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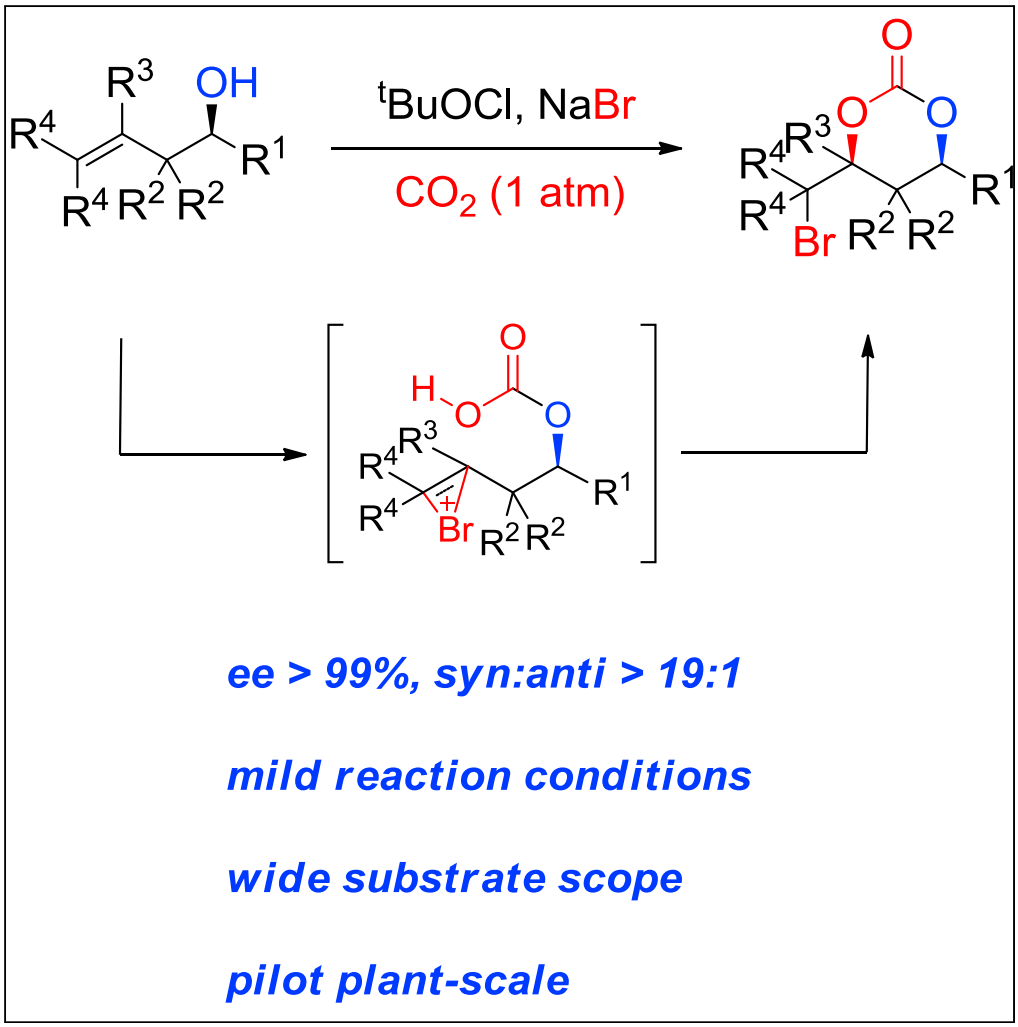

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HIGHLIGHTS

Diastereoselective carboxylation/ bromocyclization

Mild conditions

Pilot-plant-scale synthesis of statins

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Chiral Syn-1,3-diol Derivatives via a One-Pot Diastereoselective Carboxylation/ Bromocyclization of Homoallylic Alcohols

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SUMMARY

Chiral *syn*-1,3-diols are fundamental structural motifs in many natural products and drugs. The traditional Narasaka-Prasad diastereoselective reduction from chiral β-hydroxyketones is an important process for the synthesis of these functionalized *syn*-1,3-diols, but it is of limited applicability for large-scale synthesis because (1) highly diastereoselective control requires extra explosive and flammable Et_2BOMe as a chelating agent under cryogenic conditions and (2) only a few functional *syn*-1,3-diol scaffolds are available. Those involving halogen-functionalized *syn*-1,3-diols are much less common. There are no reported diastereoselective reactions involving chemical fixation of CO_2/bromocyclization of homoallylic alcohols to halogen-containing chiral *syn*-1,3-diols. Herein, we report an asymmetric synthesis of *syn*-1,3-diol derivatives via direct diastereoselective carboxylation/bromocyclization with both relative and absolute stereocontrol utilizing chiral homoallylic alcohols and CO_2 in one pot with up to 91% yield, > 99% ee, and >19:1 *dr*. The power of this methodology has been demonstrated by the asymmetric synthesis of statins at the pilot plant scale.

INTRODUCTION

Chiral *syn*-1,3-diols are ubiquitous and privileged structural motifs in many biologically active polyketide natural products, most prominently represented by the macrolide antibiotics(Norcross and Paterson, 1995; Yeung and Paterson, 2005; Merketegi et al., 2013), and a range of small-molecule drugs, particularly in the statin families (HMG-CoA reductase inhibitors) (Scheme 1) (Müller, 2005; Časar, 2010; Wu et al., 2015). In addition to direct incorporation into these molecules, chiral *syn*-1,3-diols are also fundamental building blocks that can easily be elaborated into complex natural products and bioactive molecules. The applications of chiral *syn*-1,3-diols are also a subject of increasing interest in the pharmaceutical industry (Bode et al., 2006; Gupta et al., 2013; Dechert-Schmitt et al., 2014; Kumar et al., 2017; Quirk et al., 2003; Junoy, 2007; Angelo et al., 2018). For example, a statin analog, rosuvastatin, is used to treat hypercholesterolemia and prevent cardiovascular disease (Shepard et al., 1995; LaRosa et al., 1999), and achieved sales of $4.2 billion in 2017. The unique *syn*-1,3-diols structure, together with their broad spectrum of physiological activities, fueled intense research activity into their synthesis. Benchmarked by the aldol-directed addition/reduction transformations (Lee and Lin, 2000; Yatagai and Ohnuki, 1990), a considerable number of ingenious methodologies with general utility have been developed. However, the relative and absolute stereocontrol in the construction of these structurally diverse chiral *syn*-1,3-diols still represents significant challenges. Only a few chiral *syn*-1,3-diol fragments with proper functional groups, such as aryl, acetate, nitrile and amine, are available. Those involving halogen-functionalized chiral *syn*-1,3-diols, which are versatile building blocks for the synthesis of *syn*-1,3-diol-containing natural products and drugs, are much less common. Therefore, there is still a great need for alternative, flexible, and highly stereoselective synthetic methodologies to construct chiral *syn*-1,3-diol scaffolds.

Today, the stereocontrolled synthesis of chiral *syn*-1,3-diols can be achieved by the following two strategies: (1) catalyst-controlled asymmetric reactions (Scheme 2A) (Gupta et al., 2013) and (2) substrate-controlled asymmetric induction, both of which encompass a variety of possible bond disconnections around the hydroxy groups at the C1 and C3 positions. Although various transition metal catalysts and organocatalysts have been developed, no generally applicable approach exists for the flexible synthesis of chiral *syn*-1,3-diols, and the efficient construction of chiral *syn*-1,3-diol motifs was realized mainly by a classical Narasaka-Prasad reduction, that is, by securing the chirality of a *β*-hydroxyketone precursor and

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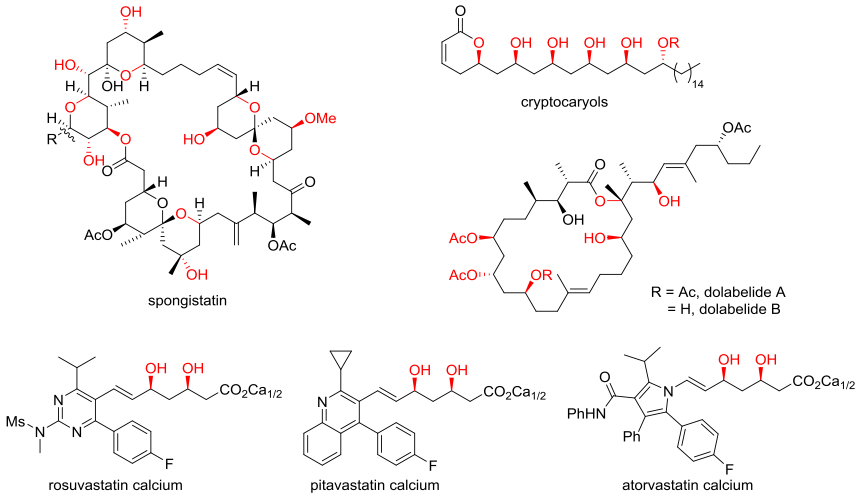


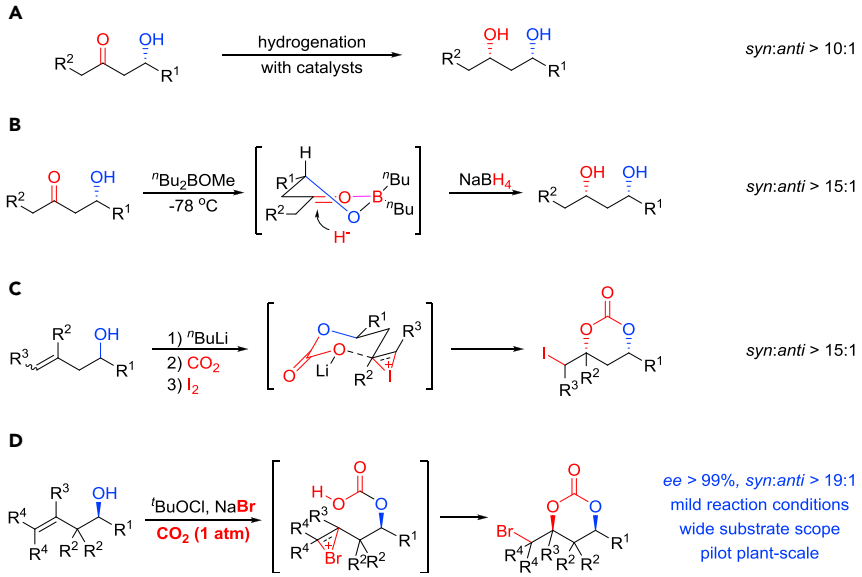
Scheme 1. 1,3-Diol Polyketide Natural Products and Drugs

then ensuring a *syn*-diastereoselective reduction using excess Et_2BOMe (Scheme 2B) (Narasak and Pai, 1984; Chen et al., 1987). Despite the considerable efficacy, cryogenic reaction conditions are required to achieve high diastereoselectivity. Notably, among several possible approaches to prepare functionalized chiral *syn*-1,3-diols, the direct diastereoselective electrophilic iodocarboxylation of homoallylic alcohols is clearly underexploited (Scheme 2C) (Ahmad et al., 1977; Bartlett et al., 1982; Duan et al., 1993; Xiong et al., 2016). Although this method requires additional transformation to extend the nucleophilic character of β-hydroxy group by forming esters such as cyclic phosphates and carbonates, the method allows the installation of the functionalized chiral *syn*-1,3-diol subunits in one step with high efficiency. However, this iodocarboxylation is limited by the inherent instability of the expensive iodo-1,3-dicarbonate products, and there are no reported diastereoselective bromocarboxylations using the chemical fixation of CO_2 with chiral homoallylic alcohols to generate chiral *syn*-1,3-diols.

In our attempt to synthesize chiral *syn*-1,3-diol building blocks, we envisioned that CO_2 could be an ideal oxygen source to introduce the second hydroxy group when using homoallylic alcohols. However, due to its thermodynamic stability, the chemical fixation of CO_2 and its application in the production of valuable fine chemicals still represent major challenges (Klankermayer et al., 2016; Liu et al., 2015; Appel et al., 2013; Sakakura et al., 2007). In previous transformations involving CO_2 fixation to unsaturated alcohols, strong bases (such as ^{n}BuLi, Scheme 2C), or high CO_2 pressures, were generally required (Cardill et al., 1981; Bongini et al., 1982; Tirado and Prieto, 1993; Kielland et al., 2013; Yu and He, 2015). In 2010, Minakata and coworkers described an innovative and extremely mild procedure for the synthesis of *trans*-1,2-diol (Minakata et al., 2010). Inspired by these fundamental results, we hypothesized that a transient alkylcarbonic acid, *in situ* prepared from CO_2 and a homoallylic alcohol, could react with a cyclic bromonium intermediate in the presence of ^{t}BuOCl and NaBr to give *syn*-1,3-diols (Scheme 2D). Moreover, the chirality of *syn*-1,3-diols could be obtained via chiral homoallylic alcohol transfer. Herein, we described the first stereocontrolled synthesis of chiral *syn*-1,3-diol motifs via a one-pot CO_2 fixation/bromocyclization using various chiral homoallylic alcohols under extremely mild conditions in up to 91% yield, >99% ee, and >19:1 *dr*. This 1,3-asymmetric induction methodology was successfully applied in the asymmetric total synthesis of statins on the pilot plant scale.

RESULTS AND DISCUSSION

To validate the feasibility of our hypothesis, we first investigated the reaction using chiral homoallylic alcohol (**1a**) and ^{t}BuOCl (2 equiv) with KBr (1.5 equiv) under a balloon of CO_2 in acetonitrile at −20°C. As shown in Table 1, the desired chiral six-membered cyclic bromocarbonate **2a** was generated in 16% isolated yield with excellent diastereoselectivity (>19:1, entry 1). To improve the efficiency of this bromocyclization, a variety of solvents were evaluated. Switching to a less polar solvent, THF, resulted in only 10% yield but good diastereoselectivity (entry 2). When using dichloromethane or ethyl acetate, the desired product was not formed even after a longer reaction time (entries 3 and 4). In comparison,



Scheme 2. Methods for the Synthesis of *syn*-1,3-Diols

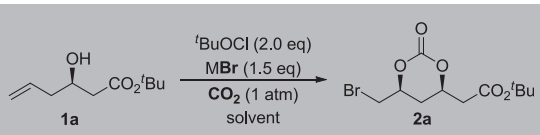
(A–D) (A) Hydrogenation of 1,3-hydroxyketones to chiral *syn*-1,3-diols. (B) Cryogenic Narasaka-Prasad reduction to chiral *syn*-1,3-diols (currently dominates in the industry). (C) ^{n}BuLi-mediated iodocarboxylation to racemic *syn*-1,3-diols. (D) This work: substrate-induced diastereoselective bromocarboxylation to chiral *syn*-1,3-diols.

the use of DMF (N,N-Dimethylformamide) as the solvent tremendously improved the yield of 2a to 65% (entry 5), which can be attributed to the good solubility of NaBr in DMF. However, kindred dimethylacetamide (DMA) led to an inferior yield (entry 6). When protic solvents, such as MeOH or HOAc, were employed, consumption of substrate **1** was detected, but no bromocarbonate product was detected (entries 7 and 8).

We next investigated other representative alkali metal bromides, including NaBr, NH_4Br, and LiBr (entries 9–11). NaBr proved to be a superior bromination reagent with high reactivity and selectivity, giving the desired product in 73% yield in 1 hr (entry 11). In contrast, more soluble bromides, NH_4Br and LiBr, failed to produce expected bromocarbonate **2a** (entries 9 and 10). The reaction temperatures were also examined, and the reaction yields were dependent on the temperatures. Increasing the temperature led to decreased reaction yields and diastereoselectivities (entries 12–15). In contrast, the formation of **2a** could be improved by conducting the reaction at lower temperatures. At −40°C, the reaction afforded the optimal results with 86% yield and >19:1 diastereoselectivity within 3 hr (entry 16). When the temperature was decreased further, the yield of the reaction remained essentially the same (entry 17).

Changing the equivalence of ^{t}BuOCl and CO_2 was also discussed. Decreasing the amount of ^{t}BuOCl significantly decreased the yield of this reaction (entries 18 and 19), whereas increasing the amount did not improve the yield (entry 20). Simultaneously, improving the pressure of CO_2 slightly improved the yield but special equipment was needed, which made the procedure impractical (entries 21, 22). Thus, we selected ^{t}BuOCl (2 equiv) with NaBr(1.5 equiv) under a balloon of CO_2 in DMF and at −40°C as the reaction conditions. Notably, when using iodide as the nucleophile, no desired *syn*-1,3-diol was produced, suggesting that iodide was not suitable for this reaction.

With the optimized reaction conditions in hand, we investigated the substrate scope of this reaction with various chiral homoallylic alcohols. As illustrated in Table 2, this new system indicated excellent substrate compatibility, giving the desired carbonate products in good to excellent isolated yields and diastereoselectivities. First, the ester-containing substrates performed well and afforded the desired *syn*-isomer products in excellent yields (79%–86%) and high diastereoselectivities (>19:1) (**2a-e**). Replacing the ester groups with various oxy groups, including electron-rich benzyloxy (**2f, 2g**), electron-deficient p-toluenesulfonic ester (OT)s (**2h**), or sterically bulky alkoxy (**2i, 2j**) or silyloxy groups (**2k, 2l**), all led to



Entry	MBr	^{t}BuOCl (eq)	CO_2 (atm)	Solvent	Temp (°C)	T (h)	Yield (%)[a,b]	dr[c]
1	KBr	2	1	MeCN	−20	3	16	>19:1
2	KBr	2	1	THF	−20	3	10	>19:1
3	KBr	2	1	DCM	−20	5	<5	–
4	KBr	2	1	EA	−20	5	<5	–
5	KBr	2	1	DMF	−20	1.5	65	>19:1
6	KBr	2	1	DMAc	−20	1	21	>19:1
7	KBr	2	1	MeOH	−20	5	<5	–
8	KBr	2	1	HOAc	−20	5	<5	–
9	NH_4Br	2	1	DMF	−20	2	<5	–
10	LiBr	2	1	DMF	−20	1.5	<5	–
11	NaBr	2	1	DMF	−20	1	73	>19:1
12	NaBr	2	1	DMF	r.t	0.5	35	>19:1
13	NaBr	2	1	DMF	0	0.5	52	>19:1
14	NaBr	2	1	DMF	−10	1	61	>19:1
15	NaBr	2	1	DMF	−30	2	81	>19:1
16	NaBr	2	1	DMF	−40	3	86	>19:1
17	NaBr	2	1	DMF	−50	3	84	>19:1
18	NaBr	1.5	1	DMF	−40	3	69	>19:1
19	NaBr	1	1	DMF	−40	3	41	>19:1
20	NaBr	2.5	1	DMF	−40	3	87	>19:1
21	NaBr	2	5	DMF	−40	3	88	>19:1
22	NaBr	2	10	DMF	−40	3	87	>19:1

Table 1. Screening Conditions for the Bromocarboxylation of Chiral Homoallylic Alcohols

THF, tetrahydrofuran; EA, ethyl acetate; DCM, dichloromethane.

[a]General conditions: **1a** (1 mmol, 1.0 equiv), CO_2 (x atm), ^{t}BuOCl (x mmol), MBr (x mmol), solvent (6 mL).

[b]Isolated yields of **2a**.

[c]The diastereoselectivity was determined by ^{1}H NMR.

bromocarbonate products in identical performances. With general alkyl (**2m**), benzyl (**2n, 2o**), or aryl substituents (**2p, 2q**), this reaction also worked well and produced the desired products. In addition, heterocycles, such as thienyl (**2r**), reacted smoothly to give the desired product in good yield and diastereoselectivity. Moreover, some highly reactive functional groups, such as Cl (**2s**) and CN (**2t**), were also tolerated under these reaction conditions. Substrates bearing geminal substituents were also converted into the corresponding products (**2u**). Notably, when homoallylic alcohols with mono- (**2v, 2w**) or disubstituted (**2x, 2y**) double bonds were used, the carbonate products were generated in moderate yields (25%–45%), but the good diastereoselectivities remained. To further evaluate the synthetic utility of this method, we attempted to use the opposite configuration of the (*S*)-homoallylic alcohols. Fortunately, satisfactory yields and diastereoselectivities were obtained with all these substrates, which not only highlighted the excellent substrate compatibility but also implied the great potential of this new method for

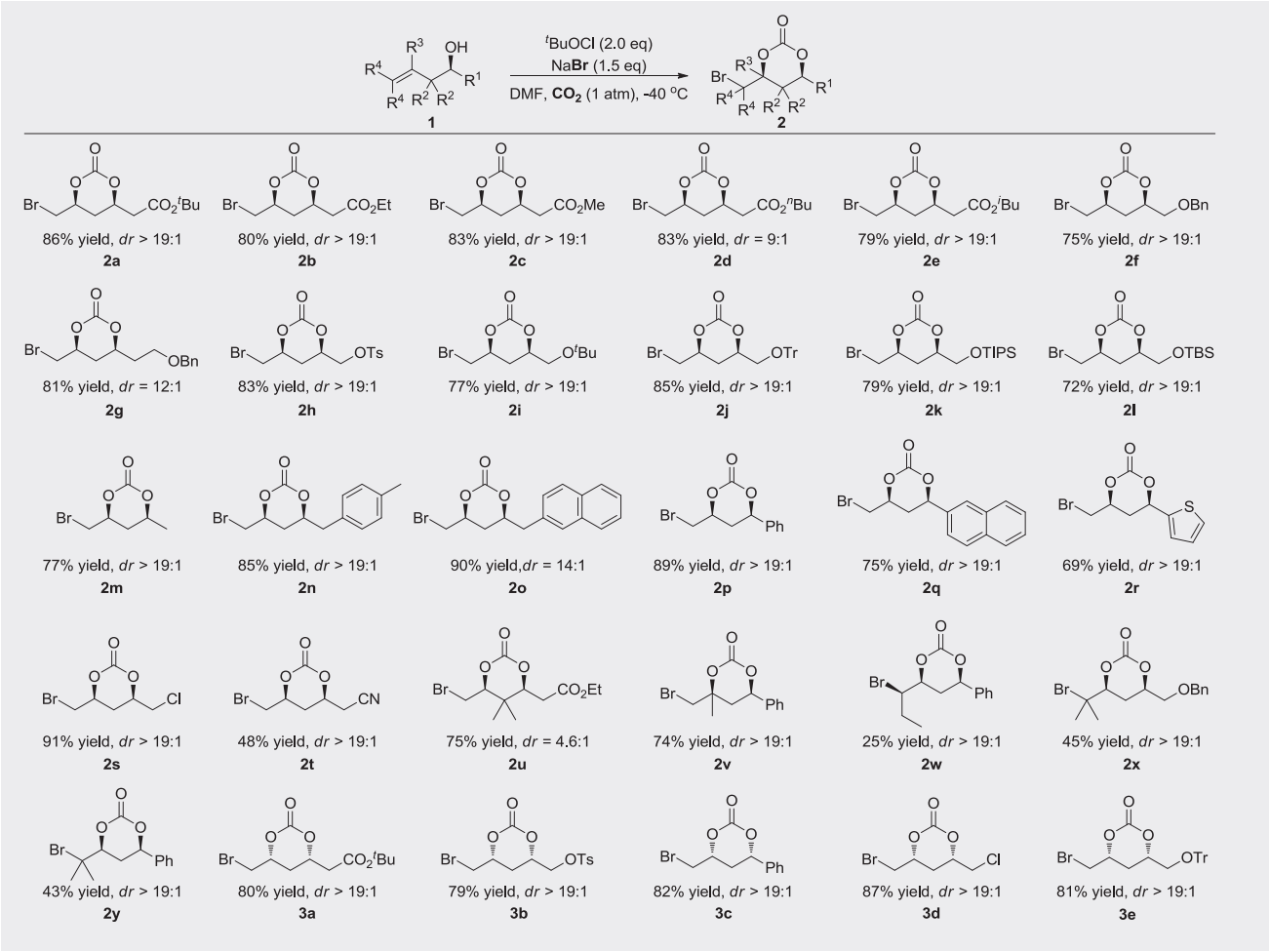
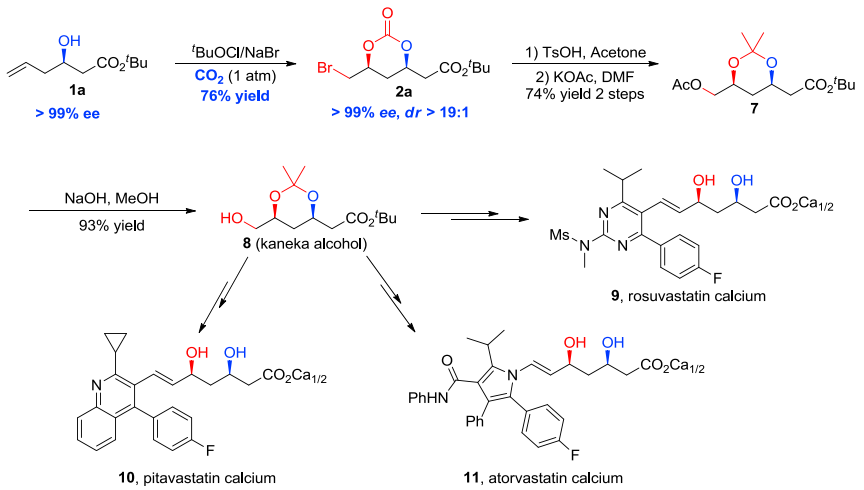


Table 2. Survey of the Substrate Scope in the Diastereoselective Bromocarboxylation of Chiral Homoallylicalcohols

synthesizing chiral *syn*-1,3-diols (**3a**-**e**). More importantly, the enantiopurity of the starting material was retained, and 99% ee was detected in all cases after purification.

Industrial Application

The aforementioned chiral *syn*-1,3-diol-bromocarbonates are valuable building blocks for the asymmetric synthesis of *syn*-1,3-diol-containing natural products and drugs, and the power of this methodology was demonstrated in the pilot-plant-scale synthesis of chiral *syn*-1,3-diol-derived statins, including rosuvastatin, pitavastatin, and atorvastatin. As depicted in Scheme 3, chiral homoallylic alcohol **1a** was subjected to ^{t}BuOCl and NaBr in DMF at −40°C under a continuously bubbling CO_2 system to give, after crystallization, pure bromocarbonate product **2a** in 76% yield, >99% ee, and >19:1 *dr* without column chromatography isolation. Compound **2a** was then converted to acetate **7** in two steps via acetonidation (Clive et al., 1990; Radl et al., 2002; Beck et al., 1995) followed by an S_N2 reaction with a total yield of 74%. Subsequent hydrolysis of the acetate proceeded smoothly to give Kaneka alcohol **8** in 93% yield (Fan et al., 2011; Sun et al., 2007), which could be transformed to the final rosuvastatin **9** via known procedures (Wess et al., 1990). Moreover, from the general intermediate Kaneka alcohol **8**, other statins in this family, such as pitavastatin **10** (Choi and Shin, 2008) and atorvastatin **11** (Rádl, 2003), could be easily prepared on scales up to kilograms. Notably, asymmetric total syntheses of statins have been well documented in the literature (Chen et al., 2014; Xiong et al., 2015). However, this methodology is the first example using CO_2 as oxygen source to construct the important chiral *syn*-1,3-diol structure. Right now, this procedure was patented and processed in a pharmaceutical company (Chen et al., 2017).



Scheme 3. Pilot-Plant-Scale Synthesis of Statins

Conclusion

In summary, we have developed a one-pot diastereocontrolled synthesis of chiral *syn*-1,3-diol derivatives via CO_2 fixation/bromocyclization using *in situ*-generated ^{t}BuOBr in excellent yield and with both relative and absolute stereocontrol. This transformation is tolerant of a wide range of functional groups and can easily be scaled up to the hectogram scale without racemization, providing ready access to a broad range of chiral *syn*-1,3-diol products. Further application of this method to the synthesis of statins highlighted the great synthetic capability of this methodology. Ongoing new synthetic approach toward chiral *syn*-1,3-diol-containing natural products and medicines using this method is now underway in our laboratory.

Limitations of Study

Excess amounts of oxidant and source of bromides are generally needed. Substitutions on the alkenes also inhibited this reaction with decreased reactivity.

METHODS

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

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods and 95 figures and can be found with this article online at https://doi.org/10.1016/j.isci.2018.11.010.

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AUTHOR CONTRIBUTIONS

Methodology, G.H. and F.C.; Investigation, G.H. and M.L.; Writing – Original Draft, G.H.; Writing – Review & Editing, H.P., and F.C.; Supervision, H.P.

DECLARATION OF INTERESTS

The authors declare no competing financial interest.

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Supplemental Information

Chiral Syn-1,3-diol Derivatives via a One-Pot Diastereoselective Carboxylation/ Bromocyclization of Homoallylic Alcohols

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Supplemental Information

Functionalized chiral *syn*-1,3-diol derivatives via a one-pot diastereoselective carboxylation/bromocyclization of homoallylic alcohols

Guan-xin Huang, Min-jie Liu, Fang-jun Xiong, Ge Meng, Yuan Tao, Yan Wu, Hai-hui Peng* and Fen-er Chen*

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

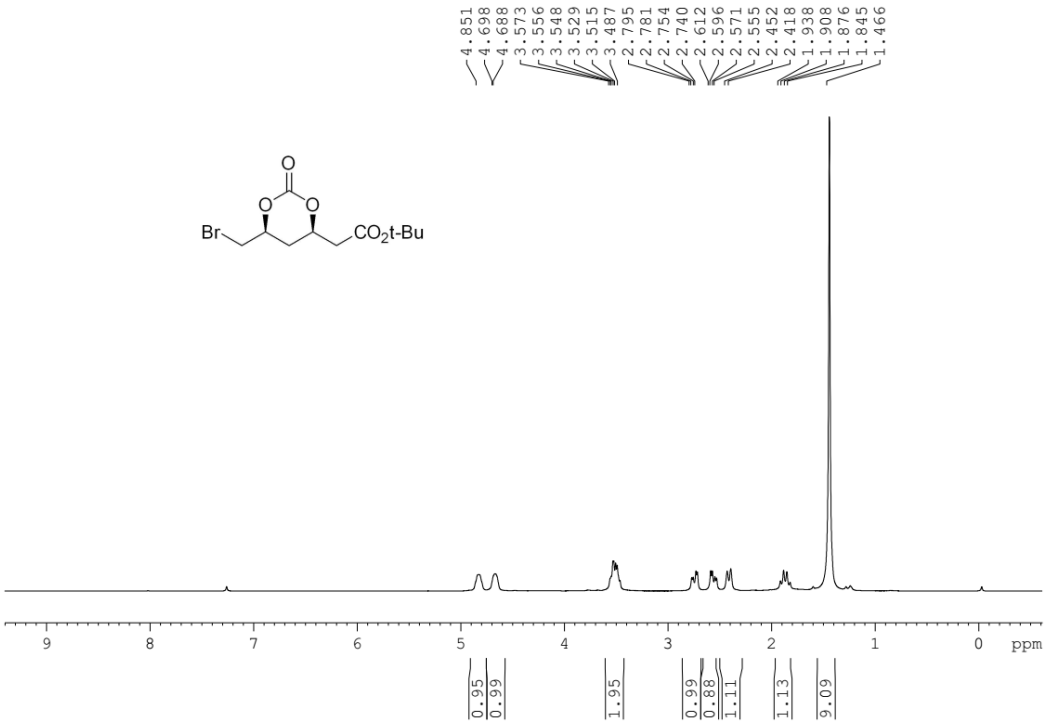


Figure S1. ^{1}H NMR spectrum of compound **2a**, related to **Table 2**.

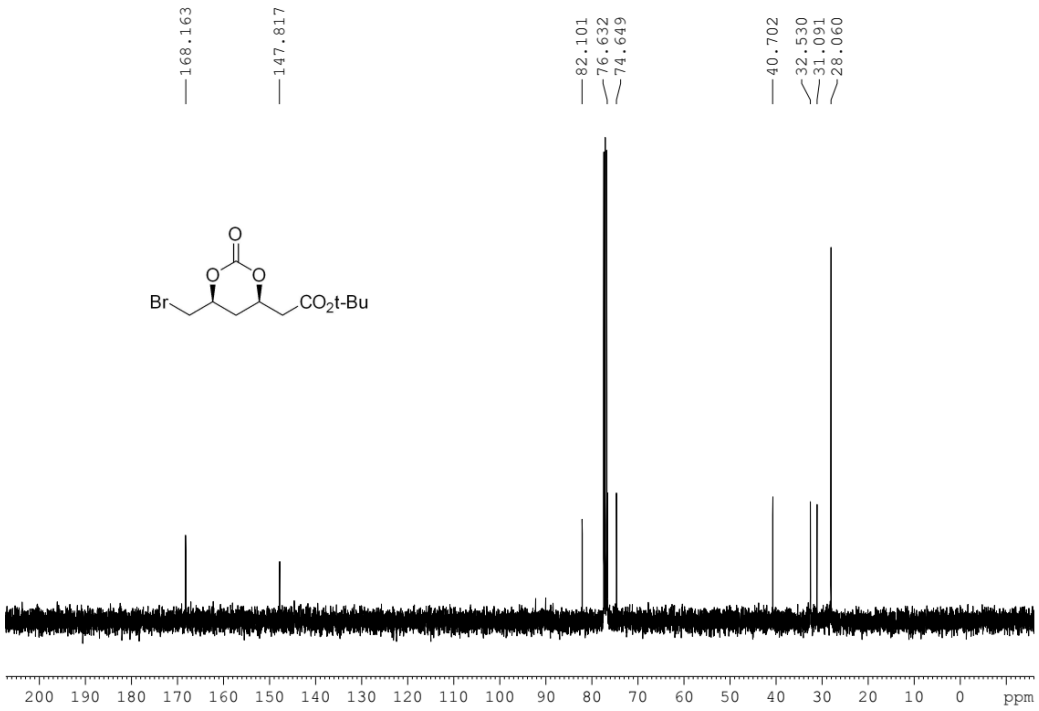
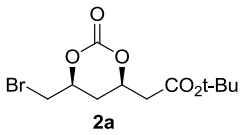
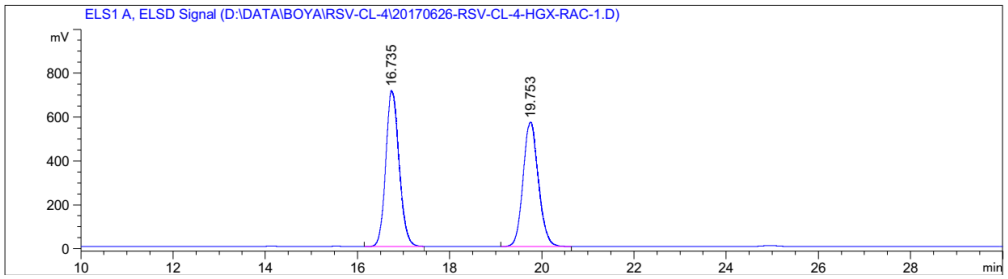


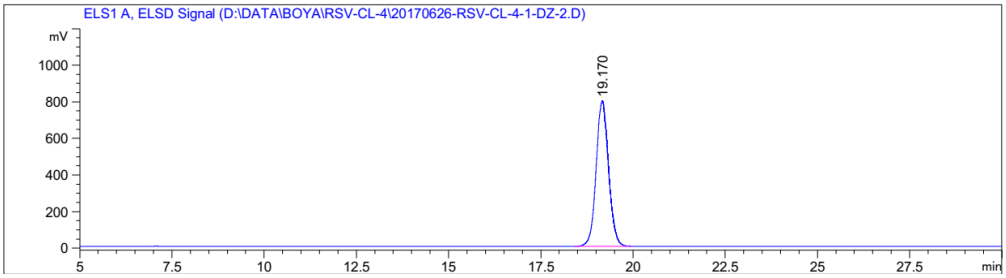
Figure S2. ^{13}C NMR spectrum of compound **2a**, related to **Table 2**.



2a



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mV*s]	峰高 [mV]	峰面积 %
1	16.735	VV	0.2425	1.42954e4	711.08325	52.1860
2	19.753	VV	0.2769	1.30977e4	567.28394	47.8140



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1	19.170	VV	0.2769	1.86613e4	796.24957	100.0000

Figure S3. HPLC Analysis of compound **2a**.

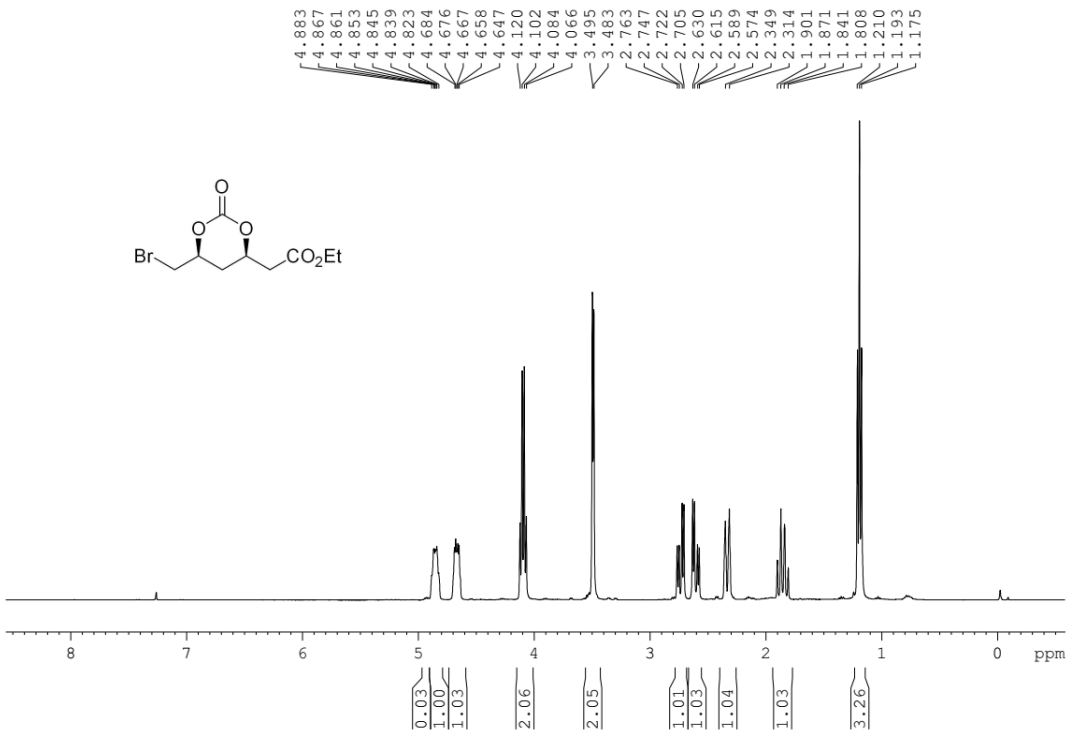


Figure S4. [1]H NMR spectrum of compound **2b**, related to **Table 2**.

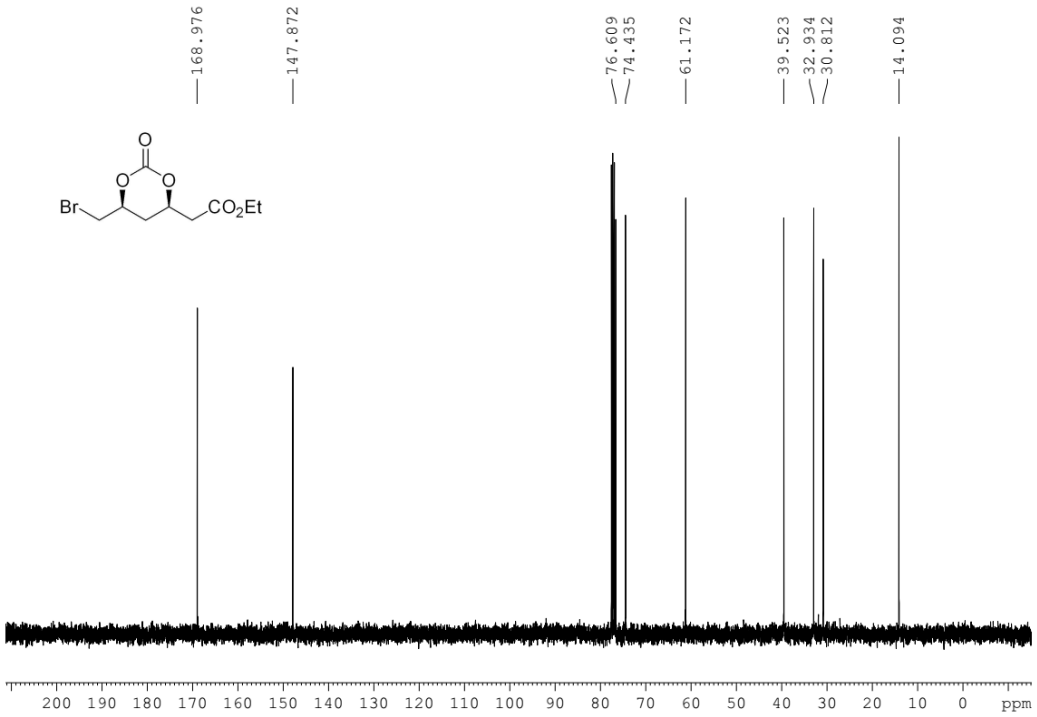


Figure S5. [13]C NMR spectrum of compound **2b**, related to **Table 2**.

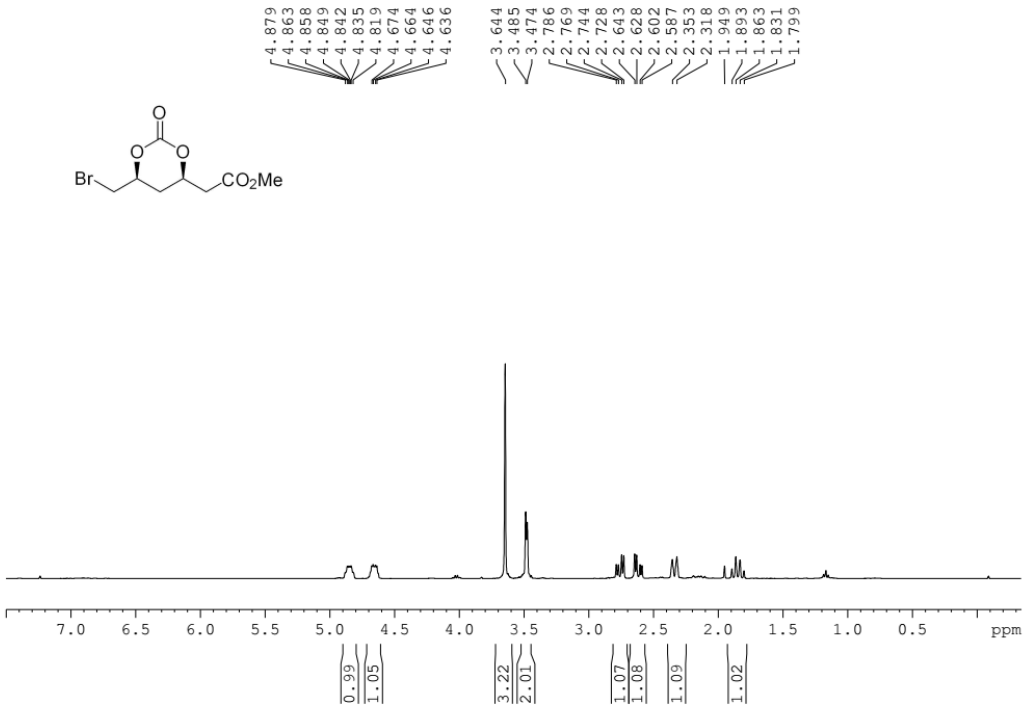


Figure S6. [1]H NMR spectrum of compound **2c**, related to **Table 2**.

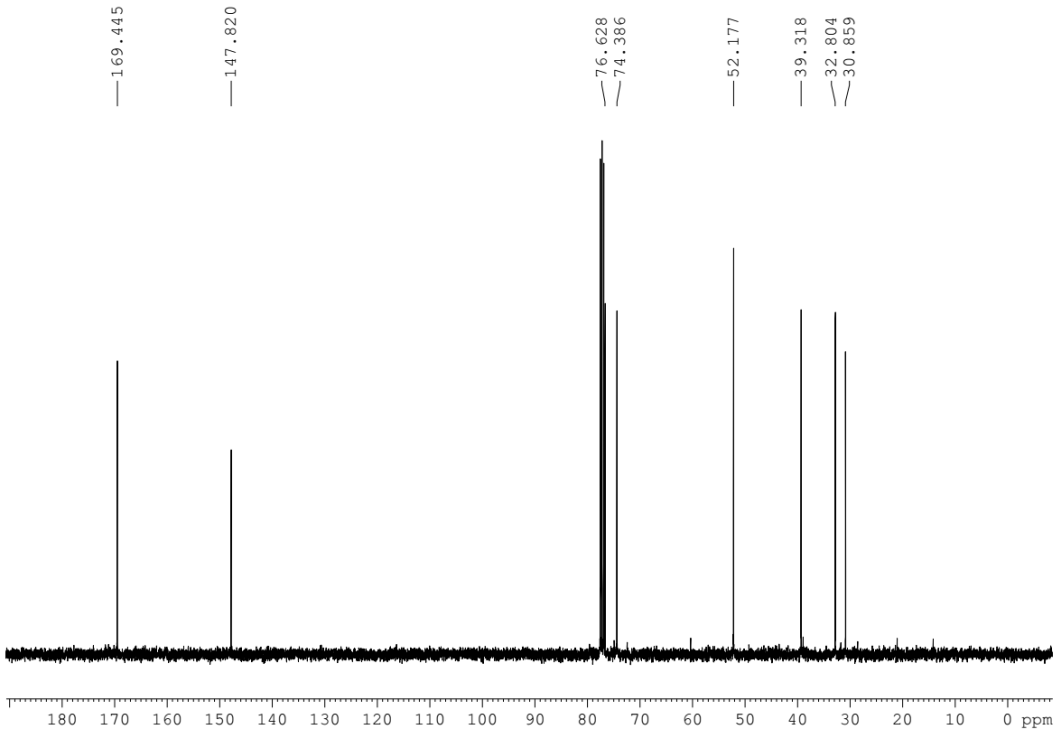


Figure S7. [13]C NMR spectrum of compound **2c**, related to **Table 2**.

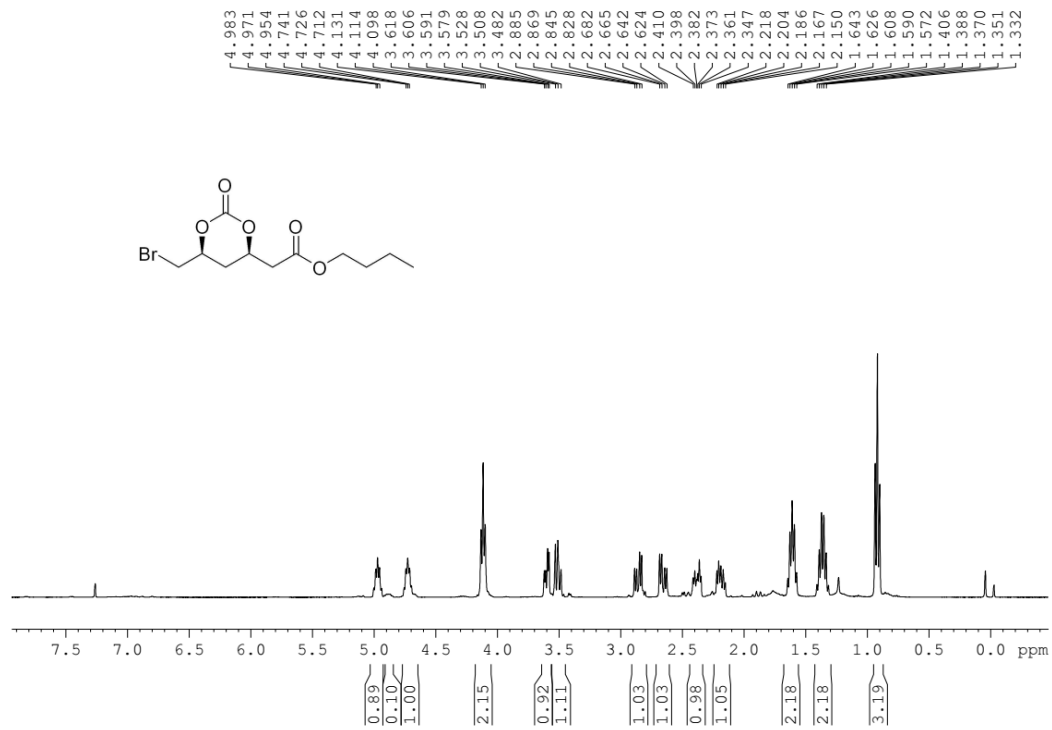


Figure S8. [1]H NMR spectrum of compound **2d**, related to **Table 2**.

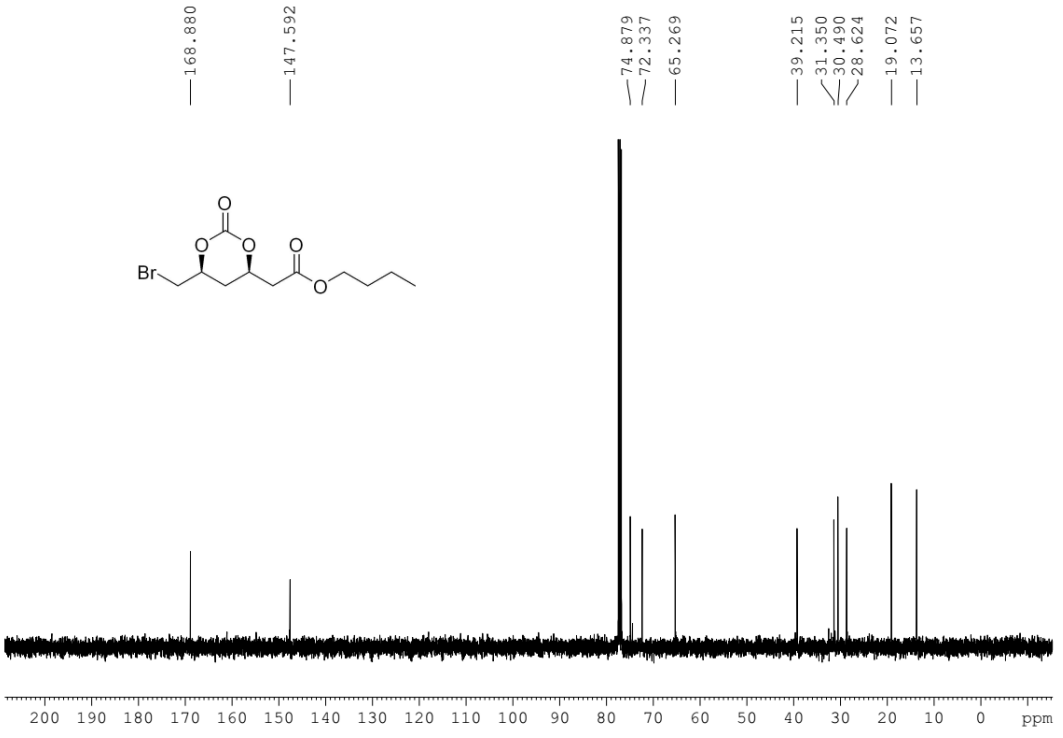


Figure S9. [13]C NMR spectrum of compound **2d**, related to **Table 2**.

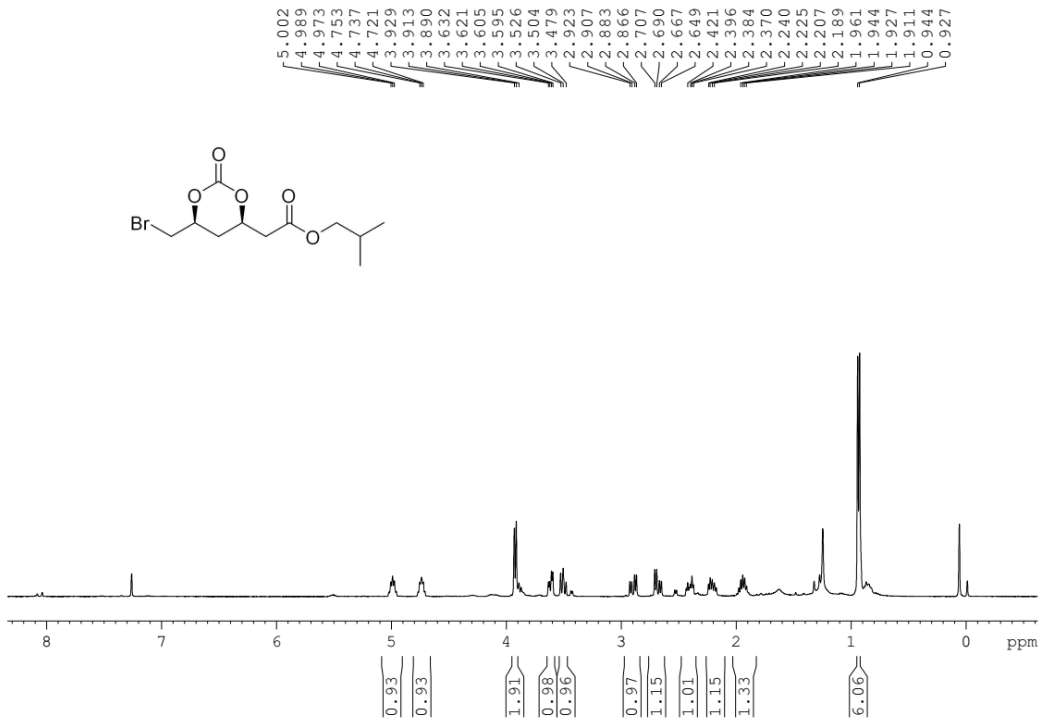


Figure S10. [1]H NMR spectrum of compound **2e**, related to **Table 2**.

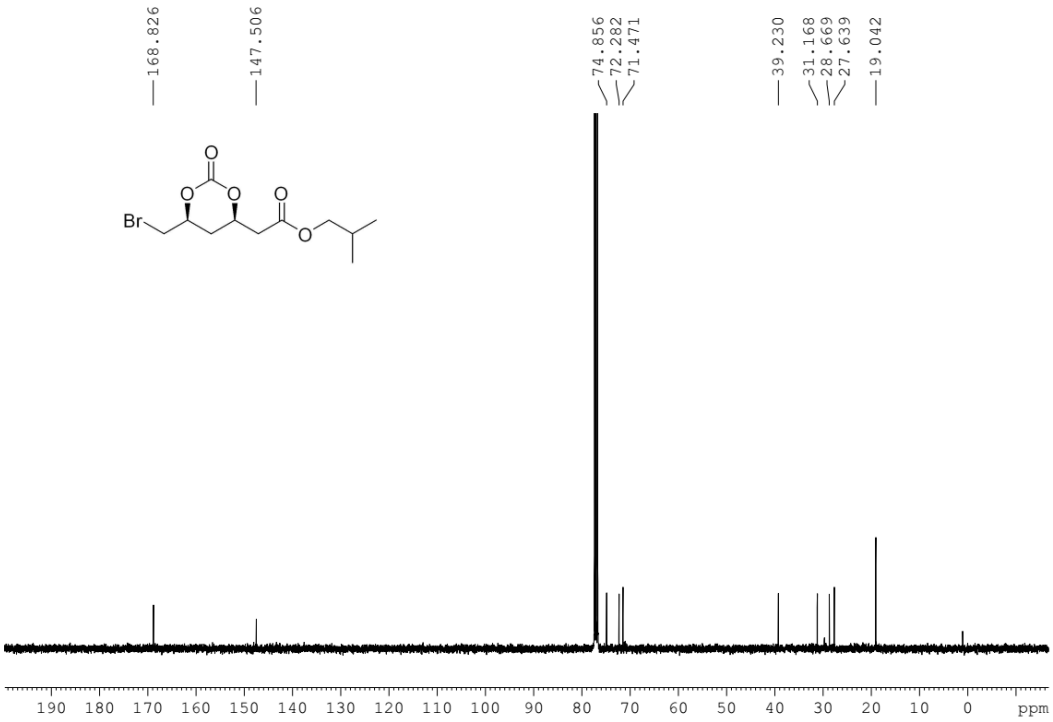


Figure S11. [13]C NMR spectrum of compound **2e**, related to **Table 2**.

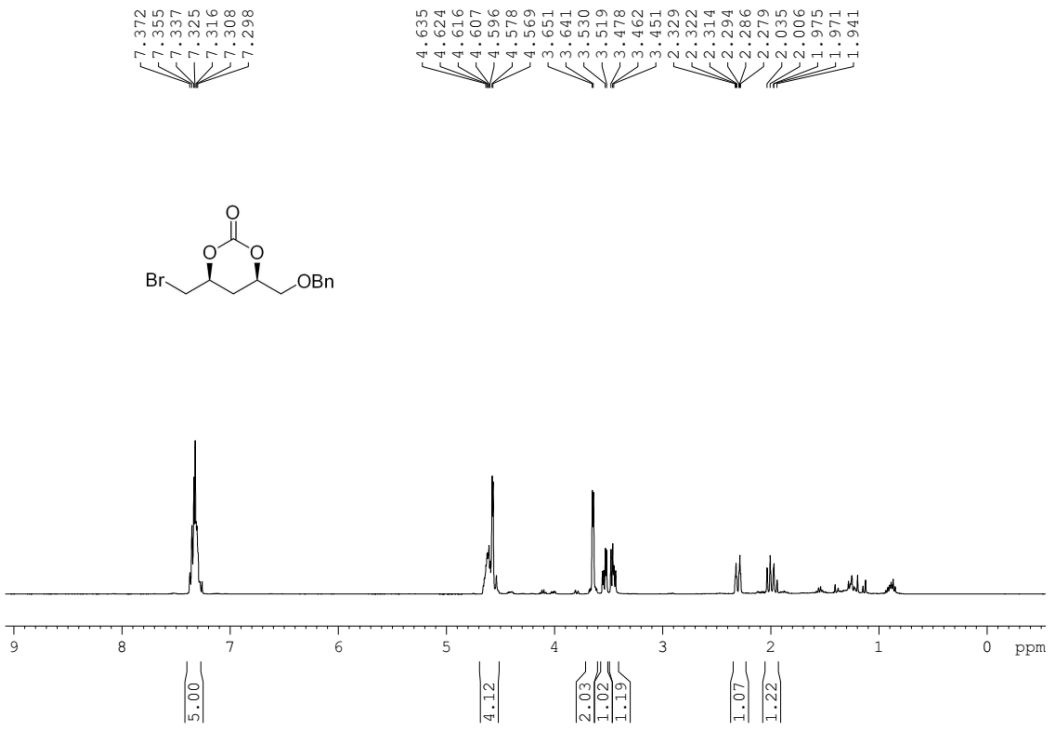


Figure S12. [1]H NMR spectrum of compound **2f**, related to **Table 2**.

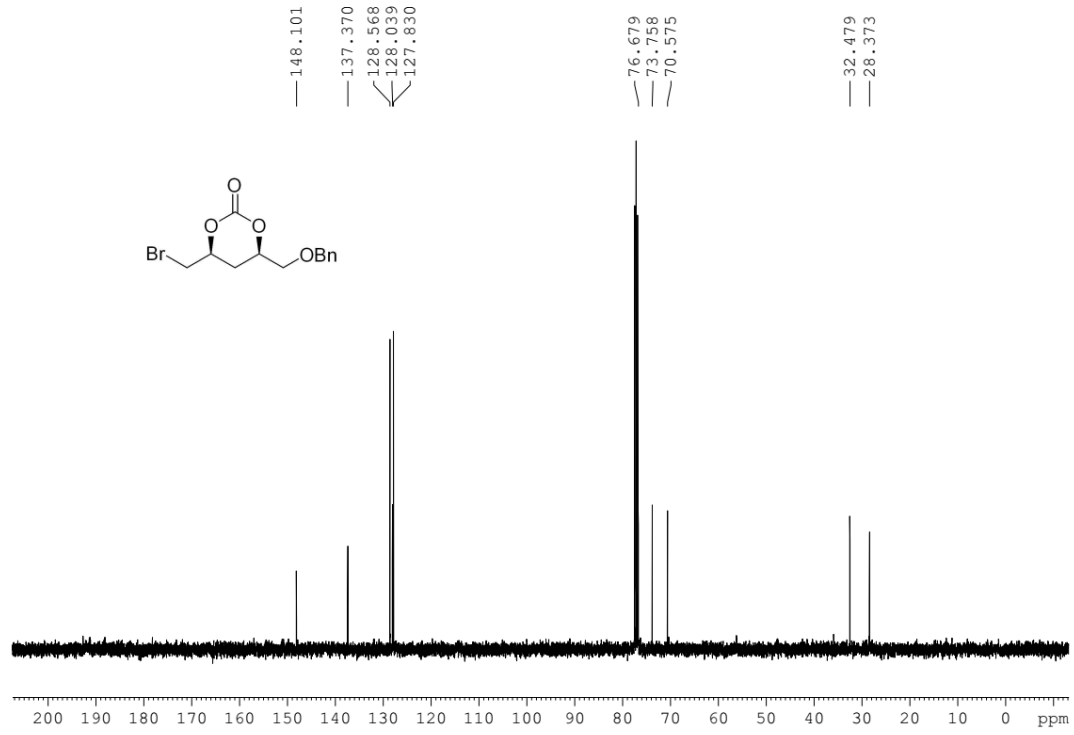


Figure S13. [13]C NMR spectrum of compound **2f**, related to **Table 2**.

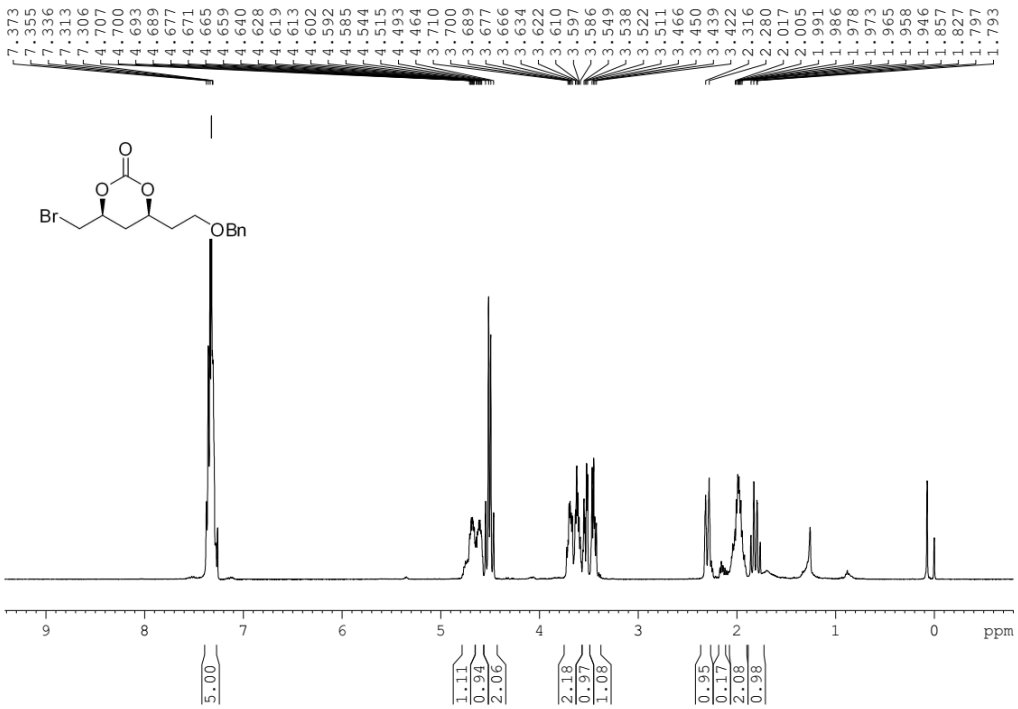


Figure S14. ^{1}H NMR spectrum of compound **2g**, related to **Table 2**.

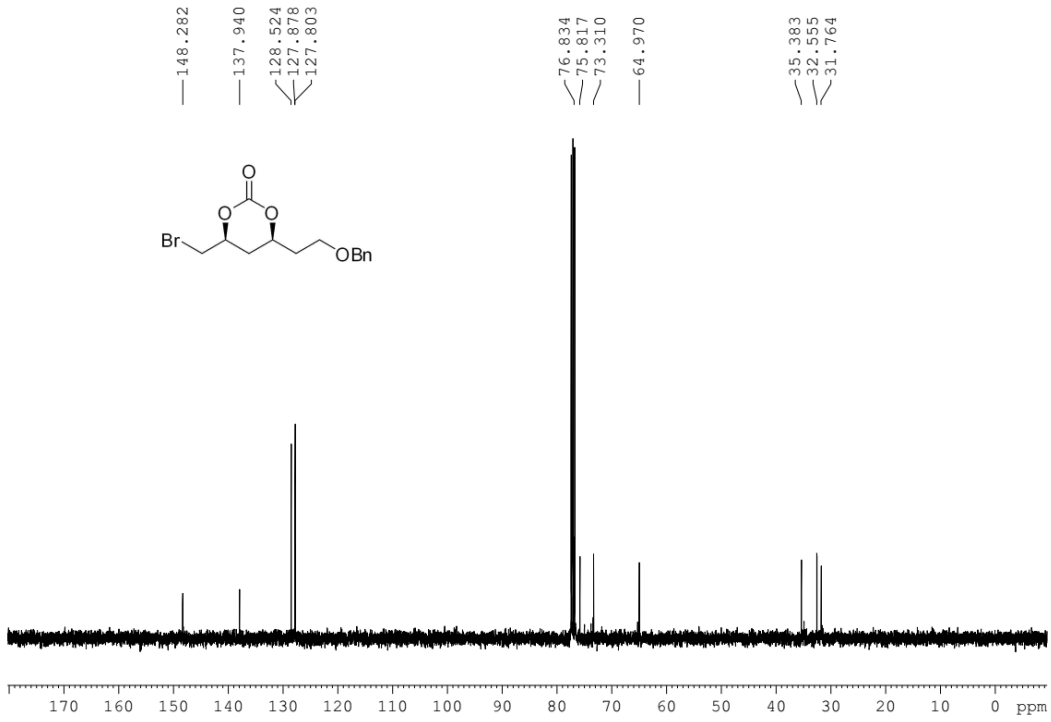


Figure S15. ^{13}C NMR spectrum of compound **2g**, related to **Table 2**.

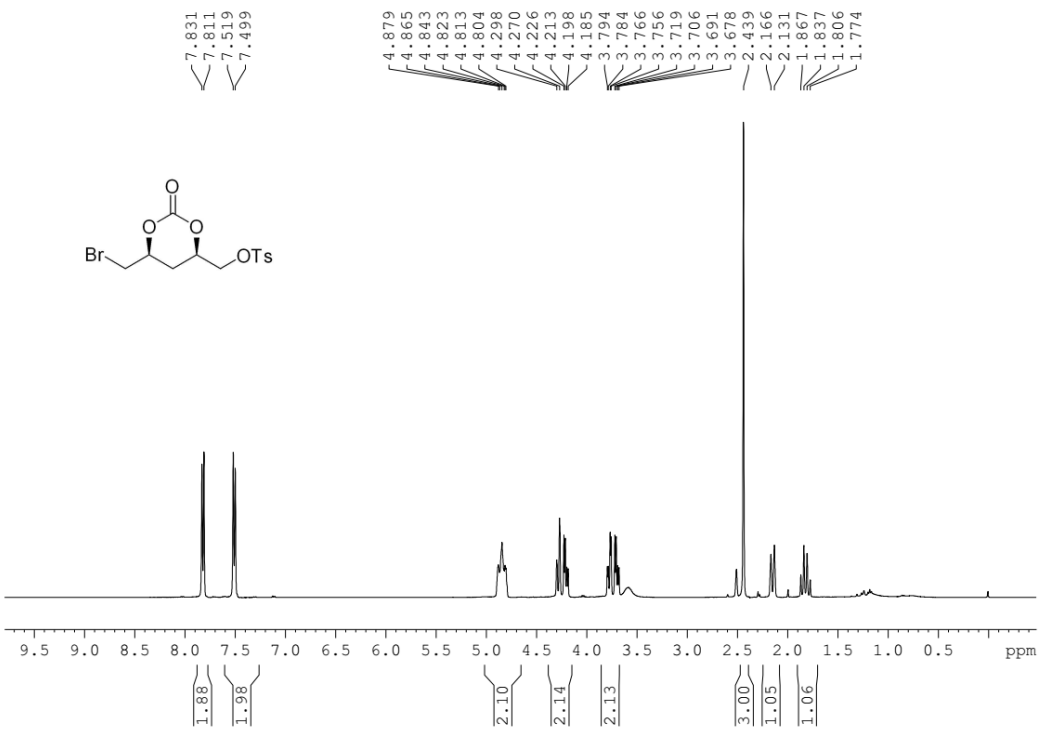


Figure S16. [1]H NMR spectrum of compound **2h**, related to **Table 2**.

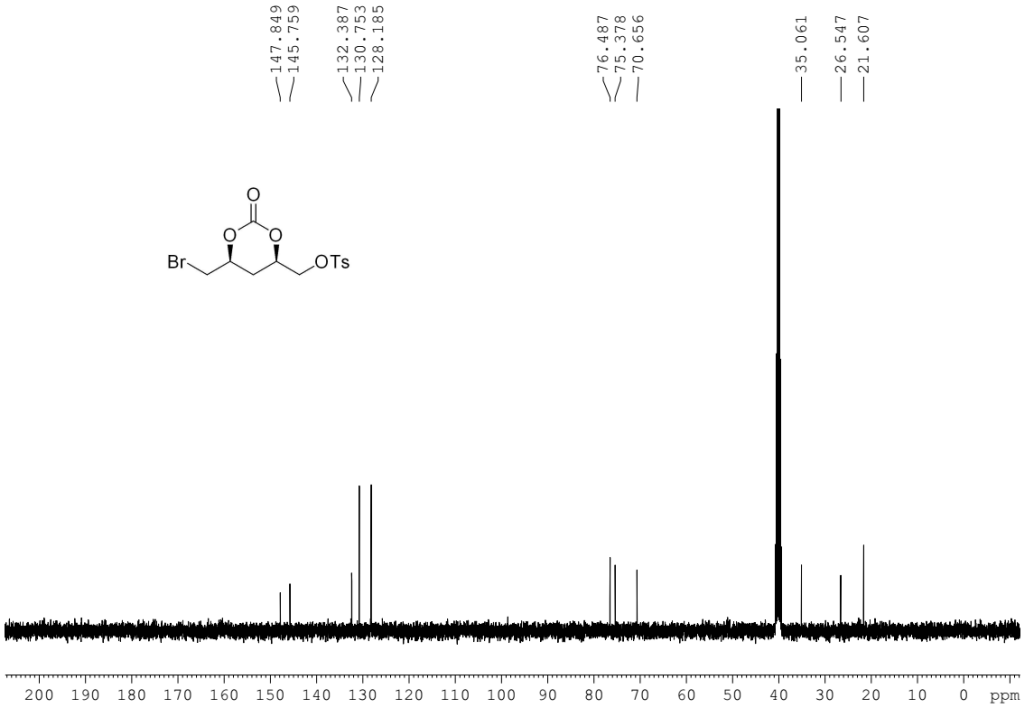
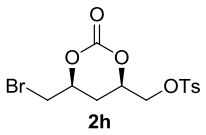
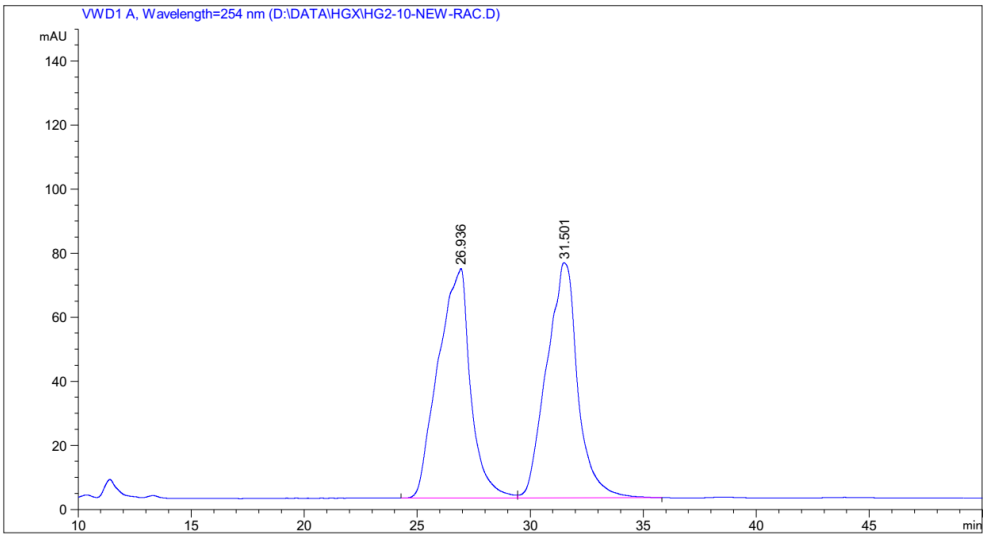


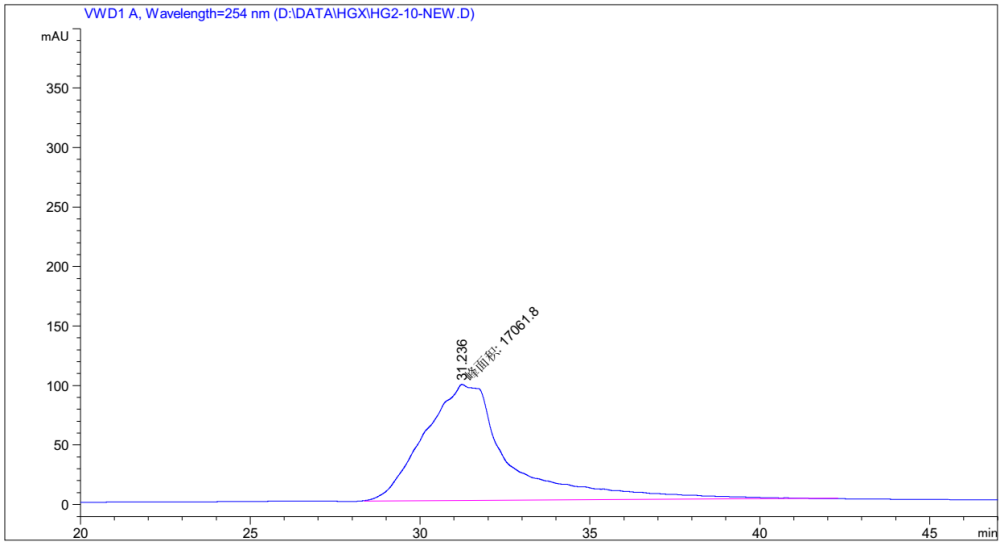
Figure S17. [13]C NMR spectrum of compound **2h**, related to **Table 2**.



2h



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.936	BV	1.2536	7131.73389	71.63023	50.4070
2	31.501	VB	1.3073	7016.55664	73.39655	49.5930



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1	31.236	MM	2.9145	1.70618e4	97.56672	100.0000

Figure S18. HPLC Analysis of compound **2h**.

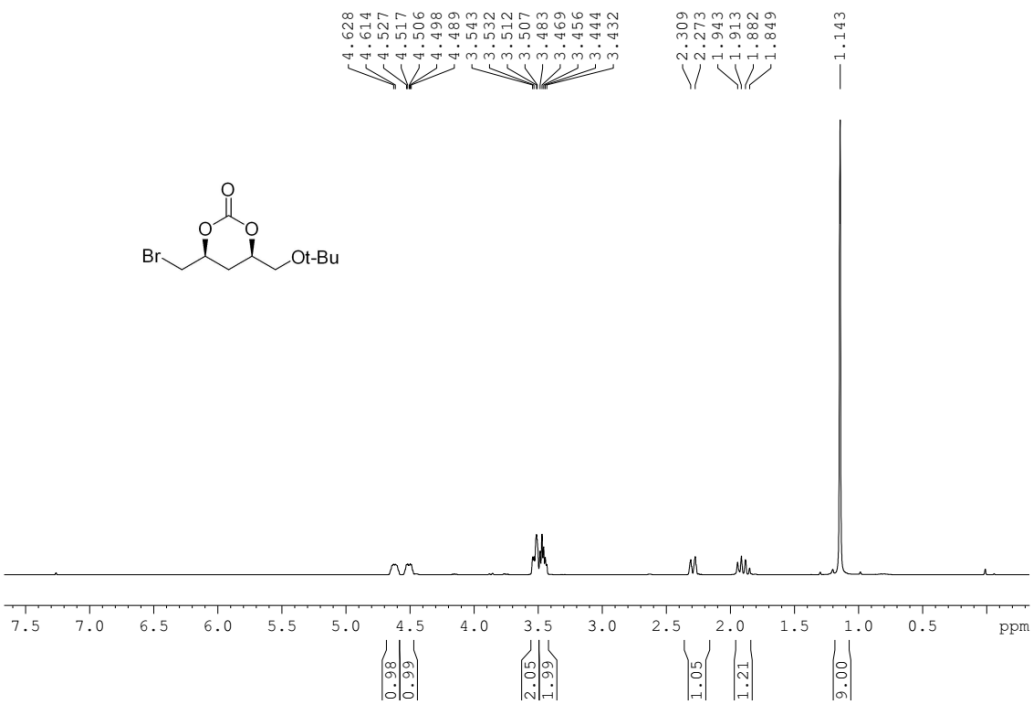


Figure S19. ^{1}H NMR spectrum of compound **2i**, related to **Table 2**.

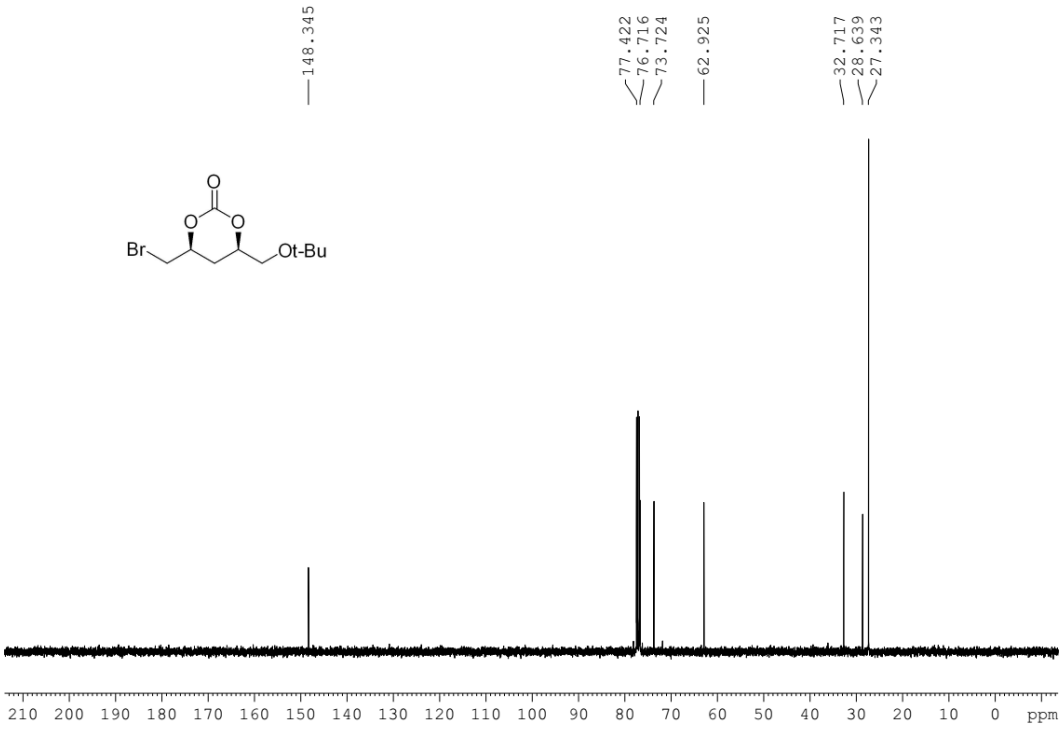


Figure S20. ^{13}C NMR spectrum of compound **2i**, related to **Table 2**.

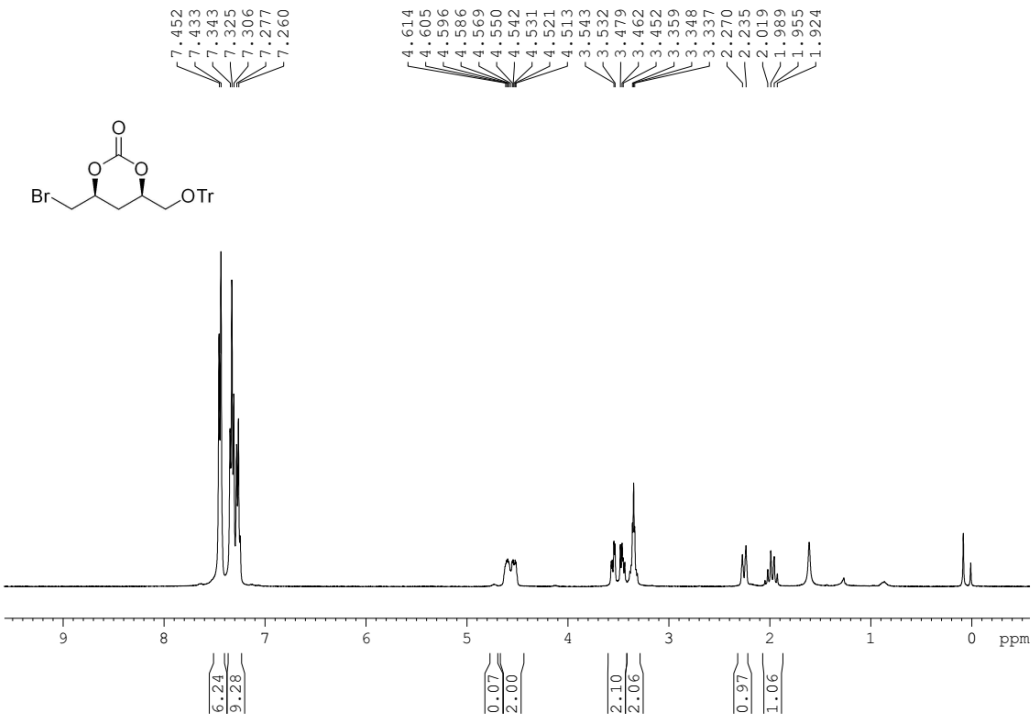


Figure S21. [1]H NMR spectrum of compound **2j**, related to **Table 2**.

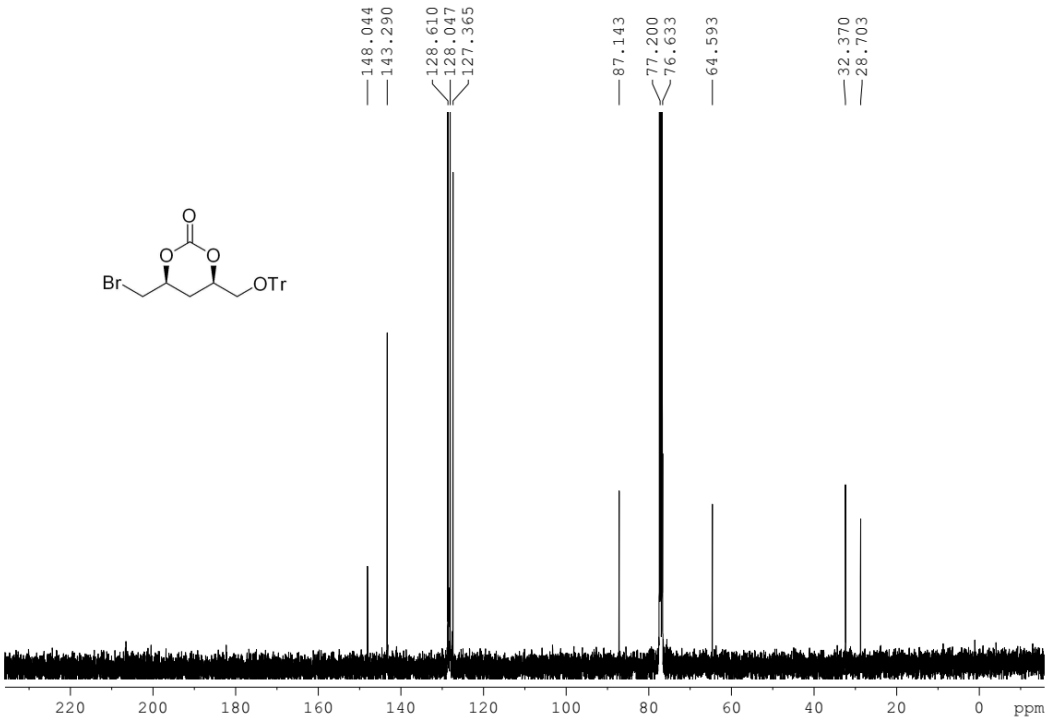


Figure S22. [13]C NMR spectrum of compound **2j**, related to **Table 2**.

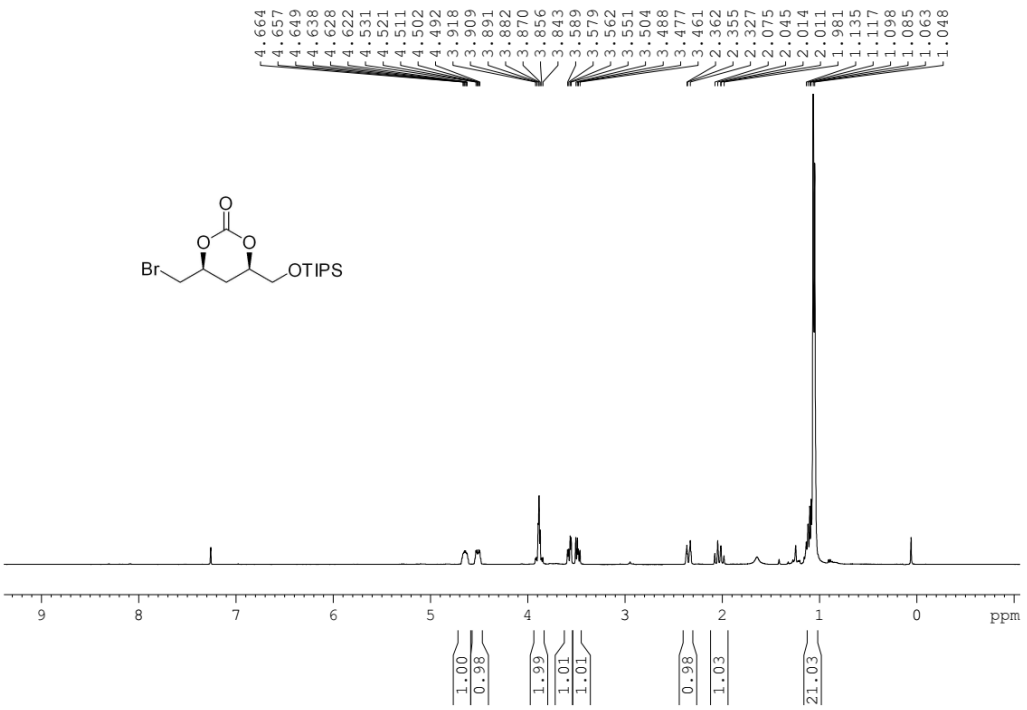


Figure S23. [1]H NMR spectrum of compound **2k**, related to **Table 2**.

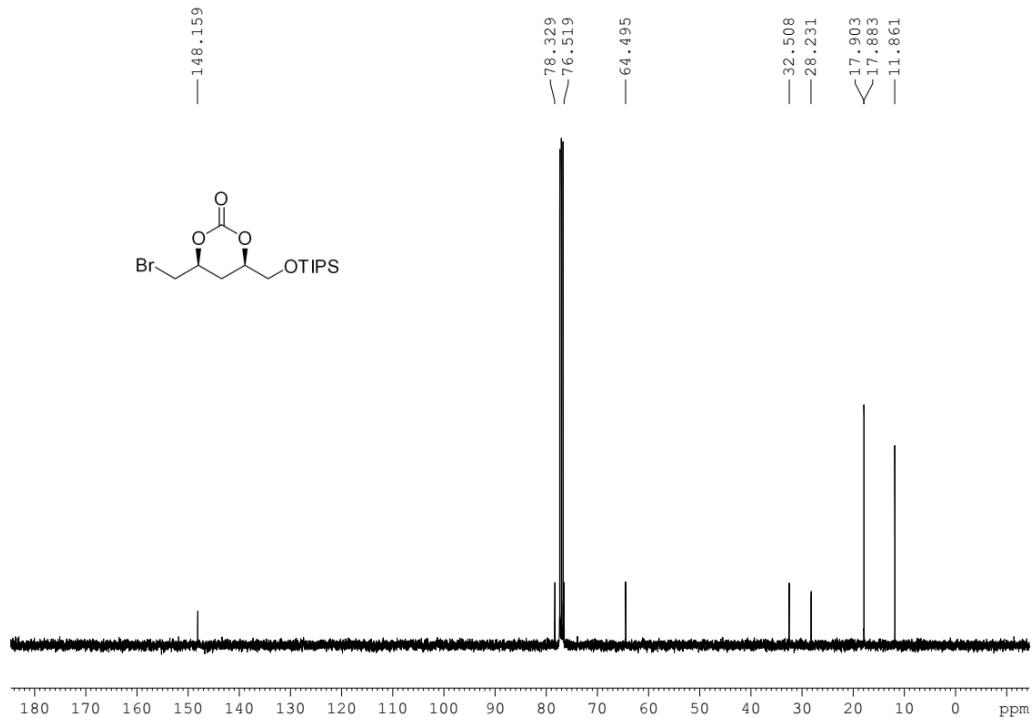


Figure S24. [13]C NMR spectrum of compound **2k**, related to **Table 2**.

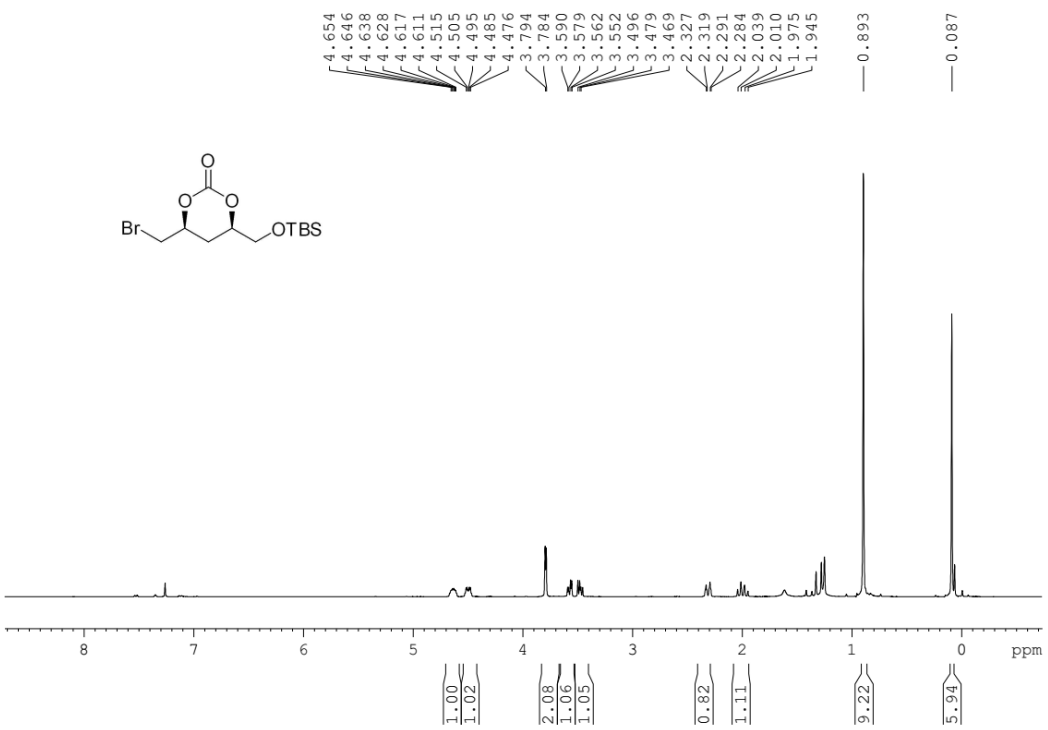


Figure S25. [1]H NMR spectrum of compound **2l**, related to **Table 2**.

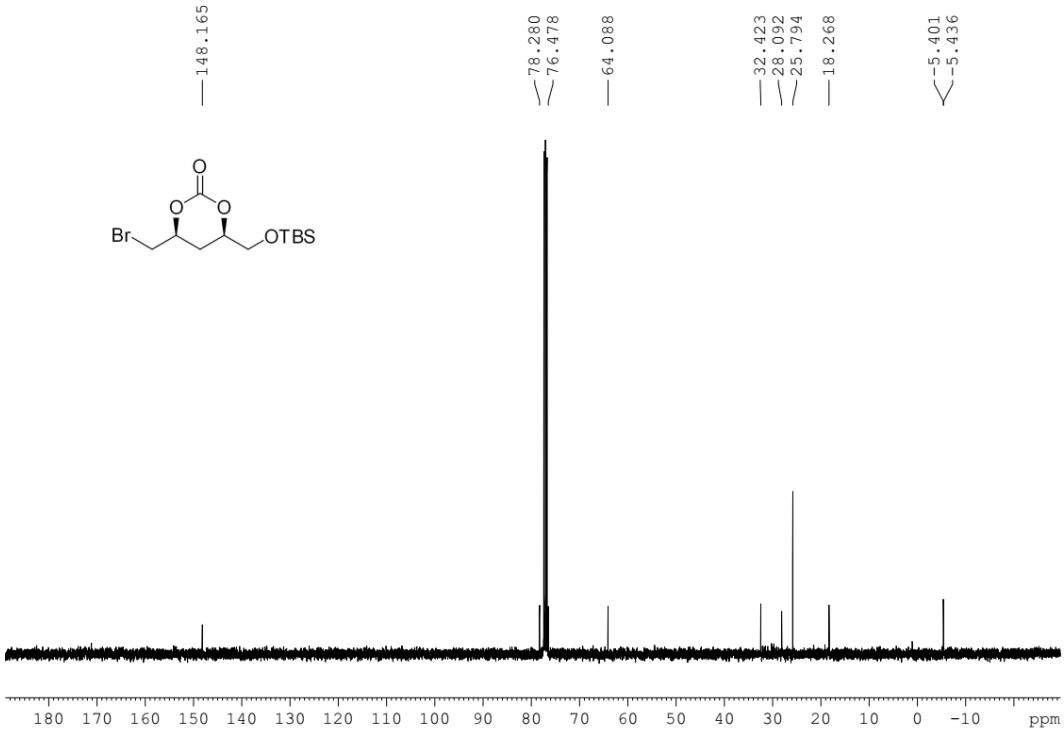


Figure S26. [13]C NMR spectrum of compound **2l**, related to **Table 2**.

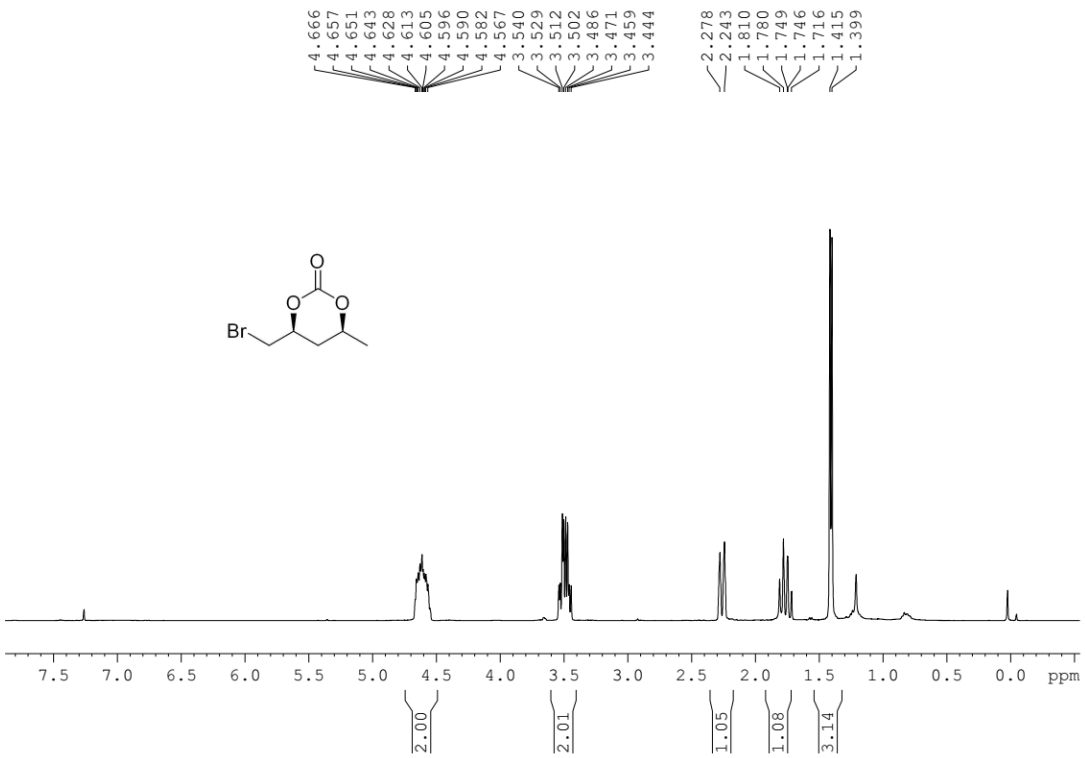


Figure S27. [1]H NMR spectrum of compound **2m**, related to **Table 2**.

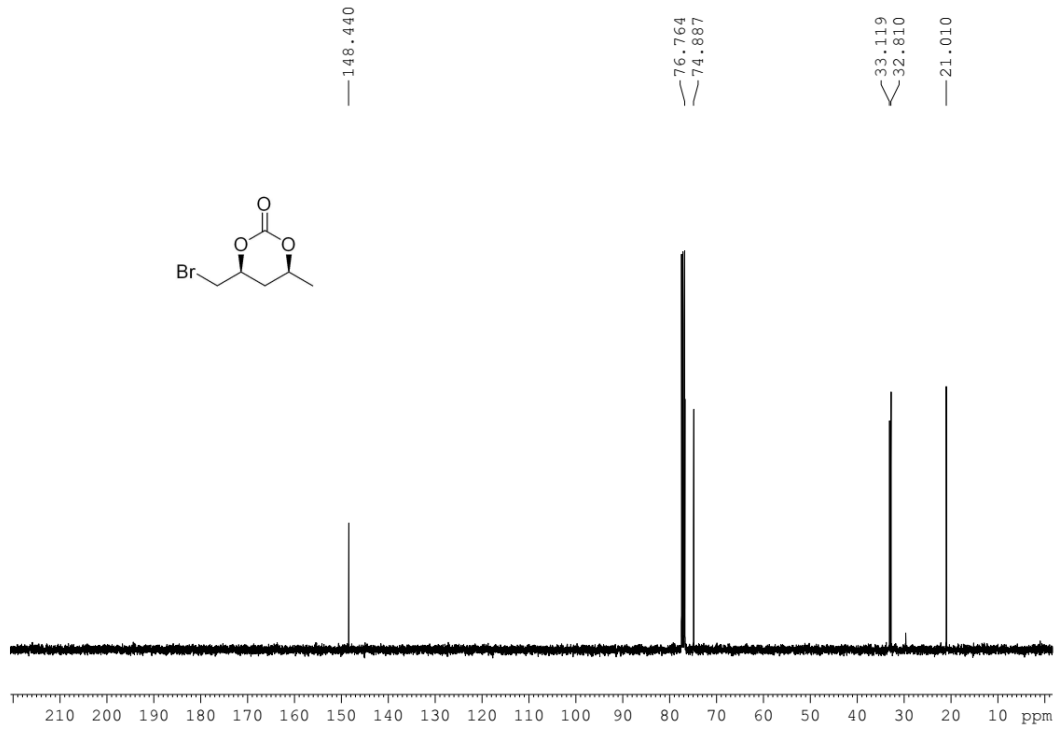


Figure S28. [13]C NMR spectrum of compound **2m**, related to **Table 2**.

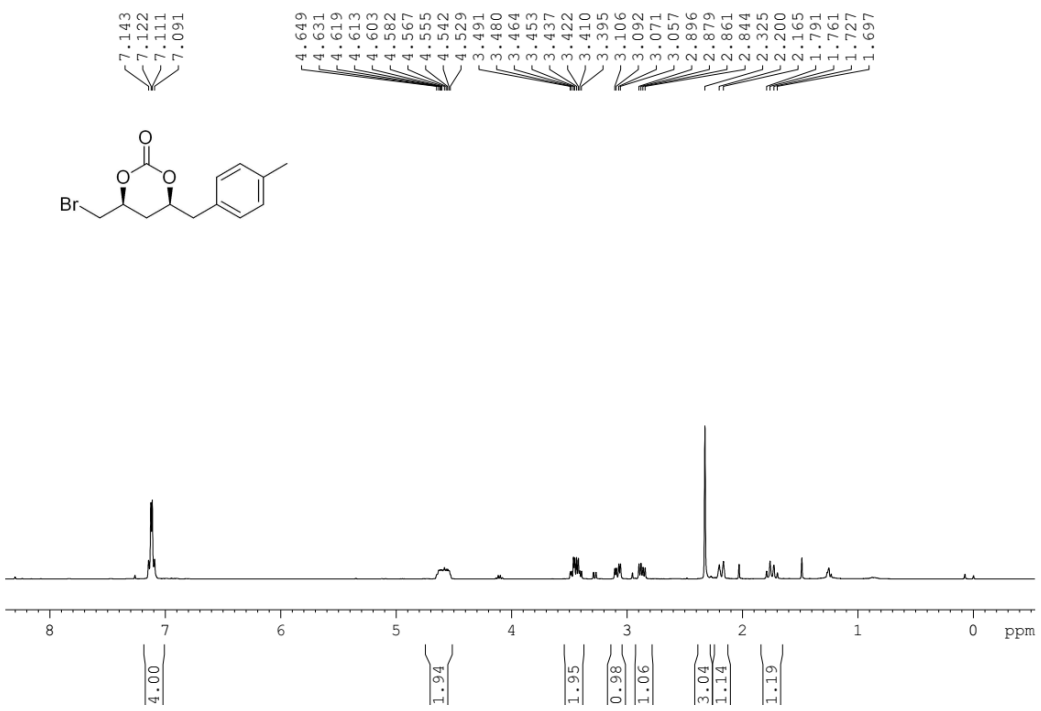


Figure S29. ^{1}H NMR spectrum of compound **2n**, related to **Table 2**.

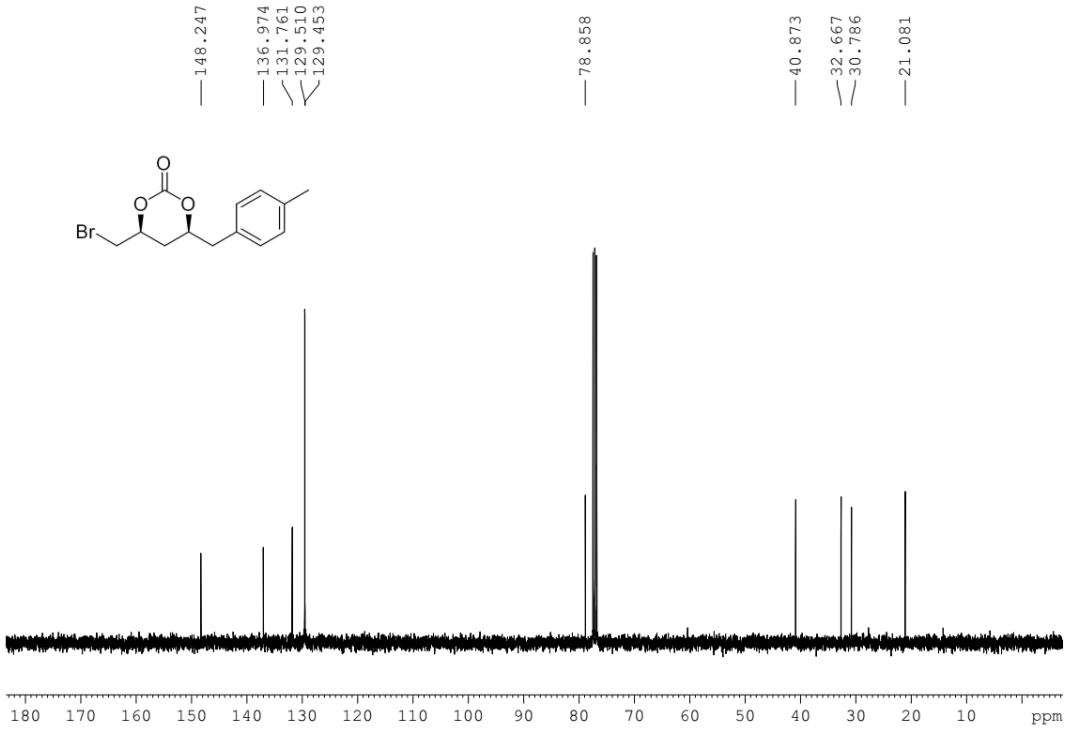


Figure S30. ^{13}C NMR spectrum of compound **2n**, related to **Table 2**.

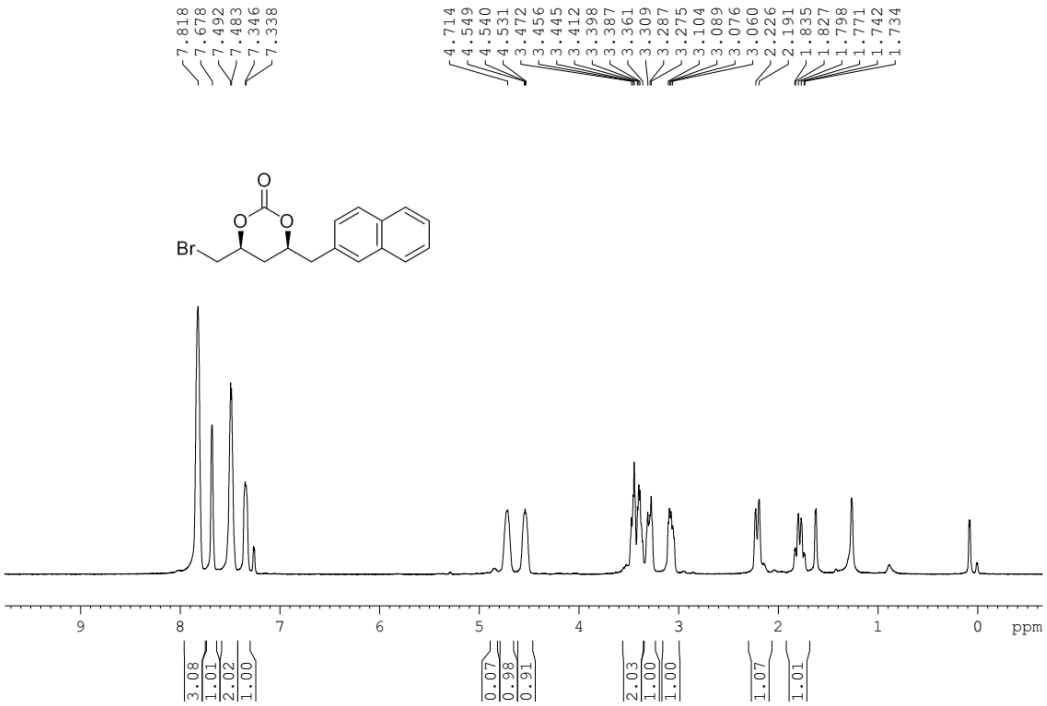


Figure S31. [1]H NMR spectrum of compound **2o**, related to **Table 2**.

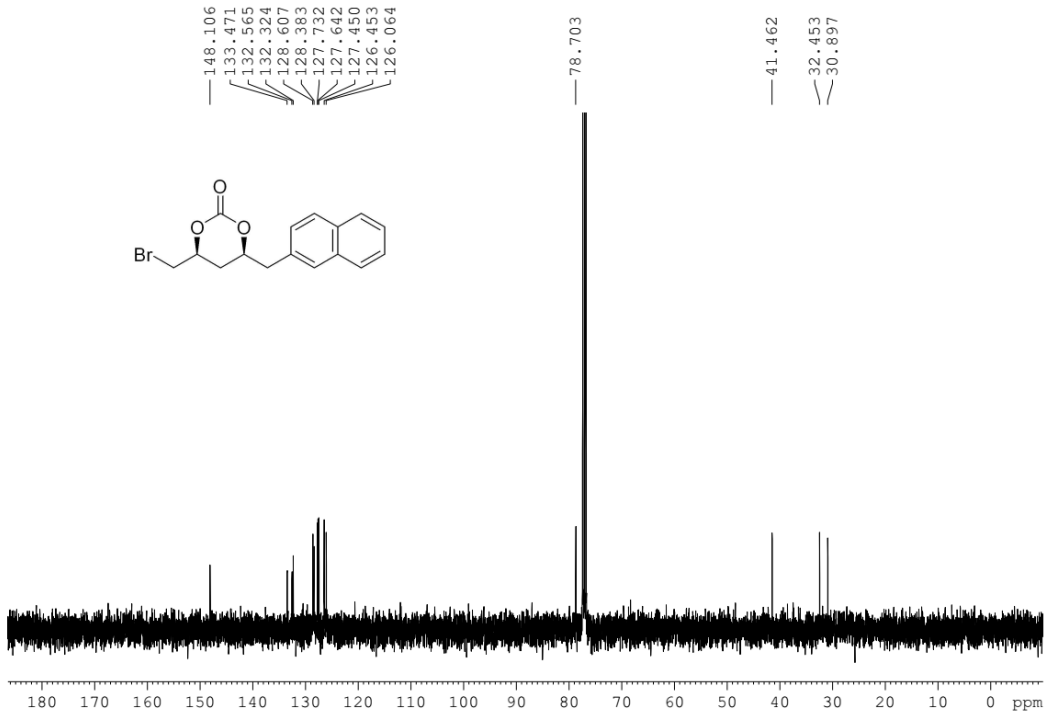


Figure S32. [13]C NMR spectrum of compound **2o**, related to **Table 2**.

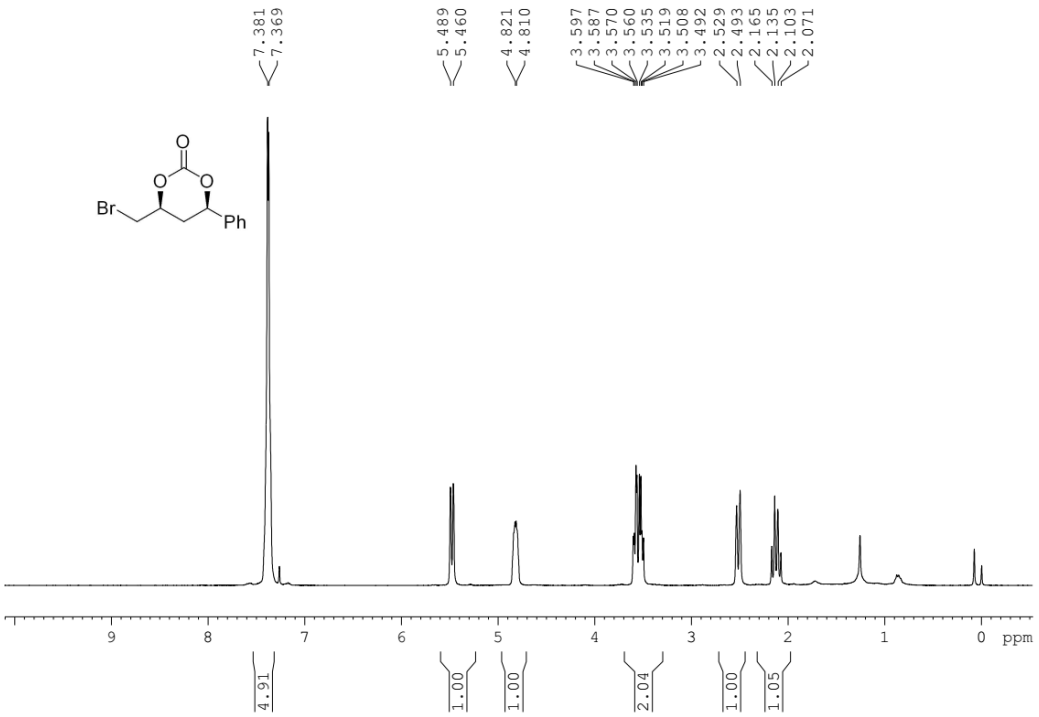


Figure S33. [1]H NMR spectrum of compound **2p**, related to **Table 2**.

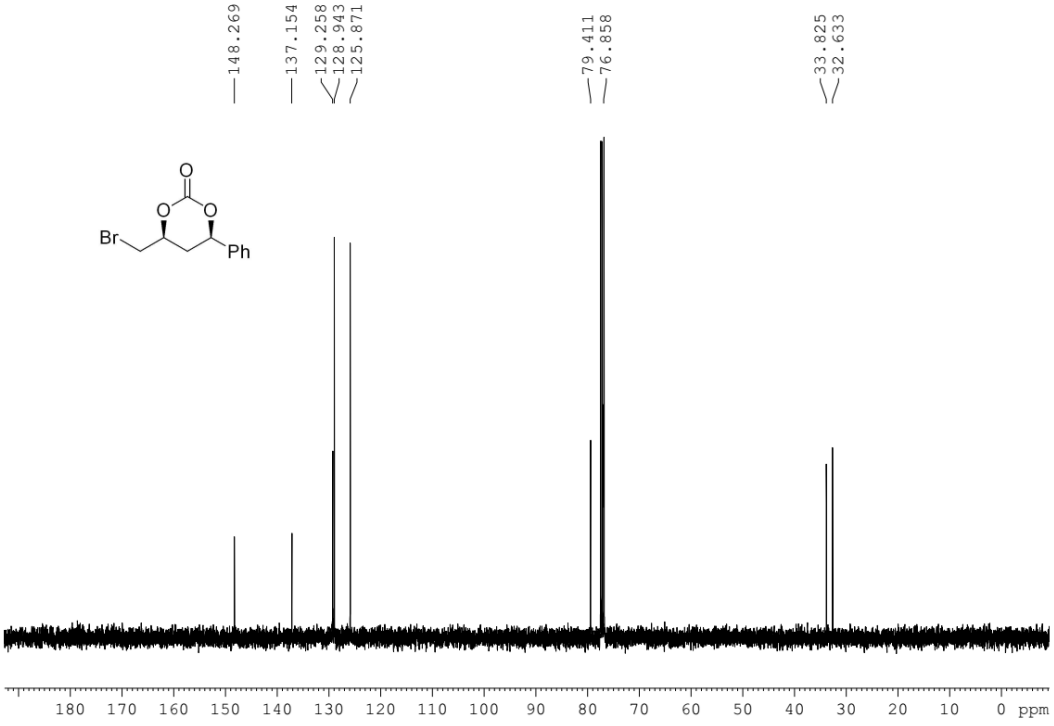
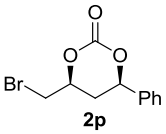
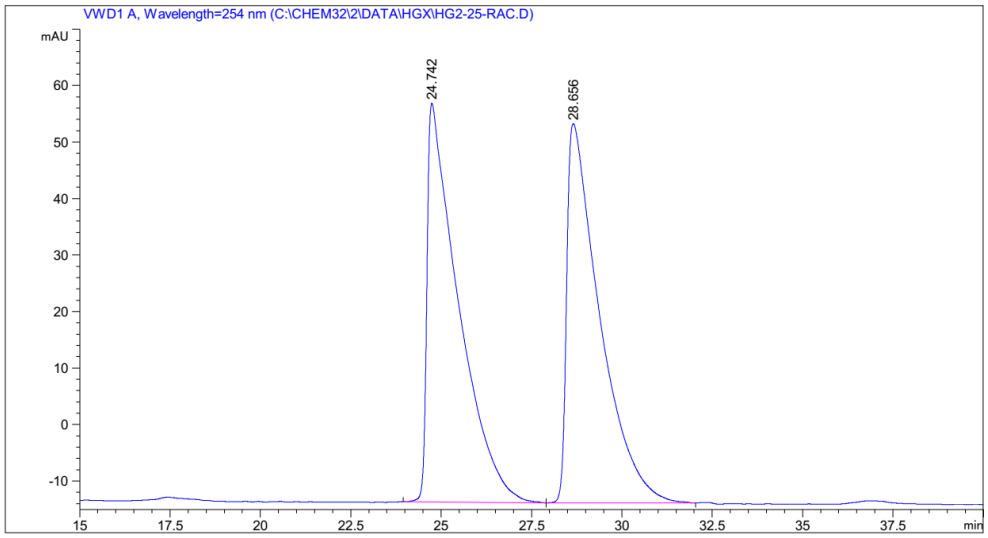


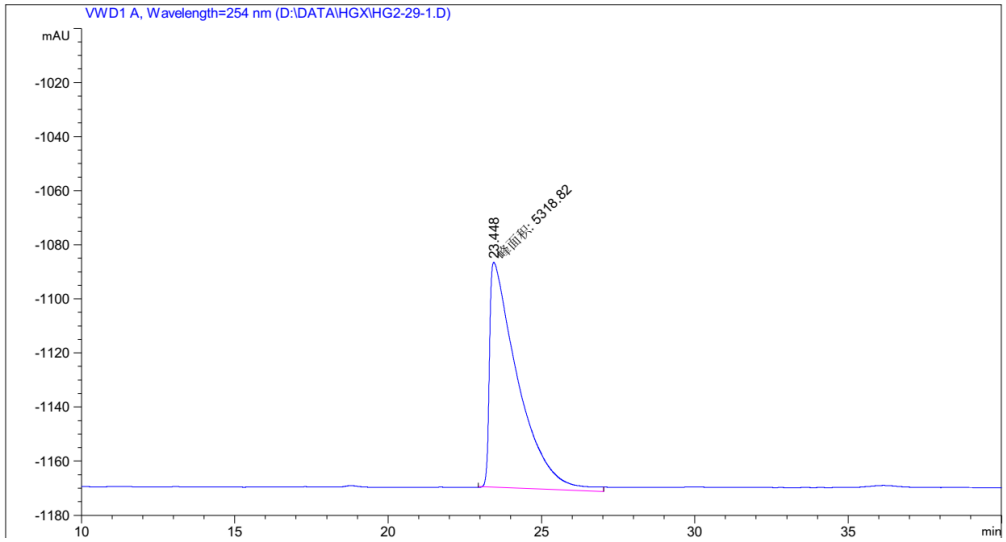
Figure S34. [13]C NMR spectrum of compound **2p**, related to **Table 2**.



2p



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	24.742	BB	0.7760	4240.38721	70.57394	50.0188
2	28.656	BB	0.8768	4237.19238	67.08855	49.9812



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	23.448	MM	1.0678	5318.81982	83.01678	100.0000

Figure S35. HPLC Analysis of compound **2p**.

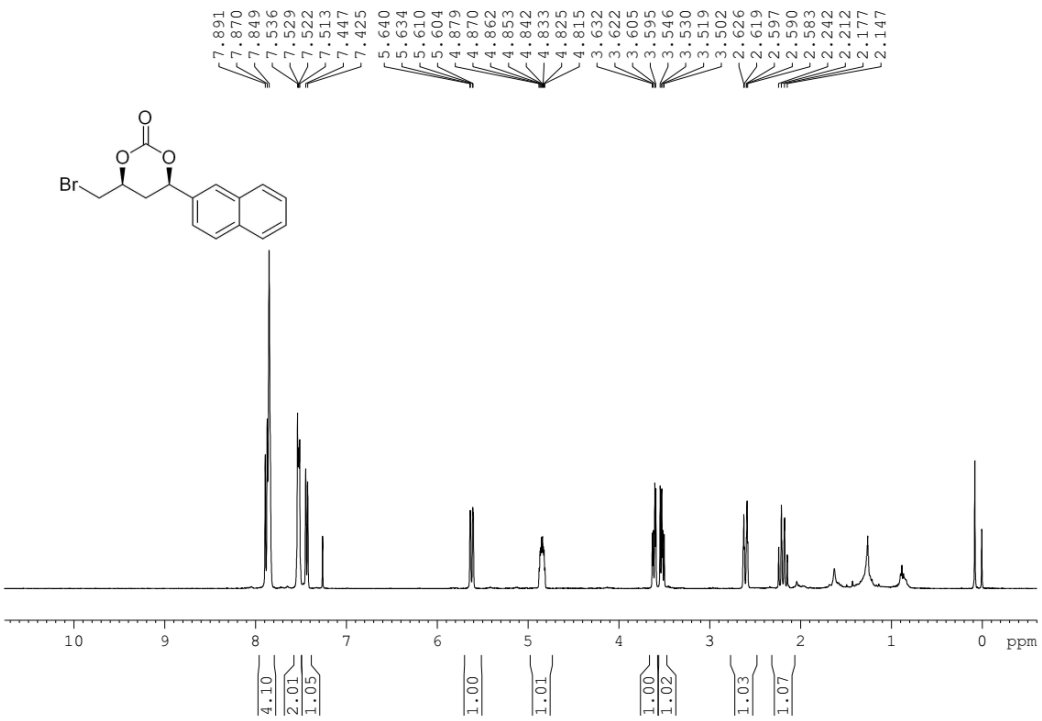


Figure S36. ^{1}H NMR spectrum of compound **2q**, related to **Table 2**.

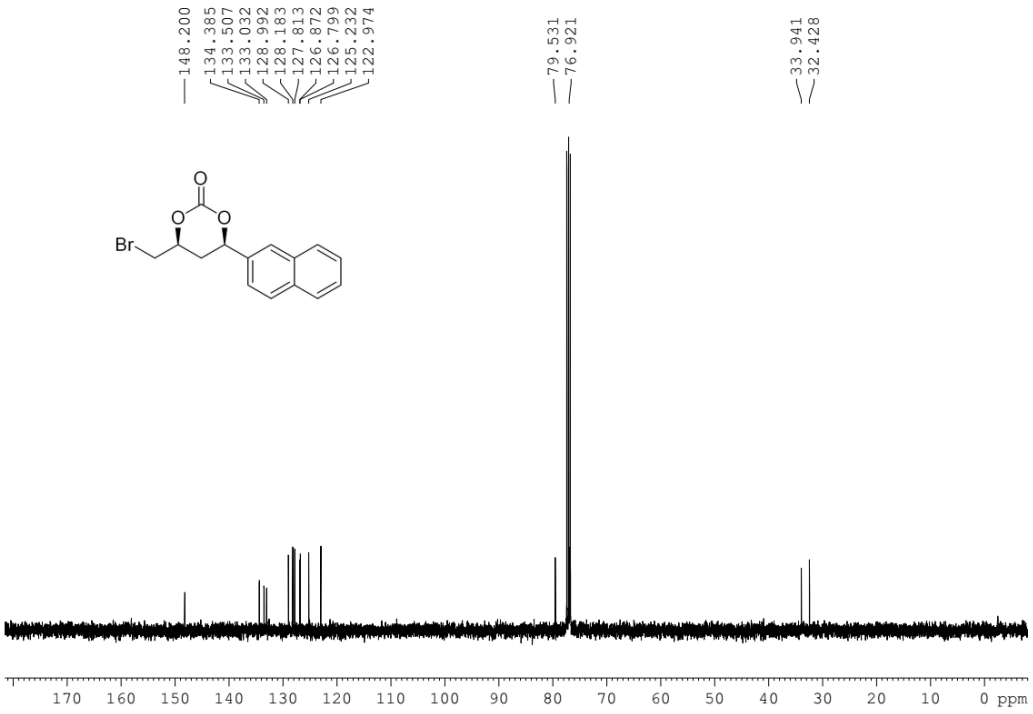


Figure S37. ^{13}C NMR spectrum of compound **2q**, related to **Table 2**.

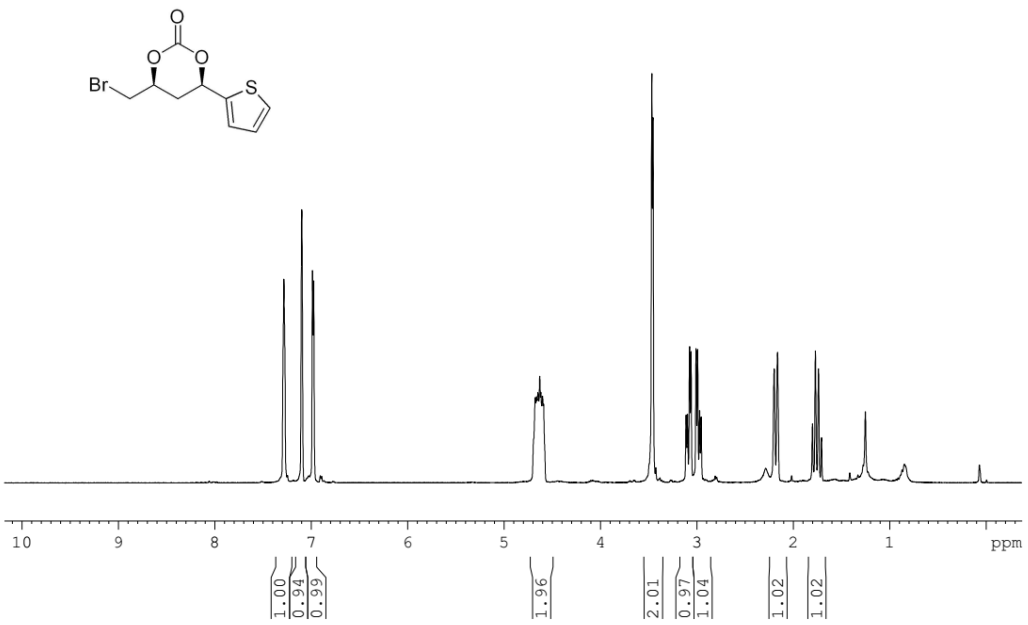


Figure S38. [1]H NMR spectrum of compound **2r**, related to **Table 2**.

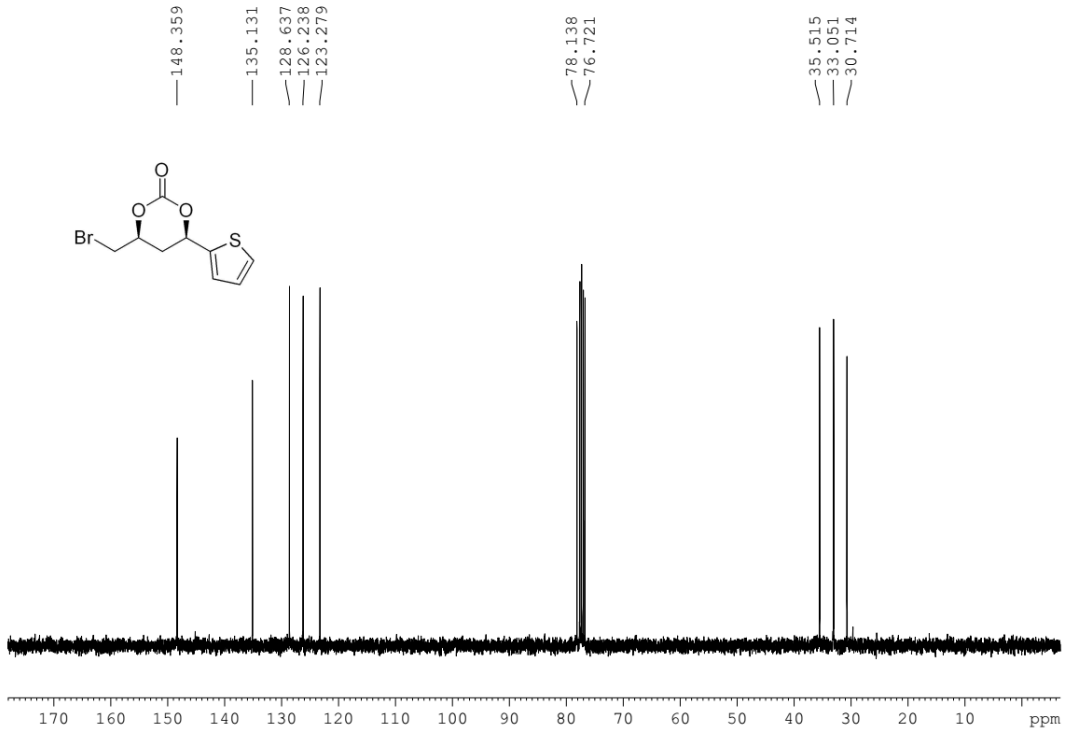


Figure S39. [13]C NMR spectrum of compound **2r**, related to **Table 2**.

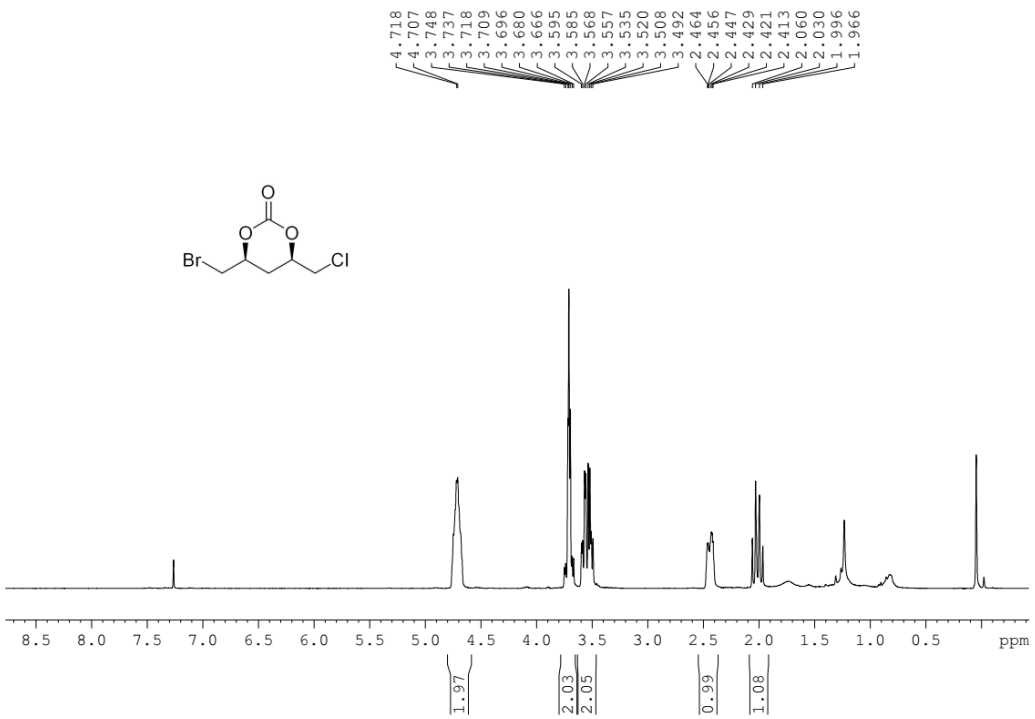


Figure S40. ^{1}H NMR spectrum of compound **2s**, related to **Table 2**.

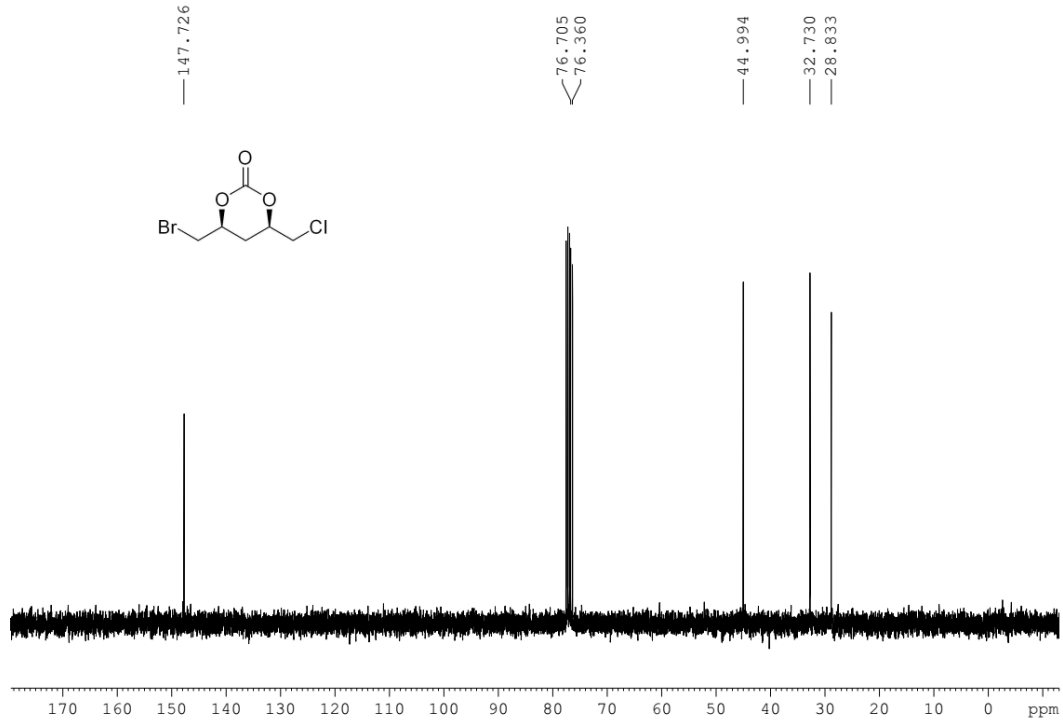
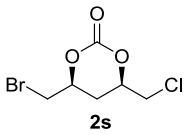
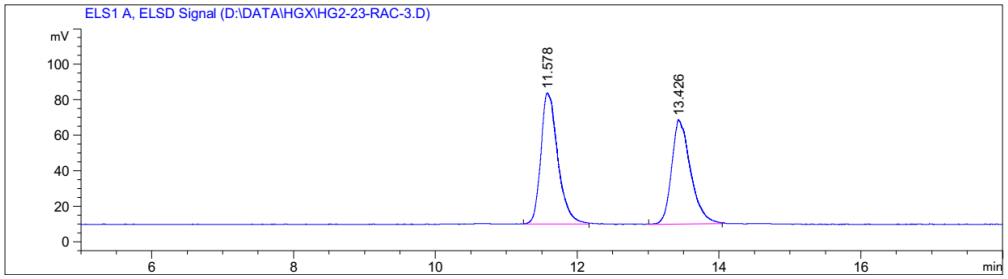


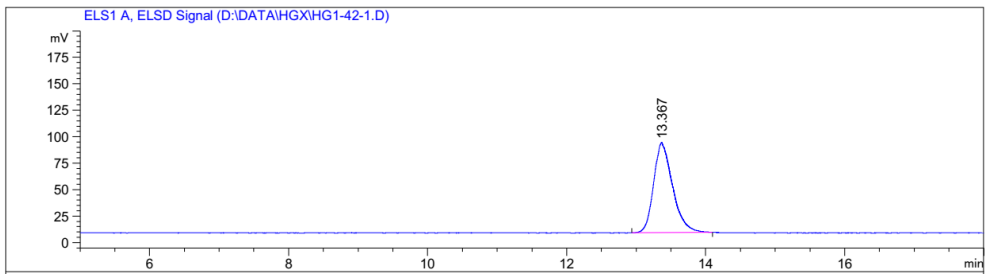
Figure S41. ^{13}C NMR spectrum of compound **2s**, related to **Table 2**.



2s



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mV*s]	峰高 [mV]	峰面积 %
1	11.578	VV	0.2039	1227.34460	74.04911	52.9897
2	13.426	VV	0.2237	1088.84937	58.88310	47.0103



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mV*s]	峰高 [mV]	峰面积 %
1	13.367	VB	0.2270	1616.07397	85.32702	100.0000

Figure S42. HPLC Analysis of compound **2s**.

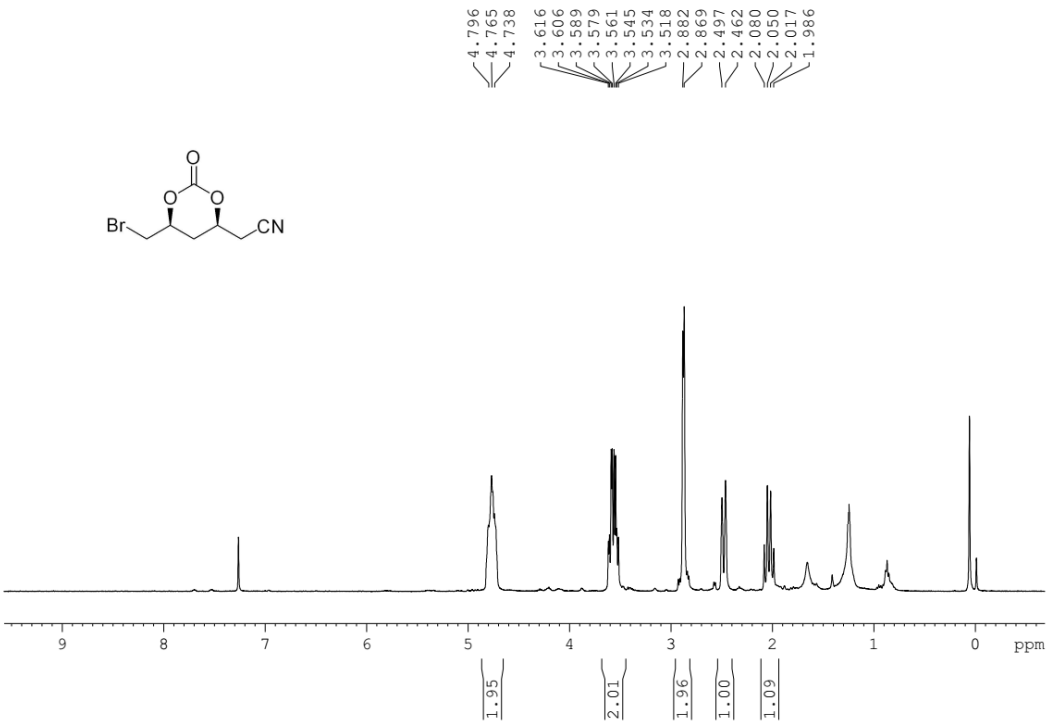


Figure S43. [1]H NMR spectrum of compound **2t**, related to **Table 2**.

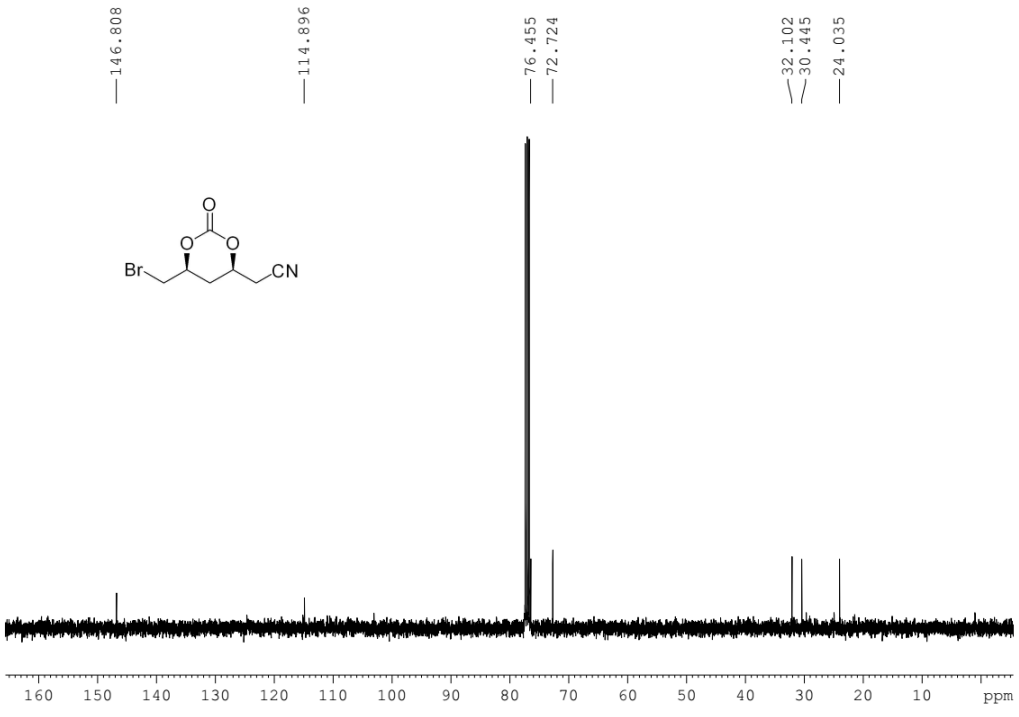


Figure S44. [13]C NMR spectrum of compound **2t**, related to **Table 2**.

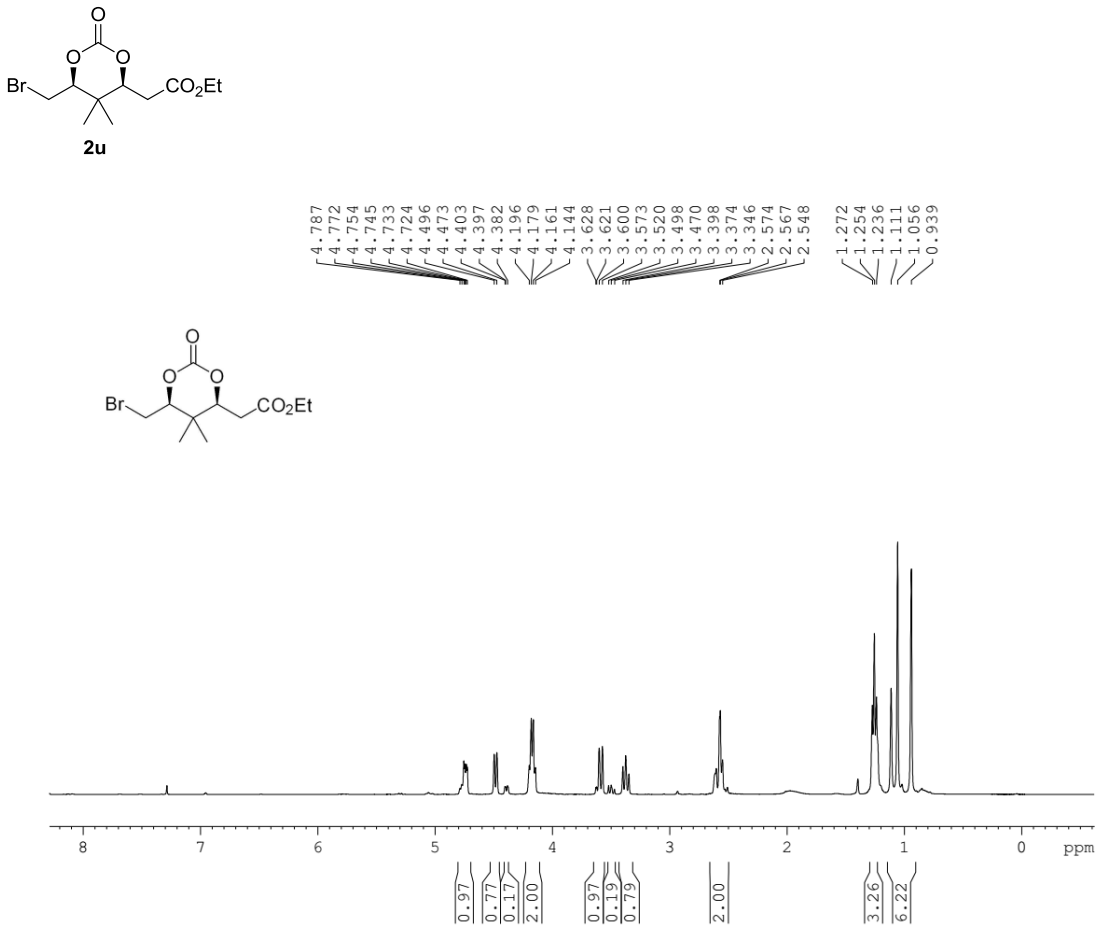


Figure S45. [1]H NMR spectrum of compound **2u**, related to **Table 2**.

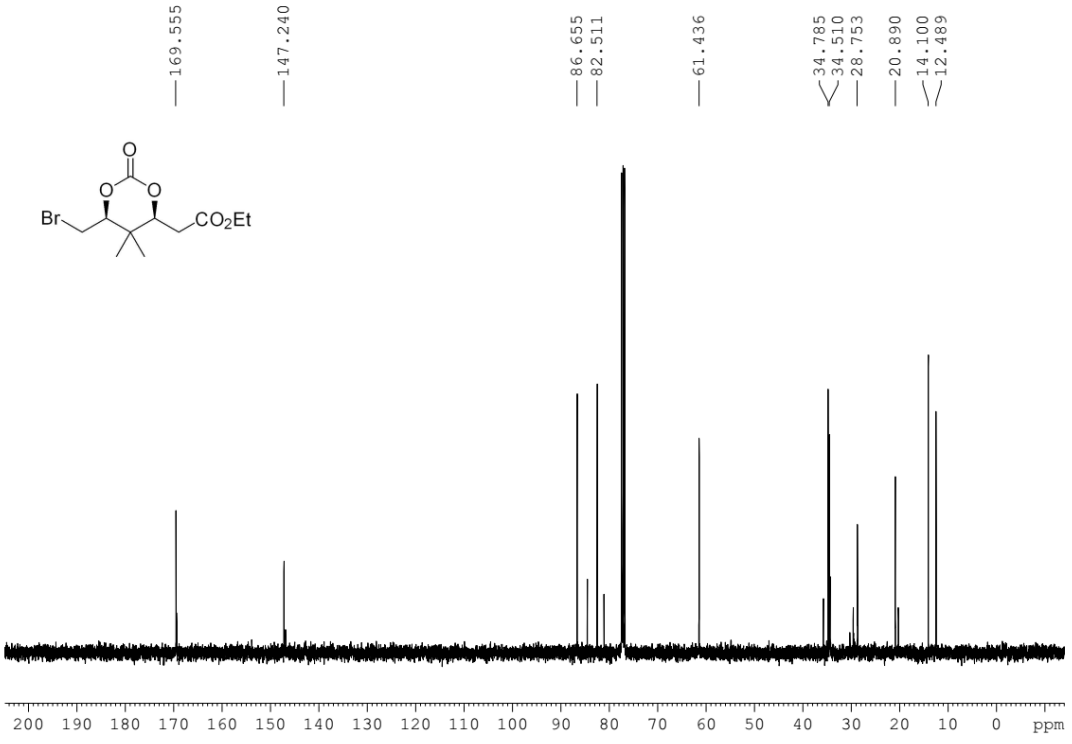


Figure S46. [13]C NMR spectrum of compound **2u**, related to **Table 2**.

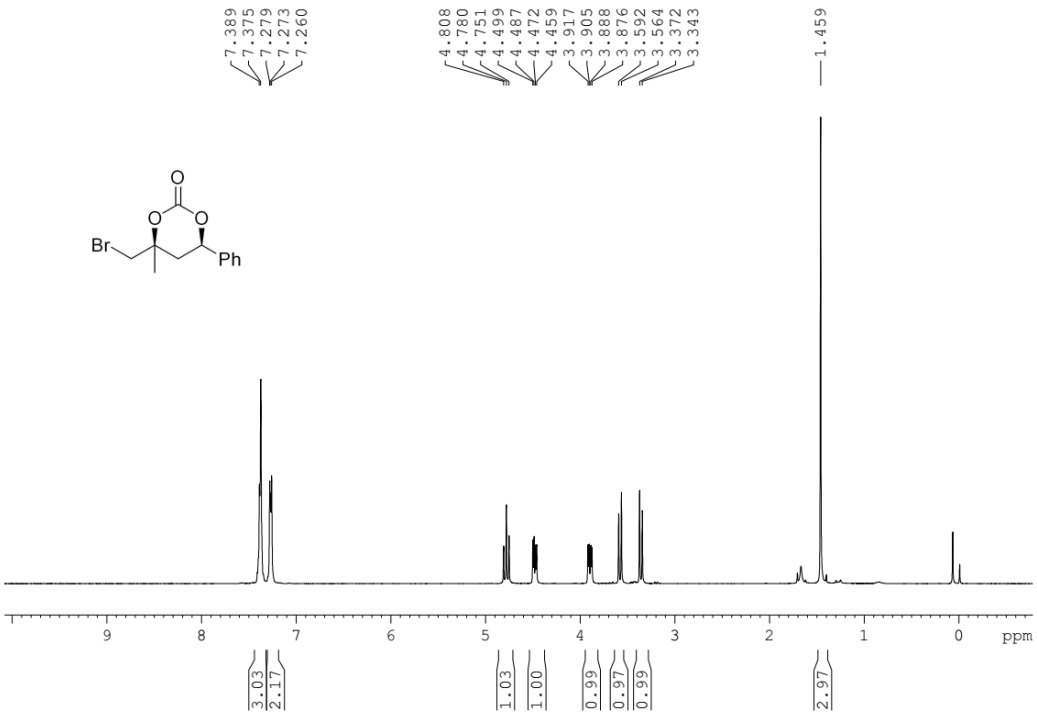


Figure S47. [1]H NMR spectrum of compound **2v**, related to **Table 2**.

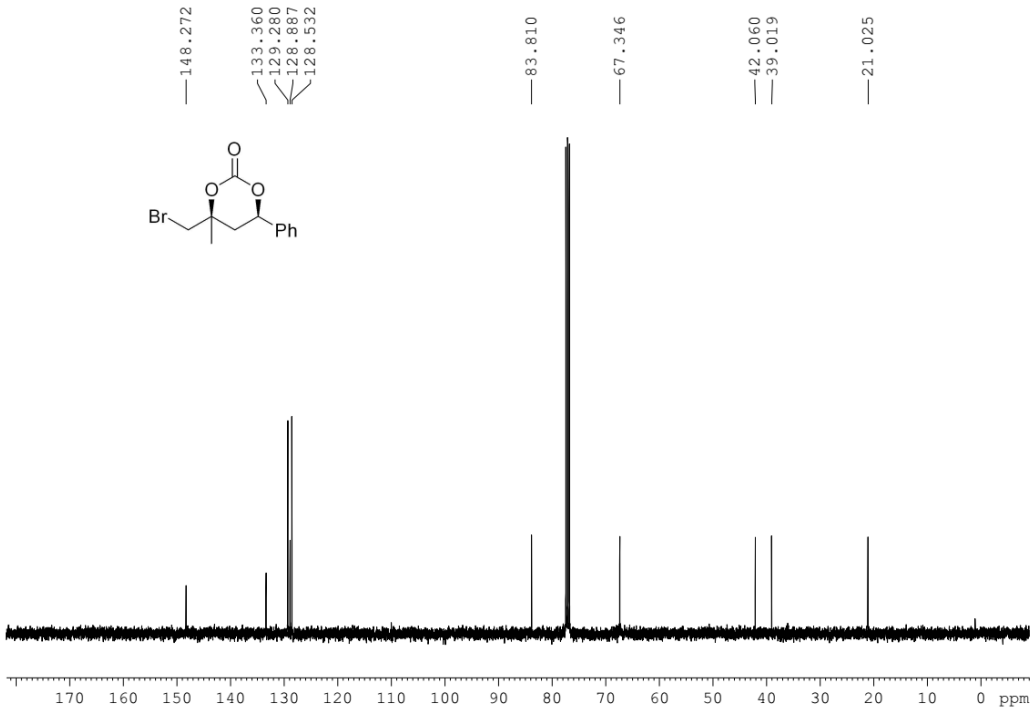


Figure S48. [13]C NMR spectrum of compound **2v**, related to **Table 2**.

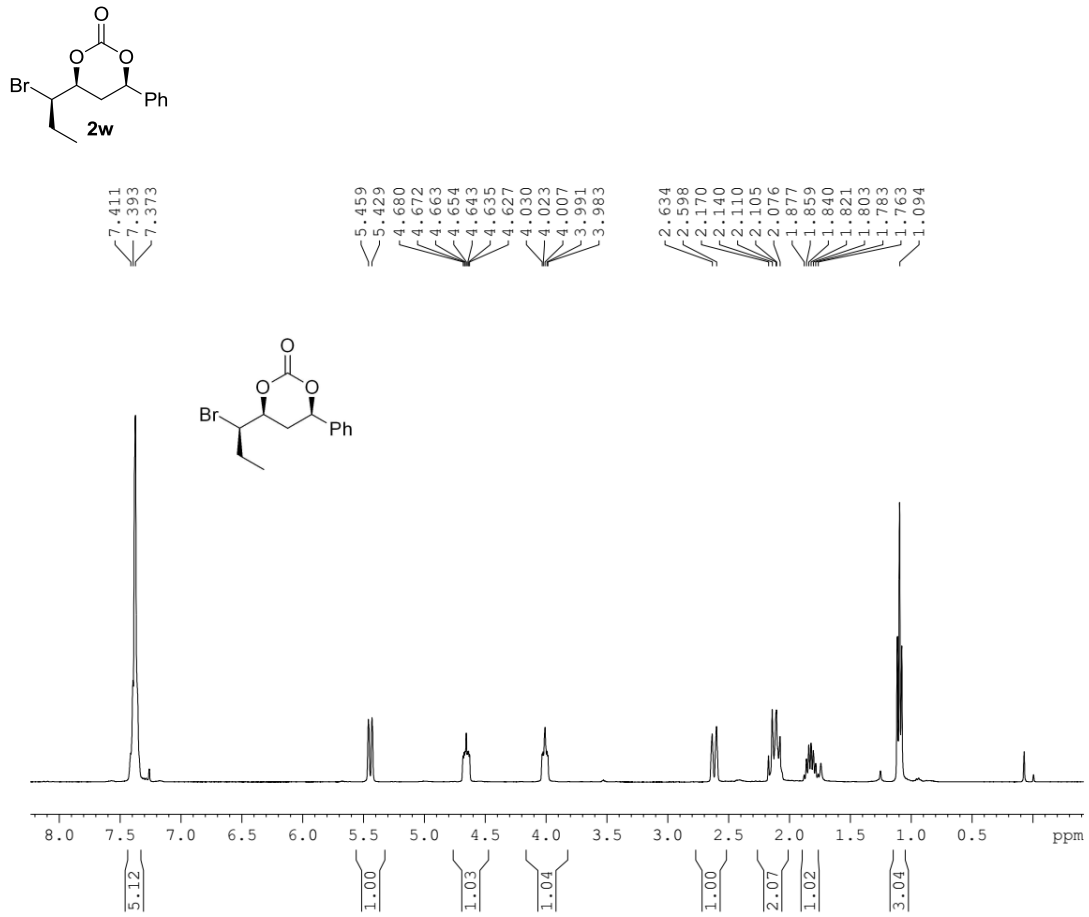


Figure S49. [1]H NMR spectrum of compound **2w**, related to **Table 2**.

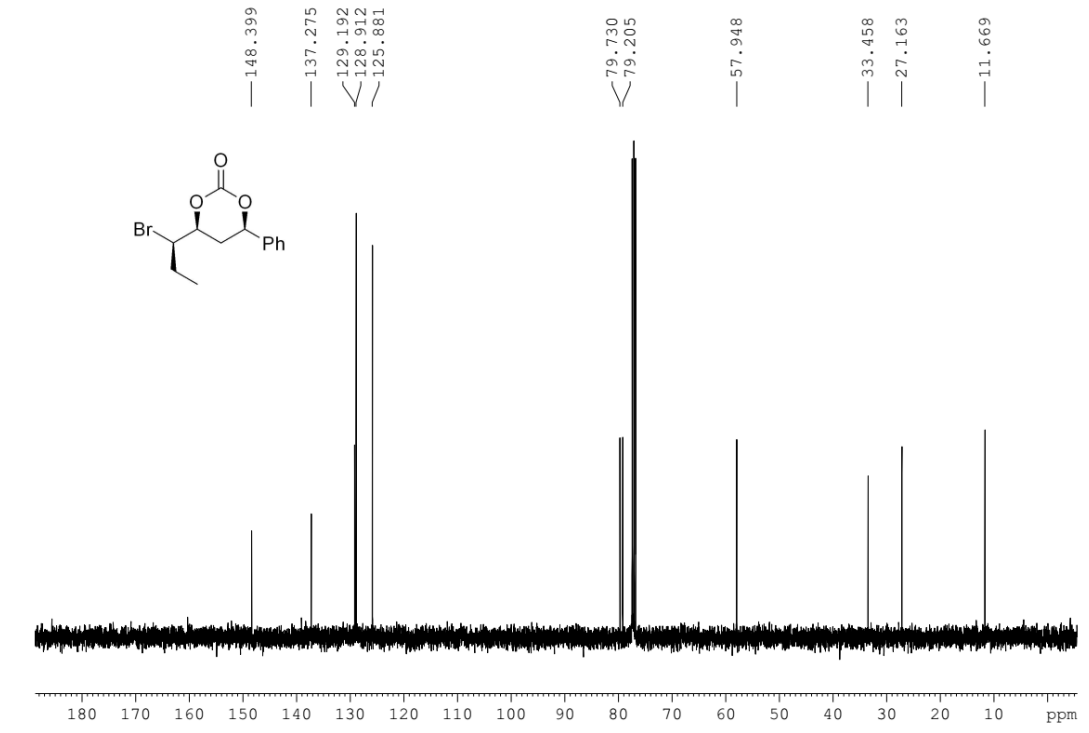


Figure S50. [13]C NMR spectrum of compound **2w**, related to **Table 2**.

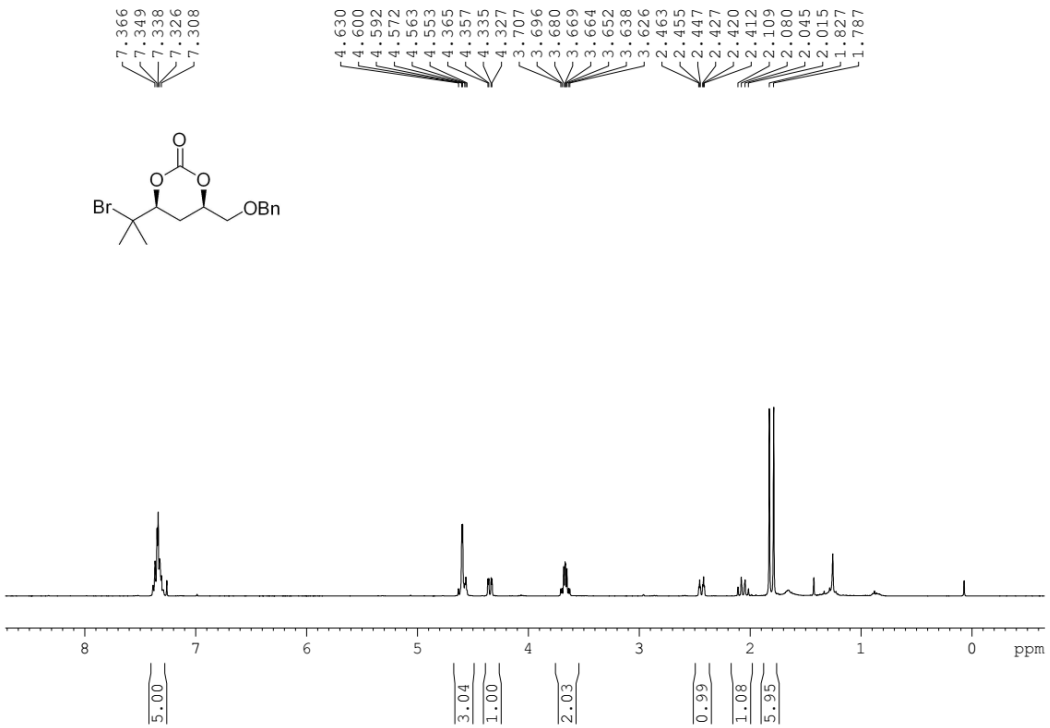


Figure S51. [1]H NMR spectrum of compound **2x**, related to **Table 2**.

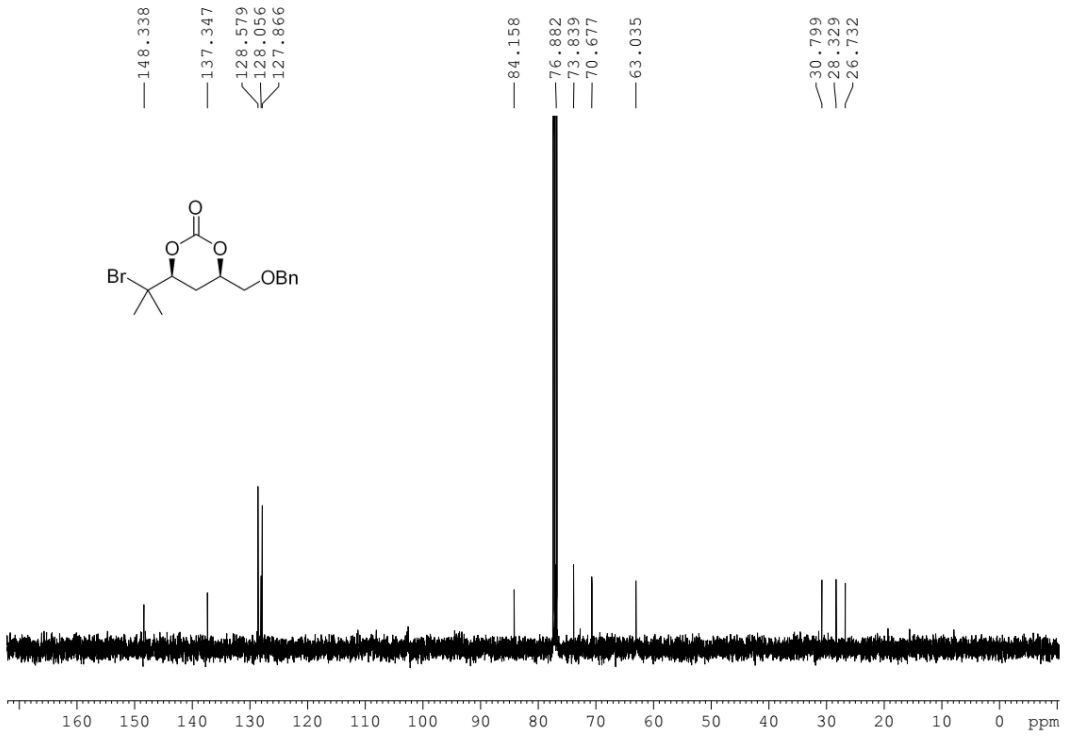


Figure S52. [13]C NMR spectrum of compound **2x**, related to **Table 2**.

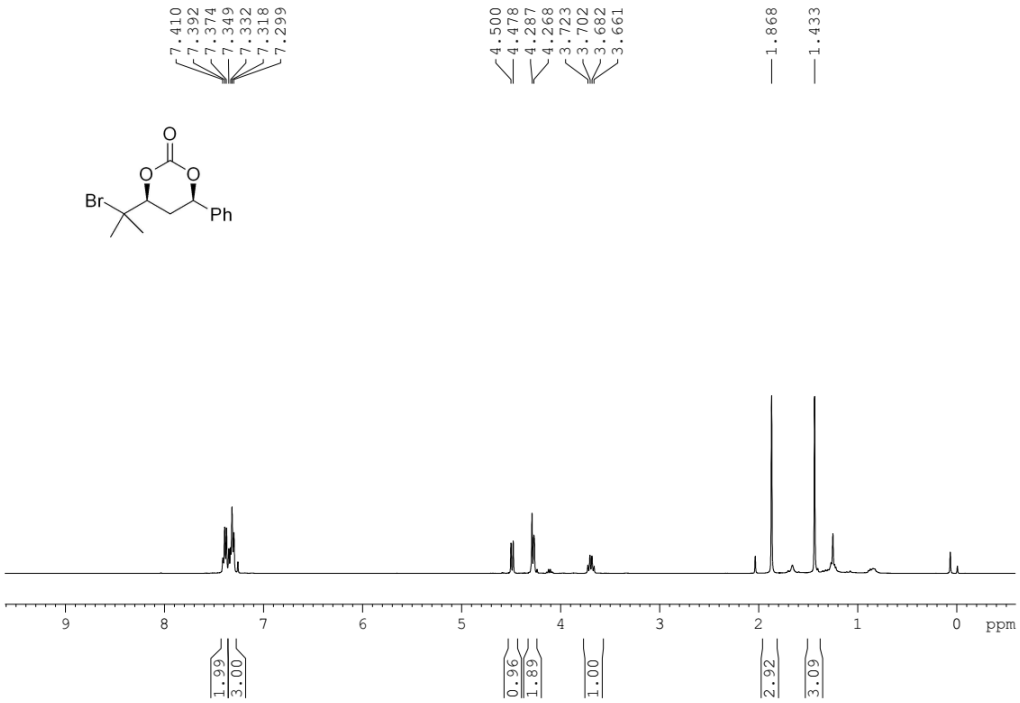


Figure S53. [1]H NMR spectrum of compound **2y**, related to **Table 2**.

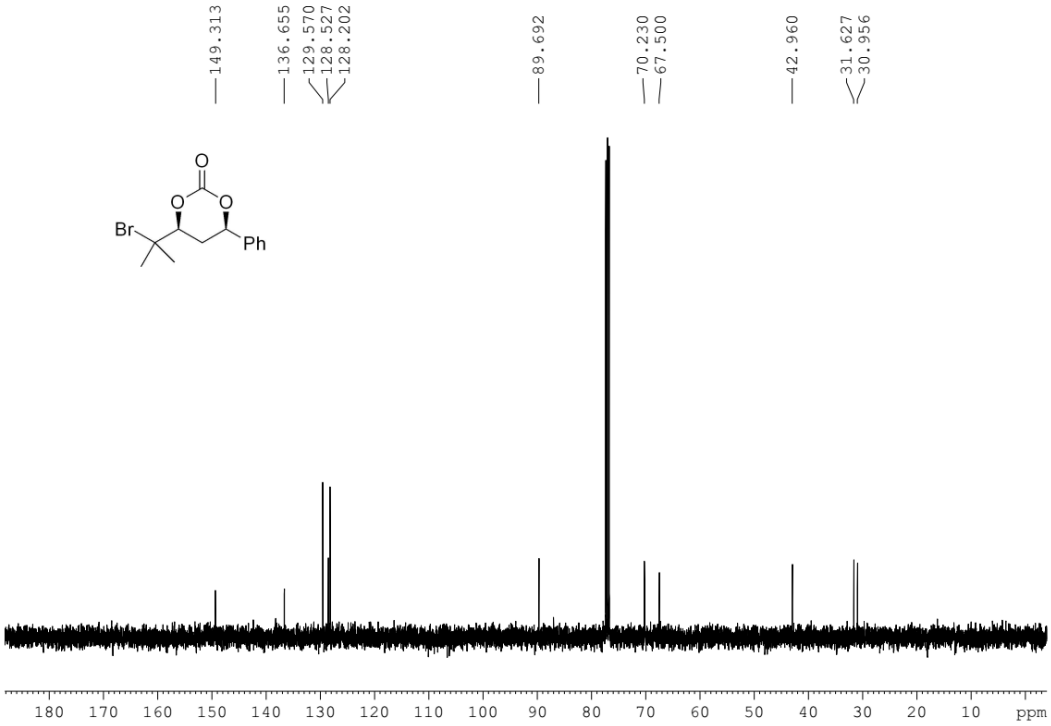


Figure S54. [13]C NMR spectrum of compound **2y**, related to **Table 2**.

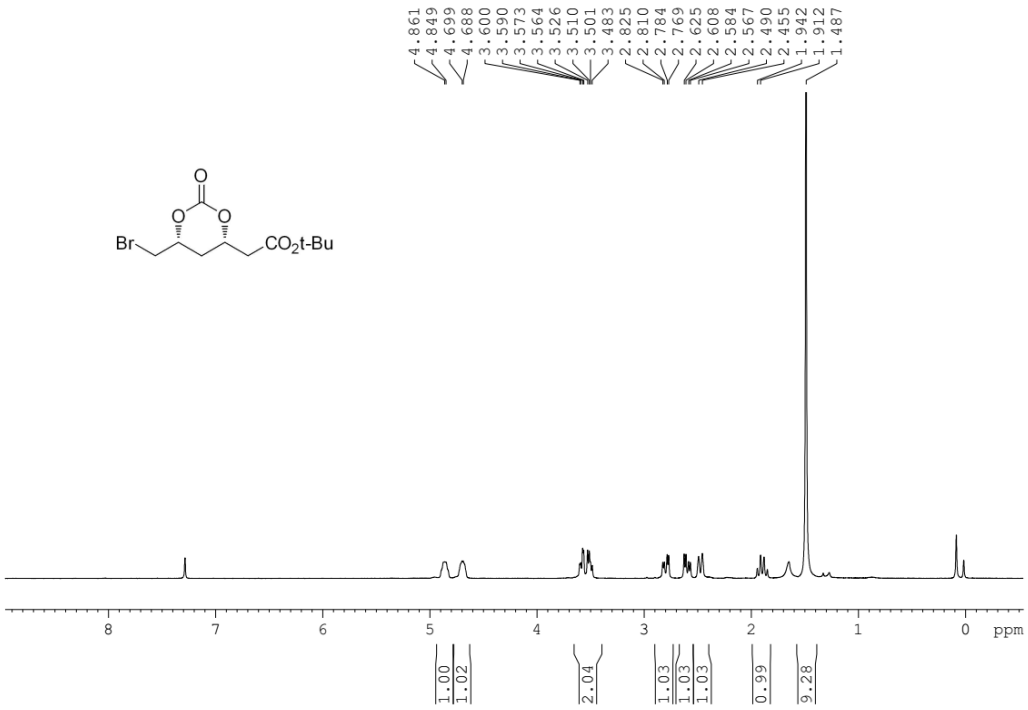


Figure S55. ^{1}H NMR spectrum of compound **3a**, related to **Table 2**.

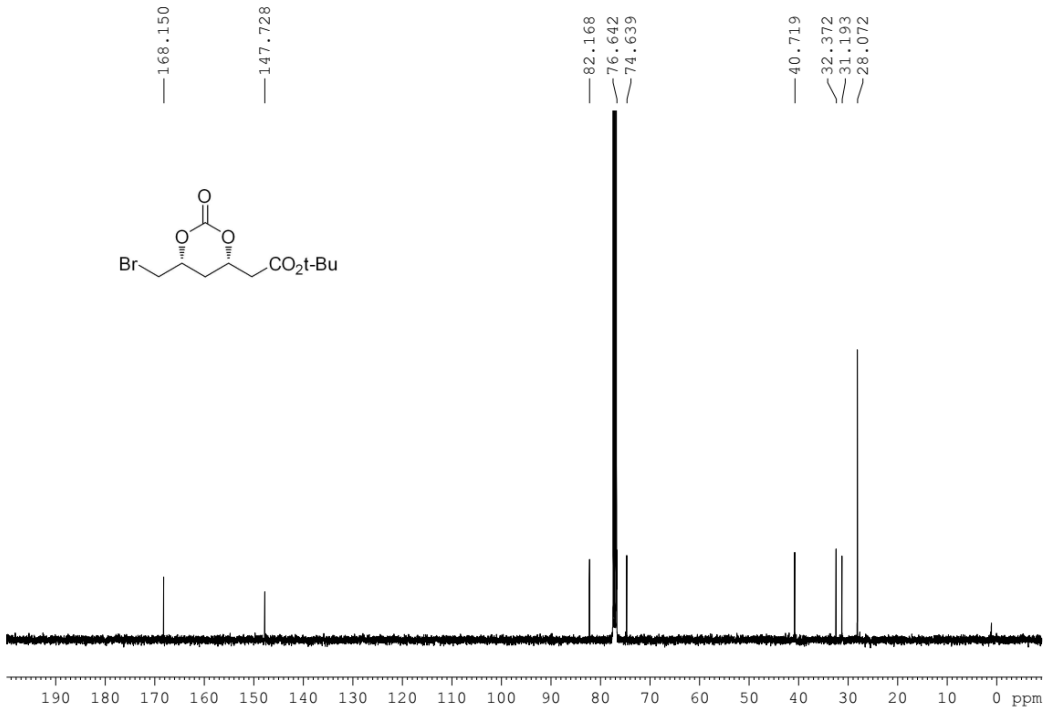


Figure S56. ^{13}C NMR spectrum of compound **3a**, related to **Table 2**.

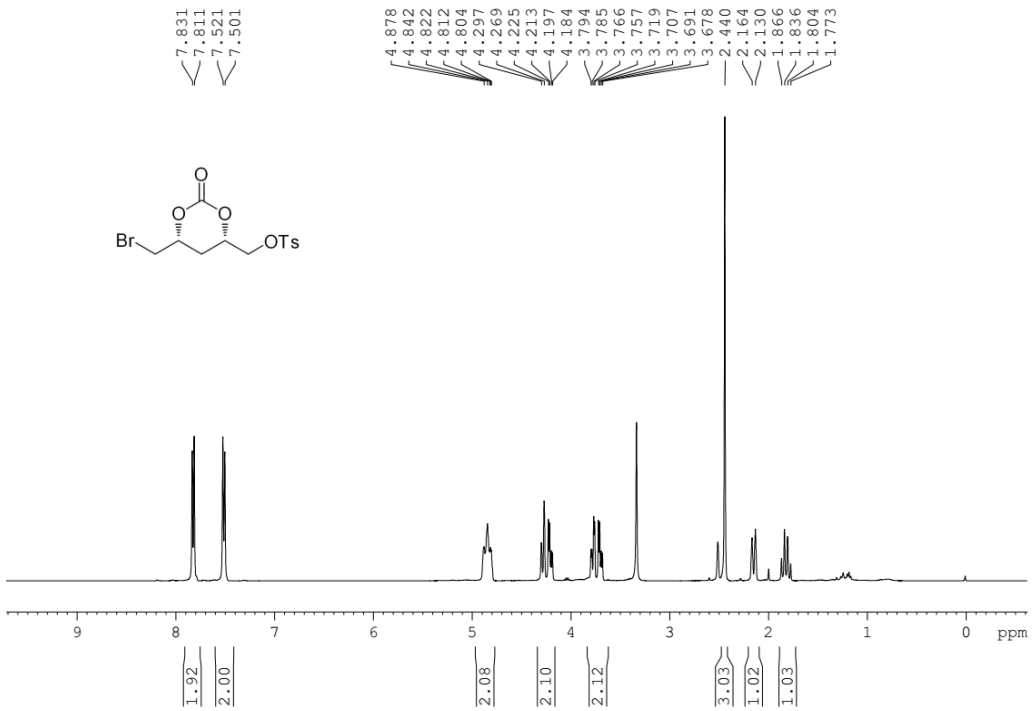


Figure S57. [1]H NMR spectrum of compound **3b**, related to **Table 2**.

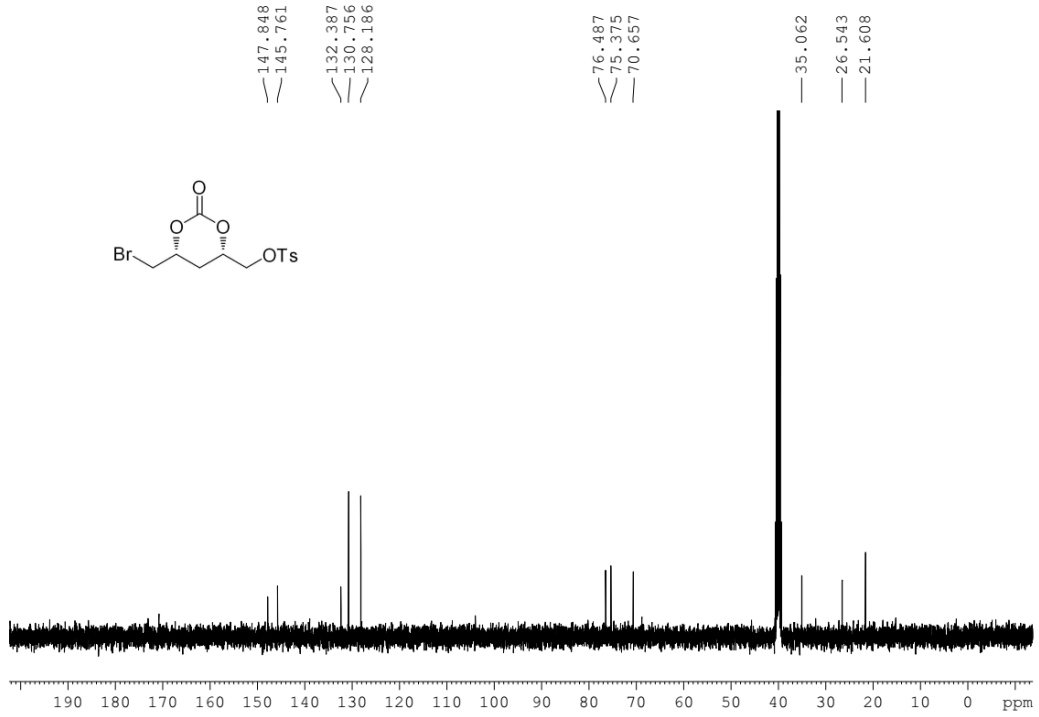
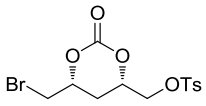
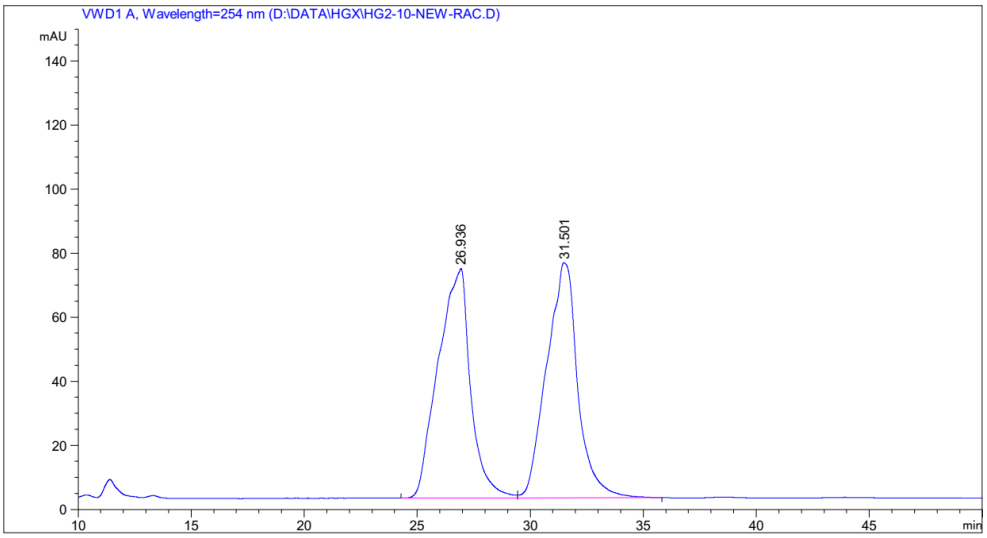


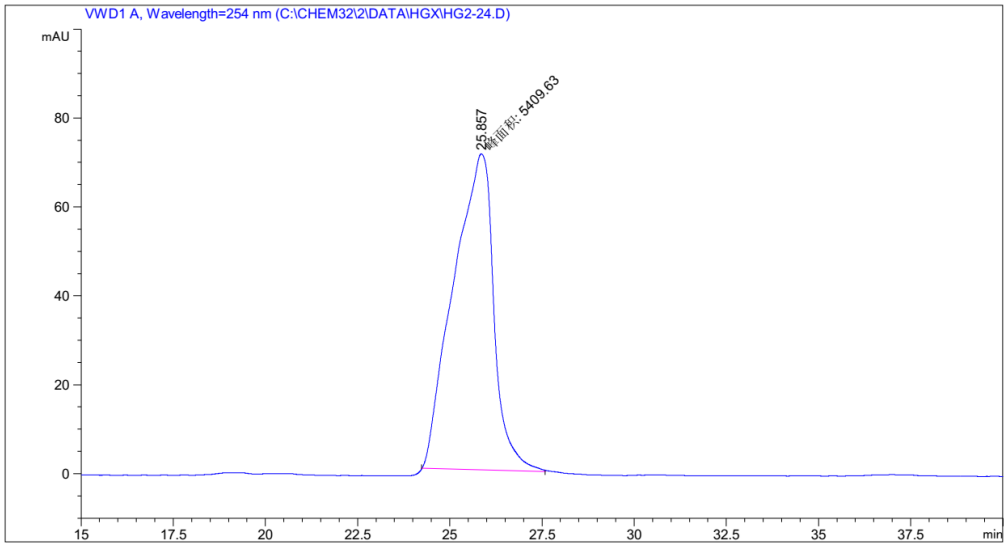
Figure S58. [1]H NMR spectrum of compound **3c**, related to **Table 2**.



3b



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.936	BV	1.2536	7131.73389	71.63023	50.4070
2	31.501	VB	1.3073	7016.55664	73.39655	49.5930



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	25.857	MM	1.2683	5409.62549	71.08970	100.0000

Figure S59. HPLC Analysis of compound **3b**.

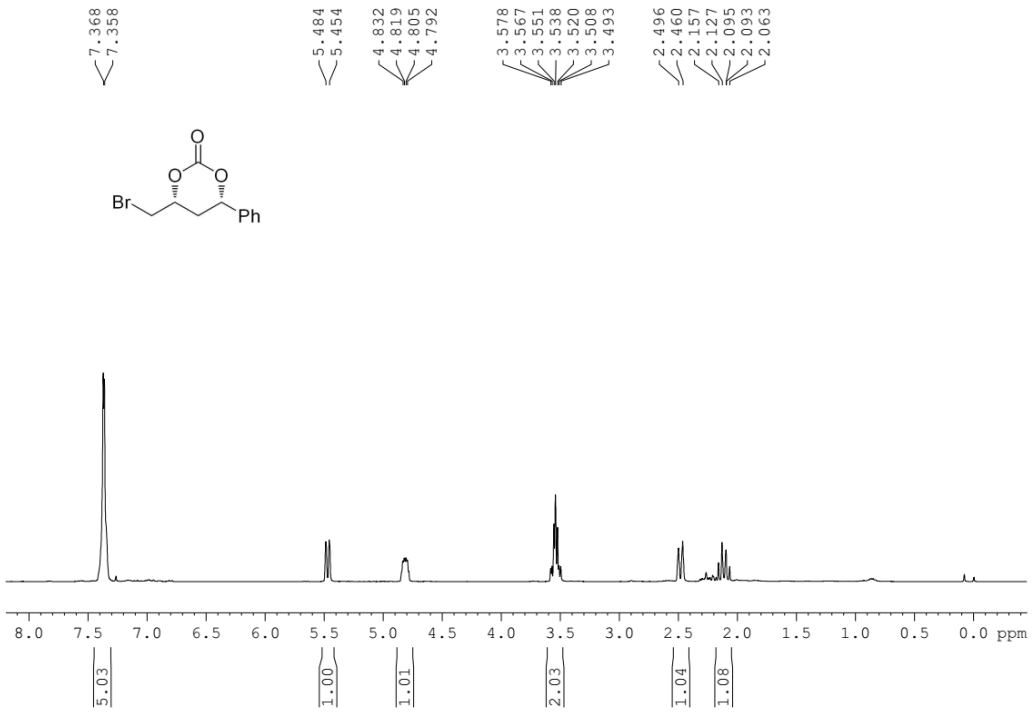


Figure S60. [1]H NMR spectrum of compound **3c**, related to **Table 2**.

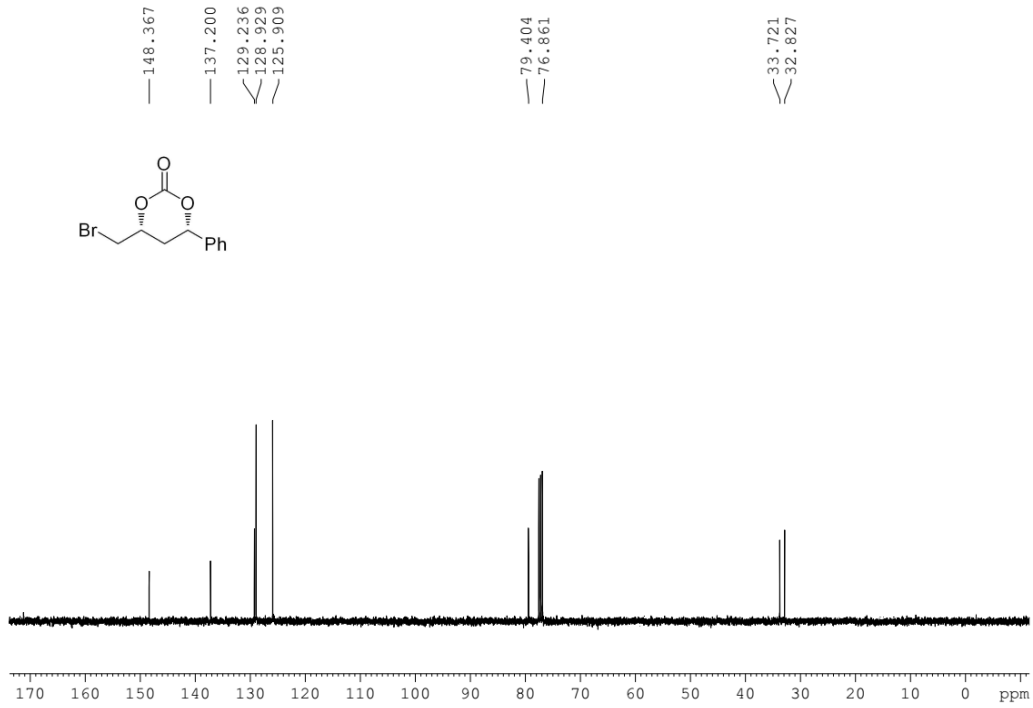


Figure S61. [13]C NMR spectrum of compound **3c**, related to **Table 2**.

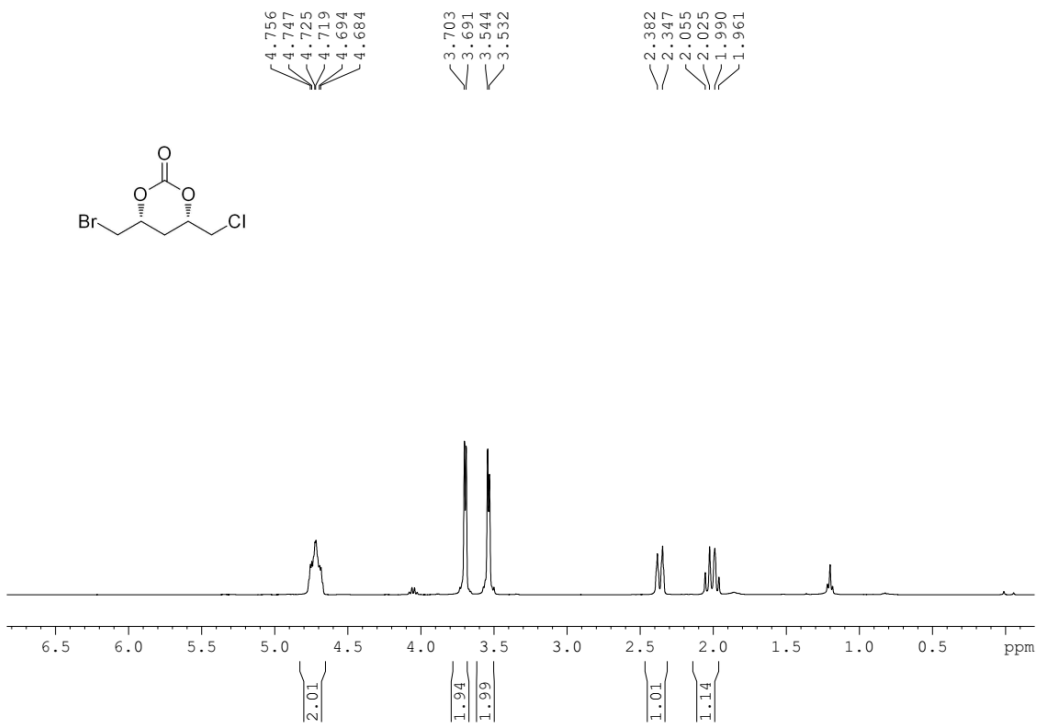


Figure S62. [1]H NMR spectrum of compound **3d**, related to **Table 2**.

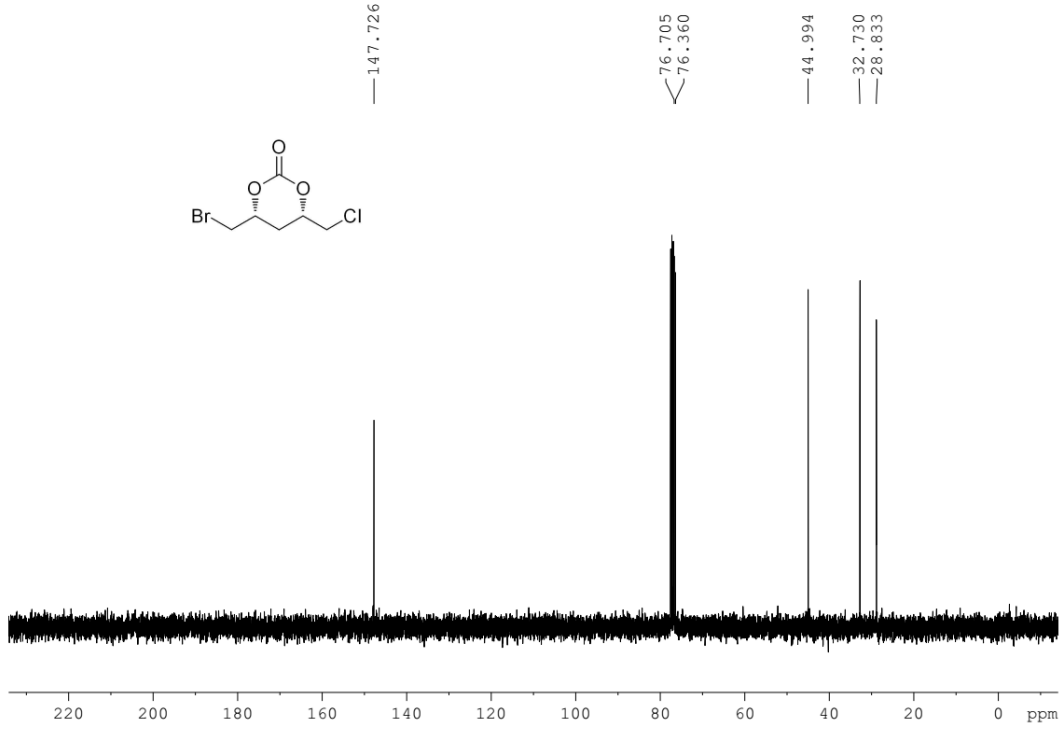
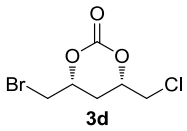
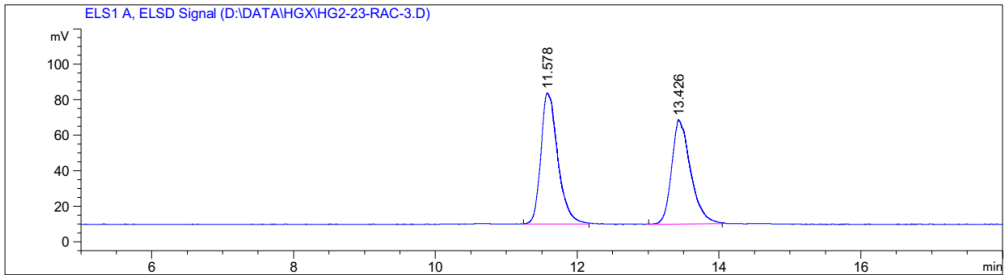


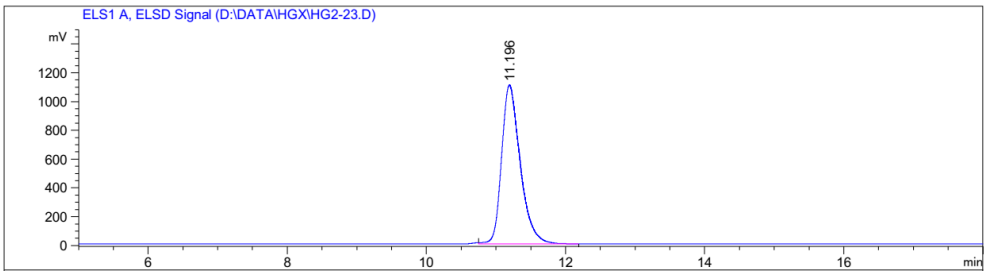
Figure S63. [13]C NMR spectrum of compound **3d**, related to **Table 2**.



3d



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mV*s]	峰高 [mV]	峰面积 %
1	11.578	VV	0.2039	1227.34460	74.04911	52.9897
2	13.426	VV	0.2237	1088.84937	58.88310	47.0103



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mV*s]	峰高 [mV]	峰面积 %
1	11.196	VV	0.2278	2.05617e4	1106.31018	100.0000

Figure S64. HPLC Analysis of compound **3d**.

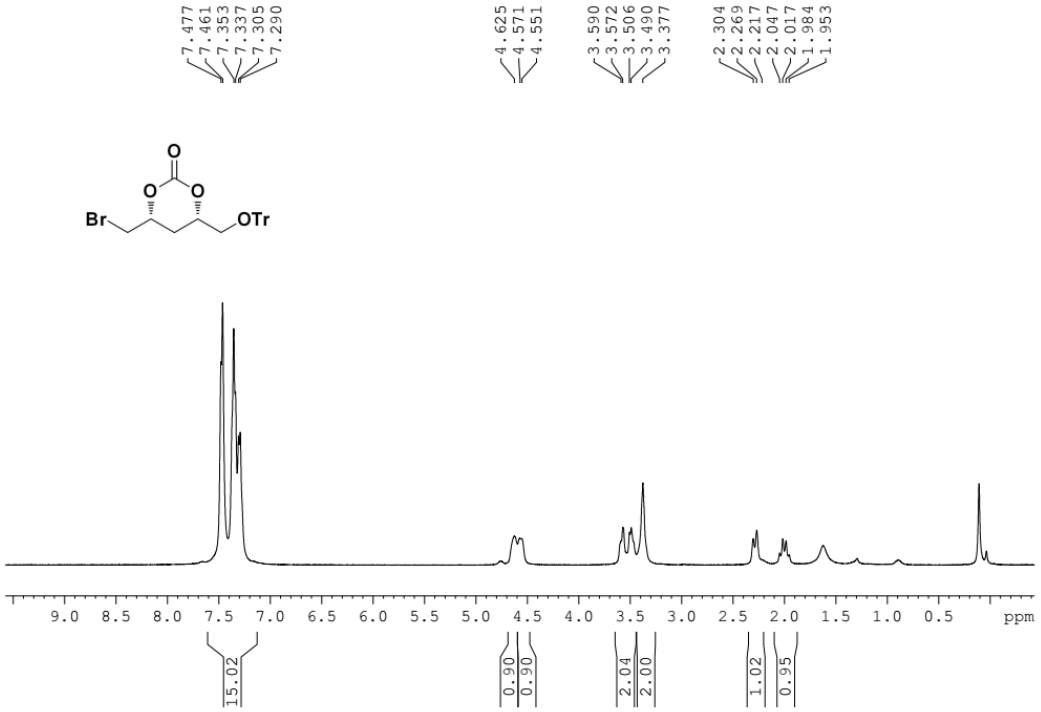


Figure S65. [1]H NMR spectrum of compound **3e**, related to **Table 2**.

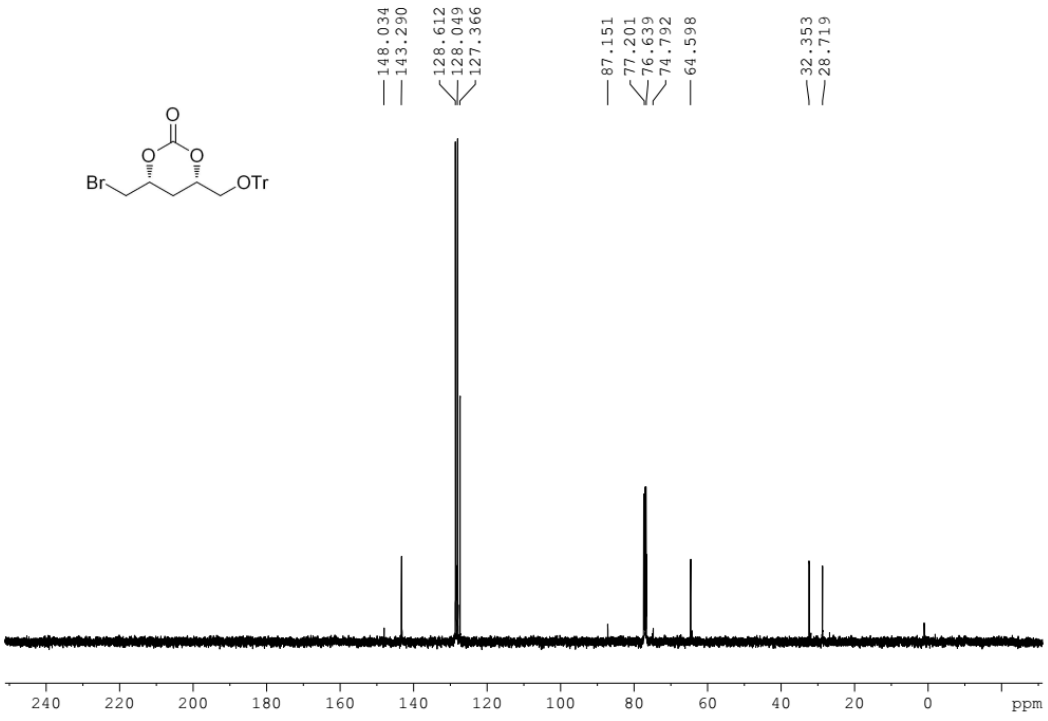


Figure S66. [13]C NMR spectrum of compound **3e**, related to **Table 2**.

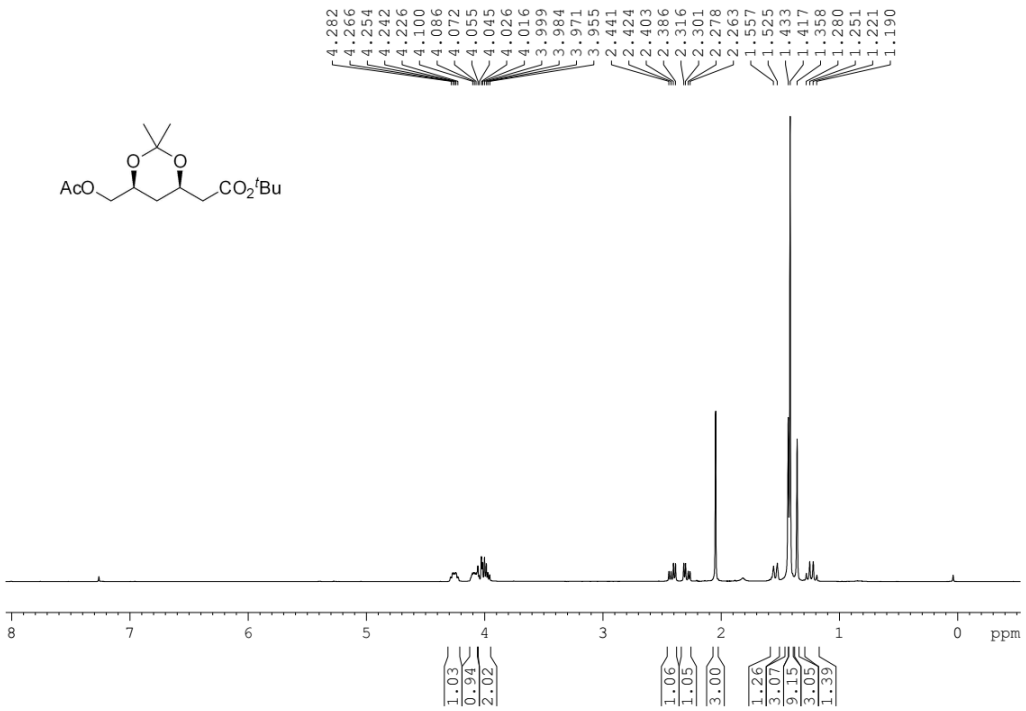


Figure S67. ^{1}H NMR spectrum of compound **7**, related to **Scheme 3**.

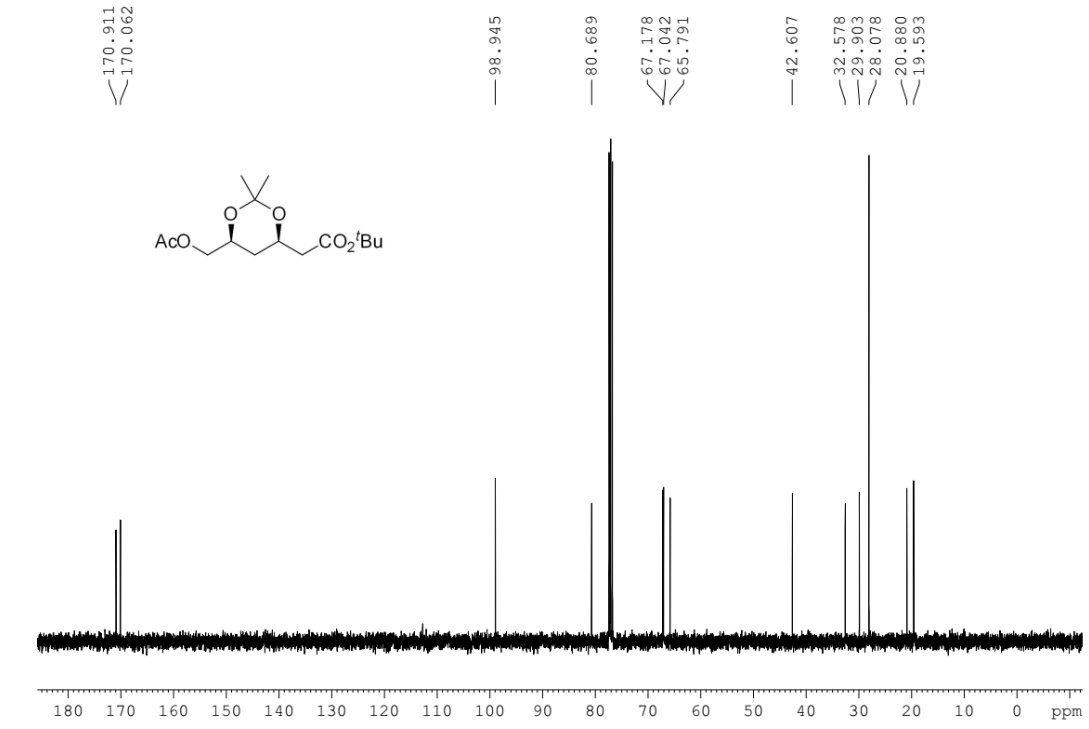
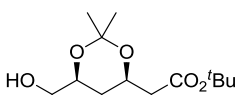


Figure S68. ^{13}C NMR spectrum of compound **7**, related to **Scheme 3**.



8

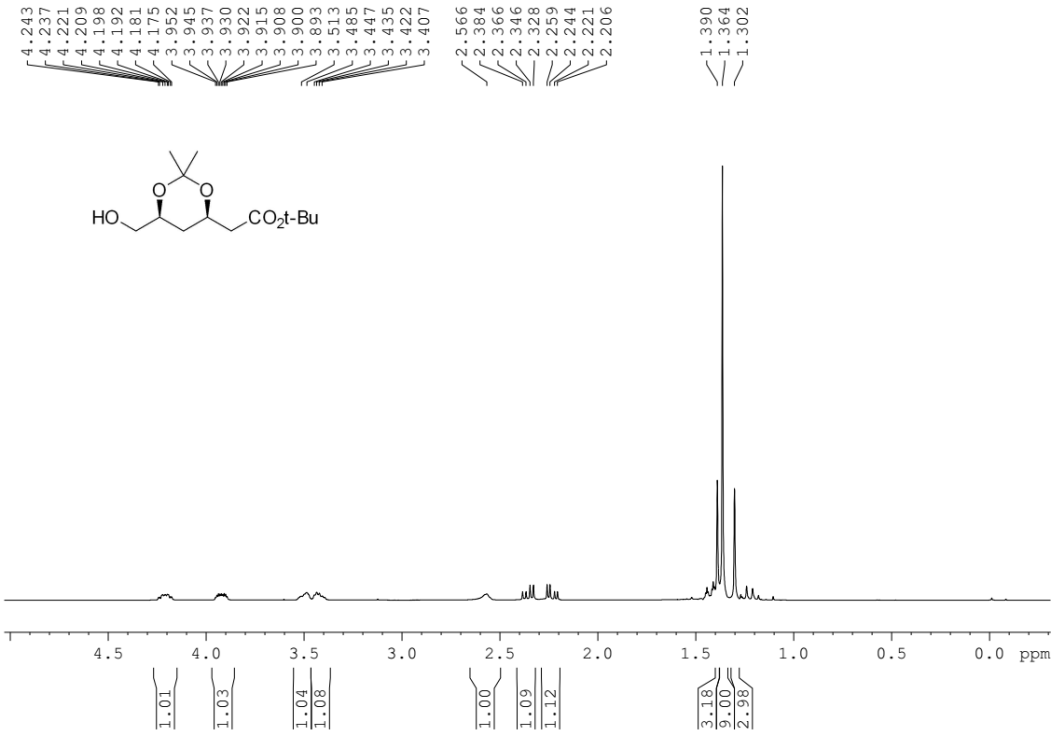


Figure S69. ^{1}H NMR spectrum of compound **8**, related to **Scheme 3**.

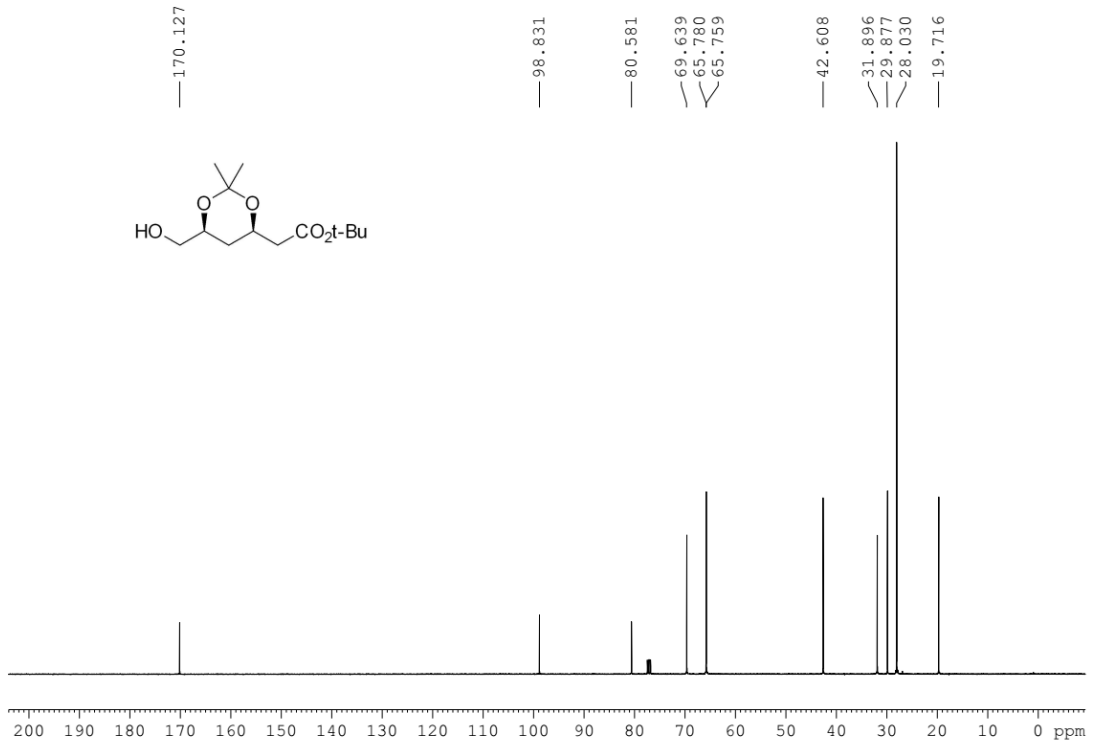


Figure S70. ^{13}C NMR spectrum of compound **8**, related to **Scheme 3**.

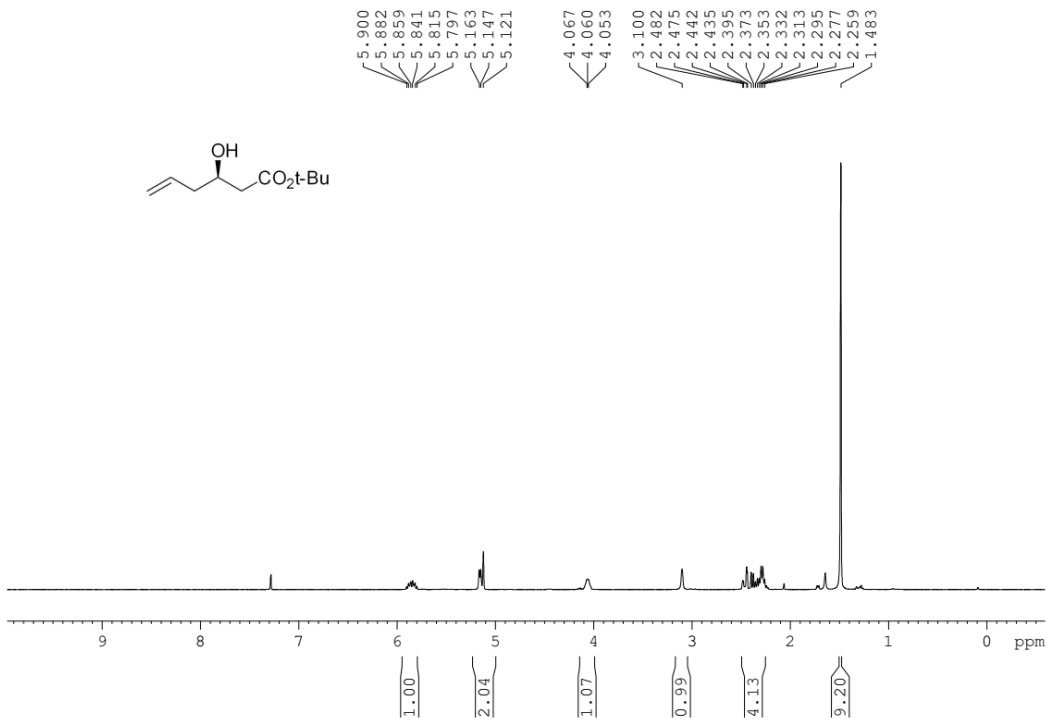


Figure S71. [1]H NMR spectrum of compound **1a**, related to **Table 2**.

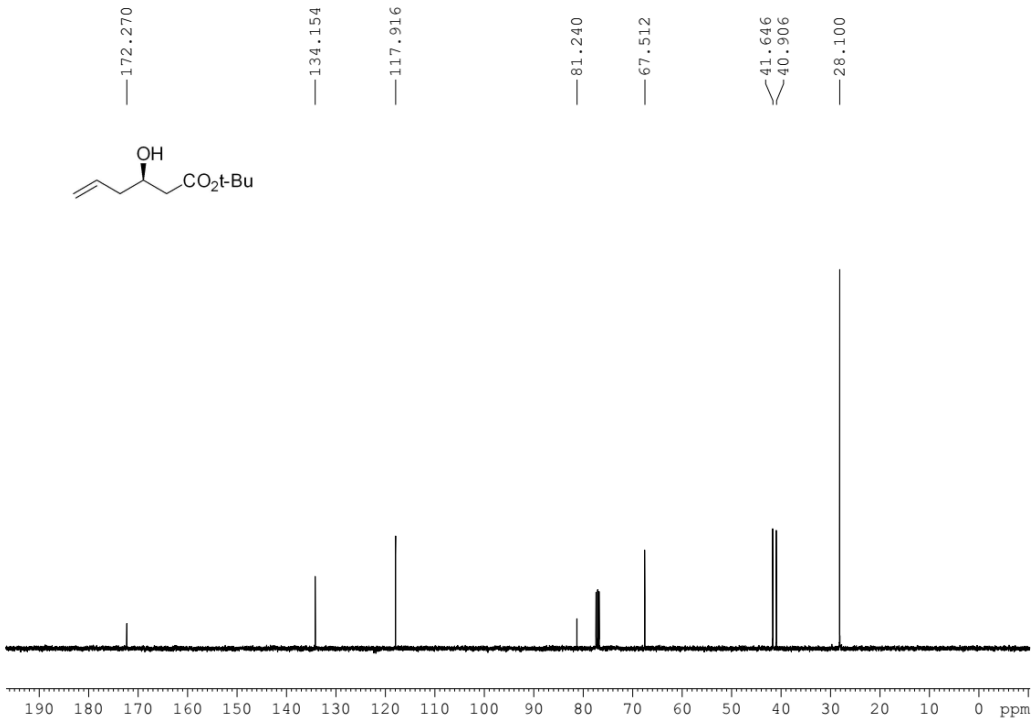
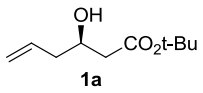
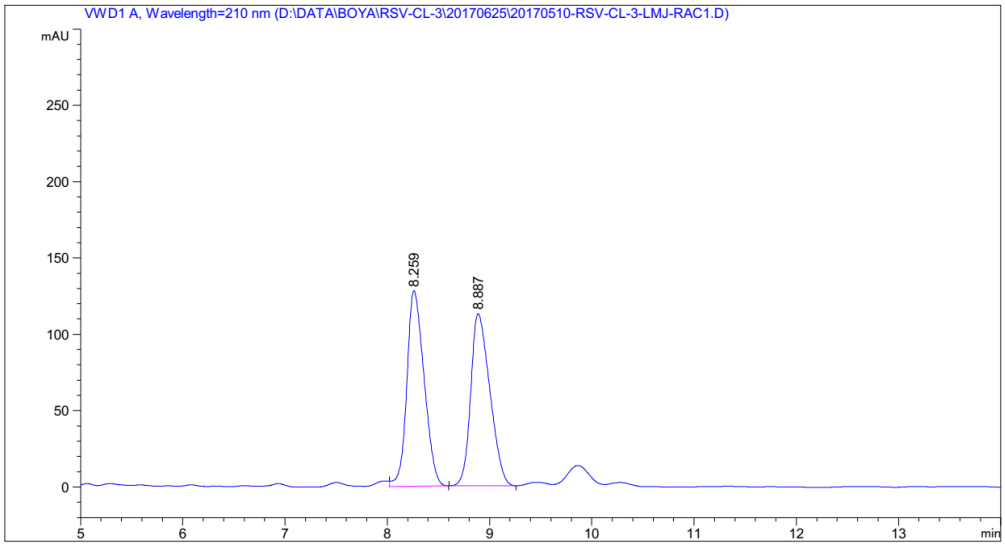


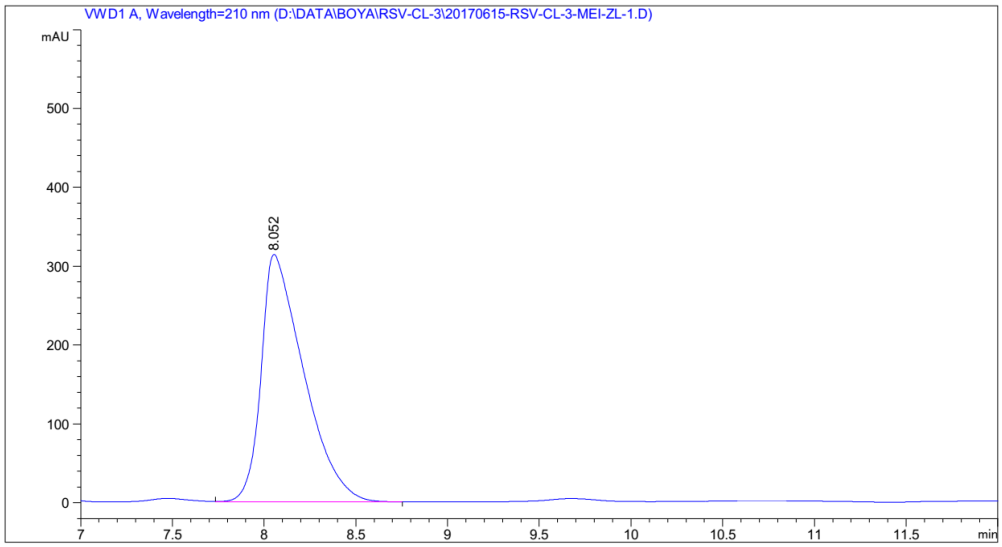
Figure S72. [13]C NMR spectrum of compound **1a**, related to **Table 2**.



1a



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.259	VB	0.1816	1499.51733	128.07930	50.5706
2	8.887	BB	0.2016	1465.67859	112.80564	49.4294



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.052	VB	0.2423	5062.34033	313.71506	100.0000

Figure S73. HPLC Analysis of compound **1a**.

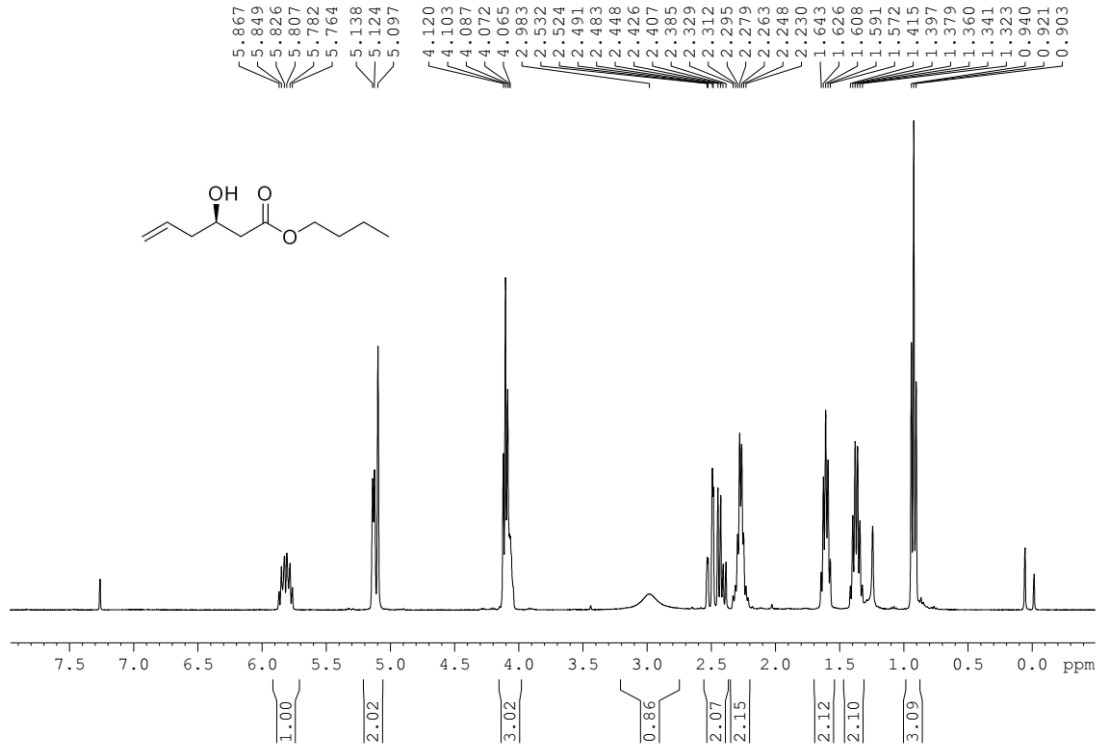


Figure S74. [1]H NMR spectrum of compound **1d**, related to **Table 2**.

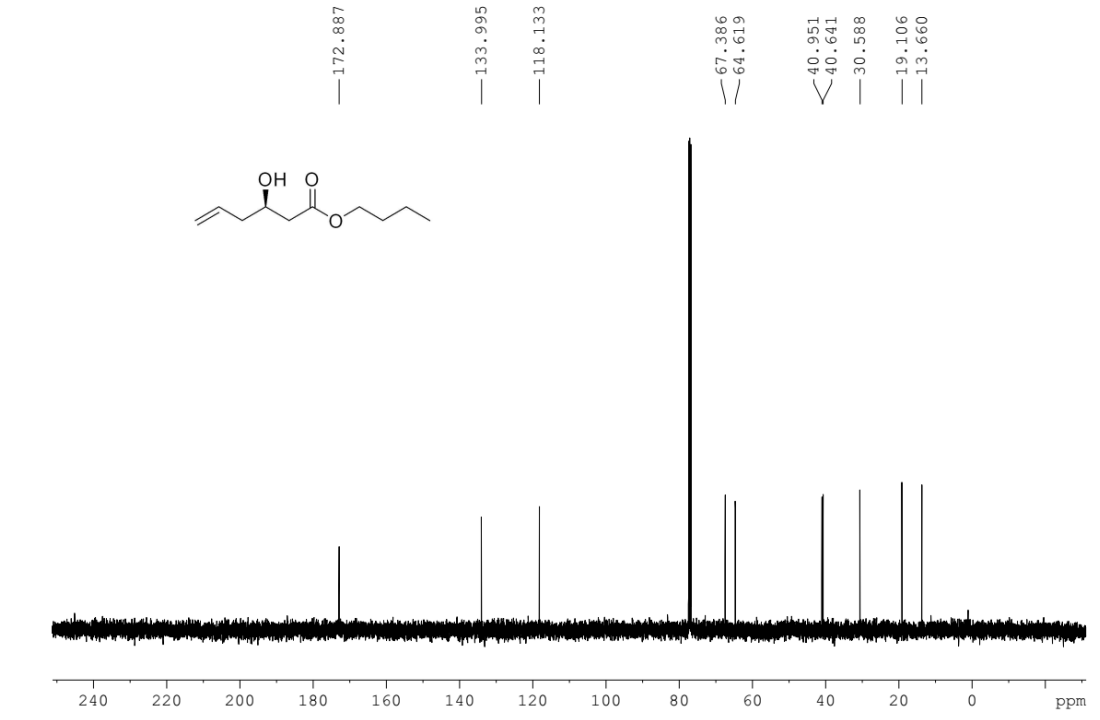


Figure S75. [13]C NMR spectrum of compound **1d**, related to **Table 2**.

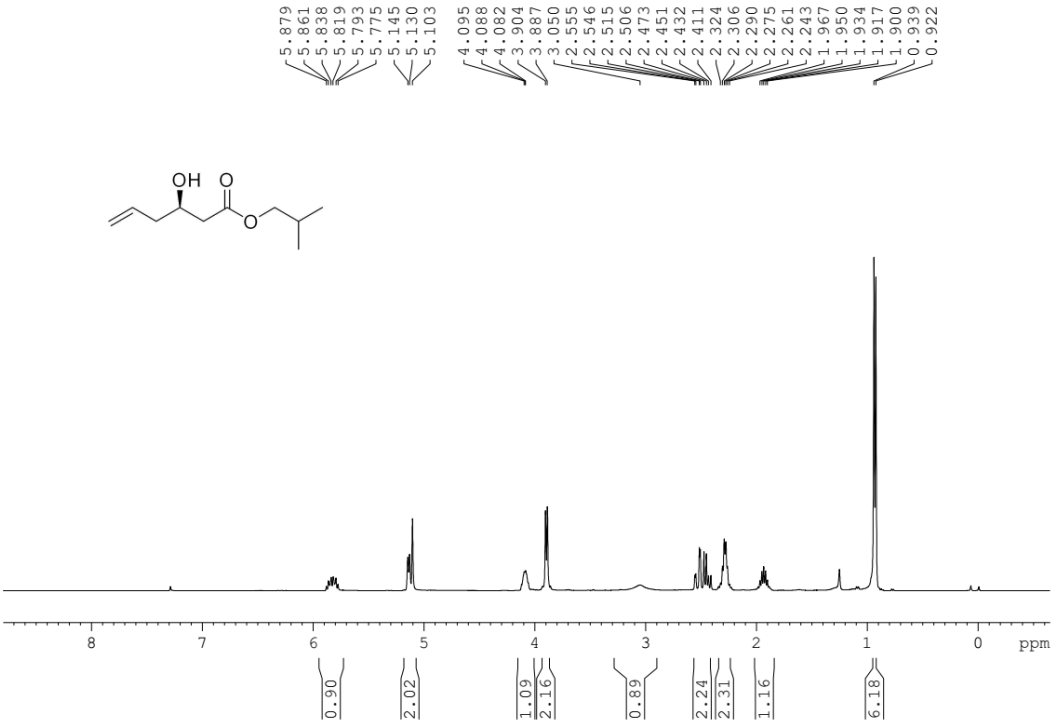


Figure S76. ^{1}H NMR spectrum of compound **1e**, related to **Table 2**.

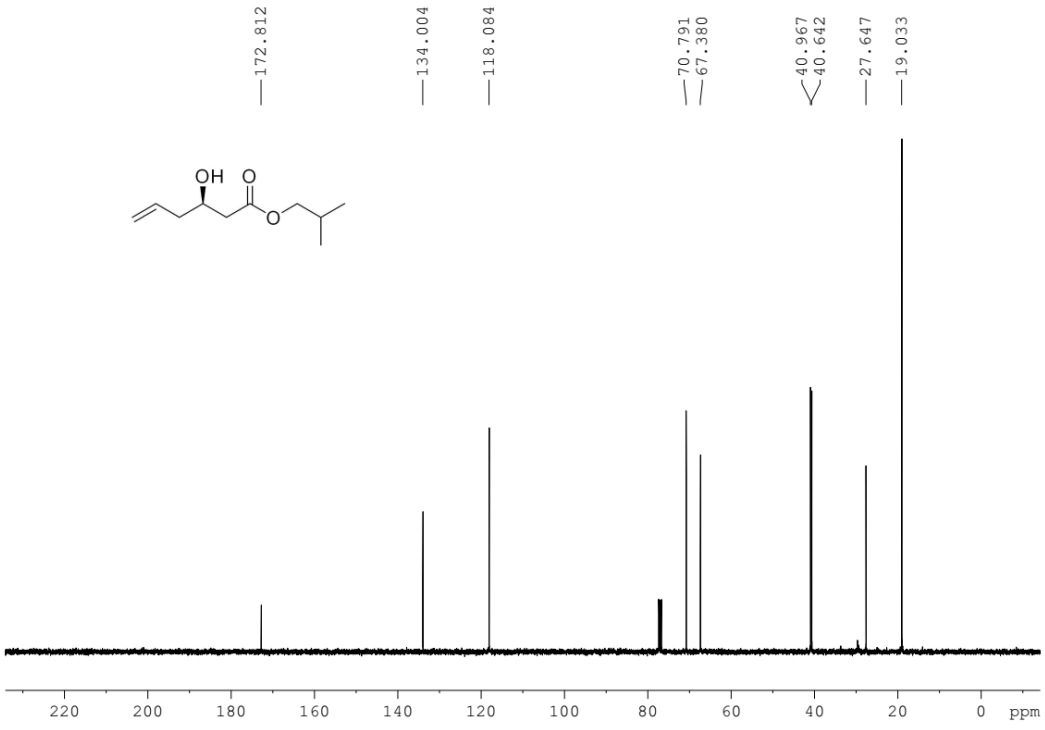


Figure S77. ^{13}C NMR spectrum of compound **1e**, related to **Table 2**.

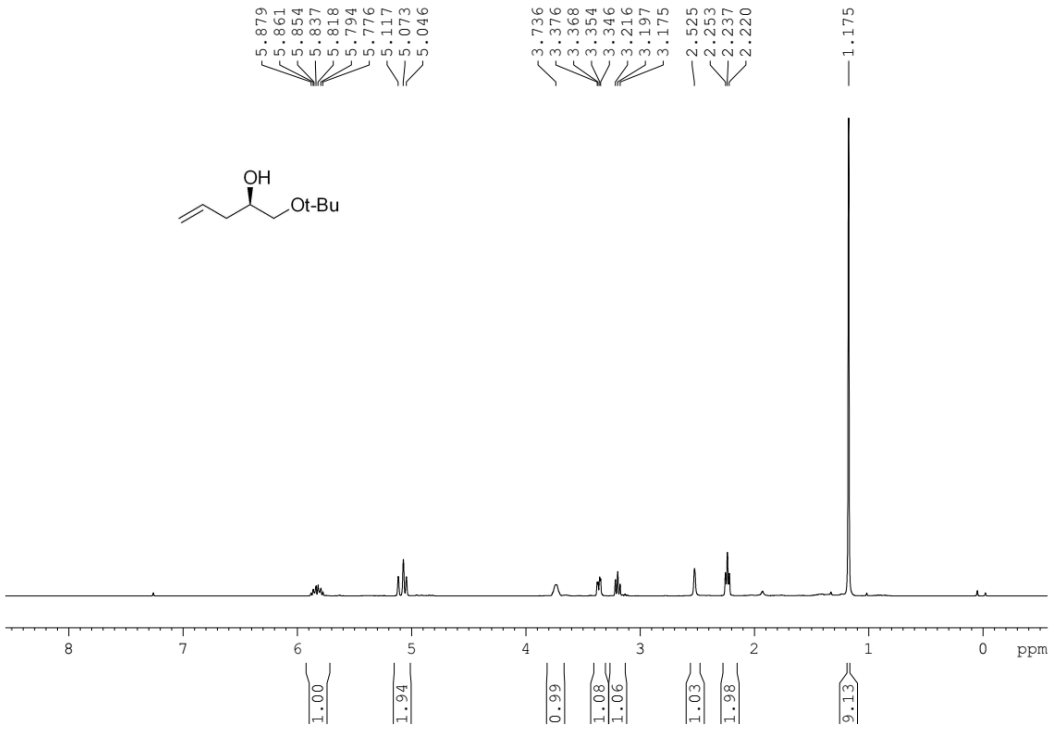


Figure S78. [1]H NMR spectrum of compound **1i**, related to **Table 2**.

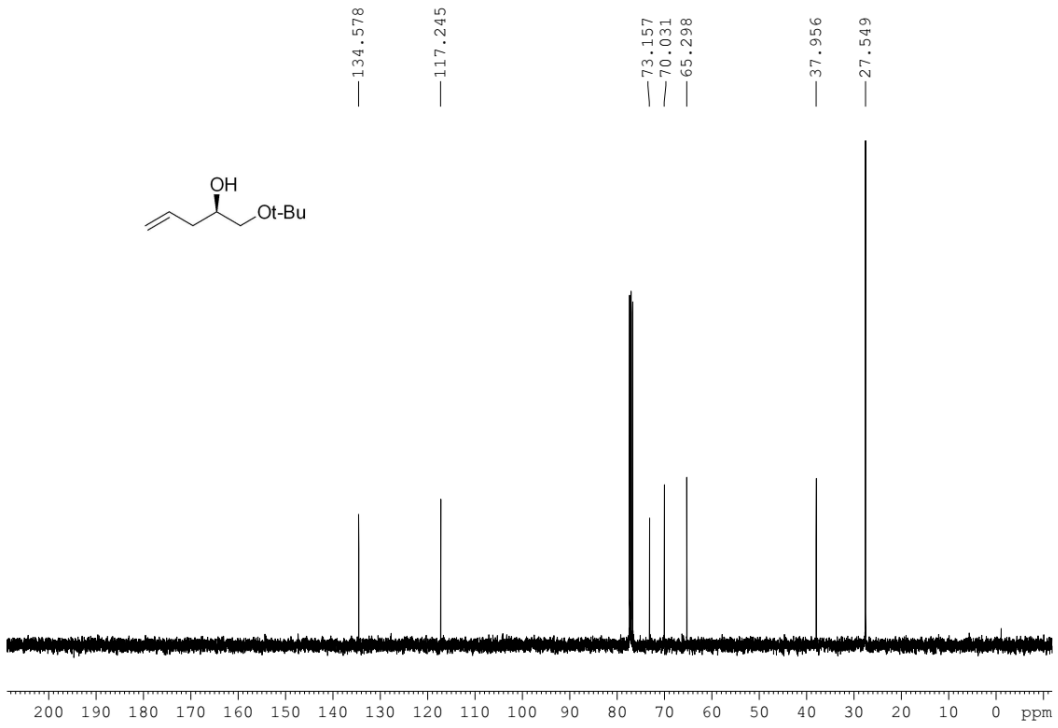


Figure S79. [1]C NMR spectrum of compound **1i**, related to **Table 2**.

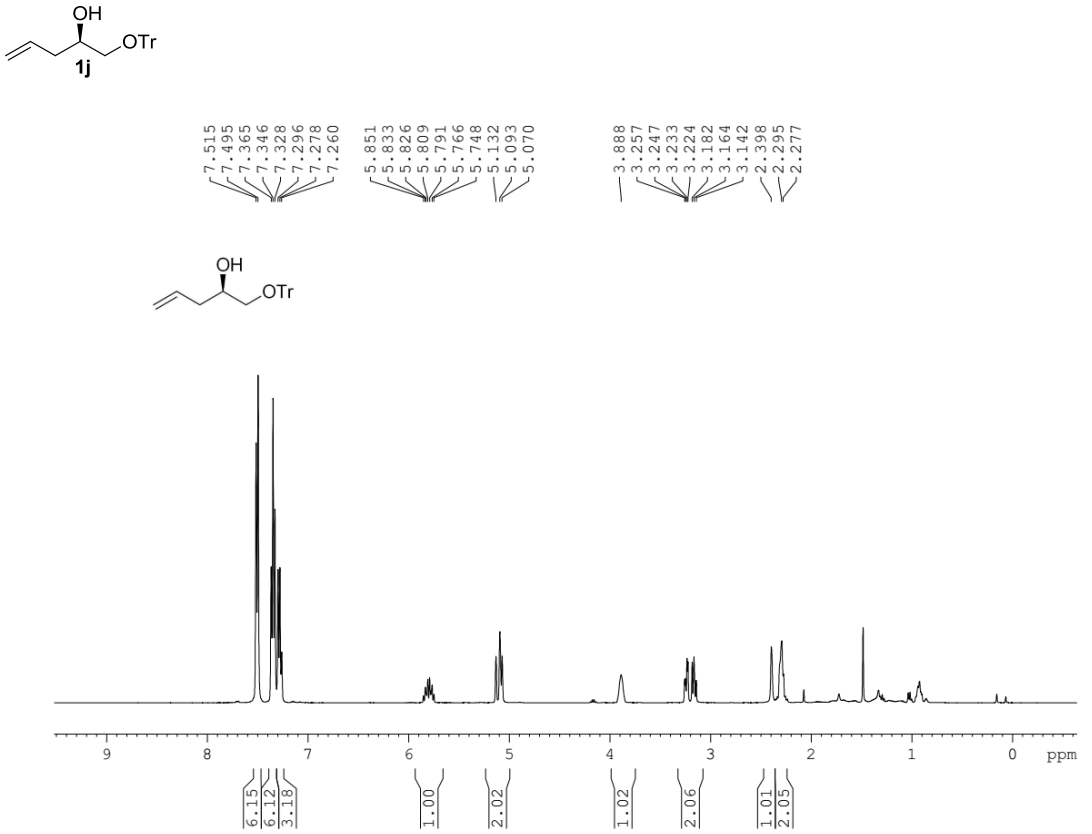


Figure S80. [1]H NMR spectrum of compound **1j**, related to **Table 2**.

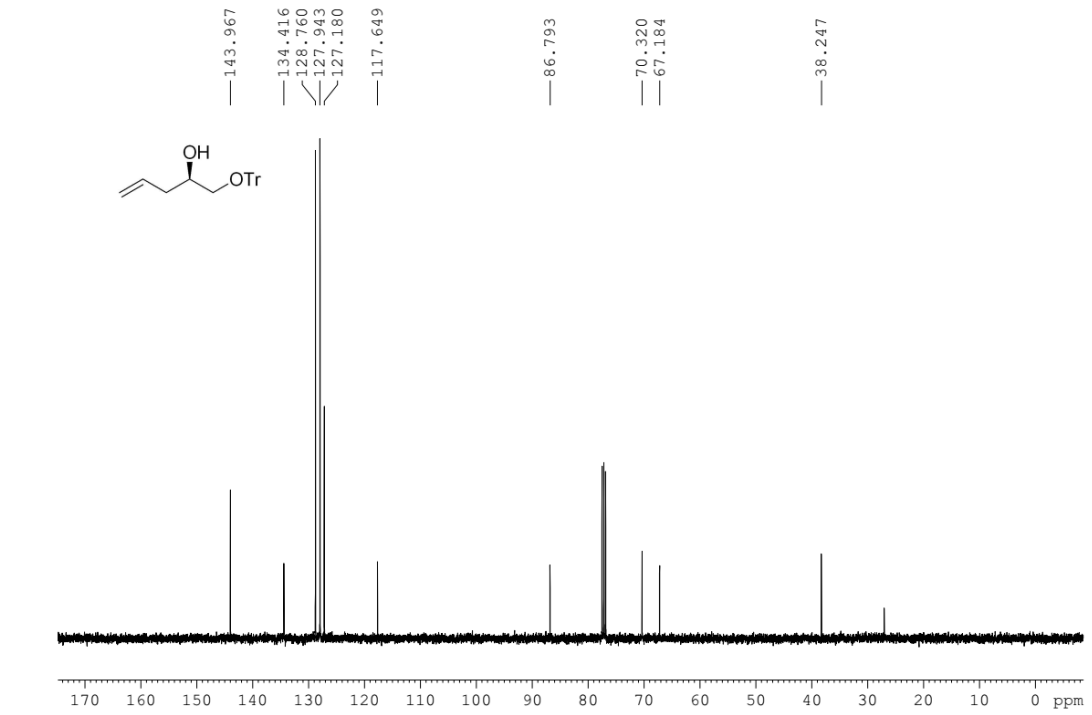


Figure S81. [13]C NMR spectrum of compound **1j**, related to **Table 2**.

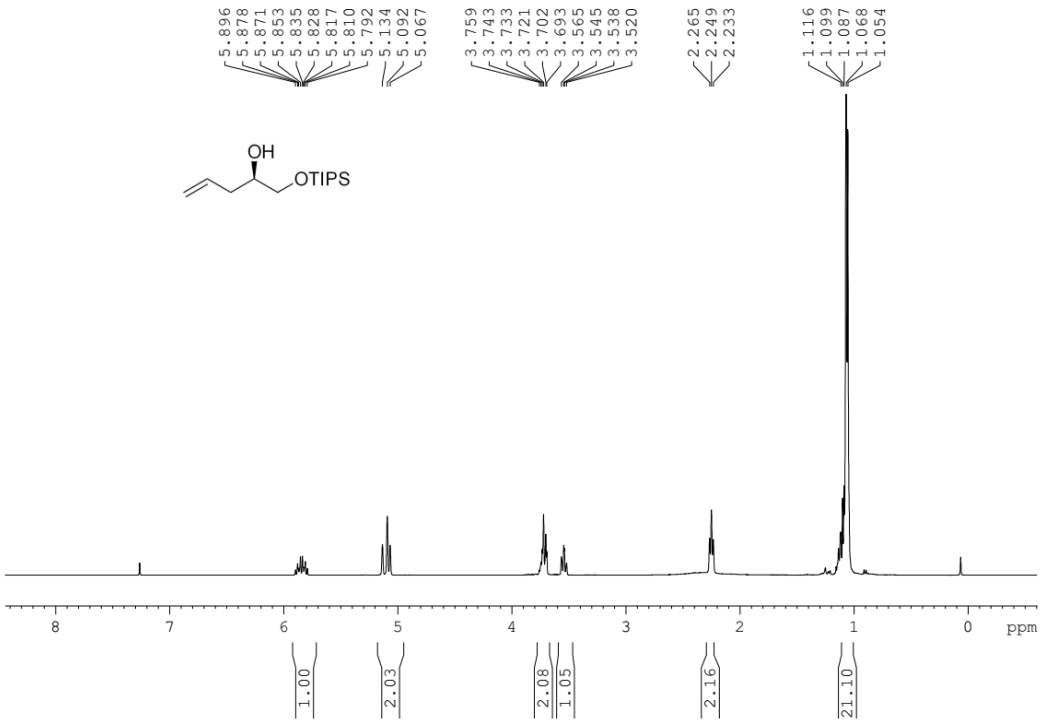


Figure S82. ^{1}H NMR spectrum of compound **1k**, related to **Table 2**.

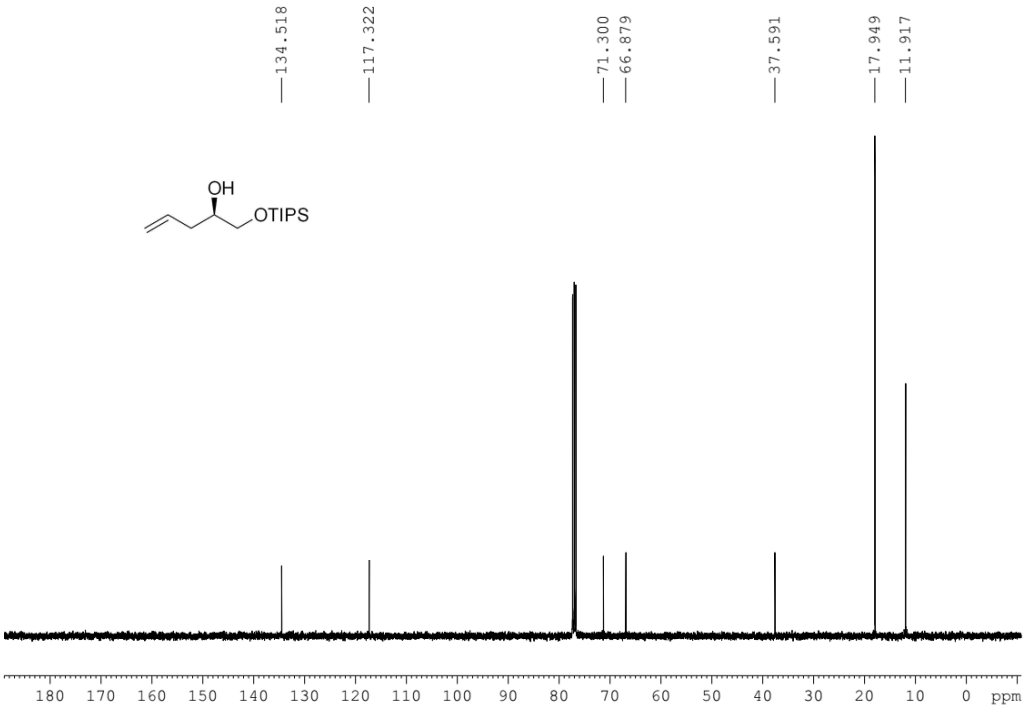


Figure S83. ^{13}C NMR spectrum of compound **1k**, related to **Table 2**.

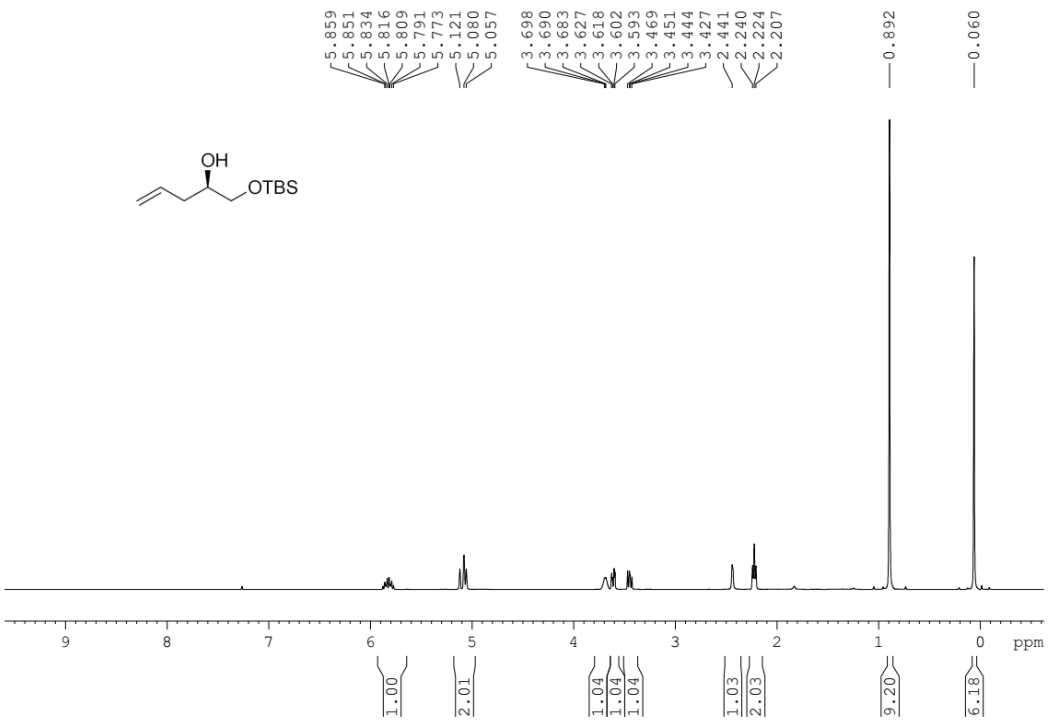


Figure S84. ^{1}H NMR spectrum of compound **1l**, related to **Table 2**.

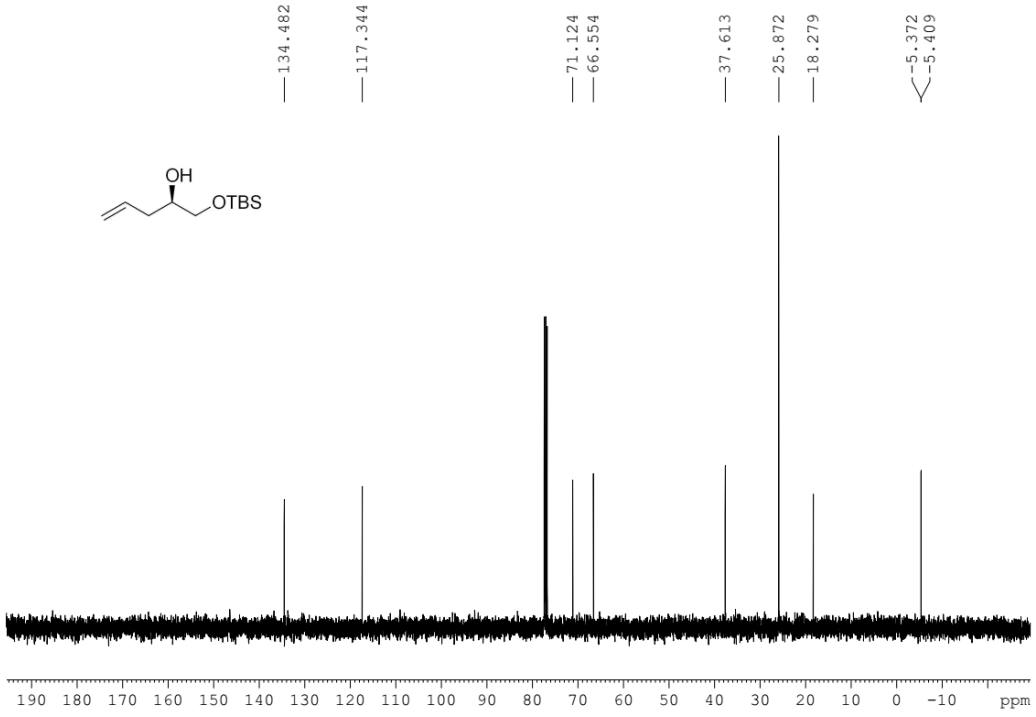


Figure S85. ^{13}C NMR spectrum of compound **1l**, related to **Table 2**.

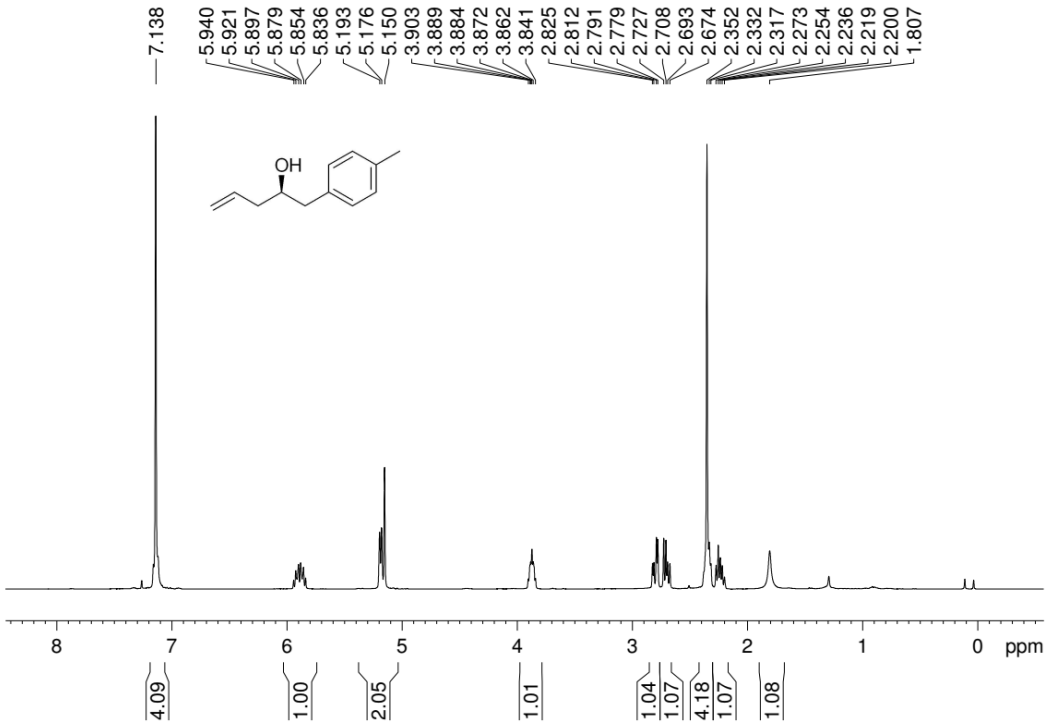


Figure S86. ^{1}H NMR spectrum of compound **1n**, related to **Table 2**.

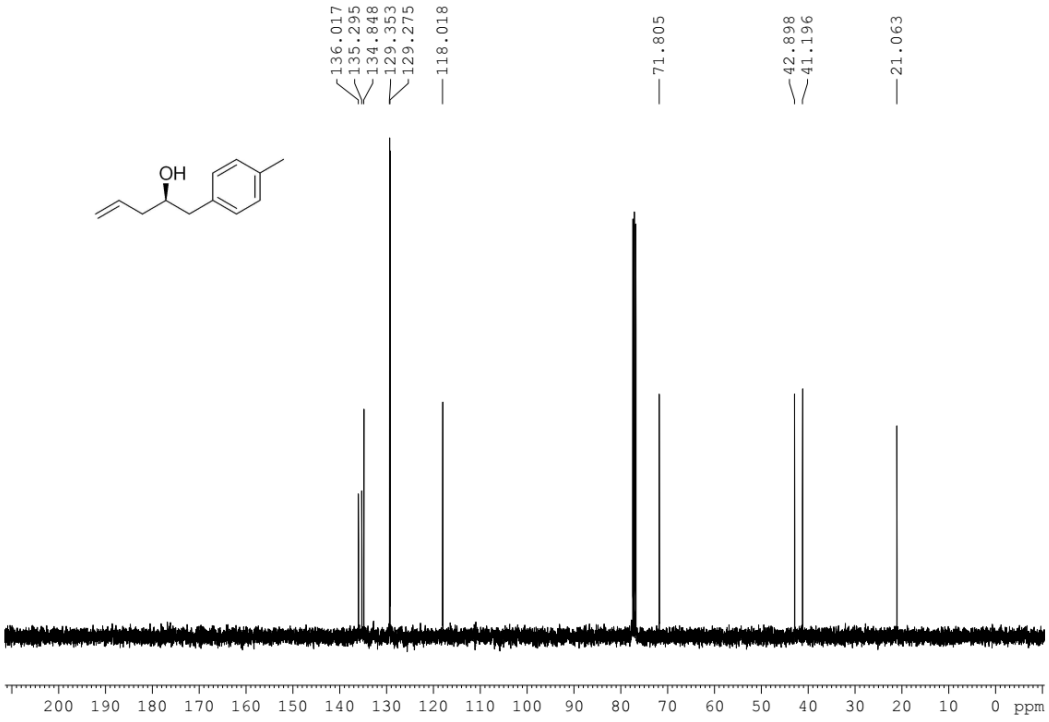


Figure S87. ^{13}C NMR spectrum of compound **1n**, related to **Table 2**.

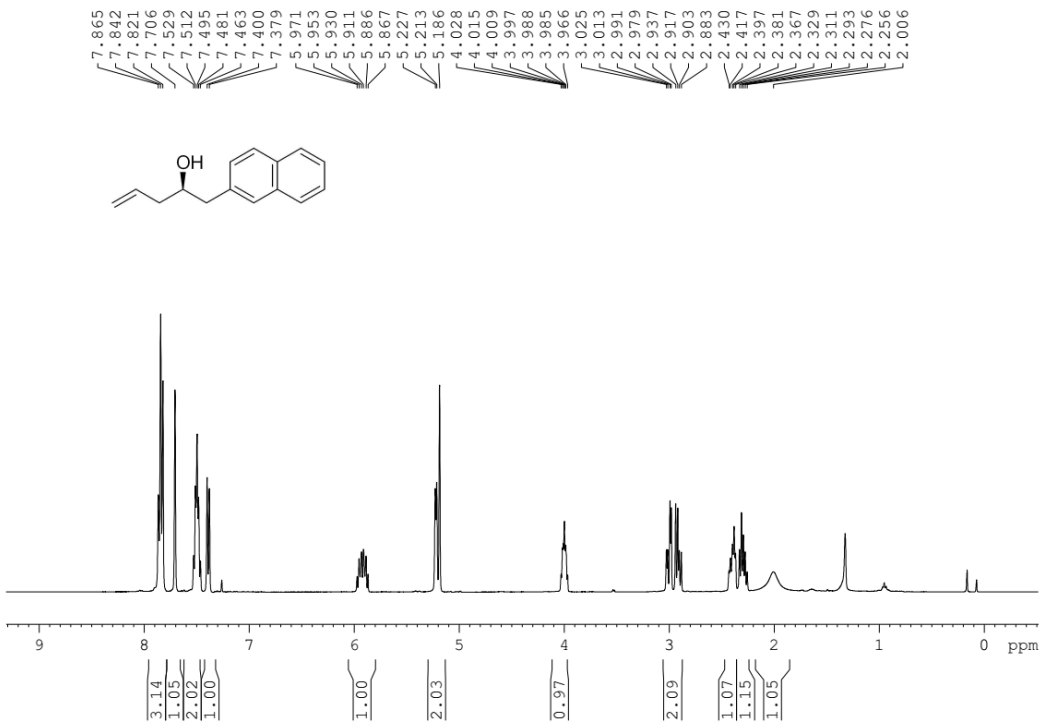


Figure S88. ^{1}H NMR spectrum of compound **1o**, related to **Table 2**.

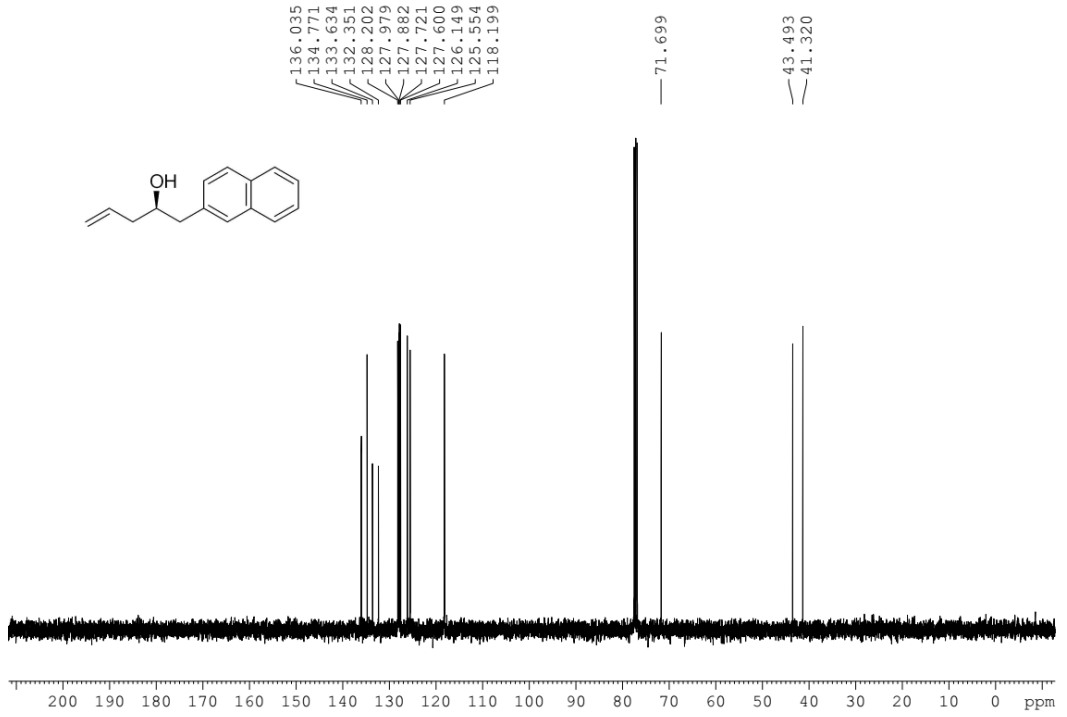


Figure S89. ^{13}C NMR spectrum of compound **1o**, related to **Table 2**.

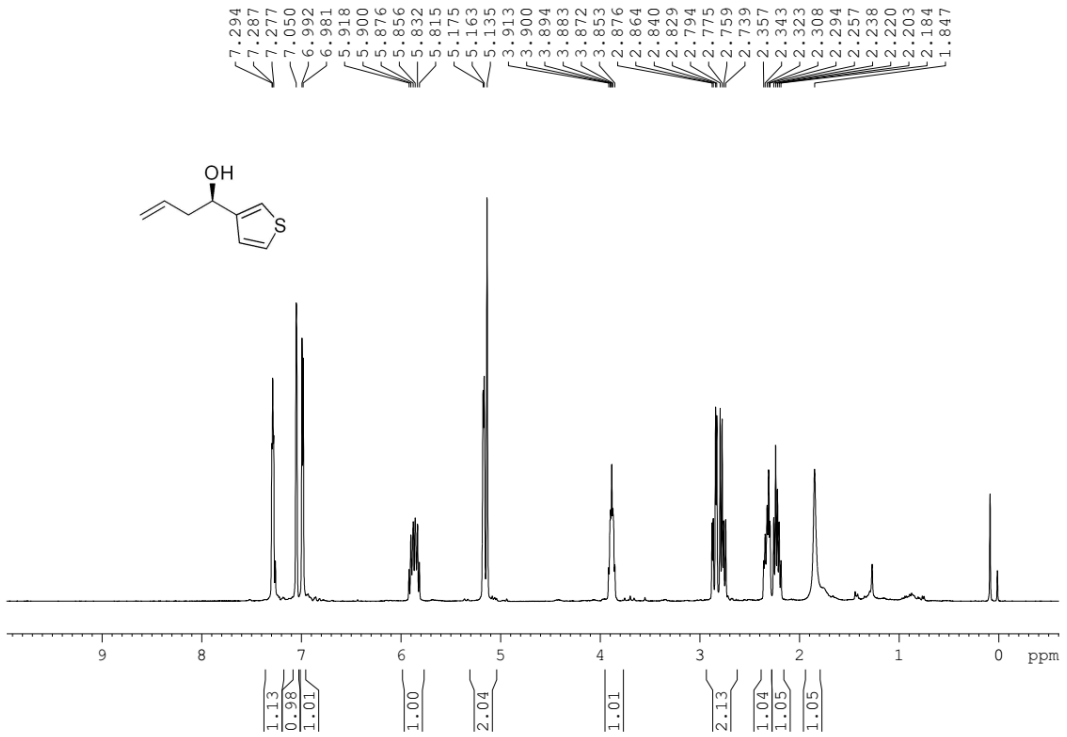


Figure S90. ^{1}H NMR spectrum of compound **1r**, related to **Table 2**.

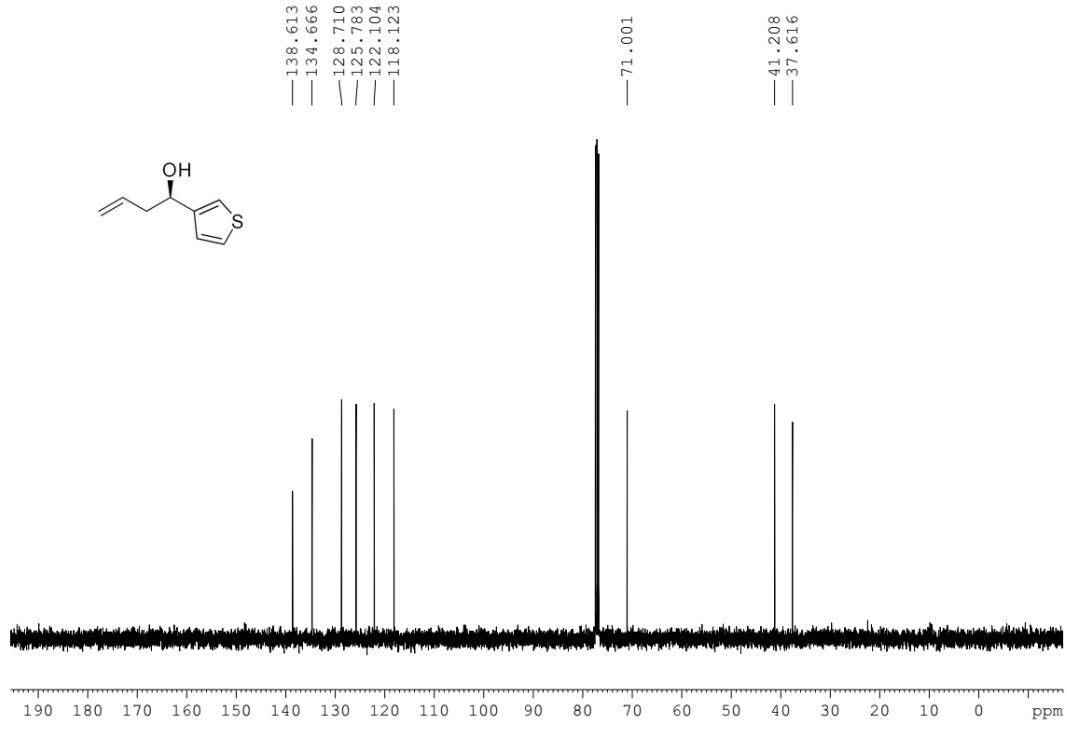


Figure S91. ^{13}C NMR spectrum of compound **1r**, related to **Table 2**.

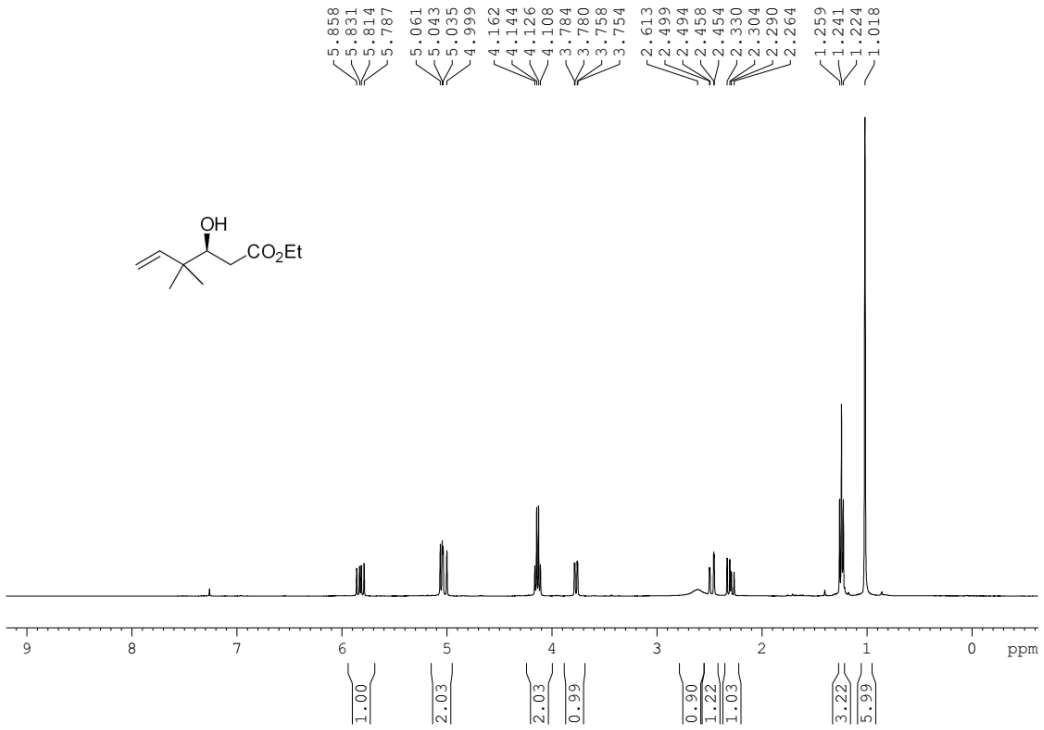


Figure S92. [1]H NMR spectrum of compound **1u**, related to **Table 2**.

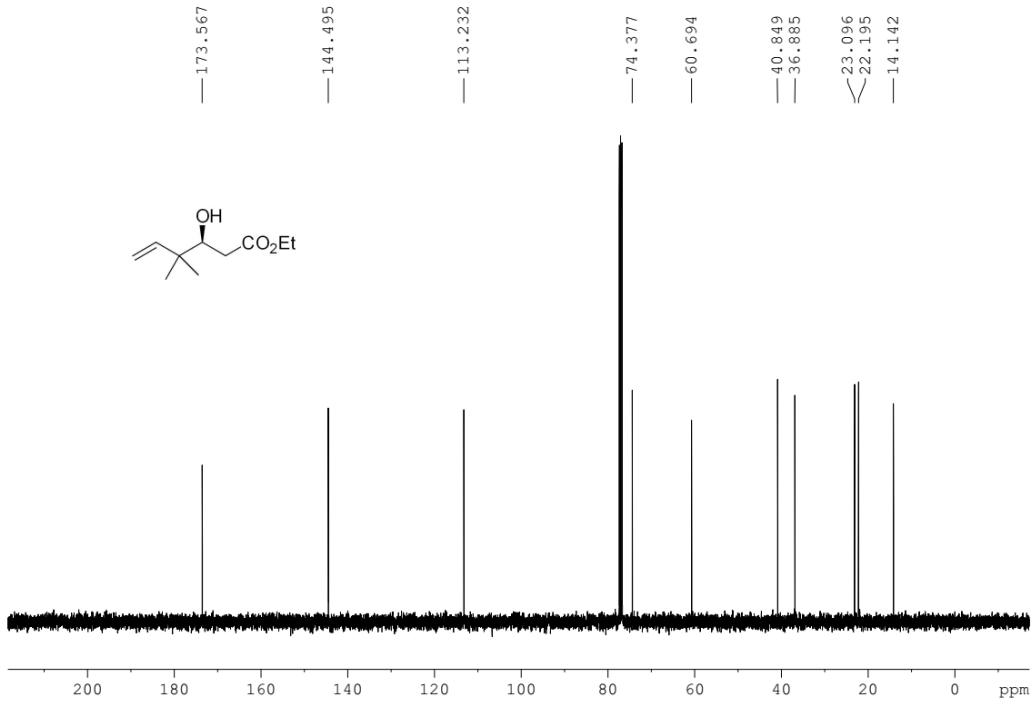


Figure S93. [13]C NMR spectrum of compound **1u**, related to **Table 2**.

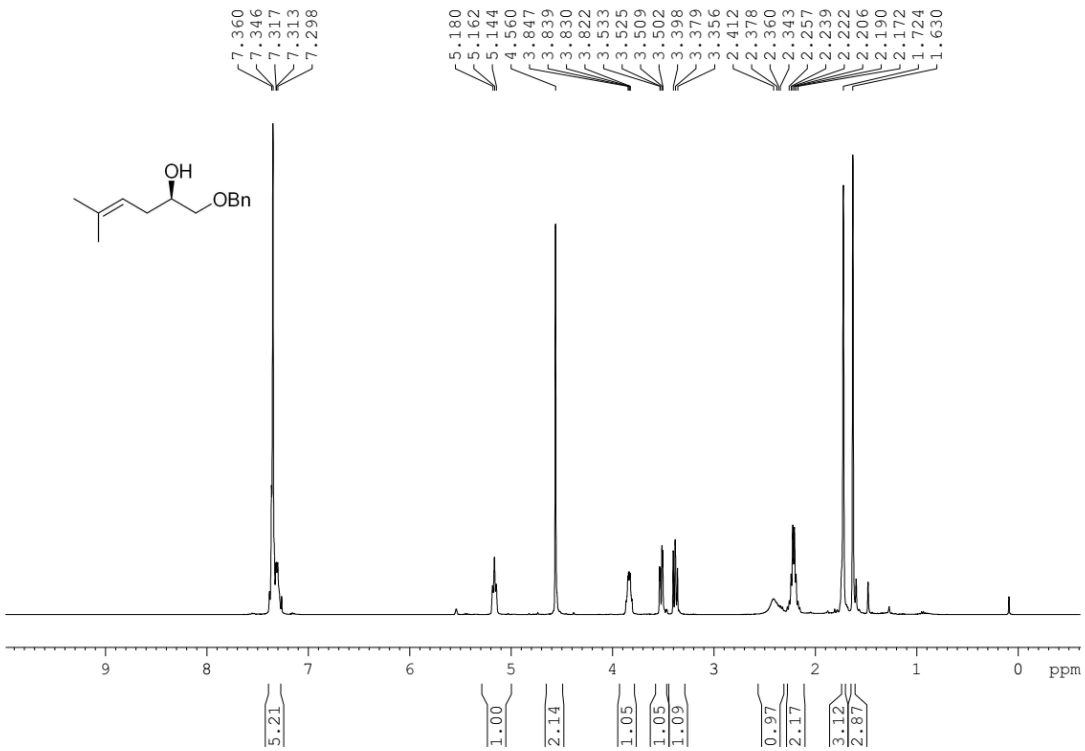


Figure S94. [1]H NMR spectrum of compound **1x**, related to **Table 2**.

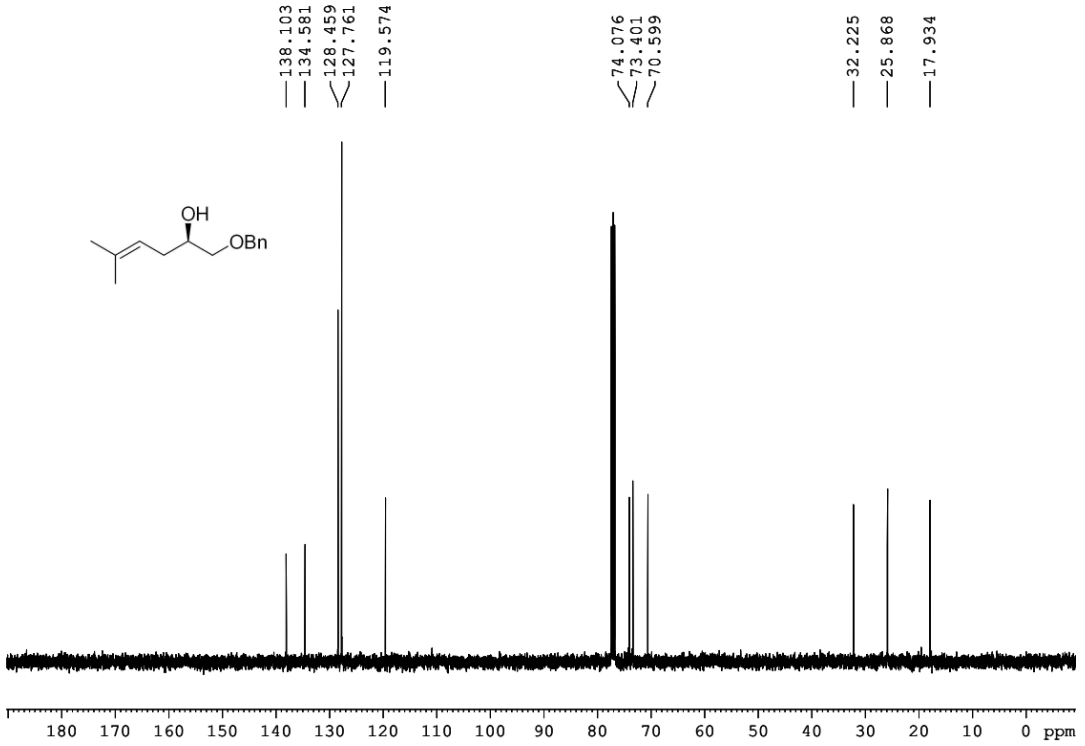
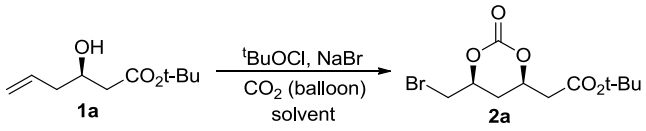


Figure S95. [13]C NMR spectrum of compound **1x**, related to **Table 2**.

Transparent Methods

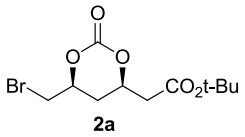
Thin-layer chromatography (TLC) carried out on 0.25 mm silica gel platesvisualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or iodine. Flash column chromatography was performed on silica gel (300-400 mesh). NMR spectraswere recorded on Bruker AM400 (400 MHz). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Optical rotations were taken on JASCO P1020. High-resolution mass spectra were recorded on Bruker ApeXIII 7.0 TESLA FTMS. Enantiomeric excesses were determined by chiral HPLC using a Agilent instrument.

General procedure for the synthesis of chiral cyclic bromocarbonates:



Chiral homoallylic alcohol (1.0 mmol) was added to a mixture of NaBr (154.3 mg, 1.5 mmol) and DMF (6 mL) under a balloon of CO_2 and stirred for 15 minutes. t-BuOCl (217.2 mg, 2.0 mmol) was added dropwise in the dark at -40 ℃ and the reaction mixture was stirred at -40 ℃ for 3 h. The reaction was quenched by adding aqueous $Na_2S_2O_3$ and the solution was diluted with EtOAc (50 mL) and washed with saturated brine water (4×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel with petroleum ether-ethyl acetate (petroleum ether/ethyl acetate 4:1) as eluent to give the desired product.

Spectroscopic Data of Products



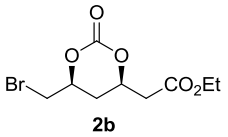
Tert-butyl2-((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetate (2a): white solid; actual mass 265.7 mg, yield 86%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): 4.83 (m, 1H), 4.70 (m, 1H), 3.51 (dq, J = 18.7, 4.9 Hz, 2H), 2.74 (dd, J = 16.4, 6.1 Hz, 1H), 2.56 (dd, J = 16.4, 6.8 Hz, 1H), 2.42 (d, J = 13.6, 1H), 1.86 (q, J = 12.0, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 147.8, 82.1, 76.6, 74.6, 40.7, 32.5, 31.1, 28.1.

HRMS (ESI) calcd. $(C_{11}H_{17}BrNaO_5)^+$ 331.0152, found 331.0148.

$[\alpha]^{20}_D$ -8.8 (c 1.00, $CHCl_3$).

HPLC (Daicel CHIRALPAK IA, ELSD Signal, Hexane : Isopropanol = 85 : 15, Flow rate = 1

mL/min, λ = 210 nm): t_R = 19.2 min (major enantiomer). (> 99% ee)

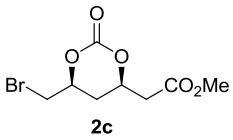


2b

Ethyl 2-((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl) acetate (2b): Colorless oil; actual mass 224.8 mg, yield 80%, *dr* > 19:1. ^{1}H NMR (400 MHz,$CDCl_3$): δ 4.88-4.82 (m, 1H), 4.68-4.65 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 4.9 Hz, 2H), 2.73 (dd, *J* = 16.6, 6.6 Hz, 1H), 2.60 (dd, *J* = 16.6, 6.1 Hz, 1H), 2.33 (dd, *J* = 14.1, 3.3 Hz, 1H), 1.86 (q, *J* =12.8 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 147.9, 76.6, 74.4, 61.2, 39.5, 32.9, 30.8, 14.1.

HRMS (ESI) calcd. $(C_9H_{13}BrNaO_5)^+$ 302.9839, found 302.9845.

$[\alpha]^{20}_D$ -6.1 (c 1.00, $CHCl_3$).

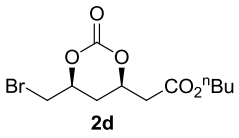


2c

Methyl 2-((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetate (2c): Colorless oil; actual mass 221.7 mg, yield 83%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88-4.82 (m, 1H), 4.67-4.64 (m, 1H), 3.64 (s, 3H), 3.48 (d, *J* = 4.7, 2H), 2.75 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.61 (dd, *J* = 16.6, 6.1 Hz, 1H), 2.35-2.31 (m, 1H), 1.92-1.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.8, 76.6, 74.4, 52.2, 39.3, 32.8, 30.8

HRMS (ESI) calcd. $(C_8H_{11}BrNaO_5)^+$ 288.9682, found 288.9685.

$[\alpha]^{20}_D$ -6.7 (c 1.40, $CHCl_3$).

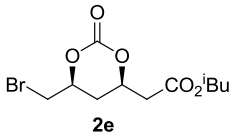


2d

Butyl2-((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetate (2d): Colorless oil; actual mass 256.5 mg, yield 83%, *dr* = 9:1. ^{1}H NMR (400 MHz, $CDCl_3$): 5.00-4.96 (m, 1H), 4.74-4.71 (m, 1H), 4.14 (t, *J* = 6.8 Hz, 2H), 3.62 (dd, *J* = 11.0, 4.7 Hz, 1H), 3.53 (dd, *J* = 9.7, 7.9 Hz, 1H), 2.88 (dd, *J* = 16.3, 6.8 Hz, 1H), 2.68 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.41-2.35 (m, 1H), 2.22-2.15 (m, 1H), 1.64-1.57 (m, 2H), 1.40-1.31 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 147.6, 74.9, 72.3, 65.3, 39.2, 31.4, 30.5, 28.6, 19.1, 13.7.

HRMS (ESI) calcd. $(C_{11}H_{17}BrNaO_5)^+$ 331.0152, found 331.0152

$[\alpha]^{20}_D$ -7.6 (c 1.00, $CHCl_3$).

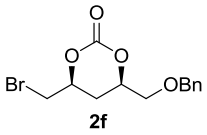


2e

Isobutyl 2-((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetate (2e): Colorless oil; actual mass 244.1 mg, yield 79%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.01-4.97 (m, 1H), 4.75-4.72 (m, 1H), 3.91 (t, *J* = 8.1 Hz, 2H), 3.61 (dd, *J* = 10.5, 4.6 Hz,1H), 3.50 (dd, *J* = 11.5, 8.8 Hz, 1H), 2.89 (dd, *J* = 16.5, 6.8 Hz, 1H), 2.67 (dd, *J* = 15.8, 6.8 Hz, 1H), 2.42-2.37 (m, 1H), 2.24-2.19 (m, 1H), 1.96-1.91 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 147.5, 74.9, 72.3, 71.5, 39.2, 31.2, 28.7, 27.6, 19.0.

HRMS (ESI) calcd. $(C_{11}H_{17}BrNaO_5)^+$ 331.0152, found 331.0157

$[\alpha]^{20}_D$ -8.5 (c 0.92, $CHCl_3$).

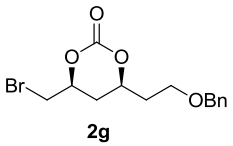


2f

(4*R*,6*S*)-4-((benzyloxy)methyl)-6-(bromomethyl)-1,3-dioxan-2-one(2f): Colorless oil; actual mass 236.4 mg, yield 75%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.33 (m, 5H), 4.63 – 4.40 (m, 2H), 4.58-4,57 (m, 2H), 3.64 (d, *J* = 4.3 Hz, 2H), 3.52 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.46 (dd, *J* = 11.4, 6.8 Hz, 1H), 2.30 (m, 1H), 2.00 (qd, *J* = 11.5, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 137.4, 128.6, 128.0, 127.8, 76.7, 73.8, 70.6, 32.5, 28.4.

HRMS (ESI) calcd. $(C_{13}H_{15}BrNaO_4)^+$ 337.0046, found 337.0051.

$[\alpha]^{20}_D$ -17.1 (c 0.5, $CHCl_3$).

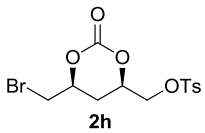


2g

(4*S*,6*S*)-4-(2-(benzyloxy)ethyl)-6-(bromomethyl)-1,3-dioxan-2-one (2g): Colorless oil; actual mass 244.1 mg, yield 81%, *dr* =12:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 5H), 4.77-4.65 (m, 1H), 4.64-4.58 (m, 1H), 4.50 (q, *J* = 11.6 Hz, 2H), 3.72-3.67 (m, 1H), 3.63-3.58 (m, 1H), 3.56-3.51 (dd, *J* = 10.7, 4.5 Hz,1H), 3.47-3.42 (dd, *J* = 11.1, 6.8 Hz,1H), 2.31-2.28 (m, 1H), 2.04-1.95 (m, 2H), 1.88-1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.9, 128.5, 127.9, 127.8, 76.8, 75.8, 73.3, 65.0, 35.4, 32.6, 31.8.

HRMS (ESI) calcd. $(C_{14}H_{17}BrNaO_4)^+$ 351.0202, found 351.0209.

$[\alpha]^{20}_D$ -27.8 (c 0.95, $CHCl_3$).



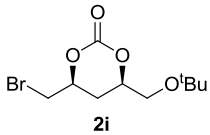
2h

((4*R*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)methyl4-methyl benzene sulfonate (2h): white solid; actual mass 314.7 mg, yield 83%, *dr* >19:1. ^{1}H NMR (400 MHz, DMSO): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 4.85 (m, 2H), 4.28 (dd, *J* = 11.4, 2.2 Hz, 1H), 4.21 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.78 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.70 (dd, *J* = 11.3, 5.2 Hz, 1H), 2.44 (s, 3H), 2.17-2.13 (m, 1H), 1.82 (q, *J* = 12.0 Hz 1H). ^{13}C NMR (100 MHz, DMSO) δ 147.8, 145.8, 132.4, 130.8, 128.2, 76.5, 75.4, 70.7, 35.1, 26.5, 21.6.

HRMS (ESI) calcd. $(C_{13}H_{15}BrNaO_4S)^+$ 400.9665, found 400.9673.

$[\alpha]^{20}_D$ -33.8 (c 0.50, $CHCl_3$).

HPLC (Daicel CHIRALPAK IA, Hexane: Isopropanol = 80 : 20, Flow rate = 1 mL/min, λ = 254 nm):t_R = 31.2 min (major enantiomer). (> 99% ee)

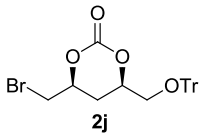


2i

(4*S*,6*R*)-4-(bromomethyl)-6-(tert-butoxymethyl)-1,3-dioxan-2-one (2i): Colorless oil; actual mass 216.4 mg, yield 77%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63-4.61 (m, 1H), 4.53-4.49 (m, 1H), 3.54-3.51 (m, 2H), 3.49-3.43 (m, 2H), 2.31-2.27 (m, 1H), 1.94-1.85 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 77.4, 76.7, 73.7, 62.9, 32.7, 28.6, 27.3.

HRMS (ESI) calcd. $(C_{10}H_{17}BrNaO_4)^+$ 303.0202, found 303.0207.

$[\alpha]^{20}_D$ -11.1 (c 0.9, $CHCl_3$).

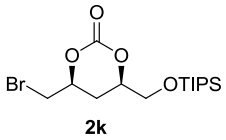


2j

(4*S*,6*R*)-4-(bromomethyl)-6-((trityloxy)methyl)-1,3-dioxan-2-one (2j): white solid; actual mass 397.3 mg, yield 85%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.6 Hz, 6H), 7.34-7.26 (m, 9H), 4.61-4.51 (m, 2H), 3.54 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.46 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.36-3.34 (m, 2H), 2.27-2.24 (m, 1H), 2.02-1.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 143.3, 128.6, 128.0, 127.4, 87.1, 77.2, 76.6, 64.6, 32.4, 28.7.

HRMS (ESI) calcd. $(C_{25}H_{23}BrNaO_4)^+$ 489.0672, found 489.0663.

$[\alpha]^{20}_D$ -13.1 (c 0.50, $CHCl_3$).

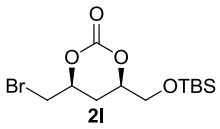


2k

(4*S*,6*R*)-4-(bromomethyl)-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-2-one (2k): Colorless oil; actual mass 301.3 mg, yield 79%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66-4.62 (m, 1H), 4.52-4.49 (m,1H), 3.92-3.84 (m,2H), 3.57 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.48 (dd, *J* = 11.0, 6.6 Hz, 1H), 2.36-2.32 (m,1H), 2.07-1.98 (m,1H),1.13-1.05 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 78.3, 76.5, 64.5, 32.5, 28.2, 17.9, 17.9, 11.9.

HRMS (ESI) calcd. $(C_{15}H_{29}BrNaO_4Si)^+$ 403.0911, found 403.0915.

$[\alpha]^{20}_D$ -29.1 (c 0.5, $CHCl_3$).

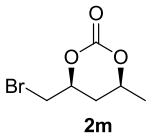


2l

(4*S*,6*R*)-4-(bromomethyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)-1,3-dioxan-2-one (2l): Colorless oil; actual mass 244.3 mg, yield 72%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65-4.61 (m, 1H), 4.51-4.48 (m, 1H), 3.79 (d, *J* = 4.3 Hz, 2H), 3.54 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.33-2.29 (m, 1H), 2.04-1.95 (m, 1H), 0.89 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 78.3, 76.5, 64.1, 32.42, 28.1, 25.8, 18.3.

HRMS (ESI) calcd. $(C_{12}H_{23}BrNaO_4Si)^+$ 361.0441, found 361.0449.

$[\alpha]^{20}_D$ -21.8 (c 0.6, $CHCl_3$).

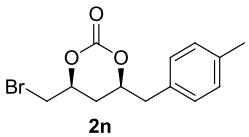


2m

(4*S*,6*S*)-4-(bromomethyl)-6-methyl-1,3-dioxan-2-one (2m): Colorless oil; actual mass 161.0 mg, yield 77%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67-4.57 (m, 2H), 3.49 (qd, *J* = 10.7, 4.1 Hz, 2H), 2.27 (d, *J* = 14.5 Hz, 1H), 1.77 (q, *J* = 11.8 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 76.8, 74.9, 33.1, 32.8, 21.0.

HRMS (ESI) calcd. $(C_6H_9BrNaO_3)^+$ 230.9627, found 230.9617.

$[\alpha]^{20}_D$ -9.7 (c 1.8, $CHCl_3$).



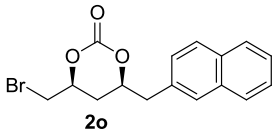
2n

(4*S*,6*S*)-4-(bromomethyl)-6-(4-methylbenzyl)-1,3-dioxan-2- one (2n): white solid; actual mass 254.3 mg, yield 85%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.09 (m, 4H), 4.65-4.53 (m, 2H), 3.44 (qd, *J* = 11.2, 4.4 Hz, 2H), 3.08 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.87 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.3 (s, 1H), 2.20-2.17 (m, 1H), 1.75 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 137.0, 131.8, 129.5,

129.5, 78.9, 40.9, 32.7, 30.8, 21.1.

HRMS (ESI) calcd. $(C_{13}H_{15}BrNaO_3)^+$ 321.0097, found 321.0109.

$[\alpha]^{20}_D$ 5.1 (c 0.8, $CHCl_3$).

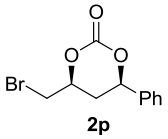


2o

(4*S*,6*S*)-4-(bromomethyl)-6-(naphthalen-2-ylmethyl)-1,3-dioxan-2-one (2o): white solid; actual mass 301.7 mg, yield 90%, *dr* = 14:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.34 (m, 7H), 4.71-4.53 (m, 2H), 3.72-3.45 (m, 2H), 3.31-3.28 (m, 1H), 3.10-3.06 (m, 1H), 2.22 (d, *J* =12.3 Hz, 1H), 1.78 (q, *J* =12.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 133.5, 132.6, 132.3, 128.6, 128.4 127.7, 127.6, 127.4, 126.5, 126.1, 78.7, 41.5, 32.5, 30.9.

HRMS (ESI) calcd. $(C_{16}H_{15}BrNaO_3)^+$ 357.0097, found 357.0085.

$[\alpha]^{20}_D$ -15.8 (c 0.7, $CHCl_3$).



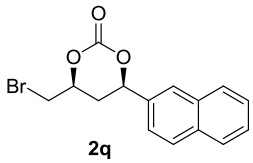
2p

(4*S*,6*R*)-4-(bromomethyl)-6-phenyl-1,3-dioxan-2-one (2p): white solid; actual mass 241.3 mg, yield 89%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.37 (m, 5H), 5.48 (d, *J* = 12.3 Hz, 1H), 4.82-4.81 (m, 1H), 3.53 (qd, *J* = 10.8, 4.2 Hz, 2H), 2.52 (d, *J* = 13.8 Hz, 1H), 2.12 (q, *J* = 12.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.2 129.3, 128.9, 125.9, 79.4, 76.9, 33.8, 32.6.

HRMS (ESI) calcd. $(C_{11}H_{11}BrNaO_3)^+$ 292.9784, found 292.9784.

$[\alpha]^{20}_D$ -60.5 (c 0.5, $CHCl_3$).

HPLC (Daicel CHIRALPAK IB, Hexane : Isopropanol = 85 :15, Flow rate = 1 mL/min, λ = 254 nm):t_R = 23.4 min (major enantiomer). (> 99% ee)

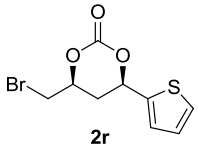


2q

(4S,6R)-4-(bromomethyl)-6-(naphthalen-2-yl)-1,3-dioxan-2-one (2q): white solid; actual mass 240.9 mg, yield 75%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.85 (m, 4H), 7.54-7.51 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 5.64-5.60 (m, 2H), 4.88-4.82 (m, 1H), 3.61 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.52 (dd, *J* = 11.0, 6.6 Hz, 1H), 2.63-2.58 (m, 1H), 2.20 (q, *J* = 11.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 134.4, 133.5, 133.0, 129.0, 128.2, 127.8, 126.9, 126.8, 125.2, 123.0, 79.5, 76.9, 33.9, 32.4.

HRMS (ESI) calcd. $(C_{15}H_{13}BrNaO_3)^+$ 342.9940, found 342.9942.

$[\alpha]^{20}_D$ -67.5 (c 0.6, $CHCl_3$).

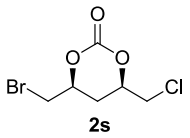


2r

(4*S*,6*R*)-4-(bromomethyl)-6-(thiophen-2-yl)-1,3-dioxan-2-one (2r): Colorless oil; actual mass 191.2 mg, yield 69%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.10 (s, 1H), 6.98 (d, *J* = 4.9 Hz, 1H), 4.68-4.59 (m, 2H), 3.46 (d, *J* = 4.6 Hz, 2H), 3.03 (qd, *J* = 14.5, 5.7 Hz, 2H), 2.19 (d, *J* = 13.8 Hz, 1H), 1.76 (q, *J* = 11.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 135.1, 128.6, 126.2, 123.3, 78.1, 76.7, 35.5, 33.1, 30.7.

HRMS (ESI) calcd. $(C_9H_9BrNaO_3S)^+$ 298.9348, found 298.9353.

$[\alpha]^{20}_D$ -7.5 (c 0.8, $CHCl_3$).



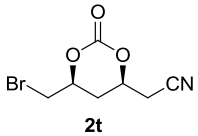
2s

(4*S*,6*R*)-4-(bromomethyl)-6-(chloromethyl)-1,3-dioxan-2-one (2s): Colorless oil; actual mass 221.6 mg, yield 91%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76-4.68 (m, 2H), 3.70 (d, *J* = 4.7, 2H), 3.54 (d, *J* = 5.1, 2H), 2.38-2.35 (m, 2H), 2.01 (q, *J* = 12.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 76.7, 76.4, 45.0, 32.7, 28.8.

HRMS (ESI) calcd. $(C_6H_8BrClNaO_3)^+$ 264.9238, found 264.9247.

$[\alpha]^{20}_D$ -6.4 (c 1.3, $CHCl_3$).

HPLC (Daicel CHIRALPAK IA, ELSD Signal, Hexane : Isopropanol = 85 : 15, Flow rate = 1 mL/min, λ = 210 nm):t_R = 13.4 min (major enantiomer). (> 99% ee)

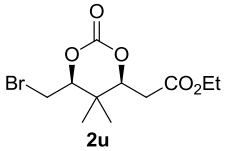


2t

2-((4*S*,6*S*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetonitrile (2t): Colorless oil; actual mass 112.3 mg, yield 48%, *dr* >19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80-4.74 (m, 2H), 3.62-3.52 (m, 2H), 2.87 (d, *J* = 5.4, 2H), 2.48 (*J* = 14.3, 1H), 2.03 (q, *J* = 12.2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 114.9, 76.5, 72.7, 32.1, 30.4, 24.0.

HRMS (ESI) calcd. $(C_7H_8BrNNaO_3)^+$ 255.9580, found 255.9592.

$[\alpha]^{20}_D$ -10.2 (c 1.1, $CHCl_3$).



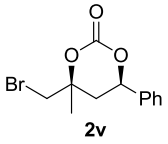
2u

Ethyl2-((4*S*,6*S*)-6-(bromomethyl)-5,5-dimethyl-2-oxo-1,3–dioxan-4-yl)

acetate (2u): Colorless oil; actual mass 231.7 mg, yield 75%, *dr* = 4 : 1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79-4.72 (m, 1H), 4.50-4.47 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 3.63-3.62 (m, 1H), 3.74 (t, *J* = 10.1 Hz, 1H), 2.57-2.55 (m, 2H), 1.27-1.24 (m, 3H), 1.11-0.94 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 147.2, 86.7, 82.5, 61.4, 34.8, 34.5, 28.8, 20.9, 14.1, 12.5.

HRMS (ESI) calcd. $(C_{11}H_{17}BrNaO_5)^+$ 331.0152, found 331.0153.

$[\alpha]^{20}_D$ -9.7 (c 1.0, $CHCl_3$).

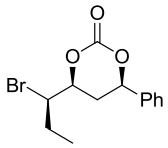


2v

(4*R*,6*R*)-4-(bromomethyl)-4-methyl-6-phenyl-1,3-dioxan-2-one (2v): white solid; actual mass 211.0 mg, yield 74%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.26 (m, 5H), 4.77 (t, *J* =11.2 Hz, 1H), 4.87 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.89 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.36 (d, *J* = 11.8 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 133.4, 129.3, 128.9, 128.5, 83.8, 67.3, 42.1, 39.0, 21.0.

HRMS (ESI) calcd. $(C_{12}H_{13}BrNaO_3)^+$ 306.9940, found 306.9947.

$[\alpha]^{20}_D$ -47.5 (c 0.7, $CHCl_3$).

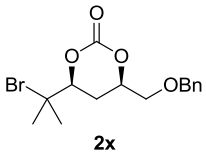


2w

(4*S*,6*R*)-4-((R)-1-bromopropyl)-6-phenyl-1,3-dioxan-2-one (2w): Colorless oil; actual mass 74.8 mg, yield 25%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.37 (m, 5H), 5.44 (d, *J* = 12.0 Hz, 1H), 4.68-4.63 (m, 1H), 4.03-3.98 (m, 1H), 2.62 (d, *J* = 13.9 Hz, 1H), 2.17-2.08 (m, 2H), 1.88-1.76 (m, 1H), 1.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 137.3, 129.2, 128.9, 125.9, 79.7, 79.2, 57.9, 33.5, 27.2, 11.7.

HRMS (ESI) calcd. $(C_{13}H_{15}BrNaO_3)^+$ 321.0097, found 321.0094.

$[\alpha]^{20}_D$ -29.6 (c 0.4, $CHCl_3$).

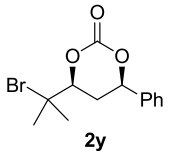


2x

(4*R*,6*S*)-4-((benzyloxy)methyl)-6-(2-bromopropan-2-yl)-1,3-dioxan-2-one (2x): Colorless oil; actual mass 154.4 mg, yield 45%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 5H), 4.60-4.59 (m, 2H), 4.57-4.55 (m, 1H), 4.35 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.71-3.63 (m, 2H), 2.44 (dt, *J* = 14.1, 3.1 Hz, 1H), 2.65 (q, *J* = 11.8 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.3, 128.6, 128.1, 127.9, 84.2, 76.9, 73.8, 70.7, 63.0, 30.8, 28.3, 26.7.

HRMS (ESI) calcd. $(C_{15}H_{19}BrNaO_4)^+$ 365.0359, found 365.0363.

$[\alpha]^{20}_D$ -41.7 (c 0.6, $CHCl_3$).

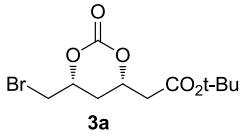


2y

(4*S*,6*R*)-4-(2-bromopropan-2-yl)-6-phenyl-1,3-dioxan-2-one (2y): Colorless oil; actual mass 128.6 mg, yield 43%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.30 (m, 5H), 4.48 (d, *J* = 8.8 Hz, 1H), 4.29-4.27 9 (m, 2H), 3.69 (q, *J* = 8.2 Hz, 1H), 1.87 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 136.7, 129.6, 128.5, 128.2, 89.7, 70.2, 67.5, 43.0, 31.6, 31.0.

HRMS (ESI) calcd. $(C_{13}H_{15}BrNaO_3)^+$ 321.0097, found 321.0097.

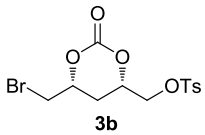
$[\alpha]^{20}_D$ -33.3 (c 0.7, $CHCl_3$).



3a

Tert-butyl2-((4*S*,6*R*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)acetate (3a): white solid; actual mass 247.2 mg, yield 80%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86-4.85 (m, 1H), 4.70-4.69 (m, 1H), 3.60-3.48 (m, 2H), 2.80 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.59 (dd, *J* = 16.7, 6.3 Hz, 1H), 2.46 (d, *J* = 14.2 Hz, 1H), 1.92 (q, *J* =12.2 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 147.2, 82.2, 76.6, 74.6, 40.7, 32.4, 31.2, 28.1.

$[\alpha]^{20}_D$ 5.1 (c 1.00, $CHCl_3$).

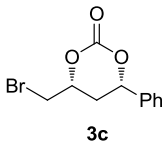


3b

((4*S*,6*R*)-6-(bromomethyl)-2-oxo-1,3-dioxan-4-yl)methyl4-methylbenzenesulfonate (3b): white solid; actual mass 299.6 mg, yield 79%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* =7.7 Hz, 2H), 4.88-4.80 (m, 2H), 4.30-4.18 (m, 2H), 3.79-3.68 (m, 2H), 2.44 (s, 3H), 2.16-2.13 (m, 1H), 1.82 (q, *J* =12.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 145.8, 132.4, 130.8, 128.2, 76.5, 75.4, 70.7, 35.1, 26.5, 21.6.

$[\alpha]^{20}_D$ 33.1 (c 0.7, $CHCl_3$).

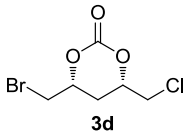
HPLC (Daicel CHIRALPAK IA, Hexane : Isopropanol = 85 : 15, Flow rate = 1 mL/min, λ = 254 nm):t_R = 25.9 min (major enantiomer). (> 99% ee)



3c

(4*R*,6*S*)-4-(bromomethyl)-6-phenyl-1,3-dioxan-2-one (3c): white solid; actual mass 222.2 mg, yield 82%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.36 (m, 5H), 5.48 (d, *J* = 12.3 Hz, 1H), 4.82-4.79 (m, 1H), 3.53 (qd, *J* = 10.8, 4.2 Hz, 2H), 2.50 (d, *J* = 13.8 Hz, 1H), 2.12 (q, *J* =12.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.2 129.3, 128.9, 125.9, 79.4, 76.9, 33.8, 32.6.

$[\alpha]^{20}_D$ 59.3 (c 1.1, $CHCl_3$).

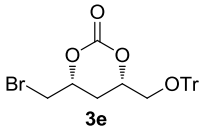


3d

(4*R*,6*S*)-4-(bromomethyl)-6-(chloromethyl)-1,3-dioxan-2-one (3d): Colorless oil; actual mass 211.8 mg, yield 87%, *dr* > 19:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 1H), 5.16-5.11 (m, 1H), 3.86 (s, 1H), 3.59 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.48 (dd, *J* = 11.3, 6.6 Hz, 1H), 2.55 (s, 1H), 2.38-2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 118.6, 70.6, 49.3, 38.7.

$[\alpha]^{20}_D$ 6.0 (c 1.3, $CHCl_3$).

HPLC (Daicel CHIRALPAK IA, ELSD Signal, Hexane : Isopropanol = 85 : 15, Flow rate = 1 mL/min, λ = 210 nm):t_R = 11.2 min (major enantiomer). (> 99% ee)

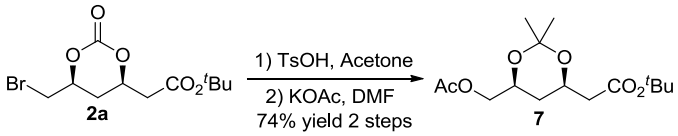


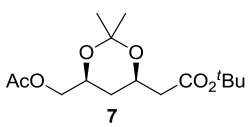
3e

(4*R*,6*R*)-4-(bromomethyl)-6-(2-(trityloxy)ethyl)-1,3-dioxan-2-one (3e): Colorless oil; actual mass 390.0 mg, yield 81%, *dr* > 19:1. ^{1}H NMR (400 MHz, CDCl3): δ 7.44 (d, *J* = 7.6 Hz, 6H), 7.34-7.26 (m, 9H), 4.61-4.51 (m, 2H), 3.54 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.46 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.36-3.34 (m, 2H), 2.27-2.24 (m, 1H), 2.02-1.92 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 148.0, 143.3, 128.6, 128.0, 127.4, 87.1, 77.2, 76.6, 64.6, 32.4, 28.7.

$[\alpha]^{20}_D$ 20.1 (c 1.1, $CHCl_3$).

Determination of absolute stereochemistry of 2a by correlation





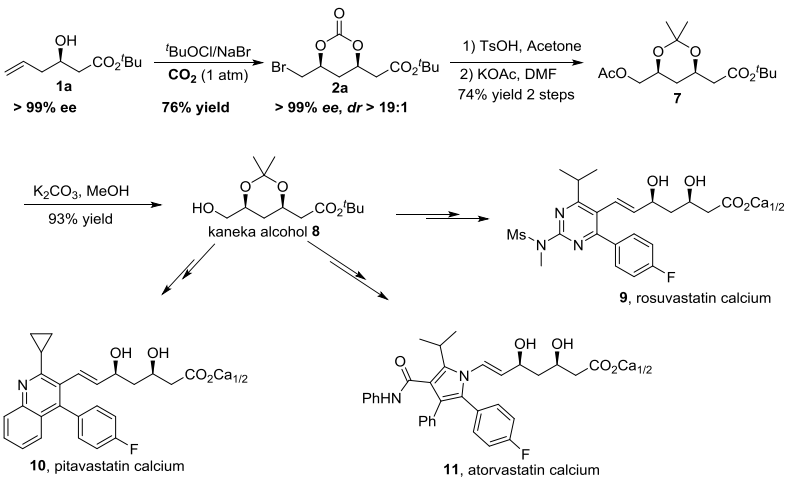
7

Tert-butyl2-((4*R*,6*S*)-6-(acetoxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetate (7): A mixture of **2a** (3.09 g, 10 mmol) and TsOH.•H_2O (0.95 g, 5 mmol) in acetone (40 mL) was stirred at r.t. for 20 h. The reaction

mixture was neutralized with sat. $NaHCO_3$ solution and acetone was evaporated. Extracted with DCM (50 mL × 3) and washed with brine, dried (Na_2SO_4) and evaporated to obtain crude compound. A mixture of the residue and AcONa (2.9 g, 35 mmol) in DMF (30 mL) was heat to 135 ^oC and stirred for 9h. After completion of the reaction, water (150 mL) and DCM (100 mL) was added and extracted with DCM (50 mL ×2) the combined organic phase was washed with water and brine, dried over Na_2SO_4, evaporated to dryness and purified by column chromatography to afford white solid. Actual mass 2.3 g, yield 74%. ^1H NMR (400 MHz, $CDCl_3$): δ 4.28-4.23 (m, 1H), 4.10-4.04 (m, 1H), 4.03- 3.96 (m, 2H), 2.42 (dd, *J* =15.1, 6.8 Hz, 1H), 2.29 (dd, *J* =15.2, 6.2 Hz, 1H), 2.05 (s, 3H), 1.56-1.52 (m, 1H), 1.43 (s, 3H), 1.42 (s, 9H), 1.36 (s, 3H), 1.23 (q, *J* =11.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.1, 98.9, 80.7, 67.2, 67.0, 65.8, 42.6, 32.6, 29.9, 28.1, 20.9, 19.6.

$[\alpha]^{20}_D$ 14.0 (c 1.0, $CHCl_3$). lit.[1] $[\alpha]^{20}_D$ 13.7 (c 1.0, $CHCl_3$).

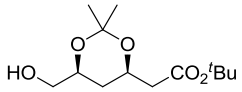
Scheme S1. Pilot-plant scale preparation of 2a and elaboration into synthetic common intermediate of statins



Chrial homoallylic alcohol **1a** (250 g, 1.35 mol) was added to a mixture of NaBr (207.7 g, 2.02 mol) and DMF (3 L) under an oxygen bag of CO_2 (the oxygen bag connected with a CO_2 cylinder) and stirred for 30 minutes. t-BuOCl (293.2 g, 2.7 mol) was added dropwise in the dark at -40 ℃ and the reaction mixture was stirred at -40 ℃ for 3 h. The reaction was quenched at -40 ℃ by adding aqueous $Na_2S_2O_3$, and the solution was diluted with EtOAc (2.5 L) and washed with saturated brine water (4×250 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum. actual mass 315.7 g, yield 76% (in 93% purity determined by

HPLC-ELSD).

To a stirred solution of **7** (2.0 g, 6.6 mmol) in MeOH (20 mL) was added K_2CO_3 (0.91 g, 6.6 mmol), the stirring was continued for 1 h and then sat. aq. NH_4Cl (5 mL) was added, the reaction mixture was washed with petroleum ether (30 mL × 3). The methanolic phase was concentrated to remove MeOH in vacuo. The residue was dissolved in EtOAc and washed with brine, dried (Na_2SO_4) and evaporated to dryness in vacuo to afford crude alcohol，and purified by column chromatography to afford oil liquid **8**. Actual mass 1.6 g, yield 93%.

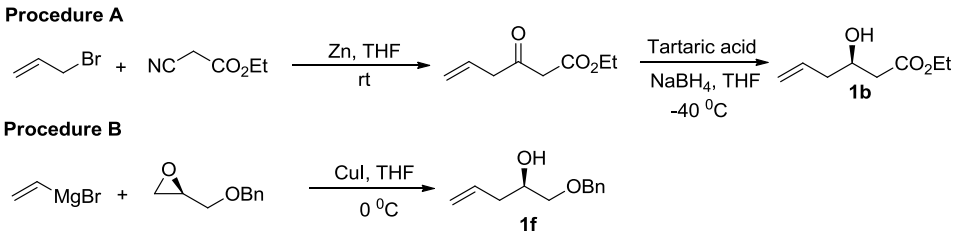


8

tert-butyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (8): ^{1}H NMR (400 MHz, CDCl3): δ 4.24-4.18 (m, 1H), 3.95-3.89 (m, 1H), 3.51-3.49 (m, 1H), 3.45-3.41 (m, 1H), 2.57 (s, 1H), 2.36 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.23 (dd, *J* = 15.1, 6.1 Hz, 1H), 1.42 (dt, *J* = 12.7, 2.6 Hz, 1H), 1.39 (s,3H), 1.36 (s, 9H), 1.30 (s,3H), 1.22 (d, *J* = 12.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 98.8, 80.6, 69.6, 65.8, 65.8, 42.6, 31.9, 29.9, 28.0, 19.7.

$[\alpha]^{20}_D$ 10.4 (c 1.0, $CHCl_3$). lit. $[\alpha]^{20}_D$ 12.0 (c 0.94, $CHCl_3$). (Fan et al., 2011)

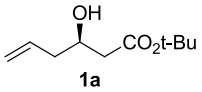
Scheme S2. General procedure for preparation of homoallylic alcohols



Procedure A (Lee et al., 2000; Yatagai et al., 1990)**:** Ethyl cyanoacetate (20.0 mmol) was added to a solution of zinc powder (60.0 mmol) and allylic bromide (30.0 mmol) in anhydrous THF (100 mL) at 0 ℃ (ice-water bath). The reaction mixture was warmed to room temperature and then stirred at room temperature. After the reaction was completed (monitored by TLC), aqueous HCl (2 M, 100 mL) was added to the reaction mixture and stirred at room temperature for 5 minutes, and the solution was diluted with EtOAc (150 mL) and washed with saturated brine water (4×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum to obtain the correlative crude ketone without any purification. After addition of (*L*)-tartaric acid (30.0 mmol)

to the stirred suspension of $NaBH_4$ (24.0 mmol) in THF (200 mL), the mixture was stirred under reflux for 4 h. The mixture was cooled -40 ℃ and then the crude ketone in THF (20 mL) was added to it with stirring. After the completion of reduction, 1 M HCl was added to the mixture until PH value indicated acidic, and the resulting mixture was stirred for 15 min. Evaporation of THF was followed by extraction of the residue with ethyl acetate (3× 50 mL). The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate and brine, and dried with Na_2SO_4, The crude product was purified by means of column chromatography on silica gel to afford the corresponding homoallylic alcohol **1e** (2.3 g) in 73% yield over 2 steps.

Procedure B(Beattie et al., 2016)**:** To a solution of (*R*)-2-((benzyloxy)methyl)oxirane (10 mmol) in Et_2O (100 mL) and copper (I) iodide (1 mmol) at -78 ℃ under N_2 was added vinyl magnesium bromide (15mL of 1M solution in THF, 15 mmol) dropwise over 5 minutes. The resulting mixture was allowed to stir for 4 h, after which saturated aqueous solution of NH_4Cl (50 mL) was added. The organics were separated and the aqueous layer extracted with Et_2O (3 x 50 mL), combined, then dried (Na_2SO_4) and concentrated in vacuo. The crude residue was then purified by column chromatography to give homoallylic alcohol **1a** as a colorless oil (3.1 g, 80%).



1a

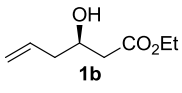
(*R*)-tert-butyl 3-hydroxyhex-5-enoate (1a) (Chen et al., 2017)**:** Colorless oil; actual mass 319.9 g, yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.80 (m, 1H), 5.15 (d, *J* = 5.8 Hz, 1H), 5.12 (s, 1H), 4.07-4.05 (m, 1H), 3.10 (s, 1H), 2.48-2.29 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 134.1, 117.9, 81.2, 67.5, 41.6, 40.9, 28.1.

HRMS (ESI) calcd. $(C_{10}H_{18}NaO_3)^+$ 209.1148, found 209.1144.

$[\alpha]^{20}_D$ -24.3 (c 1.0, $CHCl_3$).

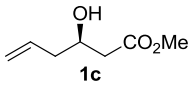
HPLC (Daicel CHIRALPAK IA, ELSD Signal, Hexane : Isopropanol = 98.5 : 1.5, Flow rate = 1 mL/min, λ = 210 nm) : t_R = 8.1 min (major enantiomer). (> 99% ee)

Spectroscopic Data of substrates



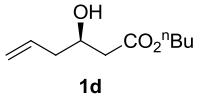
1b

(*R*)-Ethyl 3-hydroxyhex-5-enoate (1b): synthesized by procedure A. Colorless oil; actual mass 2.3 g, yield 73%. $[\alpha]^{20}_D$ -31.2 (c 1.1, $CHCl_3$). lit. $[\alpha]^{24}_D$ -14.8 (c 1.1, $CHCl_3$). (Ema et al., 2001)



1c

(*R*)-Methyl 3-hydroxyhex-5-enoate (1c): synthesized by procedure A. Colorless oil; actual mass 2.0 g, yield 78%. $[\alpha]^{20}_{D}$ -21.1 (c 0.8, $CHCl_3$). lit. $[\alpha]^{20}_{D}$ -13.5 (c 1.1, $CHCl_3$).(Bennett et al., 1988)

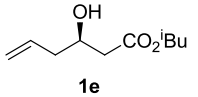


1d

(*R*)-butyl 3-hydroxyhex-5-enoate (1d): synthesized by procedure A. Colorless oil; actual mass 2.5 g, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87-5.76 (m, 1H), 5.13 (d, *J* = 6.1 Hz, 1H), 5.10 (s, 1H), 4.12-4.09 (m, 2H), 4.07-4.06 (m, 1H), 2.98 (s, 1H), 2.53-2.39 (m, 2H), 2.33-2.23 (m, 2H), 1.64-1.57 (m, 2H), 1.42-1.32 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 134.0, 118.1, 67.4, 64.6, 41.0, 40.6, 30.6, 19.1, 13.7.

HRMS (ESI) calcd. $(C_{10}H_{18}NaO_3)^+$ 209.1148, found 209.1148.

$[\alpha]^{20}_{D}$ -10.4 (c 0.9, $CHCl_3$).

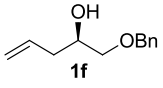


1e

(*R*)-isobutyl 3-hydroxyhex-5-enoate (1e): synthesized by procedure A. Colorless oil; actual mass 2.6 g, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.78 (m, 1H), 5.13 (d, *J* = 6.2 Hz, 1H), 5.10 (s, 1H), 4.10-4.08 (m, 1H), 3.89 (d, *J* = 6.3 Hz, 1H), 3.05 (s, 1H), 2.56-2.41 (m, 2H), 2.32-2.24 (m, 2H), 1.97-1.90 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 134.0, 118.1, 70.8, 67.4, 41.0, 40.6, 27.6, 19.0.

HRMS (ESI) calcd. $(C_{10}H_{18}NaO_3)^+$ 209.1148, found 209.1151.

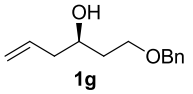
$[\alpha]^{20}_{D}$ -7.6 (c 1.0, $CHCl_3$).



1f

(*R*)-1-(benzyloxy)pent-4-en-2-ol (1f): synthesized by procedure B. Colorless oil; actual mass 3.1 g, yield 80%.

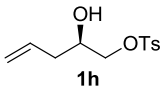
$[\alpha]^{20}_{D}$ -3.1 (c 0.70, $CHCl_3$). lit. $[\alpha]^{25}_{D}$ -6.0 (c 1.5, $CHCl_3$). (Beattie et al., 2016)



1g

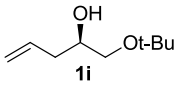
(*R*)-1-(benzyloxy)hex-5-en-3-ol (1g): synthesized by procedure B. Colorless oil; actual mass 2.3 g, yield 81%.

$[\alpha]^{20}_{D}$ -4.1 (c 1.0, $CHCl_3$). lit. $[\alpha]^{25}_{D}$ -3.33 (c 0.6, $CHCl_3$). (Rauniyar et al., 2008)



(*R*)-2-hydroxypent-4-en-1-yl 4-methylbenzenesulfonate (1h): synthesized by procedure B. Colorless oil; actual mass 4.5 g, yield 88%.

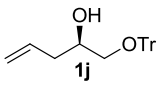
$[\alpha]^{20}_D$ -11.7 (c 1.0, $CHCl_3$). lit. $[\alpha]^{25}_D$ -9.6 (c 0.9, $CHCl_3$).(Brun, et al., 2014)



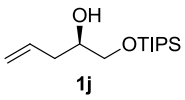
(*R*)-1-(tert-butoxy)pent-4-en-2-ol (8): synthesized by procedure B. Colorless oil; actual mass 2.7 g, yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.78 (m, 1H), 5.11-5.05 (m, 1H), 3.74 (m, 1H), 3.36 (dd, *J* =8.8, 3.1 Hz, 1H), 3.20 (t, *J* =7.9 Hz, 1H), 2.52 (s, 1H), 2.24 (t, *J* =6.8 Hz, 1H), 1.8 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 117.2, 73.2, 70.0, 65.3, 38.0, 27.5.

HRMS (ESI) calcd. $(C_9H_{18}NaO_2)^+$ 181.1199, found 181.1203.

$[\alpha]^{20}_D$ -5.4 (c 1.15, $CHCl_3$).



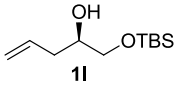
(*R*)-1-(trityloxy)pent-4-en-2-ol (1j): synthesized by procedure B. Colorless oil; actual mass 6.2 g, yield 90%. $[\alpha]^{20}_D$ -3.1 (c 0.95, $CHCl_3$). lit. $[\alpha]^{20}_D$ -7.4 (c 0.97, MeOH).(Faul et al.,1998)



(*R*)-1-((triisopropylsilyl)oxy)pent-4-en-2-ol (1j): synthesized by procedure B. Colorless oil; actual mass 4.4 g, yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.79 (m, 1H), 5.13-5.07 (m, 2H), 3.76-3.69 (m, 2H), 3.56-3.52 (m, 1H), 2.25 (t, *J* = 6.2 Hz, 2H), 1.12-1.05 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 117.3, 71.3, 66.9, 37.6, 17.9, 11.9.

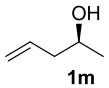
HRMS (ESI) calcd. $(C_{14}H_{30}NaO_2Si)^+$ 281.1907, found 281.1909.

$[\alpha]^{20}_D$ -7.6 (c 1.2, $CHCl_3$).



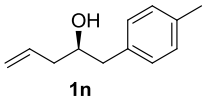
(*R*)-1-((tert-butyldimethylsilyl)oxy)pent-4-en-2-ol (1l): synthesized by procedure B. Colorless oil; actual mass 3.5 g, yield 81%.

$[\alpha]^{20}_D$ -3.7 (c 1.0, $CHCl_3$). lit.{ for (S) enantiomer, $[\alpha]^{20}_D$ 3.3 (c 0.6, $CHCl_3$)}.(Lu et al., 2013)



(*S*)-pent-4-en-2-ol (1m): synthesized by procedure B. Colorless oil; actual mass 1.3 g, yield 78%.

$[\alpha]^{20}_D$ 4.5 (c 1.2, Et_2O). lit. $[\alpha]^{25}_D$ 10.9 (c 3.2 , Et_2O).(Kumar et al., 2006)

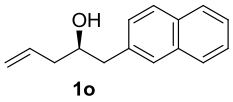


1n

(*R*)-1-(p-tolyl)pent-4-en-2-ol (1n): synthesized by procedure A. Colorless oil; actual mass 2.6 g, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (m, 4H), 5.94-5.84 (m, 1H), 5.18 (d, *J* = 6.8 Hz, 1H), 5.15 (s, 1H), 3.90-3.84 (m, 1H), 2.80 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.70 (dd, *J* = 13.2,7.8 Hz, 1H), 2.35-2.31 (m, 4H), 2.28-2.20 (m, 1H), 1.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.3, 134.8, 129.4, 129.3, 118.0. 71.8, 42.9, 41.2, 21.1.

HRMS (ESI) calcd. $(C_{12}H_{16}NaO)^+$ 199.1093, found 199.1097.

$[\alpha]^{20}_D$ -9.6 (c 0.75, $CHCl_3$).

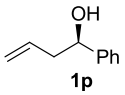


1o

(*R*)-1-(naphthalen-2-yl)pent-4-en-2-ol (1o): synthesized by procedure A. Colorless oil; actual mass 2.8 g, yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.82 (m, 3H), 7.71 (s, 1H), 7.53-7.46 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 5.97-5.87 (m, 1H), 5.22 (d, *J* = 5.4 Hz, 1H), 5.19 (s, 1H), 4.03-3.97 (m, 1H), 3.03-2.88 (m, 1H), 2.43-2.37 (m, 1H), 2.33-2.56 (m, 1H), 2.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.8, 133.6, 132.4, 128.2, 128.0, 127.9, 127.7, 127.6, 126.1, 125.6, 118.2, 71.7, 43.5, 41.3.

HRMS (ESI) calcd. $(C_{15}H_{16}NaO)^+$ 235.1093, found 235.1095.

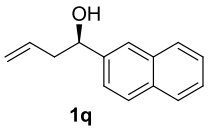
$[\alpha]^{20}_D$ -21.4 (c 1.6, $CHCl_3$).



1p

(*R*)-1-phenylbut-3-en-1-ol (1p): synthesized by procedure B. Colorless oil; actual mass 2.5 g, yield 83%

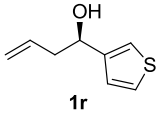
$[\alpha]^{20}_D$ 57.1 (c 1.0, $CHCl_3$). lit. $[\alpha]^{24}_D$ 55.7 (c 1.0, $CHCl_3$). (Jain et al., 2010)



1q

(*R*)-1-(naphthalen-2-yl)but-3-en-1-ol (1q): synthesized by procedure A. Colorless oil; actual mass 2.5 g, yield 64%.

$[\alpha]^{20}_D$ 37.7 (c 1.0, Benzen). lit. $[\alpha]^{25}_D$ 40.5 (c 1.0, $CHCl_3$). (Chen et al., 2015)



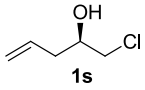
1r

(*R*)-1-(thiophen-3-yl)but-3-en-1-ol (1q): synthesized by procedure A. Colorless oil; actual mass 1.8 g, yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.28 (m, 1H), 7.05 (s, 1H), 6.99-6.98 (m, 1H), 5.92-5.81 (m, 1H), 5.17 (d, *J* = 4.7 Hz, 1H), 5.14 (s, 1H), 3.91-3.85 (m, 1H), 2.88-2.74 (m, 2H), 2.36-2.29 (m, 1H), 2.28-2.18

(m, 1H), 1.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 134.7, 128.7, 125.8, 122.1, 118.2, 77.4, 77.1, 76.8, 71.0, 41.2, 37.6.

HRMS (ESI) calcd. for $(C_8H_{10}NaOS)^+$ 177.0345, found 177.0349.

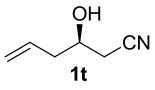
$[\alpha]^{20}_D$ 38.9 (c 1.3, $CHCl_3$).



1s

(*R*)-1-chloropent-4-en-2-ol (1s): synthesized by procedure B. Colorless oil; actual mass 2.2 g, yield 91%.

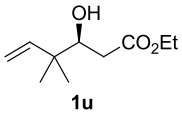
$[\alpha]^{20}_D$ -4.4 (c 1.0, $CHCl_3$). lit. $[\alpha]^{24}_D$ -4.2 (c 1.0, $CHCl_3$). (J. Donohoe et al., 2009)



1t

(*R*)-3-hydroxyhex-5-enenitrile (1t): synthesized by procedure B. Colorless oil; actual mass 4.4 g, yield 82%.

$[\alpha]^{20}_D$ -7.3(c 1.0, $CHCl_3$). lit. $[\alpha]^{24}_D$ -6.8 (c 0.8, $CHCl_3$). (Saneyoshi et al., 2010)

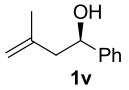


1u

(*S*)-ethyl 3-hydroxy-4,4-dimethylhex-5-enoate (1u): synthesized by procedure A. Colorless oil; actual mass 2.7 g, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (dd, *J* = 5.7, 11.1 Hz, 1H), 5.06-5.00 (m, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.78-3.75 (m, 1H), 2.61 (s, 1H), 2.50-2.45 (m, 1H), 2.33-2.26 (m, 1H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 144.5, 113.2, 113.2, 74.4, 60.7, 40.8, 36.9, 23.1, 22.2, 14.1.

HRMS (ESI) calcd. $(C_{10}H_{18}NaO_3)^+$ 209.1148, found 209.1151.

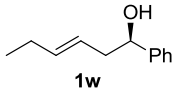
$[\alpha]^{20}_D$ -19.3 (c 1.0, $CHCl_3$).



1v

(*R*)-3-methyl-1-phenylbut-3-en-1-ol (1v): synthesized by procedure B. Colorless oil; actual mass 2.6 g, yield 80%.

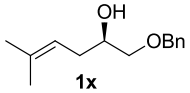
$[\alpha]^{20}_D$ 68.9 (c 1.0, $CHCl_3$). lit. $[\alpha]^{24}_D$ 65.9 (c 0.8, $CHCl_3$). (Sai et al., 2015)



1w

(*R*,*E*)-1-phenylhex-3-en-1-ol (1w): actual mass 2.5 g, yield 71%.

$[\alpha]^{20}_D$ 59.9 (c 1.0, $CHCl_3$). lit. $[\alpha]^{20}_D$ 62 (c 1.2, $CHCl_3$). (Brauns et al., 2016)



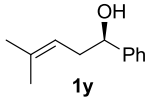
1x

(*R*)-1-(benzyloxy)-5-methylhex-4-en-2-ol (1x): synthesized by procedure B.

Colorless oil; actual mass 4.1 g, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 5H), 5.18-5.14 (m, 1H), (s, 2H), 3.85-3.82 (m, 1H), 3.53-3.50 (m, 1H), 3.40-3.56 (m, 1H), 2.41 (s, 1H), 2.26-2.17 (m, 2H), 1.72 (s, 1H), 1.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.6, 128.5, 127.8, 119.6, 74.1, 73.4, 70.6, 32.2, 25.9, 17.9.

HRMS (ESI) calcd. $(C_{14}H_{20}NaO_2)^+$ 243.1356, found 243.1359.

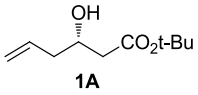
$[\alpha]^{20}_D$ -8.3 (c 1.0, $CHCl_3$).



1y

(*R*)-4-methyl-1-phenylpent-3-en-1-ol (1y): synthesized by procedure B. Colorless oil; actual mass 2.6 g, yield 74%.

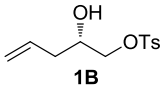
$[\alpha]^{20}_D$ 41.7 (c 0.3, MeOH). lit. $[\alpha]^{20}_D$ 38.7 (c 0.15, MeOH). (Cheng et al., 2003)



1A

(*S*)-tert-butyl 3-hydroxyhex-5-enoate (1A): synthesized by procedure A. Colorless oil; actual mass 2.6 g, yield 71%.

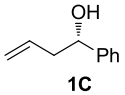
$[\alpha]^{20}_D$ 25.1 (c 1.0, $CHCl_3$).



1B

(*S*)-2-hydroxypent-4-en-1-yl 4-methylbenzenesulfonate (1B): synthesized by procedure B. Colorless oil; actual mass 4.5 g, yield 87%.

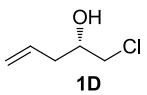
$[\alpha]^{20}_D$ 12.0 (c 1.0, $CHCl_3$).



1C

(*S*)-1-phenylbut-3-en-1-ol (1C): synthesized by procedure B. Colorless oil; actual mass 2.4 g, yield 82%.

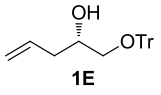
$[\alpha]^{20}_D$ -55.3 (c 1.0, $CHCl_3$).



1D

(*S*)-1-chloropent-4-en-2-ol (1D): synthesized by procedure B. Colorless oil; actual mass 2.2 g, yield 90%.

$[\alpha]^{20}_D$ 4.2 (c 1.0, $CHCl_3$).



1E

(*S*)-1-(trityloxy)pent-4-en-2-ol (1E): synthesized by procedure B. Colorless oil; actual mass 3.0 g, yield 87%.

$[\alpha]^{20}_D$ 2.4 (c 1.0, $CHCl_3$).

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