178::AID-HLCA3178>3.0.CO;2-Q.

55. Glorius F, Pfaltz A. Enantioselective Molybdenum-Catalyzed Allylic Alkylation Using Chiral Bisoxazoline Ligands. Organic letters 1999; 1 (1): 141-144. doi: 10.1021/ol990602r.

56. Kusama H, Watanabe E, Ishida K, Iwasawa N. Efficient control for the cationic platinum(II)-catalyzed concise synthesis of two types of fused carbocycles with angular oxygen functionality. Chemistry, an Asian journal 2011; 6 (9): 2273-2277. doi: 10.1002/asia.201100460.

57. Hernández A-I, Balzarini J, Karlsson A, Camarasa M-J, Pérez-Pérez M-J. Acyclic nucleoside analogues as novel inhibitors of human mitochondrial thymidine kinase. Journal of medicinal chemistry 2002; 45 (19): 4254-4263. doi: 10.1021/jm011128+.

58. Trost, BM, Schultz JE. Palladium-catalyzed asymmetric allylic alkylation strategies for the synthesis of acyclic tetrasubstitutedstereocenters. Synthesis 2019; 51 (01): 1-30. doi: 10.1055/s-0037-1610386.

59. Trost, BM. Pd- and Mo-catalyzed asymmetric allylic alkylation. Organic Process Research & Development. 2012; 16 (2): 185-194. doi: 10.1021/op200294r.

60. Trost BM, Toste FD. Regio- and enantioselectiveallylic alkylation of an unsymmetrical substrate: a working model. Journal of the American Chemical Society 1999; 121 (19): 4545-4554. doi: 10.1021/ja9828713.

61. Butts CP, Filali E, Lloyd-Jones GC, Norrby P-O. et al. Structure-based rationale for selectivity in the asymmetric allylic alkylation of cycloalkenyl esters employing the Trost 'Standard Ligand' (TSL): isolation, analysis and alkylation of the monomeric form of the cationic η3-cyclohexenyl complex [(η3-c-C6H9)Pd(TSL)]+. Journal of the American Chemical Society 2009; 131 (29): 9945-9957. doi: 10.1021/ja8099757.

62. Craig PB, Emane F, Guy CL-J, Per-Ola N, David AS. et al. CuI-catalysedenantioselective alkyl 1,4-additions to (E)-Nitroalkenes and cyclic enones with phosphino-oxazoline ligands. European Journal of Organic Chemistry 2018; 24 (12): 3122-3130. doi: 10.1002/ejoc.201800476.

63. Trost BM, Franz AW. Ruthenium-catalyzed domino redox bicycloisomerization.An atom-economical synthesis of 3.1.0- and 4.1.0carbo- and heterocycles. Journal of the American Chemical Society 2010; 132 (51): 18429. doi: 10.1021/ja1088452.

64. Sabitha G, Venkata Reddy E, Swapna R, Mallikarjun Reddy N, Yadav JS. Bismuth(III) Chloride Catalyzed Efficient and Selective Cleavage of Trityl Ethers. Synlett 2004; (7): 1276-1278. doi: 10.1055/s-2004-825602.

65. Copéret C, Ma S, Sugihara T, Negishi E-i. Cyclic carbopalladation of alkynes terminated by carbonylativeamidation. Tetrahedron 1996; 52 (35): 11529-11544. doi: 10.1016/0040-4020(96)00640-0.

66. Södergren MJ, Andersson PG. Chiral, bicyclic proline derivatives and their application as ligands for copper in the catalytic asymmetric allylic oxidation of olefins. Tetrahedron Letters 1996; 37 (42): 7577-7580. doi: 10.1016/0040-4039(96)01664-4.

67. Tran BL, Driess M, Hartwig JF. Copper-catalyzed oxidative dehydrogenative carboxylation of unactivated alkanes to allylic esters via alkenes. Journal of the American Chemical Society 2014; 136 (49): 17292-17301. doi: 10.1021/ja510093x.

68. Matsuyama K, Inoue T, Inoue Y. Self-Sensitized Diastereodifferentiating Z - E Photoisomerization of 3-, 4-, and 5-Benzoyloxycyclooctenes: Intra- versus Intermolecular Photosensitization. Synthesis 2001; 112 (08): 1167-1174. doi: 10.1055/s-2001-15062.

69. Trost BM, Malhotra S, Olson DE, Maruniak A, Du Bois J. Asymmetric synthesis of diamine derivatives via sequential palladium and rhodium catalysis. Journal of the American Chemical Society 2009; 131 (12): 4190-4191. doi: 10.1021/ja809697p.

70. Sankar U, Mahalakshmi S, Balasubramanian K. A One-Pot Stereoselective Synthesis of Electron-Deficient 4-Substituted (E,E)-1-Arylsulfonylbuta-1,3-dienes and Their Chemoselective [3+2] Cycloaddition with AzomethineYlides - A Simple Synthesis of 1,3,4-Trisubstituted Pyrrolidines and Pyrroles. Synlett 2013; 24 (12): 1533-1540. doi: 10.1055/s-0033-1339181.

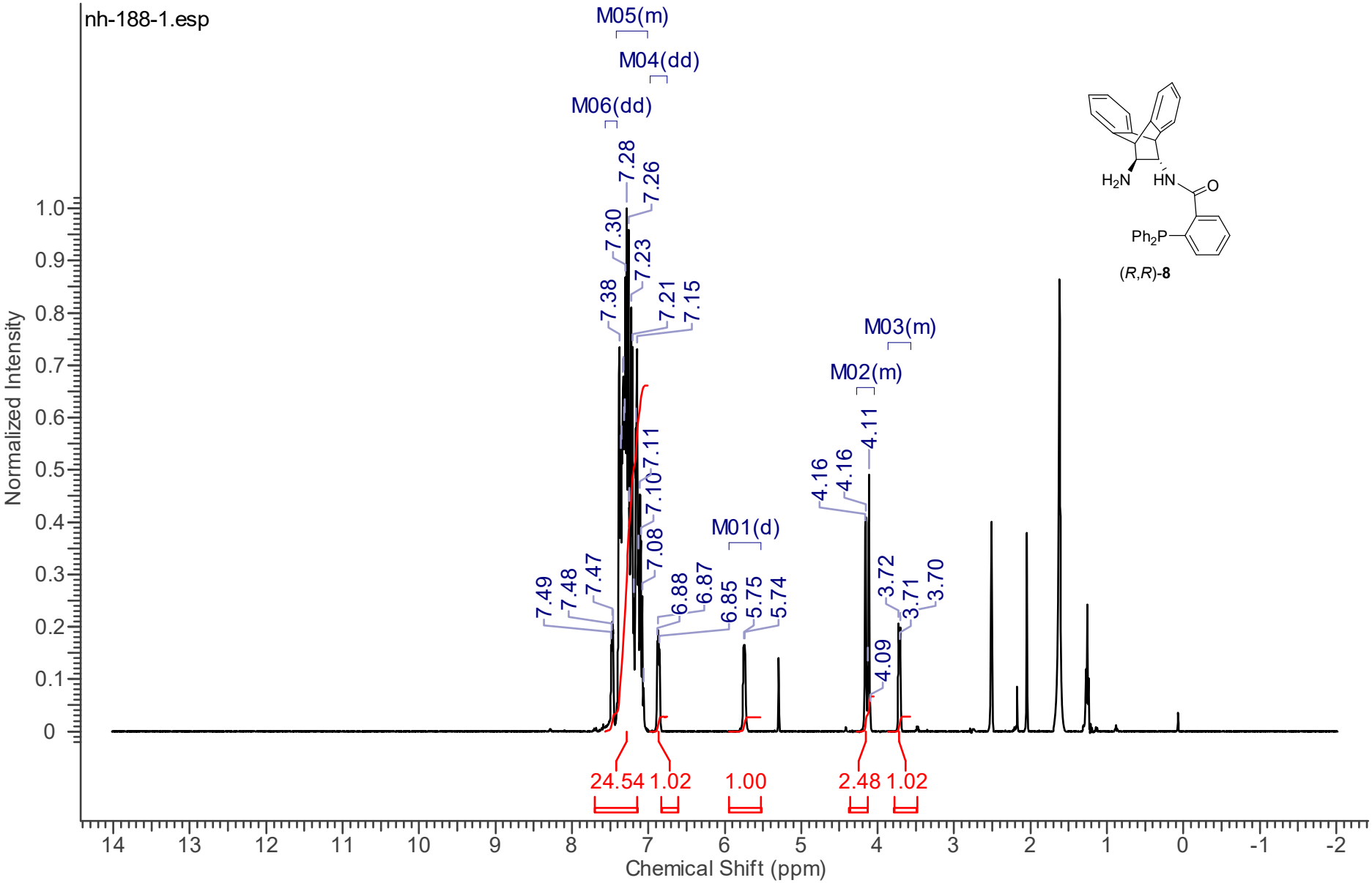
71. Kang T, Kim W-Y, Yoon Y, Kim BG, Lee H-Y. Tandem cycloaddition reactions of allenyldiazo compounds forming triquinanes via trimethylenemethanediyls. Journal of the American Chemical Society 2011; 133 (45): 18050-18053. doi: 10.1021/ja207591e.

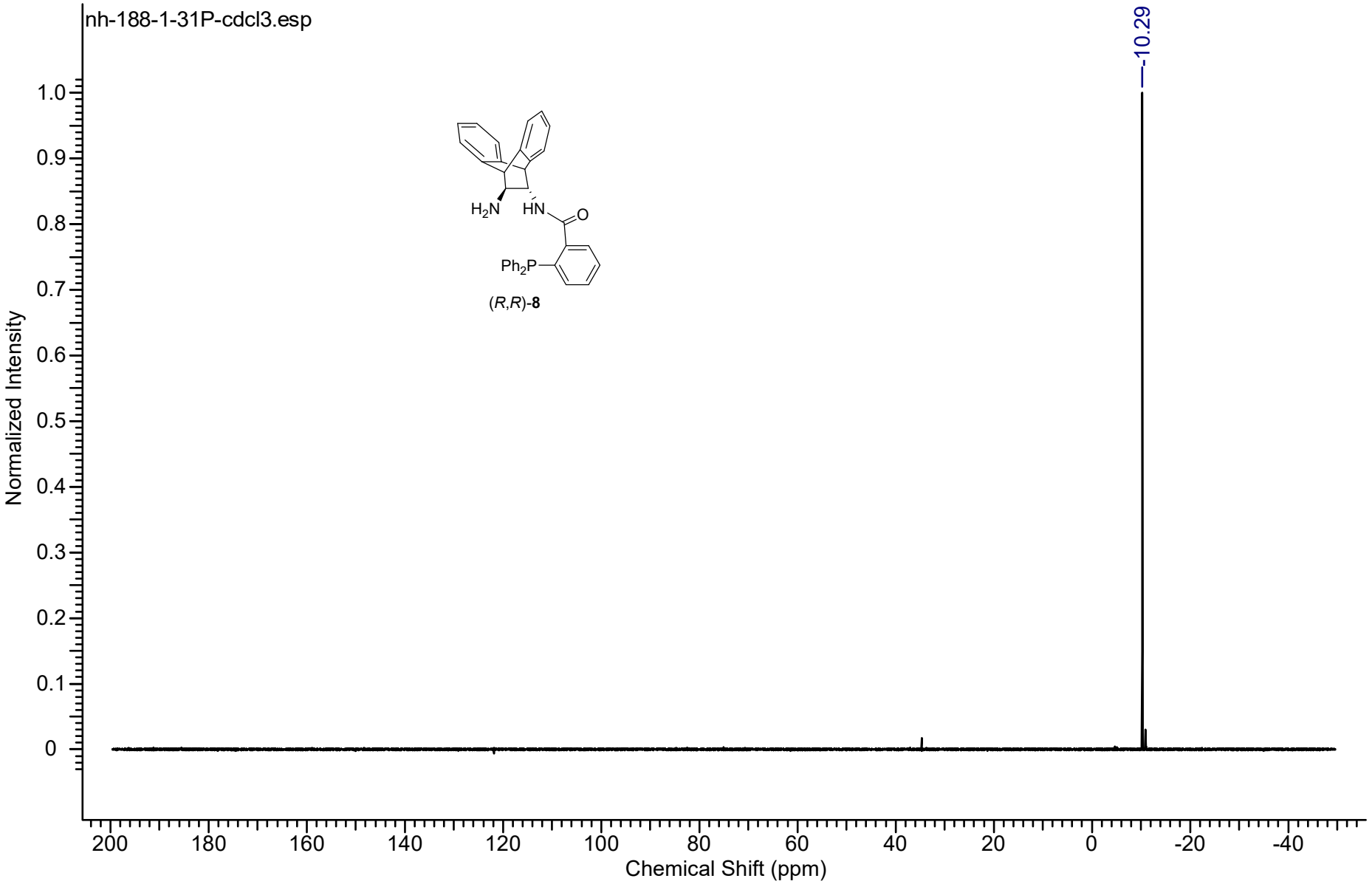
Effective synthesis of bicyclodienes via palladium-catalyzed asymmetric allylic alkylation and ruthenium-catalyzed cycloisomerization.

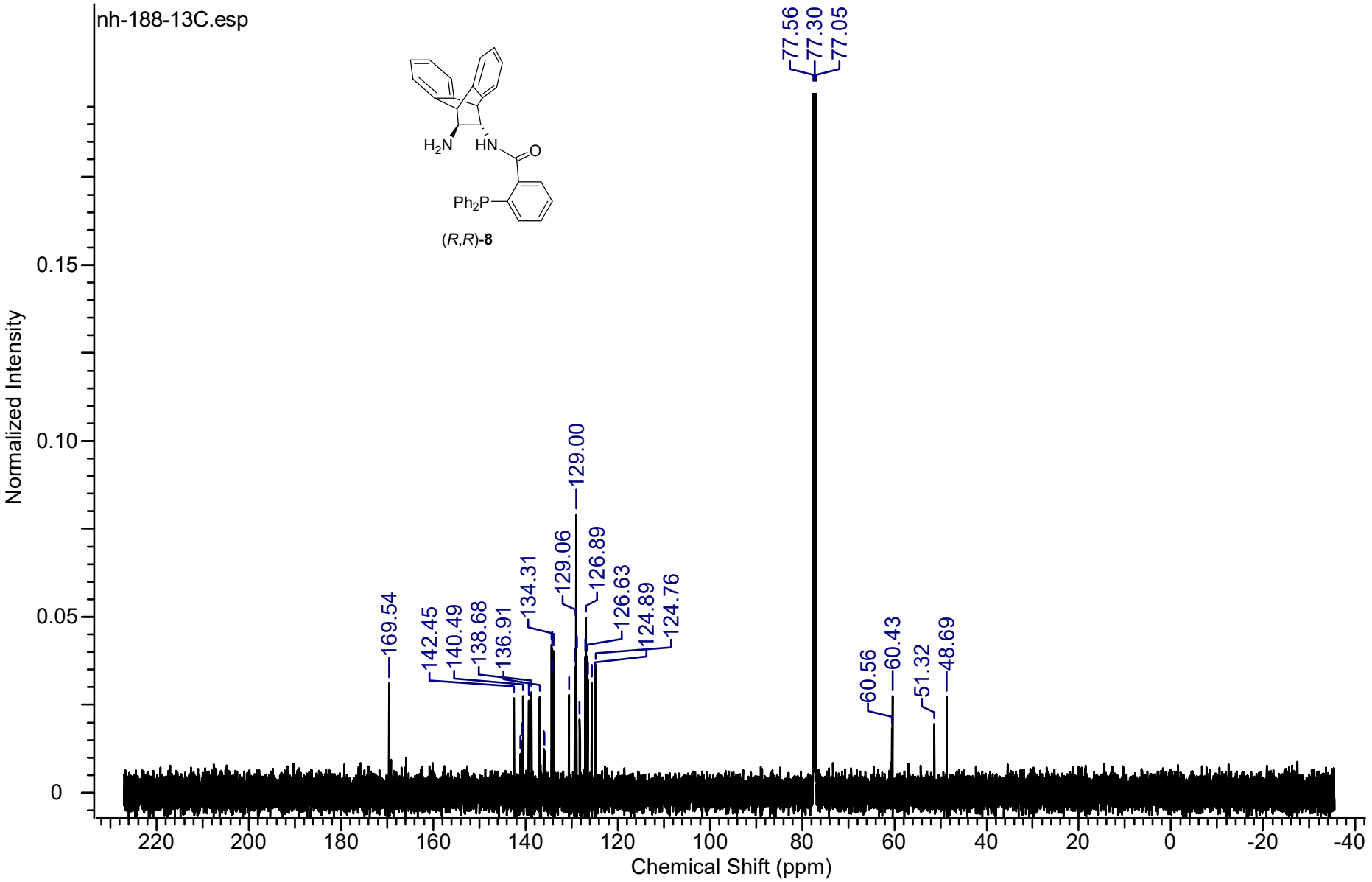
Nizam Havare*

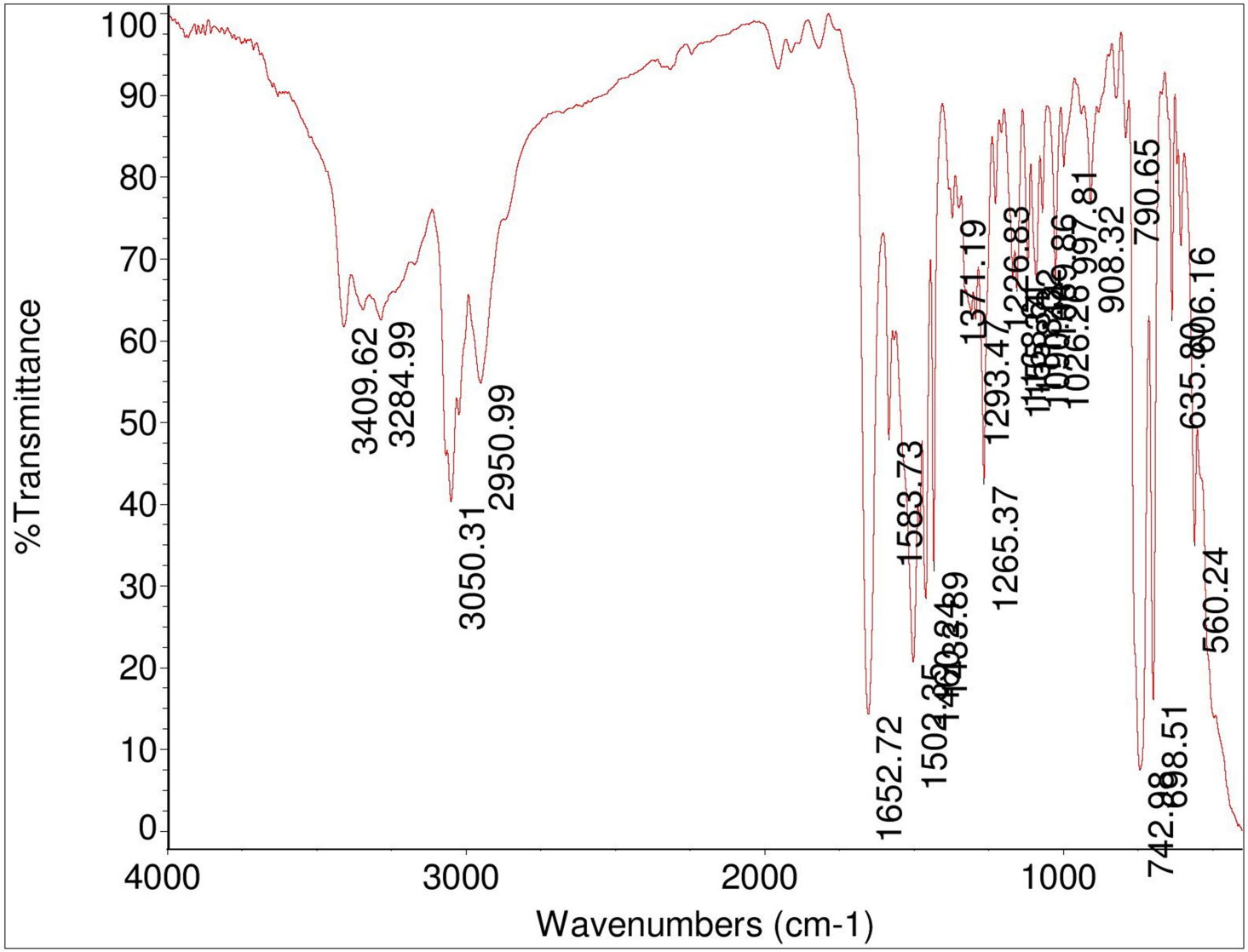
*Department of Chemistry, Stanford University, Stanford, California 94305-5580, United States

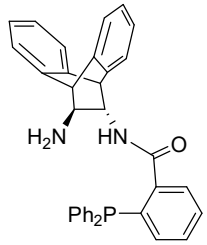
Index


nh-188-1.esp
M05(m)
M04(dd)
M06(dd)
7.28
7.26
7.30
7.23
7.38
7.21
7.15
M03(m)
M02(m)
4.11
4.16
4.16
7.11
7.10
7.08
M01(d)
7.49
7.48
7.47
6.88
6.87
6.85
5.75
5.74
3.72
3.71
3.70
4.09
24.54
1.02
1.00
2.48
1.02
Normalized Intensity
Chemical Shift (ppm)
H2N
HN
O
Ph2P
(R,R)-8


nh-188-1-31P-cdcl3.esp
10.29
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)
H2N
HN
O
Ph2P
(R,R)-8

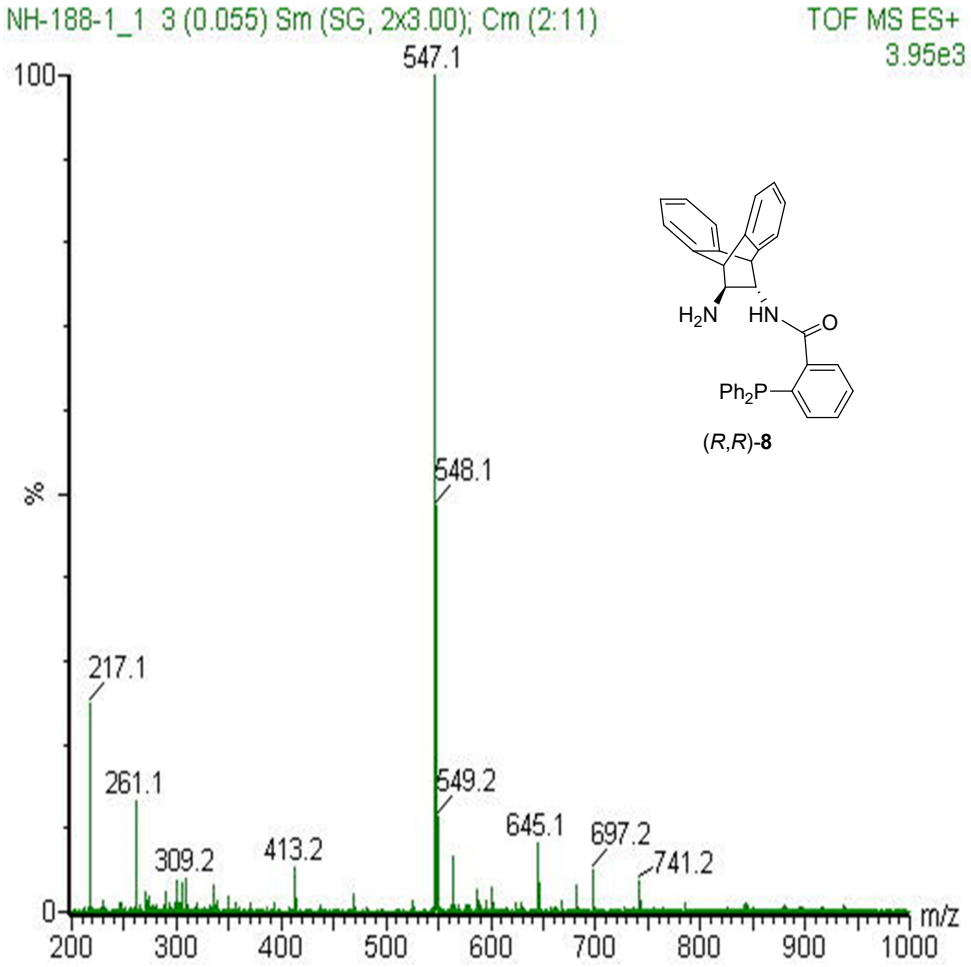

nh-188-13C.esp
77.56
77.30
77.05
H2N
HN
O
Ph2P
(R,R)-8
Normalized Intensity
0.15
0.10
0.05
0
169.54
142.45
140.49
138.68
136.91
134.31
129.06
129.00
126.89
126.63
124.89
124.76
60.56
60.43
51.32
48.69
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)


%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1000
3409.62
3284.99
3050.31
2950.99
1652.72
1583.73
1504.35
1371.19
1293.47
1265.37
1226.83
1026.28
908.32
790.65
742.89
698.51
635.80
606.16
560.24


H2N
HN
O
Ph2P

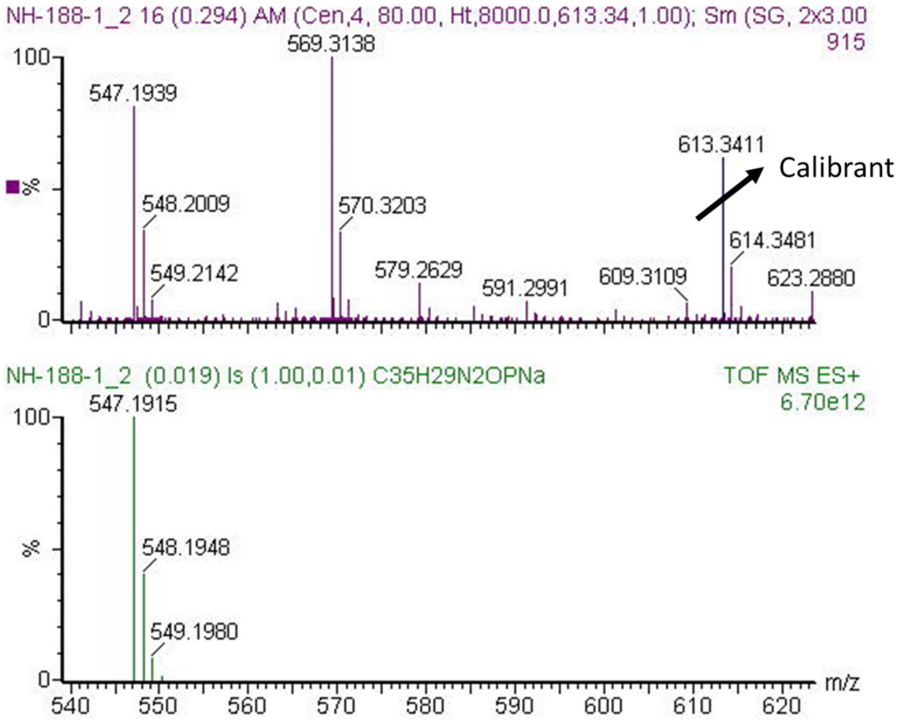
(*R*,*R*)-**8**

LRMS [M+Na]⁺

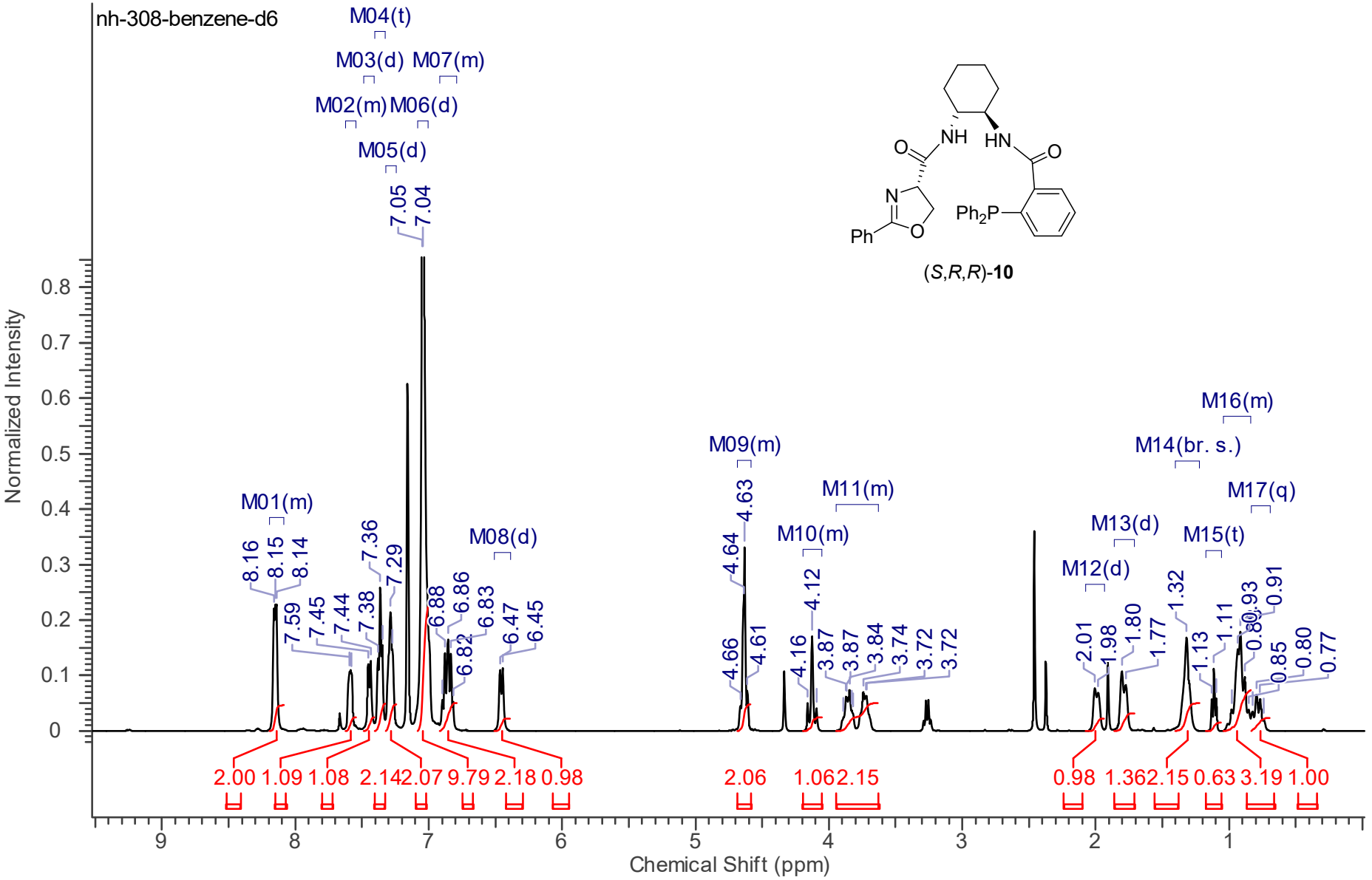


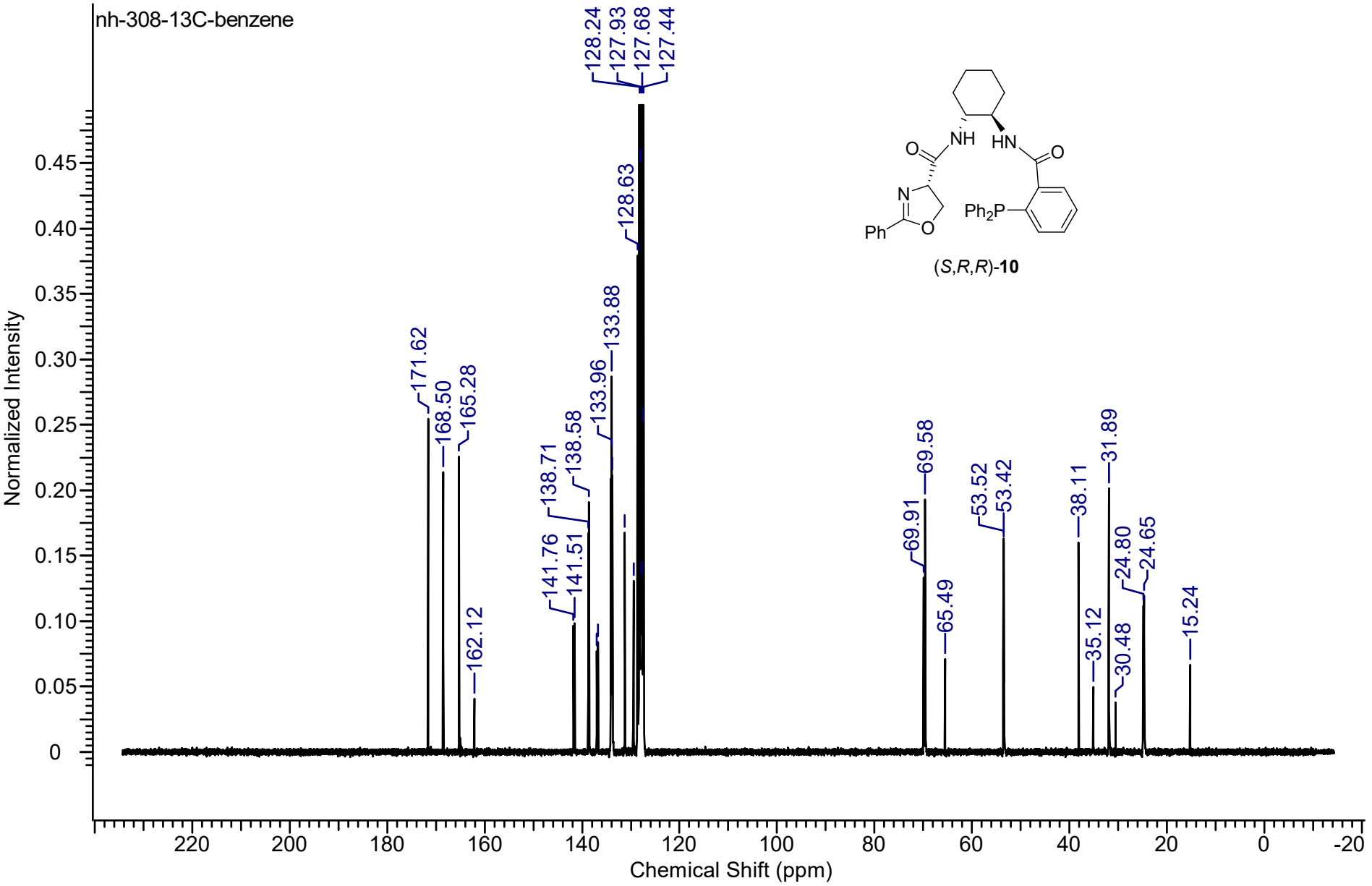
(*R*,*R*)-**8**

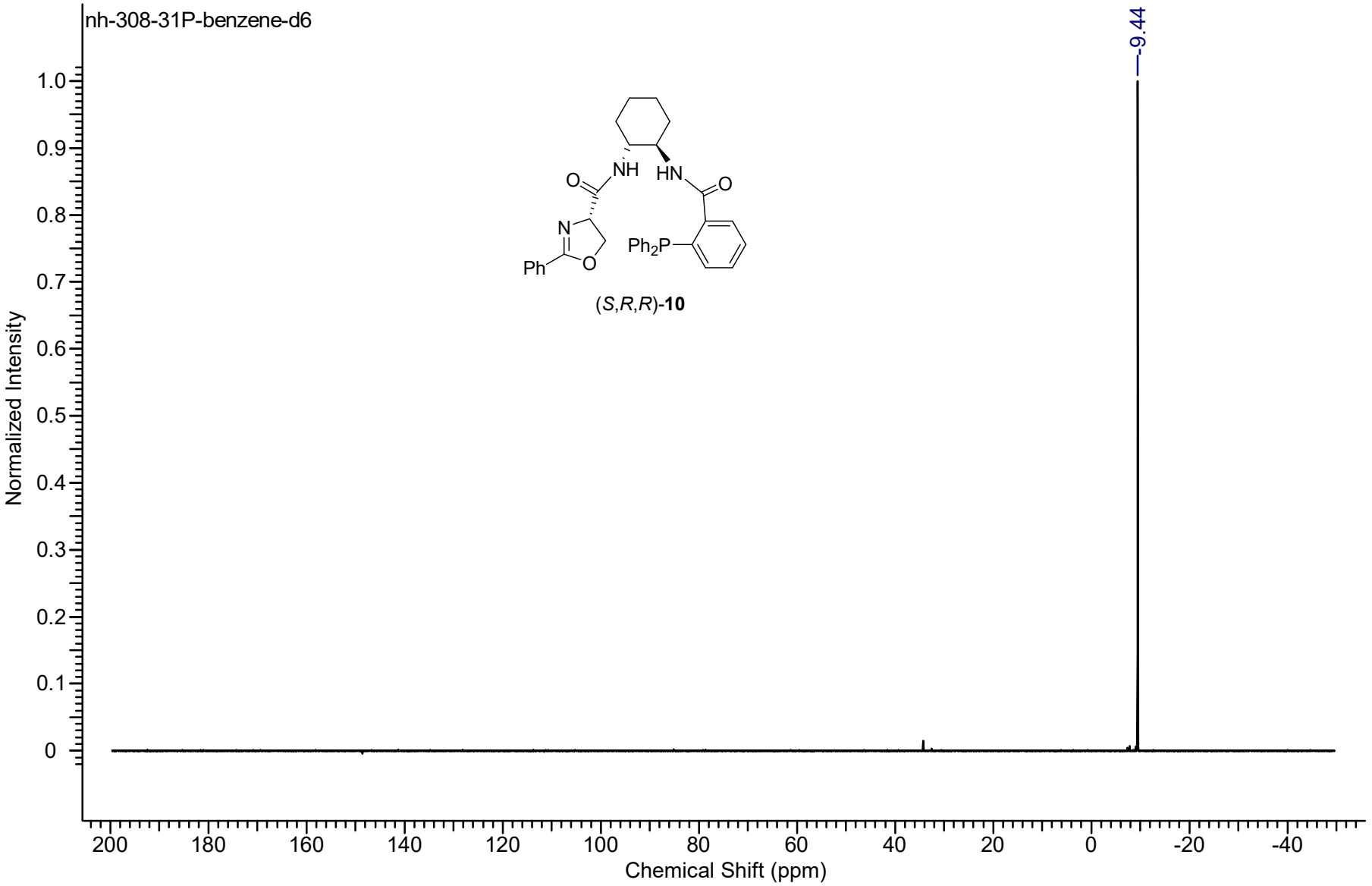
HRMS ObservedΔ = 2.4 mDa
Acceptable = ± 2.7 mDa



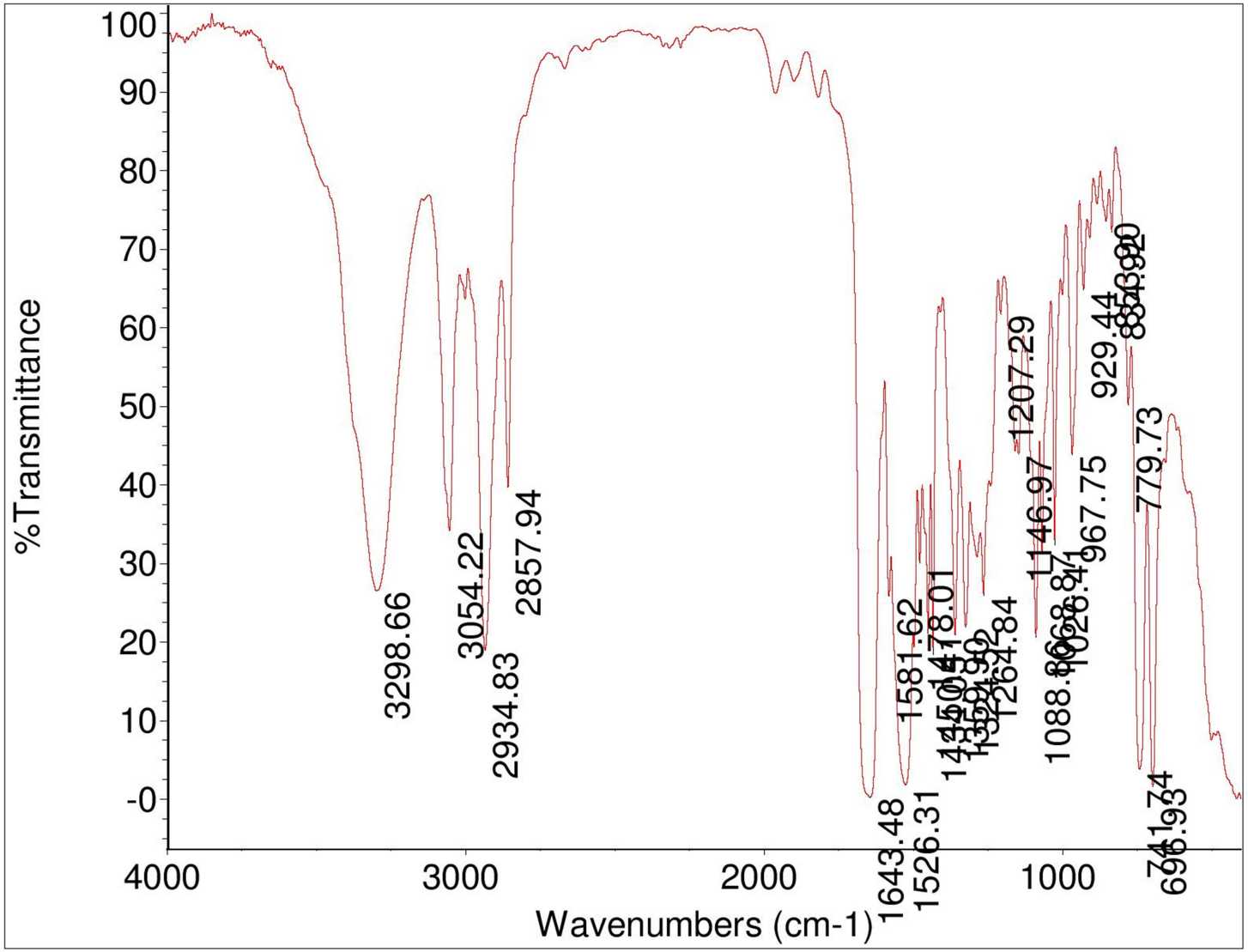
Theoretical =[M+Na]⁺

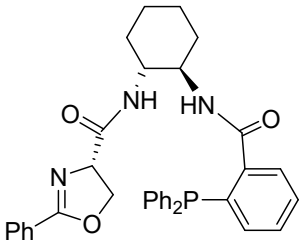

nh-308-benzene-d6
M04(t)
M03(d) M07(m)
M02(m) M06(d)
M05(d)
7.05
7.04
M01(m)
8.16
8.15
8.14
7.59
7.45
7.44
7.38
7.36
7.29
6.88
6.86
6.83
6.82
6.47
6.45
M08(d)
M09(m)
4.64
4.63
4.66
4.61
M10(m)
4.16
4.12
M11(m)
3.87
3.87
3.84
3.74
3.72
3.72
M12(d)
2.01
1.98
M13(d)
1.80
1.77
M14(br. s.)
1.32
1.13
M15(t)
1.11
0.93
0.91
M16(m)
0.80
0.85
0.80
0.77
M17(q)
2.00 1.09 1.08 2.14 2.07 9.79 2.18 0.98
2.06
1.06 2.15
0.98 1.36 2.15 0.63 3.19 1.00
Normalized Intensity
Chemical Shift (ppm)
NH
HN
O
O
N
O
Ph
Ph2P
(S,R,R)-10


nh-308-13C-benzene
128.24
127.93
127.68
127.44
128.63
133.88
133.96
138.58
138.71
141.51
141.76
171.62
168.50
165.28
162.12
69.91
69.58
65.49
53.52
53.42
38.11
31.89
35.12
30.48
24.80
24.65
15.24
NH
HN
O
O
N
O
Ph
Ph2P
(S,R,R)-10
Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


nh-308-31P-benzene-d6
-9.44
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)
NH
HN
O
O
N
O
Ph
Ph2P

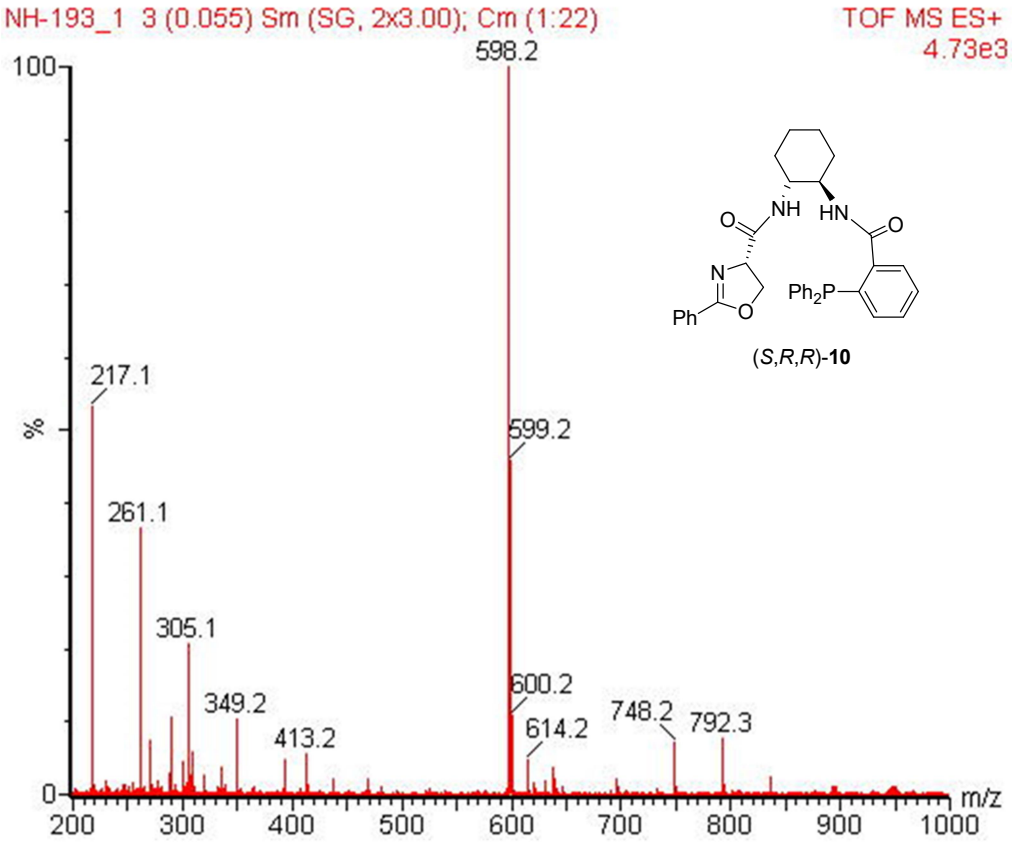
(*S*,*R*,*R*)-**10**


%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
100
90
80
70
60
50
40
30
20
10
-0
3298.66
3054.22
2934.83
2857.94
1643.48
1581.62
1526.31
1207.29
1146.97
1088.80
967.75
929.44
779.73
741.74
696.93


NH
HN
O
O
N
O
Ph
Ph2P

(*S*,*R*,*R*)-**10**

LRMS [M+Na]+

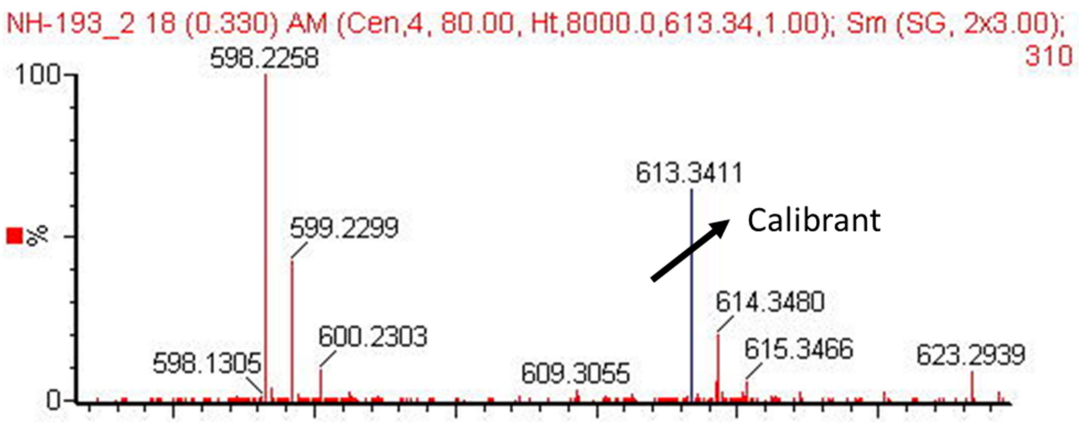


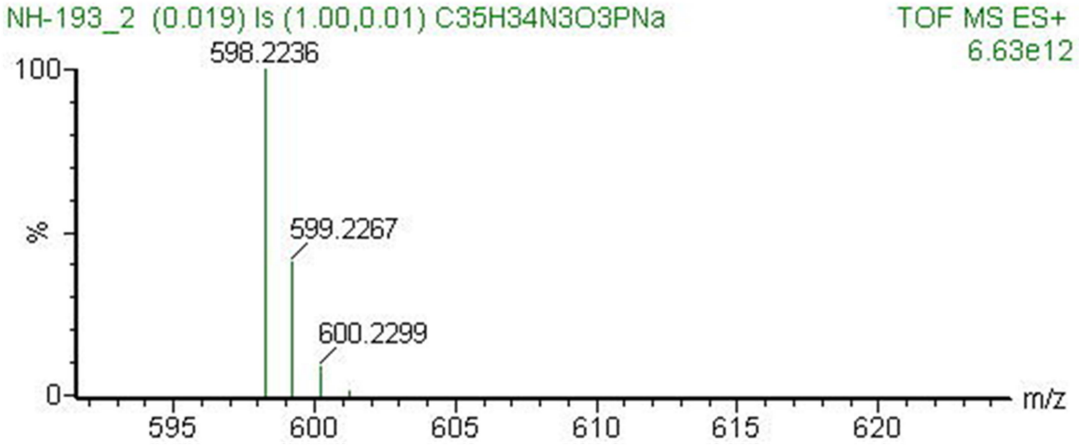
(*S*,*R*,*R*)-**10**

HRMS

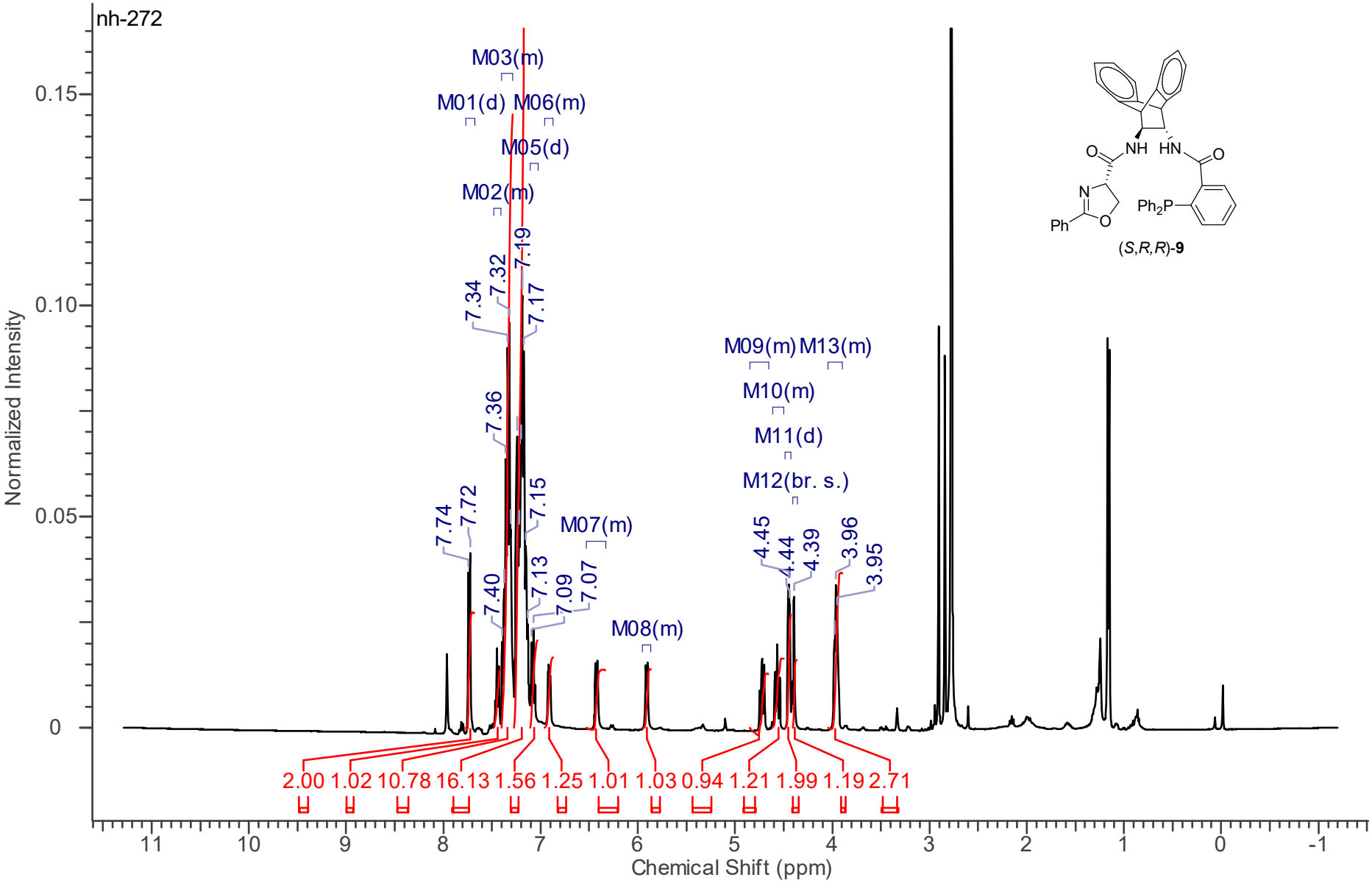
ObservedΔ = 2.2 mDa

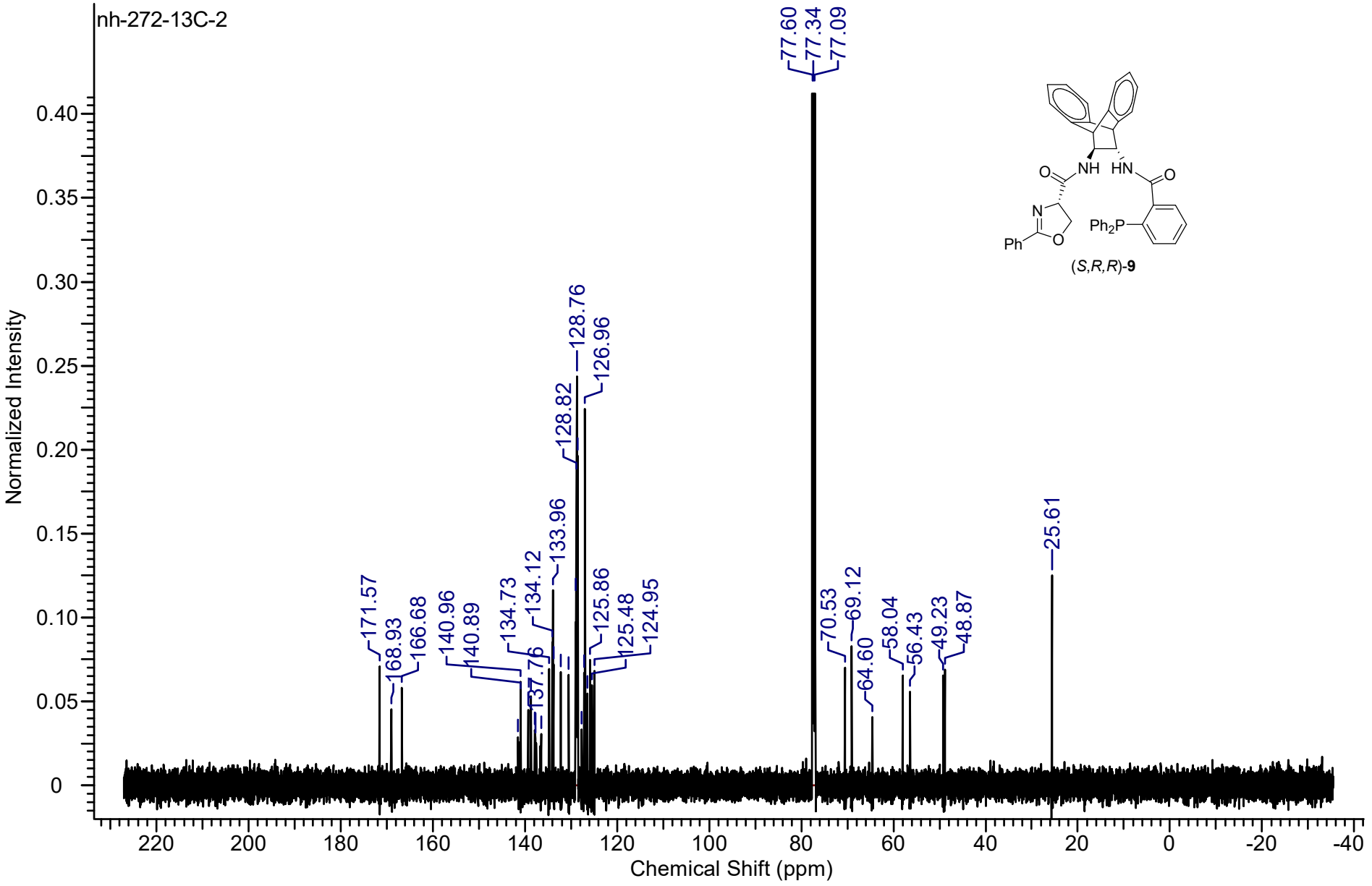
Acceptable = ± 3.0 mDa

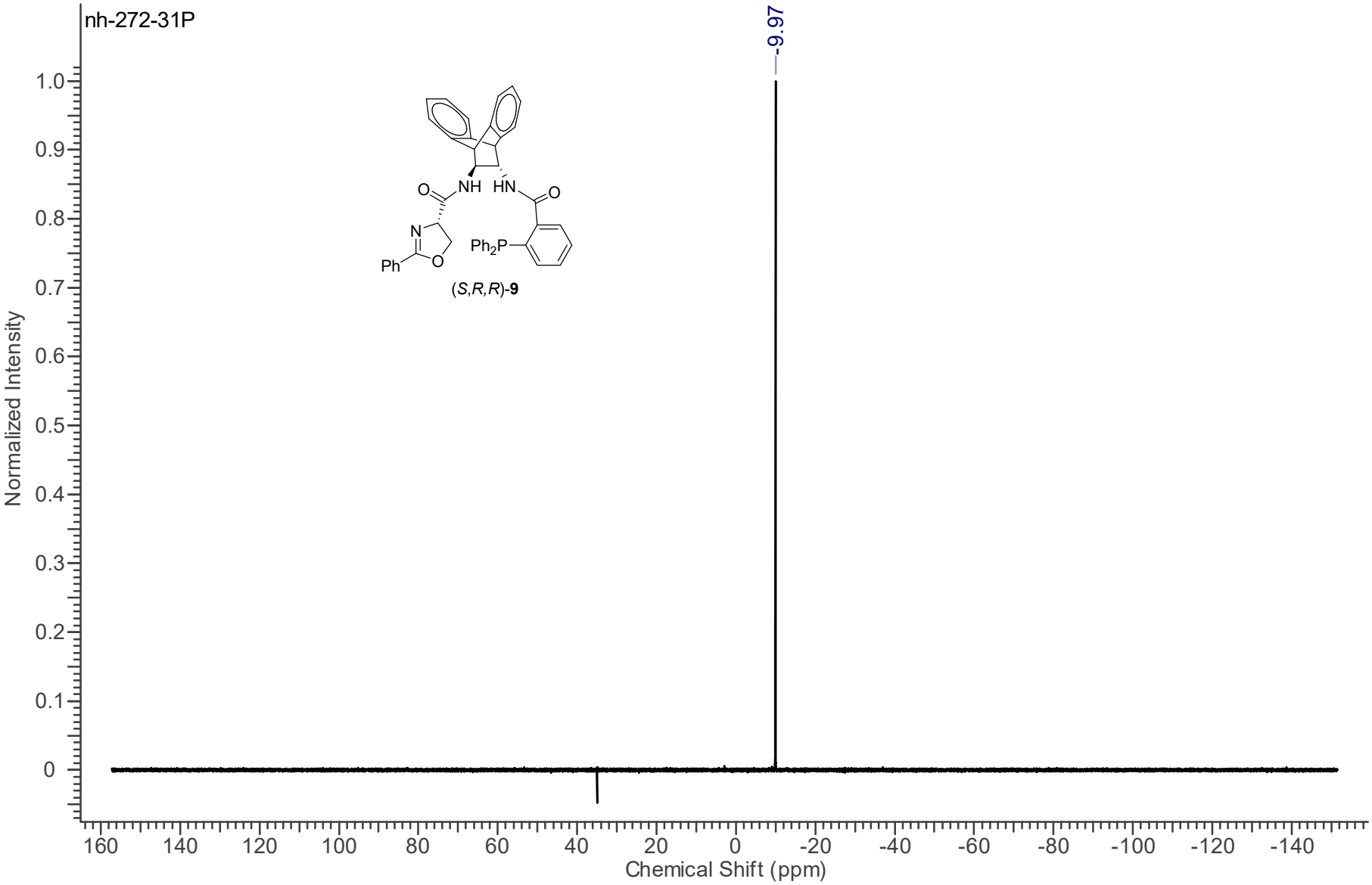


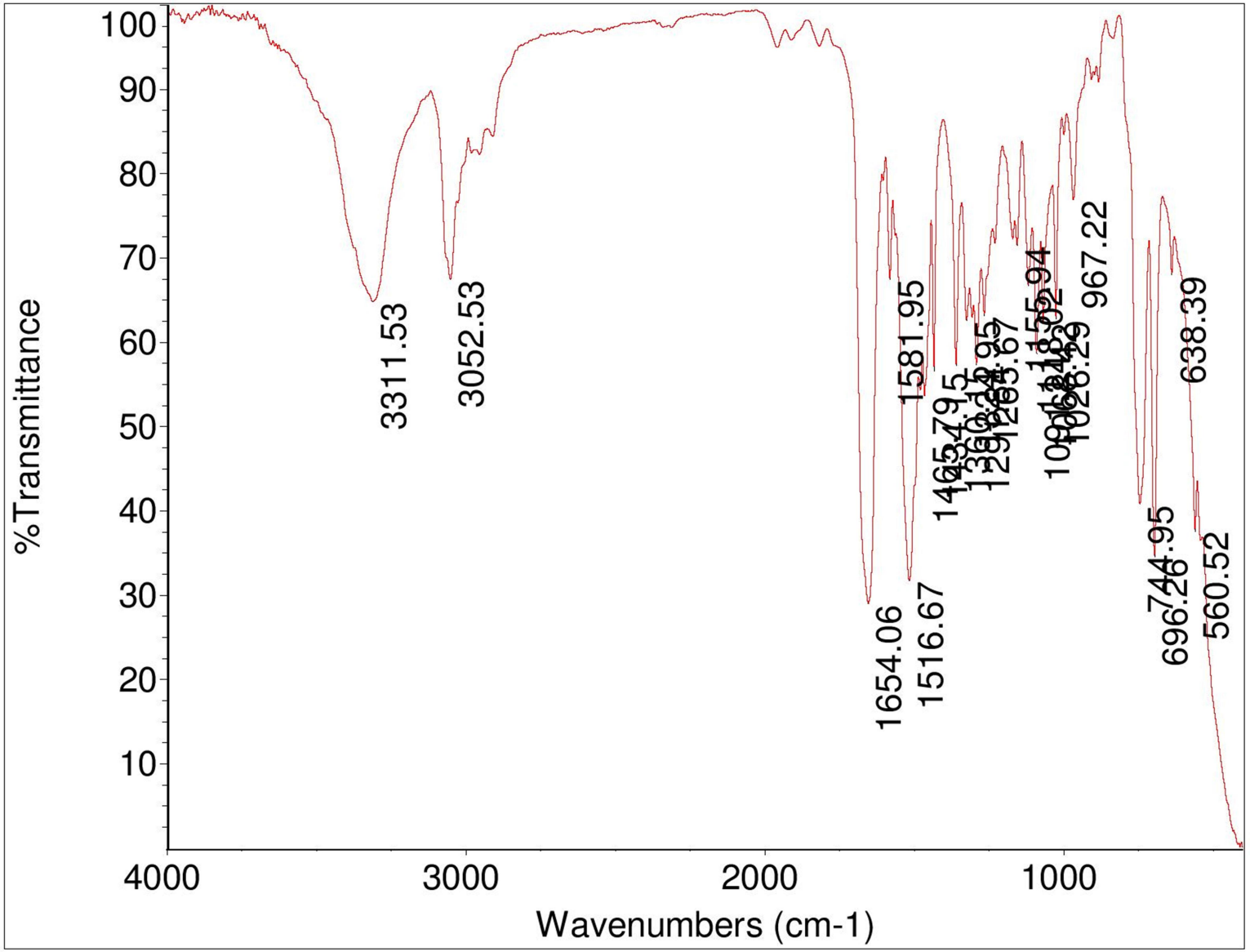


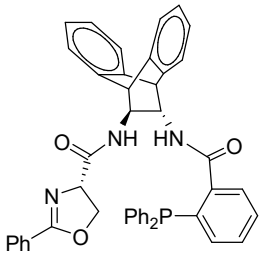
Theoretical =[M+Na]+


nh-272
M03(m)
M01(d) M06(m)
M05(d)
M02(m)
7.19
7.32
7.34
7.17
7.36
7.74
7.72
7.15
7.40
7.13
7.09
7.07
M07(m)
M08(m)
M09(m) M13(m)
M10(m)
M11(d)
M12(br. s.)
4.45
4.44
4.39
3.96
3.95
2.00 1.02 10.78 16.13 1.56 1.25 1.01 1.03 0.94 1.21 1.99 1.19 2.71
Normalized Intensity
0.15
0.10
0.05
0
11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)
NH HN
O
N
Ph
O
Ph2P
(S,R,R)-9

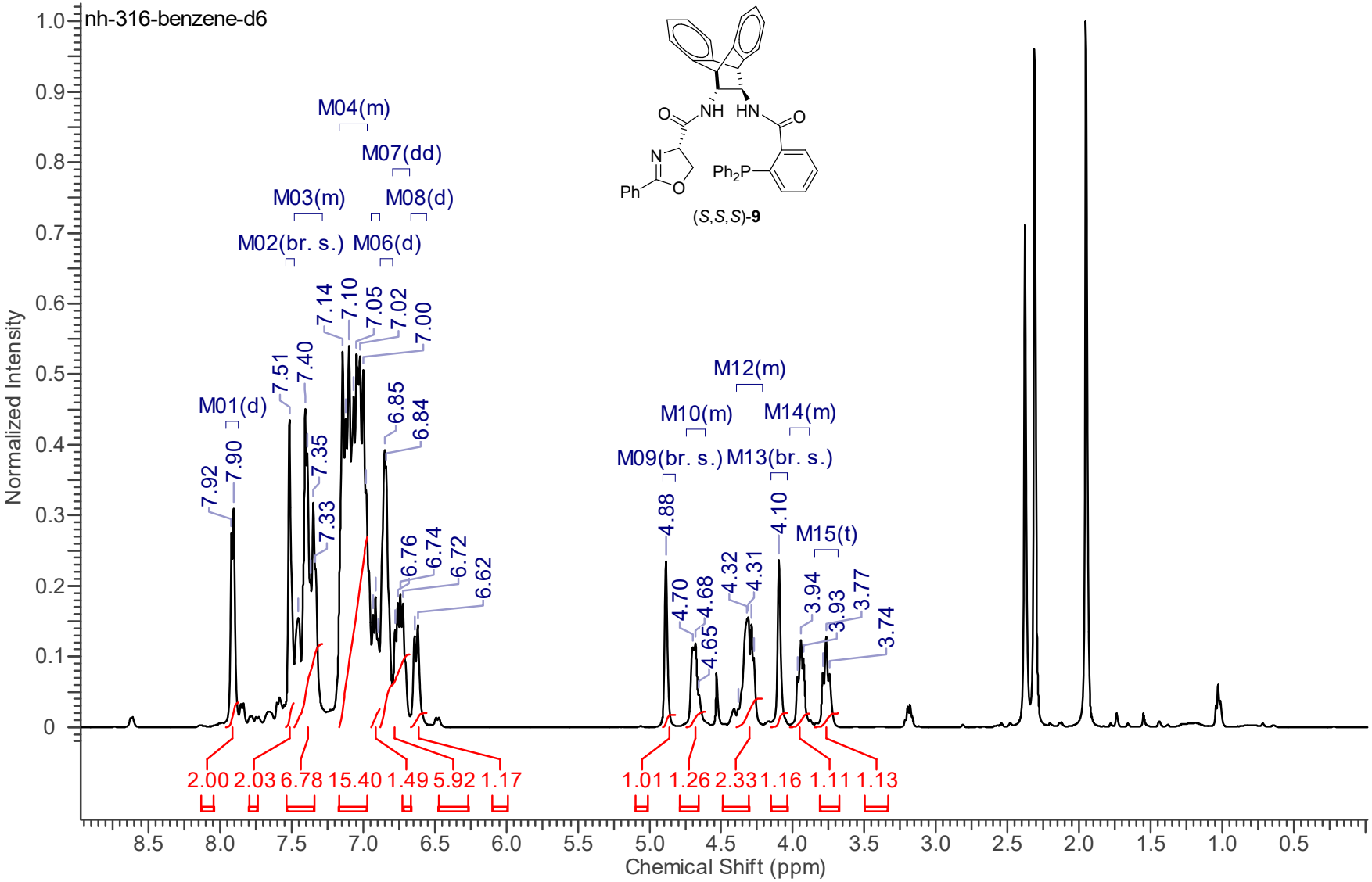

nh-272-13C-2
77.60
77.34
77.09
171.57
168.93
166.68
140.96
140.89
134.73
134.12
133.96
128.82
128.76
126.96
125.86
125.48
124.95
70.53
69.12
64.60
58.04
56.43
49.23
48.87
25.61
NH
HN
O
N
O
Ph
Ph2P
(S,R,R)-9
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)

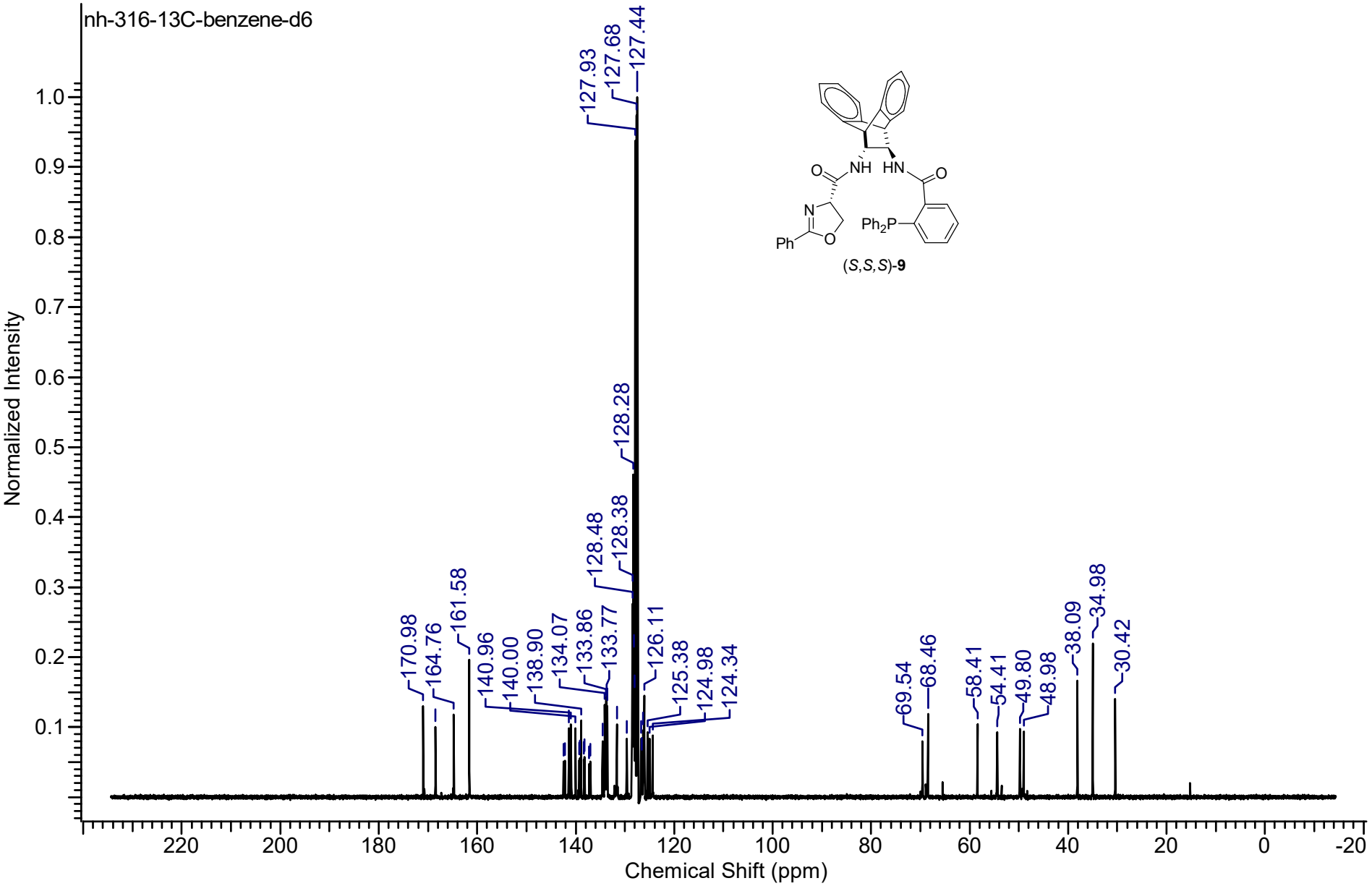

nh-272-31P
-9.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
Chemical Shift (ppm)
O
NH
HN
O
N
Ph
O
Ph2P
(S,R,R)-9

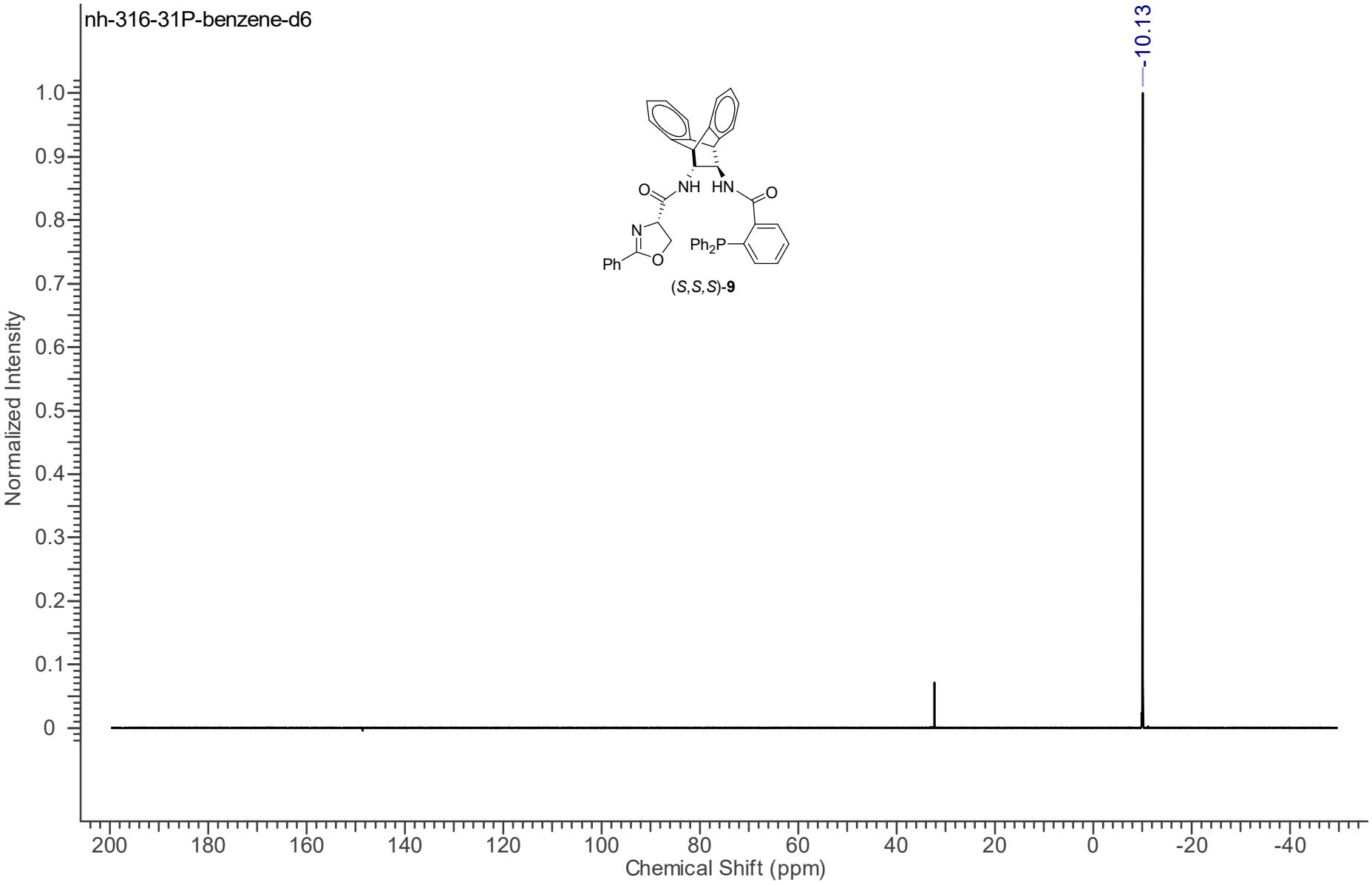

%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
3311.53
3052.53
1654.06
1581.95
1516.67
967.22
744.95
696.26
638.39
560.52

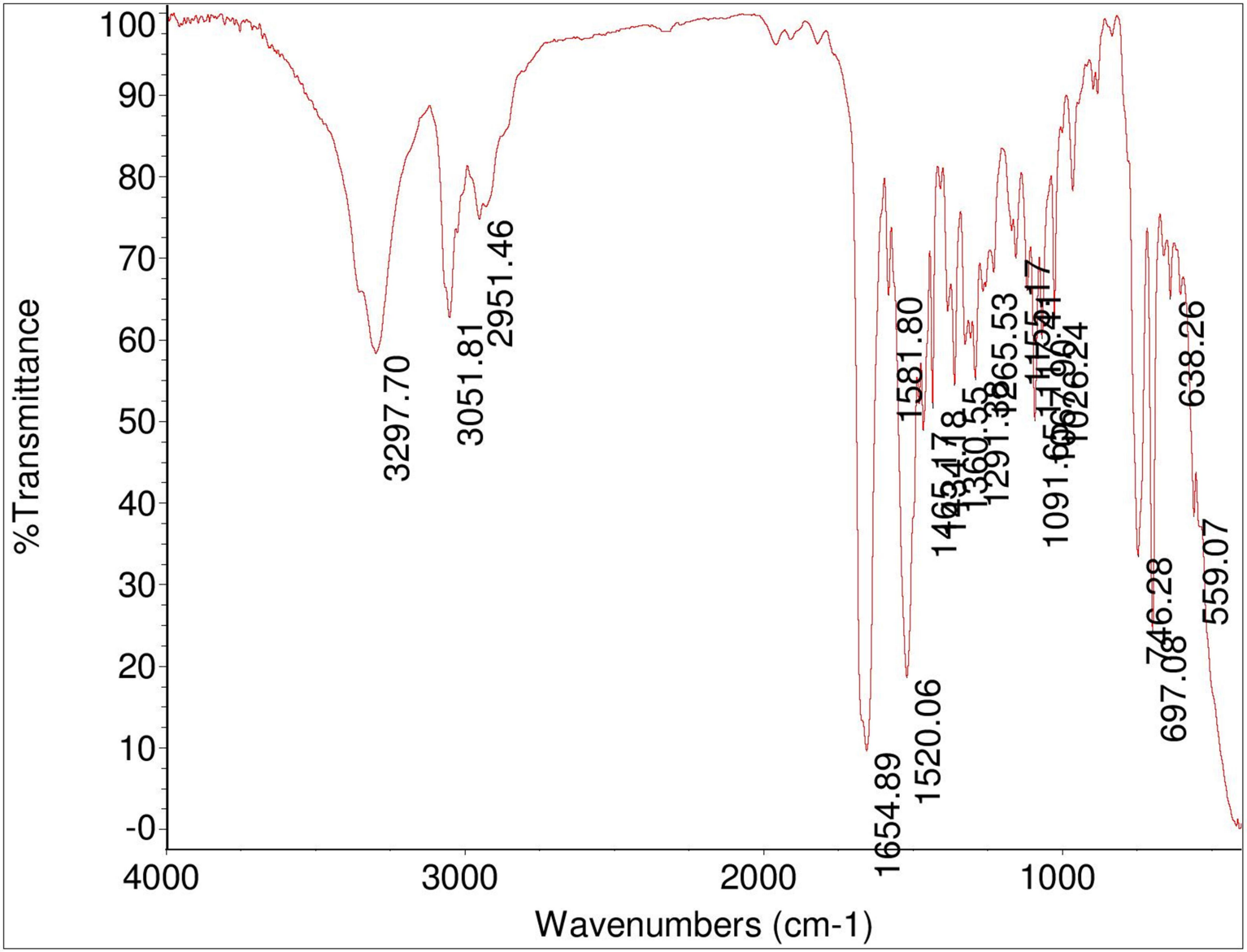

NH
HN
O
O
N
O
Ph
Ph2P

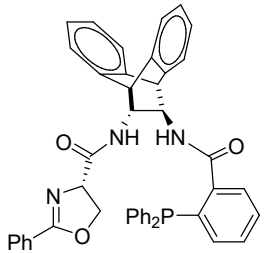
(*S*,*R*,*R*)-**9**


nh-316-benzene-d6
(S,S,S)-9
M01(d)
M02(br. s.)
M03(m)
M04(m)
M06(d)
M07(dd)
M08(d)
M09(br. s.)
M10(m)
M12(m)
M13(br. s.)
M14(m)
M15(t)
7.92
7.90
7.51
7.40
7.35
7.33
7.14
7.10
7.05
7.02
7.00
6.85
6.84
6.76
6.74
6.72
6.62
4.88
4.70
4.68
4.65
4.32
4.31
4.10
3.94
3.93
3.77
3.74
2.00 2.03 6.78 15.40 1.49 5.92 1.17
1.01 1.26 2.33 1.16 1.11 1.13
Normalized Intensity
Chemical Shift (ppm)


nh-316-13C-benzene-d6
127.93
127.68
127.44
128.28
128.48
128.38
170.98
164.76
161.58
140.96
140.00
138.90
134.07
133.86
133.77
126.11
125.38
124.98
124.34
69.54
68.46
58.41
54.41
49.80
48.98
38.09
34.98
30.42
NH
HN
O
N
Ph
Ph2P
(S,S,S)-9
Normalized Intensity
Chemical Shift (ppm)


nh-316-31P-benzene-d6
-10.13
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)
O
NH
HN
O
N
Ph
O
Ph2P
(S,S,S)-9

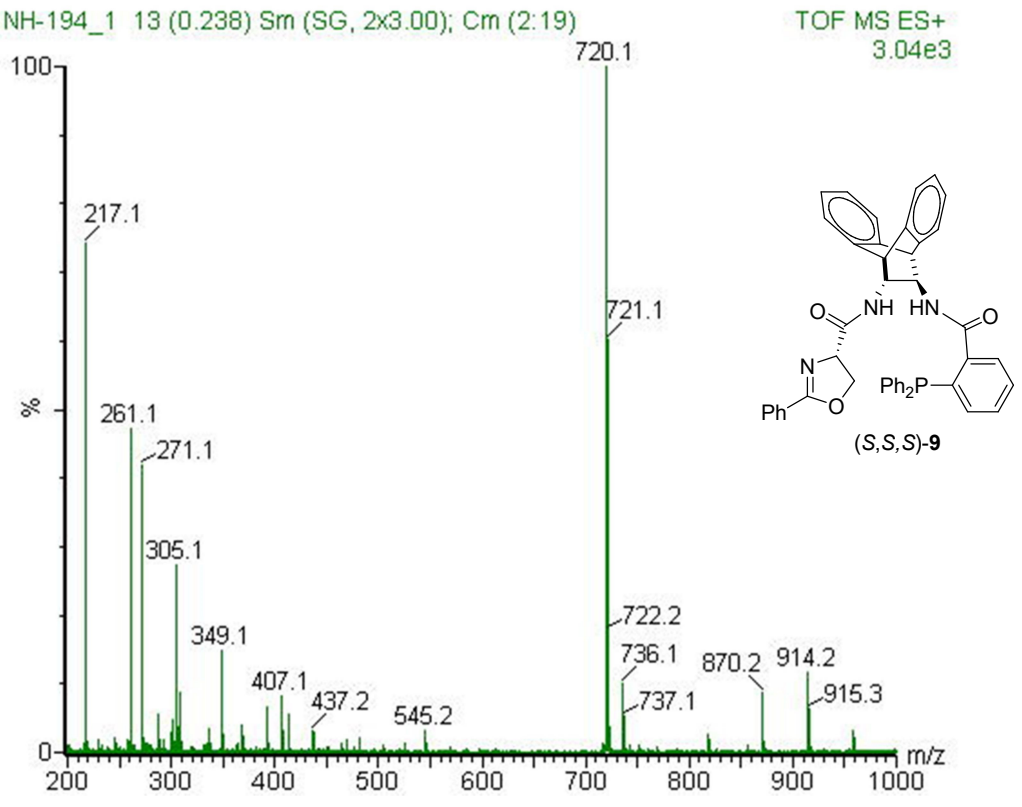

%Transmittance
100
90
80
70
60
50
40
30
20
10
-0
4000
3000
2000
1000
Wavenumbers (cm-1)
3297.70
3051.81
2951.46
1654.89
1581.80
1520.06
1465.41
1360.55
1291.38
1265.53
1091.65
1026.24
746.28
697.08
638.26
559.07


NH
HN
O
O
N
O
Ph
Ph2P

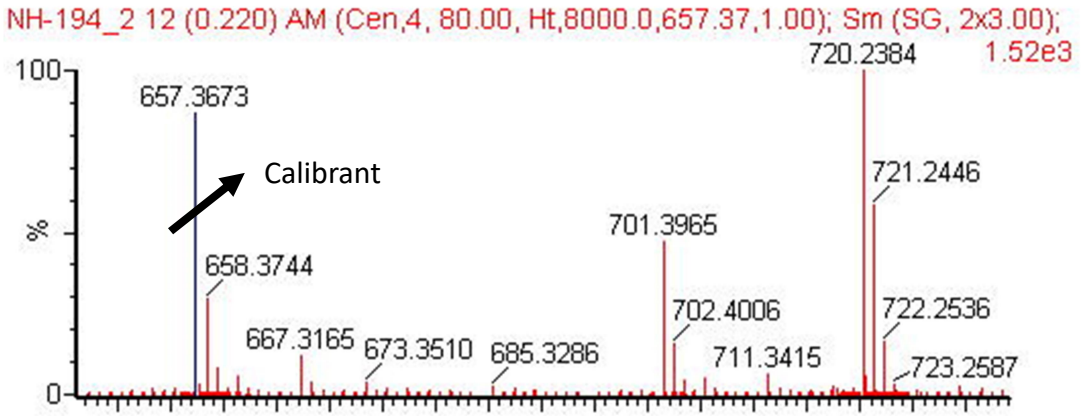
(*S*,*S*,*S*)-**9**

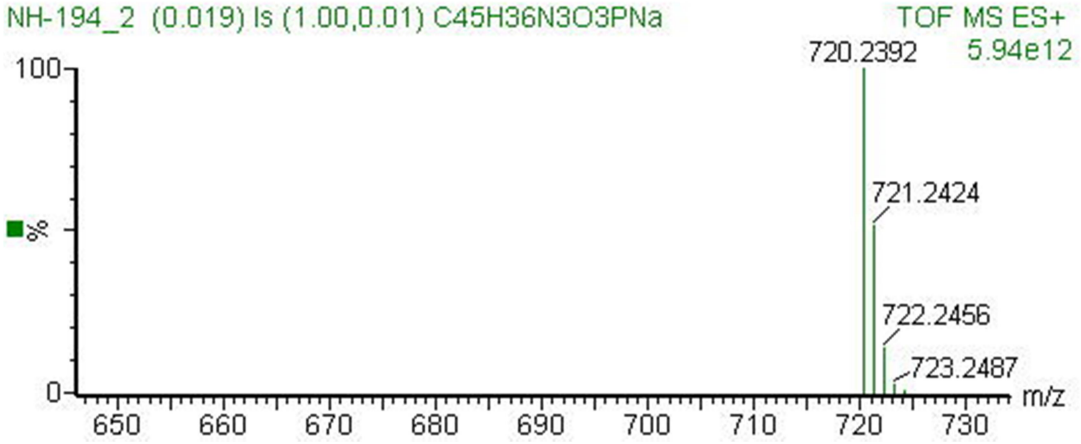
ObservedΔ = 0.8 mDa
Acceptable = ± 3.0 mDa

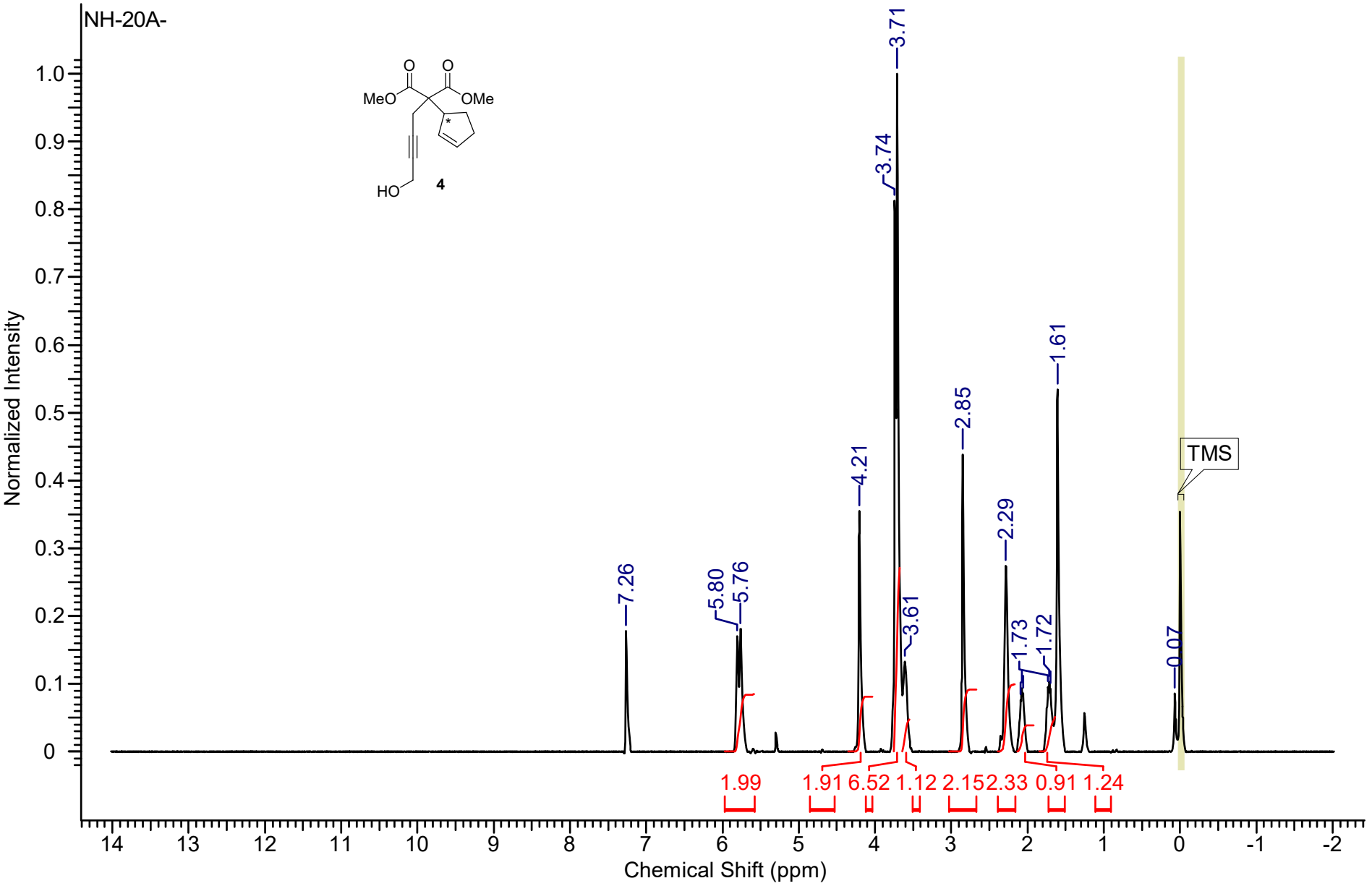
LRMS [M+Na]+

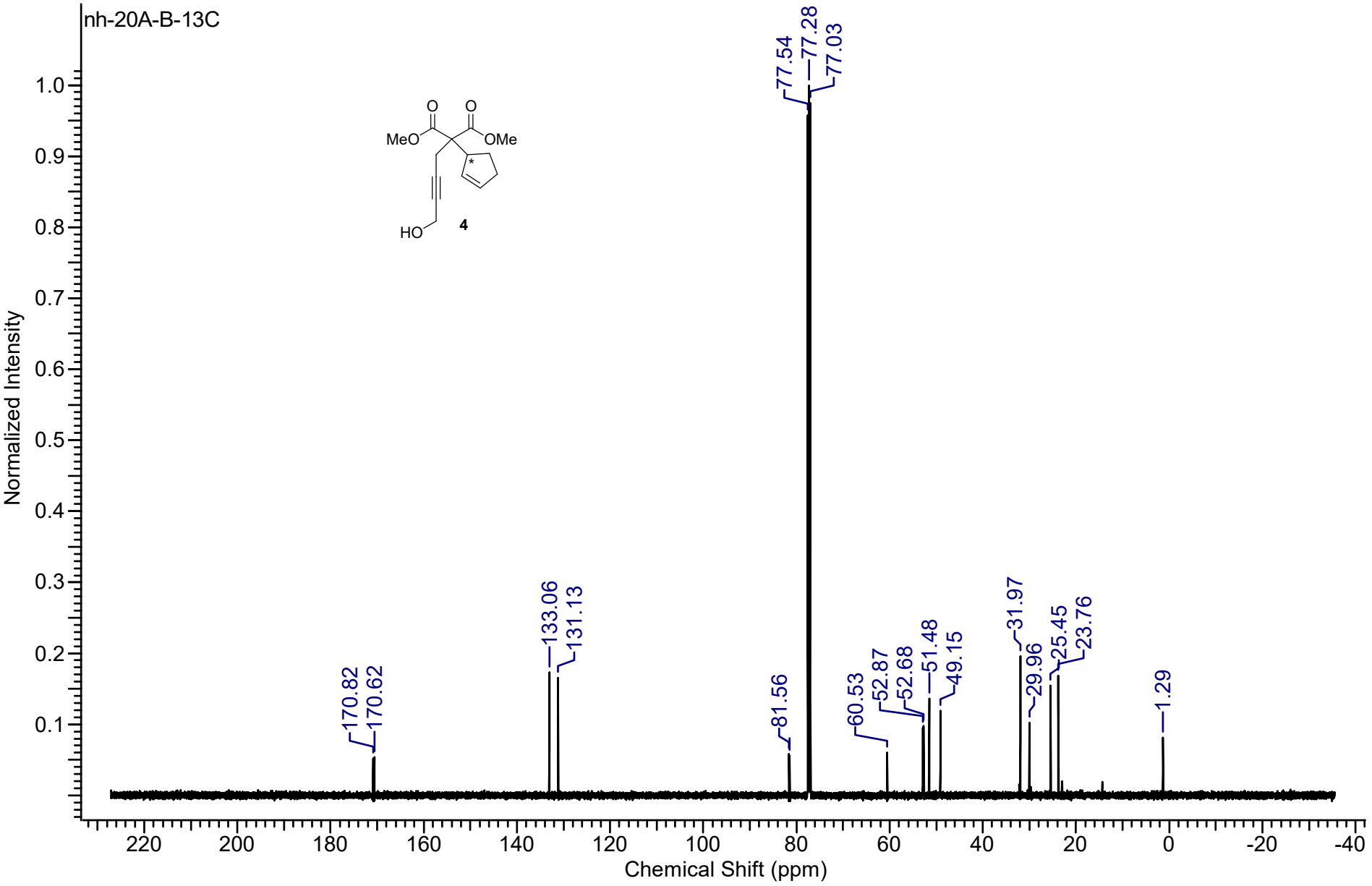


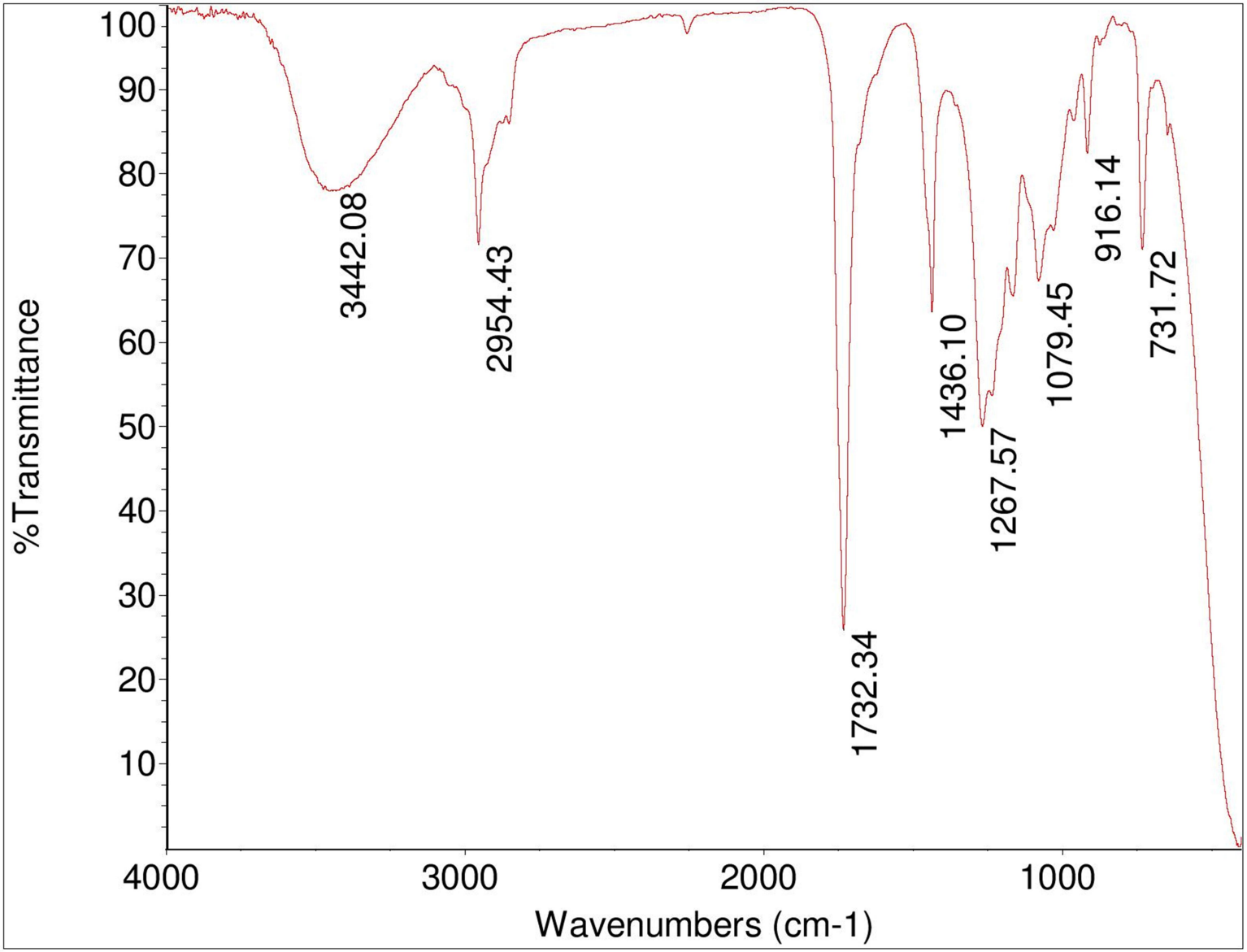
(*S*,*S*,*S*)-**9**

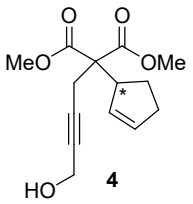





NH-20A-
MeO
OMe
HO
4
Normalized Intensity
Chemical Shift (ppm)
7.26
5.80
5.76
4.21
3.74
3.71
3.61
2.85
2.29
1.73
1.72
1.61
0.07
TMS
1.99
1.91
6.52
1.12
2.15
2.33
0.91
1.24

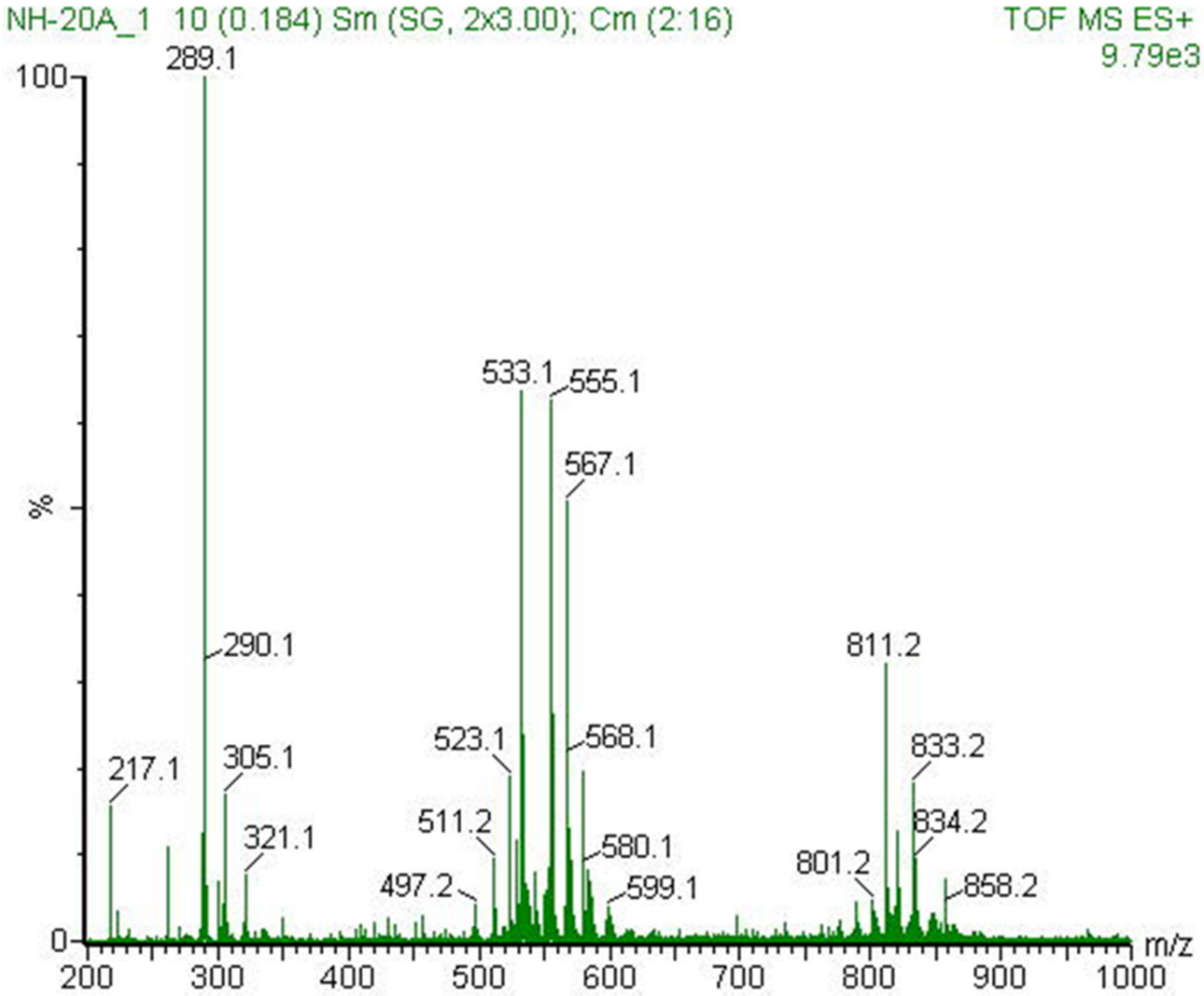

nh-20A-B-13C
MeO
OMe
HO
4
Normalized Intensity
Chemical Shift (ppm)
77.54
77.28
77.03
170.82
170.62
133.06
131.13
81.56
60.53
52.87
52.68
51.48
49.15
31.97
29.96
25.45
23.76
1.29

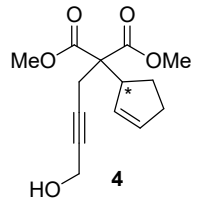

%Transmittance
100
90
80
70
60
50
40
30
20
10
3442.08
2954.43
1732.34
1436.10
1267.57
1079.45
916.14
731.72
4000
3000
2000
1000
Wavenumbers (cm-1)


MeO
OMe
HO
*

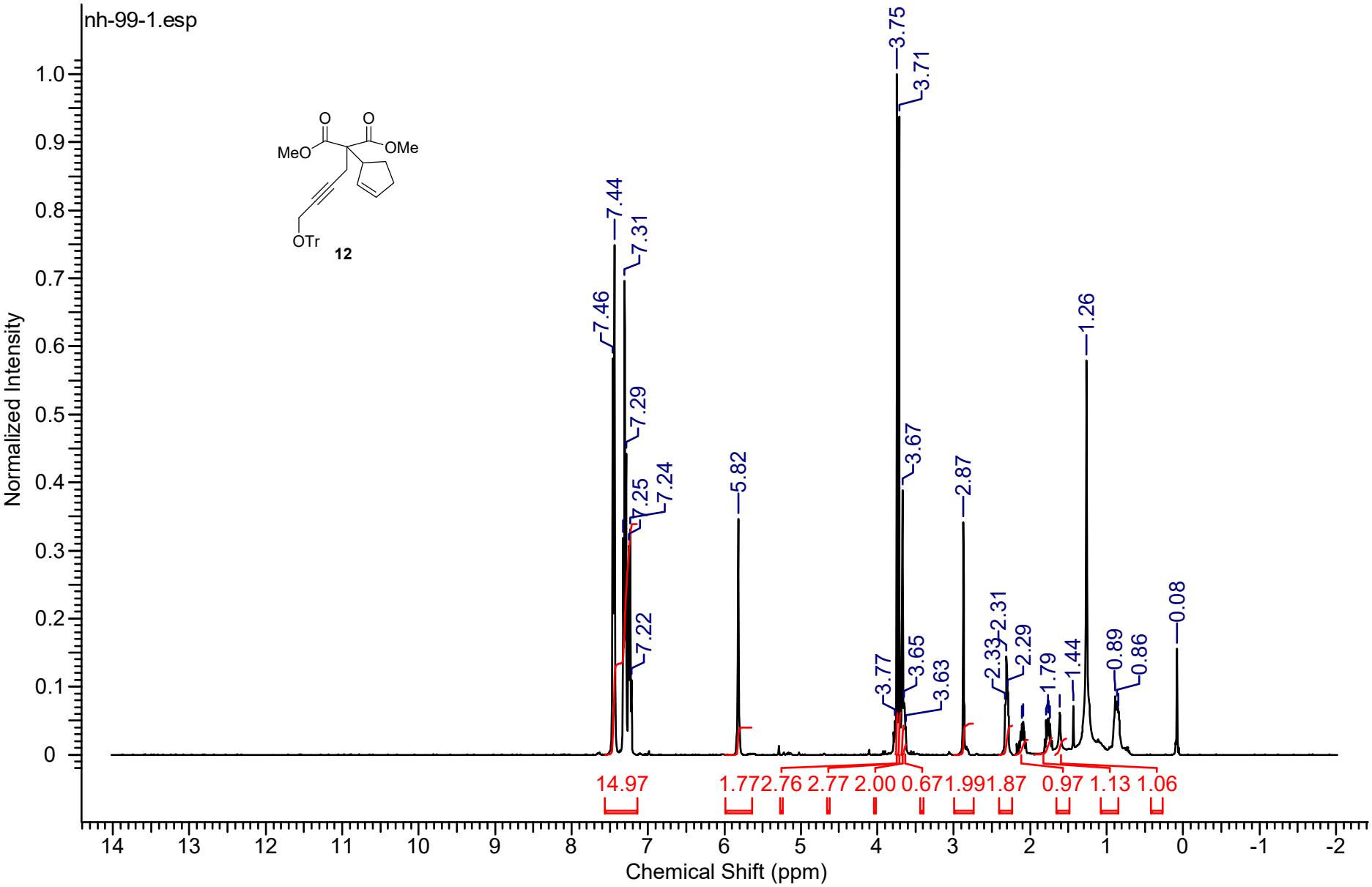
4

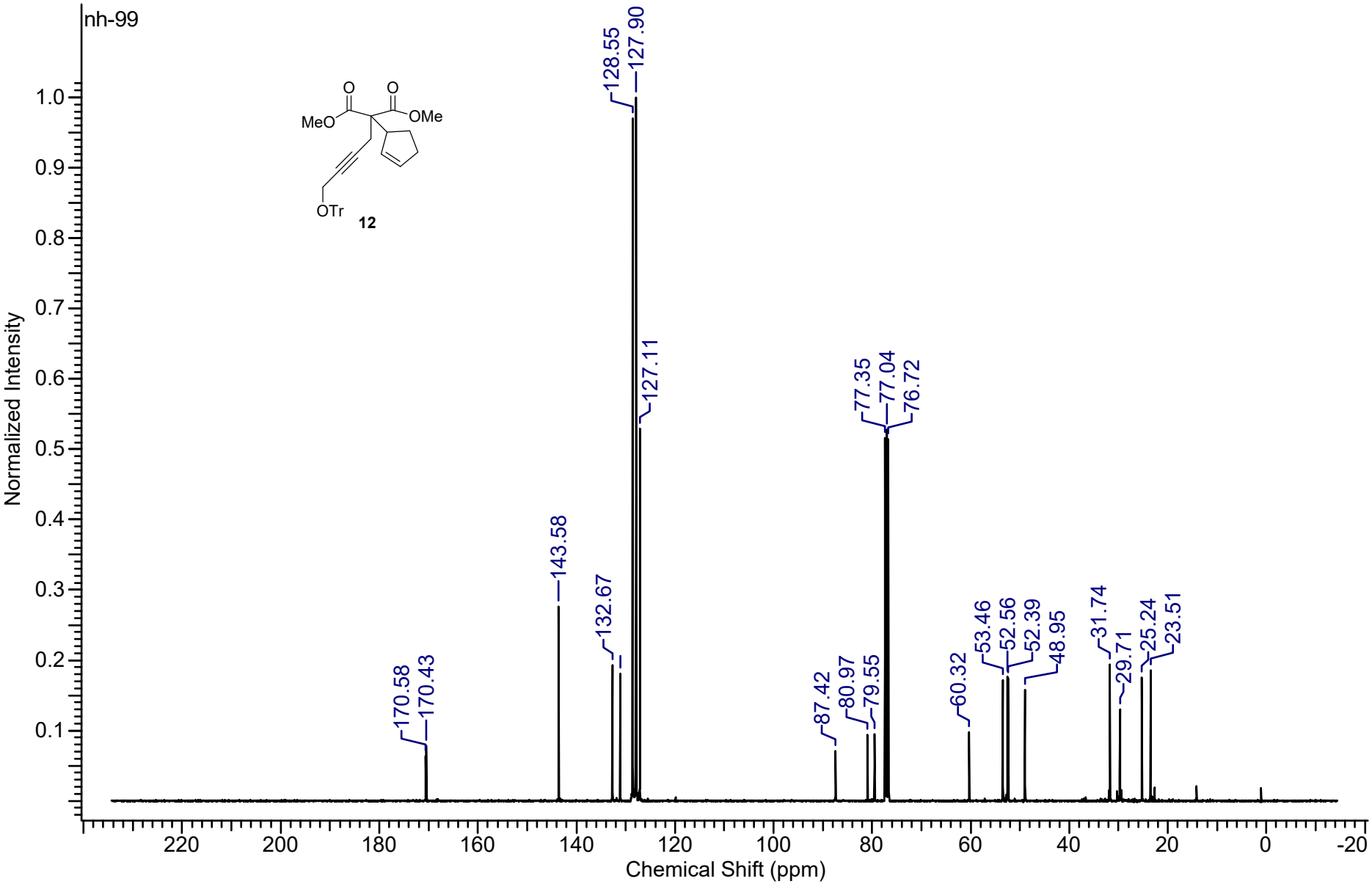
LRMS [M+Na]$^+$ [2M+Na]$^+$

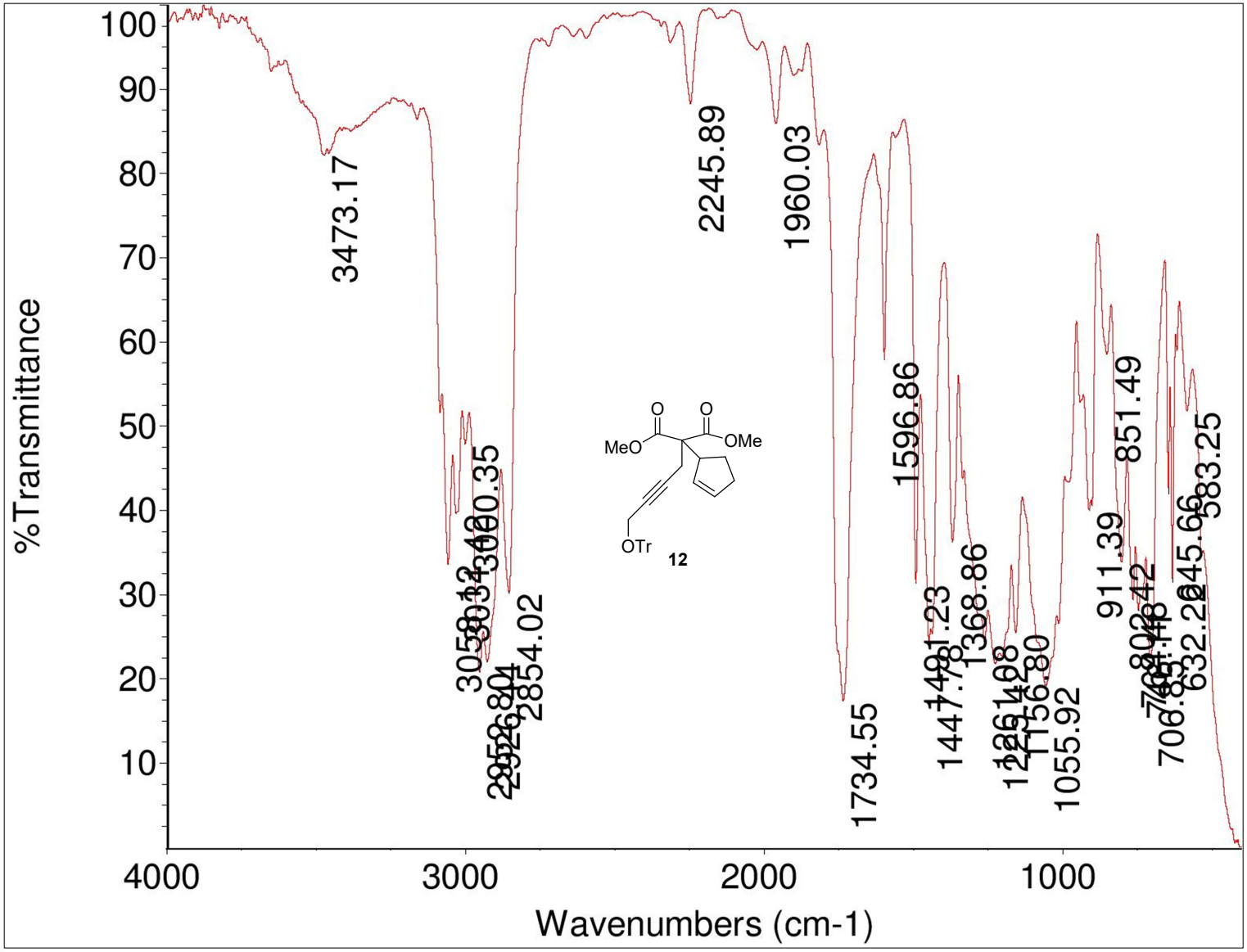




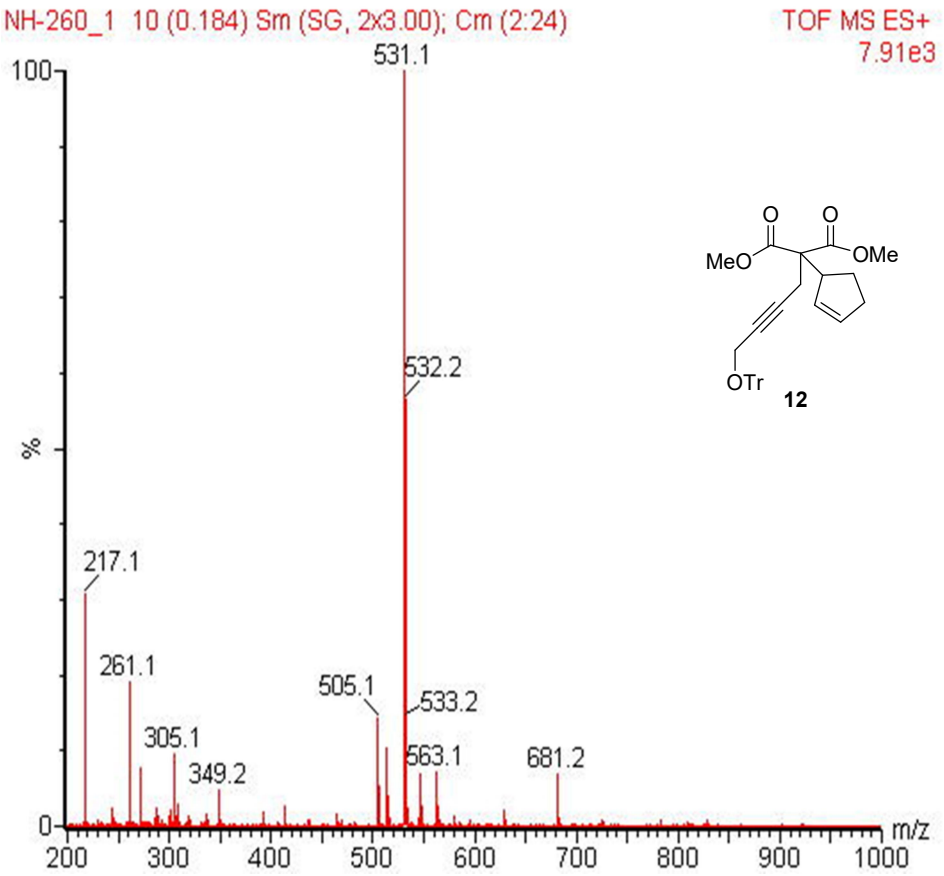
4


nh-99-1.esp
MeO
OMe
OTr
12
Normalized Intensity
Chemical Shift (ppm)
7.46
7.44
7.31
7.29
7.25
7.24
7.22
5.82
3.75
3.71
3.67
3.77
3.65
3.63
2.87
2.33
2.31
2.29
1.79
1.44
1.26
0.89
0.86
0.08
14.97
1.77
2.76
2.77
2.00
0.67
1.99
1.87
0.97
1.13
1.06


nh-99
MeO
OMe
OTr
12
Normalized Intensity
Chemical Shift (ppm)
170.58
170.43
143.58
132.67
128.55
127.90
127.11
87.42
80.97
79.55
77.35
77.04
76.72
60.32
53.46
52.56
52.39
48.95
31.74
29.71
25.24
23.51

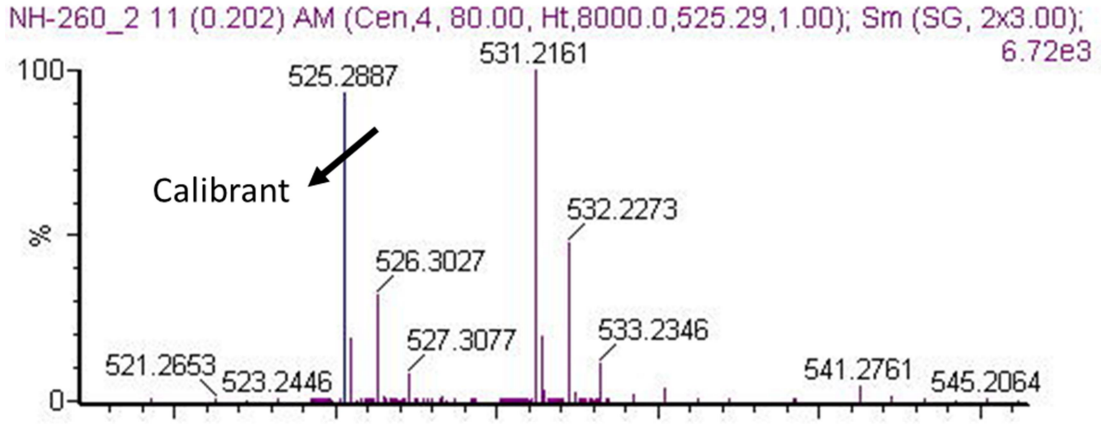

%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
100
90
80
70
60
50
40
30
20
10
3473.17
2245.89
1960.03
1596.86
1734.55
1368.86
1055.92
911.39
851.49
583.25
MeO
OMe
OTr
12

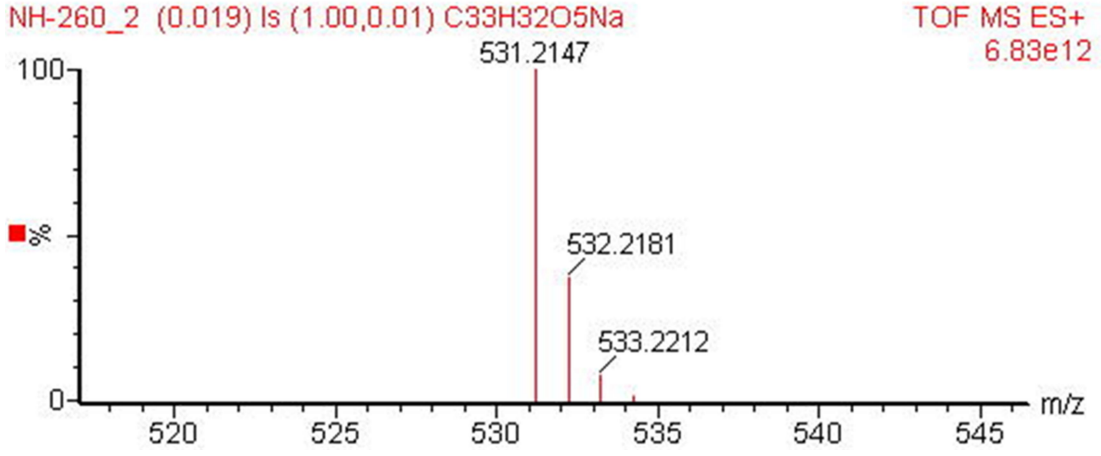
LRMS [M+Na]+



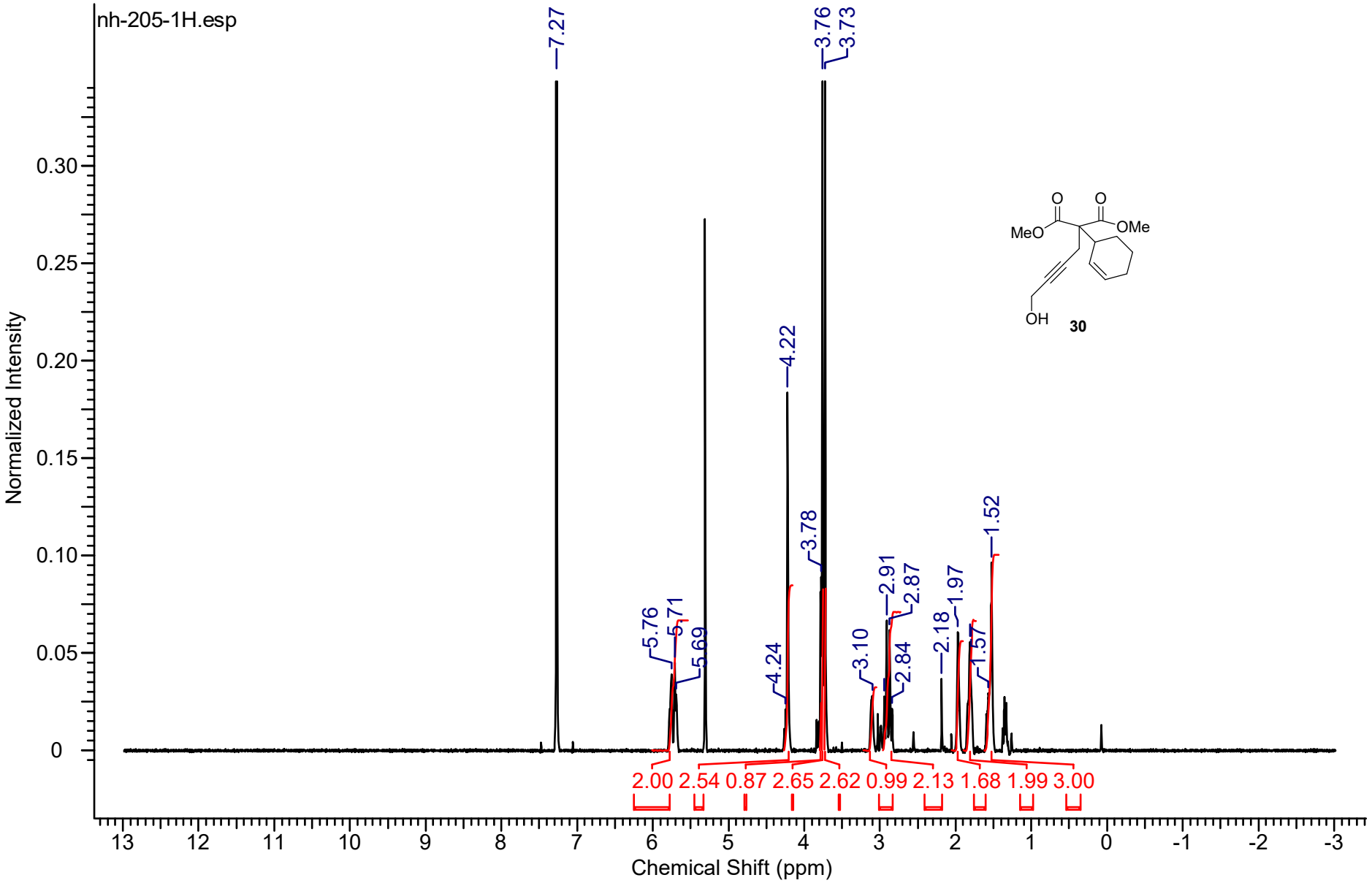
12

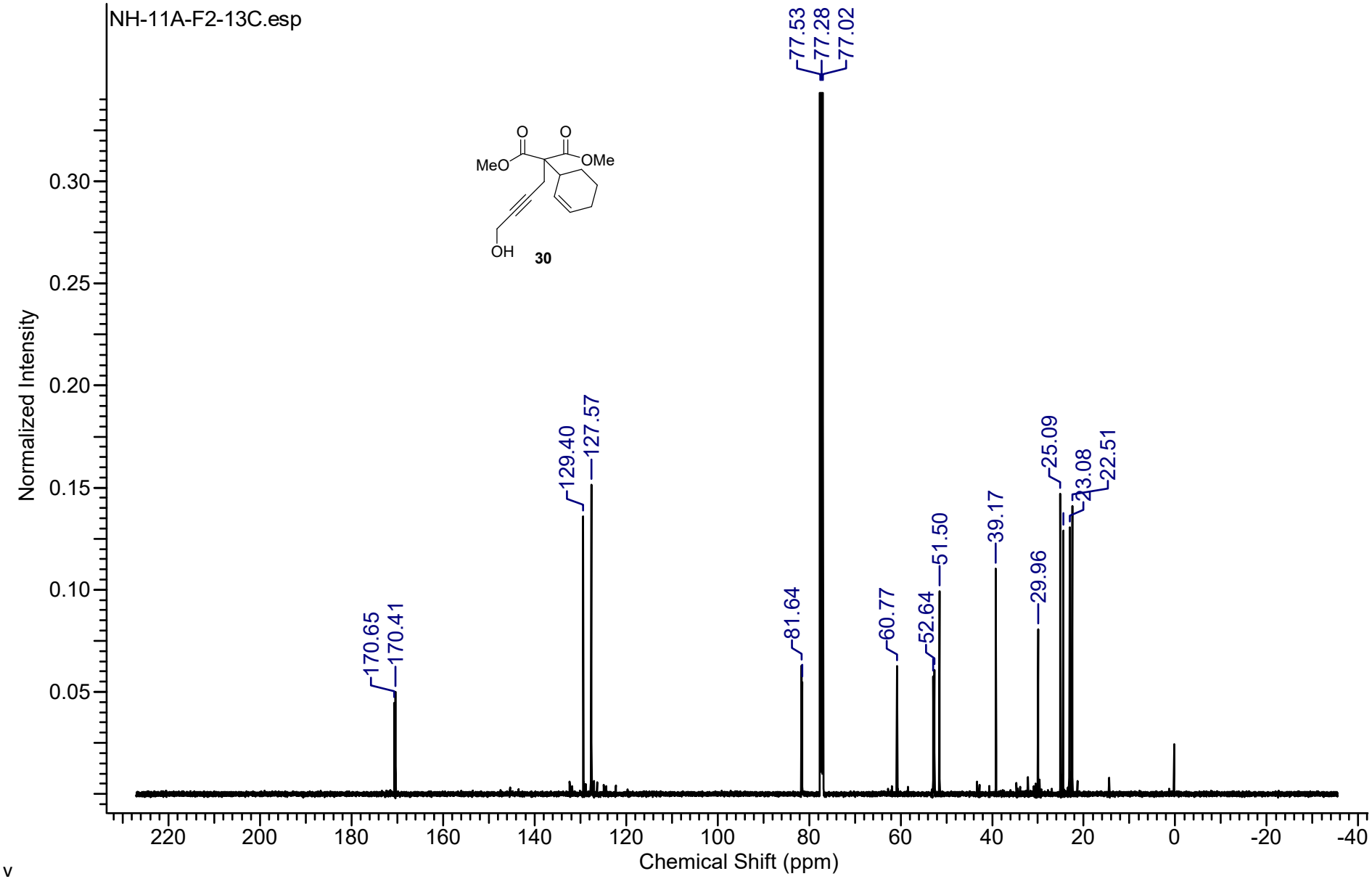
HRMS ObservedΔ = 1.4 mDa
Acceptable = ± 2.7 mDa



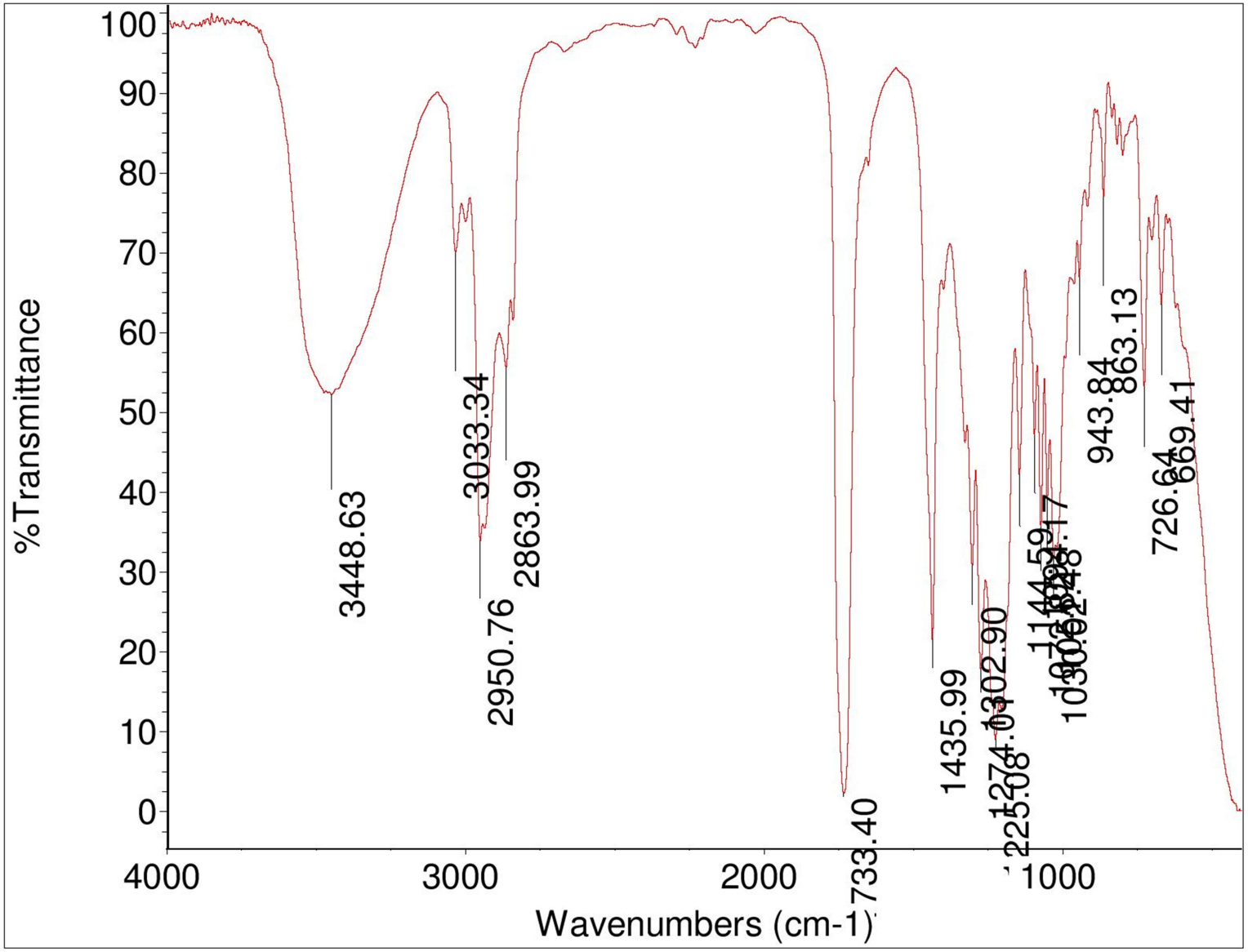


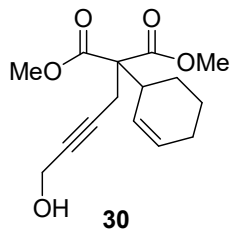
Theoretical =[M+Na]+


nh-205-1H.esp
7.27
3.76
3.73
4.22
3.78
5.76
5.71
5.69
4.24
3.10
2.91
2.87
2.84
2.18
1.97
1.57
1.52
2.00 2.54 0.87 2.65 2.62 0.99 2.13 1.68 1.99 3.00
Normalized Intensity
Chemical Shift (ppm)
MeO
OMe
OH
30


NH-11A-F2-13C.esp
77.53
77.28
77.02
MeO
OMe
O
O
OH
30
Normalized Intensity
0.30
0.25
0.20
0.15
0.10
0.05
129.40
127.57
170.65
170.41
81.64
60.77
52.64
51.50
39.17
29.96
25.09
23.08
22.51
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)

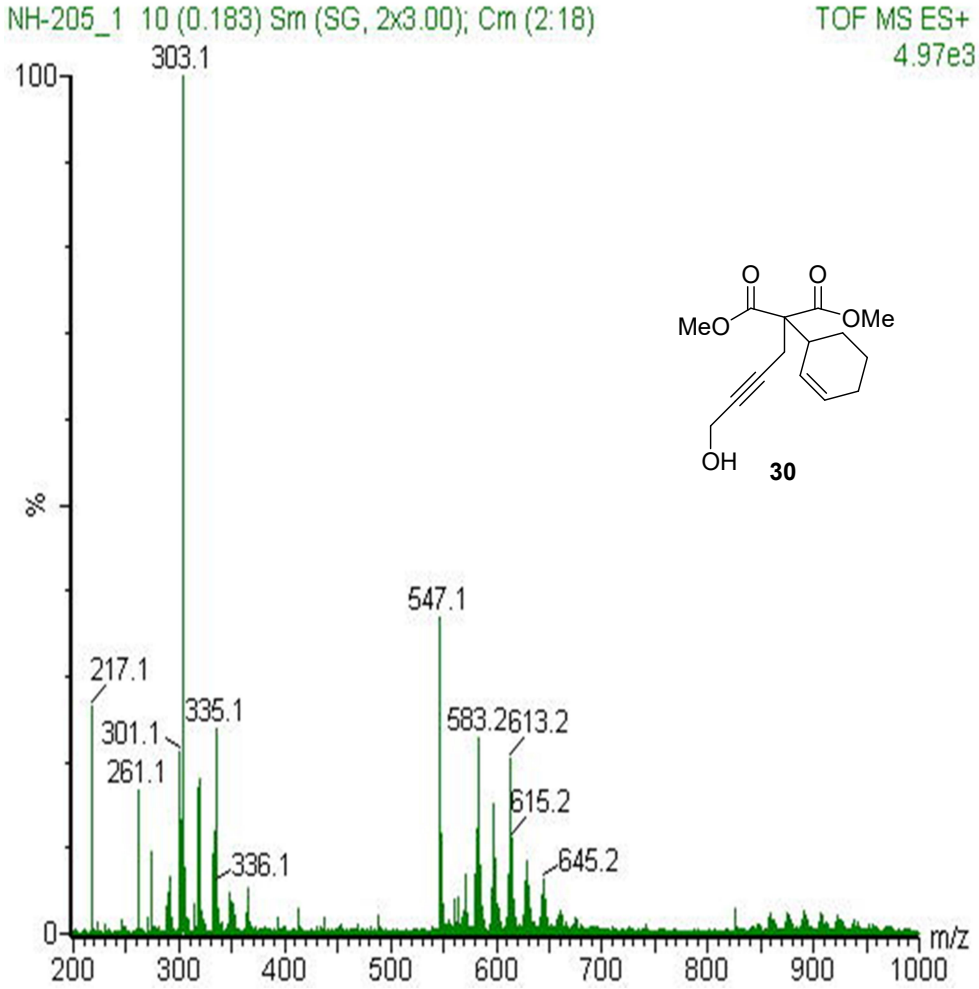
v


%Transmittance
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1000
Wavenumbers (cm-1)
3448.63
3033.34
2950.76
2863.99
1733.40
1435.99
1302.90
1225.08
1274.04
1030.62
943.84
863.13
726.64
669.41


O
O
MeO
OMe
OH

30

LRMS [M+Na]

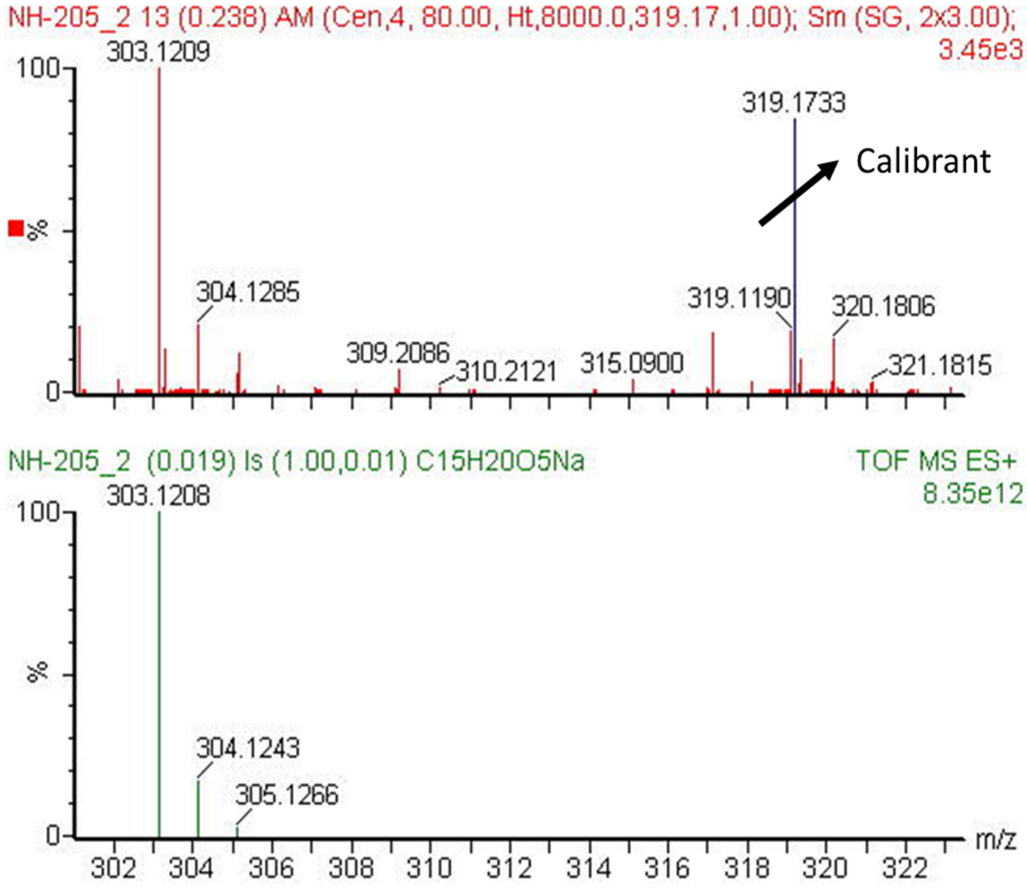


30

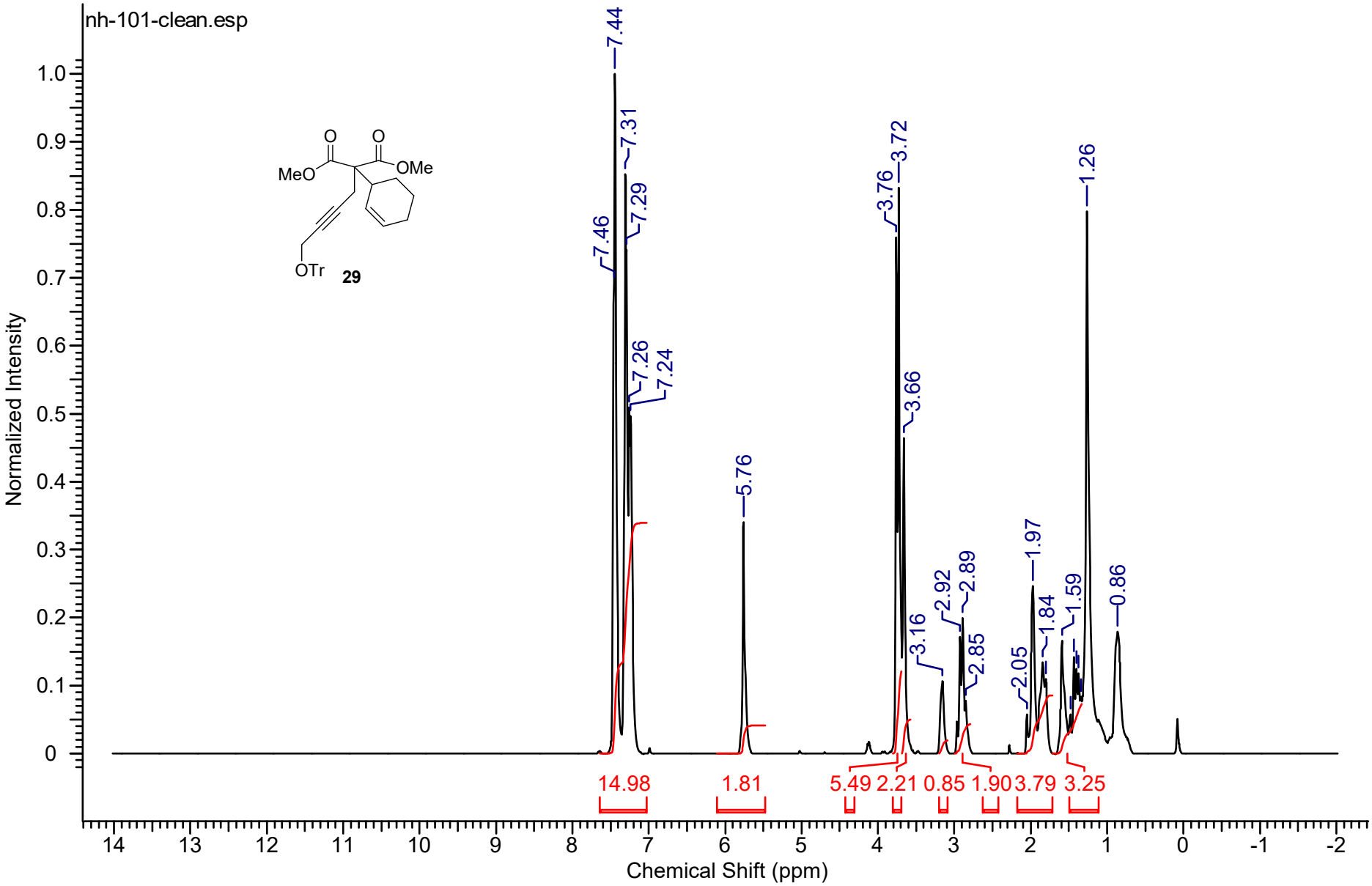
HRMS

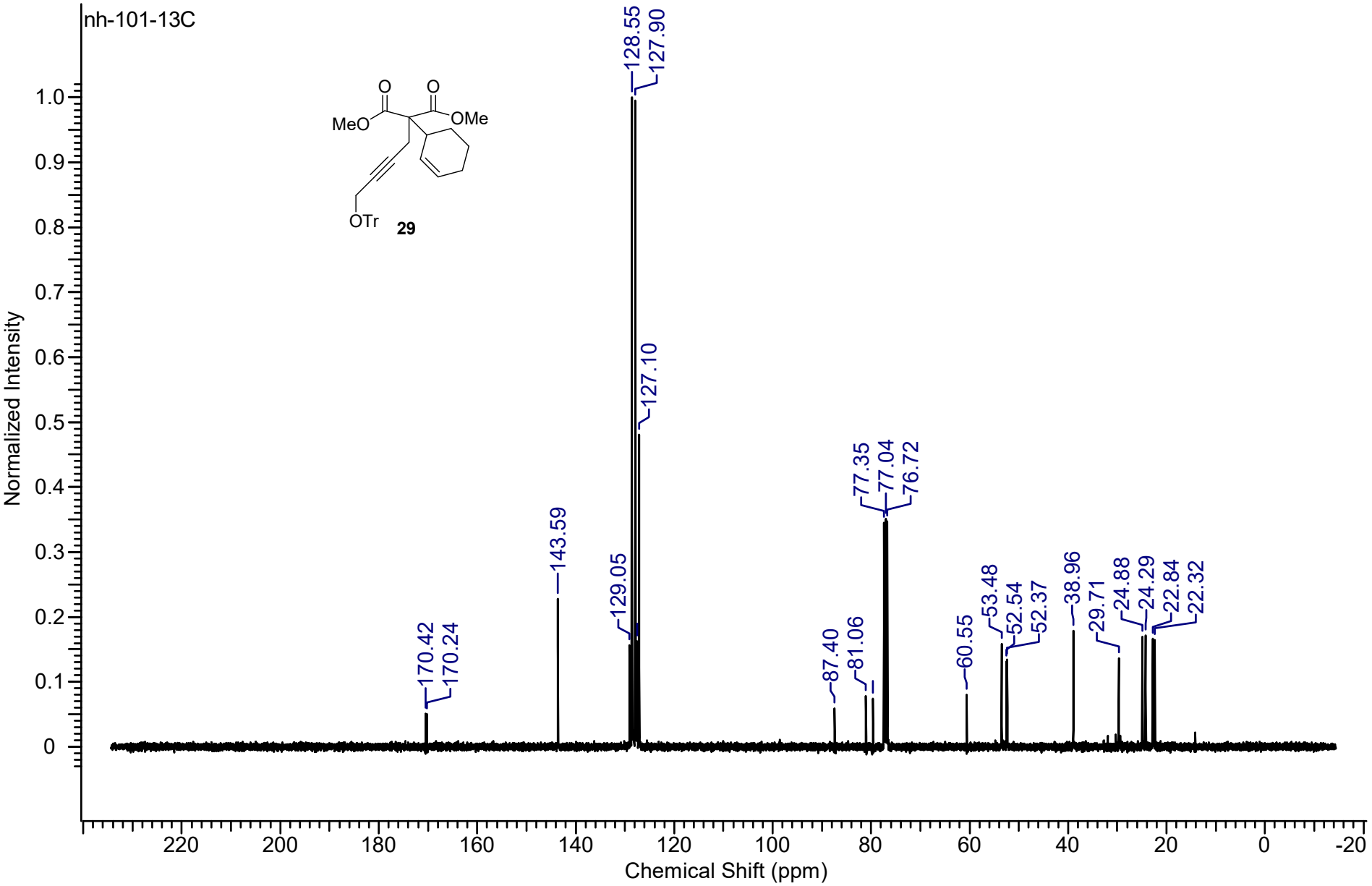
ObservedΔ = 0.1 mDa

Acceptable = ± 1.5 mDa

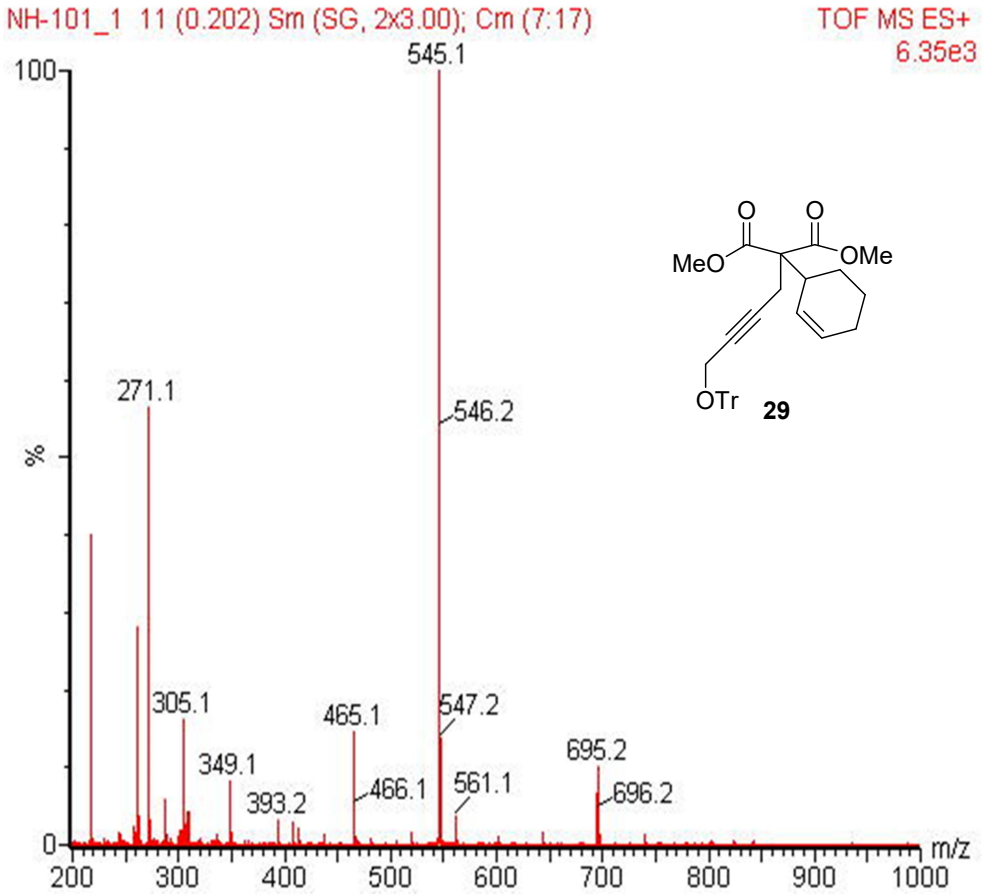


Theoretical =$[M+Na]^+$


nh-101-clean.esp
MeO
OMe
OTr
29
7.44
7.46
7.31
7.29
7.26
7.24
5.76
3.76
3.72
3.66
3.16
2.92
2.89
2.85
2.05
1.97
1.84
1.59
1.26
0.86
14.98
1.81
5.49
2.21
0.85
1.90
3.79
3.25
Normalized Intensity
Chemical Shift (ppm)

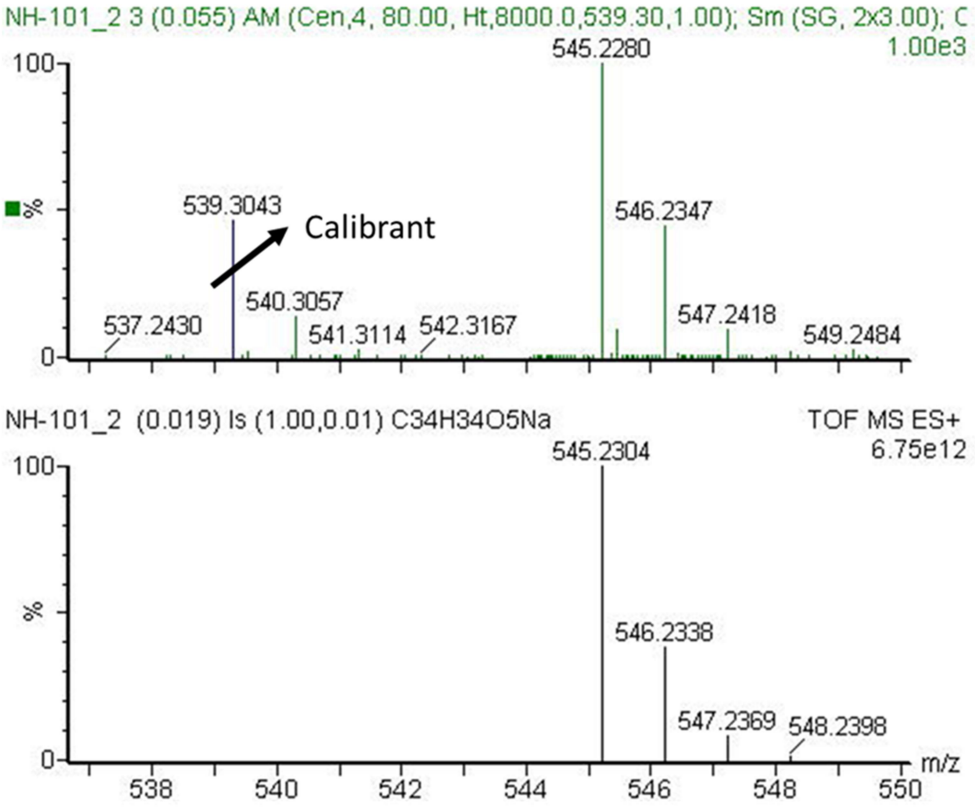

nh-101-13C
MeO
OMe
OTr
29
Normalized Intensity
Chemical Shift (ppm)
170.42
170.24
143.59
129.05
128.55
127.90
127.10
87.40
81.06
77.35
77.04
76.72
60.55
53.48
52.54
52.37
38.96
29.71
24.88
24.29
22.84
22.32

LRMS [M+Na]⁺

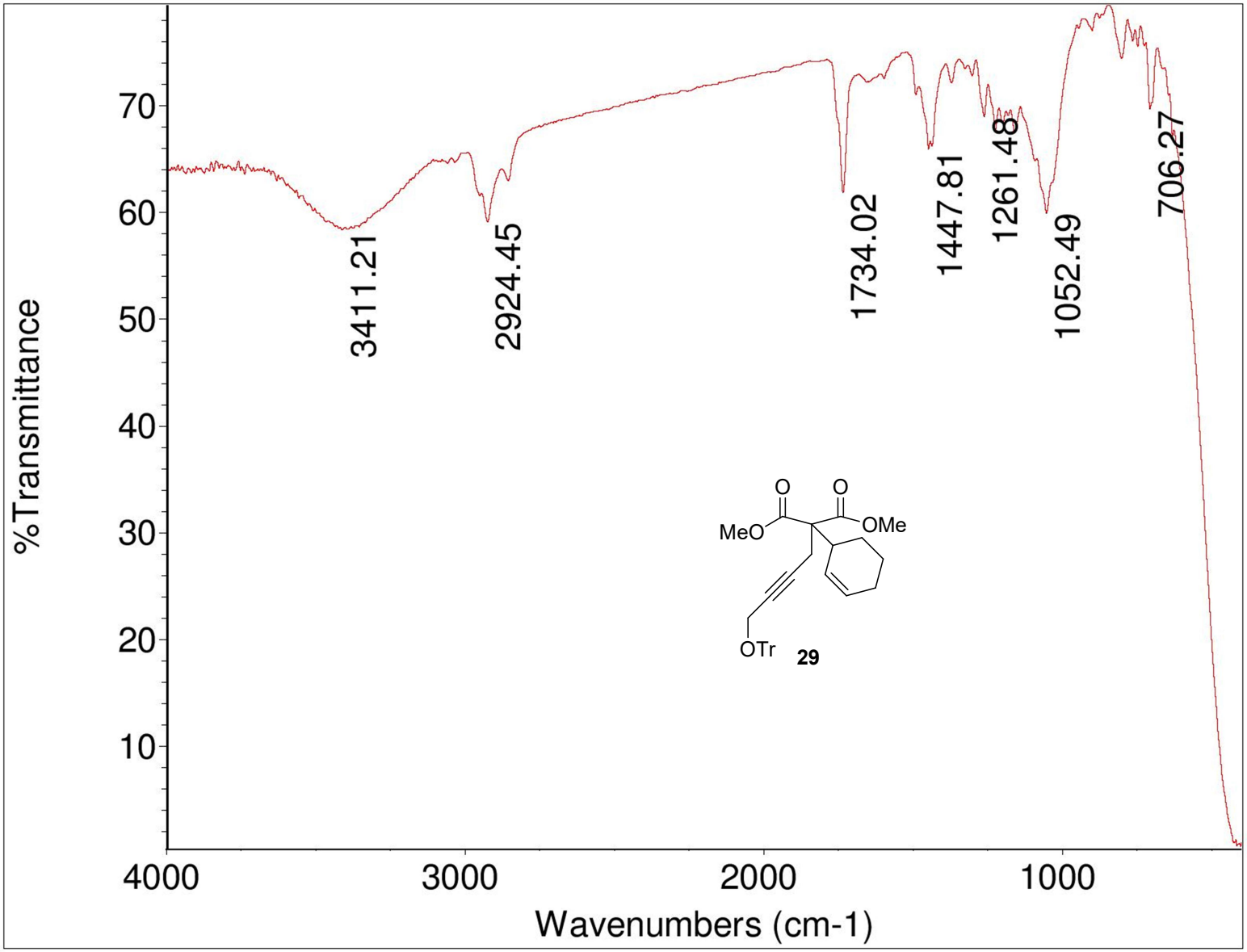


29

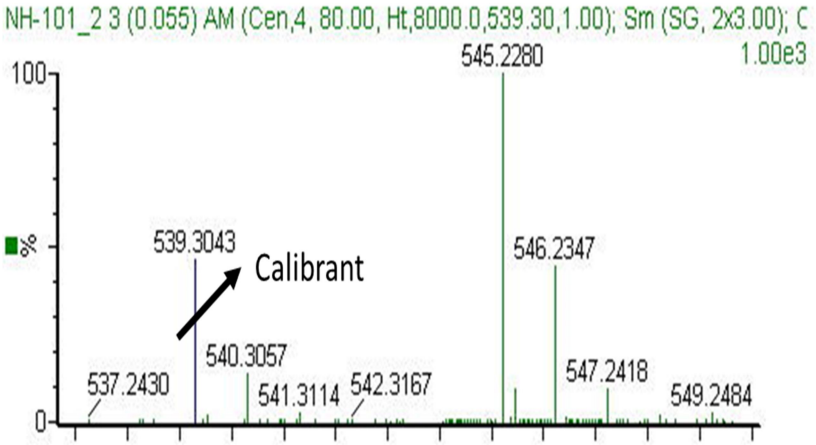
HRMS ObservedΔ = 2.4 mDa
Acceptable = ± 2.7 mDa

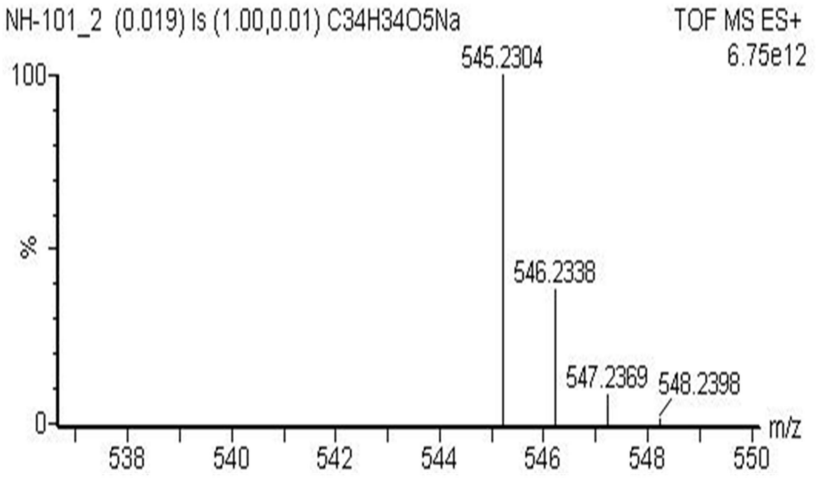


Theoretical =[M+Na]⁺


%Transmittance
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3411.21
2924.45
1734.02
1447.81
1261.48
1052.49
706.27
O
O
MeO
OMe
OTr
29

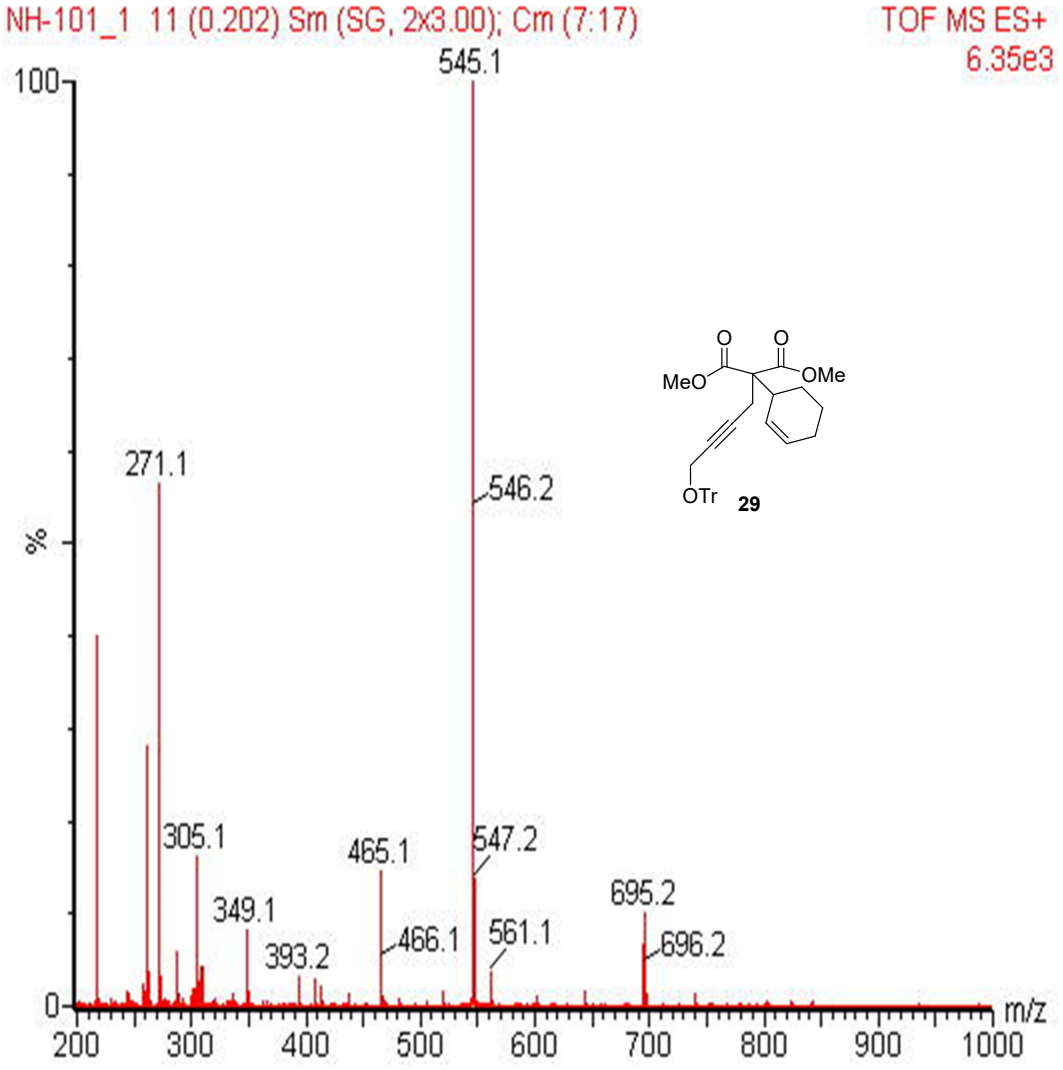
HRMS ObservedΔ = 2.4 mDa
Acceptable = ± 2.7 mDa

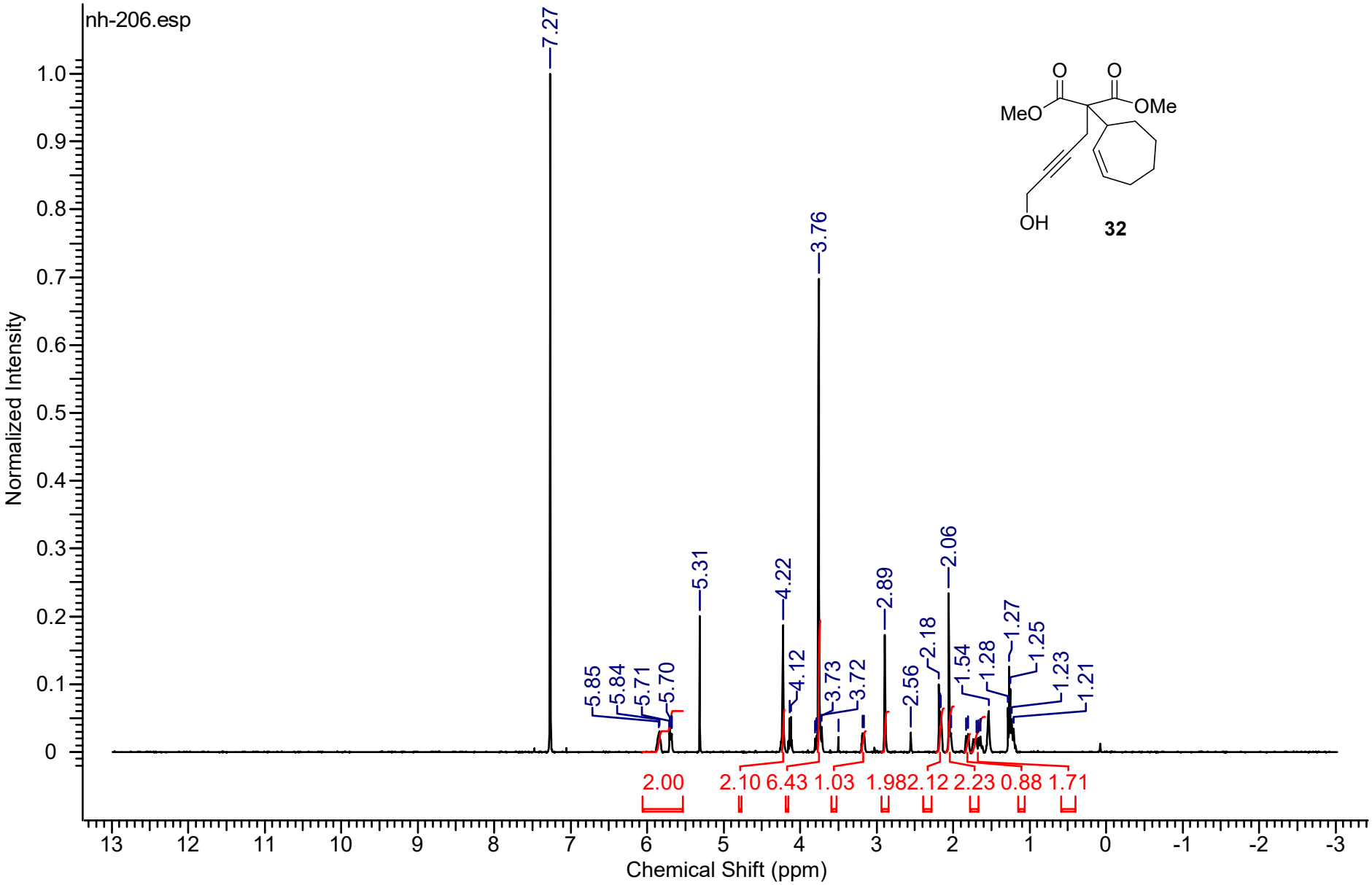


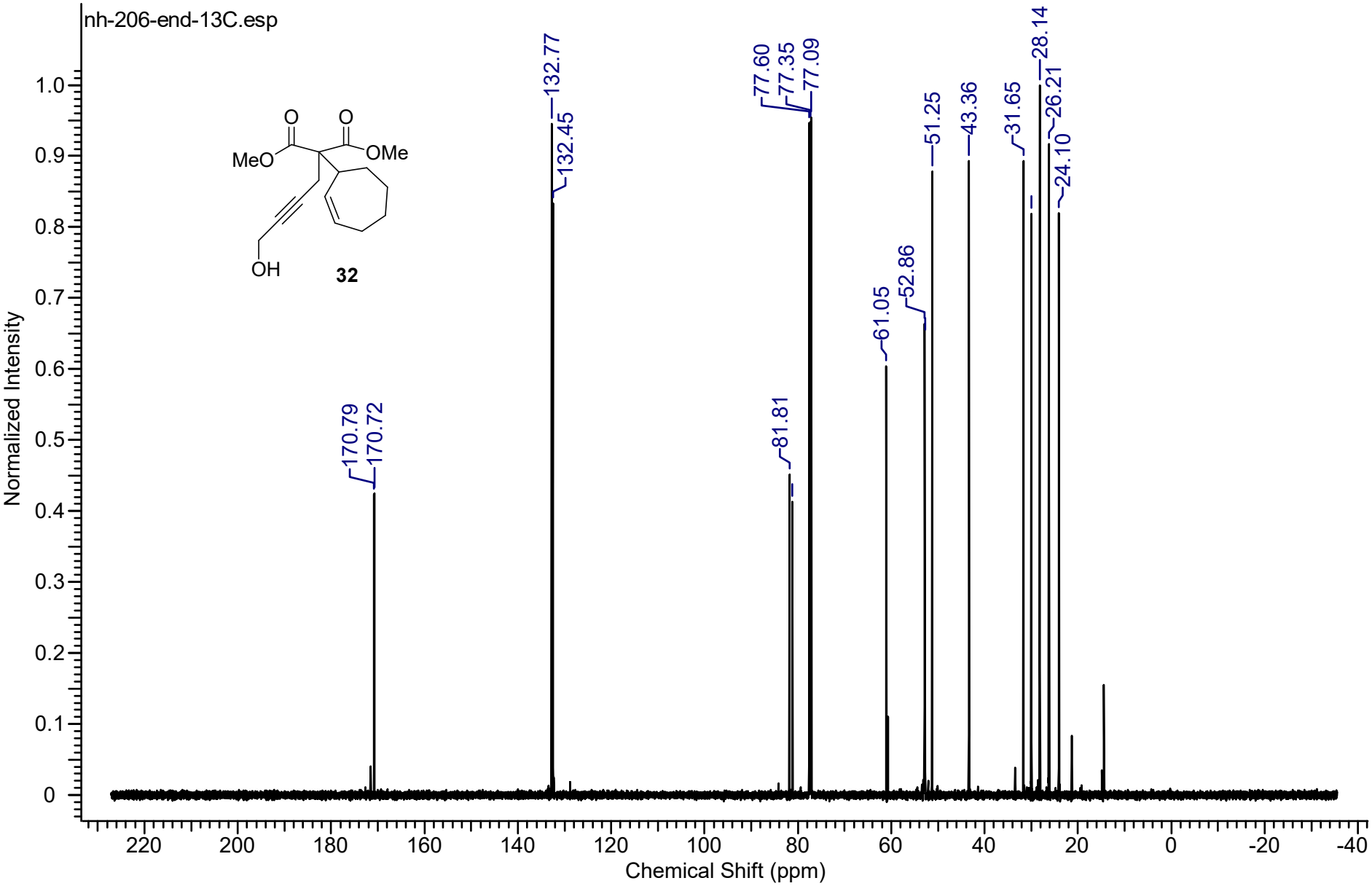


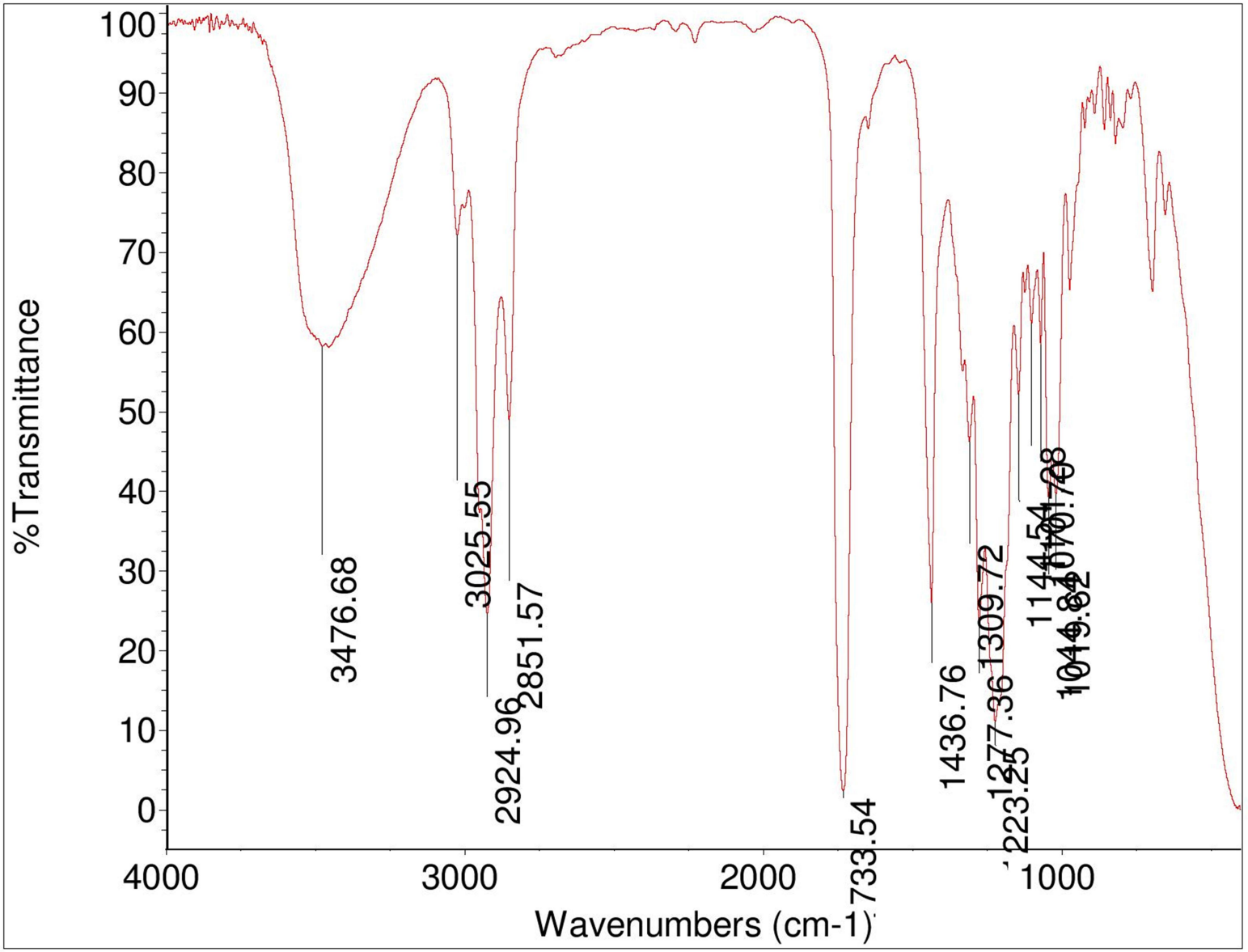
Theoretical =$[M+Na]^+$

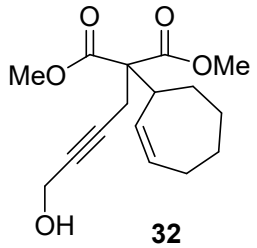
LRMS $[M+Na]^+$




nh-206.esp
7.27
3.76
5.31
4.22
2.89
2.06
2.18
1.27
1.25
1.23
1.21
1.54
1.28
5.85
5.84
5.71
5.70
4.12
3.73
3.72
2.56
2.00
2.10
6.43
1.03
1.98
2.12
2.23
0.88
1.71
Normalized Intensity
Chemical Shift (ppm)
MeO
OMe
OH
32


nh-206-end-13C.esp
MeO
OMe
O
O
OH
32
170.79
170.72
132.77
132.45
81.81
77.60
77.35
77.09
61.05
52.86
51.25
43.36
31.65
28.14
26.21
24.10
Normalized Intensity
Chemical Shift (ppm)


%Transmittance
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1000
Wavenumbers (cm-1)
3476.68
3025.55
2924.96
2851.57
1733.54
1436.76
1309.72
1277.36
1223.25
1144.54
1101.08
1070.70
1043.82
1019.82

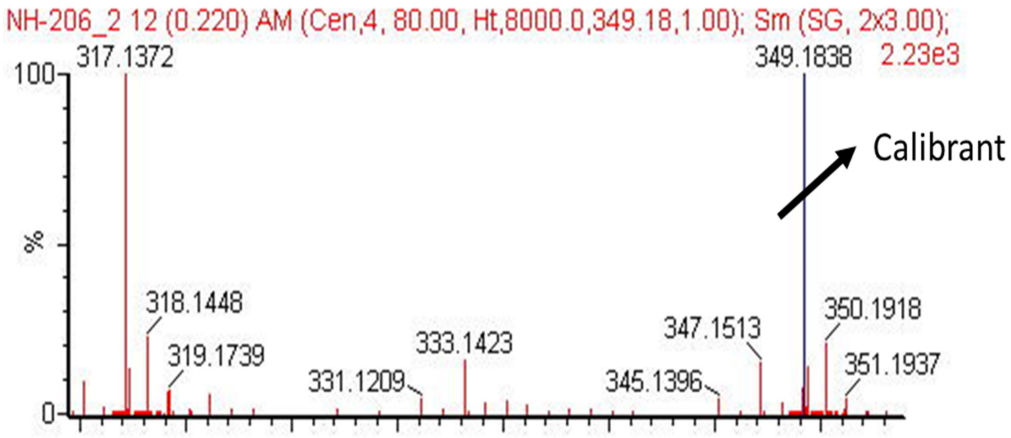

O
O
MeO
OMe
OH

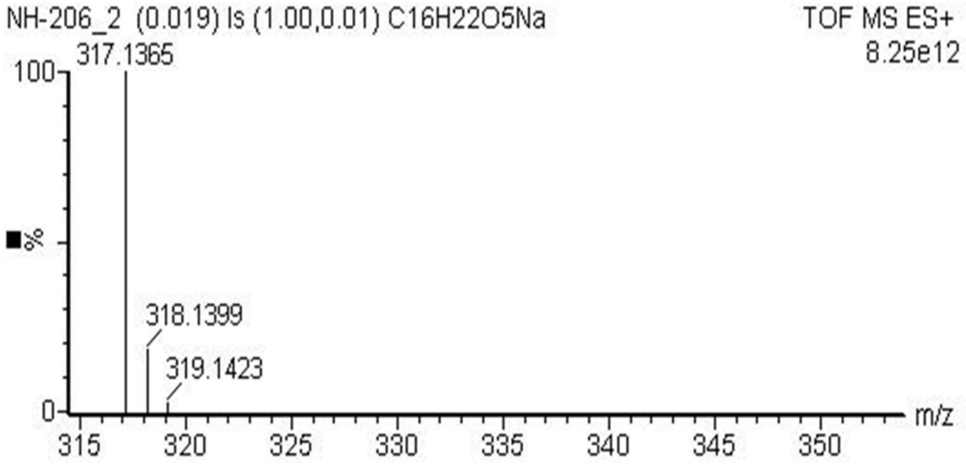
32

HRMS

ObservedΔ = 0.7 mDa

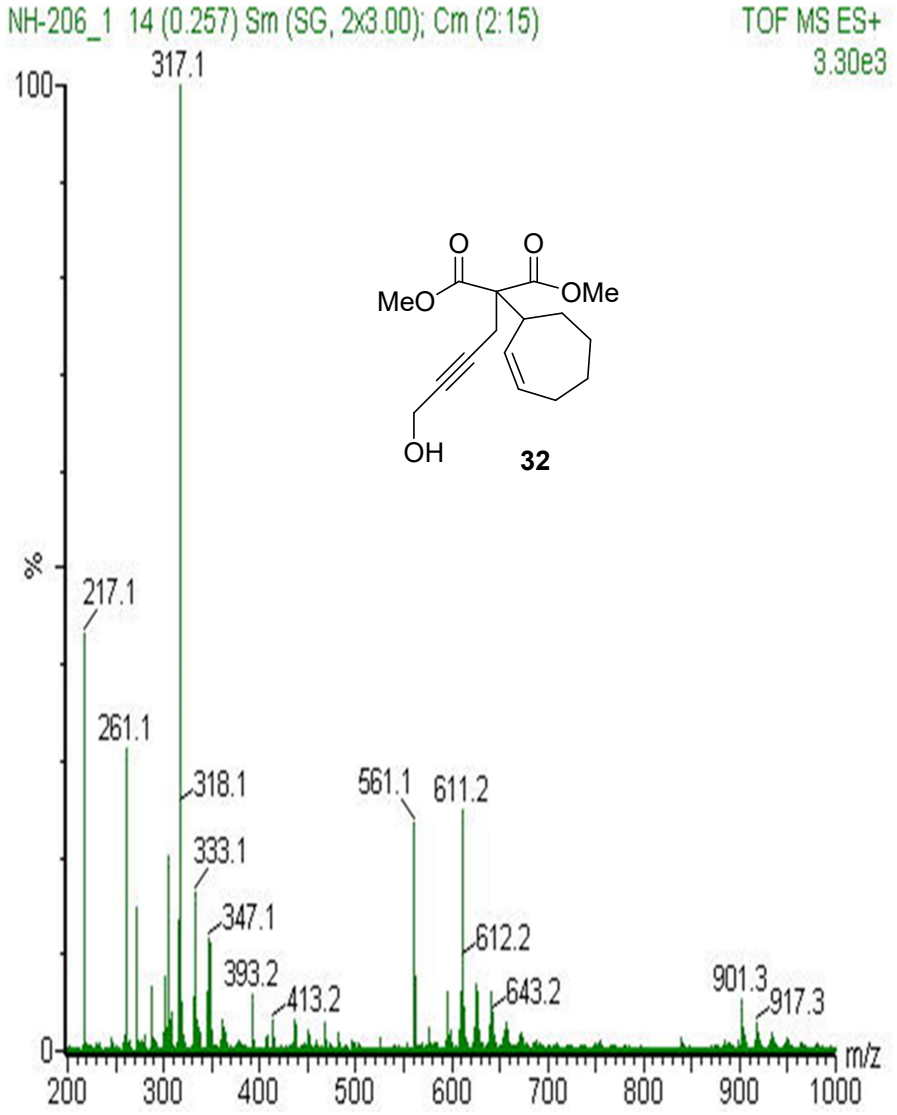
Acceptable = ± 1.6 mDa



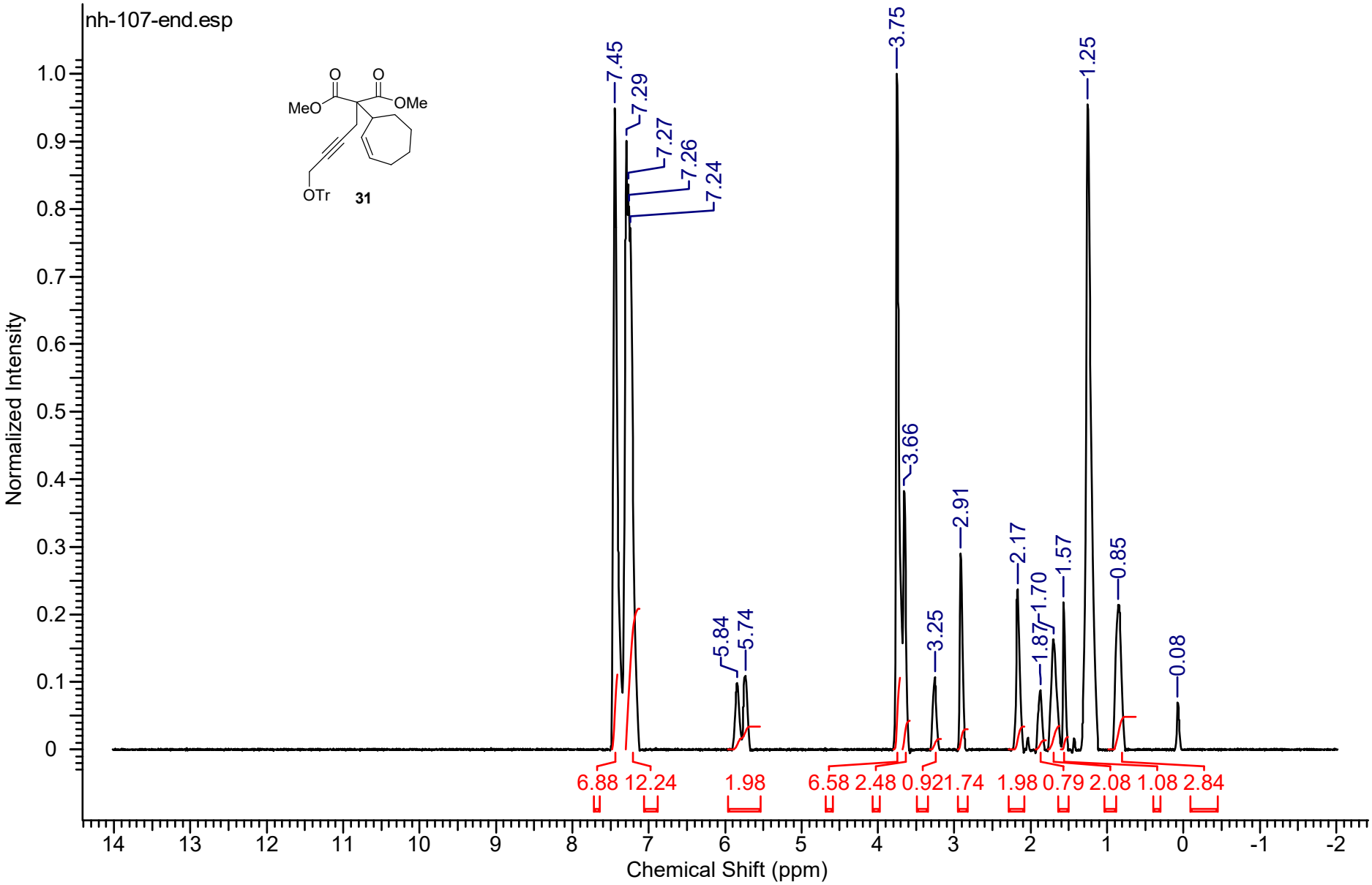


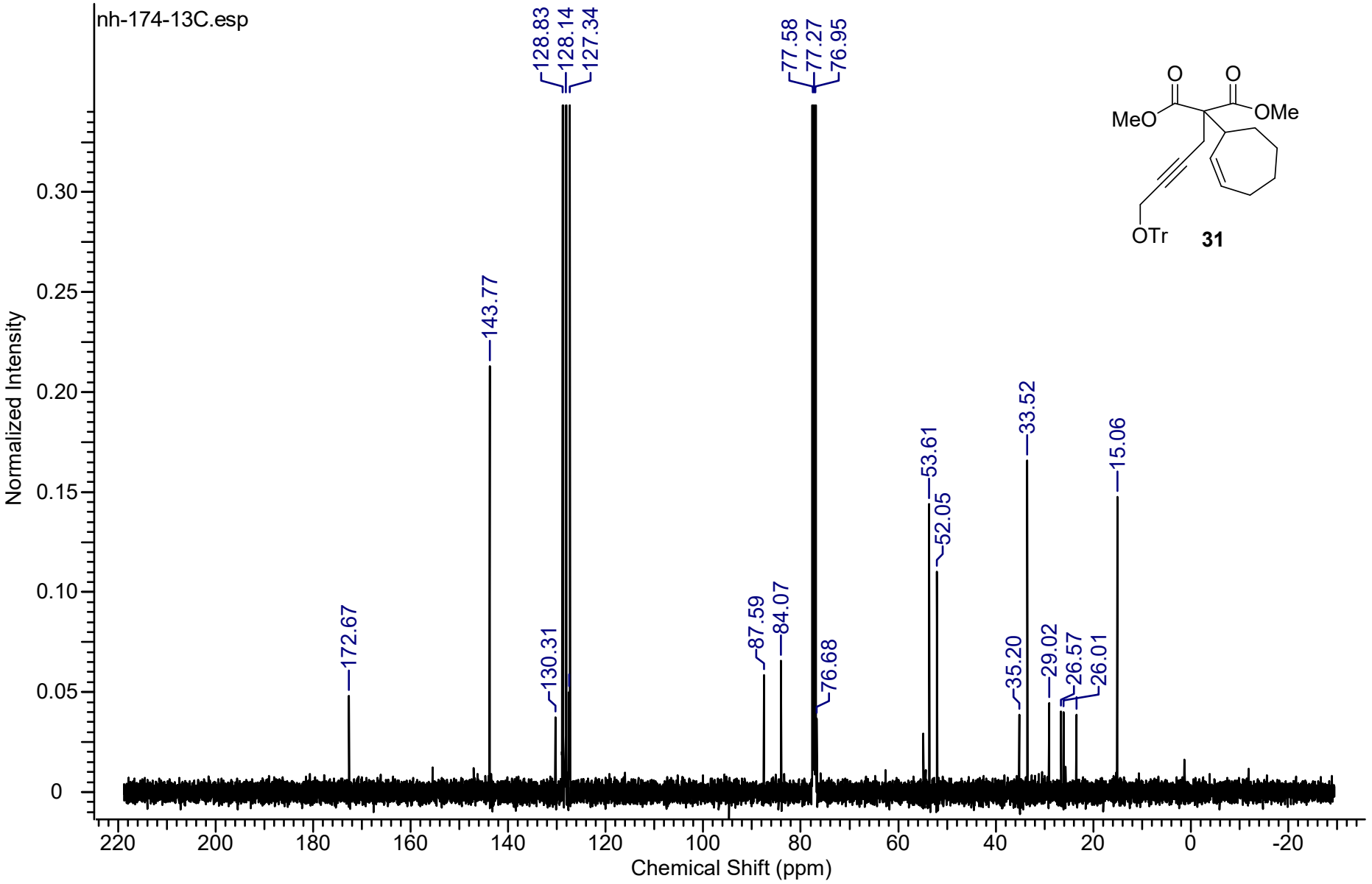
Theoretical =$[M+Na]^+$

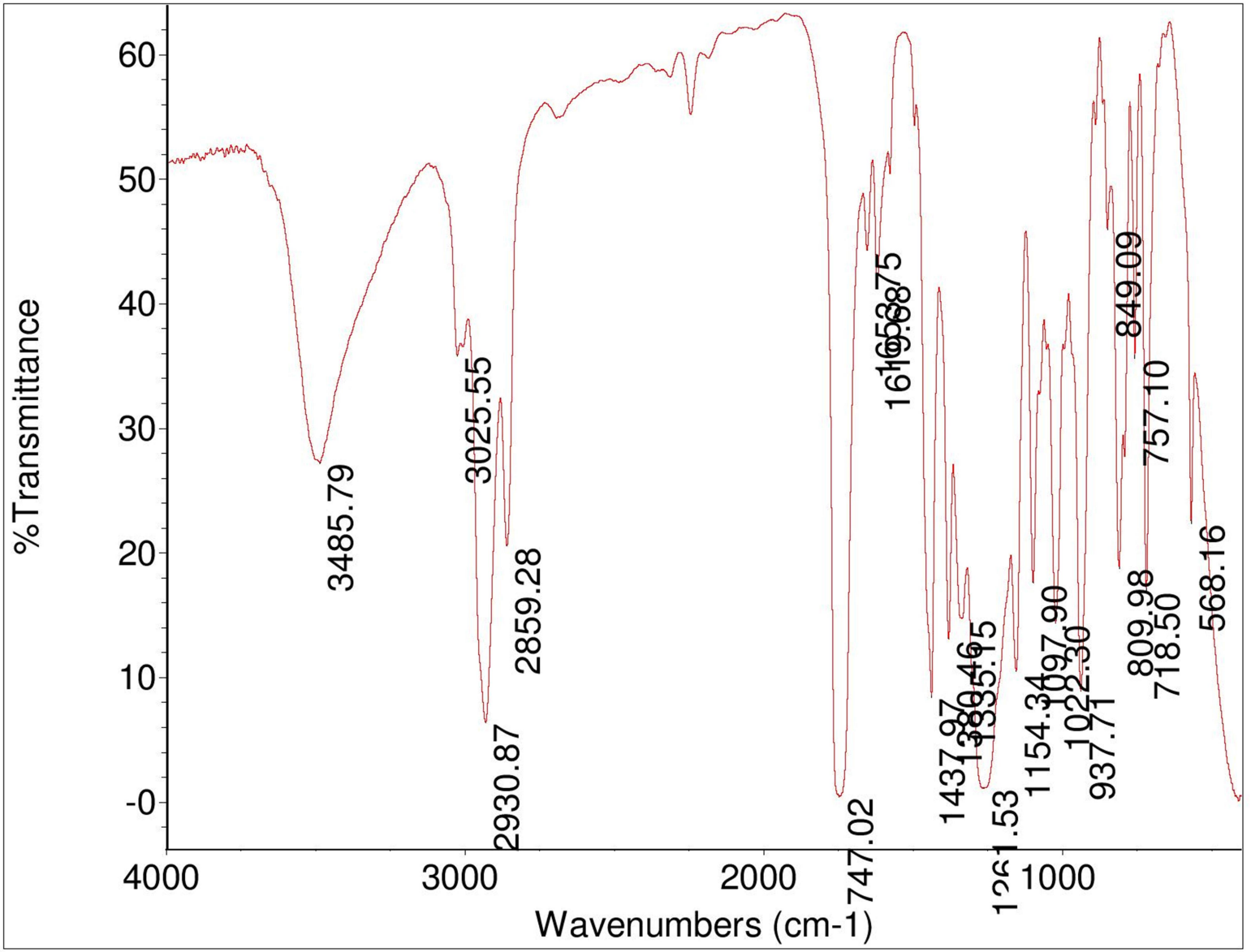
LRMS $[M+Na]^+$

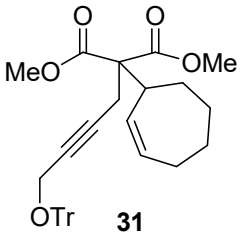


32


nh-107-end.esp
MeO
OMe
OTr
31
7.45
7.29
7.27
7.26
7.24
3.75
3.66
3.25
2.91
2.17
1.87
1.70
1.57
1.25
0.85
0.08
5.84
5.74
6.88 12.24 1.98 6.58 2.48 0.92 1.74 1.98 0.79 2.08 1.08 2.84
Normalized Intensity
Chemical Shift (ppm)

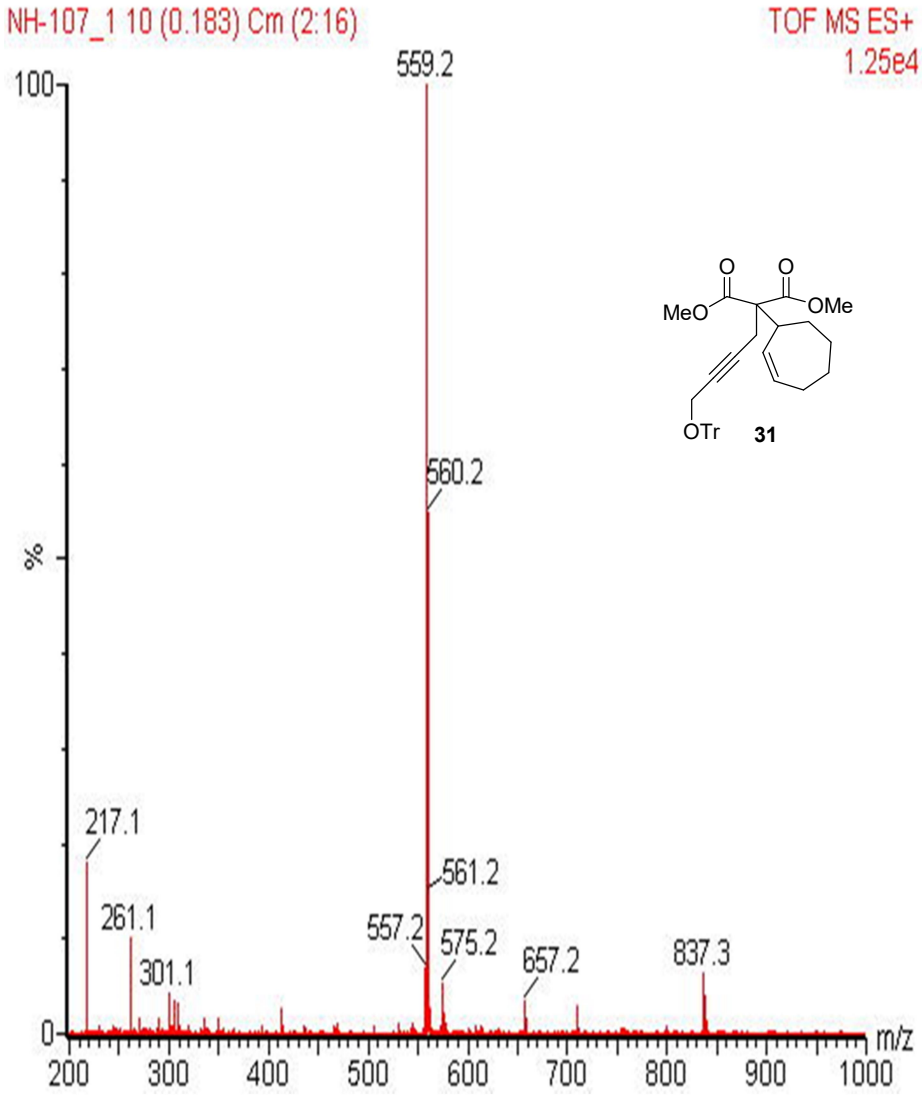

nh-174-13C.esp
128.83
128.14
127.34
77.58
77.27
76.95
143.77
172.67
130.31
87.59
84.07
76.68
53.61
52.05
33.52
35.20
29.02
26.57
26.01
15.06
Normalized Intensity
0.30
0.25
0.20
0.15
0.10
0.05
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)
O
O
MeO
OMe
OTr
31


%Transmittance
60
50
40
30
20
10
-0
4000
3000
2000
1000
Wavenumbers (cm-1)
3485.79
3025.55
2930.87
2859.28
1747.02
1653.75
1615.88
1437.97
1380.46
1335.15
1261.53
1154.34
1097.90
1022.30
937.71
849.09
809.98
757.10
718.50
568.16


MeO
O
O
OMe
OTr

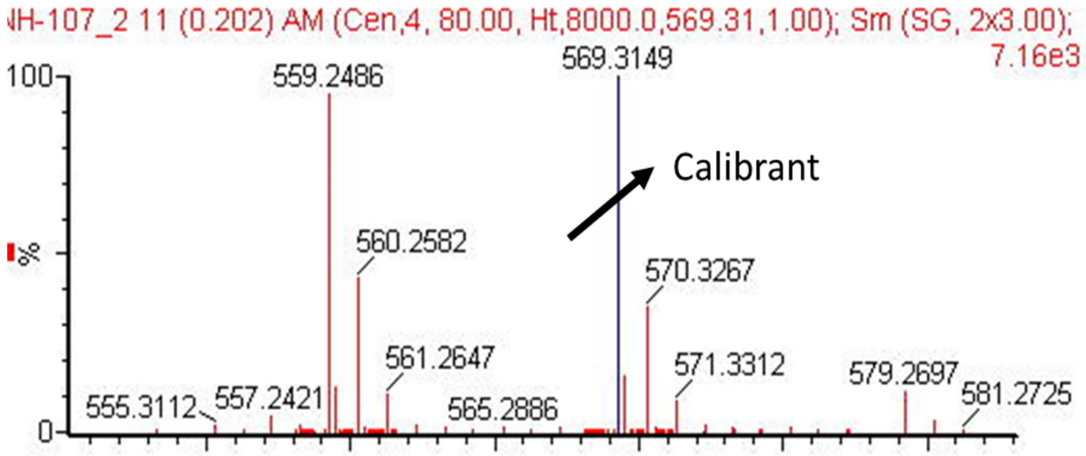
31

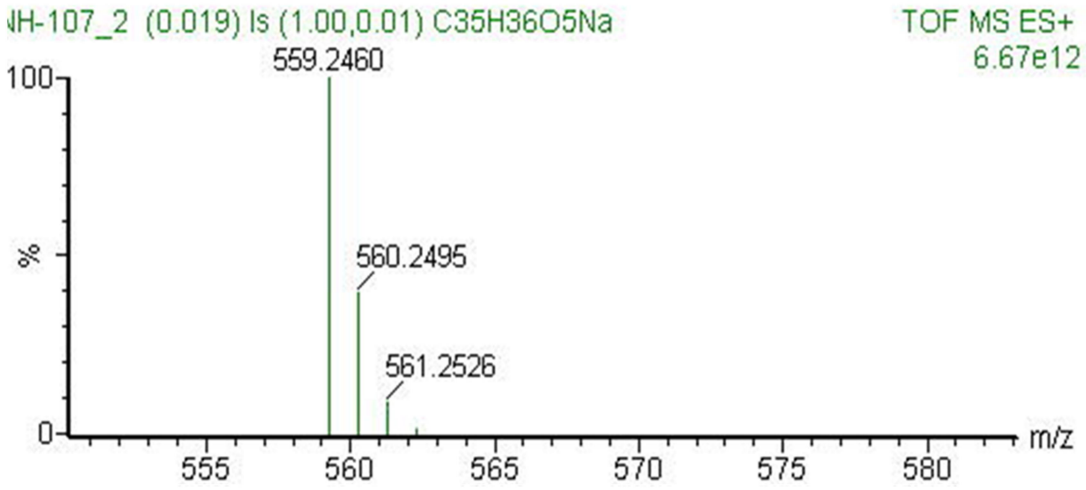
LRMS [M+Na]+



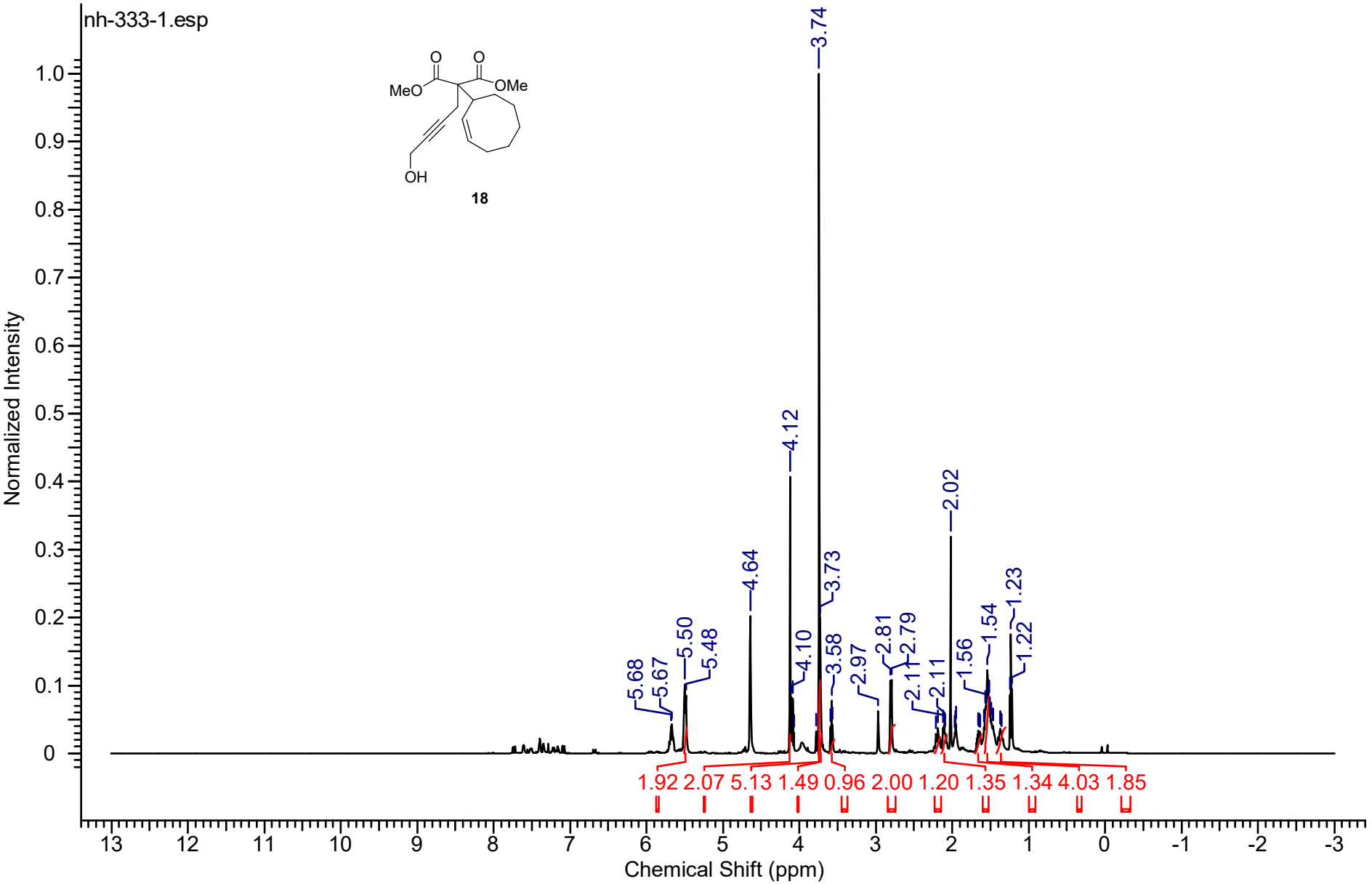
31

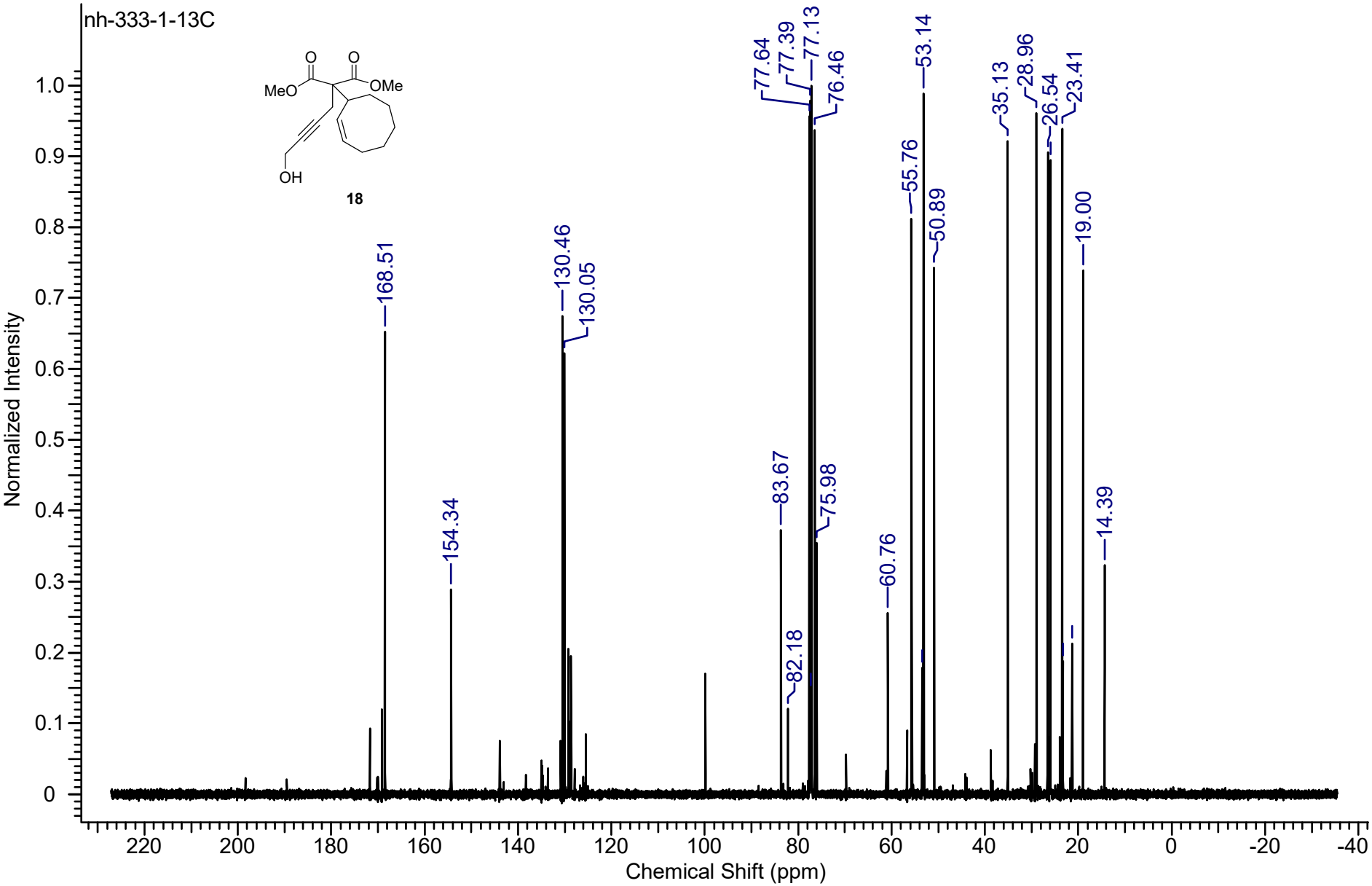
HRMS ObservedΔ = 2.6 mDa
Acceptable = ± 2.8 mDa

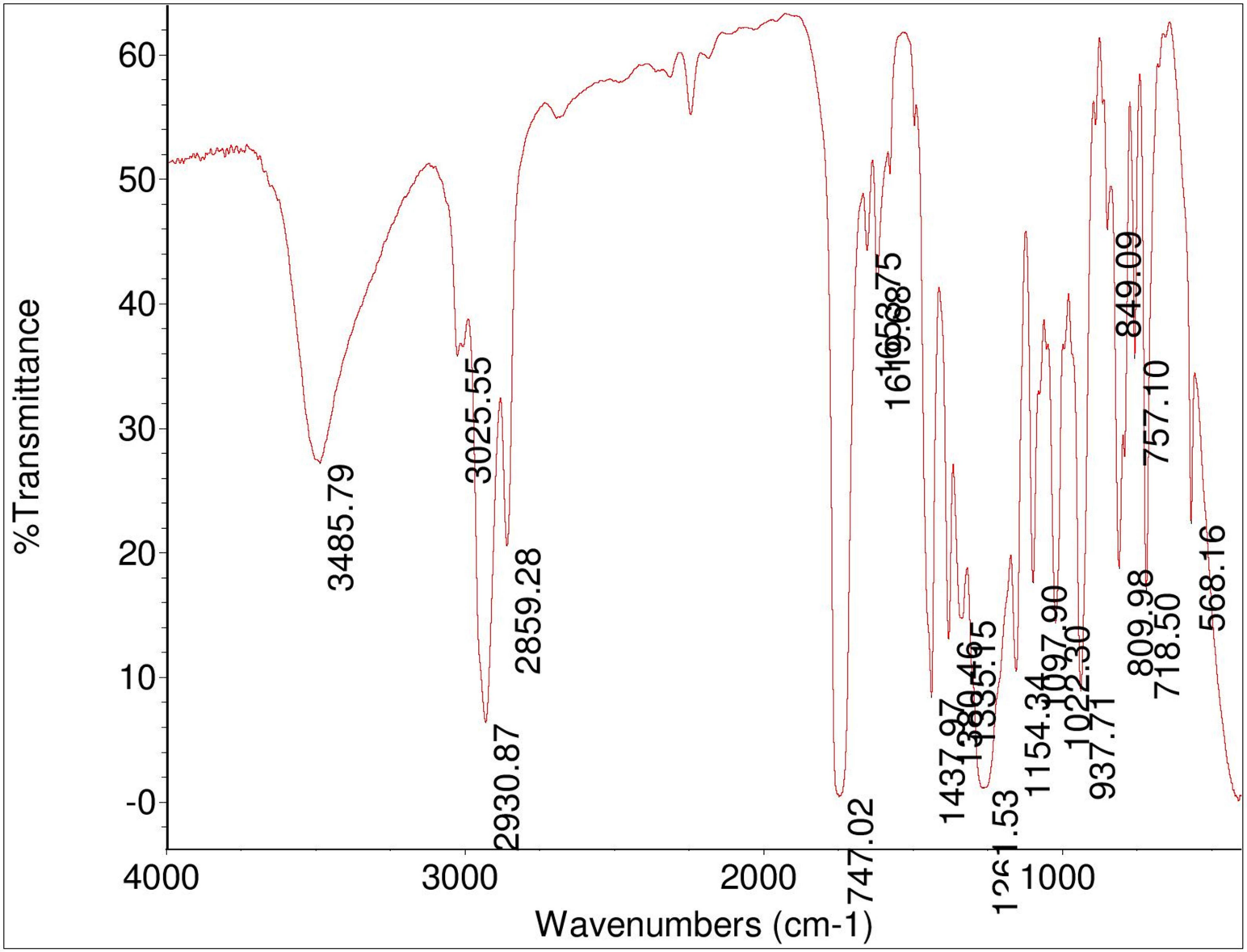


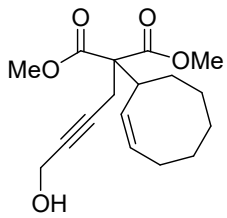


Theoretical =[M+Na]+

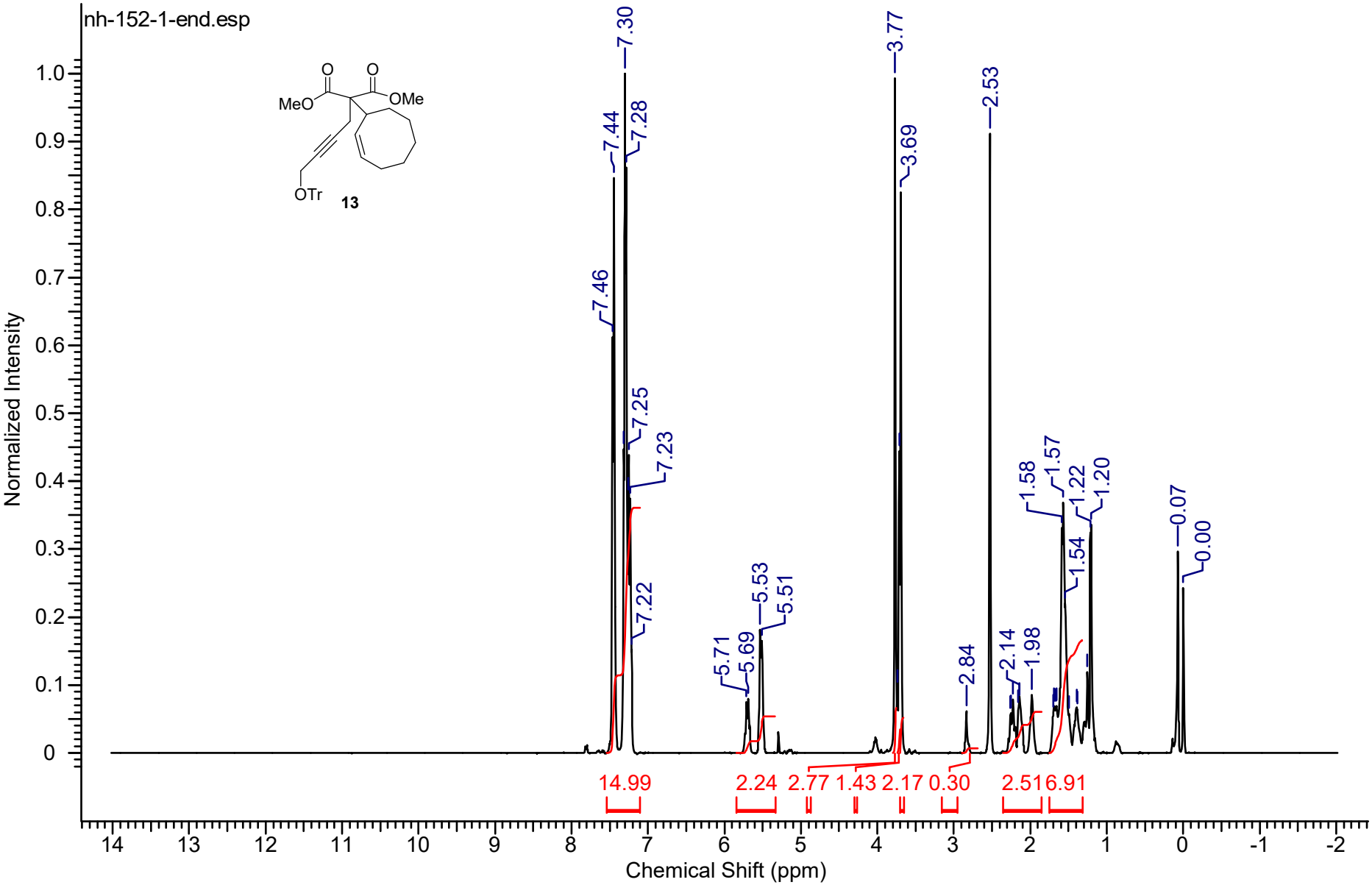

nh-333-1.esp
MeO
O
O
OMe
OH
18
3.74
4.12
4.64
3.73
4.10
2.02
5.50
5.48
5.68
5.67
3.58
2.97
2.81
2.79
2.11
2.11
1.56
1.54
1.23
1.22
1.92 2.07 5.13 1.49 0.96 2.00 1.20 1.35 1.34 4.03 1.85
Normalized Intensity
Chemical Shift (ppm)

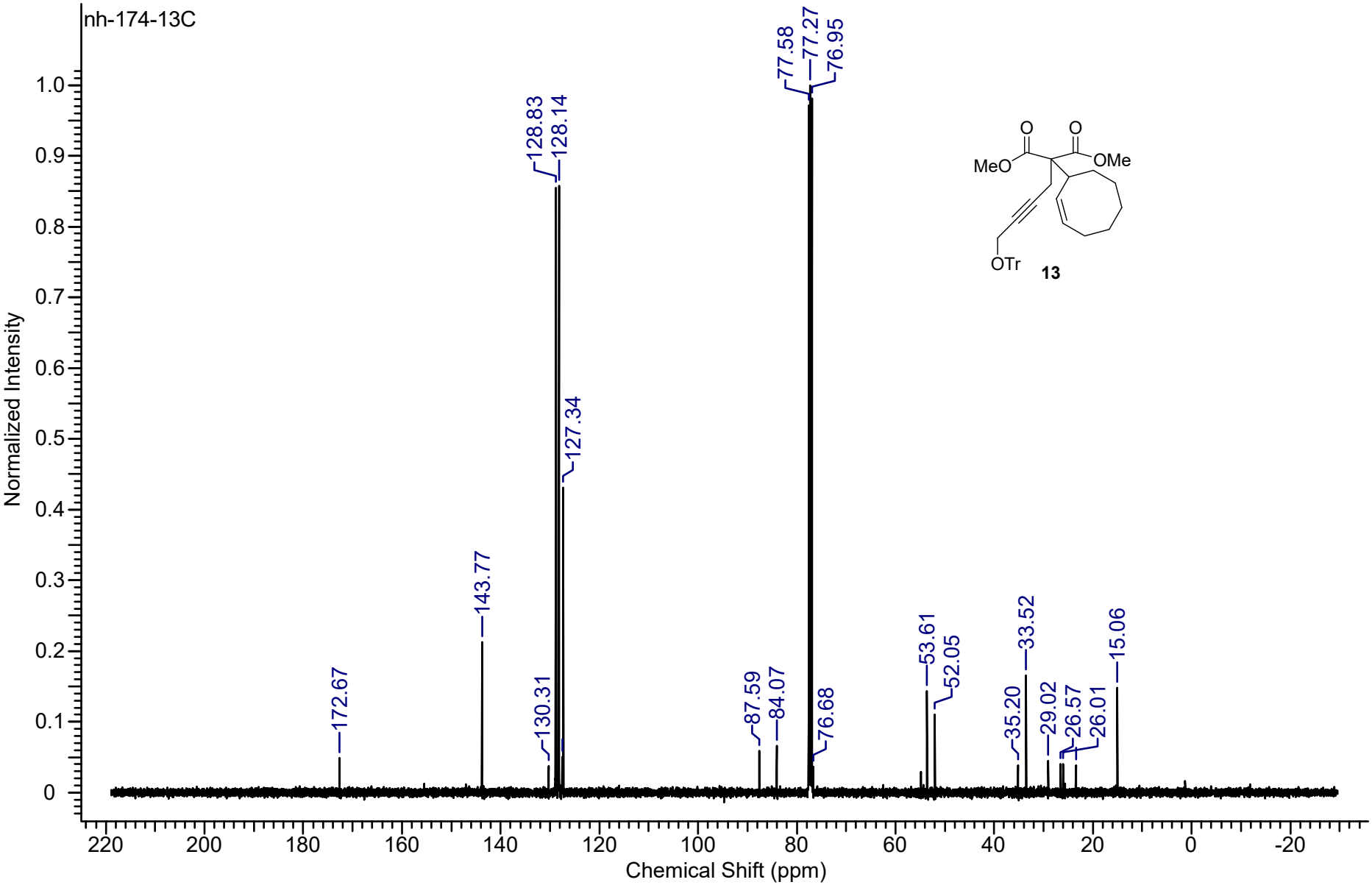

nh-333-1-13C
MeO
OMe
OH
18
Normalized Intensity
Chemical Shift (ppm)
168.51
154.34
130.46
130.05
83.67
82.18
77.64
77.39
77.13
76.46
75.98
60.76
55.76
53.14
50.89
35.13
28.96
26.54
23.41
19.00
14.39

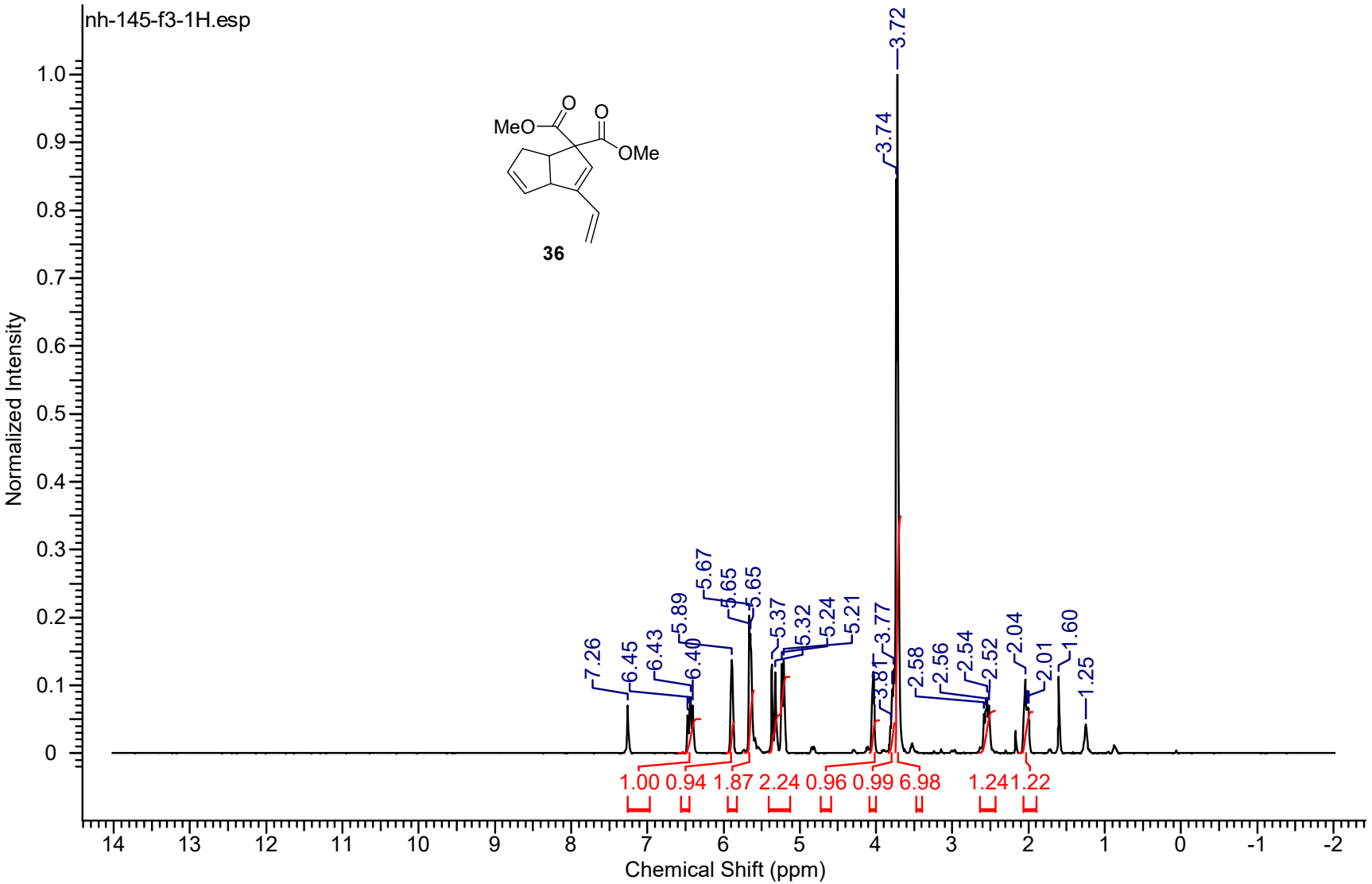

%Transmittance
60
50
40
30
20
10
-0
4000
3000
2000
1000
Wavenumbers (cm-1)
3485.79
3025.55
2930.87
2859.28
1747.02
1615.88
1437.97
1380.46
1335.15
1261.53
1154.34
1097.90
1022.30
937.71
849.09
809.98
757.10
718.50
568.16

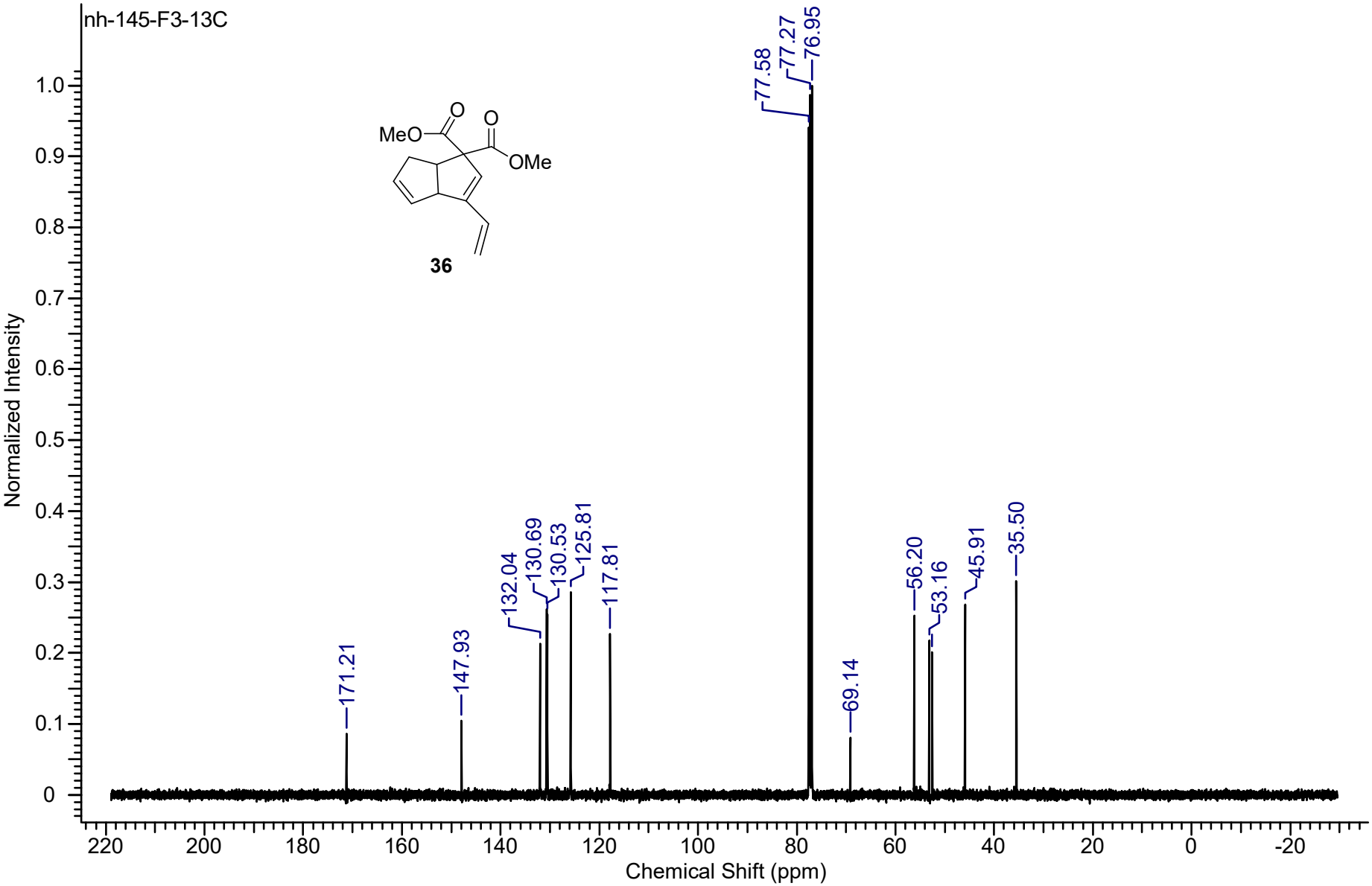

MeO
O
O
OMe
OH

18

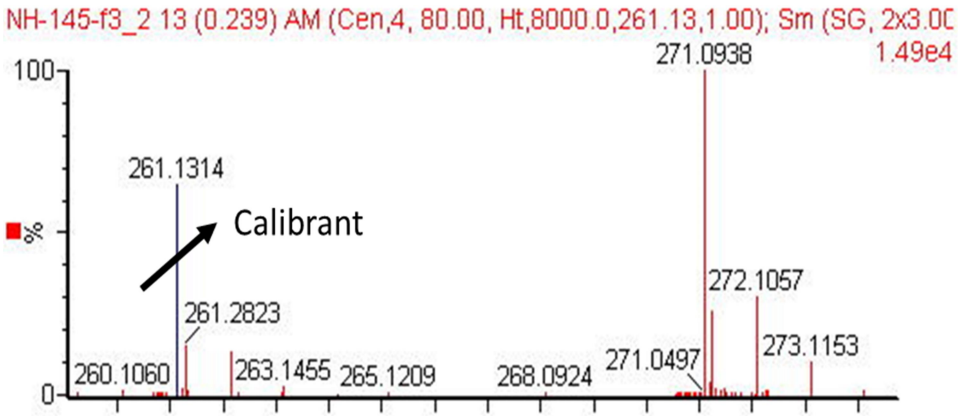

nh-152-1-end.esp
MeO
OMe
OTr
13
7.30
7.44
7.28
3.77
3.69
2.53
7.46
7.25
7.23
7.22
5.71
5.69
5.53
5.51
2.84
2.14
1.98
1.58
1.57
1.22
1.20
1.54
0.07
0.00
14.99
2.24
2.77
1.43
2.17
0.30
2.51
6.91
Normalized Intensity
Chemical Shift (ppm)

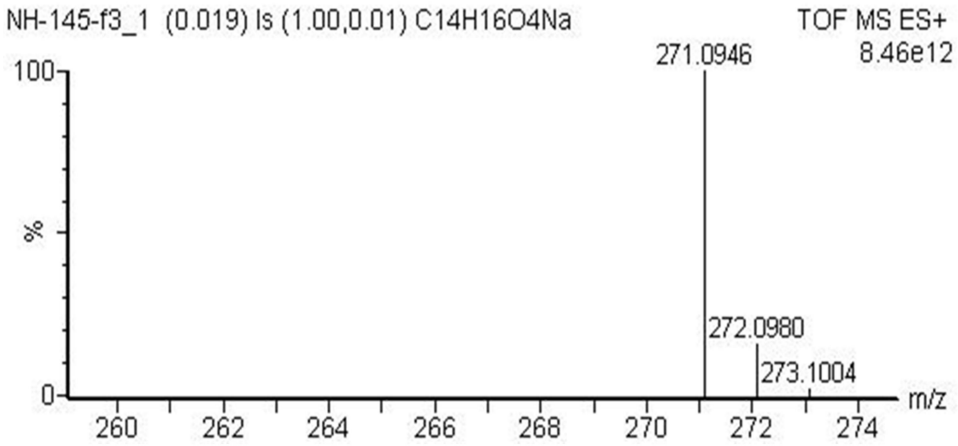

nh-174-13C
Normalized Intensity
Chemical Shift (ppm)
77.58
77.27
76.95
128.83
128.14
127.34
143.77
172.67
130.31
87.59
84.07
76.68
53.61
52.05
35.20
33.52
29.02
26.57
26.01
15.06
MeO
OMe
OTr
13


nh-145-f3-1H.esp
MeO
O
O
OMe
36
Normalized Intensity
Chemical Shift (ppm)
7.26
6.45
6.43
6.40
5.89
5.67
5.65
5.65
5.37
5.32
5.24
5.21
3.81
3.77
3.74
3.72
2.58
2.56
2.54
2.52
2.04
2.01
1.60
1.25
1.00 0.94 1.87 2.24 0.96 0.99 6.98 1.24 1.22


nh-145-F3-13C
MeO
O
O
OMe
36
77.58
77.27
76.95
171.21
147.93
132.04
130.69
130.53
125.81
117.81
69.14
56.20
53.16
45.91
35.50
Normalized Intensity
Chemical Shift (ppm)

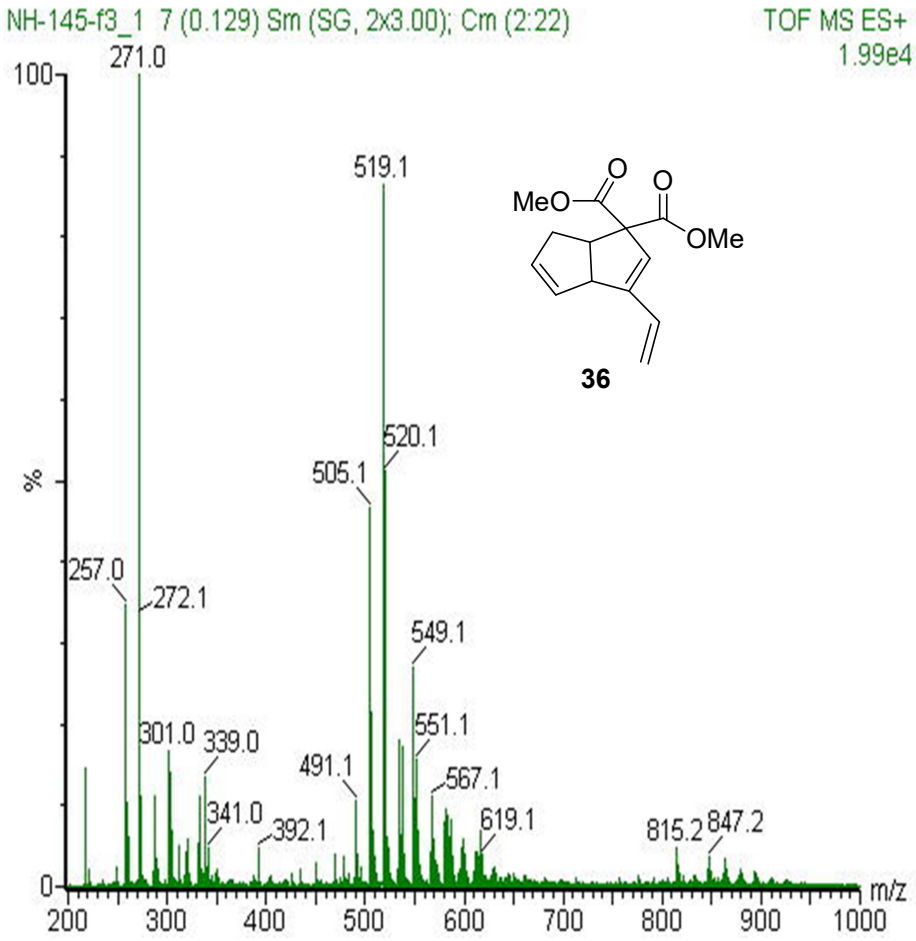
HRMS ObservedΔ = 0.8 mDa
Acceptable = ± 1.4 mDa



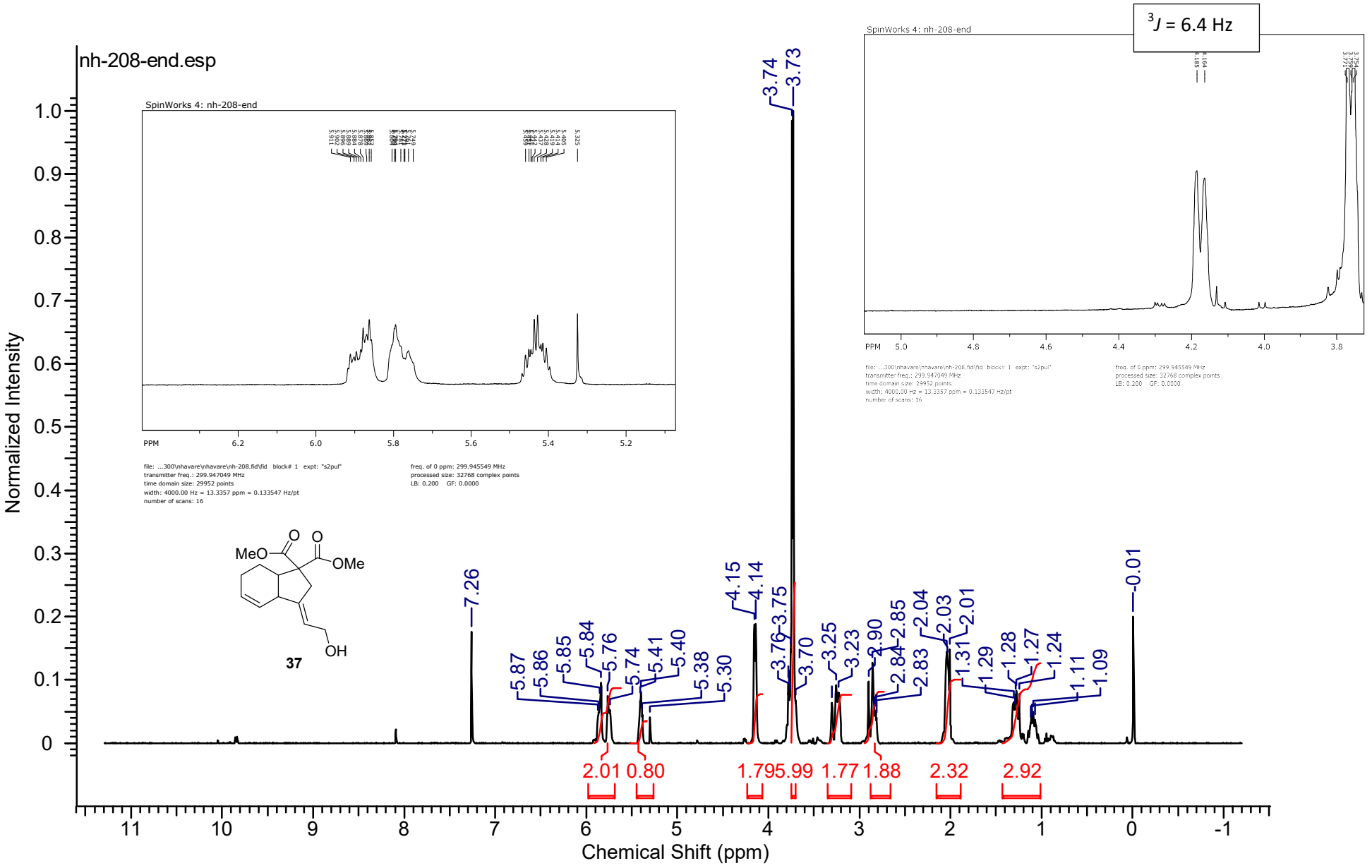


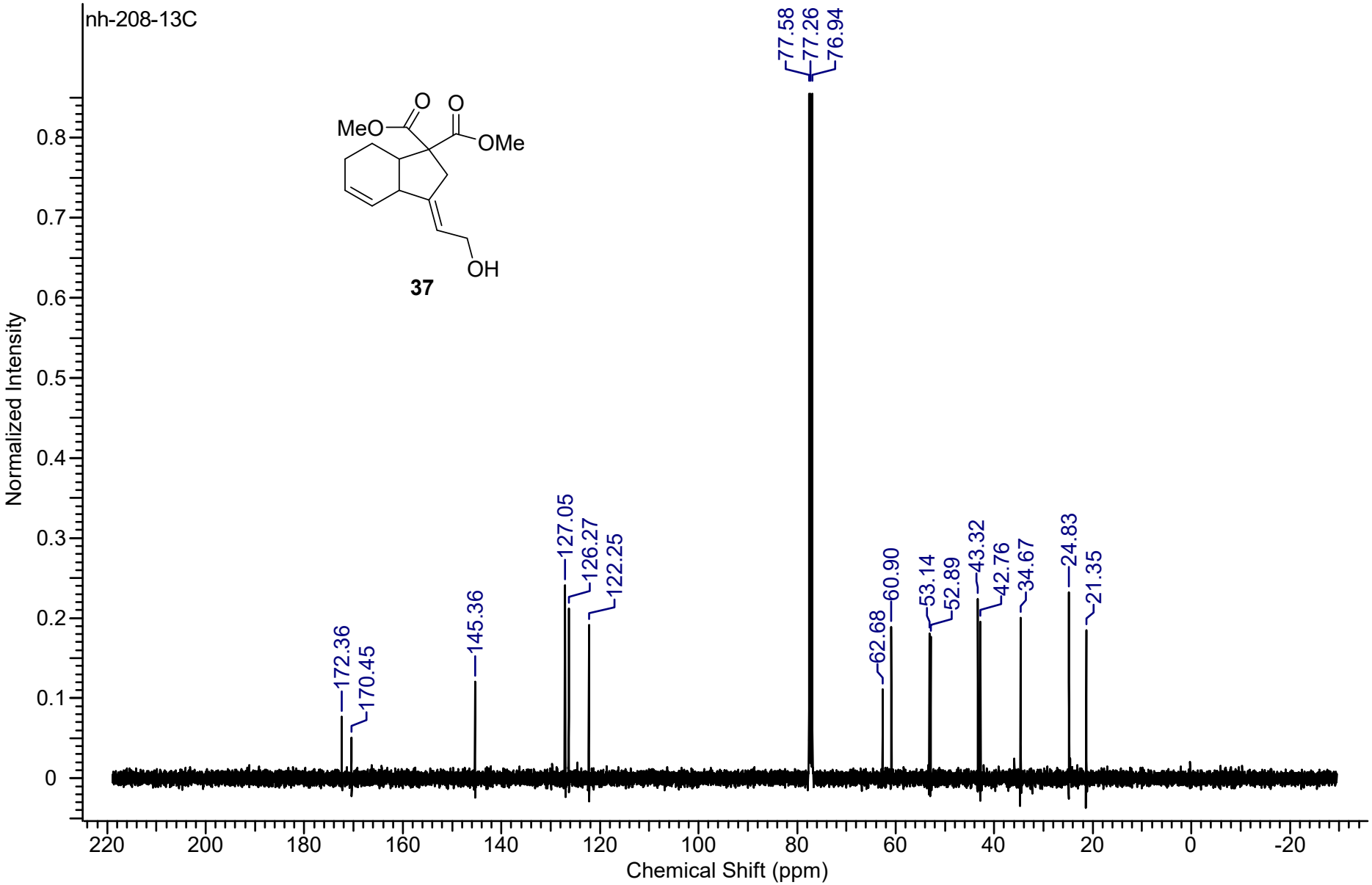
Theoretical =$[M+Na]^+$

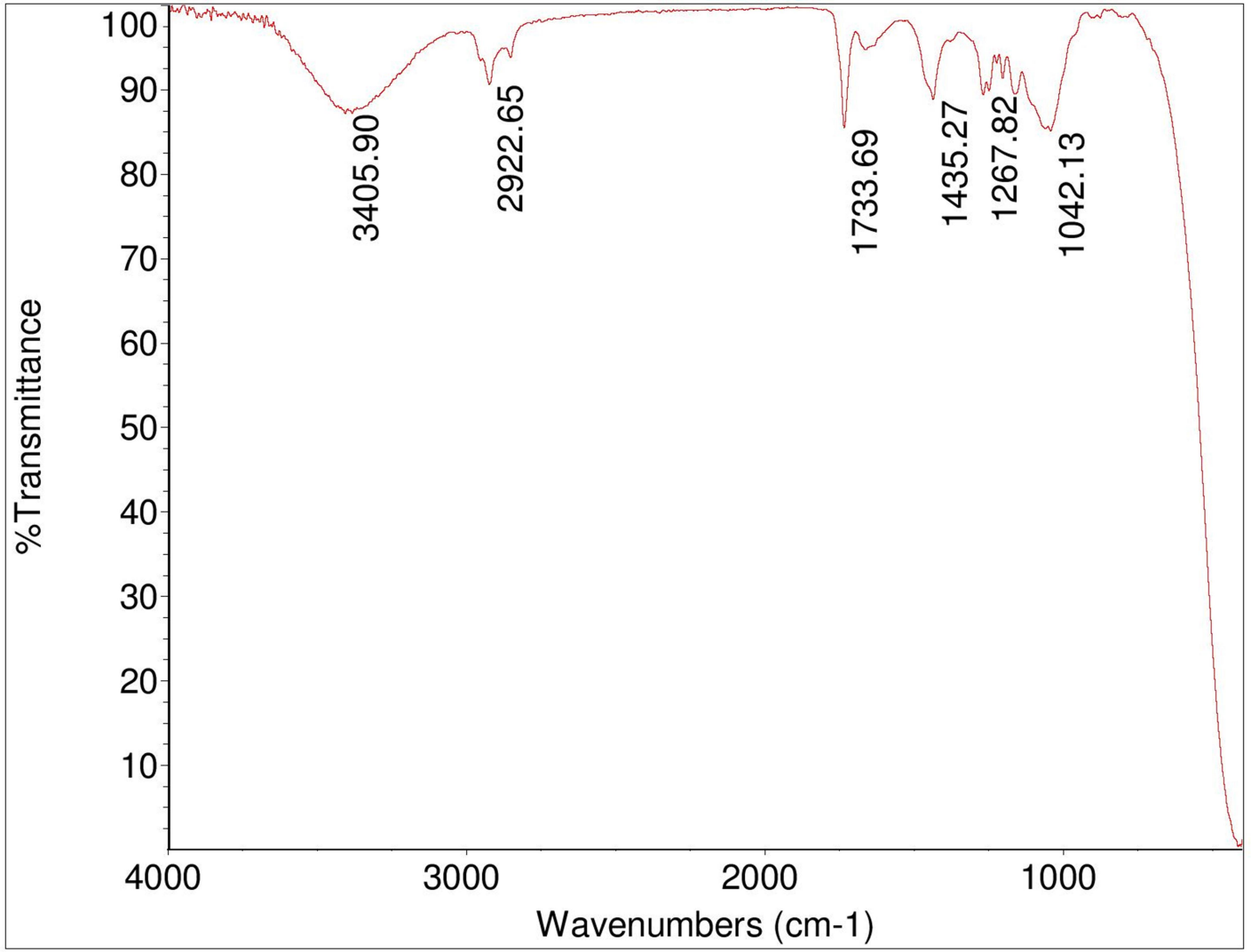
LRMS $[M+Na]^+$ $[2M+Na]^+$

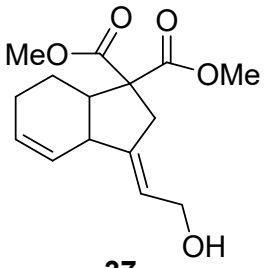


36


nh-208-end.esp
SpinWorks 4: nh-208-end
SpinWorks 4: nh-208-end
^3J = 6.4 Hz
Normalized Intensity
Chemical Shift (ppm)
MeO
OMe
OH
37
7.26
3.74
3.73
4.15
4.14
3.75
3.76
3.70
3.25
3.23
2.90
2.85
2.84
2.83
2.04
2.03
2.01
1.31
1.29
1.28
1.27
1.24
1.11
1.09
0.01
5.87
5.86
5.85
5.84
5.76
5.74
5.41
5.40
5.38
5.30
2.01
0.80
1.79
5.99
1.77
1.88
2.32
2.92

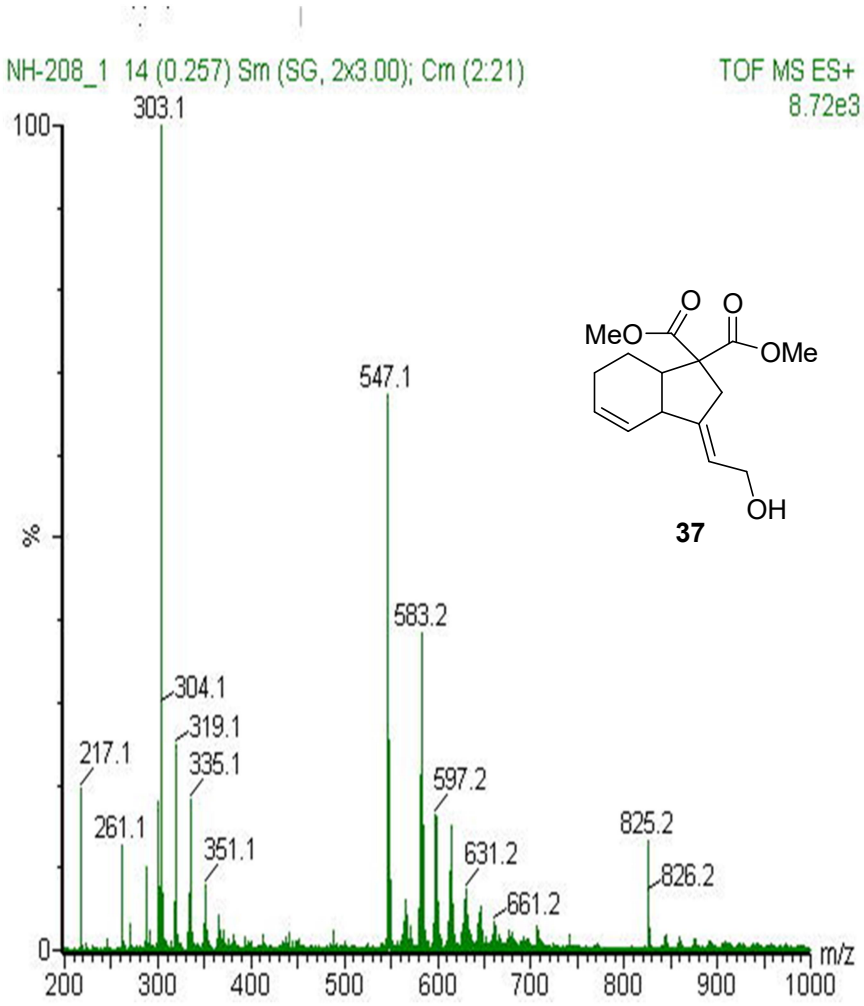

nh-208-13C
MeO
O
O
OMe
OH
37
77.58
77.26
76.94
172.36
170.45
145.36
127.05
126.27
122.25
62.68
60.90
53.14
52.89
43.32
42.76
34.67
24.83
21.35
Normalized Intensity
Chemical Shift (ppm)


100
90
80
70
60
50
40
30
20
10
%Transmittance
3405.90
2922.65
1733.69
1435.27
1267.82
1042.13
4000
3000
2000
1000
Wavenumbers (cm-1)


MeO
O
O
OMe
OH

37

LRMS [M+Na]+

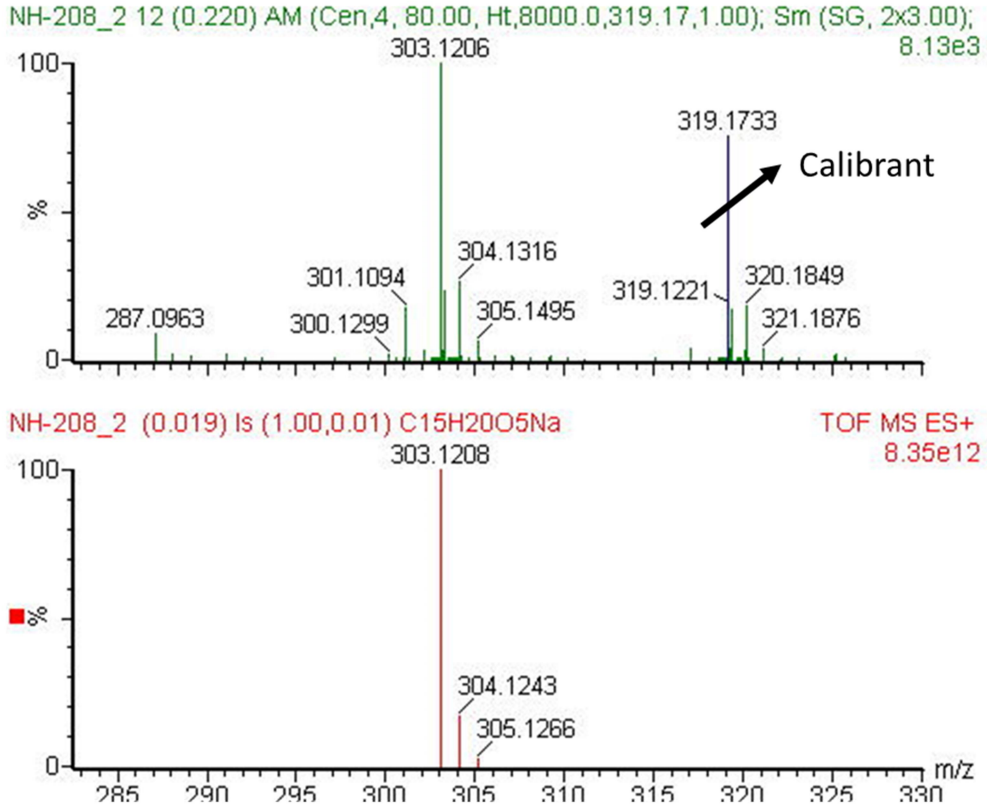


37

HRMS

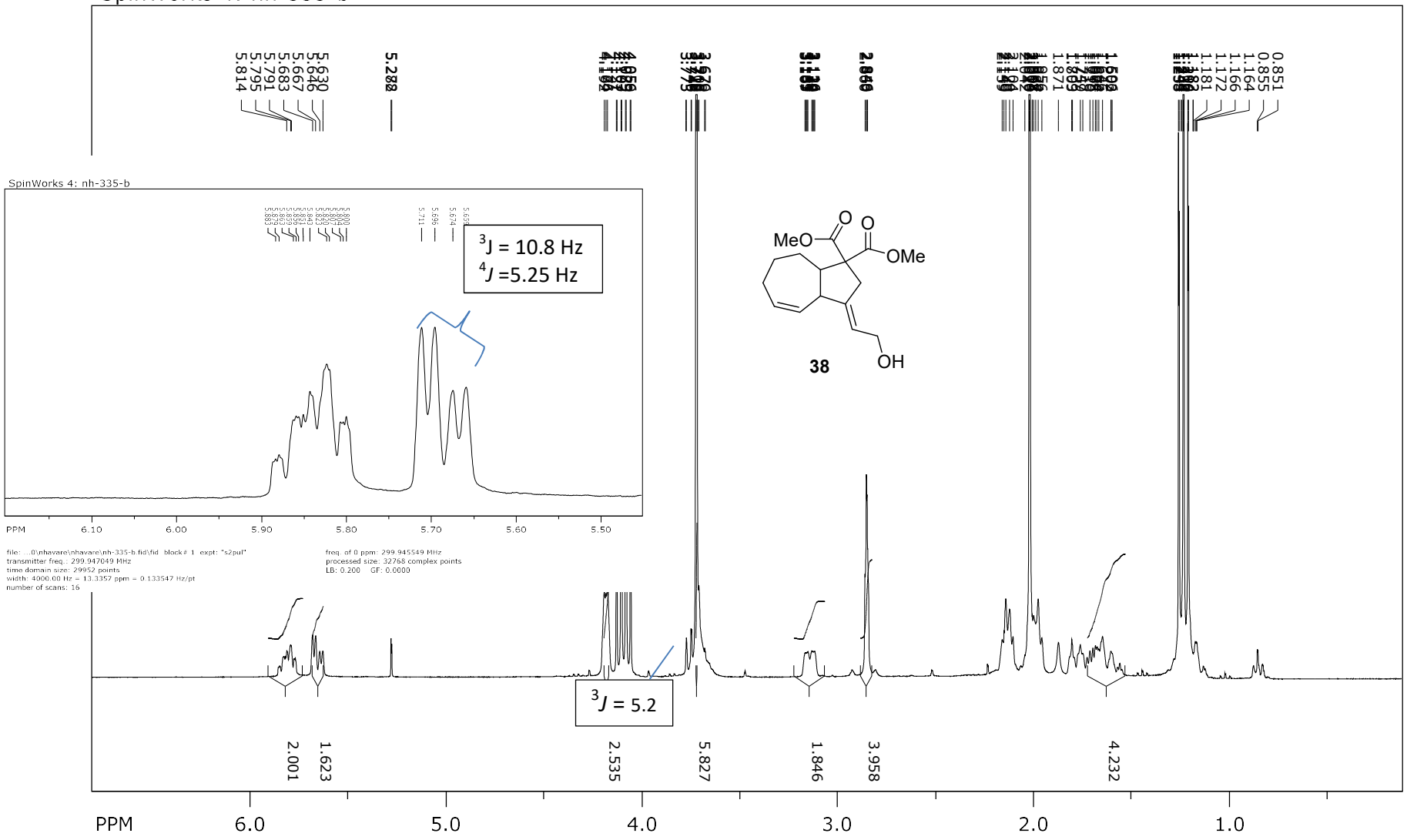
ObservedΔ = 0.2 mDa

Acceptable = ± 1.5 mDa



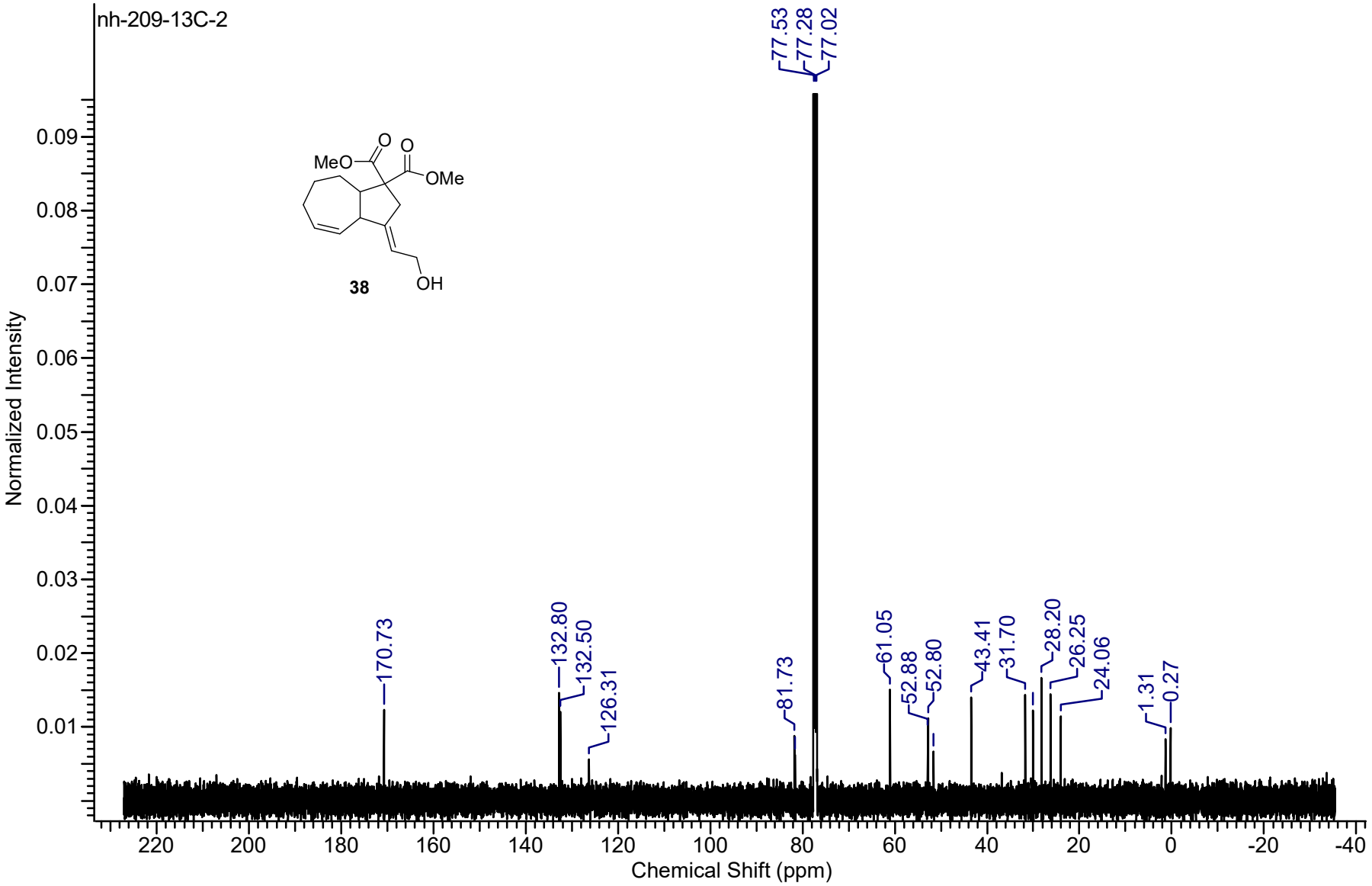
Theoretical =[M+Na]+

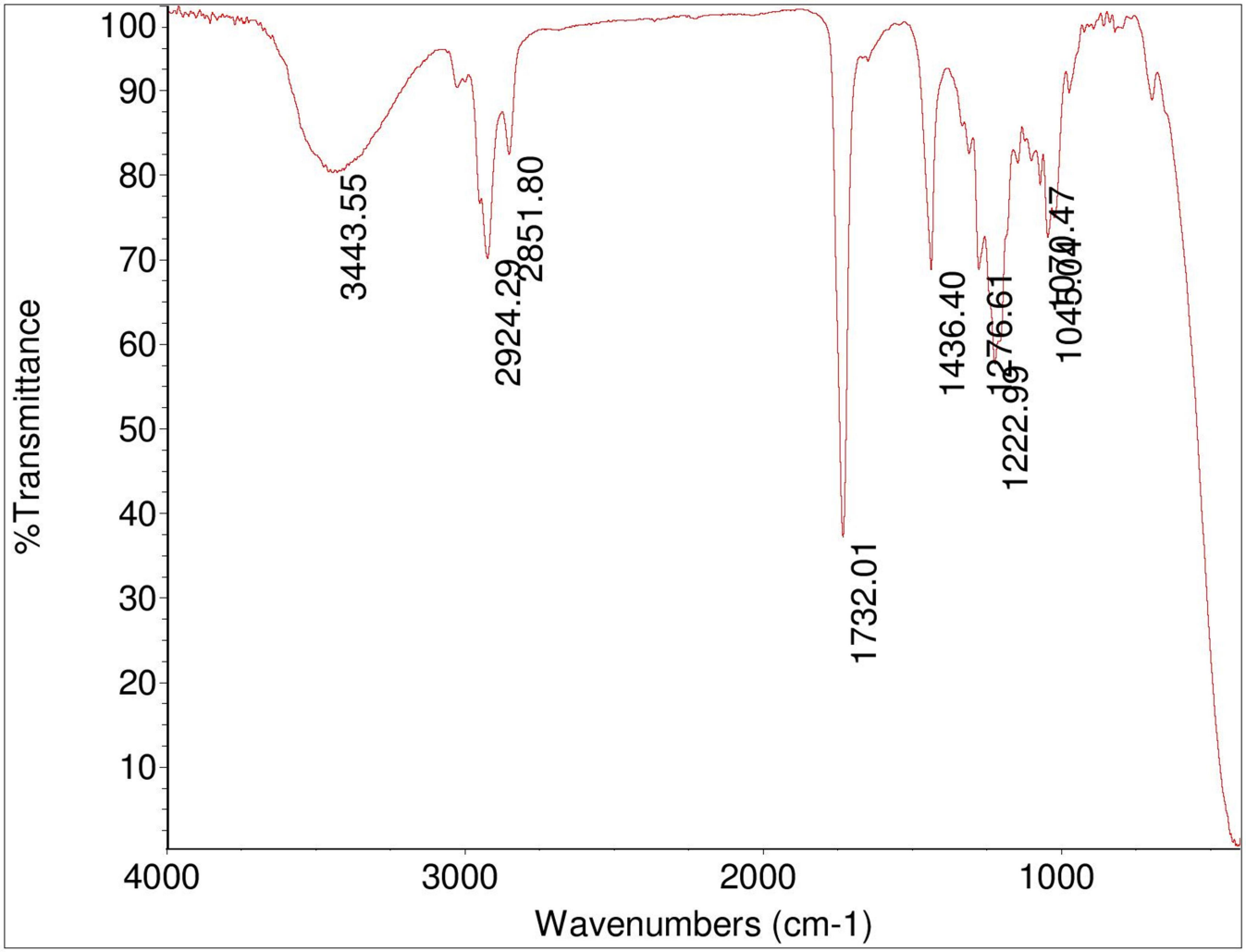
SpinWorks 4: nh-335-b

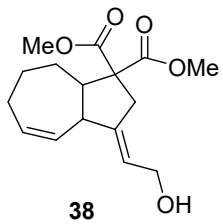


file: ...0\nhavare\nhavare\nh-335-b.fid\fid block# 1 expt: "s2pul"
transmitter freq.: 299.947049 MHz
time domain size: 29952 points
width: 4000.00 Hz = 13.3357 ppm = 0.133547 Hz/pt
number of scans: 16

freq. of 0 ppm: 299.945557 MHz
processed size: 32768 complex points
LB: 0.200 GF: 0.0000

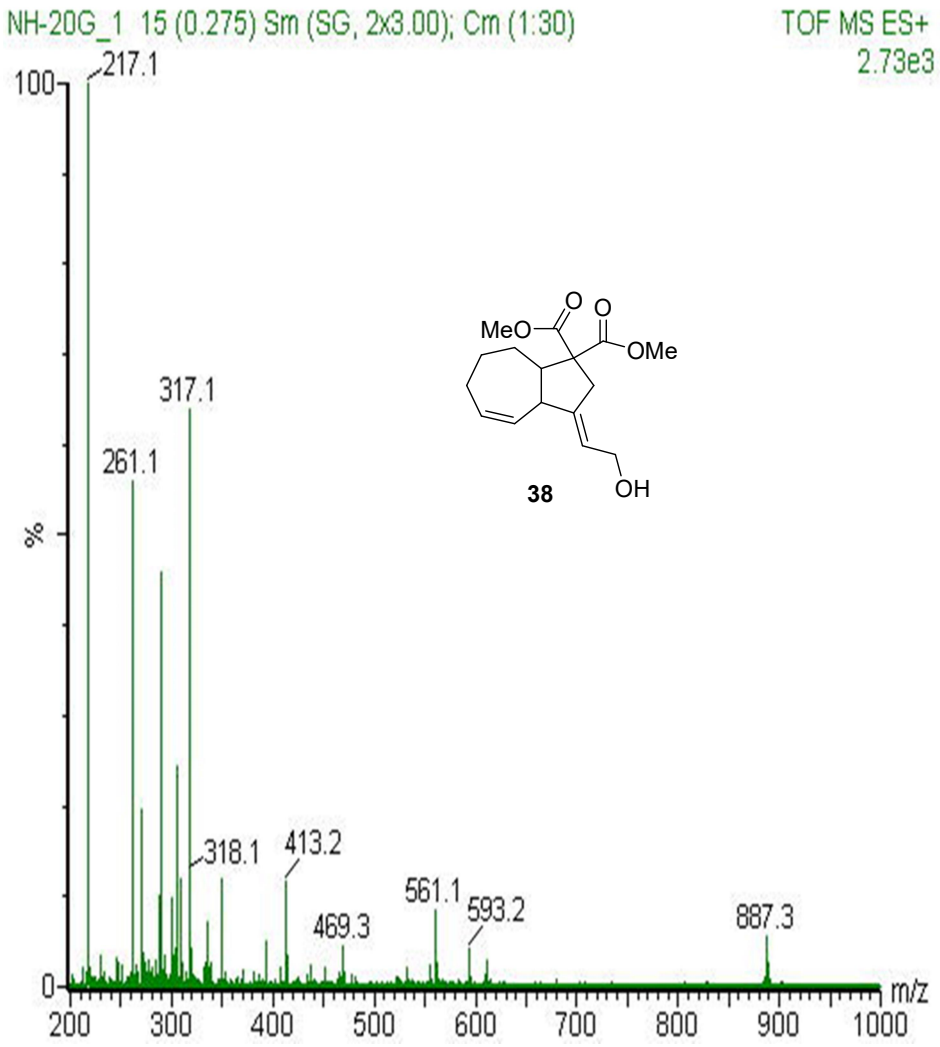

nh-209-13C-2
77.53
77.28
77.02
MeO
O
O
OMe
OH
38
170.73
132.80
132.50
126.31
81.73
61.05
52.88
52.80
43.41
31.70
28.20
26.25
24.06
1.31
0.27
Normalized Intensity
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
Chemical Shift (ppm)


%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3443.55
2924.29
2851.80
1732.01
1436.40
1276.61
1222.99
1045.74
1030.47


MeO
O
O
OMe
OH

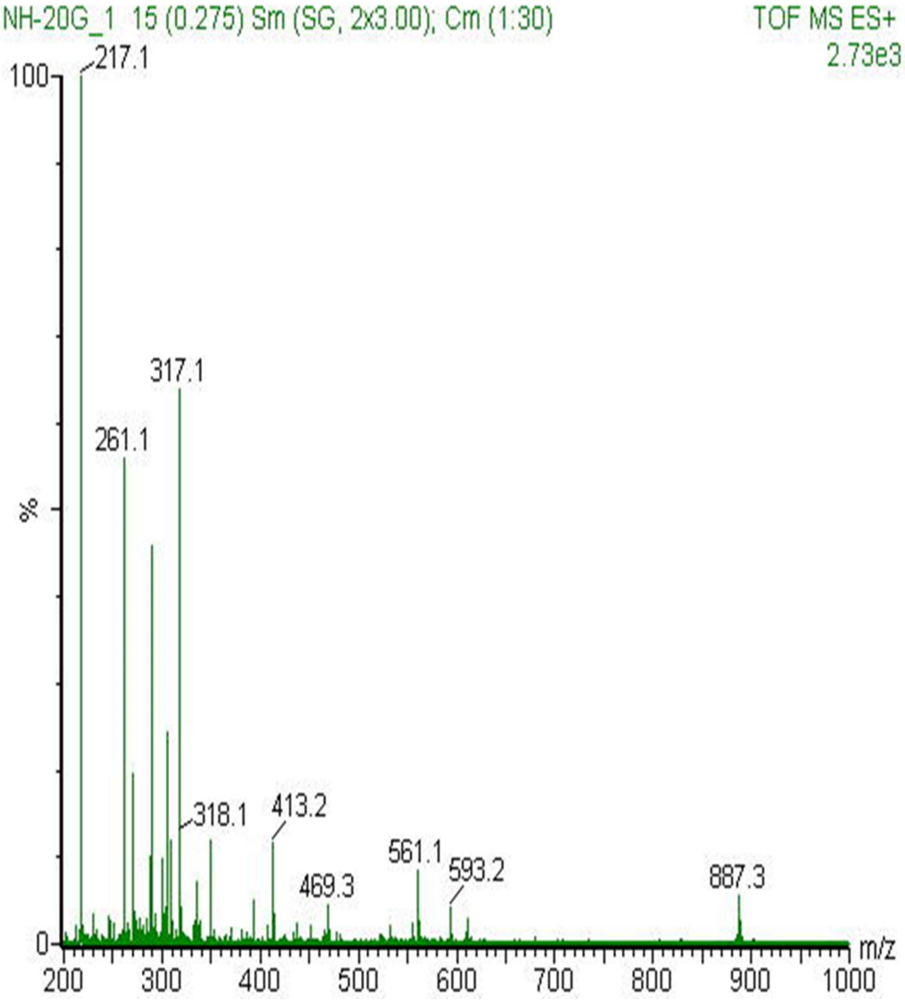
38

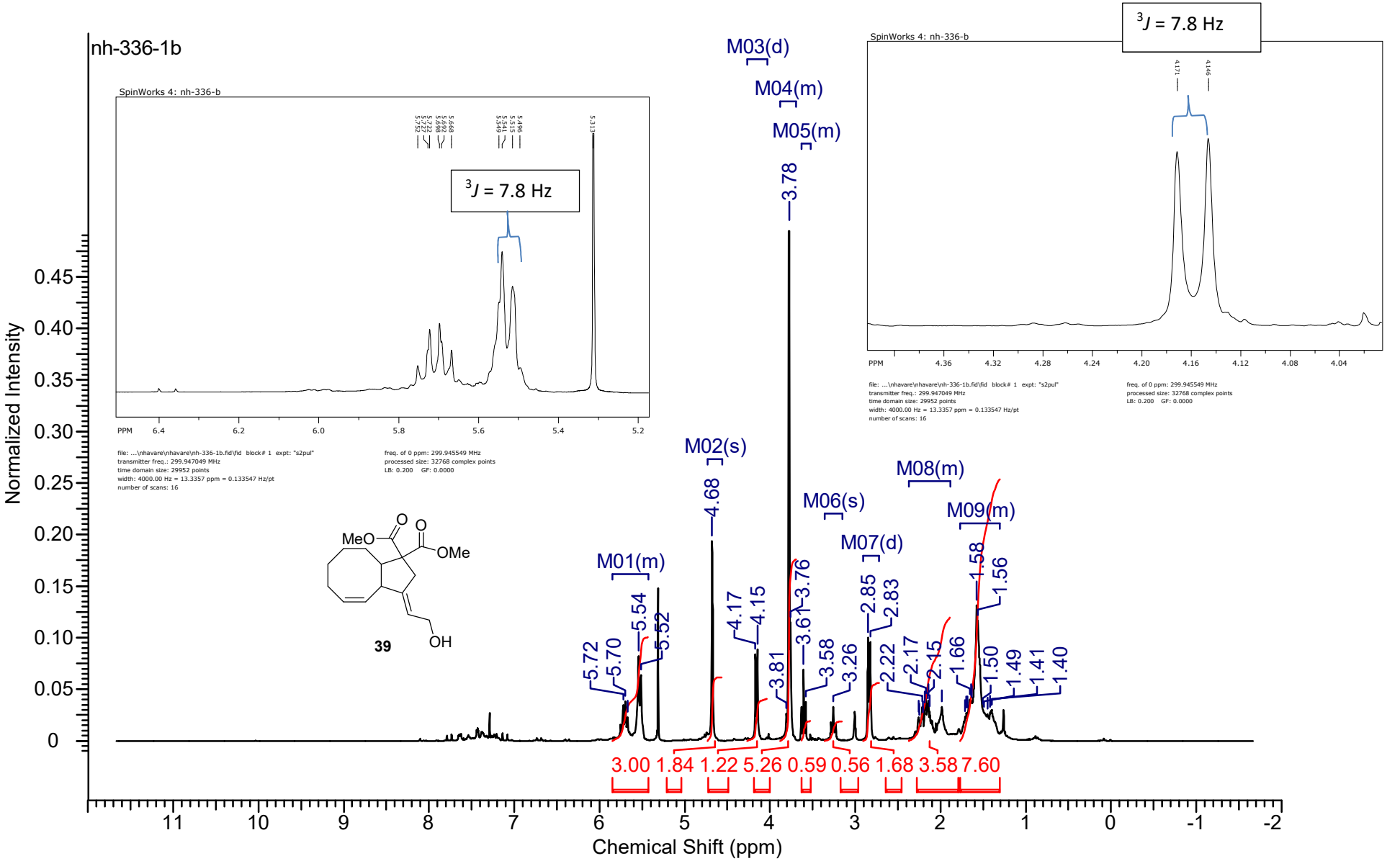
LRMS [M+Na]+

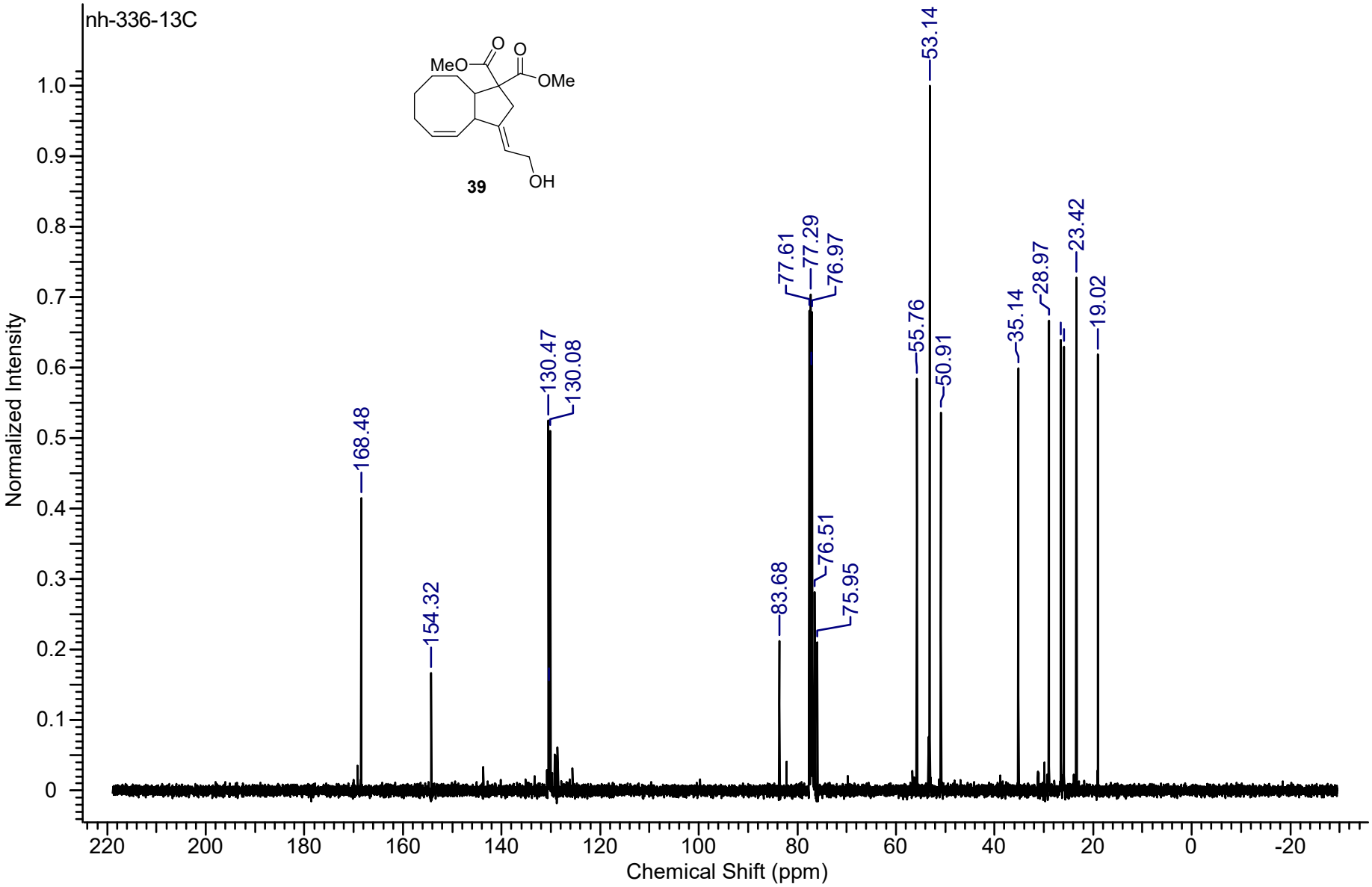


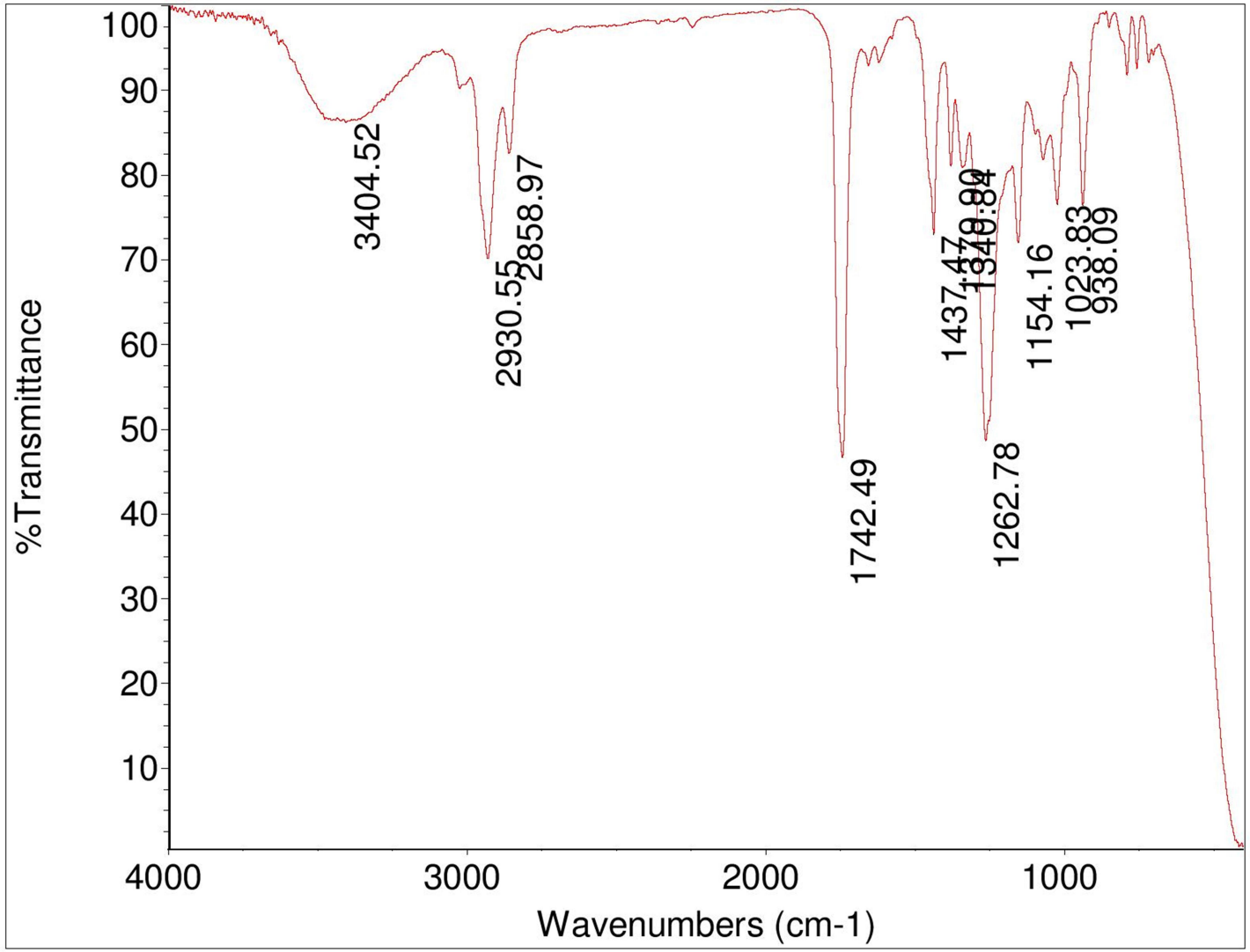
38

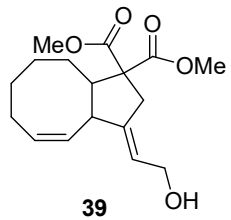
LRMS [M+Na]+




nh-336-1b
SpinWorks 4: nh-336-b
^3J = 7.8 Hz
PPM 6.4 6.2 6.0 5.8 5.6 5.4 5.2
file: ...\nhavare\nhavare\nh-336-1b.fid\fid block# 1 expt: "s2pul"
transmitter freq.: 299.947049 MHz
time domain size: 29952 points
width: 4000.00 Hz = 13.3357 ppm = 0.133547 Hz/pt
number of scans: 16
freq. of 0 ppm: 299.945549 MHz
processed size: 32768 complex points
LB: 0.200 GF: 0.0000
SpinWorks 4: nh-336-b
^3J = 7.8 Hz
PPM 4.36 4.32 4.28 4.24 4.20 4.16 4.12 4.08 4.04
file: ...\nhavare\nhavare\nh-336-1b.fid\fid block# 1 expt: "s2pul"
transmitter freq.: 299.947049 MHz
time domain size: 29952 points
width: 4000.00 Hz = 13.3357 ppm = 0.133547 Hz/pt
number of scans: 16
freq. of 0 ppm: 299.945549 MHz
processed size: 32768 complex points
LB: 0.200 GF: 0.0000
MeO
OMe
OH
39
M01(m)
M02(s)
M03(d)
M04(m)
M05(m)
M06(s)
M07(d)
M08(m)
M09(m)
3.00 1.84 1.22 5.26 0.59 0.56 1.68 3.58 7.60
Normalized Intensity
Chemical Shift (ppm)


nh-336-13C
MeO
O
O
OMe
OH
39
Normalized Intensity
Chemical Shift (ppm)
168.48
154.32
130.47
130.08
83.68
77.61
77.29
76.97
76.51
75.95
55.76
53.14
50.91
35.14
28.97
23.42
19.02


%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3404.52
2930.55
2858.97
1742.49
1437.47
1370.90
1340.84
1262.78
1154.16
1023.83
938.09


MeO
O
O
OMe
OH

39

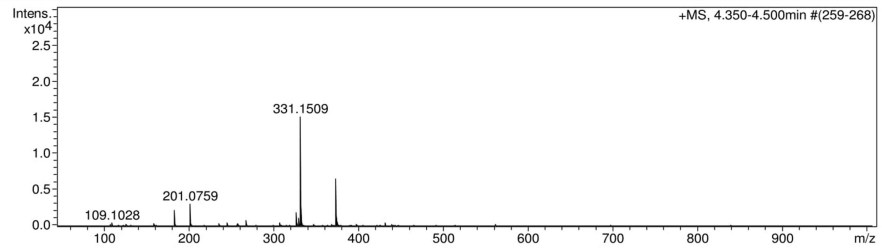
Mass Spectrum SmartFormula and Mass List Report

Analysis Info

Analysis Name	D:\Data\HRAM\170216\data\HavareN_i6574_nh-336_L1_12_01_18731.d	Acquisition Date	2/28/2017 9:47:25 PM
Method	lc_nodiv_15mins_pos_50-1000.m	Operator	BDAL@DE
Sample Name	HavareN_i6574_nh-336_L1	Instrument / Ser#	micrOTOF-Q II 10292
Comment			

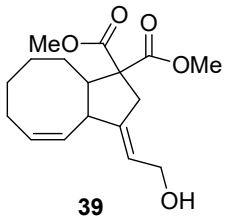
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.5 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	60.0 Vpp	Set Divert Valve	Source

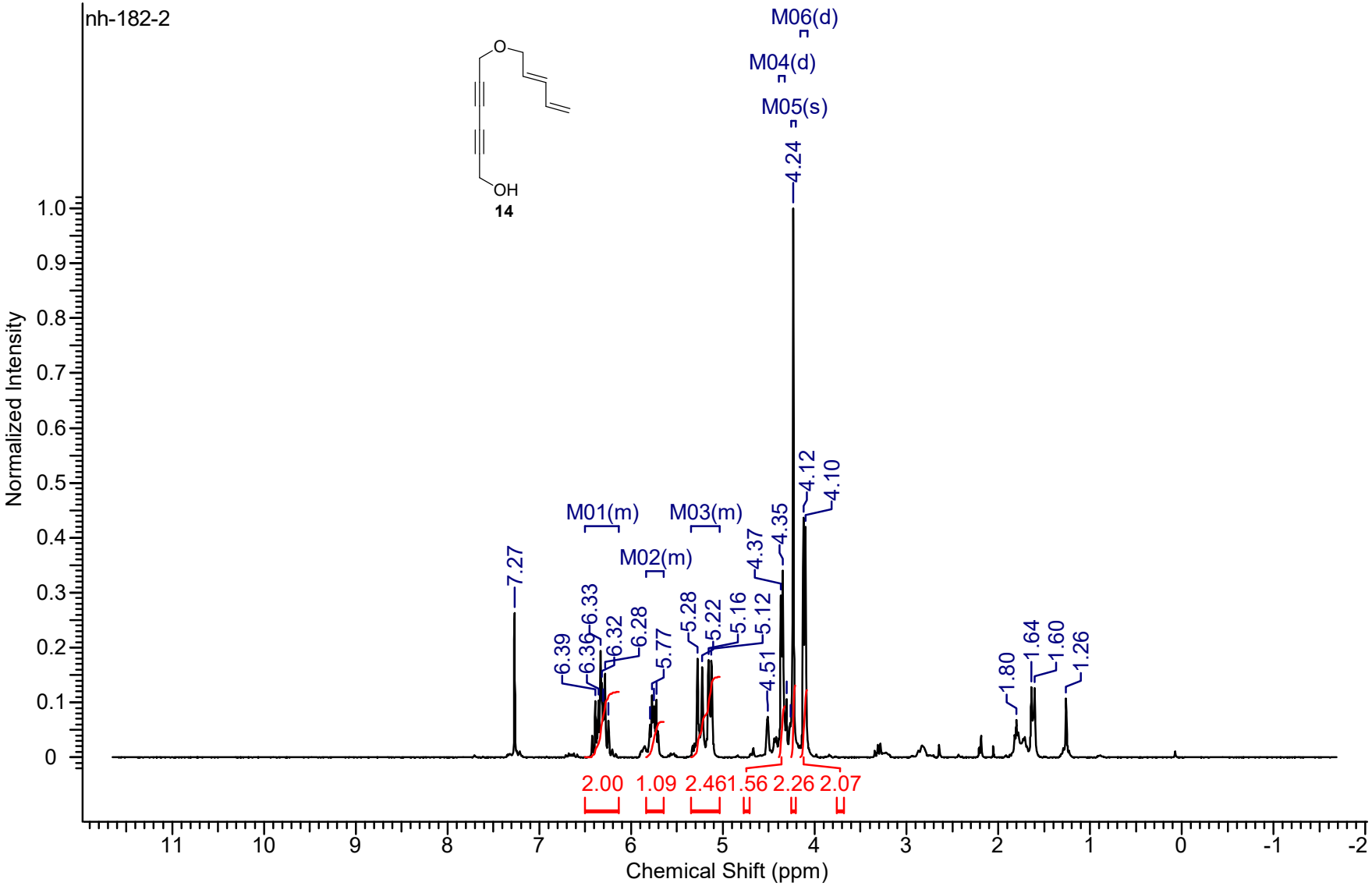


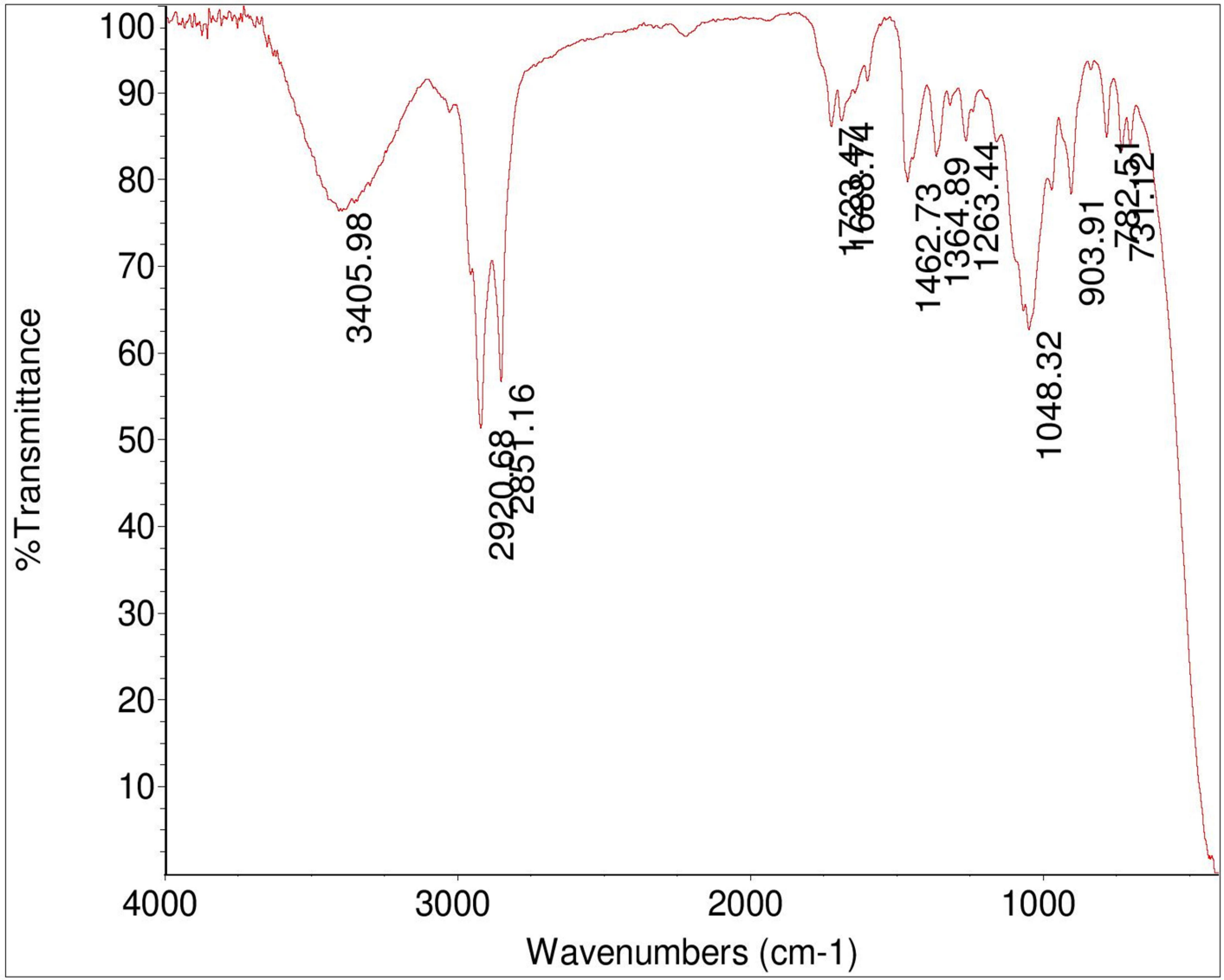
Meas. m/z	#	Formula	m/z	mSigma	err [ppm]	Score	err [mDa]	rdb	e⁻ Conf	N-Rule
331.1509	1	C 17 H 24 Na O 5	331.1516	6.3	2.1	89.34	0.7	5.5	even	ok
	2	C 15 H 19 N 6 O 3	331.1513	7.8	1.3	100.00	0.4	9.5	even	ok
	3	C 14 H 23 N 2 O 7	331.1500	8.9	-2.7	76.88	-0.9	4.5	even	ok

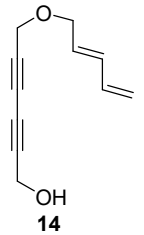
#	m/z	I	I %	Area	Res.
1	107.0866	150	1.0	3	5013
2	109.1028	379	2.5	9	4871
3	126.1285	163	1.1	4	5339
4	158.9642	349	2.3	10	5866
5	183.0650	2182	14.4	69	6161
6	184.0695	201	1.3	7	6083
7	201.0759	3067	20.3	107	6056
8	202.0782	328	2.2	11	6698
9	235.1121	271	1.8	11	6443
10	245.0665	405	2.7	17	6625
11	257.0939	332	2.2	13	7321
12	267.0479	725	4.8	32	6722
13	307.1676	410	2.7	18	7796
14	309.1692	143	0.9	7	6709
15	326.1950	1886	12.5	88	7472
16	327.1994	418	2.8	20	7652
17	329.1445	1020	6.7	54	6955
18	330.1479	232	1.5	12	7050
19	331.1509	15140	100.0	705	7652
20	332.1542	2628	17.4	127	7599
21	333.1544	456	3.0	22	8097
22	347.1236	231	1.5	11	7871
23	368.1677	223	1.5	11	8246
24	373.1246	6511	43.0	334	7925
25	374.1280	1299	8.6	67	7913
26	375.1360	553	3.7	29	8021
27	397.1456	164	1.1	10	7513
28	430.9123	469	3.1	25	8505
29	439.1189	187	1.2	12	8040



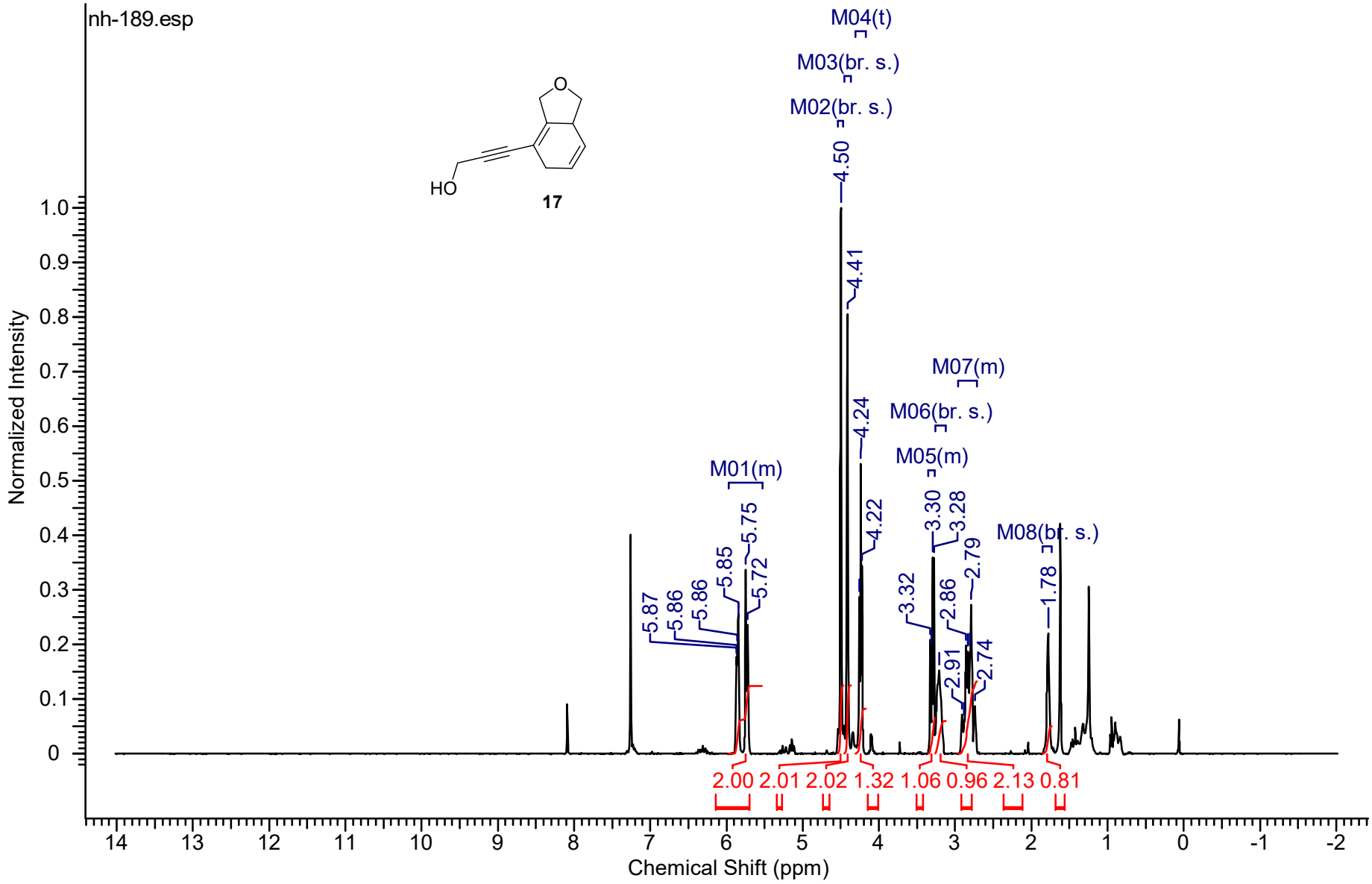
39

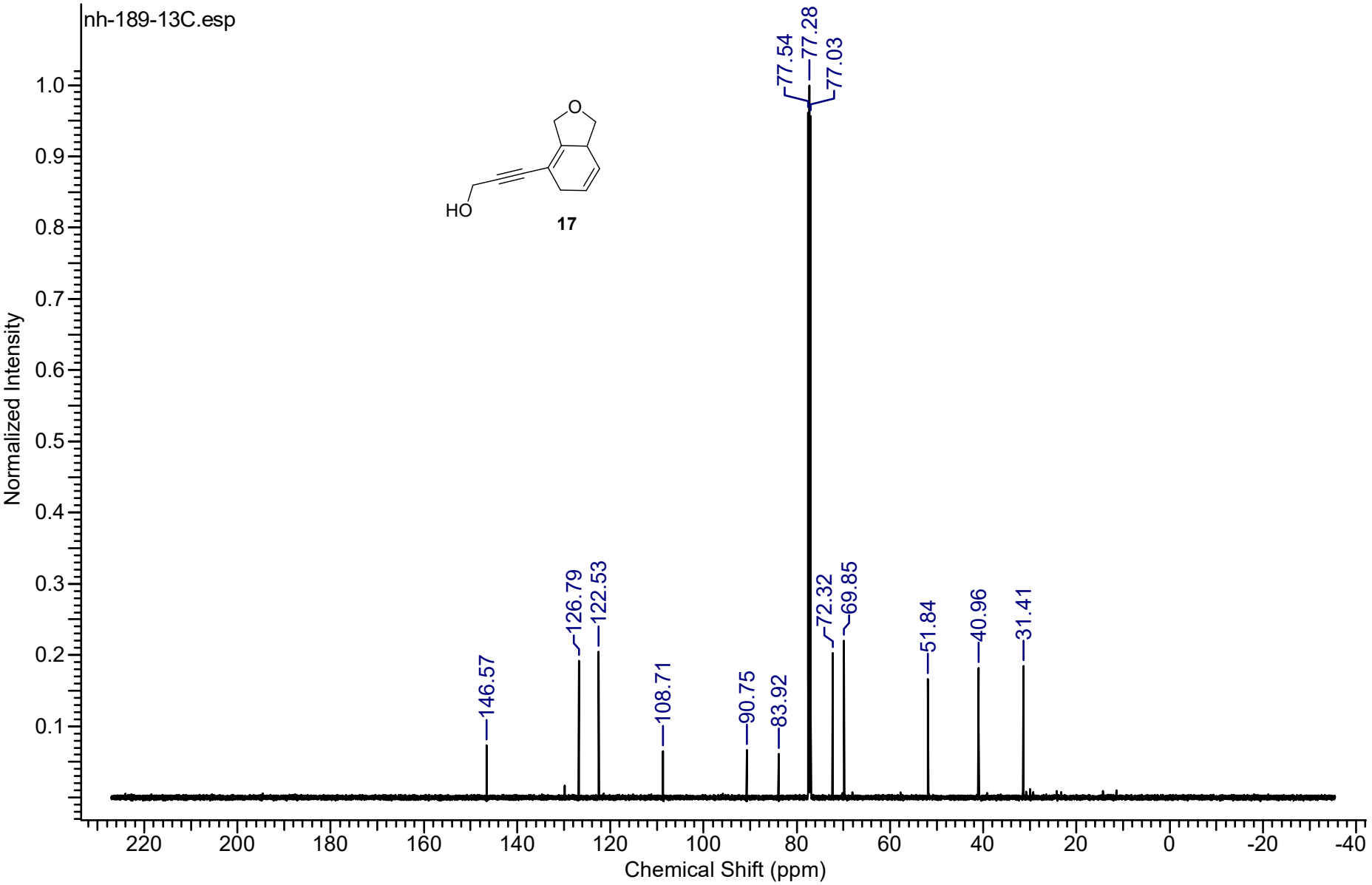

nh-182-2
O
OH
14
M06(d)
M04(d)
M05(s)
4.24
M01(m)
M03(m)
M02(m)
7.27
6.39
6.36
6.33
6.32
6.28
5.77
5.28
5.22
5.16
5.12
4.51
4.37
4.35
4.12
4.10
1.80
1.64
1.60
1.26
2.00
1.09
2.46
1.56
2.26
2.07
Normalized Intensity
Chemical Shift (ppm)

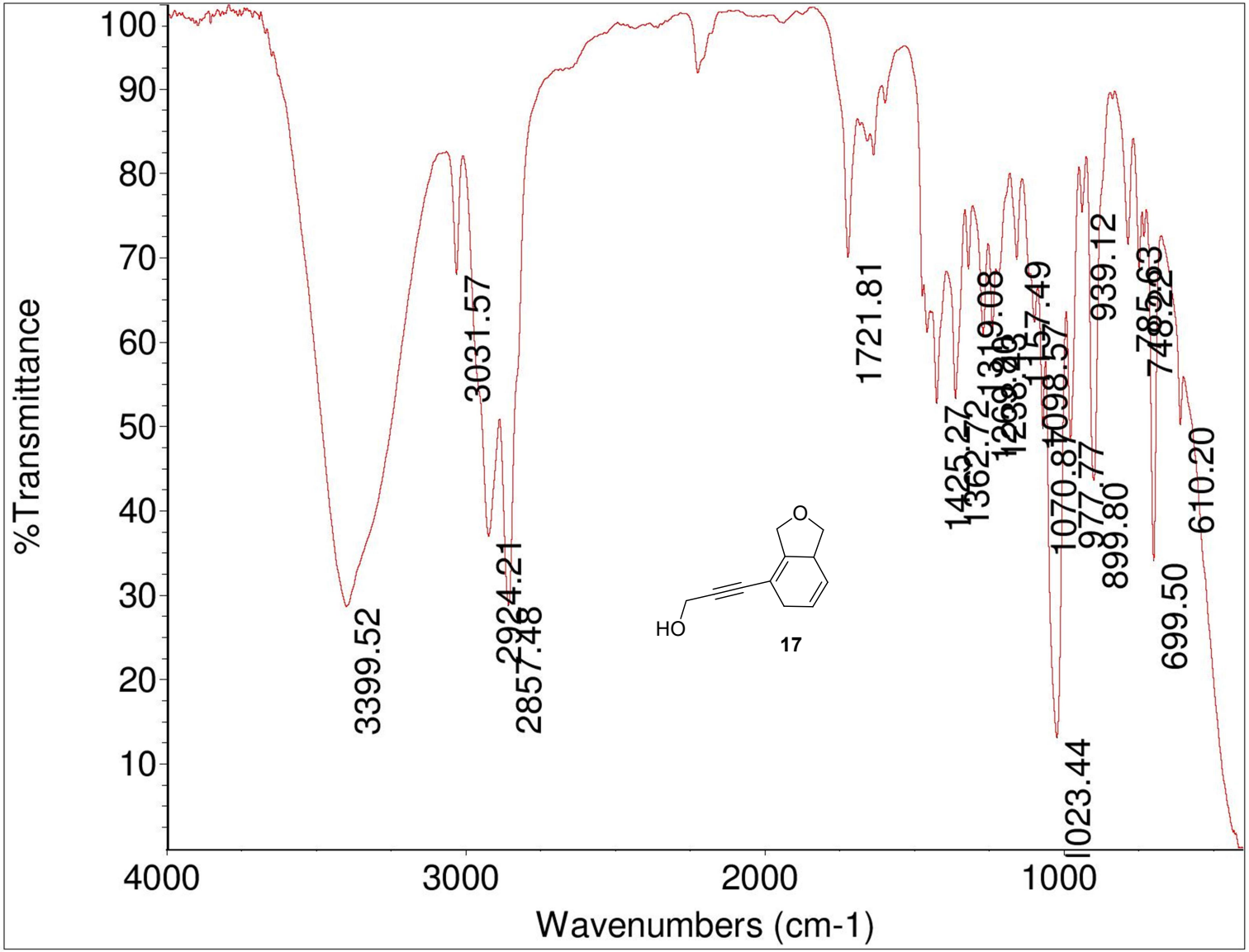

%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3405.98
2920.68
2851.16
1688.74
1462.73
1364.89
1263.44
1048.32
903.91
732.51
731.12

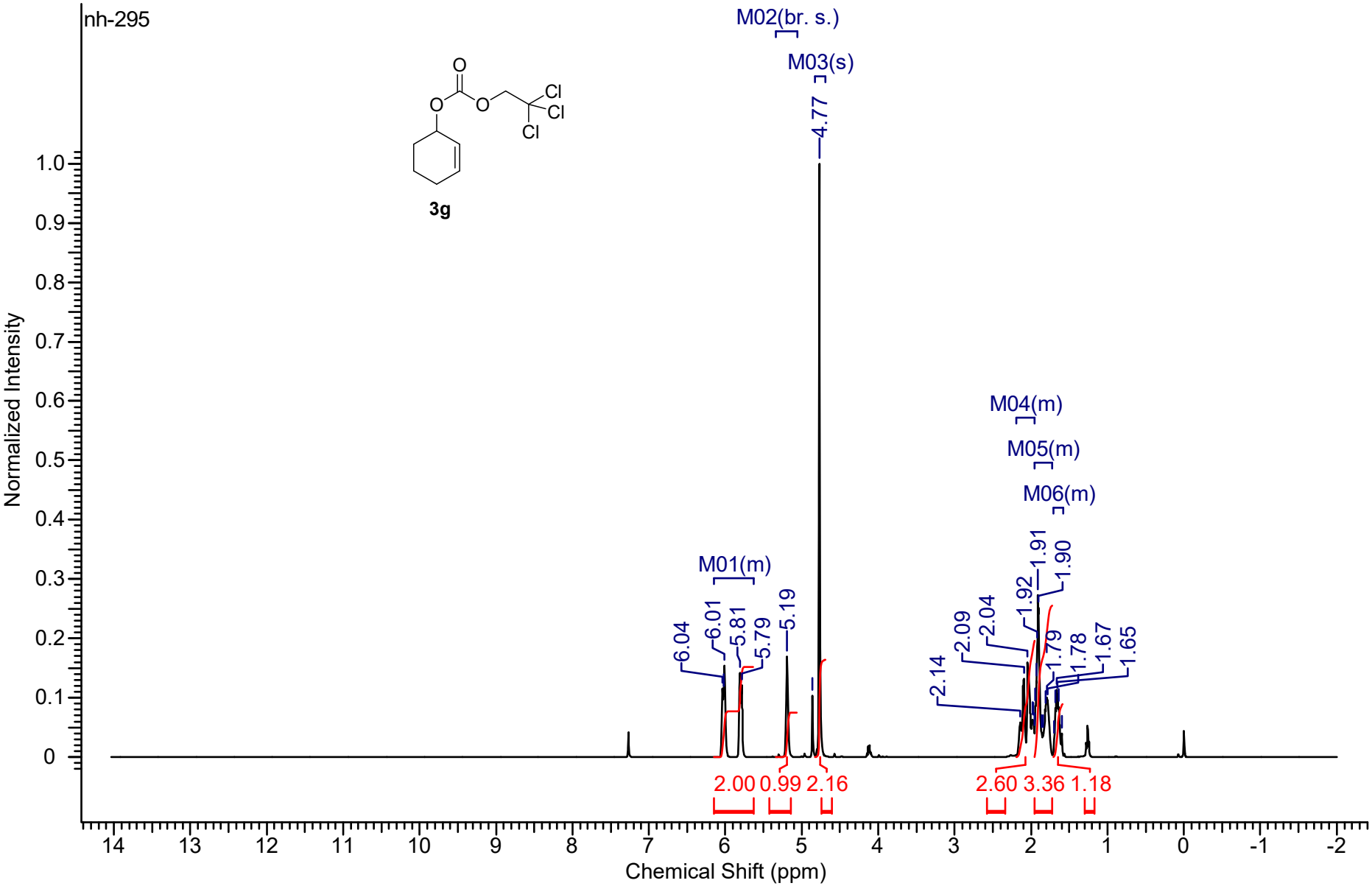

O
OH

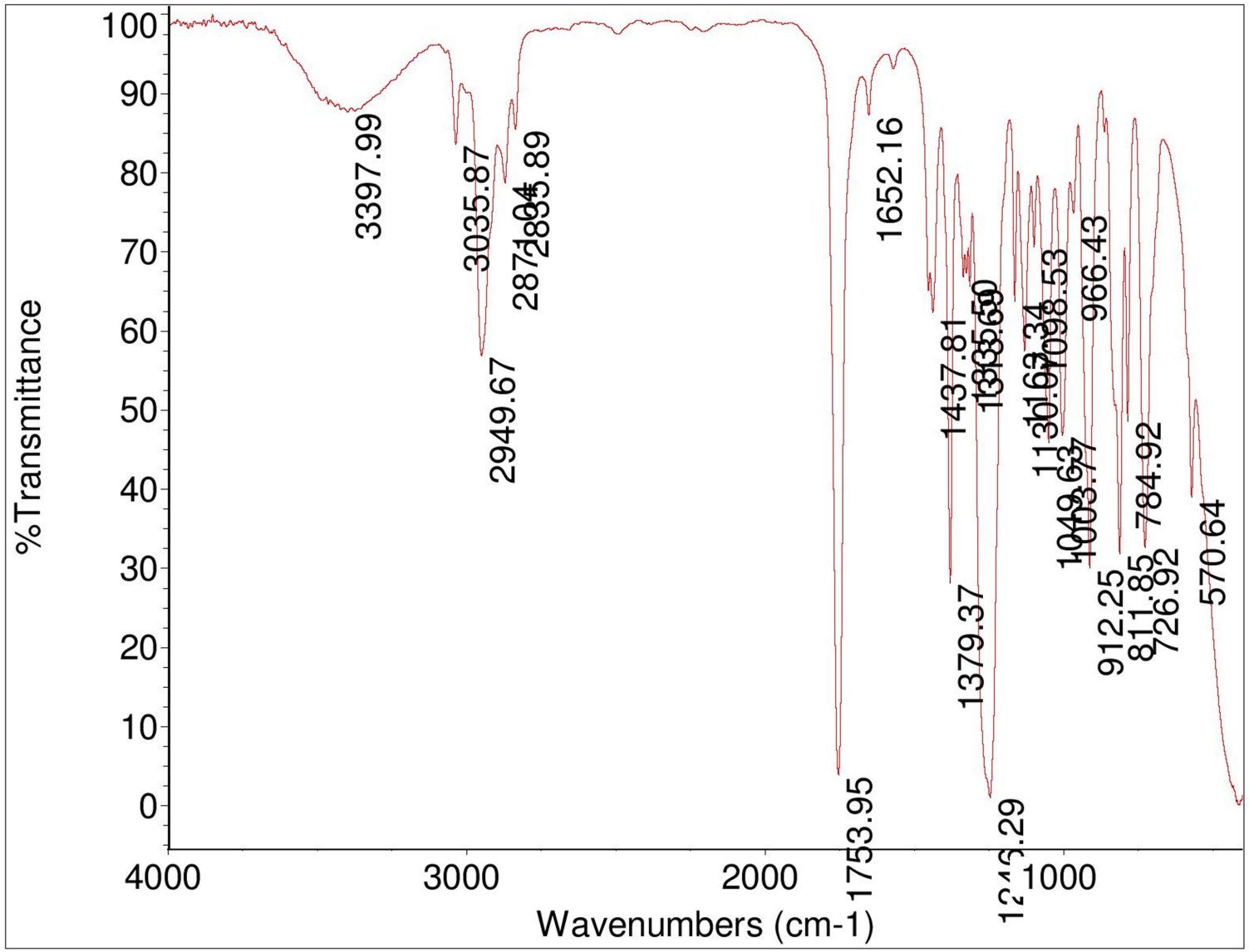
14

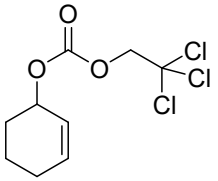

nh-189.esp
HO
O
17
M04(t)
M03(br. s.)
M02(br. s.)
4.50
4.41
M07(m)
M06(br. s.)
4.24
M05(m)
M01(m)
4.22
3.30
3.28
M08(br. s.)
5.87
5.86
5.86
5.85
5.75
5.72
3.32
2.86
2.79
1.78
2.91
2.74
2.00 2.01 2.02 1.32 1.06 0.96 2.13 0.81
Normalized Intensity
Chemical Shift (ppm)


nh-189-13C.esp
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
77.54
77.28
77.03
146.57
126.79
122.53
108.71
90.75
83.92
72.32
69.85
51.84
40.96
31.41
HO
O
17

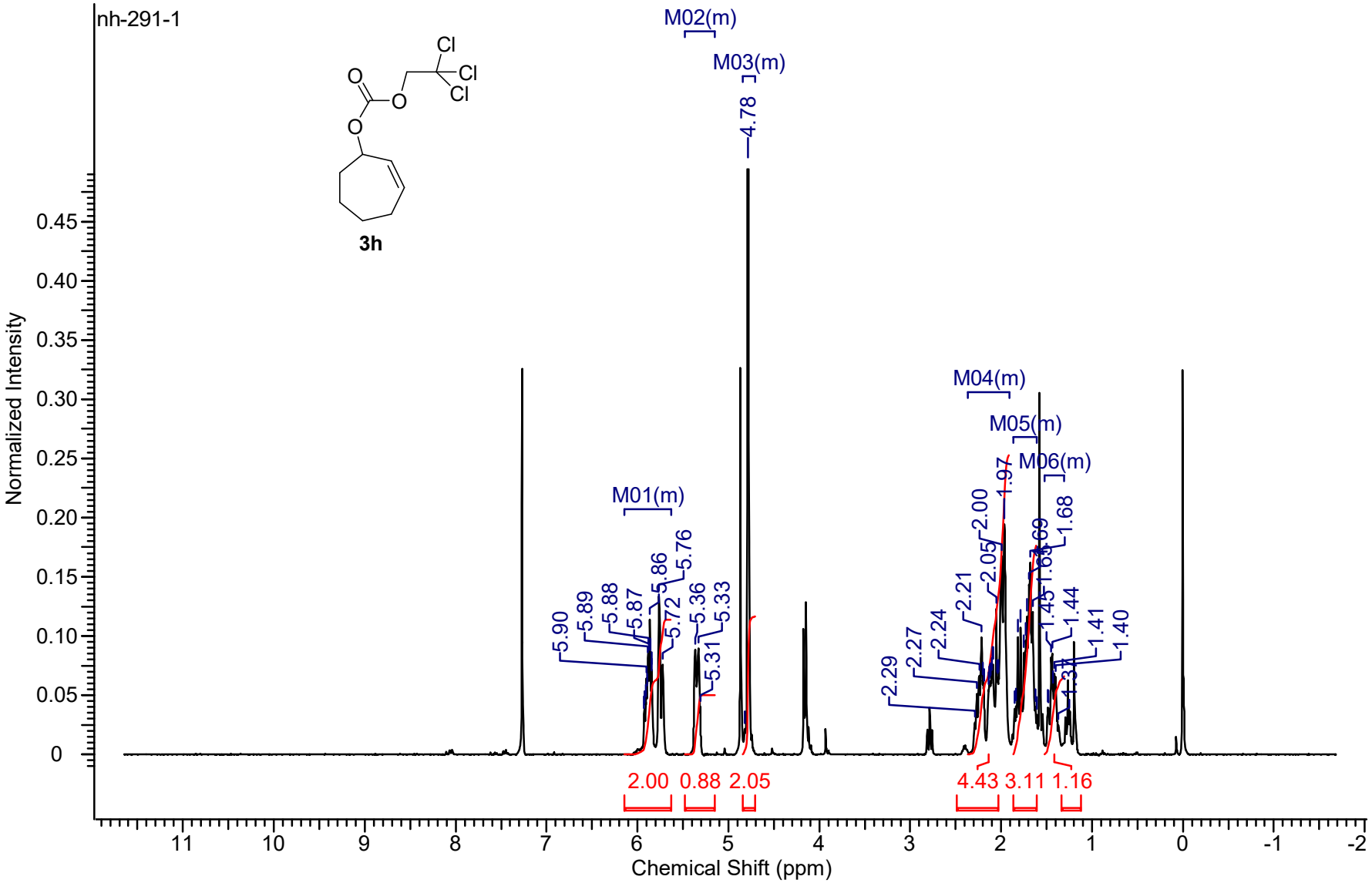

%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3399.52
3031.57
2924.21
2857.48
1721.81
1425.27
1362.72
1319.08
1157.49
1098.57
1070.87
1023.44
977.77
939.12
899.80
785.63
748.22
699.50
610.20
HO
O
17

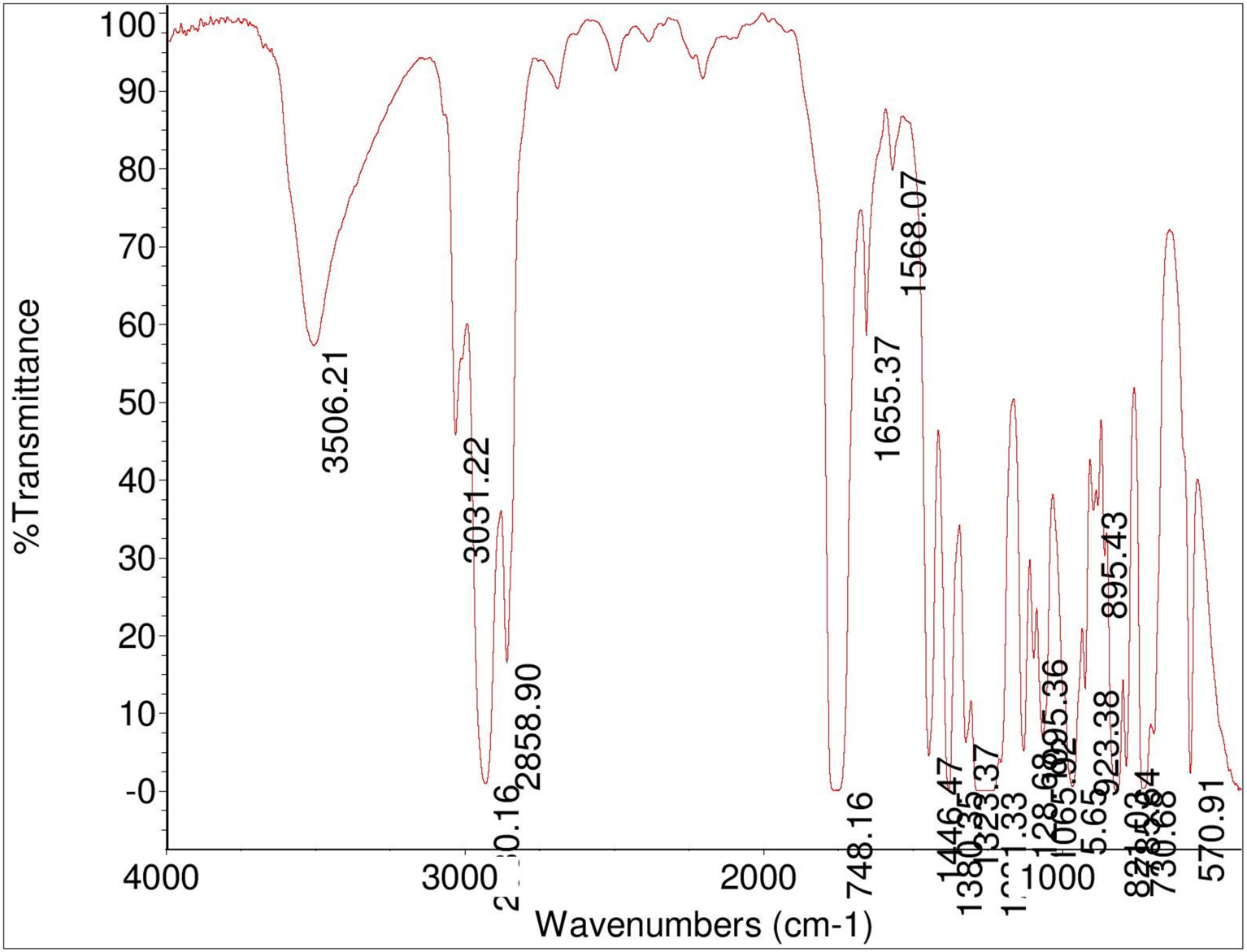

nh-295
M02(br. s.)
M03(s)
4.77
O
O
O
Cl
Cl
Cl
3g
M04(m)
M05(m)
M06(m)
M01(m)
6.04
6.01
5.81
5.79
5.19
2.14
2.09
2.04
1.92
1.91
1.90
1.79
1.78
1.67
1.65
2.00 0.99 2.16
2.60 3.36 1.18
Normalized Intensity
Chemical Shift (ppm)

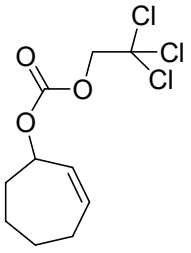

%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
100
90
80
70
60
50
40
30
20
10
0
3397.99
3035.87
2949.67
1753.95
1652.16
1437.81
1379.37
966.43
912.25
811.85
784.92
726.92
570.64


O
O
O
Cl
Cl
Cl

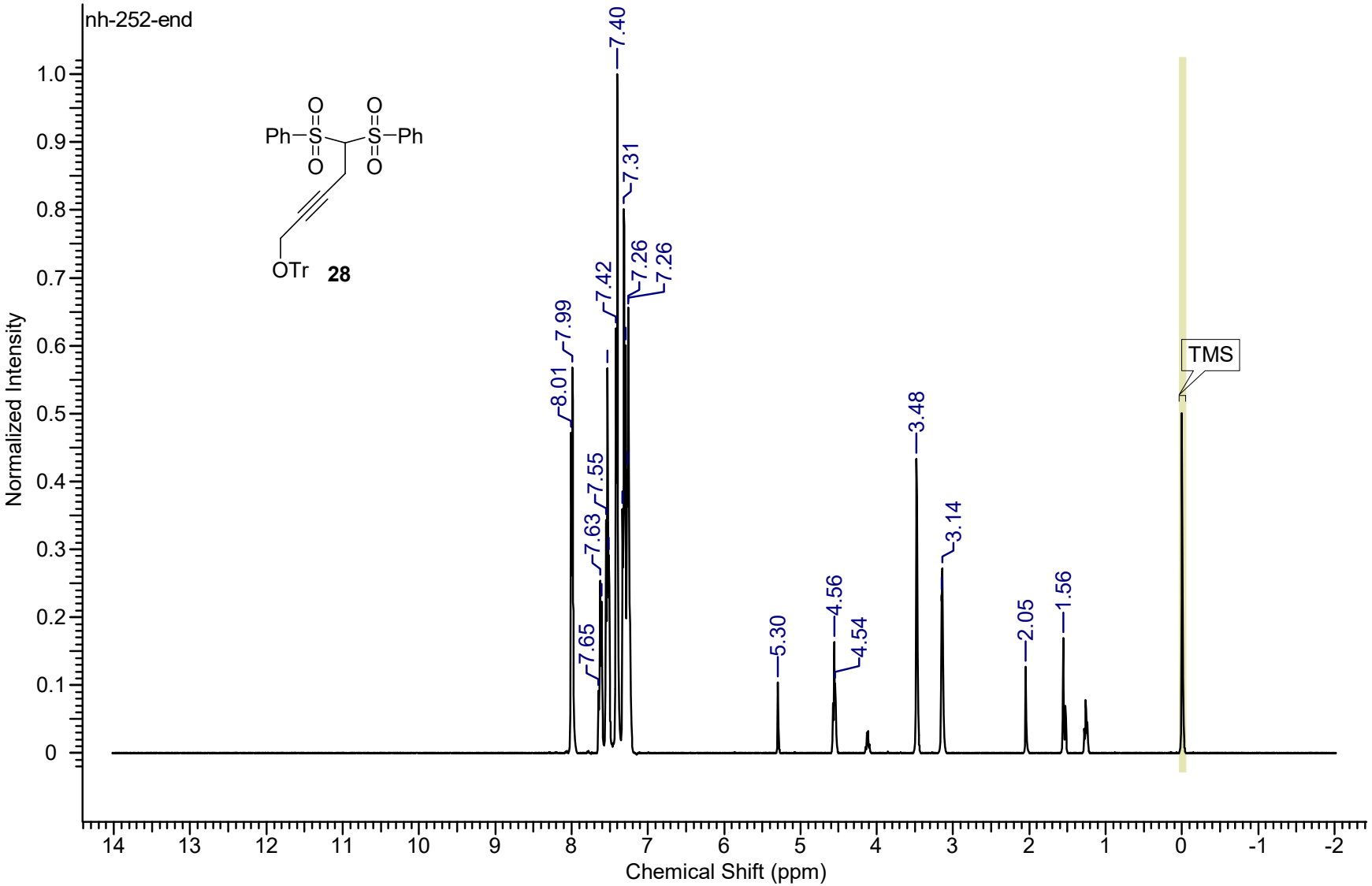
3g


nh-291-1
3h
M01(m)
M02(m)
M03(m)
M04(m)
M05(m)
M06(m)
4.78
5.90
5.89
5.88
5.87
5.86
5.76
5.72
5.36
5.33
5.31
2.29
2.27
2.24
2.21
2.05
2.00
1.97
1.68
1.45
1.44
1.41
1.40
2.00 0.88 2.05
4.43 3.11 1.16
Normalized Intensity
Chemical Shift (ppm)

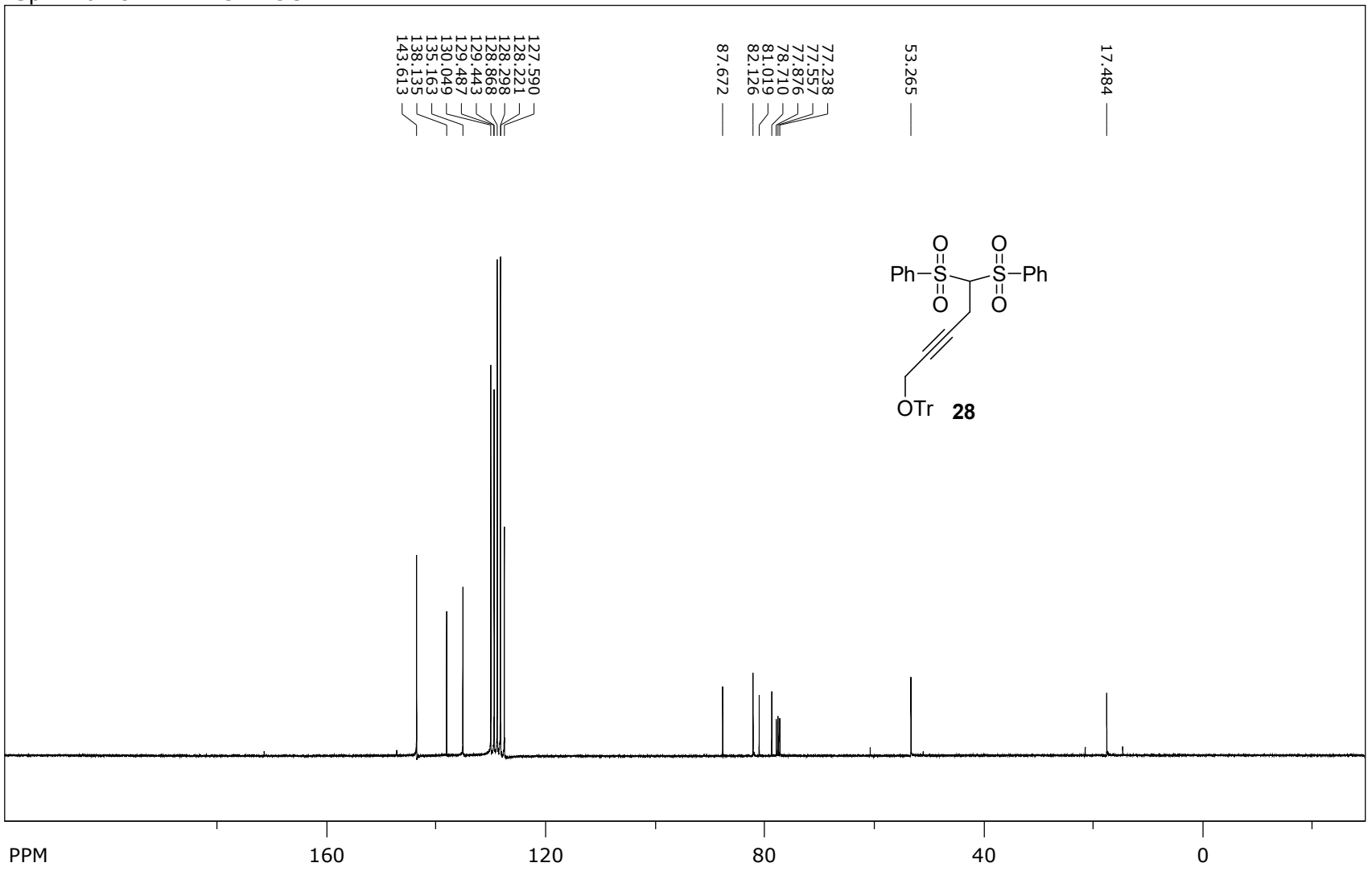

%Transmittance
Wavenumbers (cm-1)
3506.21
3031.22
2858.90
1655.37
1568.07
748.16
895.43
570.91


Cl
Cl
Cl
O
O
O

3h

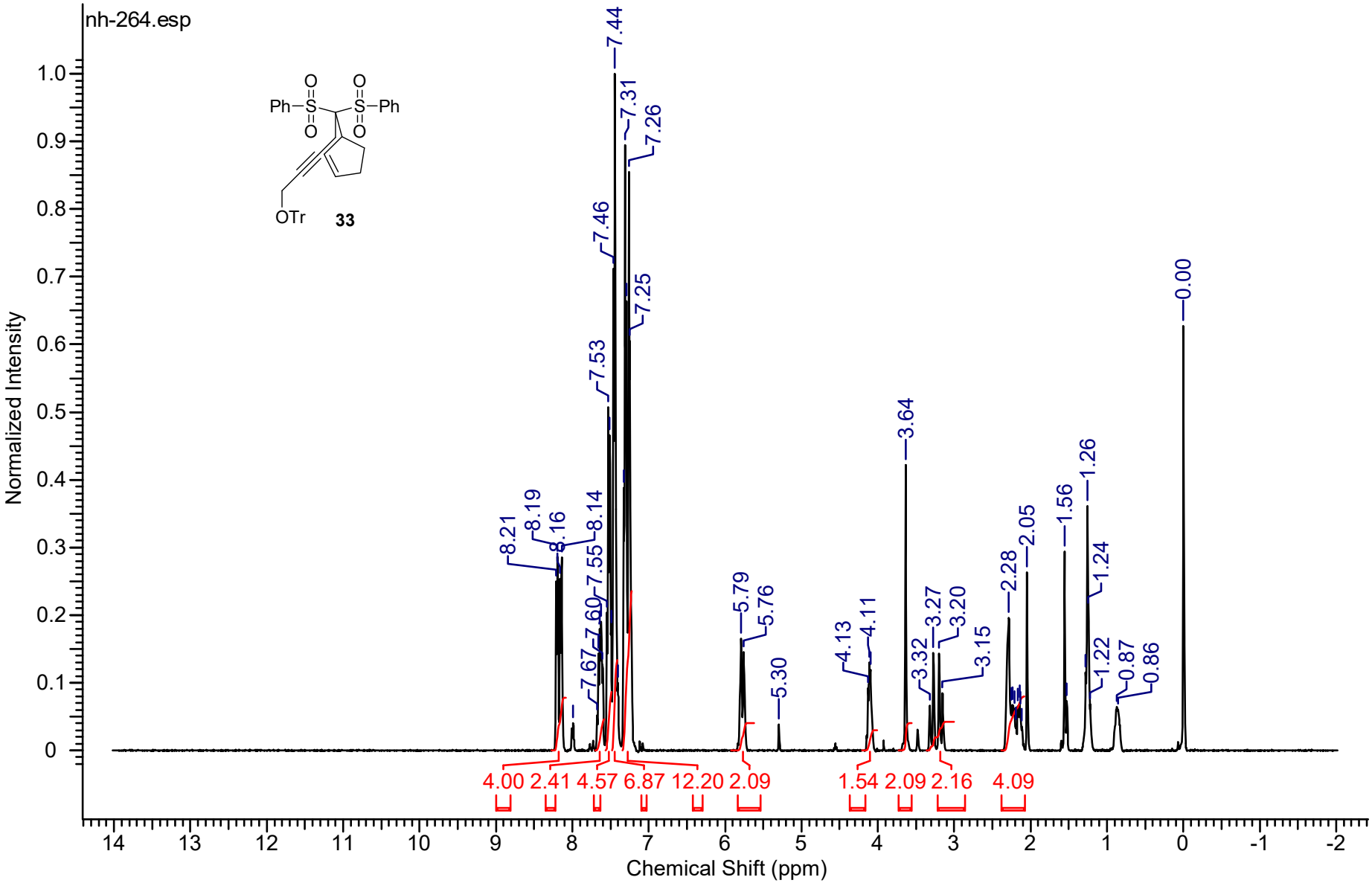

nh-252-end
Ph
S
O
O
S
Ph
OTr
28
7.40
7.31
7.26
7.26
7.42
7.99
8.01
7.55
7.63
7.65
5.30
4.56
4.54
3.48
3.14
2.05
1.56
TMS
Normalized Intensity
Chemical Shift (ppm)

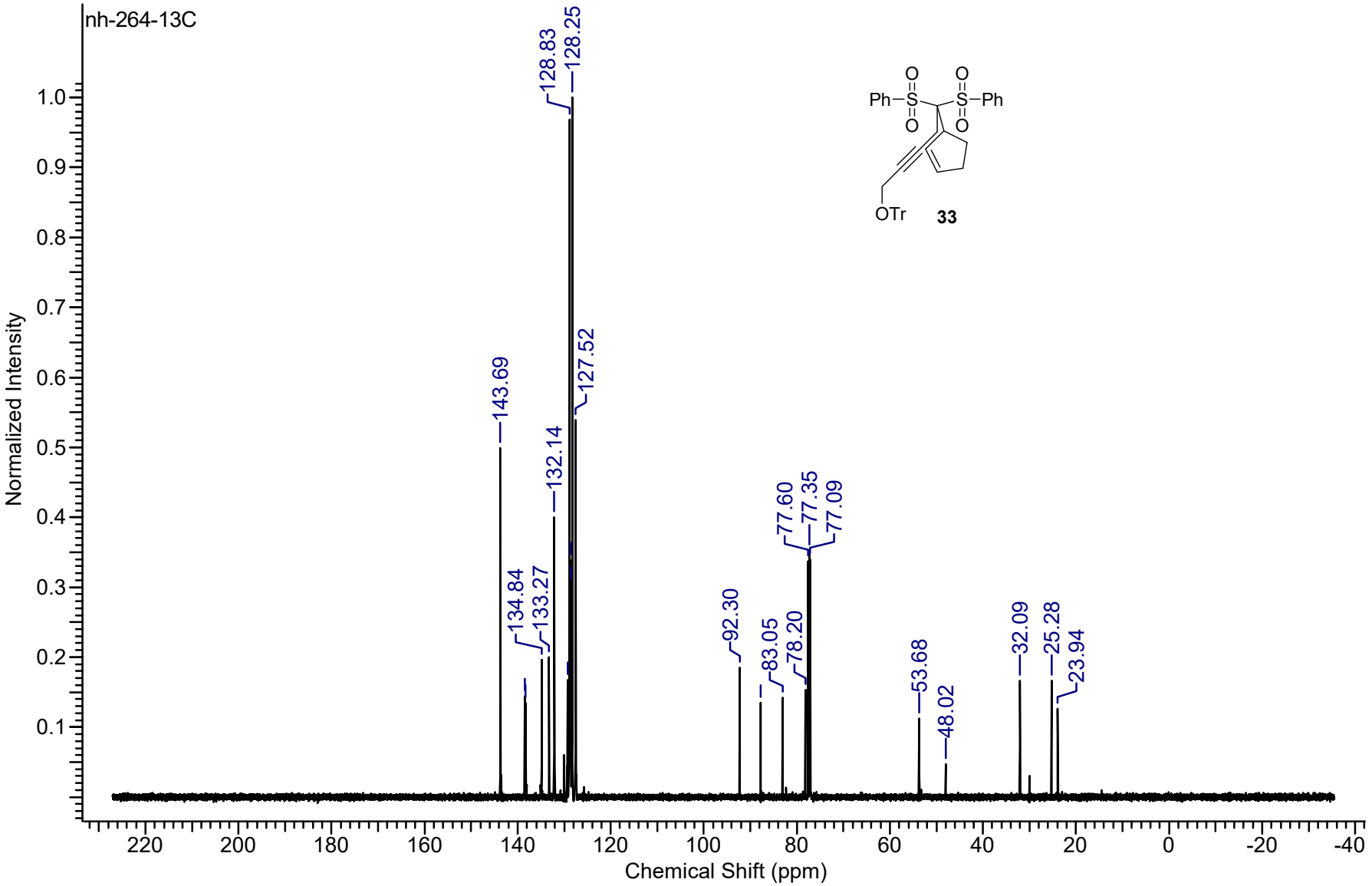
SpinWorks 4: nh-252-13C

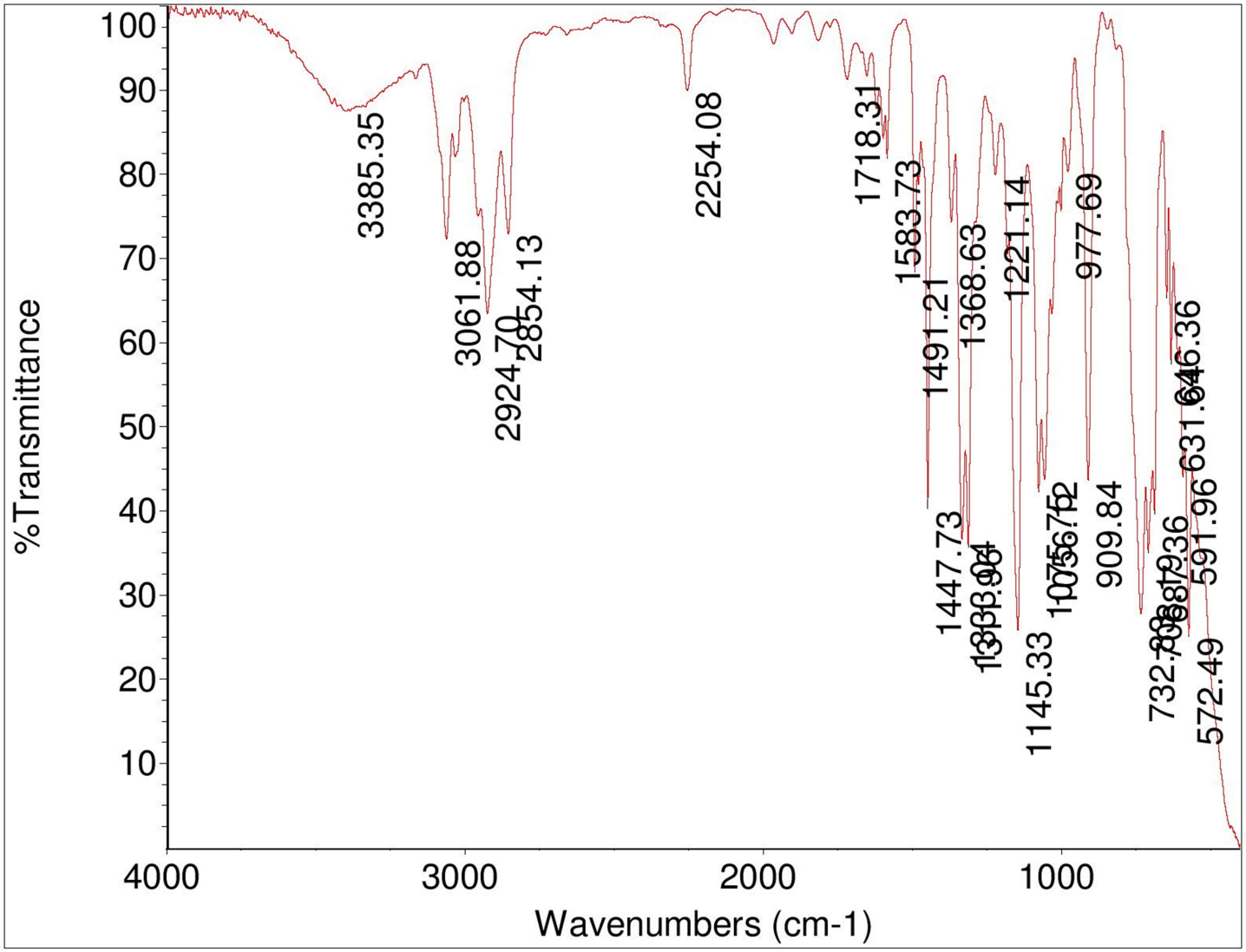


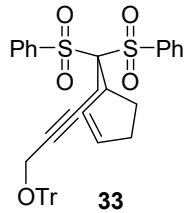
file: ...nhavare\nhavare\nh-252-13C.fid\fid block# 1 expt: "s2pul"
transmitter freq.: 100.617627 MHz
time domain size: 59968 points
width: 25000.00 Hz = 248.4654 ppm = 0.416889 Hz/pt
number of scans: 624

freq. of 0 ppm: 100.608102 MHz
processed size: 65536 complex points
LB: 0.500 GF: 0.0000

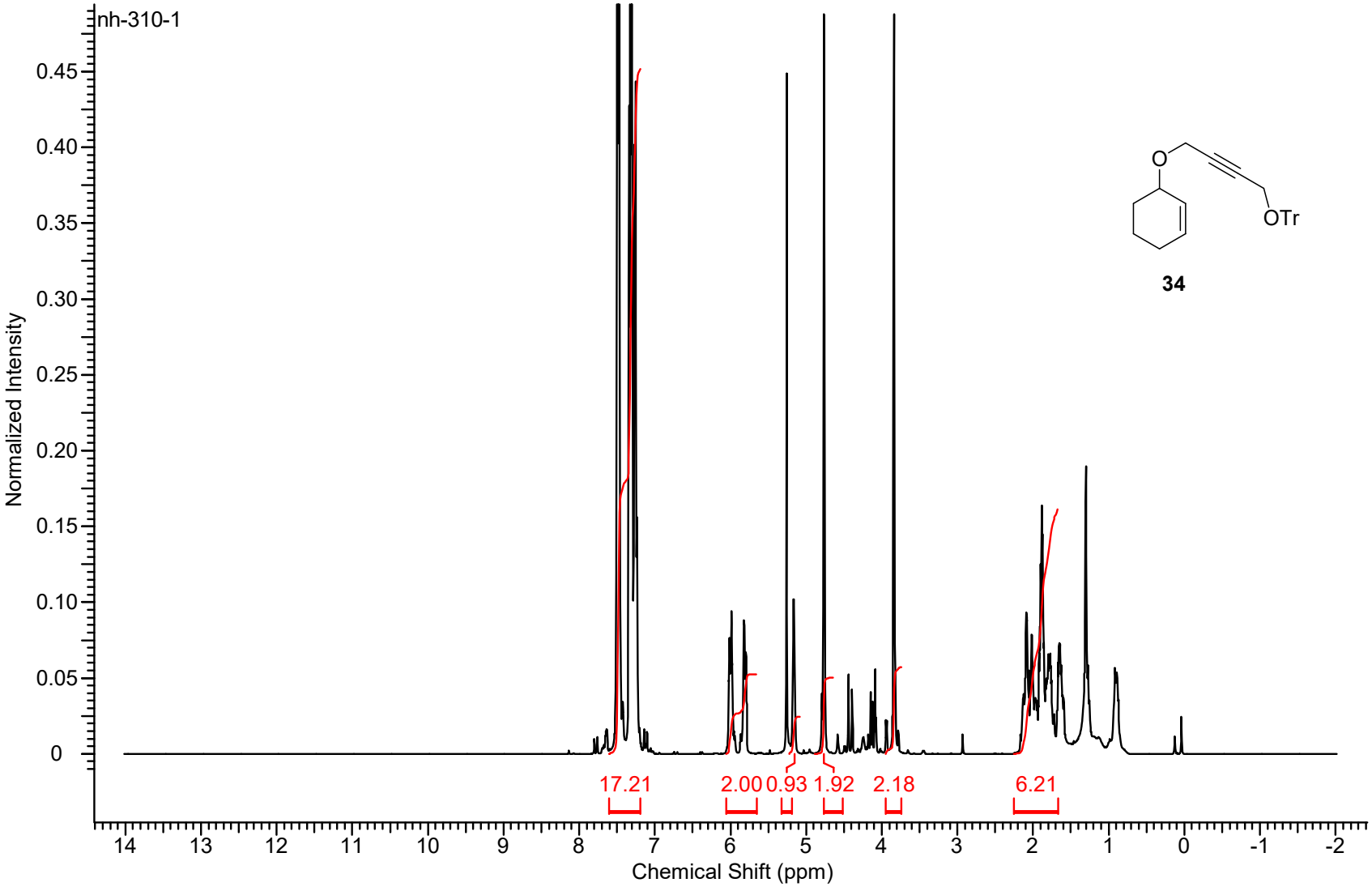

nh-264.esp
Ph
S
O
O
S
Ph
OTr
33
Normalized Intensity
Chemical Shift (ppm)
8.21
8.19
8.16
8.14
7.67
7.60
7.55
7.53
7.46
7.44
7.31
7.26
7.25
5.79
5.76
5.30
4.13
4.11
3.64
3.32
3.27
3.20
3.15
2.28
2.05
1.56
1.26
1.24
1.22
0.87
0.86
0.00
4.00 2.41 4.57 6.87 12.20 2.09
1.54 2.09 2.16 4.09

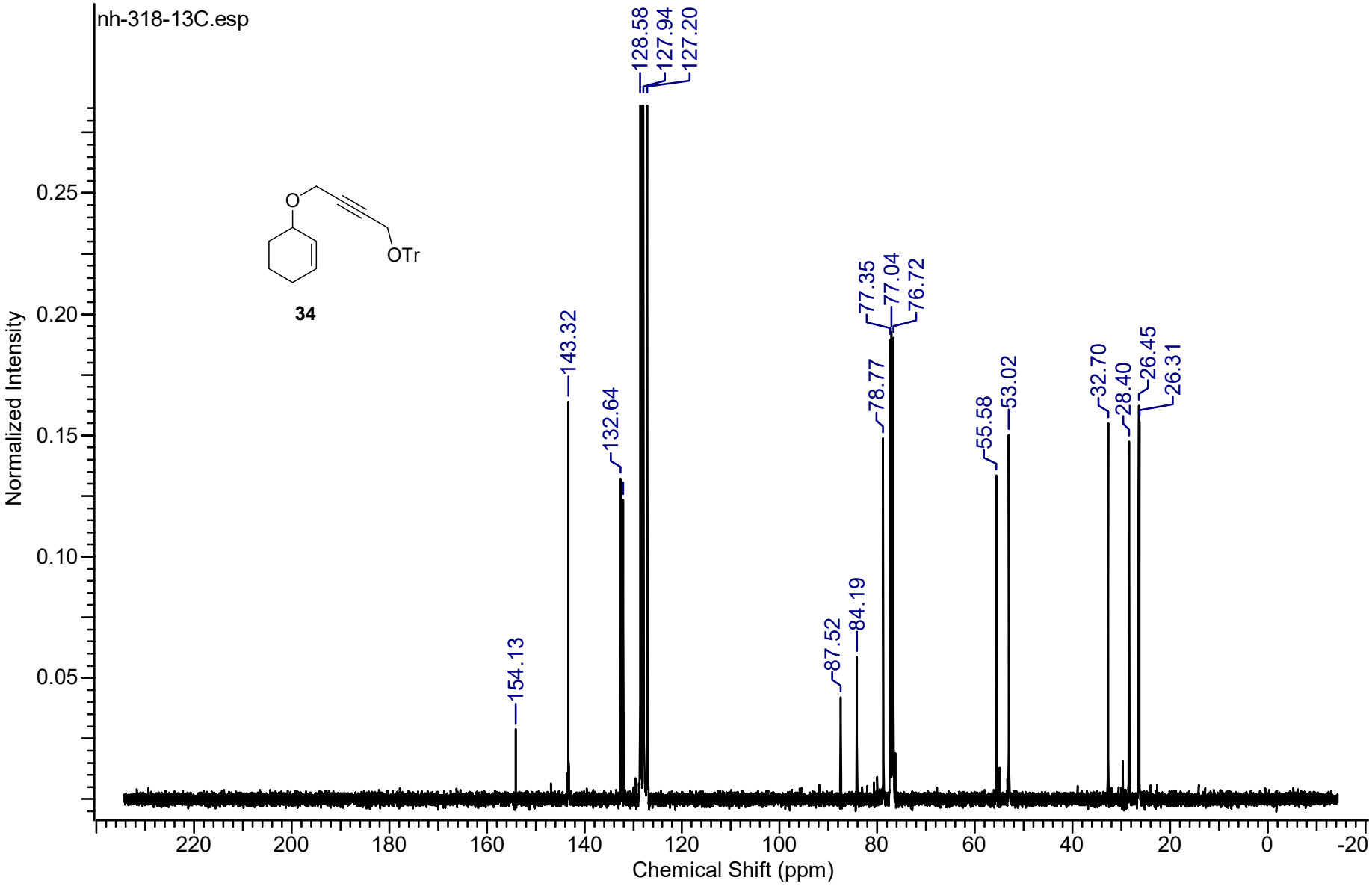

nh-264-13C
128.83
128.25
143.69
127.52
132.14
134.84
133.27
77.60
77.35
77.09
92.30
83.05
78.20
53.68
48.02
32.09
25.28
23.94
Normalized Intensity
Chemical Shift (ppm)
Ph
S
O
OTr
33

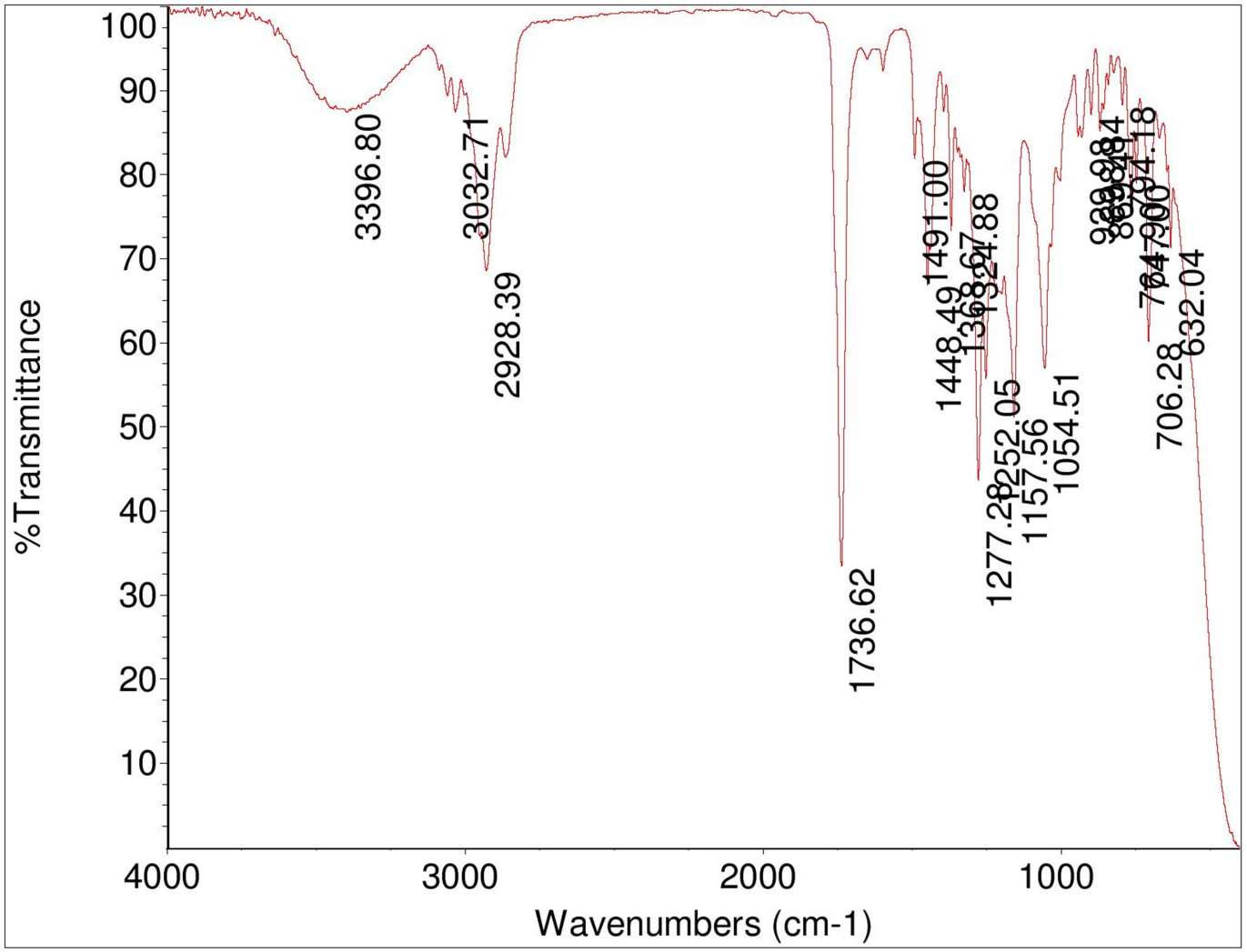

%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
100
90
80
70
60
50
40
30
20
10
3385.35
3061.88
2924.70
2854.13
2254.08
1718.31
1583.73
1491.21
1447.73
1368.63
1221.14
1145.33
977.69
909.84
732.70
631.64
591.96
572.49

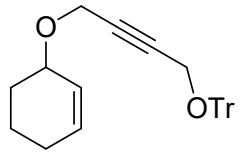

Ph
S
O
O
S
Ph
OTr

33

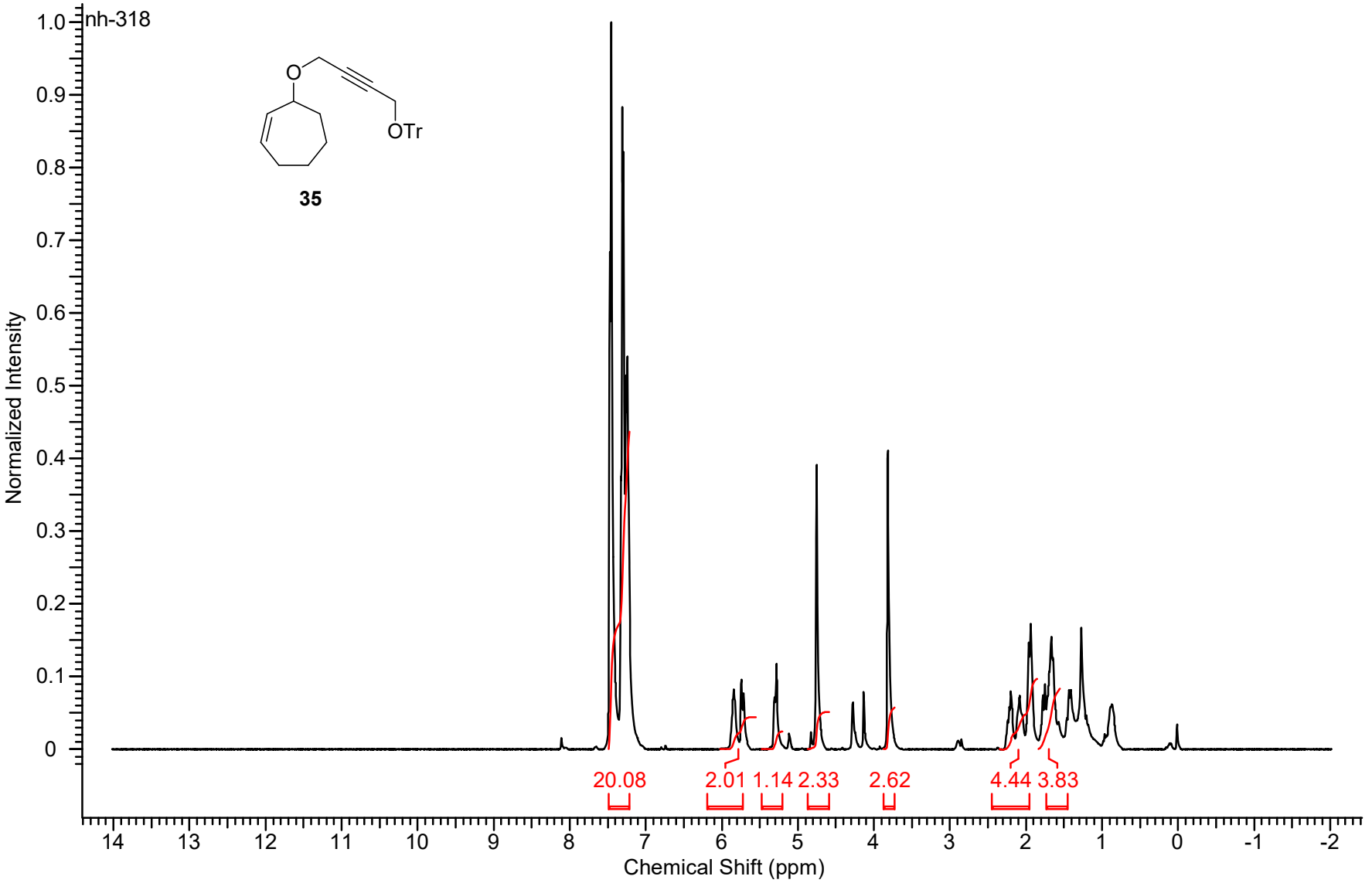

nh-310-1
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
17.21
2.00
0.93
1.92
2.18
6.21
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)
O
OTr
34

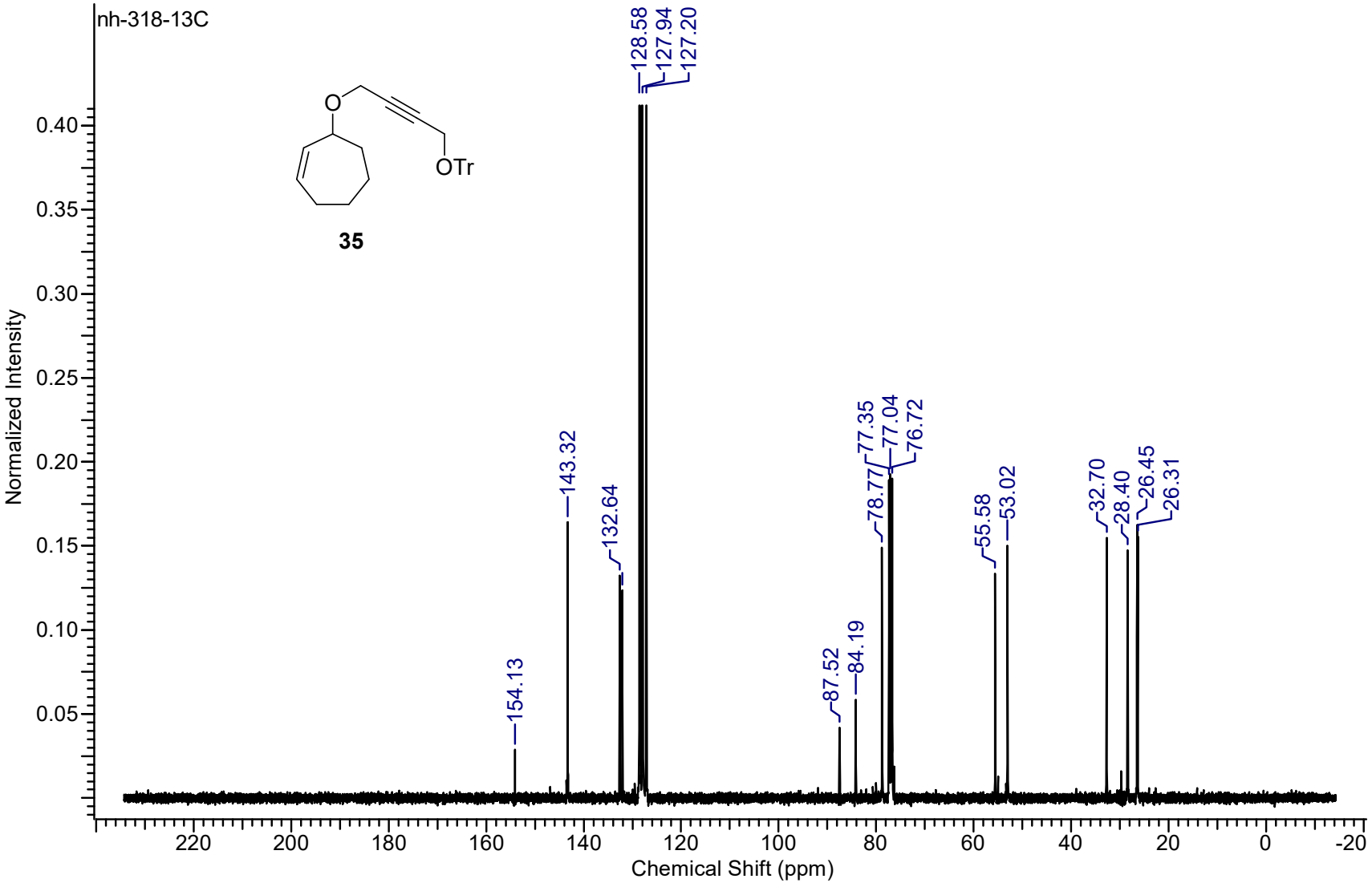

nh-318-13C.esp
128.58
127.94
127.20
77.35
77.04
76.72
143.32
132.64
78.77
55.58
53.02
32.70
28.40
26.45
26.31
154.13
87.52
84.19
O
OTr
34
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

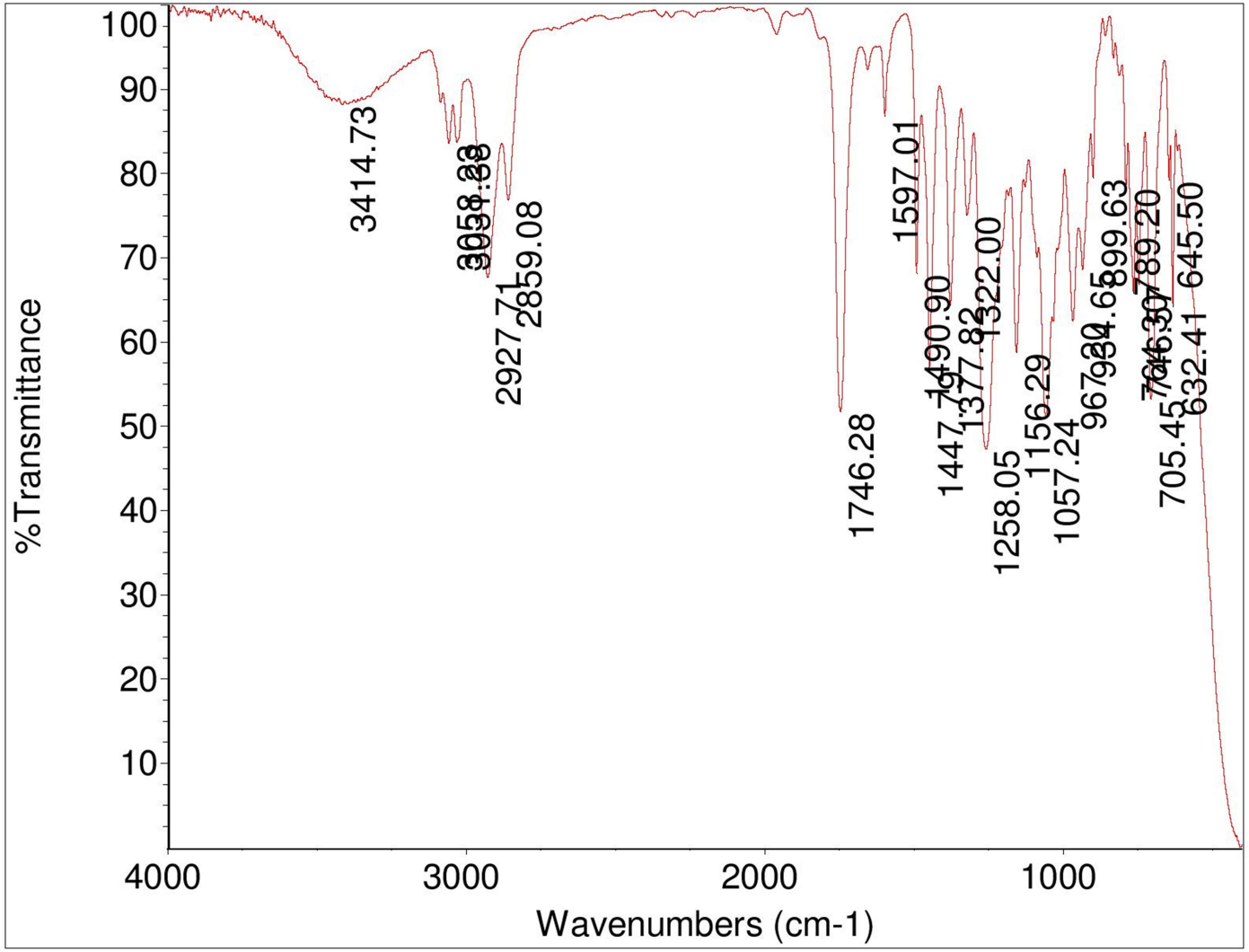

%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3000
2000
1000
Wavenumbers (cm-1)
3396.80
3032.71
2928.39
1736.62
1491.00
1448.49
1368.67
1324.88
1277.28
1252.05
1157.56
1054.51
706.28
632.04

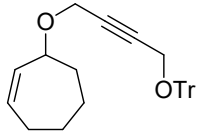

O
OTr

34


nh-318
O
OTr
35
Normalized Intensity
Chemical Shift (ppm)
20.08
2.01
1.14
2.33
2.62
4.44
3.83

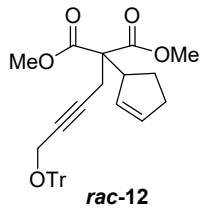

nh-318-13C
O
OTr
35
128.58
127.94
127.20
143.32
132.64
154.13
87.52
84.19
77.35
77.04
76.72
78.77
55.58
53.02
32.70
28.40
26.45
26.31
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
100
90
80
70
60
50
40
30
20
10
3414.73
2927.71
2859.08
1746.28
1597.01
1490.90
1447.79
1377.82
1322.00
1258.05
1156.29
1057.24
967.30
899.63
789.20
705.45
645.50
632.41


O
OTr

35

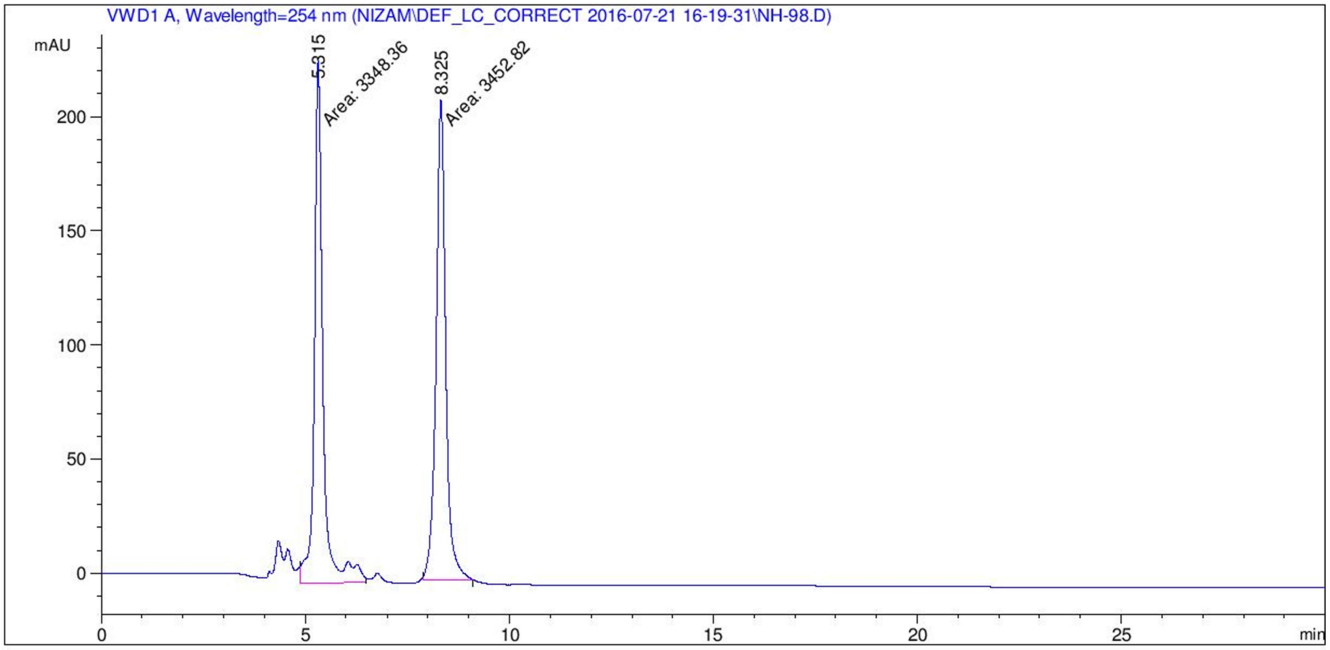
Table 2**, Entry 1**



***rac*-12**

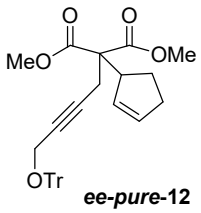
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-07-21 16-19-31\NH-98.D
Sample Name: NH-98

```
=====================================================================
Acq. Operator   : NIZAM                          Seq. Line :   2
Acq. Instrument : Instrument 1 Classic           Location : Vial 11
Injection Date  : 7/21/2016 4:39:21 PM                Inj :   1
                                                 Inj Volume : 5.0 µl
Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-07-21 16-19-31\IA, 90-10 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 10/15/2012 4:26:35 PM by Fred
Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 5/23/2015 5:47:14 PM by gnanam
Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```



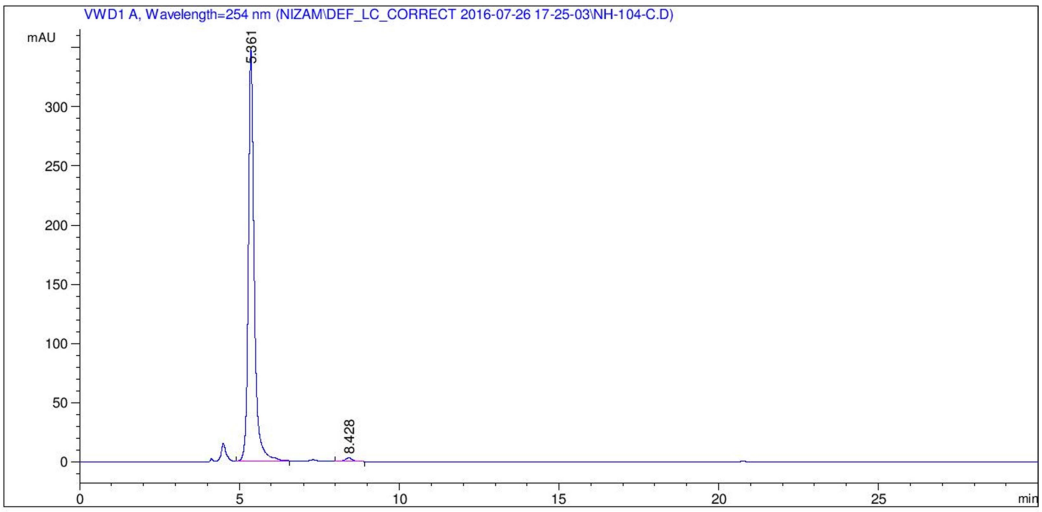

```
=====================================================================
                        Area Percent Report
=====================================================================

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


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.315 MM    0.2439 3348.35986  228.79910  49.2320
   2   8.325 MM    0.2735 3452.82373  210.39929  50.7680
```

Table 2, Entry 3



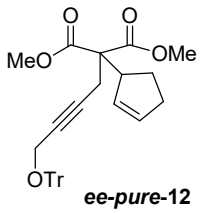
***ee-pure*-12**

```
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-07-26 17-25-03\NH-104-C.D
Sample Name: NH-104-C

    ======================================================================
    Acq. Operator   : NIZAM                        Seq. Line :   6
    Acq. Instrument : Instrument 1 Classic          Location : Vial 21
    Injection Date  : 7/26/2016 7:48:09 PM               Inj :   1
                                                  Inj Volume : 5.0 µl
    Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-07-26 17-25-03\IA, 90-10 HEPT-IPA,
                      0,8 ML-MIN,254NM,30M.M
    Last changed    : 10/15/2012 4:26:35 PM by Fred
    Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                      0,8 ML-MIN,254NM,30M.M
    Last changed    : 5/23/2015 5:47:14 PM by gnanam
    Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```




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

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


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1   5.361 BB    0.1888 4451.47021  347.36212  98.8490
       2   8.428 BB    0.2423   51.83323    3.13620   1.1510

Instrument 1 Classic 1/23/2017 3:31:58 PM MARIUS                    Page   1 of 2
```

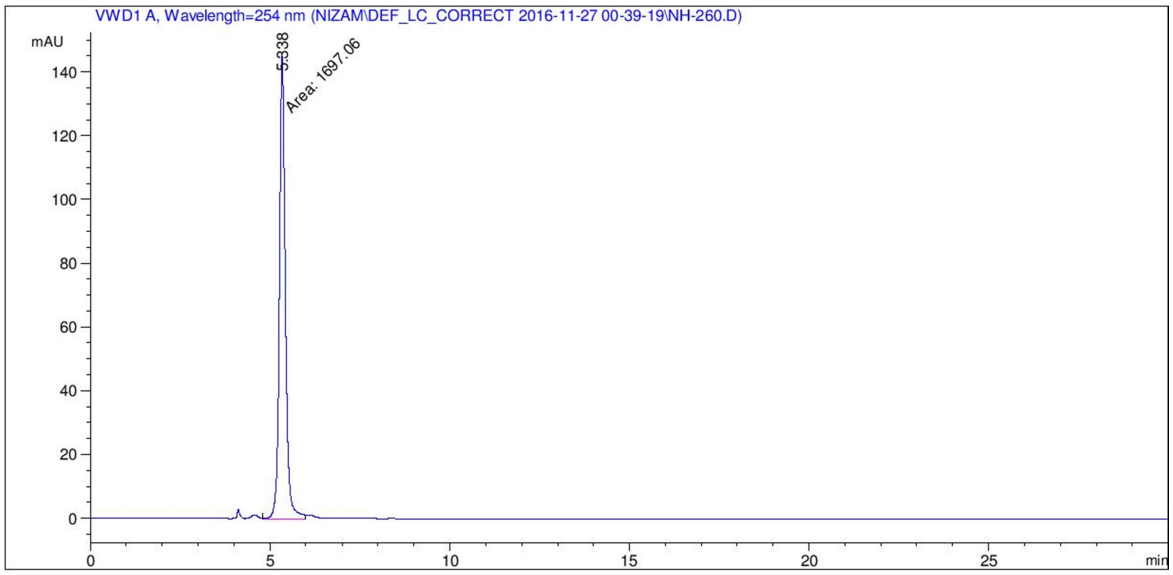
Table 2, Entry 4: Results using ligand (*S,S,S*)-**9**



***ee-pure*-12**

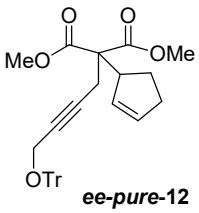
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-11-27 00-39-19\NH-260.D
Sample Name: NH-260

```
==================================================================
Acq. Operator   : NIZAM                          Seq. Line :  20
Acq. Instrument : Instrument 1 Classic           Location : Vial 21
Injection Date  : 11/27/2016 9:30:21 AM               Inj :   1
                                                 Inj Volume : 5.0 µl
Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-11-27 00-39-19\IA, 90-10 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 10/15/2012 4:26:35 PM by Fred
Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 5/23/2015 5:47:14 PM by gnanam
Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```




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

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


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.338 MM    0.1946 1697.05640  145.37408 100.0000
```

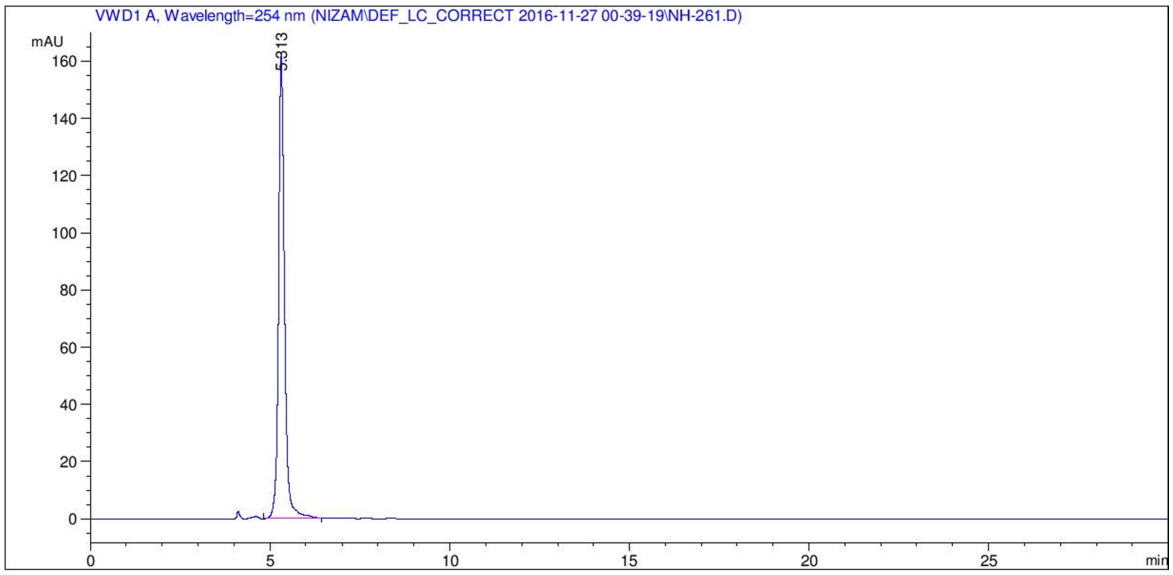
Table 2, Entry 2: Results using ligand (*S,R,R*)-**10**



***ee-pure*-12**

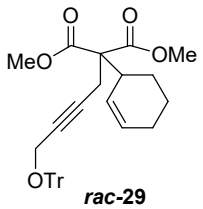
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-11-27 00-39-19\NH-261.D
Sample Name: NH-261

```
==================================================================
Acq. Operator   : NIZAM                          Seq. Line :  21
Acq. Instrument : Instrument 1 Classic            Location : Vial 31
Injection Date  : 11/27/2016 10:01:58 AM               Inj :   1
                                                 Inj Volume : 5.0 µl
Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-11-27 00-39-19\IA, 90-10 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 10/15/2012 4:26:35 PM by Fred
Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 5/23/2015 5:47:14 PM by gnanam
Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```




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

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


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.313 VB    0.1738 1886.14941  161.88745 100.0000
```

Table 2, Entry 5



***rac*-29**

```
Title       :
Run File    : c:\star\data\nizam\nh-101-b-hpt-ipa-99-1-254  nm 0.8 ml- ad.run
Method File : c:\star\data\nizam\nh-101-b-hpt-ipa-99-1-254  nm 0.8 ml- ad-1.mth
Sample ID   : Default Sample

Injection Date: 7/27/2016 4:50 PM    Calculation Date: 12/23/2016 3:28 PM

Operator    : Operator              Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFý HÚp"   Bus Address  : 80
Instrument : Instrument #1          Sample Rate  : 50.00 Hz
Channel    : 1 = 1                  Run Time     : 60.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.33 cm/min   Attenuation = 93          Zero Offset = 26%
Start Time  =    0.000   min    End Time    = 60.000  min   Min / Tick  = 1.00
```

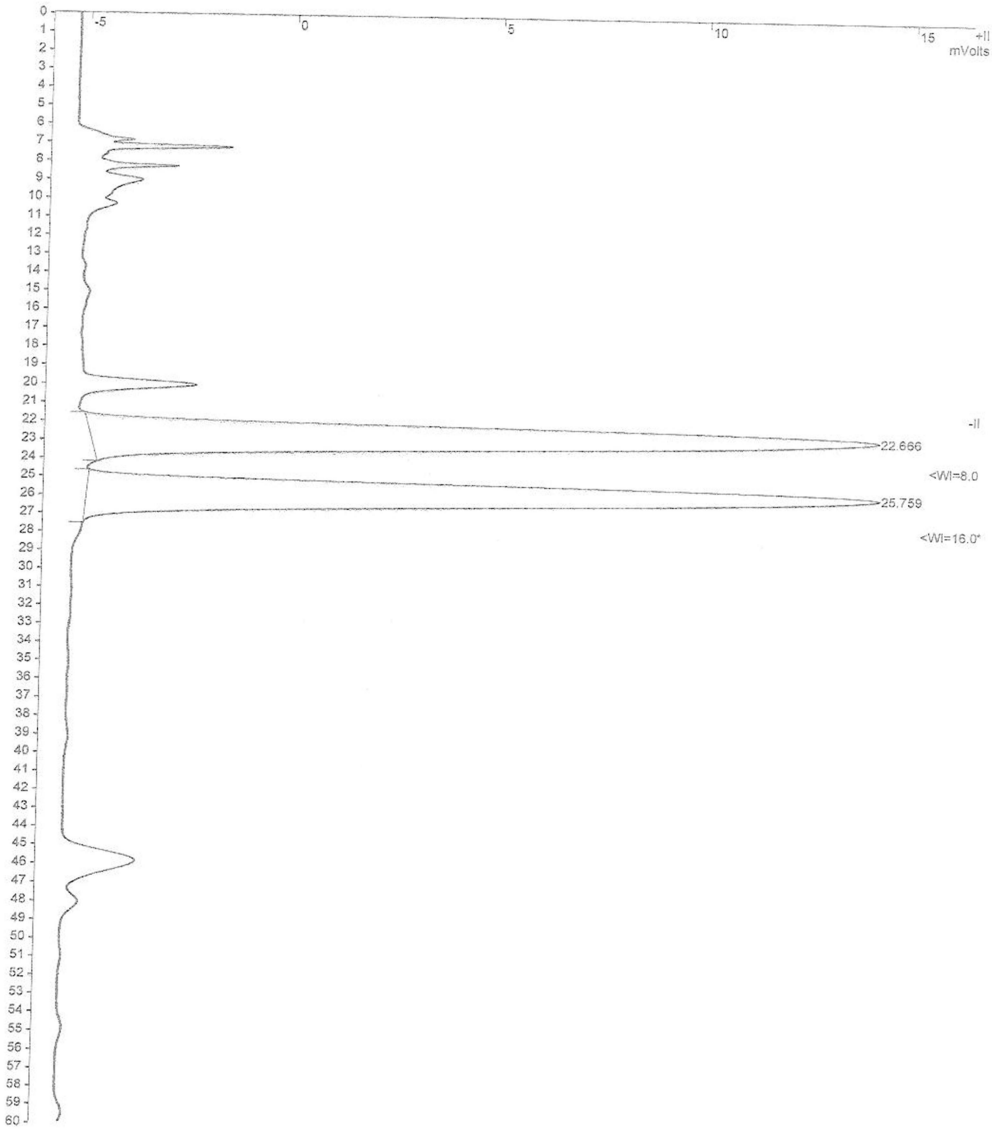
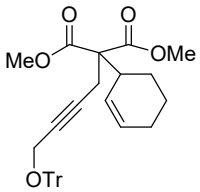


Table 2, Entry 6



***enantioenriched*-29**

```
Title       :
Run File    : c:\star\data\nizam\nh-112-hpt-ipa-99-1-254  nm 0.8 ml- ad.run
Method File : c:\star\data\nizam\nh-112-hpt-ipa-99-1-254  nm 0.8 ml- ad-1.mth
Sample ID   : Default Sample

Injection Date: 8/6/2016 8:19 PM     Calculation Date: 8/6/2016 9:19 PM

Operator    : Operator               Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFÿ HÚþ"    Bus Address  : 80
Instrument : Instrument #1           Sample Rate  : 50.00 Hz
Channel    : 1 = 1                   Run Time     : 58.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.34 cm/min   Attenuation = 144          Zero Offset = 9%
Start Time  =    0.000   min    End Time    = 58.000  min   Min / Tick  = 1.00
```

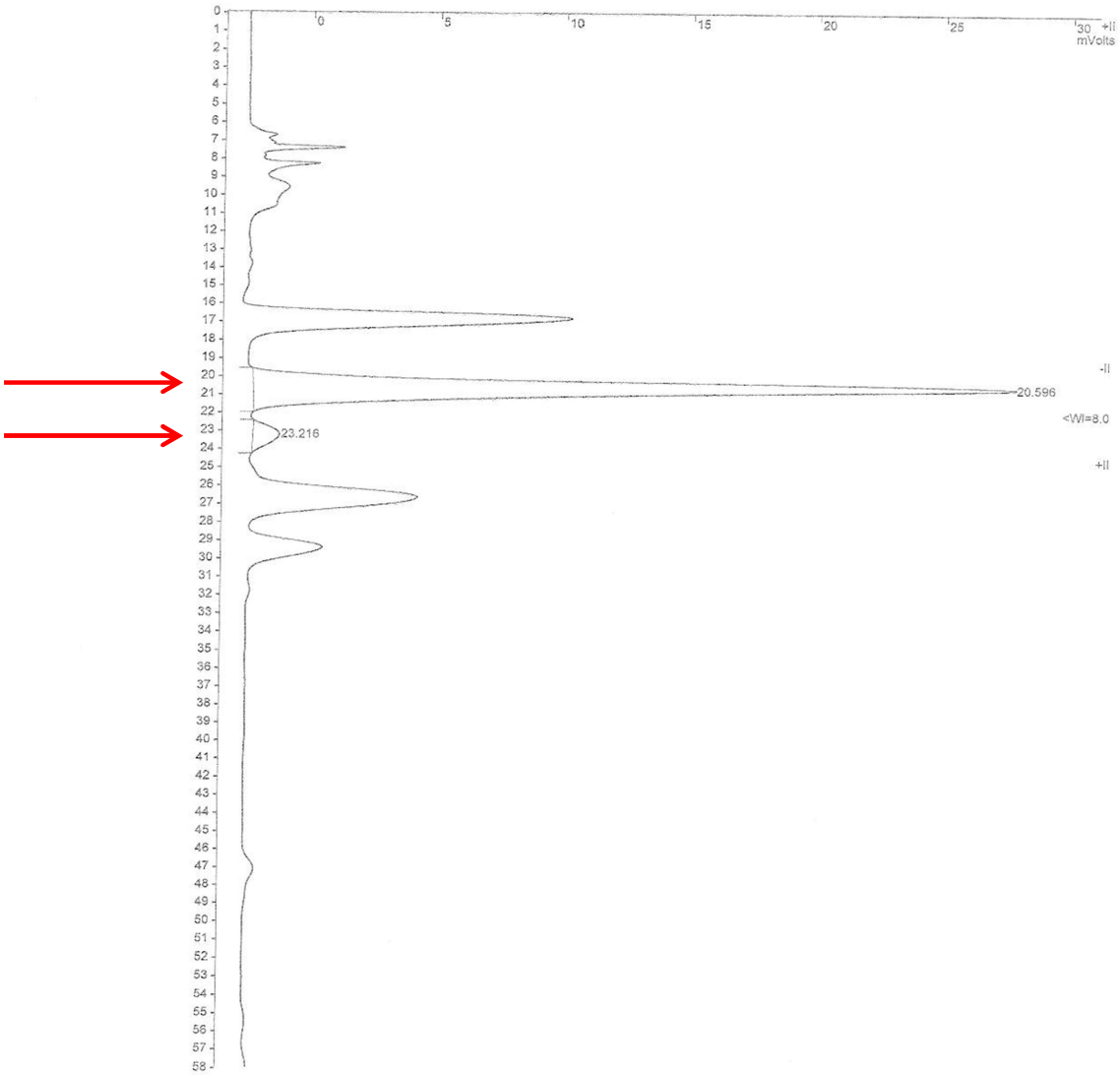
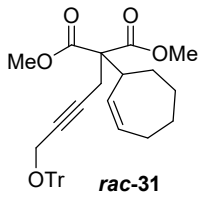


Table 2, Entry 7



***rac*-31**

After deprotection of trityl group, the racemic compound was separated using chiral GC-colomun Cyclosil B: with following method: Init Temp: 50; init time: 30; rate 1: 10; final temp. 1: 200; final time-1: 100; rate 2: 10; final-temp. 2: 50.

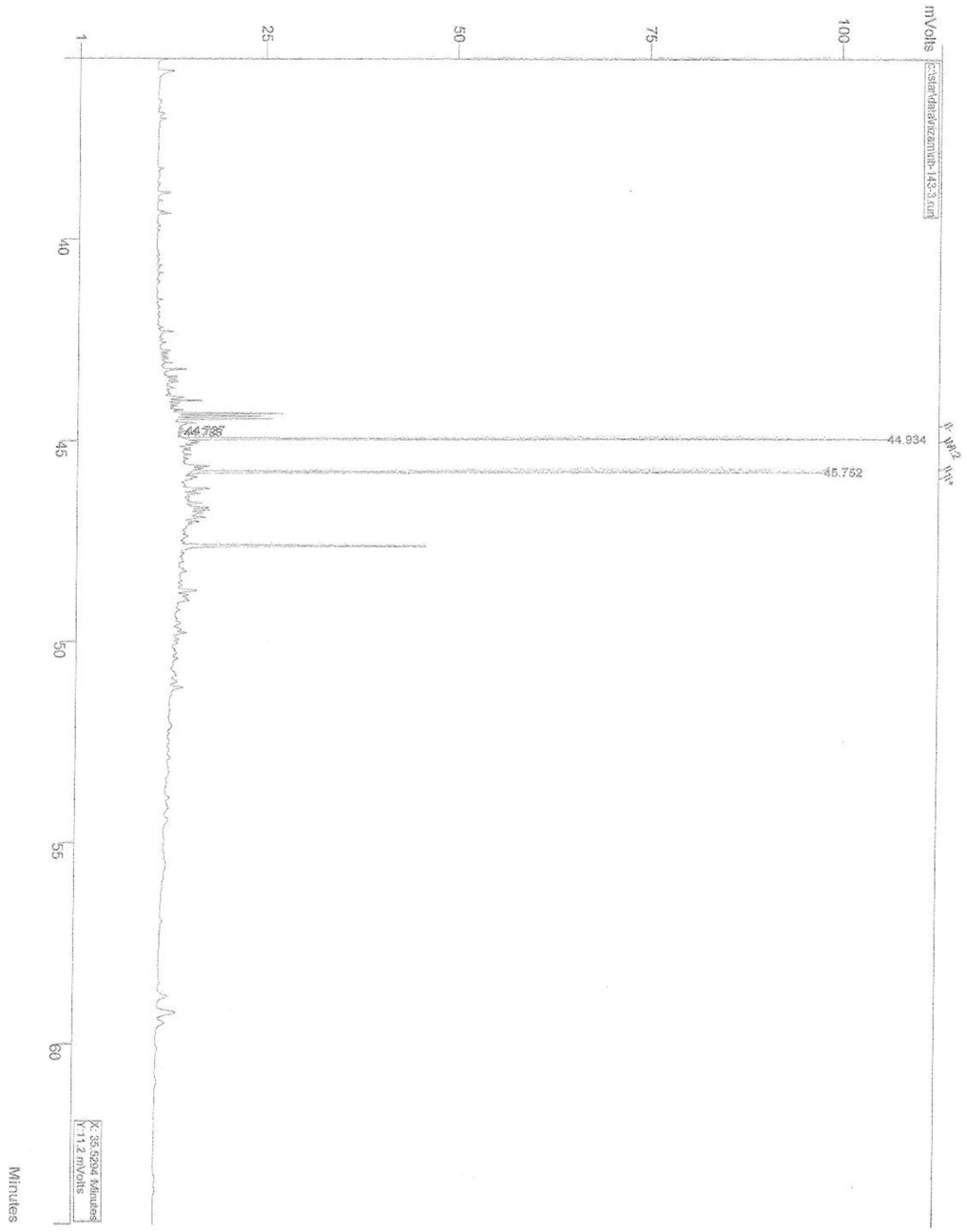
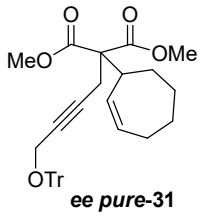


Table 2, Entry 8



***ee pure*-31**

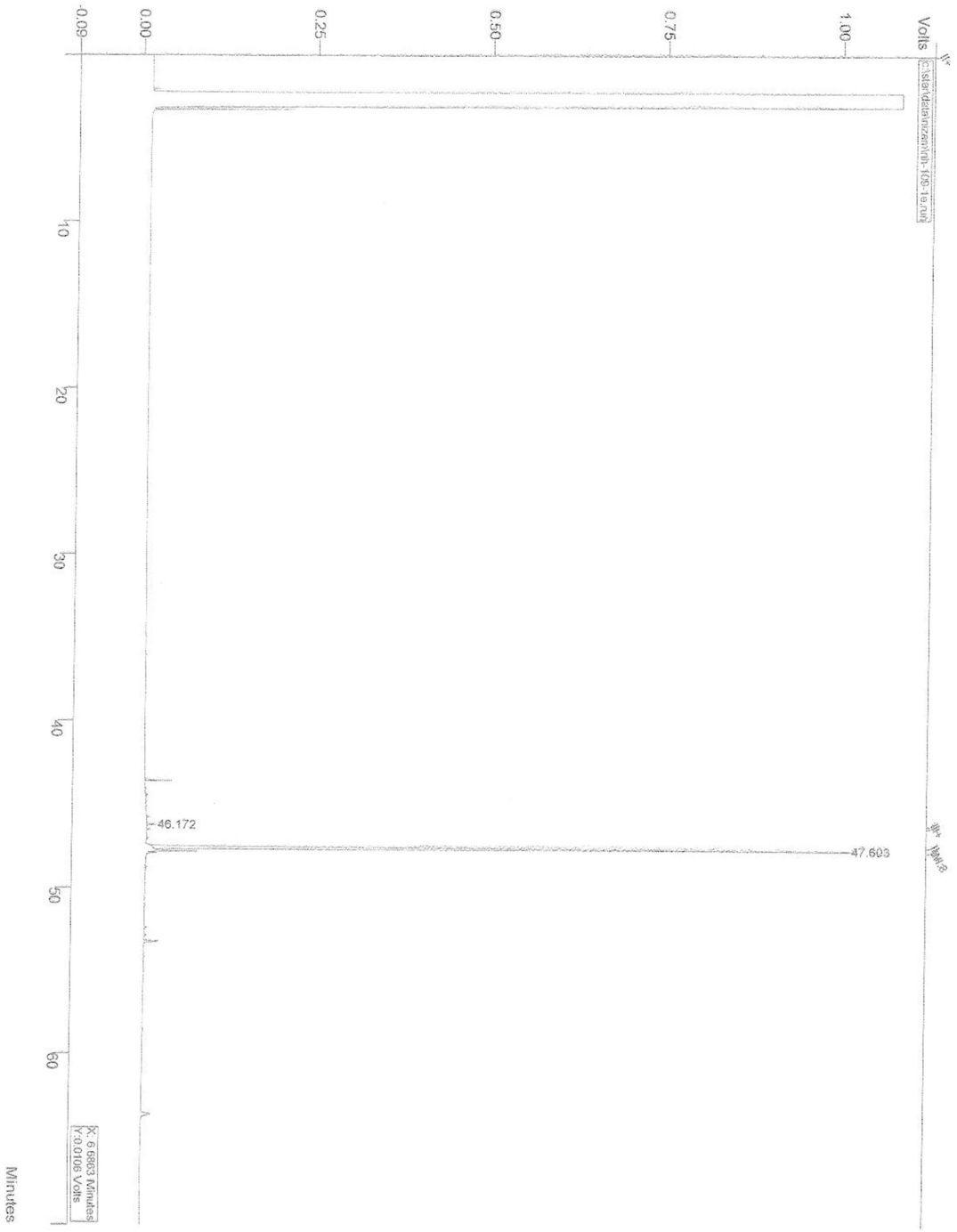
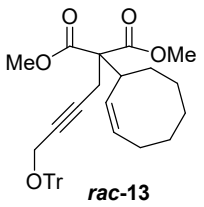


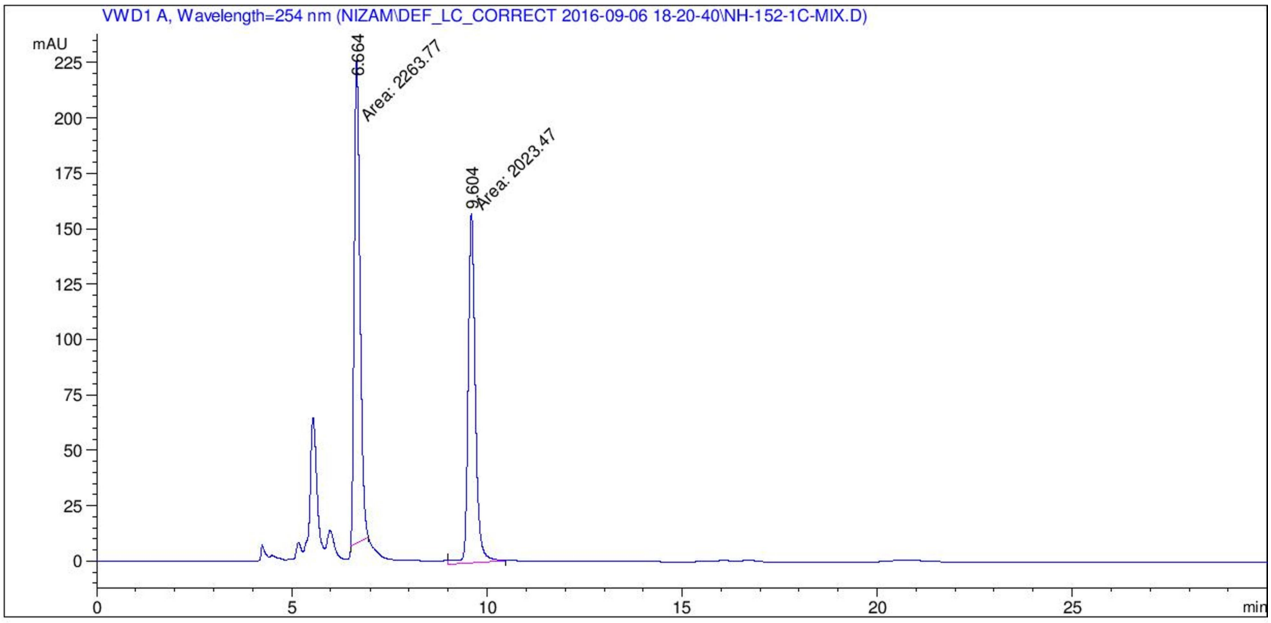
Table 2, Entry 9



***rac*-13**

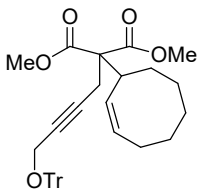
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-09-06 18-20-40\NH-152-1C-MIX.D
Sample Name: nh-152-1c-mix

```
==================================================================
Acq. Operator   : nizam                          Seq. Line :   8
Acq. Instrument : Instrument 1 Classic           Location : Vial 11
Injection Date  : 9/6/2016 9:19:17 PM                 Inj :   1
                                                 Inj Volume : 5.0 µl
Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-09-06 18-20-40\IC, 90-10 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 3/7/2011 2:58:51 PM
Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 5/23/2015 5:47:14 PM by gnanam
Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```



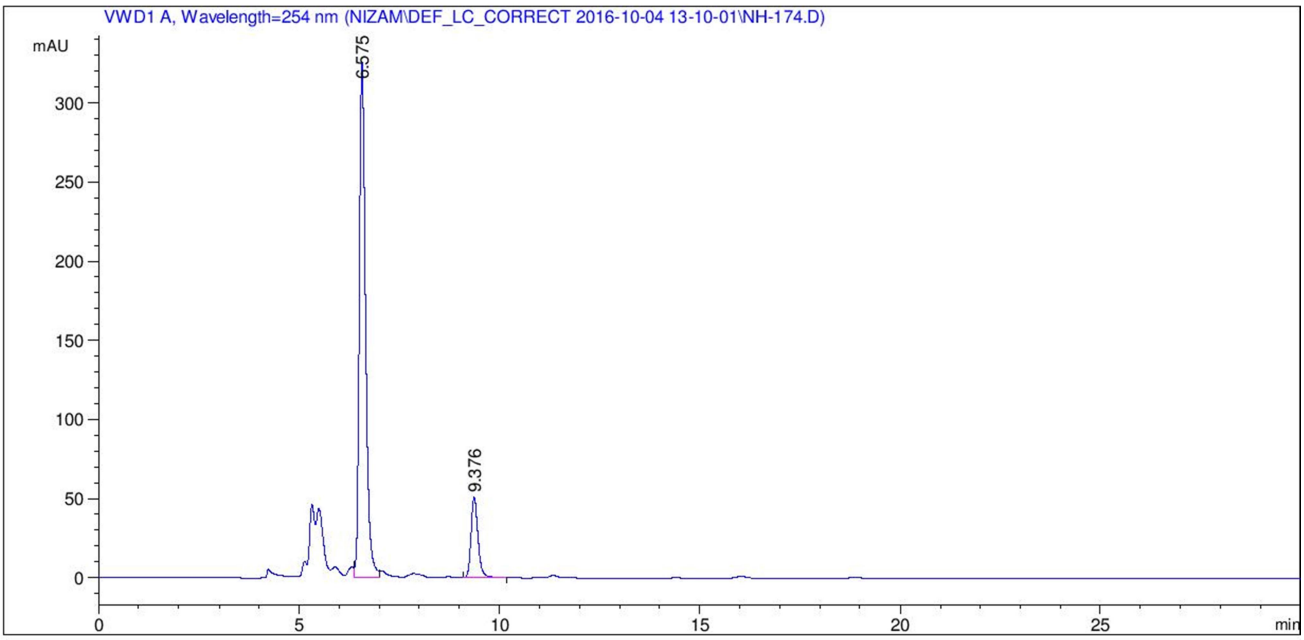

```
==================================================================
                        Area Percent Report
==================================================================

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


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.664 MM    0.1727 2263.77393  218.43097  52.8026
   2   9.604 MM    0.2140 2023.46863  157.60985  47.1974
```

Table 2, Entry 11



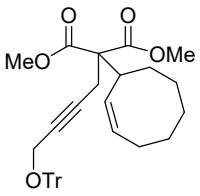
***enantioenriched*-13**

```
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-10-04 13-10-01\NH-174.D
Sample Name: NH-174

    ======================================================================
    Acq. Operator    : NIZAM                          Seq. Line :   5
    Acq. Instrument  : Instrument 1 Classic           Location : Vial 41
    Injection Date   : 10/4/2016 4:44:01 PM                Inj :   1
                                                    Inj Volume : 5.0 µl
    Acq. Method      : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-10-04 13-10-01\IC, 90-10 HEPT-IPA,
                       0,8 ML-MIN,254NM,30M.M
    Last changed     : 3/7/2011 2:58:51 PM
    Analysis Method  : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                       0,8 ML-MIN,254NM,30M.M
    Last changed     : 5/23/2015 5:47:14 PM by gnanam
    Method Info      : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```



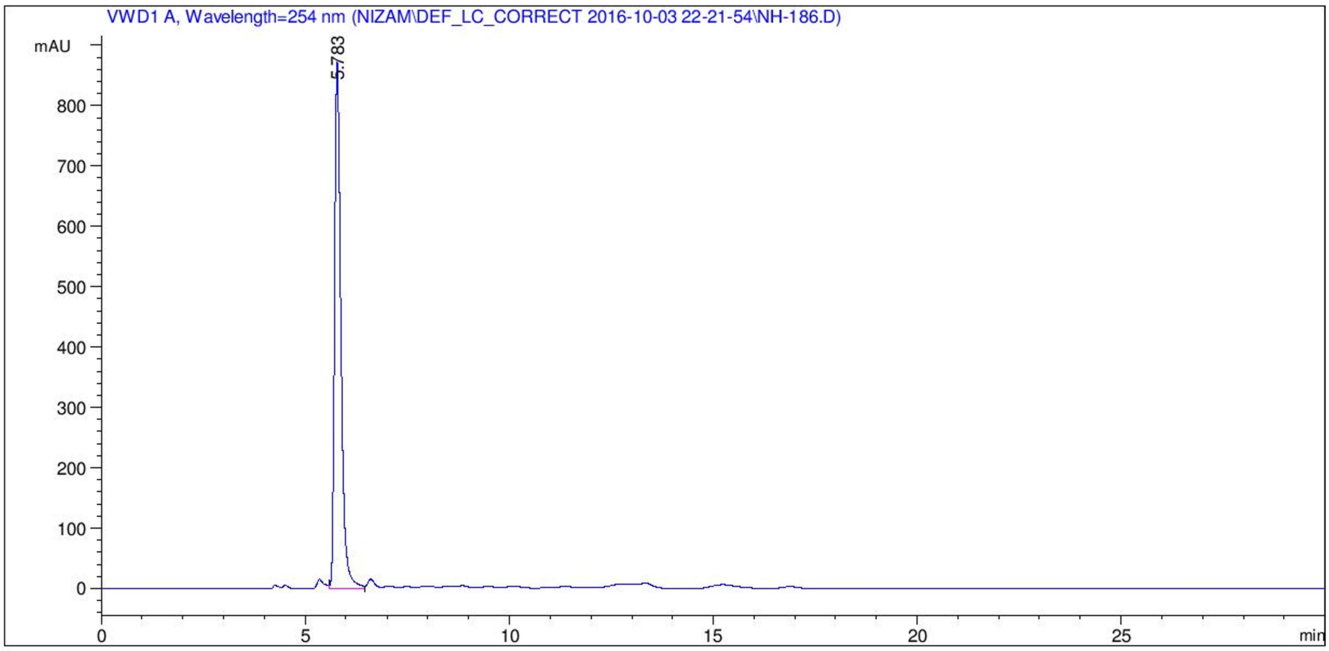

```
    ======================================================================
                              Area Percent Report
    ======================================================================

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


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1   6.575 VV    0.1663 3549.53418  326.18906  85.1267
       2   9.376 VB    0.1854  620.17120   51.05568  14.8733

Instrument 1 Classic 1/23/2017 4:22:02 PM MARIUS                    Page   1 of 2
```

Table 2, Entry 12



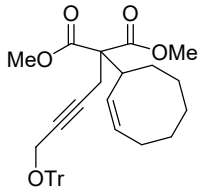
***ee pure*-13**

```
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-10-03 22-21-54\NH-186.D
Sample Name: NH-186

    ======================================================================
    Acq. Operator   : NIZAM                          Seq. Line :   4
    Acq. Instrument : Instrument 1 Classic           Location : Vial 31
    Injection Date  : 10/4/2016 12:14:27 AM               Inj :   1
                                                   Inj Volume : 5.0 µl
    Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-10-03 22-21-54\IC, 90-10 HEPT-IPA,
                      0,8 ML-MIN,254NM,30M.M
    Last changed    : 3/7/2011 2:58:51 PM
    Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                      0,8 ML-MIN,254NM,30M.M
    Last changed    : 5/23/2015 5:47:14 PM by gnanam
    Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```




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

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


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1   5.783 VV    0.1660 9468.98926  871.83289 100.0000
```

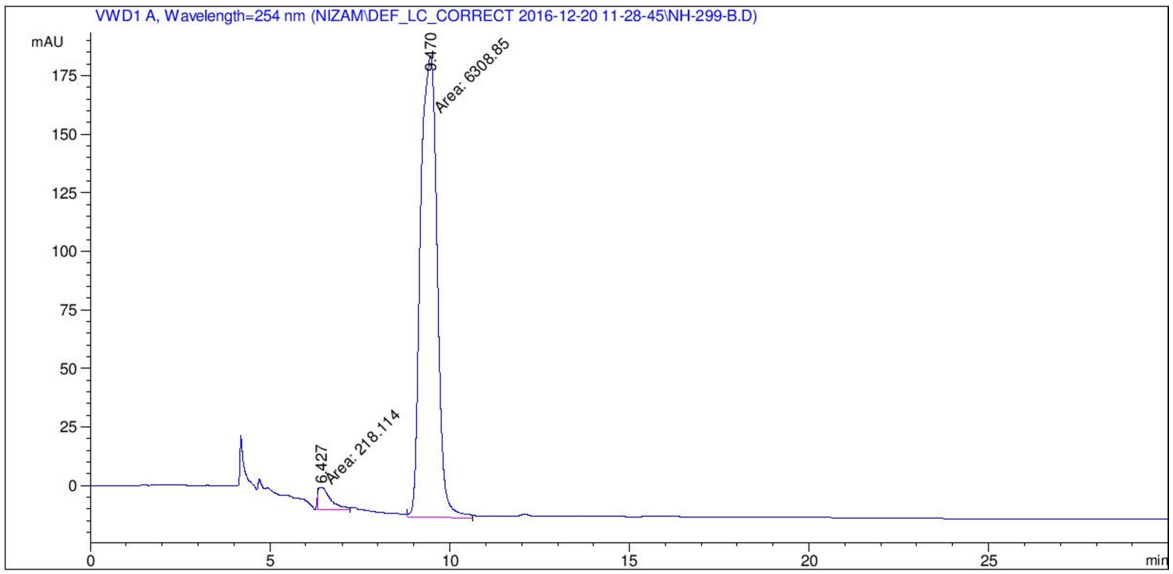
Table 2, Entry 10



***ee pure*-13**

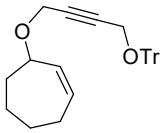
Data File C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-12-20 11-28-45\NH-299-B.D
Sample Name: NH-299-B

```
==================================================================
Acq. Operator   : NIZAM                          Seq. Line :   2
Acq. Instrument : Instrument 1 Classic            Location : Vial 11
Injection Date  : 12/20/2016 11:48:45 AM               Inj :   1
                                                 Inj Volume : 5.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 15.0 µl
Acq. Method     : C:\CHEM32\1\DATA\NIZAM\DEF_LC_CORRECT 2016-12-20 11-28-45\IC, 90-10 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 3/7/2011 2:58:51 PM
Analysis Method : C:\CHEM32\1\DATA\MARIUS\DEF_LC_CORRECT 2017-01-21 23-13-46\IA, 98-2 HEPT-IPA,
                  0,8 ML-MIN,254NM,30M.M
Last changed    : 5/23/2015 5:47:14 PM by gnanam
Method Info     : IA, 98/2 heptane/isopropanol, 0.8 ml/min, 254 nm, 30 min
```




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

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


Signal 1: VWD1 A, Wavelength=254 nm
```

Table 3, Entry 3



rac-**35**

```
Title       :
Run File    : c:\star\data\nizam\nh-312-1-hep-ipa-200-1- 254-nm-0.8ml ad.run
Method File : c:\star\data\nizam\nh-312-1-hep-ipa-200-1- 254-nm-0.8ml ad-1.mth
Sample ID   : Default Sample

Injection Date: 12/30/2016 7:52 PM    Calculation Date: 1/24/2017 3:02 PM

Operator    : Operator                Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFÝ HÚp"     Bus Address  : 80
Instrument : Instrument #1            Sample Rate  : 50.00 Hz
Channel    : 1 = 1                    Run Time     : 35.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.57 cm/min   Attenuation = 133          Zero Offset = 3%
Start Time  =   0.000   min     End Time    = 35.000  min   Min / Tick  = 1.00
```

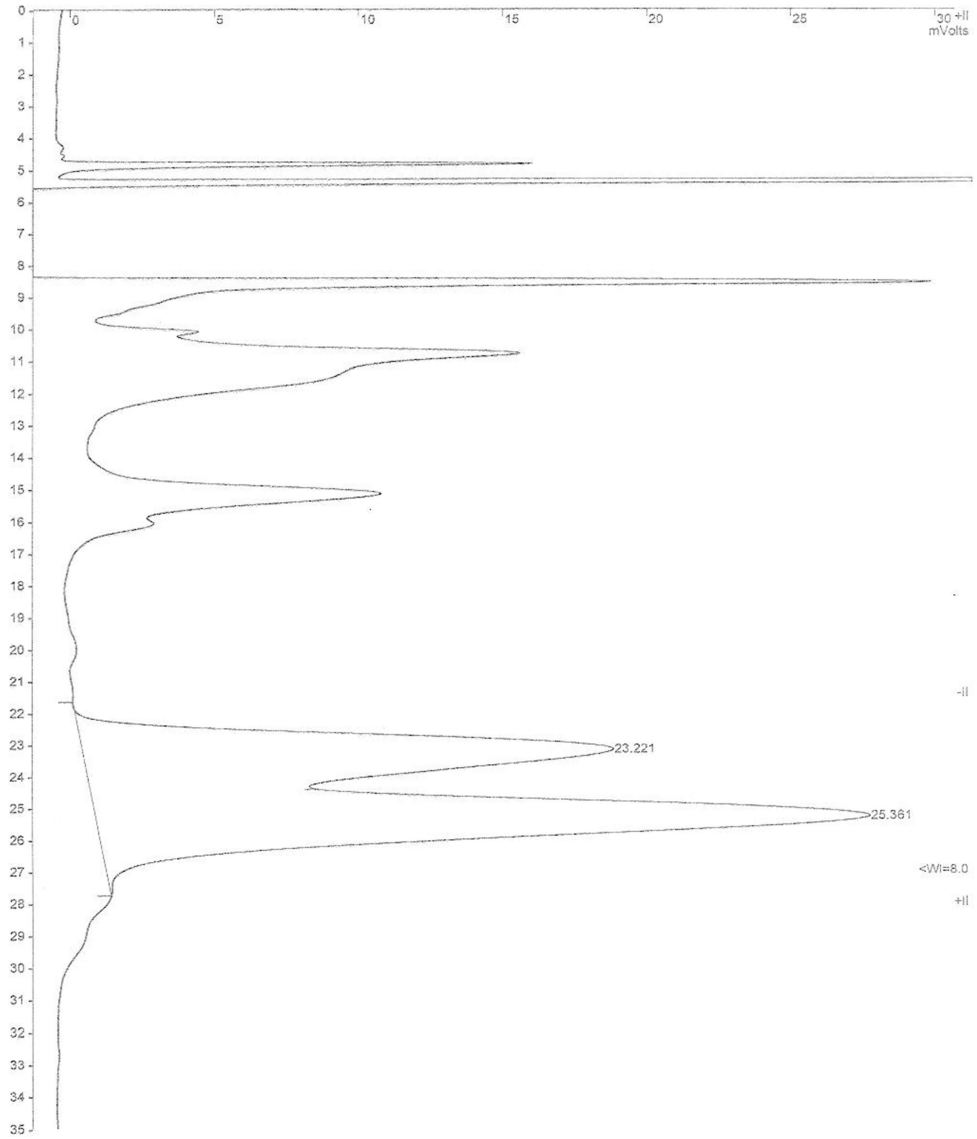
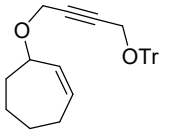


Table 3, Entry 4




```
Title       :
Run File    : c:\star\data\nizam\nh-318-1-hep-ipa-200-1- 254-nm-0.8ml ad.run enantioenriched-35
Method File : c:\star\data\nizam\nh-318-1-hep-ipa-200-1- 254-nm-0.8ml ad-1.mth
Sample ID   : Default Sample

Injection Date: 12/31/2016 2:03 PM    Calculation Date: 1/12/2017 10:28 PM

Operator    : Operator                Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFý HÚþ"     Bus Address  : 80
Instrument : Instrument #1            Sample Rate  : 50.00 Hz
Channel     : 1 = 1                   Run Time     : 60.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.33 cm/min   Attenuation = 343          Zero Offset = 2%
Start Time  =   0.000   min     End Time    = 60.000  min   Min / Tick  = 1.00
```

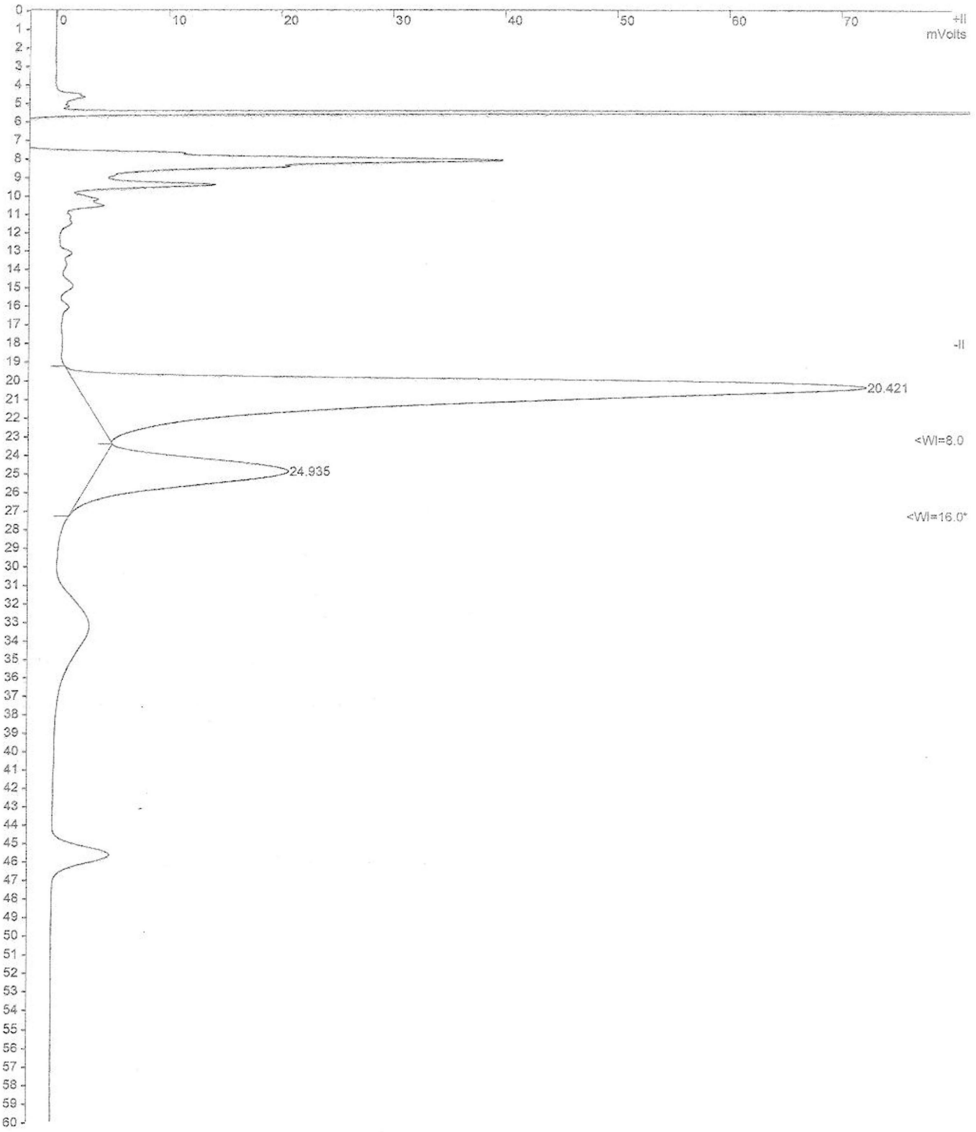
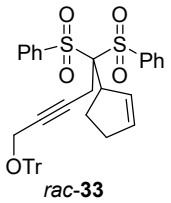


Table 2, Entry 13



rac-**33**

```
Title       :
Run File    : c:\star\data\nizam\nh-264-6-hep-ipa-90 10 254-nm-0.8ml ad.run
Method File : c:\star\data\nizam\nh-264-6-hep-ipa-90 10 254-nm-0.8ml ad-1.mth
Sample ID   : Default Sample

Injection Date: 12/16/2016 6:46 PM    Calculation Date: 1/23/2017 5:54 PM

Operator    : Operator                Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFÝ HÚÞ"     Bus Address  : 80
Instrument : Instrument #1            Sample Rate  : 50.00 Hz
Channel     : 1 = 1                   Run Time     : 56.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.35 cm/min   Attenuation = 282          Zero Offset = 15%
Start Time  =    0.000   min    End Time    = 56.000  min   Min / Tick  = 1.00
```

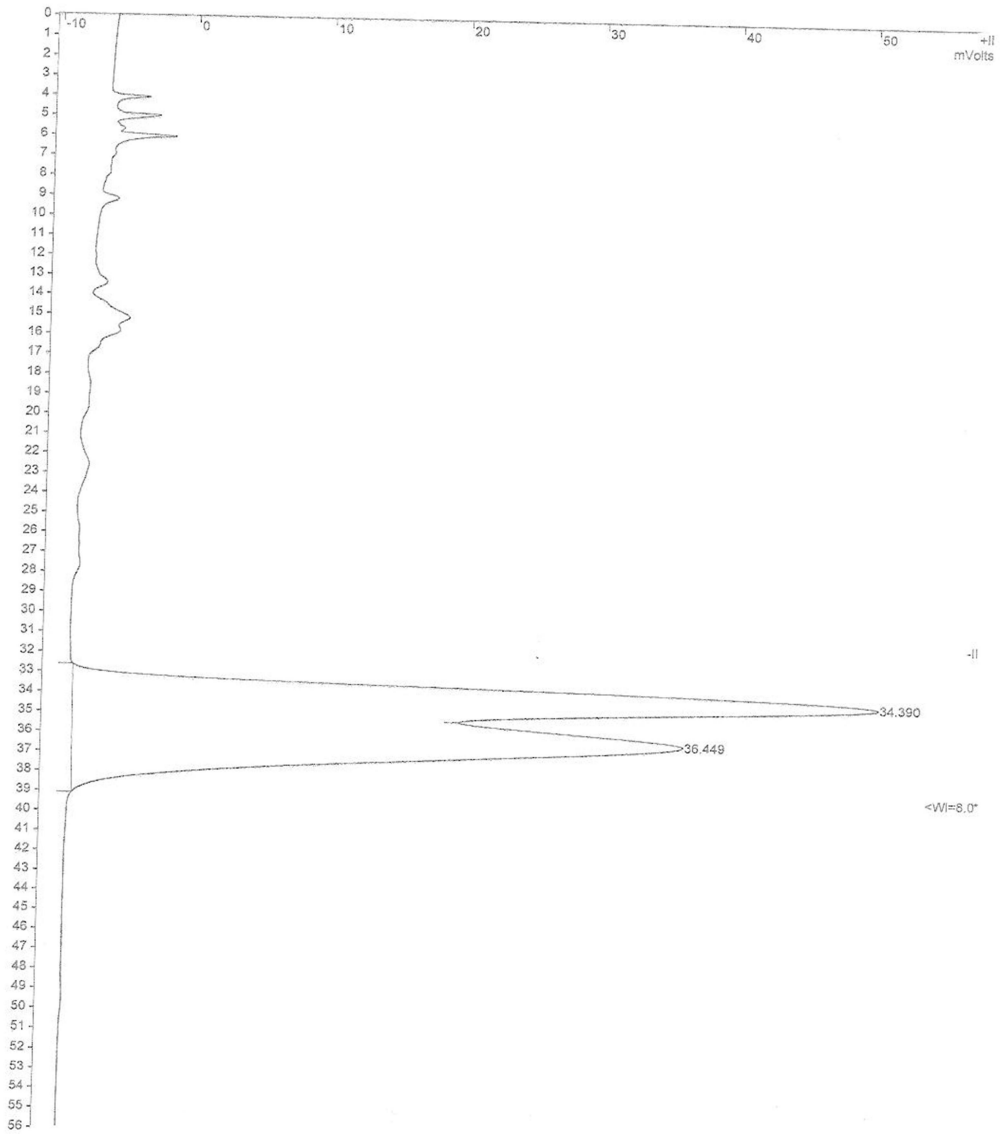
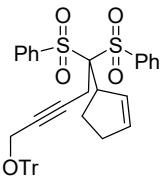


Table 2, Entry 14



enantioenriched-**33**

```
Title       :
Run File    : c:\star\data\nizam\nh-281-hep-ipa-95 5 254-nm-0.8ml ad.run
Method File : c:\star\data\nizam\nh-281-hep-ipa-95 5 254-nm-0.8ml ad-1.mth
Sample ID   : Default Sample

Injection Date: 12/19/2016 7:10 PM    Calculation Date: 1/23/2017 5:51 PM

Operator    : Operator                Detector Type: 0800 (1 Volt)
Workstation: TROST-HPLC-LEFÝ HÚÞ"     Bus Address  : 80
Instrument : Instrument #1            Sample Rate  : 50.00 Hz
Channel    : 1 = 1                    Run Time     : 100.000 min

** LC Workstation Multi Instrument (Demo) Version 6.41 ** 05000-31c8-fa9-30a1 **

Chart Speed =    0.20 cm/min   Attenuation = 1217          Zero Offset = 2%
Start Time  =    0.000   min    End Time    = 100.000 min   Min / Tick  = 1.00
```