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Graphical Abstract

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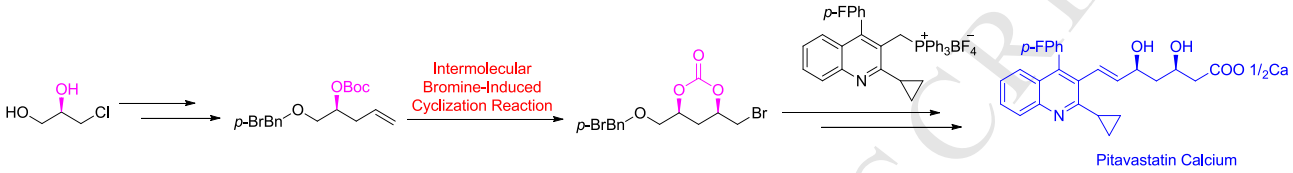

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ABSTRACT

A novel approach to synthesize pitavastatin calcium (**1**), an effective HMG-CoA reductase inhibitor, based on readily available and attractively functionalized (*R*)-3-chloro-1,2-propanediol is reported. This work highlights an intermolecular diastereoselective bromine-induced cyclization of homoallylic carbonate to meet stereochemical challenges in the synthesis of statins. An efficient route to a new triphenylphosphonium tetrafluoroborate salt of a quinoline core is also presented.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide. More than 17 million people die annually from coronary heart disease (CHD) and stroke.[1] Epidemiological evidence indicates that there is a strong correlation between hypercholesterolemia and the risk of CHD.[2] HMG-CoA reductase inhibitors, commonly referred to as statins, have been successfully used in the clinical setting to decrease the occurrence of coronary events by lowering total plasma cholesterol and the level of LDL-C.[3] Pitavastatin calcium (**1**) is an effective HMG-CoA reductase inhibitor and the active ingredient in Livalo, which is in clinical use to treat hypercholesterolemia.[4]

Given the promise of **1** as a HMG-CoA reductase inhibitor, not surprisingly, a large amount of research has been conducted toward the asymmetric synthesis of this important statin.[5] Among these endeavors, the highly convergent C_1 + C_6 Wittig-type olefination strategy using enantiomerically pure C_6-formyl side chain **2**[6] with a *syn*-1,3-diol subunit and triphenylphosphonium bromide **3** as important building blocks is considered one of the most expedient and practical approaches to develop an industrial-scale synthesis of **1** (Figure 1).[5] However, the asymmetric construction of statin side chain **2** remains challenging. The efficient chiral route to obtain this framework of statins from readily available (-)-epichlorohydrin is reliable for large-scale synthesis of **1** and other statins. However, a major problem of this synthesis is that the use of cryogenic diastereoselective borohydride reduction of a boron chelate intermediate derived from the chiral *β*-hydroxy-3-ketoester and diethylmethoxyborane as a complex agent to form the second stereogenic center (3*R*) with very high stereocontrol.[7] This drawback of the existing method prompted us to pursue an alternative practical approach to synthesize important statin **1**. Herein, we describe our recently developed novel strategy that allows the concise asymmetric synthesis of **1** and features a unique intermolecular diastereoselective bromine-induced cyclization reaction.

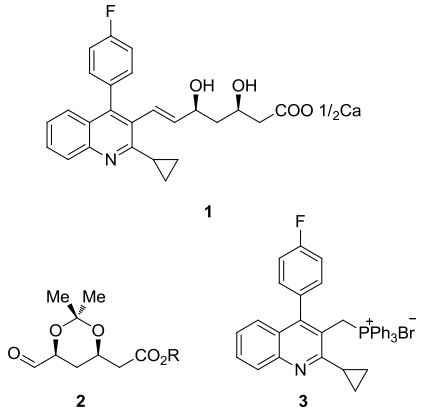

Figure 1. Structures of pitavastatin calcium (**1**), chiral C_6-formyl side chain **2** and triphenylphosphonium bromide **3**

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2. Results/Discussion

Our retrosynthetic analysis of **1** is depicted in Figure 2. Statin **1** can be disconnected into two components: chiral C_6-formyl side chain **2** containing a *syn*-1,3-diol structural unit and triphenylphosphonium tetrafluoroborate salt **4** with a quinoline core, which served as our initial targets. We anticipated that the six-carbon side chain **2** could be appended onto the quinoline core of **4** using an improved Wittig coupling reaction that would facilitate stereoselective construction of the statin side chain in the target molecule. We envisaged that aldehyde **2** could be produced from six-membered cyclic bromocarbonate **5**, which could be accessed from stereodefined homoallylic carbonate **6** *via* an intermolecular diastereoselective bromine-induced cyclization that would generate the 3*R* stereogenic center. The ultimate disconnection identified (*R*)-3-chloro-1,2-propanediol **7** as the starting material for the proposed route to **2**. Triphenylphosphonium tetrafluoroborate salt **4** could be synthesized from commercially available cyclopropyl methyl ketone **9** as a starting material *via* acetal **8** according to a series of simple functional transformations.

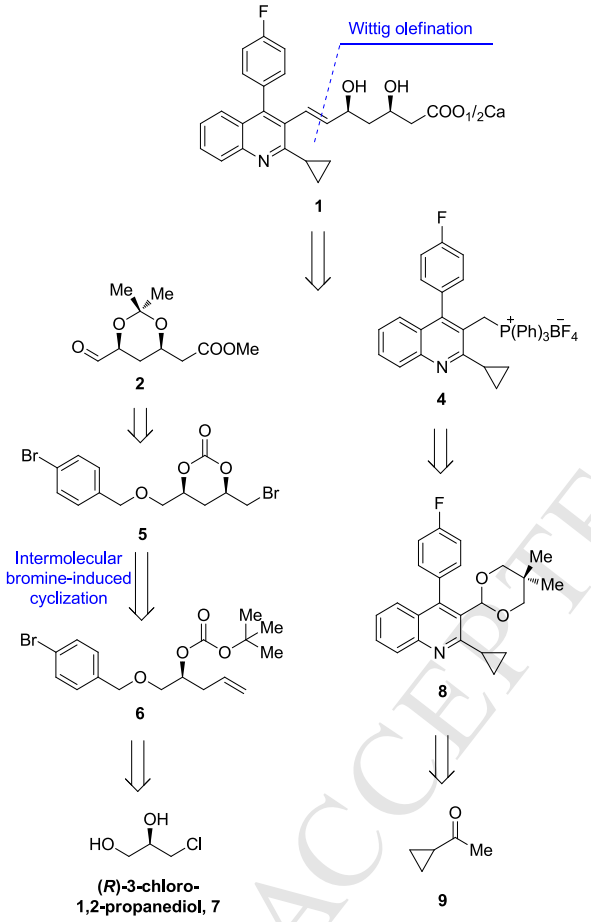
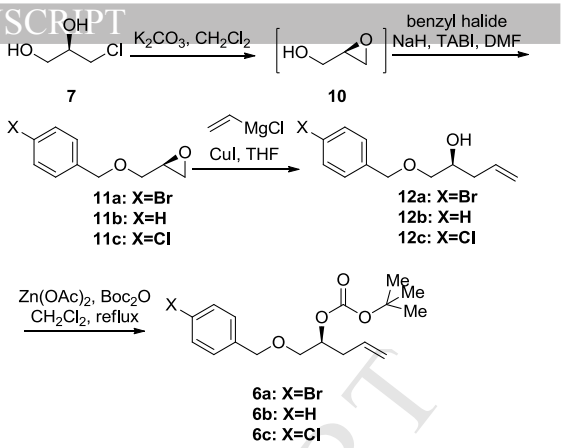


Figure 2. Retrosynthetic analysis of pitavastatin calcium (**1**)

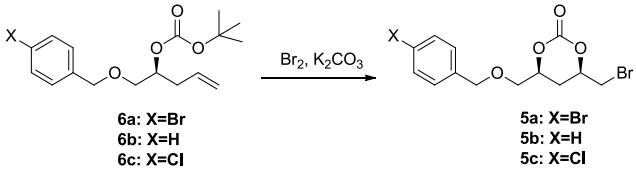
Our synthesis began by epoxidation of **7** under basic conditions (Scheme 1).[8] Protection of the primary hydroxyl group by treatment of **10** with *p*-bromobenzyl bromide, benzyl bromide, and *p*-chlorobenzyl chloride afforded the corresponding benzyl esters **11a**, **b** and **c**, respectively, in 88%–90% yield.[9] Regioselective ring opening of **11a-c** with vinylmagnesium chloride in THF at -10 °C under copper catalysis gave homoallylic alcohols **12a-c** in almost quantitative yield,[10] which were then converted to the corresponding homoallylic *tert*-butyl carbonates **6a-c** by treatment with Boc_2O in the presence of $Zn(OAc)_2$ in CH_2Cl_2 under reflux.[11]



Scheme 1. Synthesis of homoallylic *tert*-butyl carbonate **6**

Having accomplished efficient preparation of the desired homoallylic carbonates **6a-c**, their conversion to the required *syn*-bromocarbonate **5** was investigated. First, we reacted homoallylic carbonate **6a** with 1.5 equiv of bromine and 1.5 equiv of anhydrous K_2CO_3 as a base in MeCN at -20 °C for 1 h, which gave bromocarbonate **5a** in 27% yield as a single diastereomer (Table 1, entry 1). Varying the solvent indicated that CH_2Cl_2 was the most effective for this transformation (Table 1, entries 1–3). A study of the effect of temperature (Table 1, entries 3–6) indicated that the yield of **5a** increased when the reaction temperature was decreased from -20 to -40 °C, but there was slight decrease in yield when the temperature was further lowered to -80 °C. The optimized conditions, 1.5 equiv of bromine and 1.5 equiv of anhydrous K_2CO_3 in CH_2Cl_2 at -40 °C for 1 h, generated exclusively the desired bromocarbonate **5a** in an isolated yield of 55% (Table 1, entry 5). It is worth noting that the choice of protecting group on the oxygen atom of C_1 markedly affected the reactivity of the substrate in the bromine-induced intermolecular cyclization reaction. No desired product was detected when a benzyl protecting group was used, while the use of *p*-chloro benzyl as a protecting group afforded the bromocyclization product **5c** in a low yield of 18% albeit with clean conversion (Table 1, entries 7 and 8).

Table 1 Bromine-induced intermolecular cyclization of homoallylic *tert*-butyl carbonate **6**.[a]



Entry	X	Solvent	Temp(°C)	Yield(%)
1	Br	MeCN	-20	27
2	Br	PhMe	-20	26
3	Br	CH_2Cl_2	-20	33
4	Br	CH_2Cl_2	-40	55
5	Br	CH_2Cl_2	-60	52
6	Br	CH_2Cl_2	-80	48
7	H	CH_2Cl_2	-40	-
8	Cl	CH_2Cl_2	-40	18

[a]All reactions were carried out in the presence of Br_2 (1.5 equiv), K_2CO_3 (1.5 equiv) and **6a-c** (2.7 mmol).

[b]Isolated yields

A simple rationale is presented in the mechanism scheme given in Figure 3.[12] The highly diastereoselectivity of this

bromine-induced cyclization is proposed to proceed through transition state Ⅱ (favored chair conformation), leading to the *syn*-bromocarbonate **5a** as a sole product.

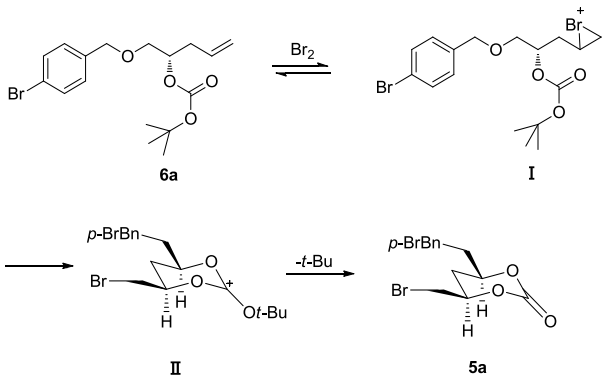


Figure 3. Proposed mechanism for the bromine-induced cyclization

Basic methanolysis of bromocarbonate **5a** efficiently provided *syn*-epoxy alcohol **13** in 84% yield (Scheme 2).[12e] Epoxide ring opening of **13** with NaCN in H_2O proceeded cleanly under mild conditions, and pure *syn*-diol nitrile **14** was isolated in 70% yield. Nitrile **14** was subjected to a Pinner reaction by treatment with a saturated solution of hydrogen chloride in MeOH at 0 °C followed by protection with 2,2-dimethoxypropane (DMP) through *p*-toluene sulfonic acid (PTSA) catalysis to provide exclusively *syn*-acetonide ester **15** (77% over two steps).

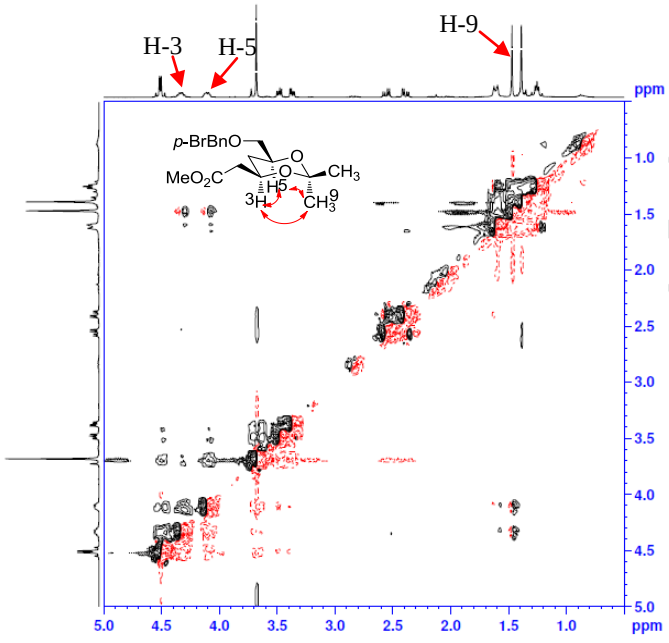
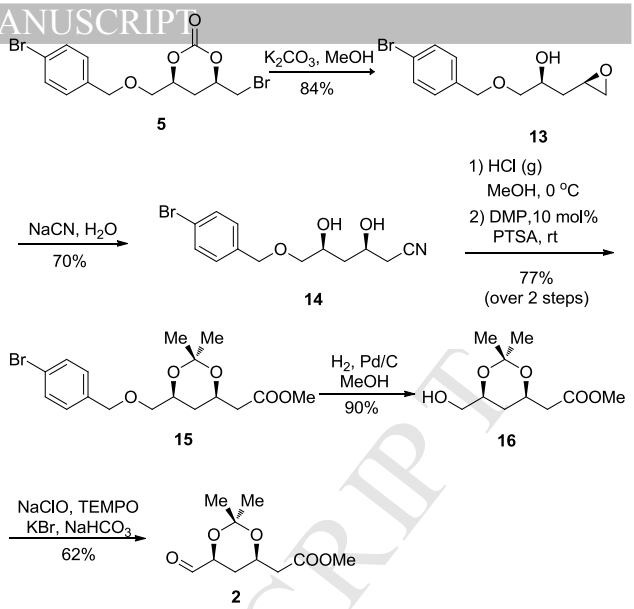


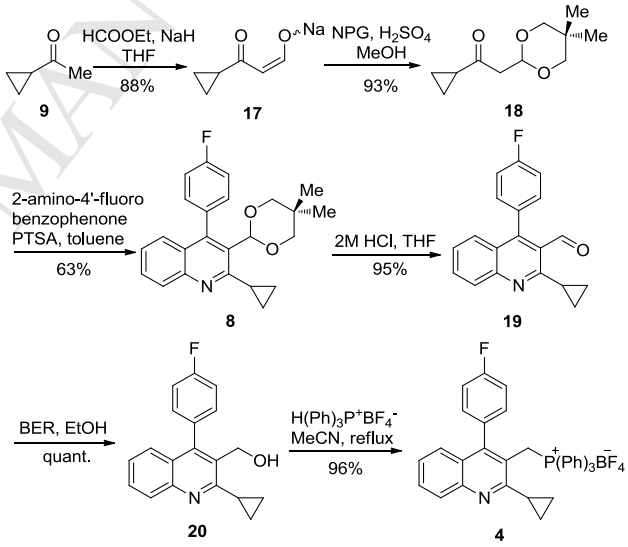
Figure 4. The NOE correlations of *syn*-acetonide **15**

The NOESY study of **15** revealed that strong NOE correlations between H-3/H-5, H-3/H-9 and H-5/H-9, which indicated H-3, H-5 and H-9 were on the same side of the molecule, and comfirmed the stereochemical assignment of **15**. (Figure 4).[6j]



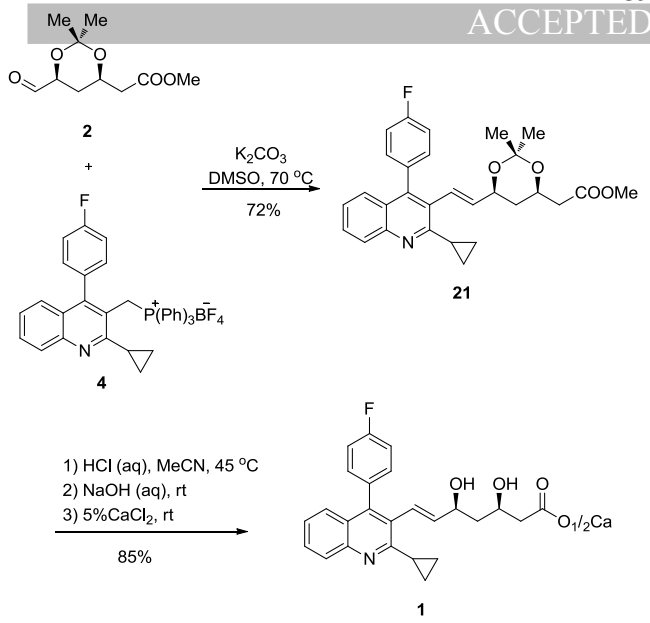
Scheme 2. Synthesis of C_6-formly side chain **2**

Removal of the 4-bromobenzyl group under hydrogenolysis conditions provided the corresponding alcohol **16** in 90% yield. Alcohol **16** was then converted into C_6-formyl side chain **2** in 68% yield under oxidizing conditions (NaClO, TEMPO, KBr, $NaHCO_3$).[13]



Scheme 3. Synthesis of triphenylphosphonium tetrafluoroborate **4**

The synthesis of new triphenylphosphonium tetrafluoroborate salt **4** began with the formation of the quinoline from cyclopropyl methyl ketone (**9**) according to an improved Nagashima protocol, as shown in Scheme 3.[14] Transformation of **9** into the derived sodium enolate **17** was achieved in 88% yield with ethyl formate in the presence of 60% NaH in THF. Salt **17** was treated immediately with neopentyl glycol (NPG) in MeOH using conc. H_2SO_4 as catalyst at room temperature to give acetal **18** in 93% yield. The Friedländer condensation of **18** and 2-amino-4'-fluoro benzophenone in the presence of PTSA in toluene afforded quinoline derivative **8** in 63% yield. Deprotection of the acetal group of **8** under acidic conditions gave quinoline aldehyde **19** in 95% yield, which was reduced with borohydride anion exchange resin (BER)[15] in EtOH to the quinoline alcohol **20** quantitatively. Alcohol **20** was converted to the corresponding triphenylphosphonium tetrafluoroborate salt **4** in 96% yield by treatment with hydrogen triphenylphosphonium tetrafluoroborate in boiling MeCN.[16,17]



Scheme 4. Synthesis of pitavastatin calcium (**1**)

With C_6-formyl side chain **2** and triphenylphosphonium tetrafluoroborates salt **4** in hand, our attention was next turned to their coupling *via* a Wittig-type olefination reaction to synthesize **1** as outlined in Scheme 4. As expected, stereoselective Wittig olefination of **2** and **4** proceeded smoothly under mild reaction conditions (K_2CO_3, DMSO, 70 °C) to furnish the (*E*)-olefin **21** as a single isomer in 72% yield. Removal of the ketal group from the resulting (*E*)-olefin followed by hydrolysis and calcium salt formation completed the synthesis of **1** with an overall yield of 85% over three steps.[5c-h]

3. Conclusion

In summary, we have demonstrated a new synthetic sequence that is robust and highly stereo-and regioselective to prepare a *syn*-1,3-diol substructure, which we applied herein to the efficient asymmetric synthesis of pitavastatin calcium (**1**). This synthetic procedure should be applicable to the synthesis of other HMG-CoA reductase inhibitors and natural products bearing similar *syn*-1,3-diol substructures.

4. Experimental Section

4.1. General

All reagents were obtained from commercial sources and used without further purification. ^{1}H (400MHz) and ^{13}C (100MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as internal standards, IR spectra were recorded on a JASCO FT/IR-4200 spectrometer, Optical rotations were measured by a JASCO P1020 digital polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Microspectrometer. HRMS were recorded on a Bruker micro TOF spectrometer.

*4.2. Genneral Procedure for the synthesis of benzy ester **11***

To a solution of (*R*)-3-bromo-1,2-propanediol (6.60 g, 60 mmol) in CH_2Cl_2 (75 mL) was added anhydrous K_2CO_3 (20.73 g, 150 mol). The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was vacuum filtered through Celite and concentrated in *vacuo* to give crude (*R*)-glycidol **10**, which was used without further purification.

Then, the solution of **10** in anhydrous DMF (10 mL) was slowly dropped into the stirred suspension of NaH (60% dispersion in mineral oil, (2.88 g, 72 mmol) in anhydrous DMF (30 mL) at 0 °C. The resultant white suspension was stirred until effervescence ceased, then benzyl bromide, *p*-chlorobenzyl chloride or *p*-bromobenzyl bromide (72 mmol) and TBAI (2.22 g, 6 mmol) were added sequentially. The reaction mixture was then allowed to warm to ambient temperature over 18 h, poured into water, and extracted with EtOAc (3 × 50 mL). The combined organic phase was then washed with water and brine, dried (anhydrous Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:20) to afford **11**

*4.2.1. (S)-2-(((4-bromobenzyl)oxy)methyl)oxirane (**11a**)*[12e]

Obtained (12.92 g, 89% over two steps) as a colorless oil. $[\alpha]_D^{25}$ +5.36 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 3.76 (dd, *J* = 2.8, 11.2 Hz, 1H), 3.39 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.16-3.20 (m, 1H), 2.79 (t, *J* = 4.4 Hz, 1H), 2.60 (dd, *J* = 2.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 131.5, 129.3, 121.6, 72.5, 70.9, 50.8, 44.1; IR (thin film, cm^{-1}) 2996, 2857, 1591, 1486, 1403, 1092, 836; MS (ESI): m/z 265 (M + Na^+).

*4.2.2. (S)-2-((benzyloxy)methyl)oxirane (**11b**)*[9b]

Obtained (8.89 g, 90% over two steps) as a colorless oil $[\alpha]_D^{20}$ -2.76 (*c* 0.8, $CHCl_3$); lit.[9b] $[\alpha]_D^{25}$ -3.0 (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 5H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 3.75 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.42 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.17-3.21 (m, 1H), 2.80 (t, *J* = 4.8 Hz, 1H), 2.61 (dd, *J* = 2.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.4, 127.7, 73.3, 70.7, 50.8, 44.2; MS (ESI): m/z 187 (M + Na^+).

*4.2.3. (S)-2-(((4-chlorobenzyl)oxy)methyl)oxir ane (**11c**)*[9c]

Obtained (10.45 g, 88% over two steps) as a colorless oil. $[\alpha]_D^{20}$ +1.66 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 3.78 (dd, *J* = 2.8, 11.2 Hz, 1H), 3.40 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.18-3.21 (m, 1H), 2.82 (t, *J* = 4.8 Hz, 1H), 2.62 (dd, *J* = 2.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 131.4, 129.2, 121.5, 72.4, 70.8, 50.7, 44.1; MS (ESI): m/z 221 (M + Na^+).

*4.3. Genneral Procedure for the synthesis of homoallylic alcohol **12***

To a solution of vinyl magnesium chloride (2.0 M in THF, 15 mL, 30 mmol) was added copper (I) iodide (190 mg, 1 mmol) and the mixture was cooled to -10 °C. A solution of 11 (20.66 mmol) in THF (17 mL) was then added dropwise over 1 h and the reaction mixture was allowed to stir at -10 °C for 10 h. The reaction was quenched with 2 M HCl and stirred for 30 min. After separation, the organic phase was washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:20) to afford **12**.

*4.3.1. (S)-1-((4-bromobenzyl)oxy)pent-4-en-2-ol (**12a**)*[12e]

Obtained (5.5 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +1.62 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.77-5.87 (m, 1H), 5.09-5.14 (m, 2H), 4.50 (s, 2H), 3.85-3.90 (m, 1H), 3.48 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.35 (dd, *J* = 7.2, 9.6 Hz, 1H), 2.33 (br s, 1H), 2.26 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.0, 131.5, 129.3, 121.6, 117.8, 73.9, 72.6, 69.7, 37.9; IR (thin film, cm^{-1}) 3469,

2927, 2863, 1643, 1488, 1099, 1068, 992; MS (ESI): m/z 293 (M + Na^+).

*4.3.2. (S)-1-(benzyloxy)pent-4-en-2-ol (**12b**)*[10]

Obtained (3.93 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ +3.2 (*c* 1.0, $CHCl_3$), lit.[10]: $[\alpha]_D^{20}$ +3.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28-7.38 (m, 5H), 5.78-5.88 (m, 1H), 5.08-5.14 (m, 2H), 4.56 (s, 2H), 3.86-3.92 (m, 1H), 3.50 (dd, *J* = 3.2, 9.6 Hz, 1H),3.36 (dd, *J* = 7.2, 9.2 Hz, 1H), 2.27 (br s, 1H), 2.27 (t, *J* = 6.8 Hz, 2H); MS (EI): m/z 192 (1), 91 (100).

*4.3.3. (S)-1-((4-chlorobenzyl)oxy)pent-4-en-2-ol (**12c**)*

Obtained (4.7 g, quant.) as a colorless oil. $[\alpha]_D^{25}$ +1.20 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.79-5.89 (m, 1H), 5.11-5.16 (m, 2H), 4.50 (s, 2H), 3.88-3.92 (m, 1H), 3.50 (dd, *J* = 3.6, 9.2 Hz, 1H), 3.37 (dd, *J* = 7.2, 9.6 Hz, 1H), 2.40 (br s, 1H), 2.28 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 134.1, 133.5, 129.0, 128.6, 117.8, 73.9, 72.5, 69.6, 37.9; HRMS (ESI-TOF) m/z calcd for C12H16ClO2 (M + H^+) 227.0839, found 227.0833.

*4.4. Genneral Procedure for the synthesis of homoallylictert-butyl carbonate **6***

To the solution of **12** (18.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added anhydrous $Zn(OAc)_2$ (0.35 g, 1.9 mmol) and di-*tert*-butyl dicarbonate (4.44 g, 20.4 mmol) sequentially at room temperature, and the resultant mixure was refluxed for 12 h. The mixture was vacuum filtered through Celite and the filtrate was washed with water and brine, dried (anhydrous Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:100) to afford **6**.

*4.4.1. (S)-1-((4-bromobenzyl)oxy)pent-4-en-2-yl tert-butyl carbonate (**6a**)*[12e]

Obtained (6.7 g, 98%) as a colorless oil. $[\alpha]_D^{25}$ +3.02 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.72-5.82 (m, 1 H), 5.07-5.14 (m, 2H), 4.86-4.91 (m, 1H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 5.2 Hz, 2H), 2.35-2.46 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 137.1, 132.9, 131.4, 129.2, 121.4, 118.2, 82.1, 74.7, 72.4, 70.8, 35.4, 27.8; IR (thin film, cm^{-1}) 2980, 2935, 2862, 1743, 1487, 1368, 1276, 1161, 1095, 1001, 918, 847, 783; MS (ESI): m/z 393 (M + Na^+).

*4.4.2. (S)-1-(benzyloxy)pent-4-en-2-yl tert-butyl carbonate (**6b**)*[12f]

Obtained (5.1 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ +3.45 (*c* 1.0, $CHCl_3$), lit.[12f] $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 5H), 5.72-5.82 (m, 1H), 5.06-5.14 (m, 2H), 4.86-4.92 (m, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.55 (d, *J* = 5.2 Hz, 2H), 2.35-2.46 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 138.0, 133.0, 128.3, 127.6, 118.1, 82.0, 74.8, 73.1, 70.6, 35.5, 27.8; MS (ESI): m/z 315 (M + Na^+).

*4.4.3. (S)-tert-butyl (1-((4-chlorobenzyl) oxy) pent -4-en-2-yl) carbonate (**6c**)*

Obtained (5.8 g, 97%) as a colorless oil. $[\alpha]_D^{25}$ +5.14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.71-5.82 (m, 1H), 5.06-5.13 (m, 2H), 4.85-4.91 (m, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 3.54 (d, *J* = 5.2 Hz, 2H), 2.38-2.43 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 136.6, 133.3, 132.9, 128.8, 128.5, 118.2, 82.0, 74.7, 72.3, 70.8, 35.4, 27.7; HRMS (ESI-TOF) m/z calcd for C17H24ClO4 (M + H^+) 327.1363, found 327.1358.

*4.5. Genneral Procedure for the synthesis of bromo–carbonate **5***

To a solution of **6** (2.7 mmol) in CH_2Cl_2 (25 mL) at -40 °C was added a solution of bromine (0.65 g, 4.05 mmol) in CH_2Cl_2 (4.05 mL) and K_2CO_3 (0.56 g, 4.05 mmol) sequentially. The reaction was maintained at -40 °C for 1 h before warmed up to ambient temperature. The reaction was quenched with saturated aqueous Na_2SO_3/$NaHCO_3$ (1:1, 10 mL) and EtOAc (50 mL). After separation, the organic phase was washed with saturated aqueous Na_2SO_3/$NaHCO_3$ and brine, dried (anhydrous Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:5) to afford **5**.

*4.5.1. (4S,6R)-4-(((4-bromobenzyl)oxy)methyl)-6-(bromomethyl)-1,3-dioxan-2-one (**5a**)*

Obtained (0.58 g, 55%) as a colorless oil. $[\alpha]_D^{25}$ +10.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.59-4.67 (m, 2H), 4.52 (s, 2H), 3.65 (m, 2H), 3.54-3.58 (m, 1H), 3.44 (dd, *J* = 6.8, 10.8 Hz, 1H), 2.30 (m, 1H), 1.95 (dt, *J* = 12.0, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 136.3, 131.6, 129.3, 121.9, 76.5, 72.9, 70.6, 32.2, 28.3; IR (thin film, cm^{-1}) 2930, 1747, 1485, 1396, 1246, 1203, 1139, 1111, 1019, 806, 760, 670; HRMS (ESI-TOF) m/z calcd for C13H18Br2NO4 (M + NH_4^+) 409.9603, found 409.9593.

*4.5.2. (4R,6S)-4-(bromomethyl)-6-(((4-chlorobenzyl)oxy)methyl)-1,3-dioxan-2-one (**5c**)*

Obtained (0.17 g, 18%) as a colorless oil). $[\alpha]_D^{15}$ +8.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.59-4.68 (m, 2H), 4.55 (d, *J* = 2.0 Hz, 2H), 3.66 (d, *J* = 4.0 Hz, 2H), 3.56 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.43 (dd, *J* = 7.2, 10.8 Hz, 1H), 2.34 (dt, *J* = 2.8, 14.4 Hz, 1H), 1.99 (dt, *J* = 12.0, 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 135.7, 133.8, 129.1, 128.7, 76.6, 73.0, 70.6, 32.1, 28.4; HRMS (ESI-TOF) m/z calcd for C13H15BrClO4 (M + H^+) 348.9842, found 348.9838.

*4.6. (S)-1-((4-bromobenzyl)oxy)-3-((R)-oxiran-2-yl)propan-2-ol (**13**)*[12e]

To a solution of **5** (0.5 g, 1.28 mmol) in anhydrous MeOH (5 mL) was added K_2CO_3 (0.44 g, 3.2 mmol). The reaction mixture was stirred at ambient temperature for 1 h before diluted with EtOAc (50 mL) and water (10 mL). After separation, the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with water and brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:5) to afford **13** (0.31 g, 84%) as a colorless oil. $[\alpha]_D^{25}$ +4.68 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.50 (s, 2H), 4.03 (br s, 1H), 3.48 (dd, *J* = 3.6, 9.6 1H), 3.43 (dd, *J* = 7.2, 9.2 Hz, 1H), 3.08-3.10 (m, 1H), 2.77 (t, *J* = 4.8 Hz, 1H), 2.63 (s, 1H), 2.49-2.51 (m, 1H), 1.81 (dt, *J* = 4.4, 14.8 Hz, 1H).1.59-1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 131.5, 129.3, 121.6, 74.0, 72.6, 68.6, 49.5, 46.6, 35.9.; IR (thin film, cm^{-1}) 3426, 2917, 1651, 1414, 1097, 802, 714, 623; MS (ESI): m/z 309 (M + Na^+).

*4.7. (3S,5S)-6-((4-bromobenzyl)oxy)-3,5-dihydroxyhexanenitrile(**14**)*

To a stirred solution of **13** (2.86 g, 10 mmol) in water (5 mL) at 0 °C was added dropwise a solution of sodium cyanide (0.734 g, 15 mmol) in water (3 mL). The reaction mixture was stirred at room temperature for 48 h and the aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic phase was washed with water and brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:2) to afford **14** (2.19 g, 70%) as a pale yellow oil. $[\alpha]_D^{25}$ +4.63 (*c* 0.9, $CHCl_3$); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.50 (s, 2H), 4.16-4.22 (m, 1H), 4.07-4.14 (m, 2H), 3.46 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.34 (dd, *J* = 7.6, 9.2 Hz, 1H), 2.98 (br s, 1H), 2.53 (d, *J* = 5.6 Hz, 2H), 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 131.7, 129.4, 121.9, 117.4, 74.0, 72.7, 70.6, 67.5, 37.9, 25.9; IR (thin film, cm^{-1}) 3443, 2920, 2862, 2356, 1411, 1072, 875, 641; HRMS (ESI-TOF) m/z calcd for C13H16BrNO3Na (M + Na^+) 336.0211, found 336.0214.

*4.8. Methyl2-((4R,6S)-6-(((4-bromobenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**15**)*

(a)A solution of **14** (3.13 g, 10 mmol) in anhydrous methanol (20 mL) was cooled to 0 °C and saturated with gaseous HCl. The reaction mixture was stirred at 0 °C for 8 h before being quenched by saturated $NaHCO_3$ solution. The solvent was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil.

(b) To a solution of the resulting yellow oil in acetone (25 mL) was added a solution of 2,2-dimethoxypropane (5.20 g, 50 mmol) in acetone (50 mL) and PTSA (190 mg, 1 mmol) sequentially at room temperature. The reaction mixture was stirred at room temperature for 24 h before being quenched by triethylamine (150 mg, 1.5 mmol) and removed solvent under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:5) to afford **15** (2.97 g, 77% over two steps) as a pale yellow oil. $[\alpha]_D^{25}$ +1.57 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.30-4.36 (m, 1H), 4.08-4.14 (m, 1H), 3.68 (s, 3H), 3.46 (dd, *J* = 5.6, 10.0 Hz, 1H), 3.35 (dd, *J* = 4.8, 10.0 Hz, 1H), 2.53 (dd, *J* = 7.2, 15.2 Hz, 1H), 2.37 (dd, *J* = 6.0, 15.2 Hz, 1H), 1.60-1.63 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.24-1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.2, 131.4, 129.3, 121.4, 98.9, 73.5, 72.6, 68.3, 65.6, 51.6, 41.2, 33.1, 29.9, 19.6; IR (thin film, cm^{-1}) 2927, 1736, 1381, 1267, 1112, 1010, 806; HRMS (ESI-TOF) m/z calcd for C17H23BrNO5Na (M + Na^+) 409.0627, found 409.0621.

*4.9. Methyl2-((4R,6S)-6-(((4-bromobenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**16**)*[6d]

A solution of **15** (1.93 g, 5 mmol) containing 20% Pd/C (0.386 g) in MeOH (10 mL) was stirred under hydrogen for 24 h. The reaction mixture was filtered through Celite and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:5) to afford **16** (0.98 g, 90%) as a pale yellow oil. $[\alpha]_D^{25}$ +11.01 (*c* 0.9, $CHCl_3$), lit.[6d] $[\alpha]_D^{25}$ +9.7 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31-4.38 (m, 1H), 3.99-4.05 (m, 1H), 3.69 (s, 3H), 3.59 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.48 (dd, *J* = 6.0, 11.2 Hz), 2.54 (dd, *J* = 7.2, 15.6 Hz, 1H), 2.37 (dd, *J* = 6.0, 15.6 Hz, 1H), 1.49 (dt, *J* = 2.4, 12.4 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.32 (d, *J* = 12.4 Hz, 1H); MS (ESI): m/z 241 (M + Na^+).

*4.10. Methyl 2-((4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**2**)*[6j]

To a solution of **16** (0.1 g, 0.46 mmol) in CH_2Cl_2 (10 mL) was added TEMPO (0.72 mg, 0.0046mmol), KBr (5.5 mg, 0.046mmol) and $NaHCO_3$ (0.4 g, 4.6 mmol) sequentially at 0 °C. A 0.5 M aqueous solution of NaClO (4.6 mL) was then added dropwise and the reaction mixture was allowed to stir at 0 °C for 15 h. The reaction was quenched with saturated aqueous Na_2SO_3 and CH_2Cl_2 (50 mL). After separation, the organic phase was washed with saturated aqueous Na_2SO_3, brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:5) to afford **2** (0.06 g, 62%) as a yellow oil. $[\alpha]_D^{25}$ -15.24 (*c* 1.0, $CHCl_3$), lit.[6j] $[\alpha]_D^{25}$ -14.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.31-4.42 (m, 2H), 3.70 (s, 3H), 2.56 (dd, *J* = 6.8, 15.6 Hz, 1H), 2.41 (dd, *J* = 6.0, 15.6 Hz, 1H), 1.83 (dt, *J* = 2.4, 13.2 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.32-1.37 (m, 1H); MS (ESI): m/z 201 (M – CH_3)$^+$.

*4.11. Sodium (Z)-3-cyclopropyl-3-oxoprop-1-en-1-olate(**17**)*[18]

A solution of cyclopropylmethyl ketone (5 g, 59.5 mmol) in anhydrous THF (10 mL) was dropped into the stirred suspension of NaH (60% dispersion in mineral oil, 2.38 g, 59.5 mmol) in anhydrous THF (50 mL) at 0 °C. The resultant white suspension was stirred for 1 h, then ethyl formate (4.85 g, 65.5 mmol) were added at 0 °C and the reaction mixture was warmed to ambient temperature and stirred overnight. The mixture was evacuated and the contents were filtered through a paper filter with a Büchner funnel. The crude yellow solid was rinsed with MTBE (10 mL) followed by hexane (20 mL). The solid was allowed to dry overnight under vacuum to afford **17** (7.0 g, 88%) as a yellow solid. ^{1}H NMR (400 MHz, D_2O) δ 9.01 (br s, 1H), 1.81-2.37 (m, 1H), 0.80-0.89 (m, 4H).

*4.12. 1-Cyclopropyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)ethanone (**18**)*

A solution of **17** (5 g, 37.3mmol) in MeOH (25 mL) was dropped into the stirred suspension of 2,2-dimethyl-1,3-propanediol (7.77 g, 74.6 mmol) and H_2SO_4 (4 g, 41 mmol) at room temperature under N_2 atmosphere. After stirring for 1 h, the reaction mixture was heated to 60 °C and then held for 8 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and EtOAc (100 mL). After separation, the organic phase was washed with saturated aqueous $NaHCO_3$ and water (3 × 50 mL), brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo* to afford **18** (6.87 g, 93%) as a yellow oil. The material was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (t, *J* = 4.8 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 2H), 3.45 (d, *J* = 10.8 Hz, 2H), 2.88 (d, *J* = 4.8 Hz, 2H), 1.96-2.02 (m, 1H), 1.19 (s, 3H), 1.05-1.07 (m, 2H), 0.87-0.90 (m, 2H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 98.8, 48.4, 30.0, 23.0, 21.8, 21.3, 11.0; HRMS (ESI-TOF) m/z calcd for C13H17BrNO3 (M + H^+) 199.1334, found 199.1324.

*4.13. 2-Cyclopropyl-3-(5,5-dimethyl-1,3-dioxan-2-yl)-4-(4-fluorophenyl) quinoline (**8**)*

To a solution of **18** (2 g, 10.1 mmol) in toluene (10 mL) was added 2-amino-4'-fluorobenzophenone (1.97 g, 9.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.57 g, 3 mmol) sequentially. The reaction was stirred at 120 °C for 24 h. During the period, the water by produced with the progress of the reaction was azeotropically removed using a Dean-Stark trap. The reaction was quenched with saturated aqueous $NaHCO_3$ and EtOAc (50 mL). After separation, the organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:100) to afford **8** (2.4 g, 63%) as a white solid. m. p 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.58-7.62 (m, 1H), 7.28-7.31 (m, 3H), 7.20-7.24 (m, 3H), 5.33 (s, 1H), 3.72 (d, *J* = 11.6 Hz, 2H), 3.35-3.40 (m, 1H), 3.31 (d, *J* = 10.8 Hz, 2H), 1.39-1.43 (m, 2H), 1.27 (s, 3H), 1.05-1.09 (m, 2H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 147.5, 146.3, 132.5 (d, *J* = 3.6 Hz), 131.5, 131.4, 129.4, 128.8, 126.7, 126.4, 125.6, 125.2, 115.4, 115.2, 102.6, 78.5, 30.3, 24.0, 22.1, 15.4, 11.1; HRMS

(ESI-TOF) m/z calcd for C24H25FNO2 ($M + H^+$) 378.1869, found 378.1862.

*4.14. 2-Cyclopropyl-4-(4-fluorophenyl)quinoline-3-carbaldehyde (**19**)*[6d]

To a solution of **8** (1 g, 2.65 mmol) in THF (10 mL) was added 2 M HCl (50 mL). The reaction mixture was stirred at 60 ^oC for 10 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and EtOAc (50 mL). After separation, the organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:100) to afford **19** (0.73 g, 95%) as a white solid. m. p 156-157 ^oC, lit.[6d] m. p 144-144.3 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.23-7.76 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.33-7.37 (m, 2H), 7.28 (s, 1H), 7.24 (s, 1H), 3.19-3.25 (m, 1H), 1.37-1.41 (m, 2H), 1.09-1.12 (m, 2H); MS (ESI): m/z 292 ($M + H^+$).

*4.15. (2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)methanol (**20**)*[5e]

To a solution of **19** (0.5 g, 1.7 mmol) in EtOH (10 mL) was added borohydride anion exchange resin (BER). The reaction mixture was stirred at room temperature for 3 h. The mixture was filtered through Celite and concentrated *in vacuo* to afford **20** (0.5 g, quant.) as a white solid. The material was carried on without further purification. mp 129-130 ^oC, lit.[5e] m. p 133.3-134.7 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.60-7.64 (m, 1H), 7.29-7.38 (m, 4H), 7.21 (t, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 2.56-2.62 (m, 1H), 1.63 (br s, 1H), 1.36-1.40 (m, 2H), 1.08-1.12 (m, 2H); MS (ESI): m/z 294 ($M + H^+$).

*4.16. Triphenylphosphoniumtetrafluoroborate salt (**4**)*

To a solution of **20** (0.5 g, 1.7 mmol) in MeCN (10 mL) was added hydrogen triphenylphosphonium tetrafluoroborate (0.6 g, 1.7 mmol). The reaction mixture was refluxed for 15 h. The mixture was concentrated in *vacuo*. The residue was recrystallized from CH_2Cl_2/MTBE to yield **4** (0.81 g, 76%) as a yellow solid. m. p: 248-250 ^oC; ^1H NMR(400 MHz, DMSO) δ 7.85-7.88 (m, 5H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.60 (m, 7H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.19-7.24 (m, 9H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 2H), 2.00-2.04 (m, 1H), 0.85 (m, 2H), 0.50 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 163.3, 160.8, 160.8, 148.0, 147.9, 146.5(d, *J* = 2.7 Hz), 135.1(d, *J* = 2.7 Hz), 133.8, 133.7, 131.4, 131.3, 131.0, 130.2, 130.1, 128.5, 128.5, 126.4, 125.8, 125.3, 125.3, 119.7, 119.6, 117.6, 116.7, 116.2, 116.0, 54.9, 25.7, 15.8, 11.3. ^{19}F NMR (376 MHz, DMSO) δ -112.85--112.78 (m), -148.18, -148.23; ^{31}P NMR (162 MHz, DMSO) 20.36; HRMS (ESI-TOF) m/z calcd for $C37H30FNP^+$ (M^+) 538.2100, found 538.2067.

*4.17. Methyl2-((4R,6S)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**21**)*[6c]

To a solution of **2** (0.2 g, 0.93 mmol) in DMSO (5 mL) was added **4** (0.53 g, 0.85 mmol) and K_2CO_3 (0.23 g, 1.7 mmol) sequentially. The reaction mixture was stirred at 70 ^oC for 3 h. The mixture was diluted with toluene (50 mL) and water (10 mL). After separation, the aqueous phase was extracted with toluene (2 × 50 mL). The combined organic phase was washed with water and brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:20) to afford **21** (0.29g, 72%) as a white solid. m. p: 128-130^oC; $[\alpha]_D^{25}$ +18.09 (*c* 0.5, $CHCl_3$); lit.[6c] m. p 133 ^oC; $[\alpha]_D^{25}$ +19.2 (*c* 0.96, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.57 (m, 1H), 7.28-7.36 (m, 2H), 7.12-7.23 (m, 4H), 6.53 (d, *J* = 16.4 Hz, 1H), 5.54 (dd, *J* = 6.0, 16.4 Hz, 1H), 4.26-4.38 (m, 2H), 3.71 (s, 3H), 2.51 (dd, *J* = 6.8, 15.6 Hz, 1H), 2.40-2.45 (m, 1H), 2.32 (dd, *J* = 6.4, 15.6 Hz, 1H), 1.46 (s, 3H), 1.35-1.38 (m, 4H), 1.25 (s, 2H), 1.03 (dd, *J* = 3.2, 8.4 Hz, 2H); MS (ESI): m/z 476 ($M + H^+$).

*4.18. Pitavastatin Calcium (**1**)*[5j]

To a solution of **21** (0.24 g, 0.5 mmol) in acetonitrile (5 mL) at 40 ^oC was added 4 M HCl (0.15 mL, 0.6 mmol). The reaction mixture was stirred for 2 h and cooled to 0 ^oC, followed by addition of 4 M NaOH until PH = 12.0. Then the mixture was stirred at 0 ^oC for 30 min before addition of 2 M HCl until PH = 9. The acetonitrile was evaporated under reduced pressure and the residue was dissolved in H_2O (2 mL). To the clear solution was added a solution of 5% $CaCl_2$. The mixture was stirred at 0 °C for 1 h before the resulting white slurry was filtrated, washed, and dried in a vacuum to afford **1** (0.18 g, 85%) as a white powder. m. p 205-210 ^oC (decomposition); $[\alpha]_D^{25}$ +23.0 (*c* 0.7, $CH_3CN:H_2O$ = 1:1), lit.[5j] m. p 225-235 ^oC (decomposition); $[\alpha]_D^{20}$ +23.2 (*c* 1.0, $CH_3CN:H_2O$ = 1:1); ^1H NMR (400 MHz, DMSO) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.23-7.38 (m, 6H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.55 (dd, *J* = 5.2, 16.0 Hz, 1H), 4.91 (br s, 1H), 4.10 (q, *J* = 5.6 Hz, 1H), 3.60-3.63 (m, 1H), 2.52 (m, 1H), 2.04 (dd, *J* = 3.6, 15.6 Hz, 1H), 1.88 (dd, *J* = 8.0, 15.2 Hz, 1H), 1.36-1.44 (m, 1H), 1.15-1.23 (m, 2H), 1.06-1.12 (m, 1H), 1.00-1.03 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 177.7, 160.9, 160.6, 147.2(d, *J* = 9.0 Hz,), 146.1, 143.9, 142.3, 133.2, 132.4, 132.3, 132.1, 132.0, 129.8, 129.2, 128.5, 125.9, 125.8, 125.0, 123.5, 115.6 (d, *J* = 4.5 Hz), 115.4 (d, *J* = 3.8 Hz), 79.3, 69.0, 67.6, 65.7, 44.6, 43.9, 15.6, 14.6, 14.4, 10.9 (d, *J* = 8.9 Hz).

References and notes

1. (a) http://www.who.int/cardiovascular_diseases/en/ (b) Gelsinger, C.; Steinhagen-Thiessen, E.; Kassner, U. *Drugs* **2012,** *72*, 1445. (c) Tang, Y. T.; Chan, S. W. *Phytother. Res.* **2014,** *28*, 1581. (d) Sinthupoom, N.; Prachayasittikul, V.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. *Eur Food Res Technol*. **2015,** *240*, 1.
2. (a) Han, K. H.; Rha, S. W.; Kang, H. J.; Bae, J. W.; Choi, B. J.; Choi, S. Y.; Gwon, H. C.; Bae, J. H.; Hong, B. K.; Choi, D. H.; Han, K. R. *J. Clin. Lipidol*. **2012,** *6*, 340. (b) Sniderman, A. D.; Tsimikas, S.; Fazio, S. *J. Am. Coll. Cardiol*. **2014,** *63*, 735.
3. (a) Tani, S.; Nagao, K.; Hirayama, A. *Am. J. Cardiovasc. Drugs* **2012,** *12*, 349. (b) Besseling, J.; Capelleveen, J.; Kastelein, J.; Hovingh, G. K. *Drugs* **2013,** *73*, 293. (c) Foody, J. M.; Toth, P. P.; Tershakovec, A. M.; Musliner, T.; Tomassini, J. E.; Lowe, R. S.; Neff, D. R.; Davis, H. R. *Clin. Lipidol*. **2014,** *9*, 441.
4. (a) Mukhtar, R.; Reid, J.; Reckless, J. *J. Clin. Pract*. **2005,** *59*, 239. (b) Corsini, A.; Ceska, R. *Curr. Med. Res. Opin.***2011,** *27*, 1551. (c) Duggan, S. T. *Drugs* **2012,** *72*, 565.
5. Selected reviews and publications: (a) Časar, Z. *Curr. Org. Chem.***2010,** *14*, 816. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114*, 2432. (c) Chen, G.; Kapa, P. K.; Loeser, E. M.; Beutler, U. WO 03064382, **2003**. (d) Matsumoto, H.; Shimizu, T. EP 1391455, **2004**. (e) Acemoglu, M.; Brodbeck, A.; Garcia, A.; Grimler, D.; Hassel, M.; Riss, B.; Schreiber, R. *Helv. Chim. Acta* **2007,** *90*, 1069. (f) Fabris, J.; Časar, Z.; Smilović, I, G. *Synthesis* **2012,** *44*, 1700. (g) Kim, H. S.; Kim, W. J.; Kim, H. C.; Sim, J. Y.; Cho, S. M.; Byun, E. Y.; Jeon, J. Y.; Lee, Y. Y. WO 2010077062, **2010**. (h) Lange, D. B. WO 2014154856, **2014**.
6. (a) Miyachi, N.; Yanagawa, Y.; Iwasaki, H.; Ohara, Y.; Hiyawa, T. *Tetrahedron Lett*. **1993,** *51*, 8267. (b) Gijsen, H. J. M.; Wong, C. H. *J. Am. Chem. Soc*. **1994,** *116*, 8422. (c) Hiyama, T.; Minami, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1995,** *68*, 364. (d) Solladie, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995,** *60*, 7774. (e) Suzuki, M.; Yanagawa, Y.; Iwasaki, H.; Kanda, H.; Yanagihara, K.; Matsumoto, H.; Ohara, Y.; Yazaki, Y.; Sakoda, R. *Bioorg. Med. Lett*. **1999,** *9*, 2977. (f) Rádl, S.; Stach, J.;

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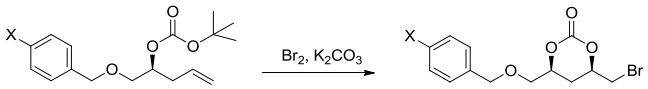
7. (a) Shin, H. L.; Choi, B. S.; Lee, K. K.; Choi, H.; Chang, J. H.; Lee, K. W.; Nam, D. H.; Kim, N. S. *Synthesis* **2004,** *16*, 2629. (b) Choi, H.; Shin, H. M. *Synlett* **2008,** 1523. (c) Sun, L.; Zhang, F. Q.; Du, T. J.; Fang, L. P.; Meng, F. M.; Liu, L. CN 102180862, **2001**; *Chem. Abstr*. **2011,** *155*, 457681.
8. (a) Srinivasulu, G.; Srinivas, K.; Rajeshwar, R. S.; Jaya, S. K. US 20060004200, **2006**. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998,** *63*, 6776.
9. (a) Plante, O. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000,** *122*, 7148. (b) Meilert, K.; Brimble, M. A. *Org. Biomol. Chem*. **2006,** *4*, 2184. (c) Fu, H.; Newcomb, M.; Wong, C. H. *J. Am. Chem. Soc.* **1991,** *113*, 5878.
10. Alam, M.; Wise, C.; Baxter, C. A.; Cleator, E.; Walkinshaw, A. *Org. Process Res. Dev*. **2012,** *16*, 435.
11. Bartoli, G.; Bosco, M.; Carlonr, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Palazzi, P.; Sambri, L. *Synlett* **2006,** 2104.
12. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem*. **1982,** *47*, 4013. (b) Duan, J. J.; Smith, A. B., III. *J. Org. Chem.* **1993,** *58*, 3703. For recent examples: (c) Smith, A. B., III.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Oiu, Y.; Salvatore, B. A; Spoors, P. G.; Duan, J. J. *J. Am. Chem. Soc*. **1999,** *121*, 10468. (d) Smith, A. B., III.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett*. **2002,** *4*, 783. (e) Smith, A. B., III.; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Boldi, A. M.; Murase, N.; Moser, W. H.; Brook, C. S.; Bennett, C. S.; Nakayama, K.; Sobukawa, M.; Lee, R. E. *Tetrahedron*. **2009,** *65*, 6470. (f) Nesbitt, C. L.; McErlean, C. *Org. Biomol. Chem.* **2011,** *9*, 2198. (g) Lee, K.; Kim, H.; Hong, J. *Org. Lett*. **2011,** *13*, 2722. (h) Reddy, D. S.; Mohapatra, D. K. *Eur. J. Org. Chem*. **2013,** *6*, 1051. (i) Brun, E. Bellosta, V.; Cossy, J. *Chem. Commun*. **2014,** *50*, 6718.
13. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987,** *52*, 2559.
14. (a) Nagashima, K.; Fukumoto, T.; Hayashibara, T.; Torihara, M. WO 2004041787, **2004**. (b) Nagashima, K.; Fukumoto, T.; Hayashibara, T.; Torihara, M. US 2006036096, **2006**.
15. Hu, M. G.; Chen, J.; Chen, F, E.; Chen, J. W. *Zhongguo Yiyao Gongye Zazhi*. **1991,** *22*, 461; *Chem. Abstr*. **1992,** *116*, 234730. (b) Parthasaradhi Reddy. B.; Parthasaradhi Reddy. K.; Muralidhara Reddy, D.; Malla Reddy. S.; Vamsi, K. B. WO 2012063254, **2012**.
16. Clark, D. A.; Fuchs, P. L. *Synthesis* **1977,** 628.
17. (a) Lieberknecbt, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1998,** 3159. (b) Shi, L.; Horn, M.; Kobayashi, S.; Mayr, H. *Chem. Eur. J*. **2009,** *15*, 8533. (c) Chen, F. E.; Xiong, F. J.; Huang, X. Y.; Li, J.; Chen, W. X.; He, Q. Q. CN 103570762, **2014**; *Chem. Abstr*. **2014,** *160*, 341276.
18. Desrosiers, J. N.; Kelly, C. B.; Fandrick, D. R.; Nummy, L.; Campbell,S. J.; Wei, X.; Sarvestani, M.; Lee, H.; Sienkiewicz, A.; Sanyal, S.; Zeng, X. Grinberg, N.; Ma, S.; Song, J. J.; Senanayake, C. H. *Org. Lett*. **2014,** *16*, 1724.

Table(s)

Table 1 Bromine-induced intermolecular cyclization of homo allylic *tert*-butyl carbonate **6**.[a]



6a: X=Br
6b: X=H
6c: X=Cl

5a: X=Br
5b: X=H
5c: X=Cl

Entry	X	Solvent	Temp(^{o}C)	Yield(%)
1	Br	MeCN	-20	27
2	Br	PhMe	-20	26
3	Br	CH_2Cl_2	-20	33
4	Br	CH_2Cl_2	-40	55
5	Br	CH_2Cl_2	-60	52
6	Br	CH_2Cl_2	-80	48
7	H	CH_2Cl_2	-40	-
8	Cl	CH_2Cl_2	-40	18

[a] All reactions were carried out in the presence of Br_2 (1.5 equiv), K_2CO_3 (1.5 equiv) and **6a-c** (2.7 mmol).

[b] Isolated yields

Figure(s)

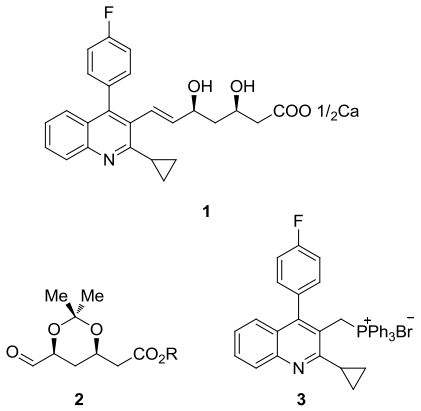


Figure 1. Structures of pitavastatin calcium (**1**), chiral C_6-formyl side chain **2** and triphenylphosphonium bromide **3**

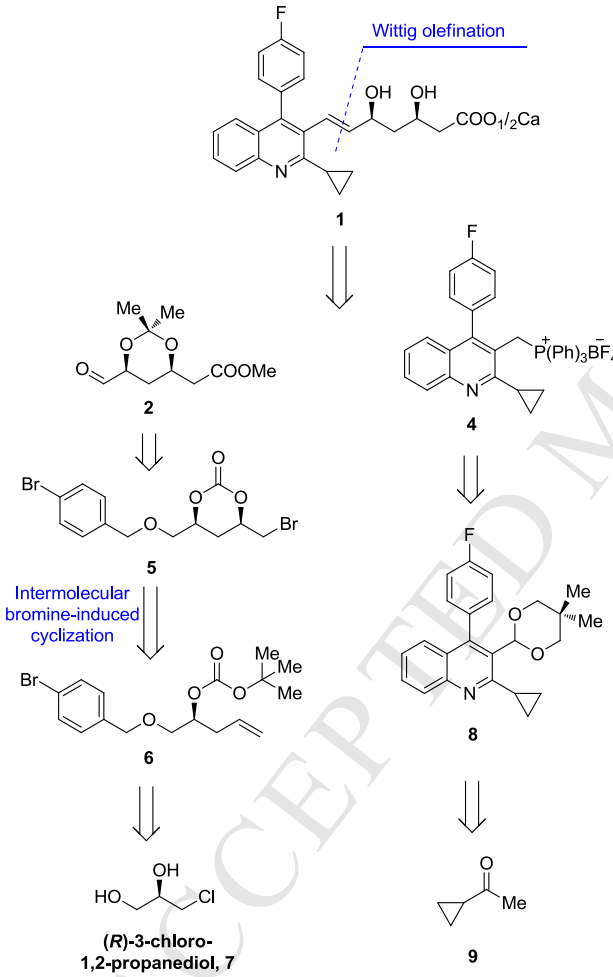


Figure 2. Retrosynthetic analysis of pitavastatin calcium (**1**)

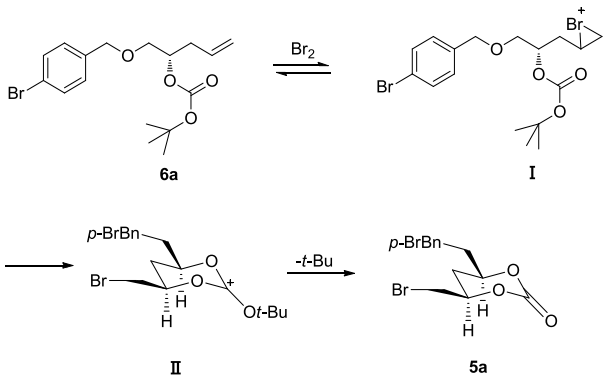


Figure 3. Proposed mechanism for the bromine-induced cyclization

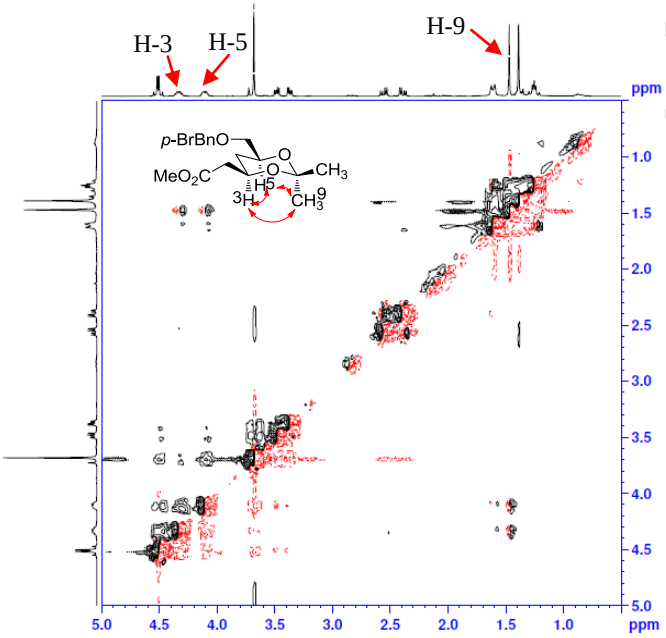


Figure 4. The NOE correlations of *syn*-acetonide **15**

SUPPORTING INFORMATION

Substrate Stereocontrol in Bromine-Induced Intermolecular Cyclization: Asymmetric Synthesis of Pitavastatin Calcium

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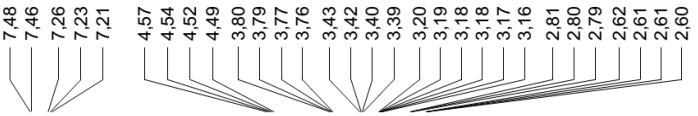
[b] *Institutes of Biomedical Science, Fudan University, 220 Handan Road, Shanghai, 200433, People's Republic of China*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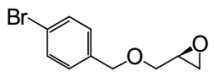
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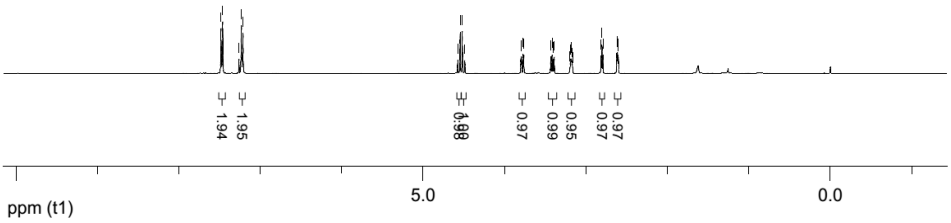
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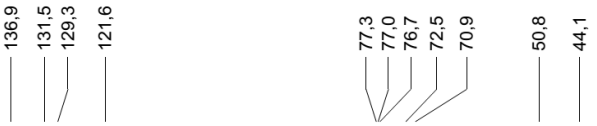
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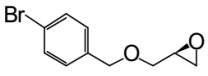
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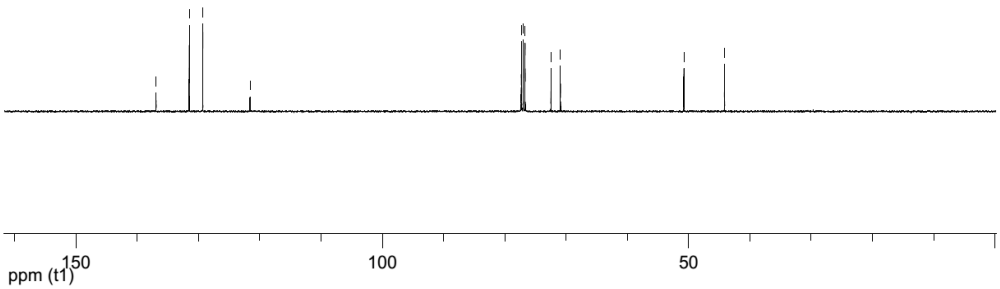
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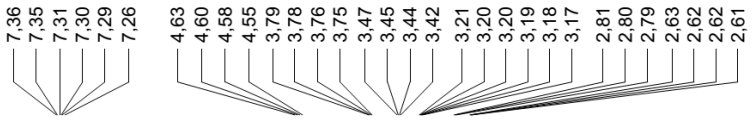
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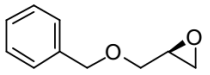

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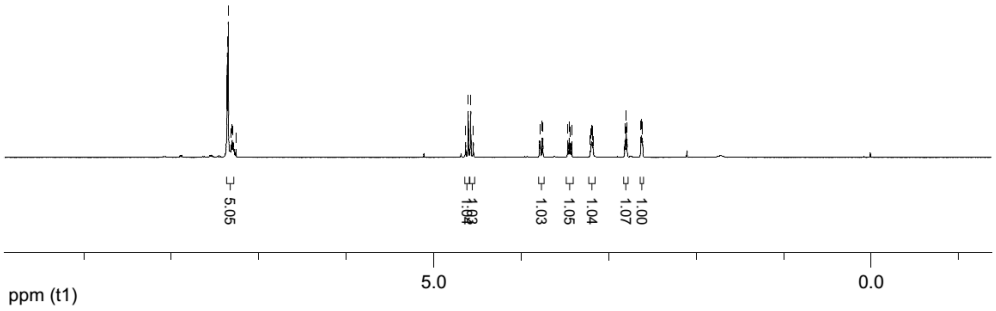
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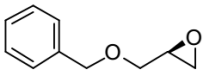

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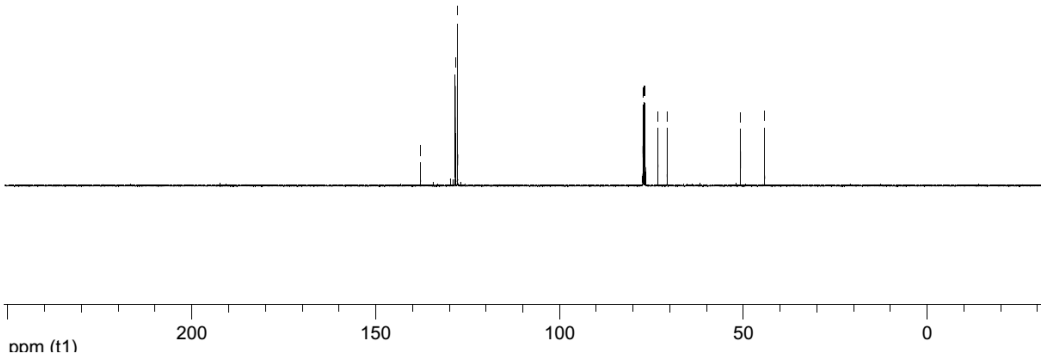
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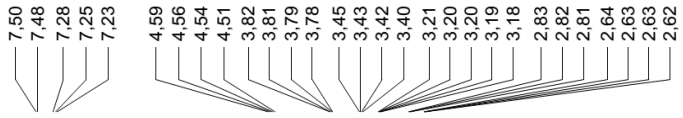
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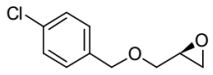
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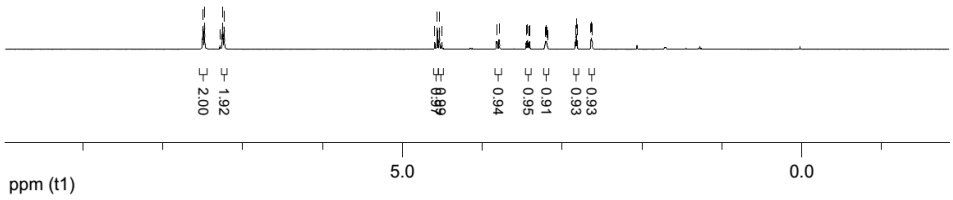
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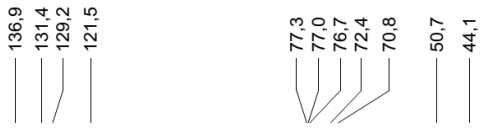
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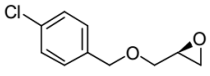
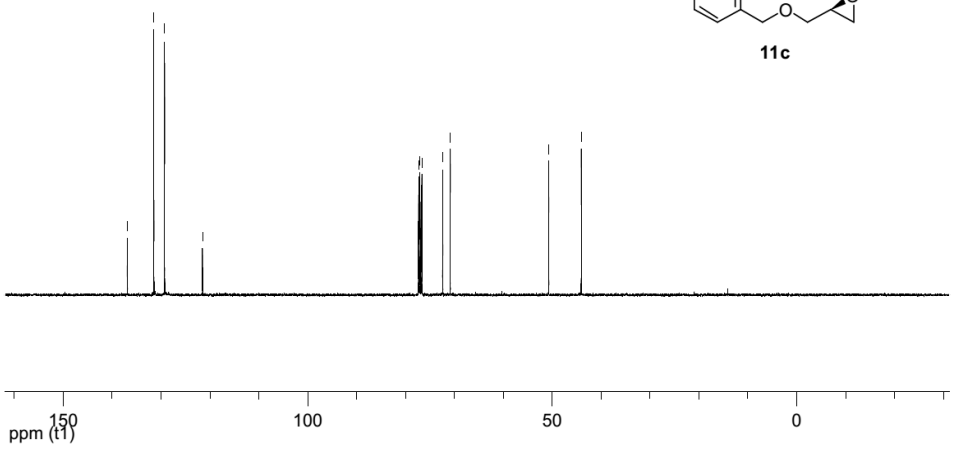

Cl
O
O

11c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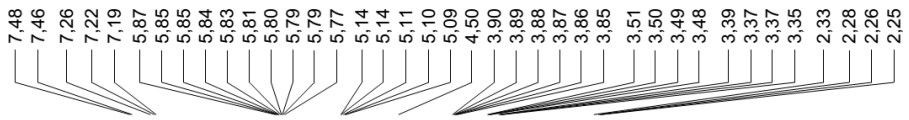
100
50
0
ppm (t1)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5,85
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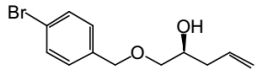
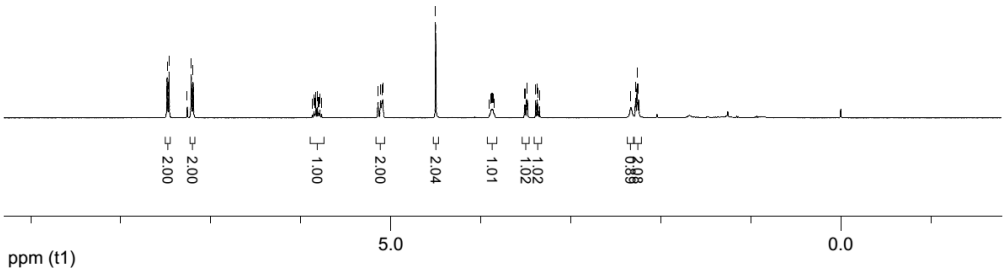
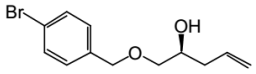
5,83
5,81
5,80
5,79
5,79
5,77
5,14
5,14
5,11
5,10
5,09
4,50
3,90
3,89
3,88
3,87
3,86
3,85
3,51
3,50
3,49
3,48
3,39
3,37
3,37
3,35
2,33
2,28
2,26
2,25


Br
OH
O

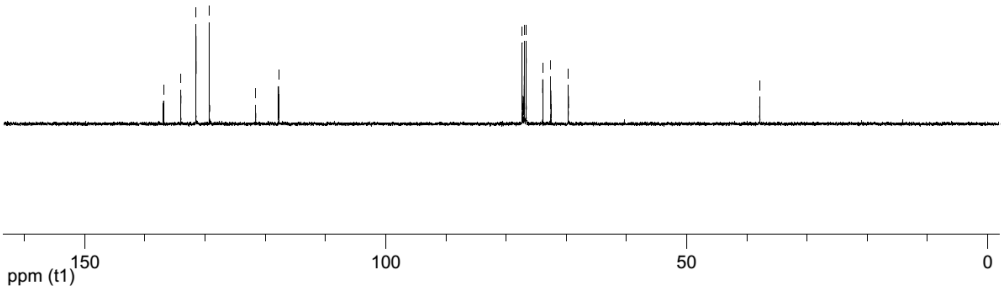
12a

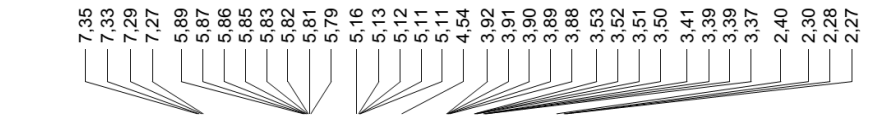

2,00
2,00
1,00
2,00
2,04
1,01
1,02
1,02
0,98
0,99
5.0
0.0
ppm (t1)


136,9
134,0
131,5
129,3
121,6
117,8
77,3
77,0
76,7
73,9
72,6
69,7
37,9


Br
OH
O

12a


150
100
50
0
ppm (t1)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5,87
5,86
5,85
5,83
5,82
5,81
5,79
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5,13
5,12
5,11
5,11
4,54
3,92
3,91
3,90
3,89
3,88
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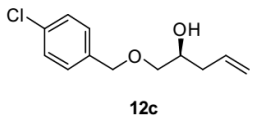
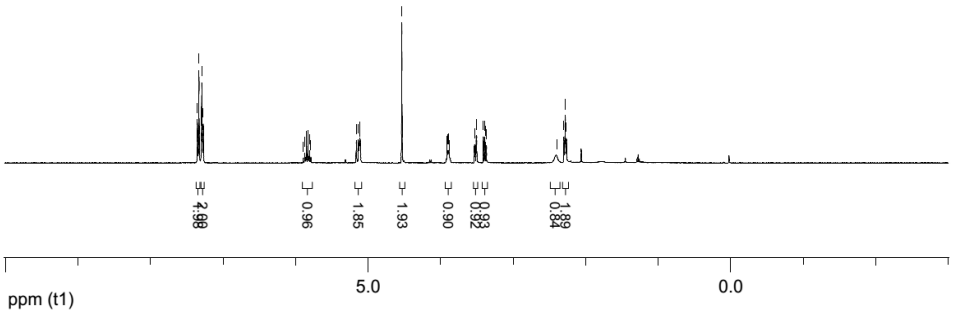
3,39
3,37
2,40
2,30
2,28
2,27


Cl
OH
O

12c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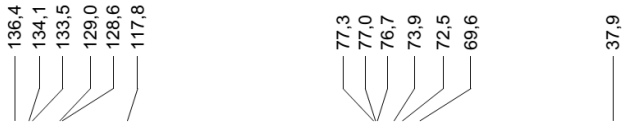
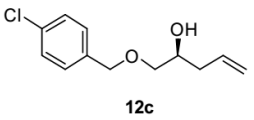
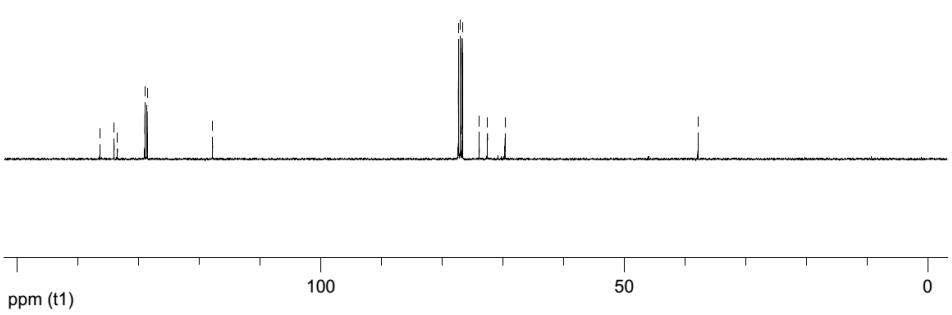
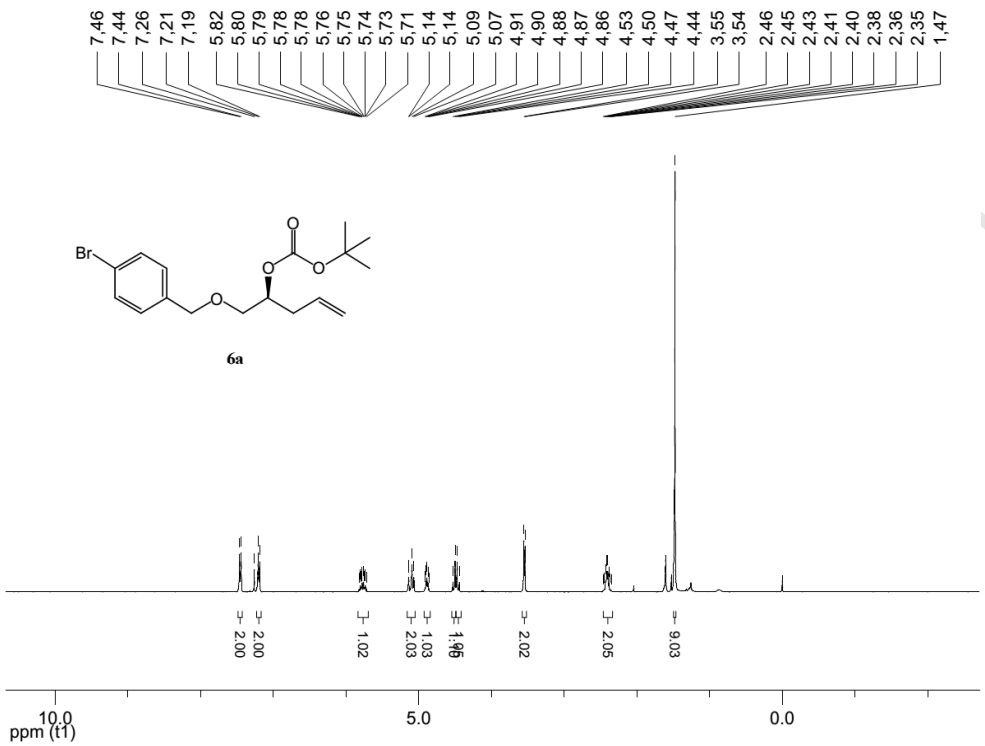
0,96
1,85
1,93
0,90
2,02
2,03
1,84
0,89
5.0
0.0
ppm (t1)


136,4
134,1
133,5
129,0
128,6
117,8
77,3
77,0
76,7
73,9
72,5
69,6
37,9


Cl
OH
O

12c


100
50
0
ppm (t1)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7,19
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5,80
5,79
5,78
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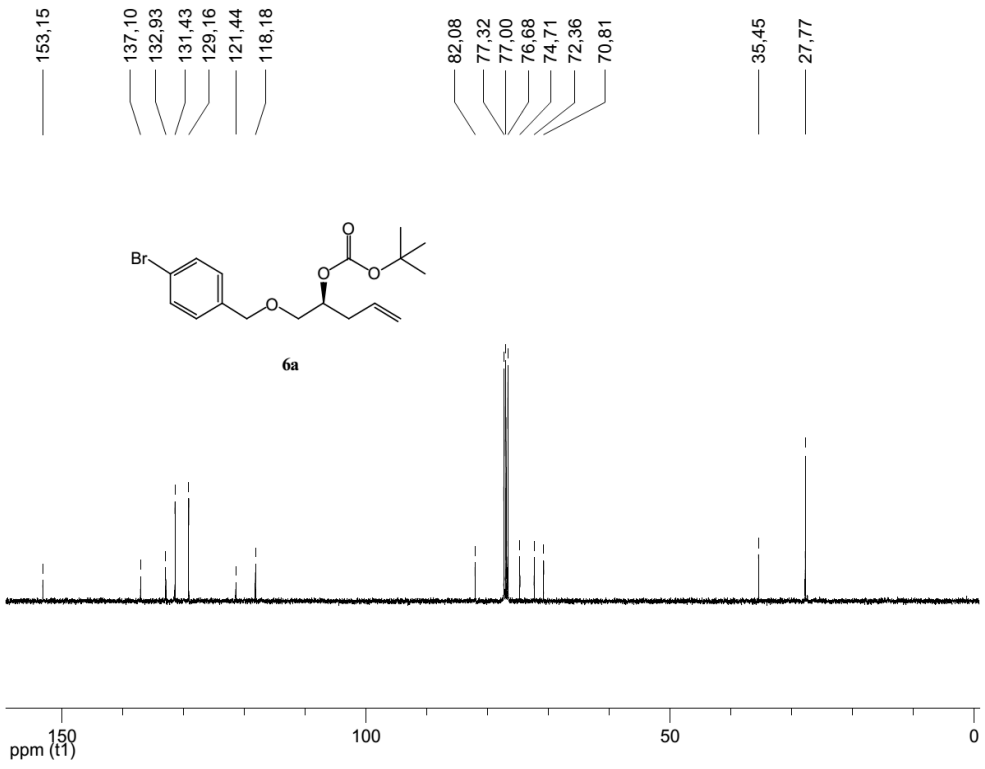
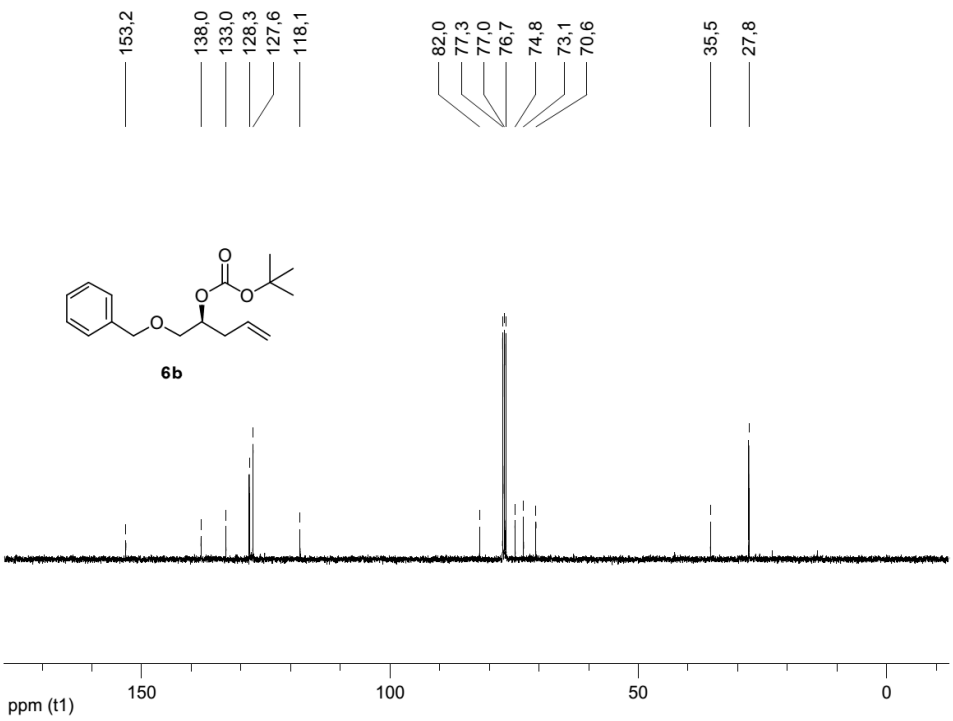
5,76
5,75
5,74
5,73
5,71
5,14
5,14
5,09
5,07
4,91
4,90
4,88
4,87
4,86
4,53
4,50
4,47
4,44
3,55
3,54
2,46
2,45
2,43
2,41
2,40
2,38
2,36
2,35
1,47
Br
O
O
O
O
6a
2,00
2,00
1,02
2,03
1,03
1,96
2,02
2,05
9,03
10.0
5.0
0.0
ppm (t1)


153,15
137,10
132,93
131,43
129,16
121,44
118,18
82,08
77,32
77,00
76,68
74,71
72,36
70,81
35,45
27,77
Br
O
O
O
O
6a
150
100
50
0
ppm (t1)


7,36
7,34
7,33
7,29
7,26
5,82
5,80
5,78
5,76
5,74
5,72
5,14
5,09
5,06
4,92
4,91
4,89
4,88
4,86
4,59
4,56
4,53
4,50
3,56
3,55
2,46
2,44
2,43
2,41
2,39
2,35
1,48
6b
5.02
1.00
1.93
0.98
1.82
1.97
9.24
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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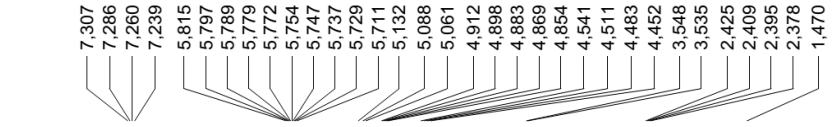
138,0
133,0
128,3
127,6
118,1
82,0
77,3
77,0
76,7
74,8
73,1
70,6
35,5
27,8
6b
ppm (t1)
150
100
50
0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7,260
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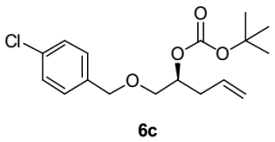
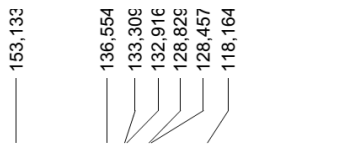
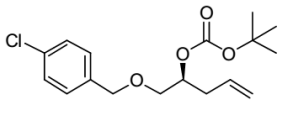
5,797
5,789
5,779
5,772
5,754
5,747
5,737
5,729
5,711
5,132
5,088
5,061
4,912
4,898
4,883
4,869
4,854
4,541
4,511
4,483
4,452
3,548
3,535
2,425
2,409
2,395
2,378
1,470


Cl
O
O
O
O

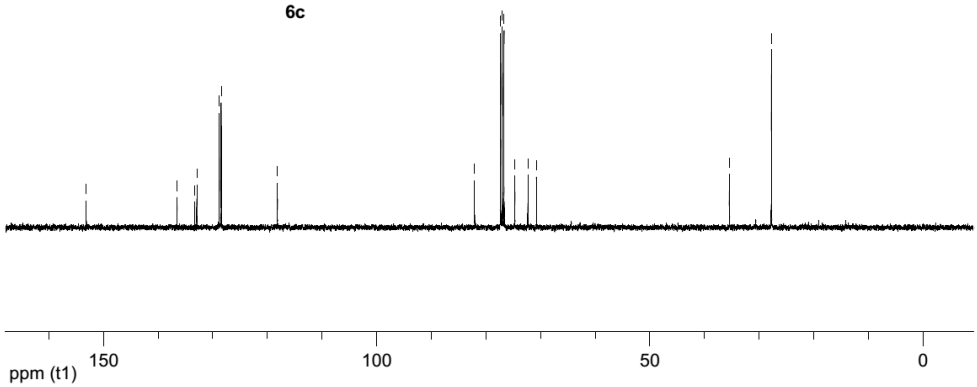
6c

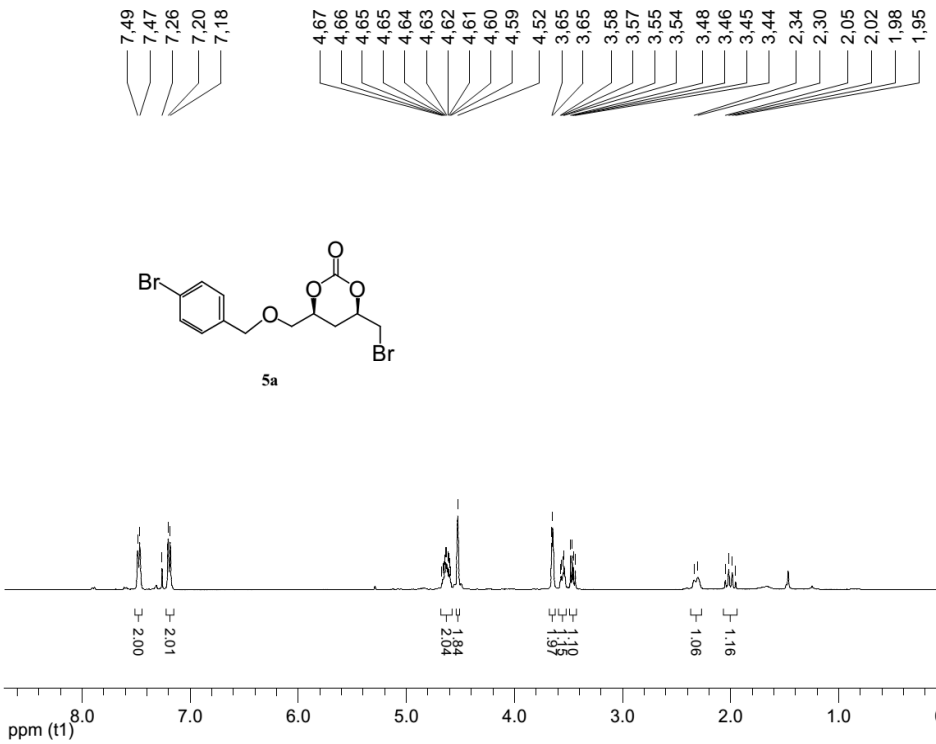
2,14
1,00
1,98
1,00
2,37
2,45
1,89
1,93
9,67
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


153,133
136,554
133,305
132,916
128,825
128,457
118,164
82,043
77,318
77,000
76,682
74,693
72,309
70,759
35,434
27,743


Cl
O
O
O
O

6c


150
100
50
0
ppm (t1)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4,65
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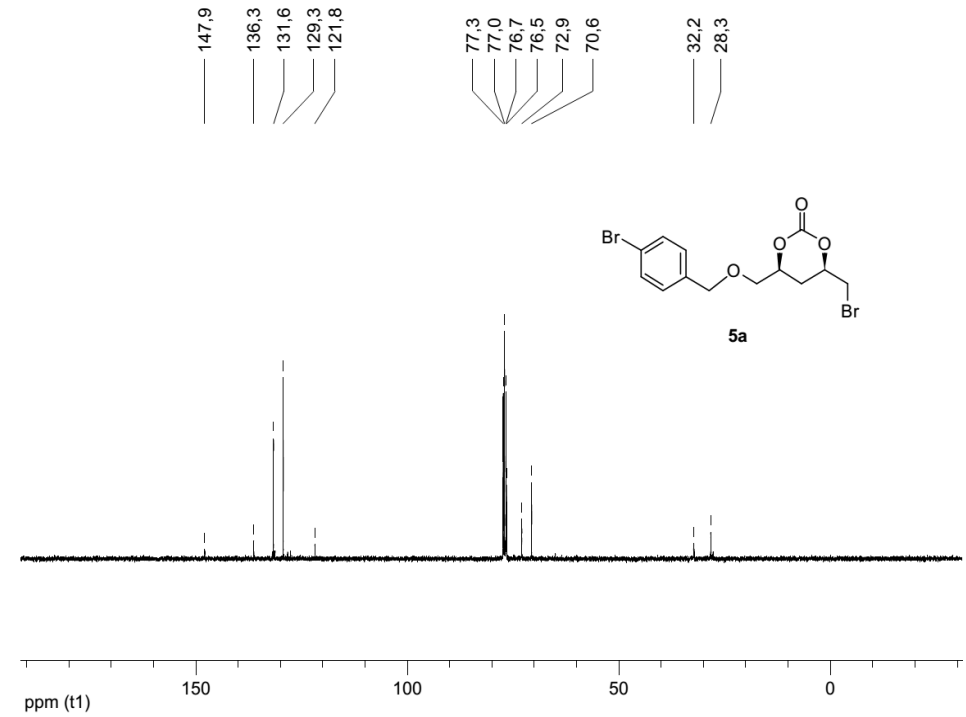
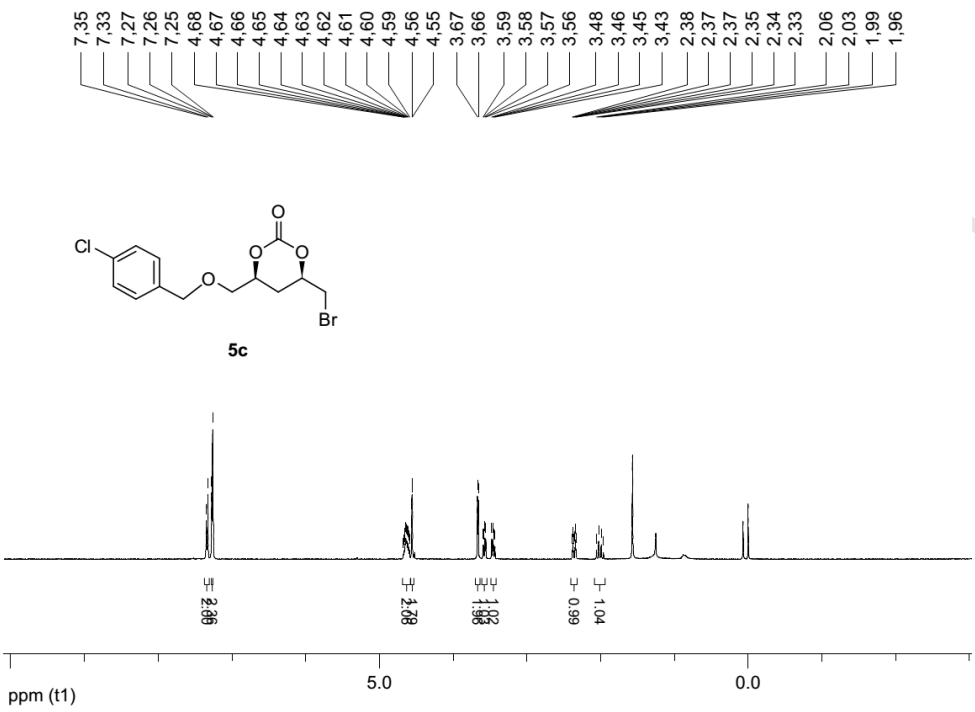
4,64
4,63
4,62
4,61
4,60
4,59
4,52
3,65
3,65
3,58
3,57
3,55
3,54
3,48
3,46
3,45
3,44
2,34
2,30
2,05
2,02
1,98
1,95
Br
O
O
O
O
Br
5a
2,00
2,01
1,84
2,04
1,19
1,17
1,06
1,16
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


147,9
136,3
131,6
129,3
121,8
77,3
77,0
76,7
76,5
72,9
70,6
32,2
28,3
Br
O
O
O
O
Br
5a
150
100
50
0
ppm (t1)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4,67
4,66
4,65
4,64
4,63
4,62
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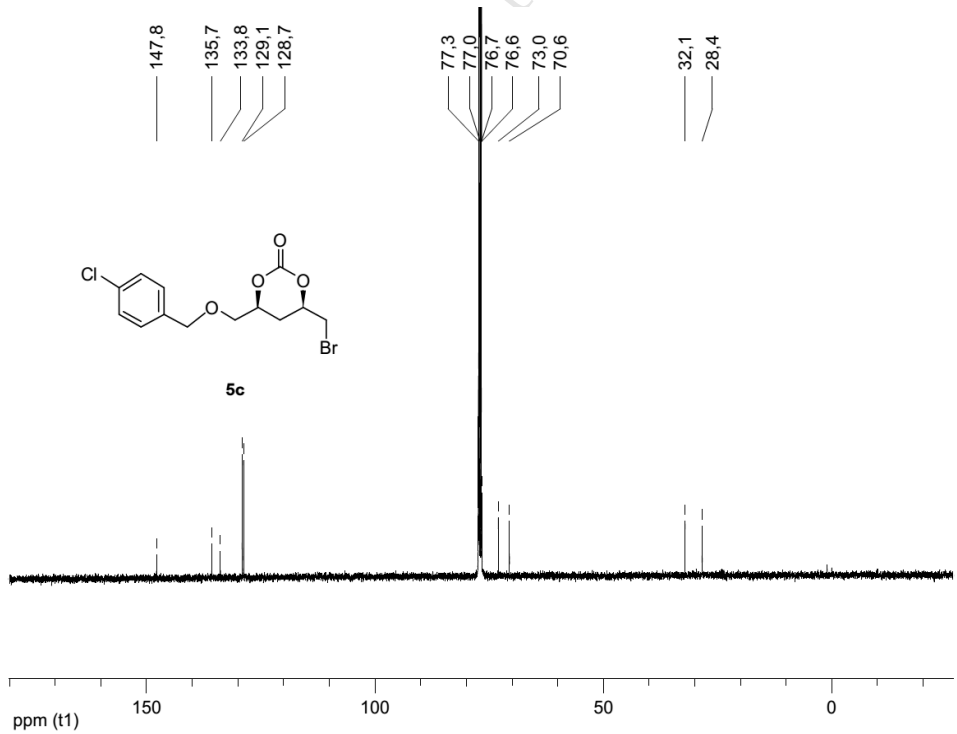
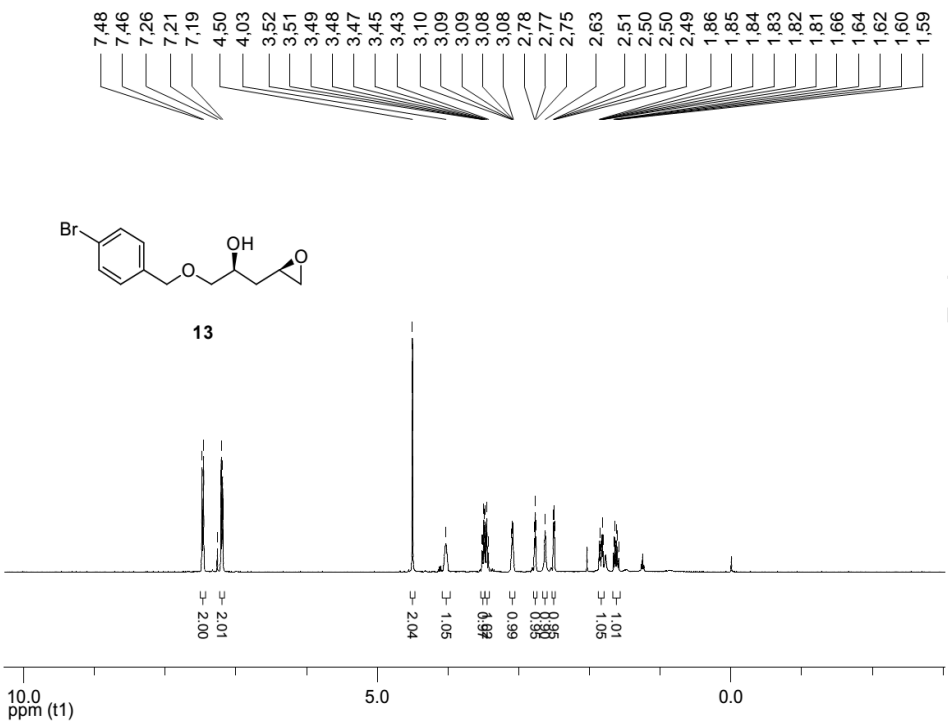
4,60
4,59
4,56
4,55
3,67
3,66
3,59
3,58
3,57
3,56
3,48
3,46
3,45
3,43
2,38
2,37
2,37
2,35
2,34
2,33
2,06
2,03
1,99
1,96
Cl
O
O
O
O
Br
5c
ppm (t1)
5.0
0.0


147,8
135,7
133,8
129,1
128,7
77,3
77,0
76,7
76,6
73,0
70,6
32,1
28,4
Cl
O
O
O
O
Br
5c
ppm (t1)
150
100
50
0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7,19
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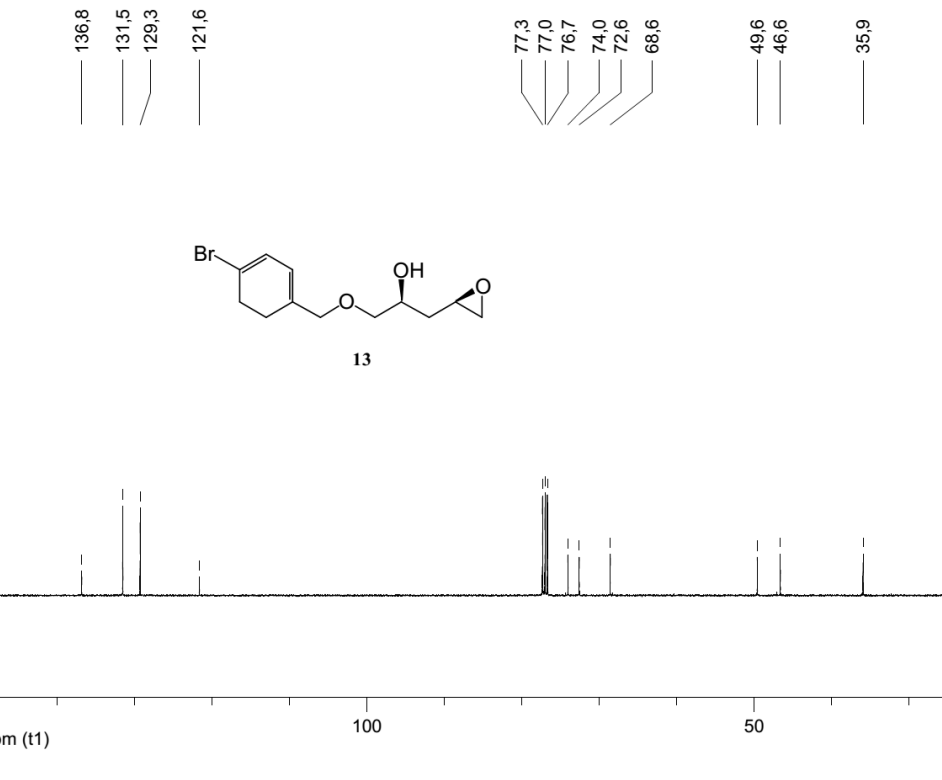
4,03
3,52
3,51
3,49
3,48
3,47
3,45
3,43
3,10
3,09
3,09
3,08
3,08
2,78
2,77
2,75
2,63
2,51
2,50
2,50
2,49
1,86
1,85
1,84
1,83
1,82
1,81
1,66
1,64
1,62
1,60
1,59
Br
OH
O
O
13
2,00
2,01
2,04
1,05
0,99
1,03
1,01
10.0
ppm (t1)
5.0
0.0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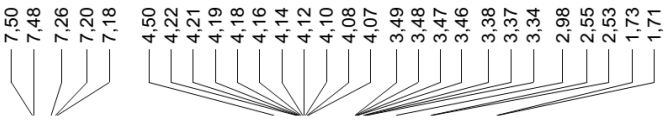
131,5
129,3
121,6
77,3
77,0
76,7
74,0
72,6
68,6
49,6
46,6
35,9
Br
OH
O
O
13
ppm (t1)
100
50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7,20
7,18
4,50
4,22
4,21
4,19
4,18
4,16
4,14
4,12
4,10
4,08
4,07
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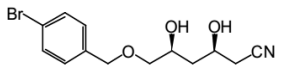
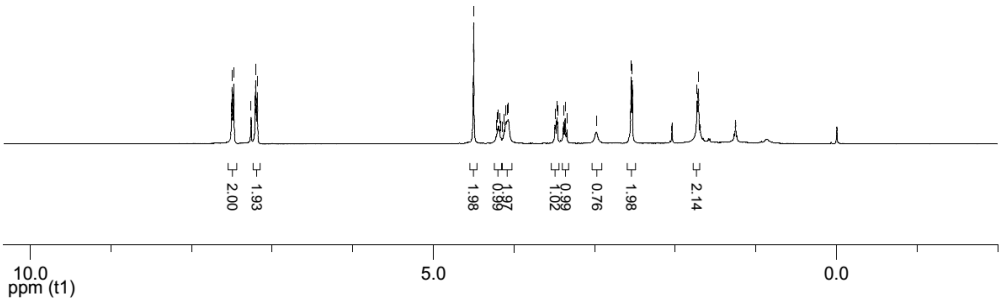
3,34
2,98
2,55
2,53
1,73
1,71


Br
OH
OH
O
CN

14


2,00
1,93
1,98
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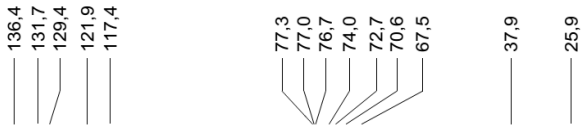
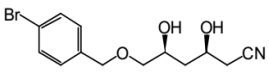
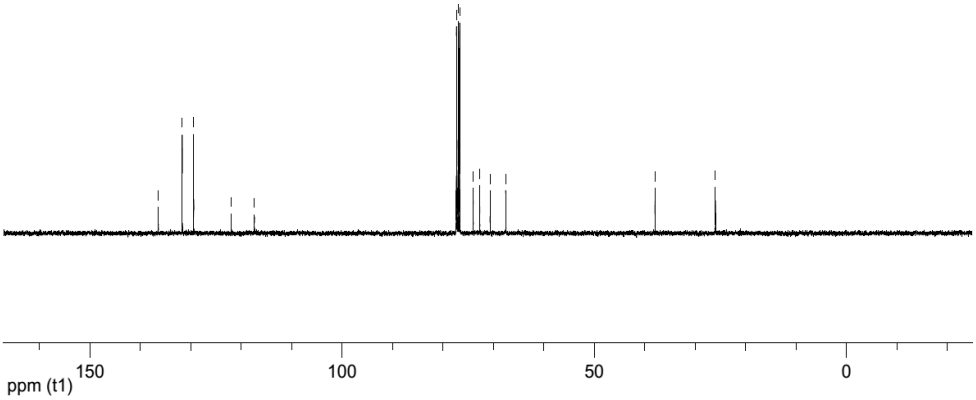
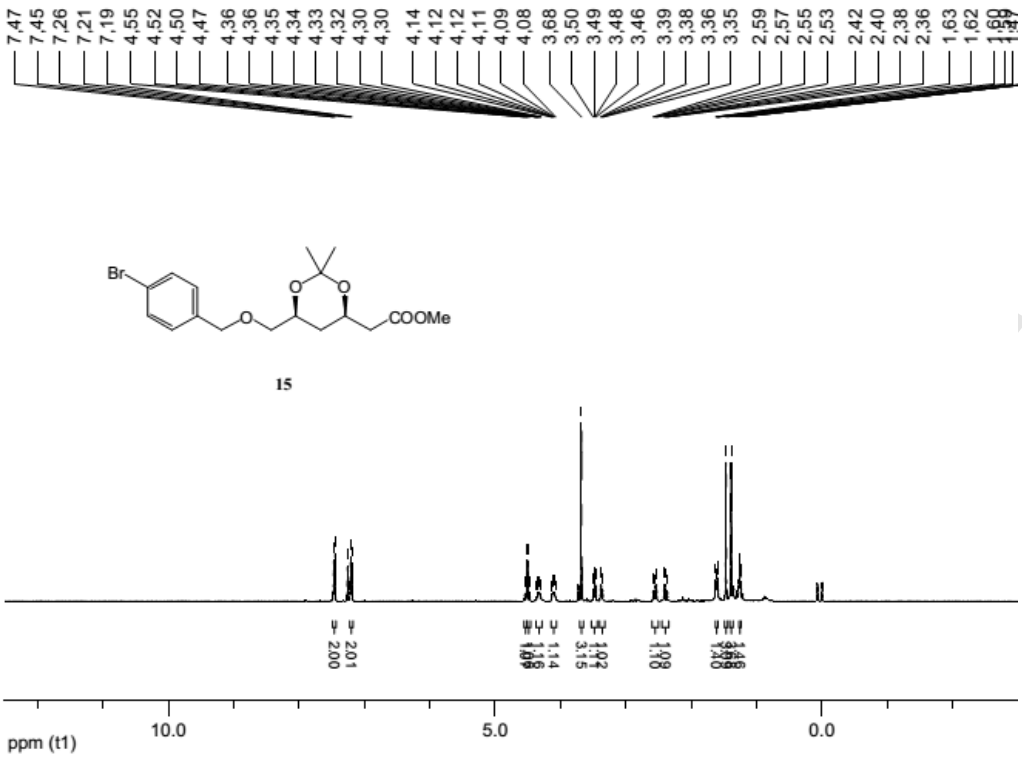
0,89
1,02
0,76
1,98
2,14
10.0
ppm (t1)
5.0
0.0


136,4
131,7
129,4
121,9
117,4
77,3
77,0
76,7
74,0
72,7
70,6
67,5
37,9
25,9


Br
OH
OH
O
CN

14


ppm (t1)
150
100
50
0


7,47
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7,21
7,19
4,55
4,52
4,50
4,47
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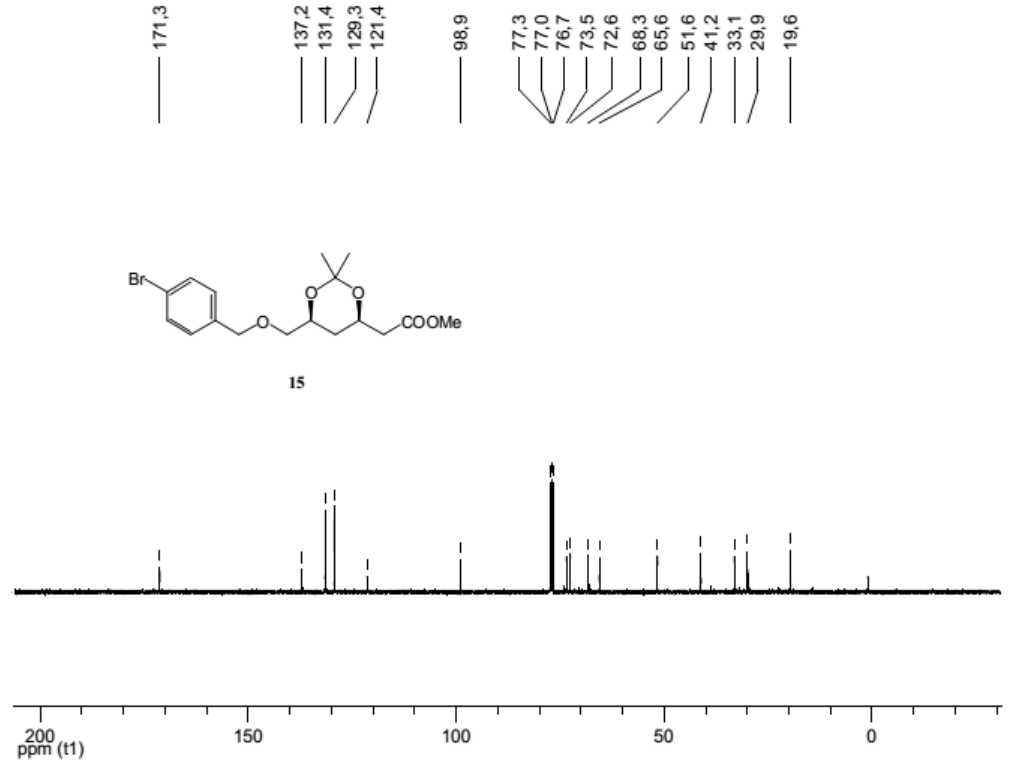
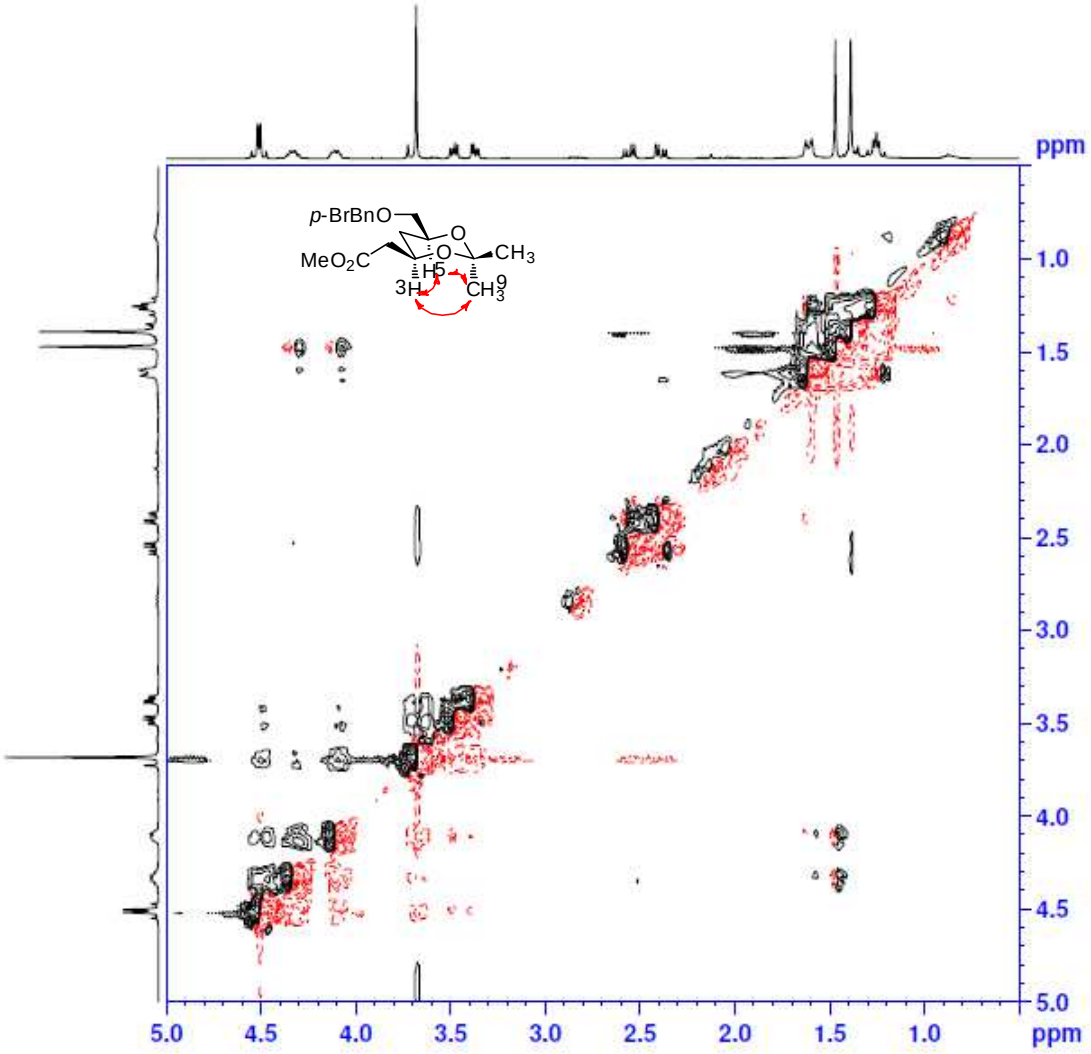
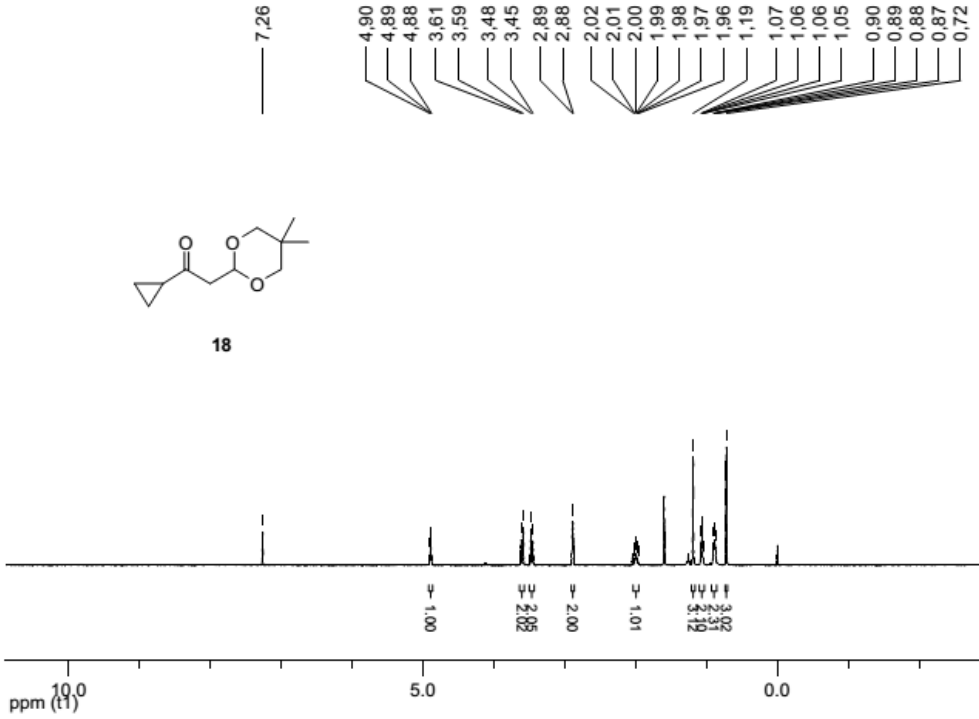
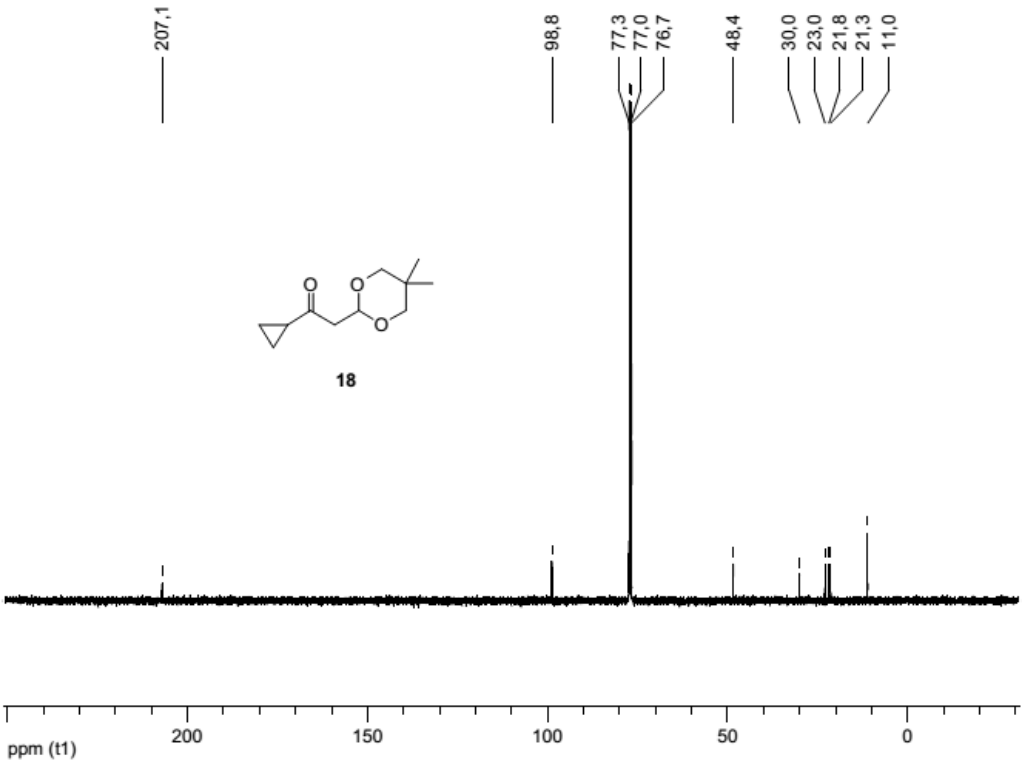
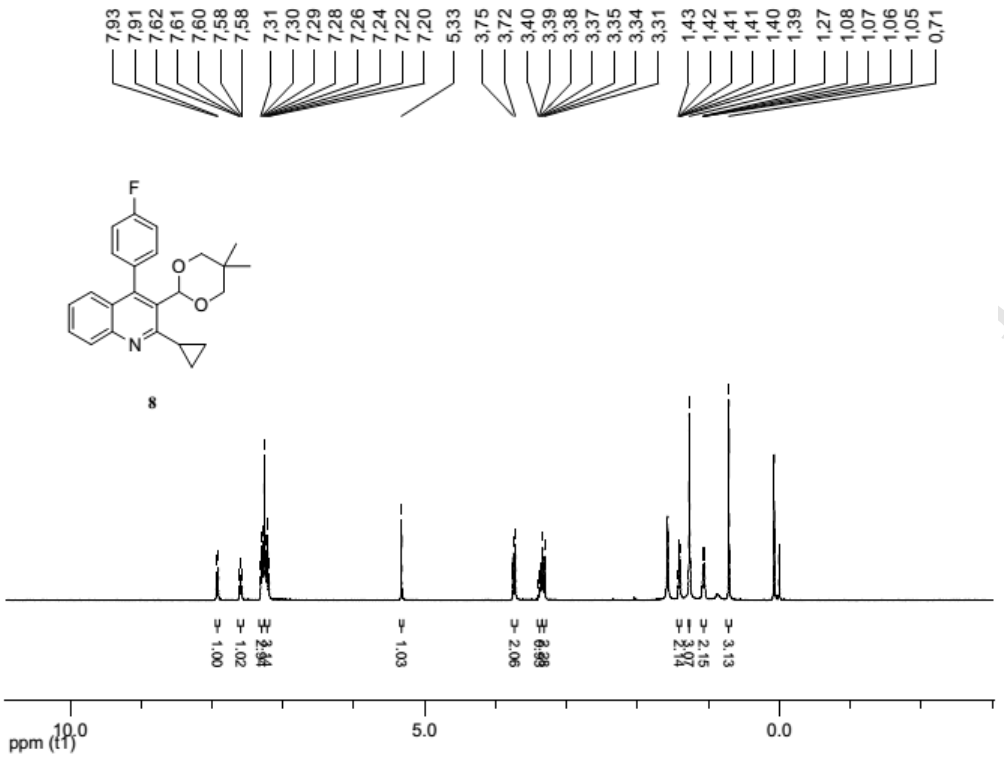
4,36
4,35
4,34
4,33
4,32
4,30
4,30
4,14
4,12
4,12
4,11
4,09
4,08
3,68
3,50
3,49
3,48
3,46
3,39
3,38
3,36
3,35
2,59
2,57
2,55
2,53
2,42
2,40
2,38
2,36
1,63
1,62
Br
O
O
O
COOMe
15
ppm (t1)
10.0
5.0
0.0

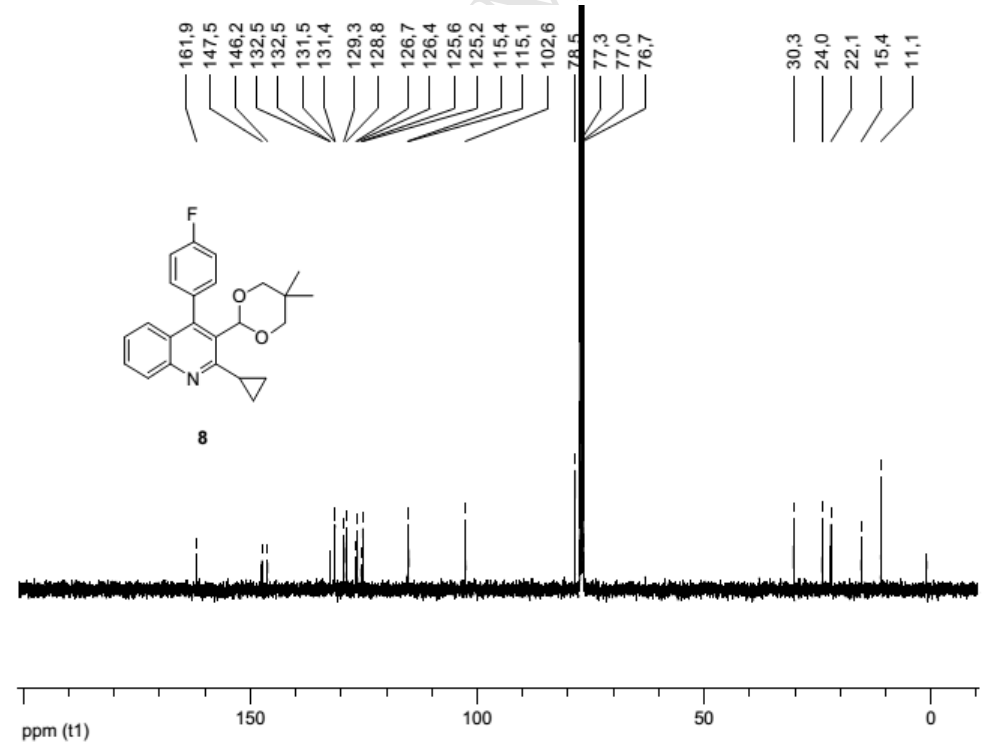

171,3
137,2
131,4
129,3
121,4
98,9
77,3
77,0
76,7
73,5
72,6
68,3
65,6
51,6
41,2
33,1
29,9
19,6
Br
O
O
O
COOMe
15
200
ppm (t1)
150
100
50
0

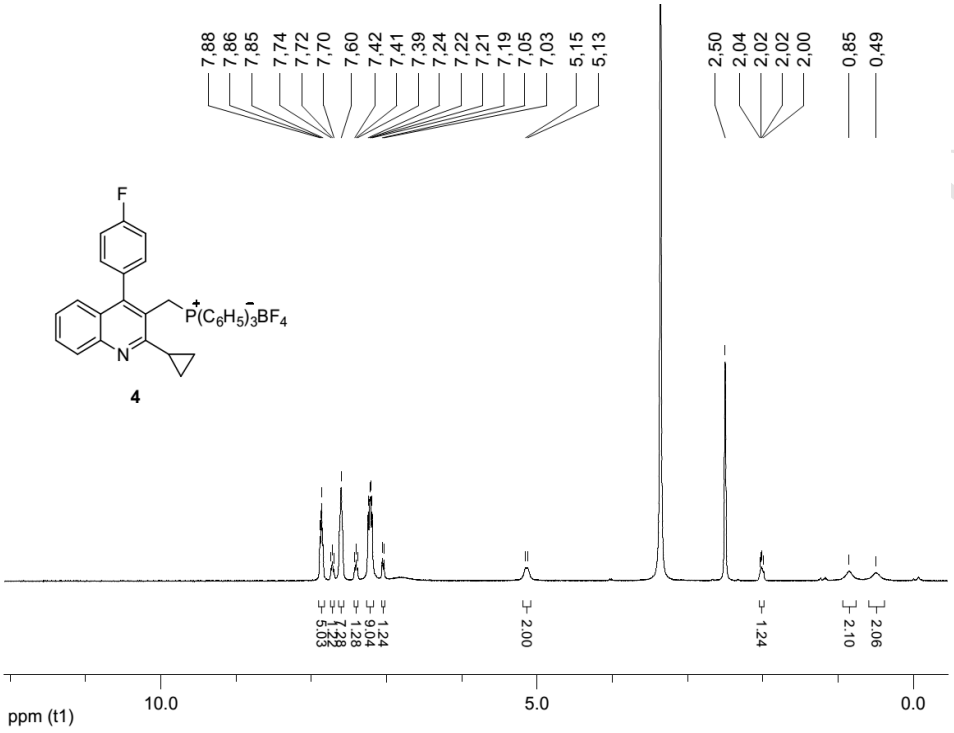


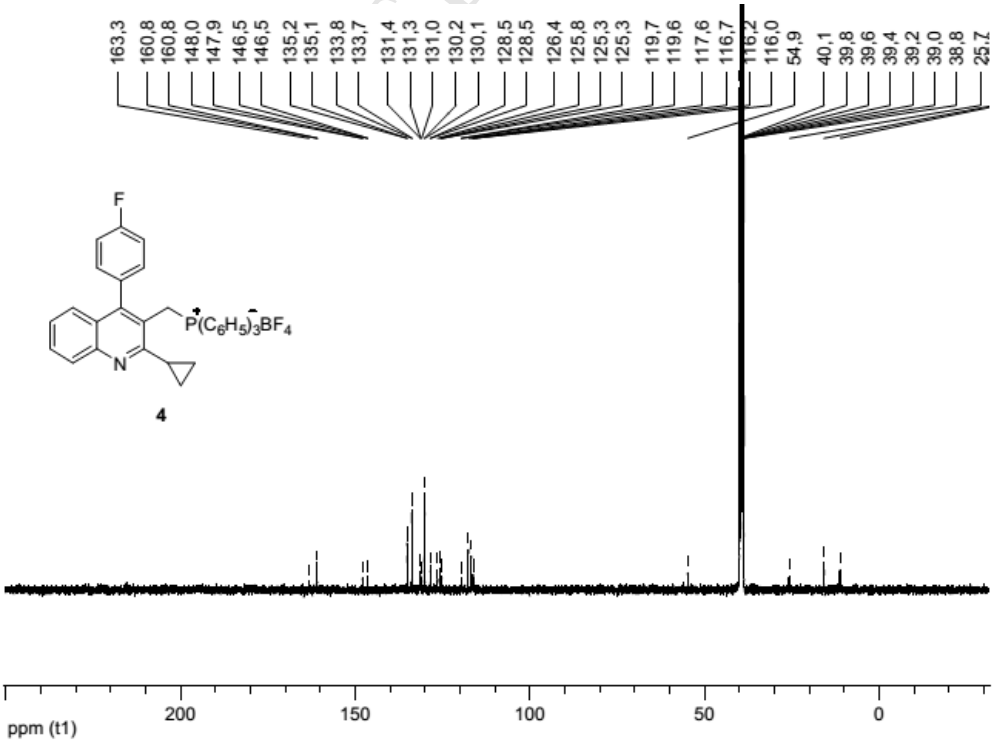

7,26
4,90
4,89
4,88
3,61
3,59
3,48
3,45
2,89
2,88
2,02
2,01
2,00
1,99
1,98
1,97
1,96
1,19
1,07
1,06
1,06
1,05
0,90
0,89
0,88
0,87
0,72
18
1.00
2.05
2.02
2.00
1.01
3.02
2.31
2.19
3.12
10.0
5.0
0.0
ppm (t1)

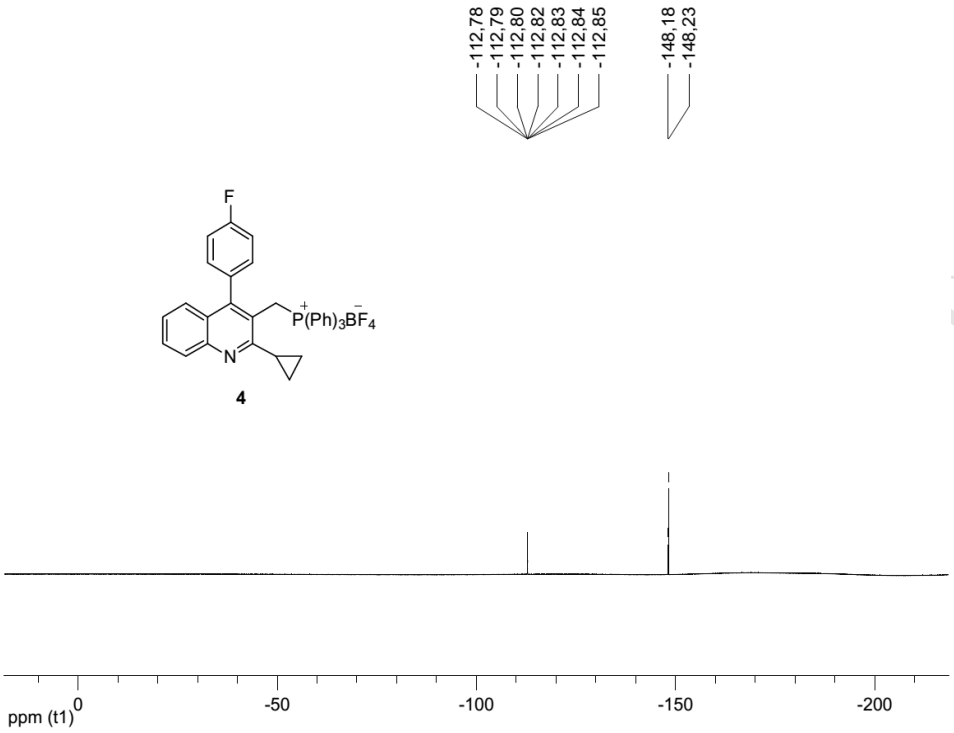

207,1
98,8
77,3
77,0
76,7
48,4
30,0
23,0
21,8
21,3
11,0
18
200
150
100
50
0
ppm (t1)

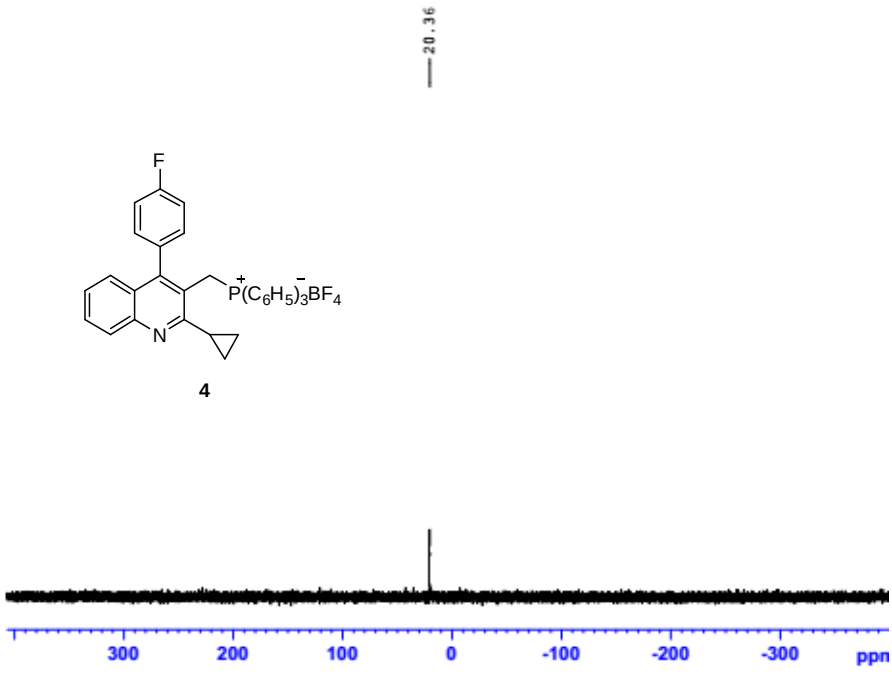

7,93
7,91
7,62
7,61
7,60
7,58
7,58
7,31
7,30
7,29
7,28
7,26
7,24
7,22
7,20
5,33
3,75
3,72
3,40
3,39
3,38
3,37
3,35
3,34
3,31
1,43
1,42
1,41
1,41
1,40
1,39
1,27
1,08
1,07
1,06
1,05
0,71
F
O
O
N
8
1,00
1,02
2,44
1,03
2,06
2,08
3,07
2,15
3,13
10.0
5.0
0.0
ppm (t1)

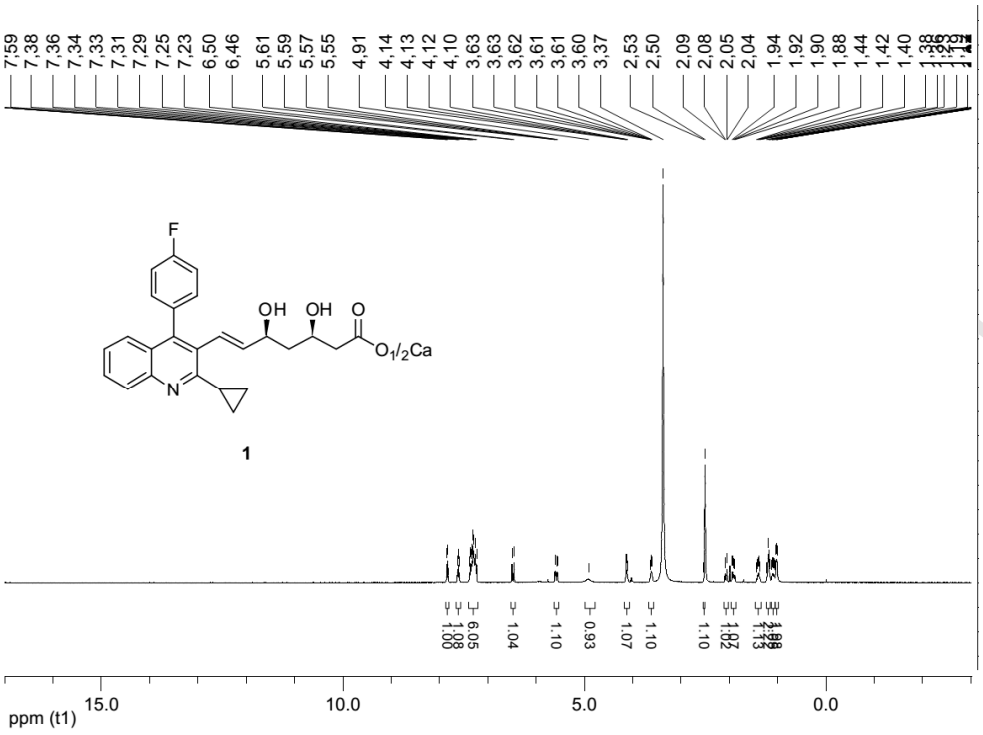

161,9
147,5
146,2
132,5
132,5
131,5
131,4
129,3
128,8
126,7
126,4
125,6
125,2
115,4
115,1
102,6
78,5
77,3
77,0
76,7
30,3
24,0
22,1
15,4
11,1
F
O
O
N
8
150
100
50
0
ppm (t1)

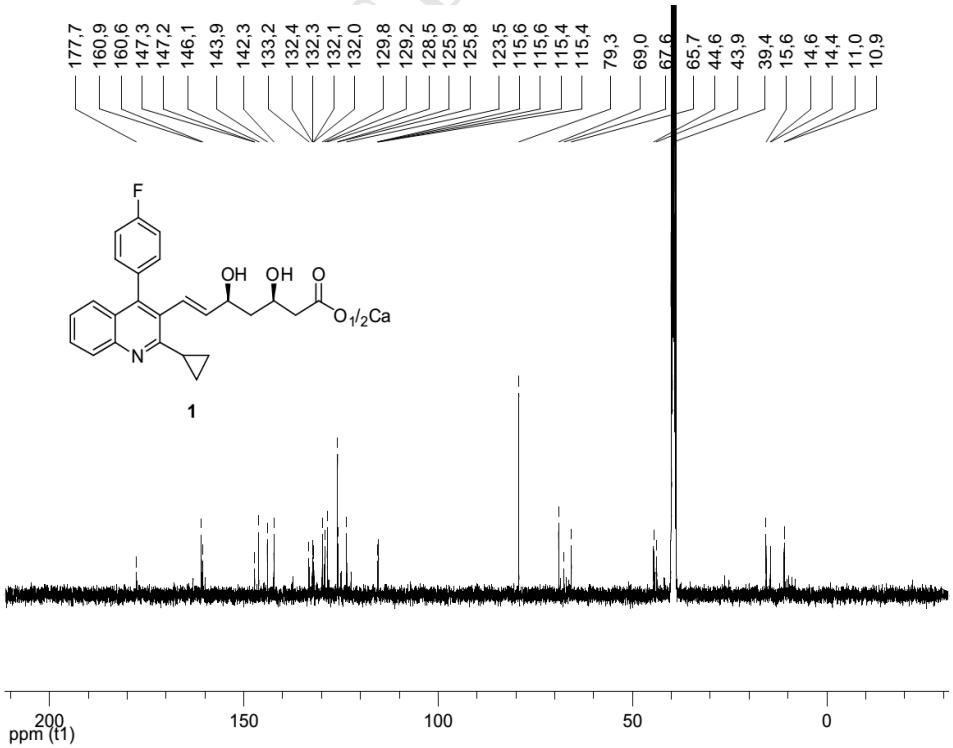

7,88
7,86
7,85
7,74
7,72
7,70
7,60
7,42
7,41
7,39
7,24
7,22
7,21
7,19
7,05
7,03
5,15
5,13
2,50
2,04
2,02
2,02
2,00
0,85
0,49
F
P(C6H5)3BF4
N
4
5,03
1,22
1,28
9,04
1,24
2,00
1,24
2,10
2,06
10.0
5.0
0.0
ppm (t1)


163,3
160,8
160,8
148,0
147,9
146,5
146,5
135,2
135,1
133,8
133,7
131,4
131,3
131,0
130,2
130,1
128,5
128,5
126,4
125,8
125,3
125,3
119,7
119,6
117,6
116,7
116,2
116,0
54,9
40,1
39,8
39,6
39,4
39,2
39,0
38,8
25,7
F
P(C6H5)3BF4
N
4
200
150
100
50
0
ppm (t1)


-112,78
-112,79
-112,80
-112,82
-112,83
-112,84
-112,85
-148,18
-148,23
F
P(Ph)3BF4
N
4
ppm (t1)
0
-50
-100
-150
-200


20,36
F
P(C6H5)3BF4
N
4
300
200
100
0
-100
-200
-300
ppm


7,59
7,38
7,36
7,34
7,33
7,31
7,29
7,25
7,23
6,50
6,46
5,61
5,59
5,57
5,55
4,91
4,14
4,13
4,12
4,10
3,63
3,63
3,62
3,61
3,61
3,60
3,37
2,53
2,50
2,09
2,08
2,05
2,04
1,94
1,92
1,90
1,88
1,44
1,42
1,40
F
OH
OH
O
O1/2Ca
N
1
1.00
1.08
6.05
1.04
1.10
0.93
1.07
1.10
1.10
1.82
ppm (t1)
15.0
10.0
5.0
0.0


177,7
160,9
160,6
147,3
147,2
146,1
143,9
142,3
133,2
132,4
132,3
132,1
132,0
129,8
129,2
128,5
125,9
125,8
123,5
115,6
115,6
115,4
115,4
79,3
69,0
67,6
65,7
44,6
43,9
39,4
15,6
14,6
14,4
11,0
10,9
F
OH
OH
O
O1/2Ca
N
1
ppm (t1)
200
150
100
50
0