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Graphical Abstract

Synthetic Studies on Statins. Part 3. A Facile Synthesis of Rosuvastatin Calcium Through Catalytic Enantioselective Allylation Strategy

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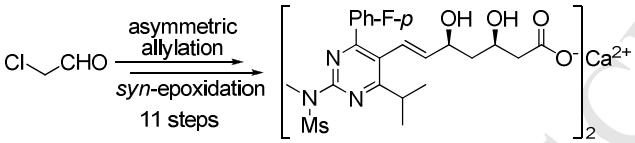
Xiaofei Chen, Fangjun Xiong, Chen Zheng, Jie Li, Fener Chen
Department of Chemistry, Institutes of Biomedical Science, Fudan University, Shanghai 200433, People's Republic of China



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Synthetic Studies on Statins. Part 3[1]. A Facile Synthesis of Rosuvastatin Calcium Through Catalytic Enantioselective Allylation Strategy

Xiaofei Chen,[a, b] Fangjun Xiong,[a] Chen Zheng,[a] Jie Li,[a] Fener Chen[a, b, *]

[a] *Department of Chemistry, Fudan University, Shanghai 200433, People's Republic of China*
[b] *Institutes of Biomedical Science, Fudan University, Shanghai 200433, People's Republic of China*
Corresponding author. Tel.: +86-21-65643809; fax: +86-21-65643811; e-mail: rfchen@fudan.edu.cn

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ABSTRACT

A concise and stereocontrolled synthesis of rosuvastatin calcium has been accomplished, with the key steps including a Keck enantioselective allylation of chloroacetaldehyde with allyltributylstannane to install 5*R*-stereocenter and a $VO(acac)_2$-catalyzed *syn*-diastereoselective epoxidation of (*S*)-1-chloropent-4-en-2-ol to set the requisite 3*R*-chirality.

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1. Introduction

Rosuvastatin calcium (Crestor, **1**, Figure 1) was marketed as a 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor by AstraZeneca in 2003, and has been billed as a "super-statin" because of its pronounced ability to reduce low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol compared with existing agents.[2] The development of a concise synthetic strategy for rosuvastatin calcium is therefore highly desired. One of the most commonly used strategies for construction of pyrimidine core attached to (3*R*,5*R*)-3,5-dihydroxy-heptenoic acid in **1** is adopted a Wittig-type olefination of the ylide **2** with the C_6 side chain aldehyde **3** (Figure 1).[3] The efficient assembly of 3*R*-*syn*-3,5-diol subunit is the key issue for the synthesis of **3**. Considerable synthetic efforts have been directed towards the development of strategies for construction of **3**, and have culminated in several new methods based on chiral pool synthesis,[4] asymmetric catalysis,[5] or the use of chiral auxiliary[6] or chemoenzymatic process.[7] One of the major industrial processes for construction of C_6 side chain involves Blaise condensation of a C_2 synthon with a C_4 synthon (starting from (*S*)-epichlorohydrin).[4h-j] One of the major limitations of this route, however, is the use of Narasaka reduction to introduce the second stereogenic center, because this reaction requires particularly harsh conditions (i.e., Et_3B or $Et_2BOMe/NaBH_4$/−78 °C). Herein, we describe the development of an efficient and alternative strategy for the synthesis of **1**, which avoids the use of Narasaka reduction.

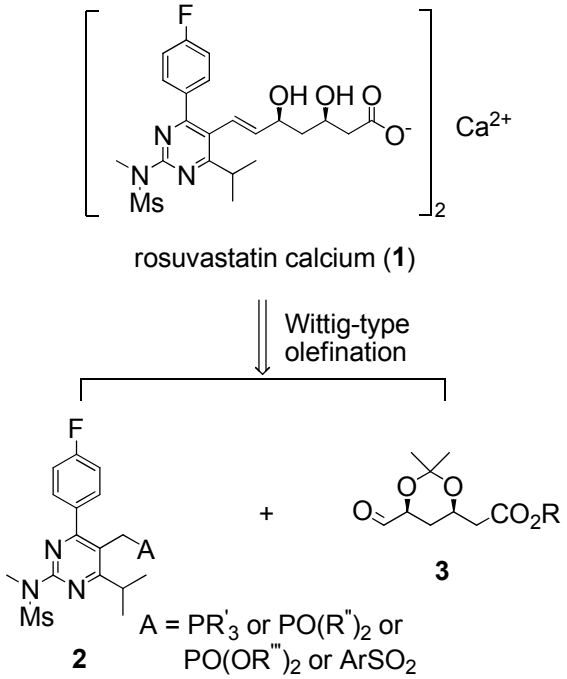

Figure 1. The chemical structures of **1**, **2** and **3**.

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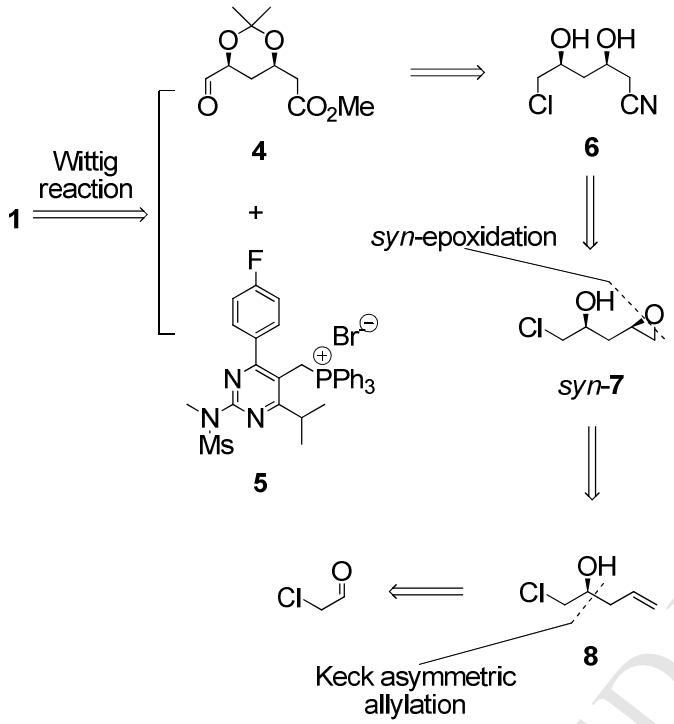
2. Results and discussion

Our retrosynthetic approach towards **1** is depicted in Scheme 1. It was envisaged that **1** could be derived from aldehyde **4** and phosphonium salt **5**. **4** could be accessed through a series of transformations from *syn*-diol **6**, which could be synthesized via epoxy addition of **7** with sodium cyanide. Compound **7** could be prepared by a $VO(acac)_2$-catalyzed *syn*-diastereoselective epoxidation of homoallylic alcohol **8**. Keck enantioselective allylation of chloroacetaldehyde with allyltributylstannane would allow for introduction of the requisite 2*R* stereochemistry in **8**.

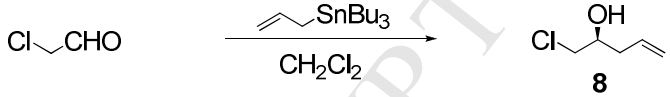


Scheme 1. Retrosynthetic strategy for **1**.

Our asymmetric synthesis of rosuvastatin calcium (**1**) commenced with anhydrous chloroacetaldehyde,[8] which was subjected to Keck asymmetric allylation[9] with allyltributylstannane in the presence of (*S*)-BINOL/$Ti(O^iPr)_4$ at −20 °C for 96 h furnished homoallylic alcohol **8** in 67% yield with the desired (*S*)-configuration, which was verified by optical rotation analysis.[10] The optical purity of **8** (94% *ee*) was determined by HPLC analysis of its benzoyl-protected derivative **9** (Table 1, entry 1). (*S*)-VANOL/$Ti(O^iPr)_4$ and (*R*)-VAPOL/$Ti(O^iPr)_4$ were screened against this reaction, but gave very low yields (41 and 37%) and poor enantioselectivities (54 and 46% *ee*) (Table 1, entries 2 and 3), and the use of (*S*)-BINOL/$FeCl_3$ and (*S*)-BINOL/$InCl_3$ gave even worse results (8 and 30% *ee*) (Table 1, entries 4 and 5).

Many researchers have explored the *syn*-epoxidation of acyclic homoallylic alcohols using a wide variety of oxidants and/or catalysts,[11] Of these, the $VO(acac)_2$/*tert*-butyl hydroperoxide (TBHP) oxidation system has become one of the most commonly used systems for this transformation.[11a] As shown in Table 2, treatment of **8** with TBHP in the presence of 5 mol% $VO(acac)_2$ afforded **7** in 69% yield as an inseparable 5:2 mixture of epimers (Table 2, entry 1). After screening other oxidants, we found that the diastereoisomeric ratio could be reduced to 2:1 using cumene hydroperoxide (CHP), whereas the use of urea hydrogen peroxide (UHP) or sodium perborate proved to be ineffective (Table 2, entries 2-4). The concentration of **8** was found to have a significant impact on the diastereoselectivity of the epoxidation, and a reduction in the concentration of substrate from 1.0 to 0.1 M led to a gradual increase in the *dr* value (from 5:2 to 3:1) (Table 2, entries 1, 5 and 6).

Table 1. Optimization of Keck asymmetric allylation of chloroacetaldehyde.[a]



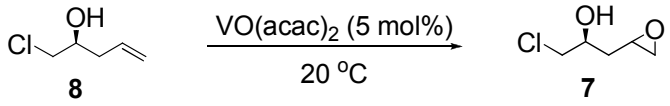
Entry	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	(*S*)-BINOL, $Ti(O^iPr)_4$	-20	96	67	94
2	(*S*)-VANOL, $Ti(O^iPr)_4$	0	96	41	54
3	(*R*)-VAPOL, $Ti(O^iPr)_4$	0	96	37	46
4	(*S*)-BINOL, $FeCl_3$	0	72	54	8
5	(*S*)-BINOL, $InCl_3$	0	60	46	30

[a] All reactions were carried out in the presence of chloroacetaldehyde (1.0 mmol), allyltributylstannane (2.0 mmol.), chiral ligands (0.22 mmol), Lewis acids (0.2 mmol) and 4Å MS in CH_2Cl_2 (10 mL).

[b] Isolated yields.

[c] The *ee* values of **8** were determined by its benzoate derivant **9**.

Table 2. Optimization of *syn*-epoxidation of homoallylic alcohol **8**.[a]



Entry	Oxidant	Solvent[b]	Time (h)	Yield[c] (%)	dr[d]
1	TBHP	CH_2Cl_2 (1.0 M)	36	69	5:2
2	CHP	CH_2Cl_2 (1.0 M)	48	67	2:1
3	UHP	THF (1.0 M)	48	---	---
4	$NaBO_3$	THF (1.0 M)	48	---	---
5	TBHP	CH_2Cl_2 (0.5 M)	60	67	13:5
6	TBHP	CH_2Cl_2 (0.1 M)	60	76	3:1

[a] All reactions were carried out in the presence of **8** (2.0 mmol), $VO(acac)_2$ (0.1 mmol), oxidants (3.0 mmol) and 3Å MS at 20 °C.

[b] In parentheses are concentration of **8**.

[c] Isolated yields.

[d] The *dr* values were determined by ^1H NMR analysis.

With requisite epoxide **7** in hand, we proceeded to investigate nucleophilic addition of sodium cyanide to allow for the introduction of cyano group to C_5 side chain. The reaction of **7** with sodium cyanide under weakly basic conditions (pH= 7.5–8.0) proceeded smoothly to afford the desired nitrile **6** in an isolated yield of 57%. The byproduct (3-*epi*-**6**) was also isolated in 17% yield (Scheme 2). Subsequent Pinner reaction of **6** with a

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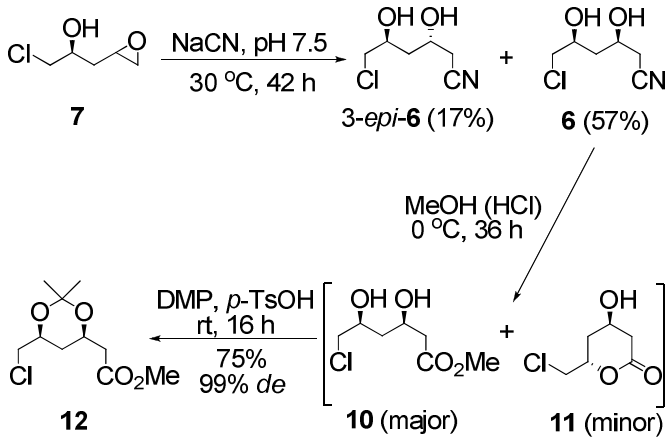
saturated solution of hydrogen chloride in methanol at 0 °C for 36 h afforded a mixture of ester **10** and lactone **11** (resulting from an intramolecular Pinner reaction), which was used directly in next reaction without further purification. Protection of the mixture with 2,2-dimethoxypropane (DMP) in the presence of 10 mol% *p*-toluenesulfonic acid gave 1,3-dioxane **12** in an overall yield of 75% over two steps with 99% *de*, which was confirmed by GC-MS analysis relative to 4-*epi*-**12** derived from 3-*epi*-**6** (Scheme 2).



Scheme 2. Synthesis of intermediate **12**

The stereochemical assignment of **12** was confirmed by a NOESY study, which revealed strong NOE correlations between H-3/H-5, H-3/H-9, and H-5/H-9. These correlations indicated that H-3, H-5, and H-9 were on the same side of the molecule (Figure 2).

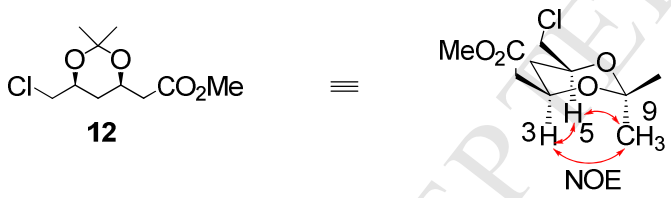
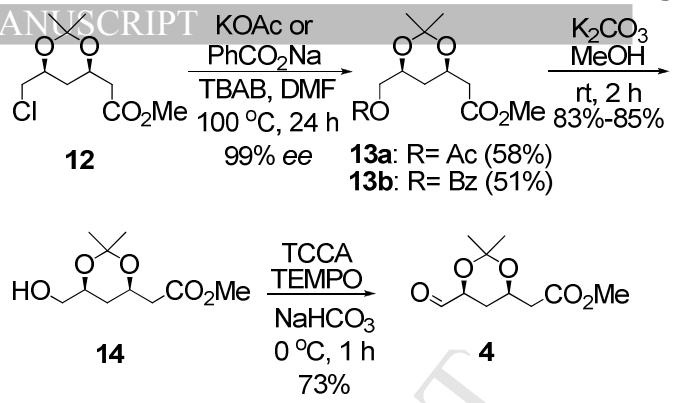


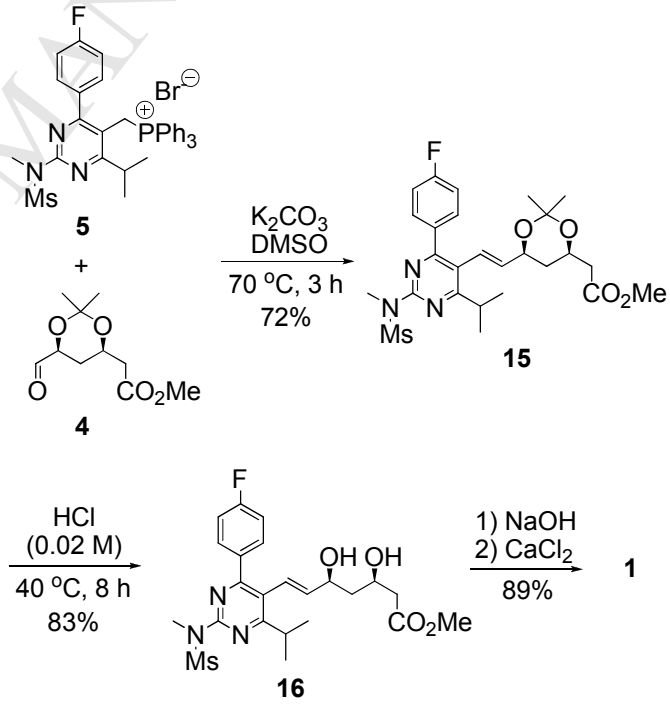
Figure 2. The NOESY correlations of intermediate **12**

Reaction of **12** with potassium acetate or sodium benzoate in the presence of tetrabutyl ammonium bromide furnished **13a** or **13b**, respectively, in moderate yields as white solids. The optical purity of **13** was only 95%, fortunately, it could be upgraded to 99% by recrystallization from *n*-heptane with recovered yields in the range of 85–88%. Compounds **13** were then hydrolyzed with aqueous potassium carbonate at room temperature for 2 h to afford alcohol **14** in excellent yields. The key building block **4** was readily synthesized in 73% yield by treatment of **14** with trichloroisocyanuric acid (TCCA) in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) (Scheme 3).[12]



Scheme 3. Synthesis of the key intermediate **4**

Finally, Wittig olefination of **4** with phosphonium salt **5**[3d] was performed under basic conditions (i.e., K_2CO_3, DMSO, 70 °C) to yield olefin **15** in 72% yield. Subsequent treatment of **15** with hydrochloric acid (0.02 mol/L, 5 mol%) in acetonitrile at 40 °C for 8 h allowed for the deprotection of ketal to give diol **16** in 83% yield, which was subjected to sequential hydrolysis and salification steps to furnish **1** in yield of 89% over two steps (Scheme 4).[3d]



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

3. Conclusions

In summary, we have developed an efficient eleven-step sequence for the synthesis of rosuvastatin calcium (**1**) starting from readily available material chloroacetaldehyde. Keck asymmetric allylation of chloroacetaldehyde with allyltributylstannane followed by a $VO(acac)_2$-catalyzed stereoselective epoxidation of the resulting homoallylic alcohol **8** allowed for rapid construction of the 3*R*-*syn*-1,3-diol subunit of

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the target. Our newly developed approach is superior to existing methodologies for preparation of **4** because it avoids the use of Narasaka reduction. Although a large number of synthetic strategies for **1** have already been reported in the literature, our newly developed strategy represents a unique approach and should provide a platform for the synthesis of **1** and its derivatives.

4. Experimental section

4.1. General

Melting points were determined on a WRS-1 digital melting point apparatus. Optical rotations were obtained on a JASCO P1020 digital polarimeter. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 spectrometer (400, 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6 using $CDCl_3$ (^{1}H, δ 7.26) or DMSO-d_6 (^{1}H, δ 2.50) and $CDCl_3$ (^{13}C, δ 77.0) or DMSO-d_6 (^{13}C δ 39.5) as internal standards. IR spectra were recorded on a Nicolet FT-IR 4200 spectrometer as KBr pellets. Mass spectra were measured on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. Enantiomeric excesses (*ee*) were determined by HPLC analysis using Chiralpak columns. Unless otherwise noted all reactions were conducted in oven-dried glassware under inert atmosphere of dried Ar or N_2. (*S*)-BINOL, (*S*)-VANOL and (*R*)-VAPOL were purchased from Aldrich.

4.2. (*S*)-1-chloropent-4-en-2-ol (**8**).

A mixture of (*S*)-BINOL (62 mg, 0.22 mmol) and 4Å MS (100 mg) in 5 mL anhydrous CH_2Cl_2 was added $Ti(O^iPr)_4$ (60 μL, 0.2 mmol). The reaction was heated at 40 ^{o}C under argon atmosphere for 1 h before cooled to room temperature and a solution of chloroacetaldehyde (1.0 mmol) in 5 mL CH_2Cl_2 was added. The contents were cooled to –20 ^{o}C and allyltributylstannane (0.62 mL, 2.0 mmol) was added. The reaction was stirred at –20 ^{o}C for 96 h before being added saturated $NaHCO_3$ (2 mL) and stirred at room temperature for 2 h. The molecular sieves were removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (20 mm Hg), then purified by column chromatography (silica gel, EtOAc/PE, 1: 15) to afford **8** (80 mg, 67%) as a pale yellow oil and recovered (*S*)-BINOL (51 mg, 83%); $[\alpha]_D^{21.1}$ +4.6 (*c* 2.0, $CHCl_3$, 94% *ee*); Lit.[10]: $[\alpha]_D^{25}$ +5.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (m, 3H), 3.48-3.52 (m, 1H), 3.60-3.63 (m, 1H), 3.87 (m, 1H), 5.13-5.19 (m, 2H), 5.76-5.86 (m, 1H); MS (EI): *m/z* (%) = 120 (1), 79 (100); IR (thin film): 3379, 2951, 1645, 991 cm^{-1}.

4.3. (*S*)-1-chloropent-4-en-2-yl benzoate (**9**).

To a stirred solution of **8** (60 mg, 0.5 mmol) and pyridine (81 μL, 1.0 mmol) in 2 mL anhydrous CH_2Cl_2 under argon atmosphere at 0 ^{o}C was added benzoyl chloride (70 μL, 0.6 mmol). The reaction mixture was stirred at room temperature for 3 h before being quenched by the addition of 10 mL brine. The mixture was extracted with 30 mL EtOAc, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, then purified by column chromatography (silica gel, PE) to afford **9** (106 mg, 95%) as a colorless oil; *ee*: 94%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), *n*-hexane/ *i*-propanol = 98/2, 0.3 mL/min, 254 nm, 30 ^{o}C, *t* (major) = 16.9 min, *t* (minor) = 17.6 min; $[\alpha]_D^{21.3}$ -2.0 (*c* 2.0, $CHCl_3$, 94% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (t, *J* = 6.6 Hz, 2H), 3.73 (dd, *J* = 5.2, 12.0 Hz, 1H), 3.77 (dd, *J* = 4.8, 12.0 Hz, 1H), 5.16 (dd, *J* = 1.2, 10.0 Hz, 1H), 5.22 (dd, *J* = 1.2, 16.8 Hz, 1H), 5.30-5.36 (m, 1H), 5.77-5.87 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 45.0, 72.5, 119.1, 128.4, 129.7, 129.9, 132.1, 133.2, 165.7; MS (EI): *m/z* (%) = 224 (1), 105 (100); HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{14}ClO_2$ ($M + H^+$) 225.0677, found 225.0679; IR (thin film): 2926, 1723, 1271, 992, 706 cm^{-1}.

4.4. (2*S*)-1-chloro-3-(oxiran-2-yl)propan-2-ol (**7**).

A mixture of **8** (240 mg, 2.0 mmol), $VO(acac)_2$ (26 mg, 0.1 mmol) and 3Å MS (100 mg) in 20 mL anhydrous CH_2Cl_2 was added TBHP (0.9 mL, 3.3 M in toluene)[13] under argon atmosphere at 0 ^{o}C. The reaction was stirred at 20 ^{o}C for 60 h before being quenched by the addition of 10 mL saturated sodium sulfite. The molecular sieves were removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:4) to afford **7**[14] (colorless oil, 207 mg, 76%) as an inseparable 3:1 mixture of epimers. *syn*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (ddd, *J* = 6.8, 14.0, 21.6 Hz, 1H), 1.87 (dt, *J* = 4.4, 14.0 Hz, 1H), 2.46 (dd, *J* = 2.8, 4.4 Hz, 1H), 2.71 (t, *J* = 4.4 Hz, 1H), 3.02 (m, 1H), 3.34 (br s, 1H), 3.49-3.57 (m, 2H), 3.96 (m, 1H); *anti*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (ddd, *J* = 4.0, 7.6, 14.4 Hz, 1H), 1.95 (dt, *J* = 4.4, 14.0 Hz, 1H), 2.49 (dd, *J* = 2.8, 4.4 Hz, 1H), 2.75 (t, *J* = 4.4 Hz, 1H), 3.06 (m, 1H), 3.34 (br s, 1H), 3.40-3.57 (m, 2H), 3.93-3.95 (m, 1H); MS (EI): *m/z* (%) = 135 (1), 57 (100); IR (thin film): 3396, 2955, 1719, 1641cm^{-1}.

4.5. (5*S*)-6-chloro-3,5-dihydroxyhexanenitrile (**6** and 3-*epi*-**6**).

To a stirred solution of **7** (6.8 g, 50 mmol) in 10 mL water at 0 ^{o}C was added dropwise a solution of sodium cyanide (2.94 g, 60 mmol) in 15 mL water maintained pH = 7.5-8.0 by saturated citric acid. The reaction was stirred at 30 ^{o}C for 42 h and the aqueous layer was extracted with EtOAc (5 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:1) to afford **6** (4.64 g, 57%) as a pale yellow oil and 3-*epi*-**6** (1.38 g, 17%) as a white solid. **6**: $[\alpha]_D^{28.1}$ +3.4 (*c* 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73-1.83 (m, 2H), 2.55 (dd, *J* = 6.0, 16.8 Hz, 1H), 2.62 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.50 (dd, *J* = 6.0, 11.2 Hz, 1H), 3.56 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.98 (br s, 1H), 4.06 (m, 1H), 4.17 (m, 1H), 4.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 38.9, 49.1, 66.6, 70.6, 117.7; MS (EI): *m/z* (%) = 163 (1), 68 (100); HRMS (ESI-TOF) *m/z* calcd for $C_6H_9{}^{35}ClNO_2$ ($M - H^-$) 162.0316, found 162.0312; IR (thin film): 3400, 2256, 1723, 1641, 974 cm^{-1}. 3-*epi*-**6**: mp 46-48 ^{o}C; $[\alpha]_D^{28.4}$ -30.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43-1.50 (m, 1H), 1.57-1.66 (m, 1H), 2.56 (dd, *J* = 6.0, 16.8 Hz, 1H), 2.65 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.51 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.56 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.80-3.87 (m, 1H), 3.89-3.96 (m, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 5.27 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 40.8, 50.3, 63.2, 66.8, 119.1; MS (EI): *m/z* (%) = 163 (1), 68 (100); HRMS (ESI-TOF) *m/z* calcd for $C_6H_9{}^{35}ClNO_2$ ($M - H^-$) 162.0316, found 162.0310; IR (thin film): 3392, 2955, 2252, 1413, 930 cm^{-1}.

4.6. methyl 2-((6*S*)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan -4-yl) acetate (**12** and 4-*epi*-**12**).

To a stirred solution of **6** (3.3 g, 20 mmol) in 40 mL dry methanol saturated with hydrogen chloride under argon atmosphere was reacted at 0 ^{o}C for 36 h before being quenched by saturated $NaHCO_3$ solution. The methanol was evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced

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pressure to afford a mixture of **10** and **11** that was pure enough to be used in next step. To a stirred solution of a mixture of **10** and **11** and 2,2-dimethoxypropane (12 mL, 100 mmol) in 50 mL acetone under argon atmosphere at room temperature was added 4-methylbenzenesulfonic acid monohydrate (380 mg, 2.0 mmol). The mixture was stirred at room temperature for 16 h before being quenched by the addition of 0.3 mL triethylamine and removed solvent under reduced pressure. the residue was purified by column chromatography (silica gel, EtOAc/PE, 1:8) to afford **12** (pale yellow oil, 75% from **6**); diastereomeric excess: 99%, t_R = 14.2 min, the *de* value was measured by GC-MS: Agilent, HP-5MS column (30 m × 0.25 mm × 0.25 μm), injector temperature: 280 °C, oven temperature program from 50 °C (2 min) to 280 °C at 10 °C/min, carrier gas: He, flow rate: 0.9 mL/min, ionization energy 70 eV in the electronic ionization (EI) mode; $[\alpha]_D^{28.3}$ +3.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (dt, *J* = 11.6, 12.8 Hz, 1H), 1.35 (s, 3H), 1.43 (s, 3H), 1.75 (dt, *J* = 2.4, 12.8 Hz, 1H), 2.38 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.54 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.36 (dd, *J* = 6.0, 11.2 Hz, 1H), 3.48 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.65 (s, 3H), 4.01-4.07 (m, 1H), 4.27-4.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 29.7, 33.8, 40.9, 46.9, 51.6, 65.5, 69.0, 99.2, 171.0; MS (EI): *m/z* (%) = 221 (100), 59 (90); IR (thin film): 2994, 1737, 988, 950 cm^{-1}.

4-*epi*-**12** was prepared by the similar procedure of **12**: (pale yellow oil, 73% from 3-*epi*-**6**); 99% *de*, t_R = 13.6 min; $[\alpha]_D^{22.4}$ -23.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.37 (s, 3H), 1.71 (ddd, *J* = 6.4, 9.6, 12.8 Hz, 1H), 1.80 (ddd, *J* = 6.0, 9.2, 12.8 Hz, 1H), 2.45 (dd, *J* = 5.2, 15.6 Hz, 1H), 2.55 (dd, *J* = 8.4, 15.6 Hz, 1H), 3.46-3.54 (m, 2H), 3.67 (s, 3H), 3.98-4.05 (m, 1H), 4.24-4.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.6, 35.3, 40.3, 46.7, 51.6, 63.3, 66.8, 101.1, 171.1; MS (EI): *m/z* (%) = 221 (100), 59 (80); HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{17}ClNaO_4$ (M + Na^+) 259.0707, found 259.0701; IR (thin film): 2990, 2955, 1740, 1440, 999 cm^{-1}.

4.7. General procedure for synthesis of **13**.

To a stirred solution of **12** (710 mg, 3 mmol), potassium acetate or sodium benzoate (15 mmol) and TBAB (966 mg, 3 mmol) in 20 mL DMF under argon atmosphere was heated to 100 °C for 24 h before added 150 mL petroleum ether. The organic phase was washed with water (3 × 20 mL) and brine (3 × 20 mL), then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:15) to afford **13**. **13a**[6c]: (white solid, 453 mg, 58%), mp 48-49 °C (*n*-heptane), Lit.[6c] mp 49-50 °C; The *ee* value of **13a** was upgraded to over 99% by recrystallization using *n*-heptane (recovered yield: 85%) and determined by HPLC analysis of its derivant **13b**, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), *n*-hexane/*i*-propanol = 90/10, 0.3 mL/min, 254 nm, 30 °C, *t* (major) = 21.0 min, *t* (minor) = 26.5 min; $[\alpha]_D^{12.2}$ +16.2 (*c* 1.0, $CHCl_3$, 99% *ee*), Lit.[6c] $[\alpha]_D$ +12 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19-1.28 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.57 (dt, *J* = 2.0, 12.4 Hz, lH), 2.05 (s, 3H), 2.38 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.54 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.66 (s, 3H), 3.96-4.05 (m, 2H), 4.06-4.11 (m, 1H), 4.28-4.34 (m, 1H); MS (EI): *m/z* (%) = 245 (70), 59 (100); IR (KBr): 3002, 2959, 1736, 1719, 1460, 941 cm^{-1}. **13b**[7e]: (white solid, 492 mg, 51%), mp 80–81 °C (*n*-heptane); The *ee* value of **13b** was upgraded from 95% to over 99% by recrystallization using *n*-heptane (recovered yield: 88%) and determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm), *n*-hexane/*i*-propanol = 90/10, 0.3 mL/min, 254 nm, 30 °C, *t* (major) = 21.0 min, *t* (minor) = 26.5 min; $[\alpha]_D^{12.8}$ +5.7 (*c* 1.0, $CHCl_3$, 99% *ee*), Lit.[7e] $[\alpha]_D^{20}$ +2.4 (*c* 0.9, $CHCl_3$, 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.40 (m, 1H), 1.40 (s, 3H), 1.48 (s, 3H), 1.68 (dt, *J* = 2.0, 12.4 Hz, lH), 2.42 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.58 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.68 (s, 3H), 4.25-4.31 (m, 1H), 4.28 (s, 2H), 4.33-4.40 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H); MS (EI): *m/z* (%) = 307 (30), 105 (100); IR (KBr): 2980, 1730, 1712, 991, 945 cm^{-1}.

4.8. methyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**14**).

To a stirred solution of **13** (2 mmol) in 5 mL methanol and 2 mL water at 0 °C was added potassium carbonate (690 mg, 5 mmol). The reaction mixture was stirred at room temperature for 2 h before being quenched by the addition of NH_4Cl. The methanol was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:2) to afford **14** as colorless oil (yields: 85% from **13a**, 83% from **13b**); $[\alpha]_D^{15.2}$ +9.9 (*c* 2.0, $CHCl_3$), Lit.[6c] $[\alpha]_D$ +9.7 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-1.34 (m, 1H), 1.37 (s, 3H), 1.46 (s, 3H), 1.50 (dt, *J* = 2.4, 12.4 Hz, lH), 2.19 (br s, 1H), 2.38 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.55 (dd, *J* = 7.2, 15.6 Hz, 1H), 3.45-3.50 (m, 1H), 3.55-3.62 (m, 1H), 3.67 (s, 3H), 3.98-4.02 (m, 1H), 4.30-4.36 (m, 1H); MS (EI): *m/z* (%) = 217 (1), 59 (100); IR (thin film): 3460, 2994, 1737, 1084, 992 cm^{-1}.

4.9. methyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl) acetate **(4)**.

To a stirred solution of **14** (654 mg, 3 mmol), TEMPO (5 mg, 0.03 mmol) and $NaHCO_3$ (2.0 g, 24 mmol) in 15 mL CH_2Cl_2 and 15 mL water at 0 °C was added TCCA (852 mg, 90% purity, 3.3 mmol) in batches. The reaction mixture was stirred at 0 °C for 1 h before being extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **4** as a pale yellow oil (473 mg, 73%) that was pure enough to be used in next step; $[\alpha]_D^{13.3}$ -15.9 (*c* 1.0, $CHCl_3$), Lit.[7b] $[\alpha]_D$ -14.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29-1.39 (m, 1H), 1.44 (s, 3H), 1.48 (s, 3H), 1.84 (dt, *J* = 2.4, 12.8 Hz, lH), 2.42 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.57 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.68 (s, 3H), 4.28-4.38 (m, 2H), 9.57 (s, 1H); MS (EI): *m/z* (%) = 201 (30), 59 (100); IR (thin film): 2994, 2952, 1736, 1440, 999 cm^{-1}.

4.10. methyl 2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isoprop -yl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**15**).

To a stirred solution of **4** (298 mg, 1.38 mmol), **5** (849 mg, 1.25 mmol) and potassium carbonate (173 mg, 1.25 mmol) in 10 mL anhydrous DMSO under argon atmosphere was heated to 70 °C for 3 h before added 100 mL EtOAc. The organic phase was washed with water (3 × 20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:12) to afford **15** (482 mg, 72%) as a white solid; mp 122–124 °C, Lit.[15]: mp 130–132 °C; $[\alpha]_D^{12.3}$ +5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.21 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 1.53-1.58 (m, 1H), 2.38 (dd, *J* = 6.4, 16.0 Hz, 1 H), 2.57 (dd, *J* = 6.4, 16.0 Hz, 1 H), 3.37 (hept, *J* = 6.8 Hz,1H), 3.51 (s, 3H), 3.57 (s, 3H), 3.70 (s, 3H), 4.29-4.36 (m, 1H), 4.41-4.45 (m, 1H), 5.46 (dd, *J* = 5.6, 16.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 5.2, 8.0 Hz, 2H); MS (ESI): *m/z* = 536 (M + H^+), 558 (M + Na^+); IR (KBr): 2996, 2951, 1739, 1600, 1442, 1152, 968, 848 cm^{-1}.

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4.11. (3*R*,5*S*,*E*)-methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate (**16**).

To a stirred solution of **15** (268 mg, 0.5 mmol) in 5 mL acetonitrile at 40 ^{o}C was added hydrochloric acid (1.25 mL, 0.02 M, 0.025 mmol) dropwise. The reaction mixture was stirred at 40 ^{o}C for 8 h before being quenched by Et_3N and removed solvent under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:1) to afford **16**[16] (205 mg, 83%) as a colorless spumy solid; $[\alpha]_D^{13.5}$ -4.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.8 Hz, 6H), 1.35-1.60 (m, 2H), 2.43-2.51 (m, 2H), 3.36 (hept, *J* = 6.8 Hz,1H), 3.51 (s, 3H), 3.56 (s, 3H), 3.72 (s, 3H), 4.21 (m, 1H), 4.45 (m, 1H), 5.46 (dd, *J* = 5.2, 16.0 Hz, 1 H), 6.63 (d, *J* = 16.0 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 6.0, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.6, 32.1, 33.1, 41.1, 41.8, 42.4, 51.9, 68.4, 71.9, 115.0 (d, $J_{C\text{-}F}$ = 21.5 Hz), 121.4, 122.7, 132.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 134.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 139.3, 157.2, 163.2 (d, $J_{C\text{-}F}$ = 248.2 Hz), 163.5, 172.9, 174.9; MS (ESI): *m/z* = 496 (M + H^+), 518 (M + Na^+); IR (KBr): 3462, 2966, 2931, 2871, 1732, 1548, 1438, 1386, 1152, 964, 840, 795 cm^{-1}.

4.12. Rosuvastatin calcium (**1**).

To a stirred solution of **16** (149 mg, 0.3 mmol) in MeOH (2 mL) at 0 ^{o}C was added NaOH (0.36 mL, 1.0 M, 0.36 mmol), then reacted at 0 ^{o}C for 1 h before being added the solution of $CaCl_2$ (1.5 mL, 0.2 M, 0.3 mmol). The mixture was stirred at 20 ^{o}C for 0.5 h before filtrated the resulting white slurry, washed and dried in vacuum to afford **1** (133 mg, 89%) as a white powder; mp 145-149 ^{o}C, Lit.[17]: mp 145-150 ^{o}C; $[\alpha]_D^{14.5}$ -7.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.0 Hz, 6H), 1.28-1.36 (m, 1H), 1.47-1.54 (m, 1H), 1.97-2.03 (m, 1H), 2.12-2.16 (m, 1H), 3.36-3.43 (m, 1H), 3.43 (s, 3H) 3.54 (s, 3H), 3.76 (m, 1H), 4.20 (m, 1H), 5.52 (dd, *J* = 5.6, 16.0 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 6.0, 8.0 Hz, 2H); MS (ESI): *m/z* = 482 (acid, M + H^+), 504 (acid, M + Na^+); IR (KBr): 3376, 2973, 2931, 2875, 1604, 1548, 1442, 1073, 968, 844, 776 cm^{-1}.

Supplementary data

Copies of ^{1}H, ^{13}C NMR, HPLC and GC-MS spectra for the compounds. Supplementary data related to this article can be found at ……

References and Notes

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Synthetic Studies on Statins. Part 3. A Facile Synthesis of Rosuvastatin Calcium Through Catalytic Enantioselective Allylation Strategy

Xiaofei Chen,[a,b] Fangjun Xiong,[a] Chen Zheng,[a] Jie Li,[a] Fener Chen[*a, b]

a Department of Chemistry, Fudan University, Shanghai 200433, People's Republic of China

b Institutes of Biomedical Science, Fudan University, Shanghai 200433, People's Republic of China

Fax: (+86)-21-65643811

E-mail: rfchen@fudan.edu.cn

Supporting Information

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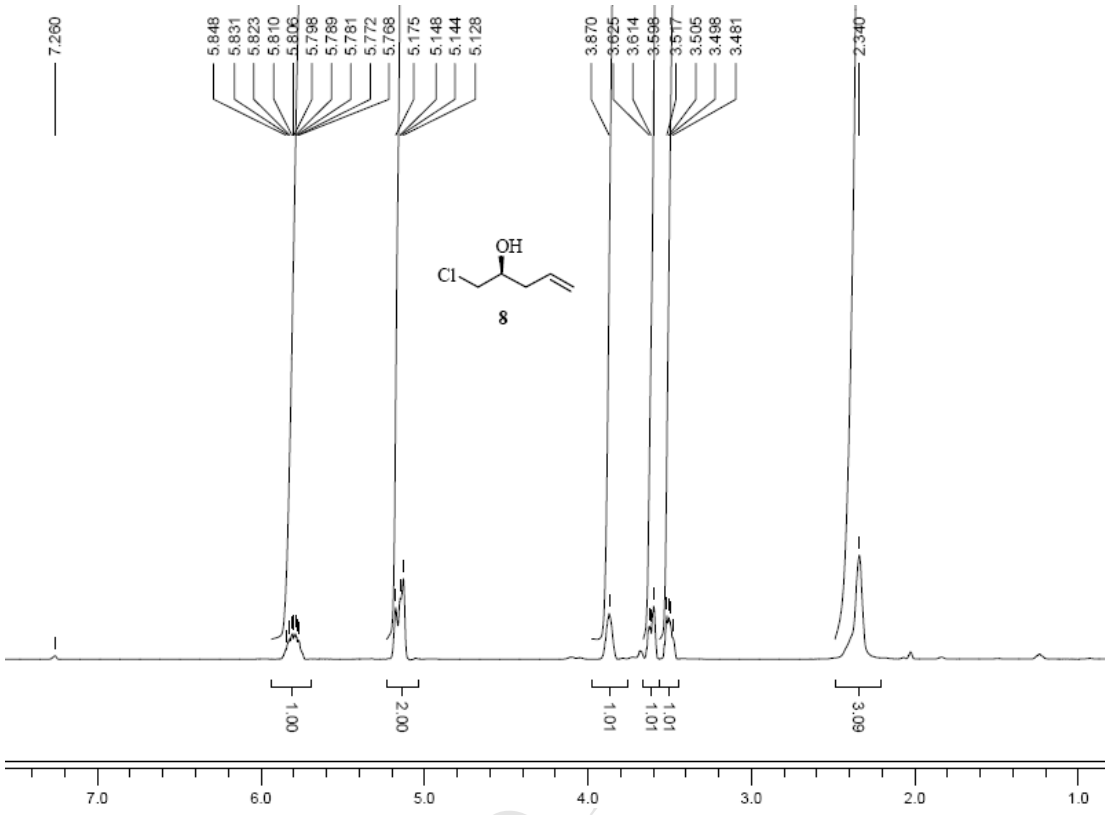
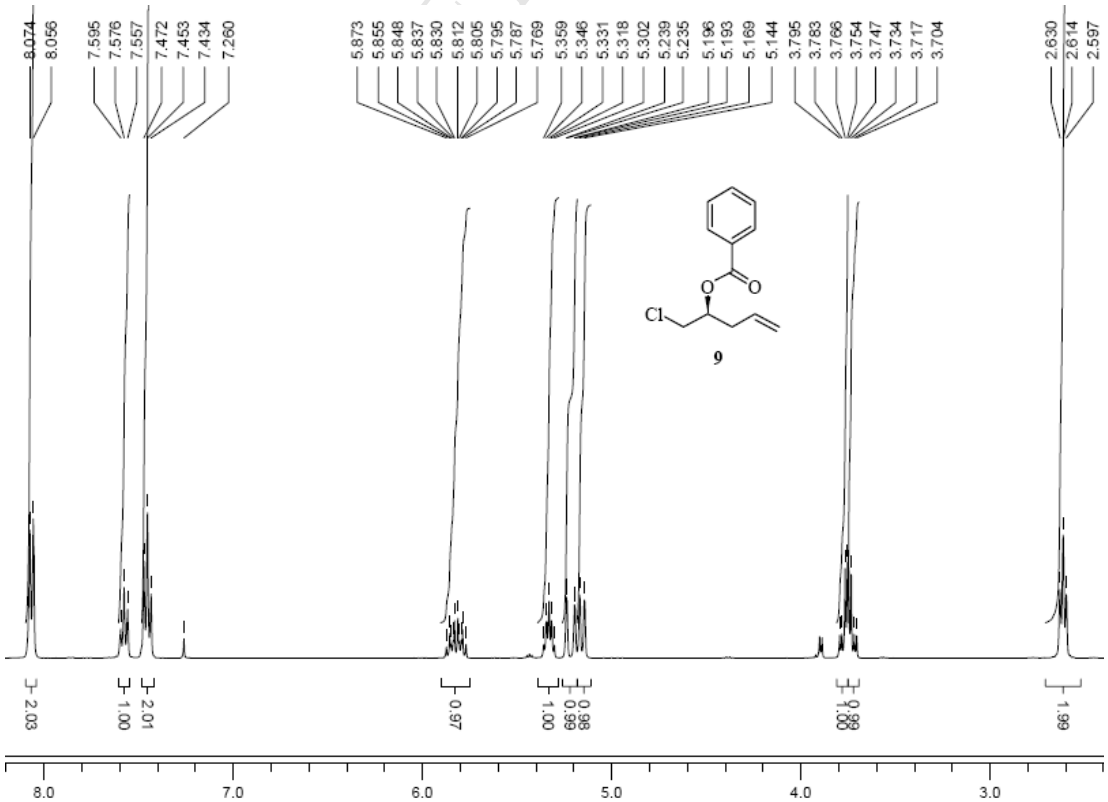
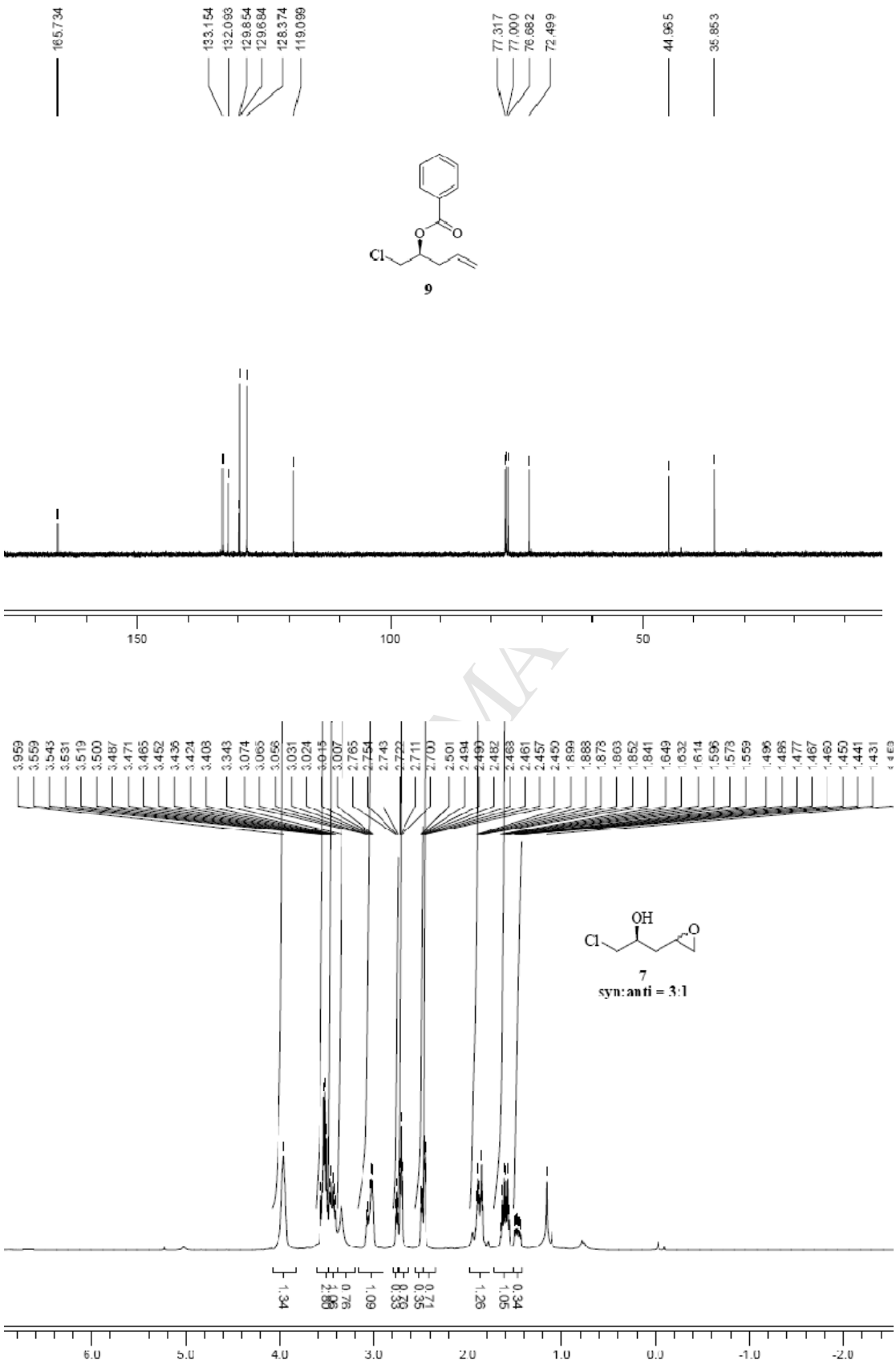
Copies of ^{1}H NMR, ^{13}C NMR and NOESY spectra



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35.853
Cl
O
O
9
150
100
50
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3.559
3.543
3.531
3.519
3.500
3.487
3.471
3.465
3.452
3.436
3.424
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3.066
3.056
3.031
3.024
3.015
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2.700
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2.490
2.482
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2.461
2.457
2.450
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1.873
1.863
1.852
1.841
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1.632
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1.573
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1.477
1.467
1.460
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1.441
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Cl
O
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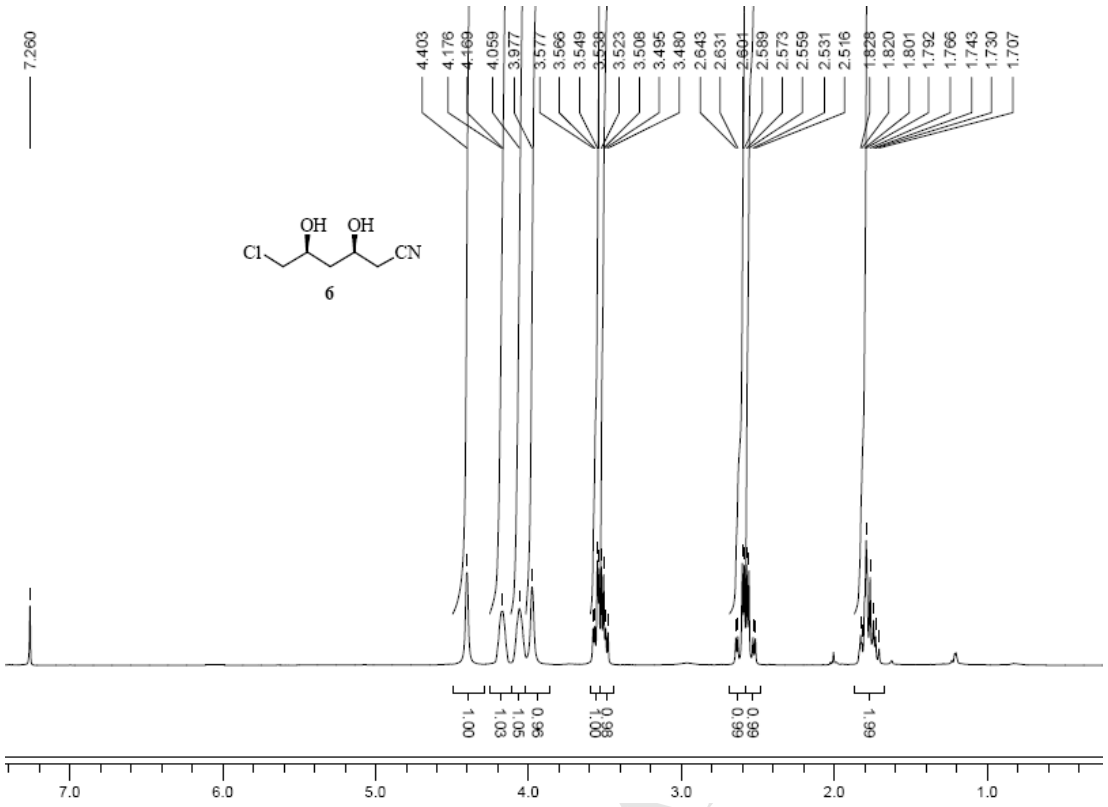
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2.531
2.516
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1.820
1.801
1.792
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1.743
1.730
1.707
OH OH
Cl CN
6
1.00
1.03
1.05
0.96
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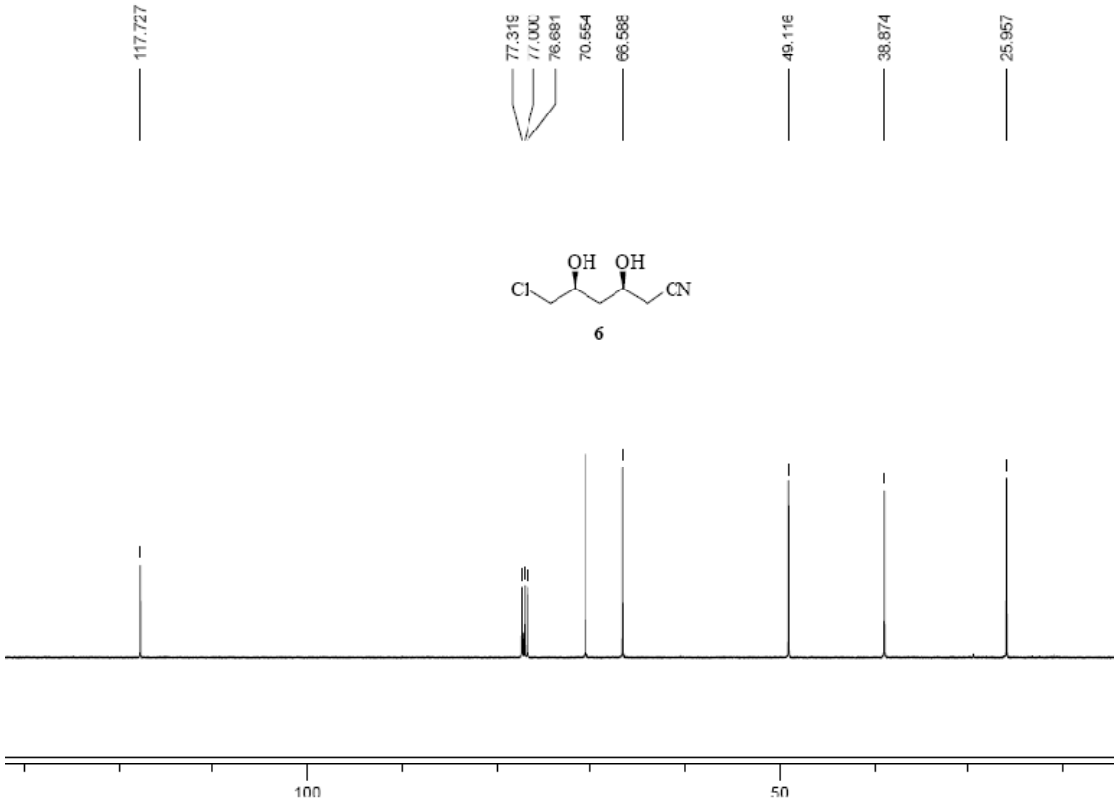
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Cl CN
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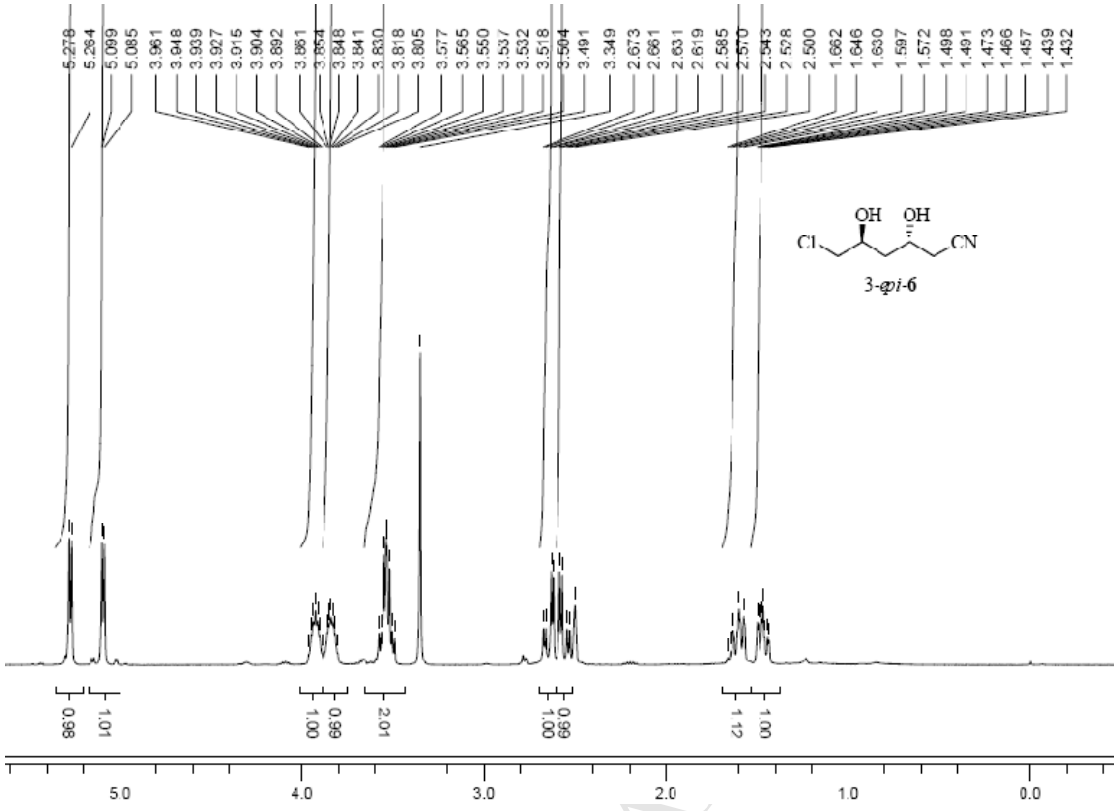
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3.830
3.818
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3.518
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2.585
2.570
2.543
2.528
2.500
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1.473
1.466
1.457
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1.432
OH
OH
Cl
CN
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1.00
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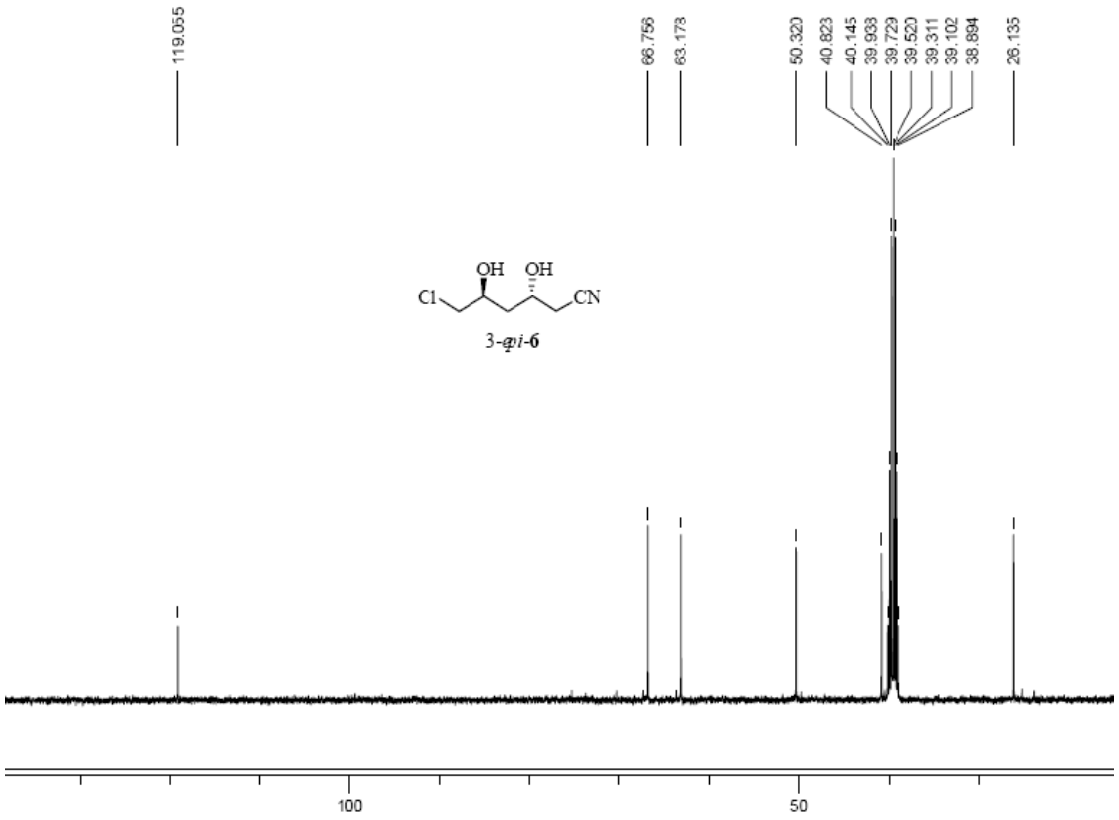
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OH
Cl
CN
3-epi-6
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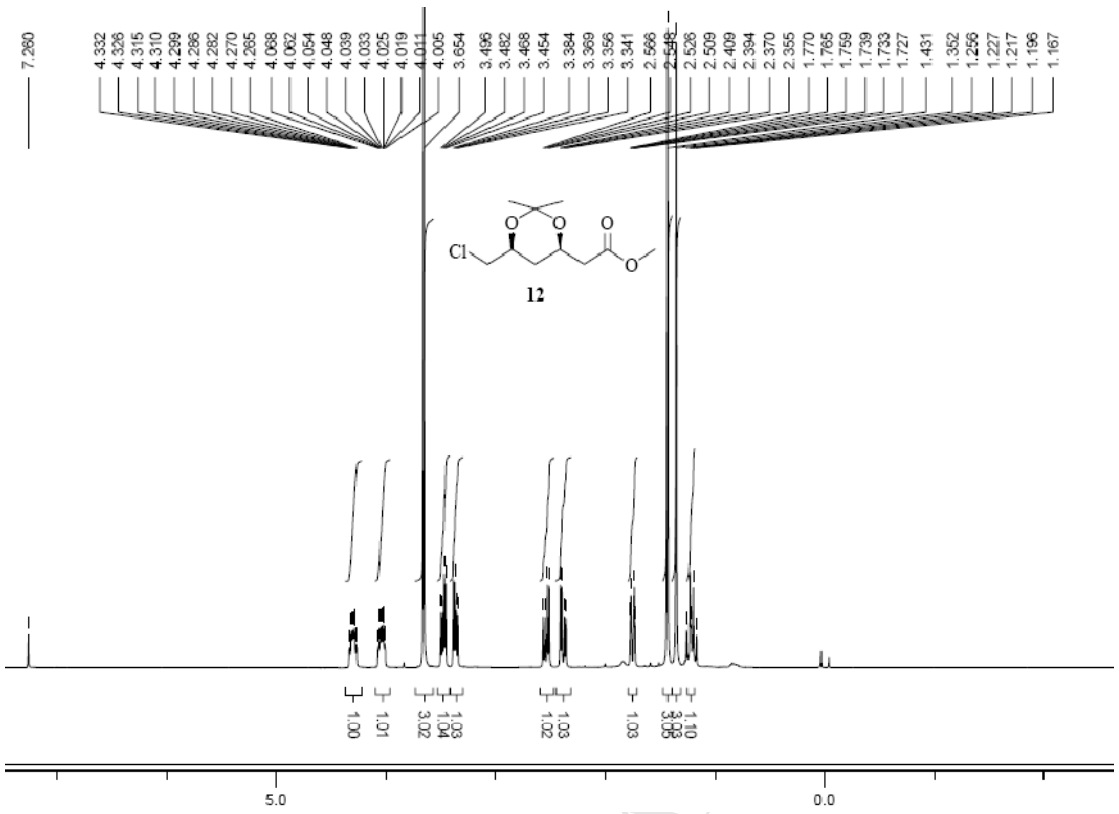
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4.068
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4.054
4.048
4.039
4.033
4.025
4.019
4.011
4.005
3.654
3.496
3.482
3.468
3.454
3.384
3.369
3.356
3.341
2.566
2.548
2.526
2.509
2.409
2.394
2.370
2.355
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1.759
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1.733
1.727
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1.217
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O
O
O
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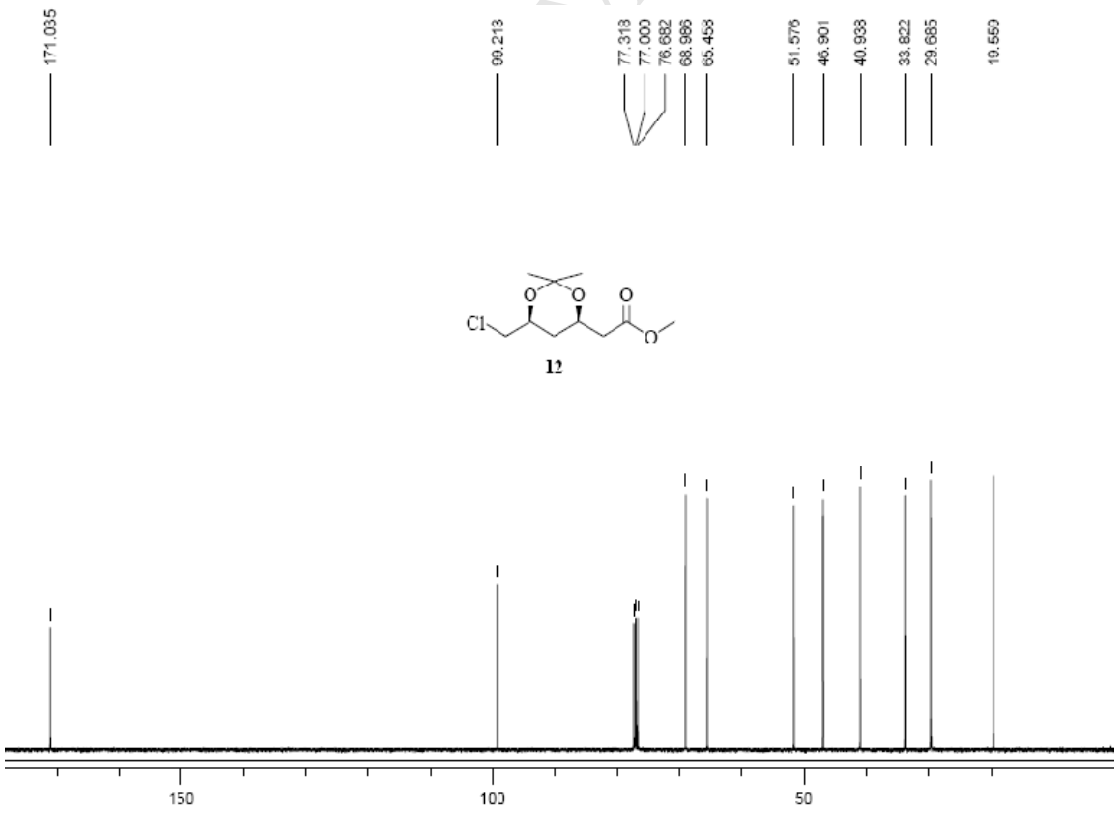
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29.685
19.559
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O
O
O
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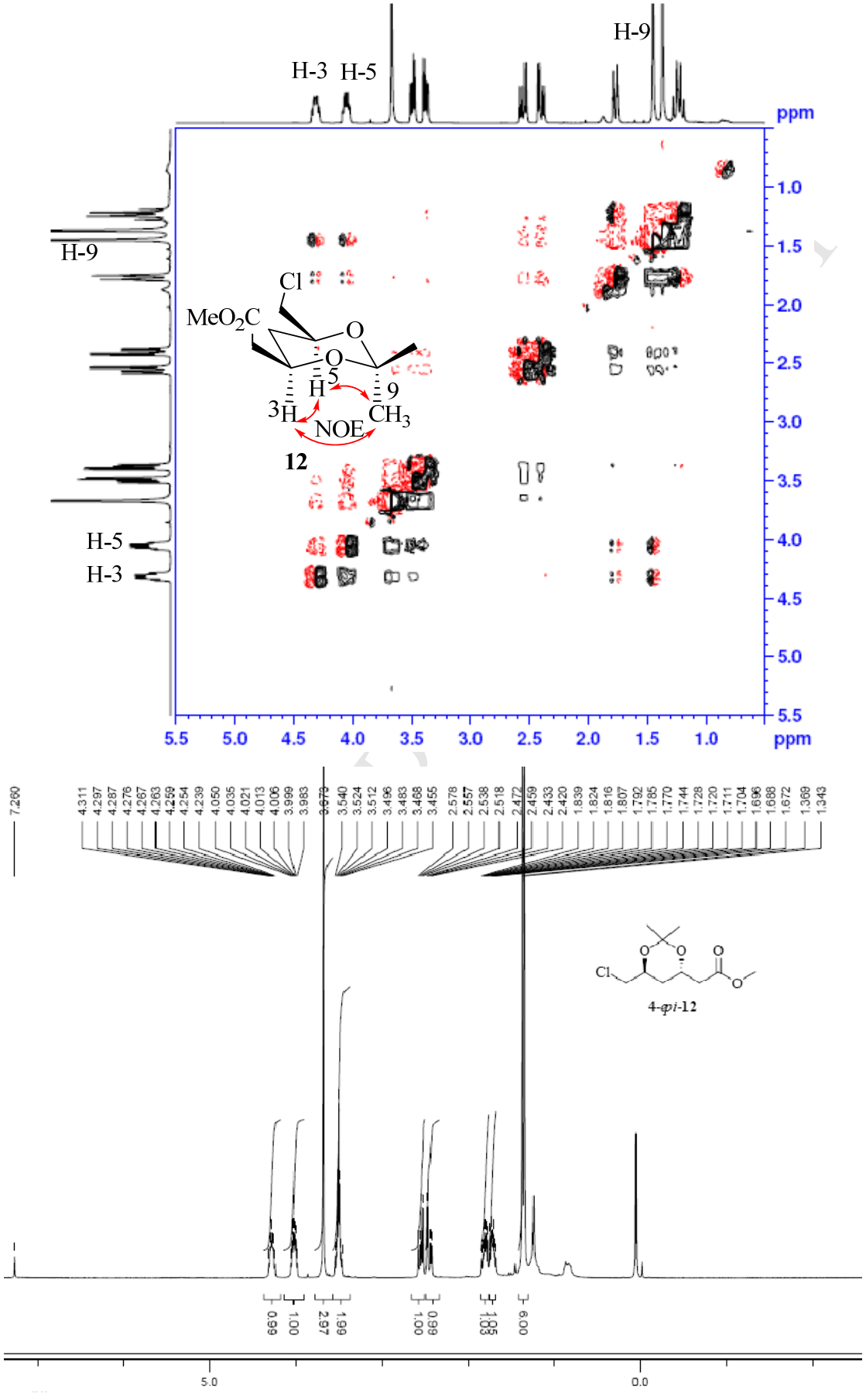
100
50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H-5
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H-9
Cl
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O
H
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9
3H
CH3
NOE
12
H-5
H-3
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
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4.263
4.259
4.254
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4.050
4.035
4.021
4.013
4.006
3.999
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2.433
2.420
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1.824
1.816
1.807
1.792
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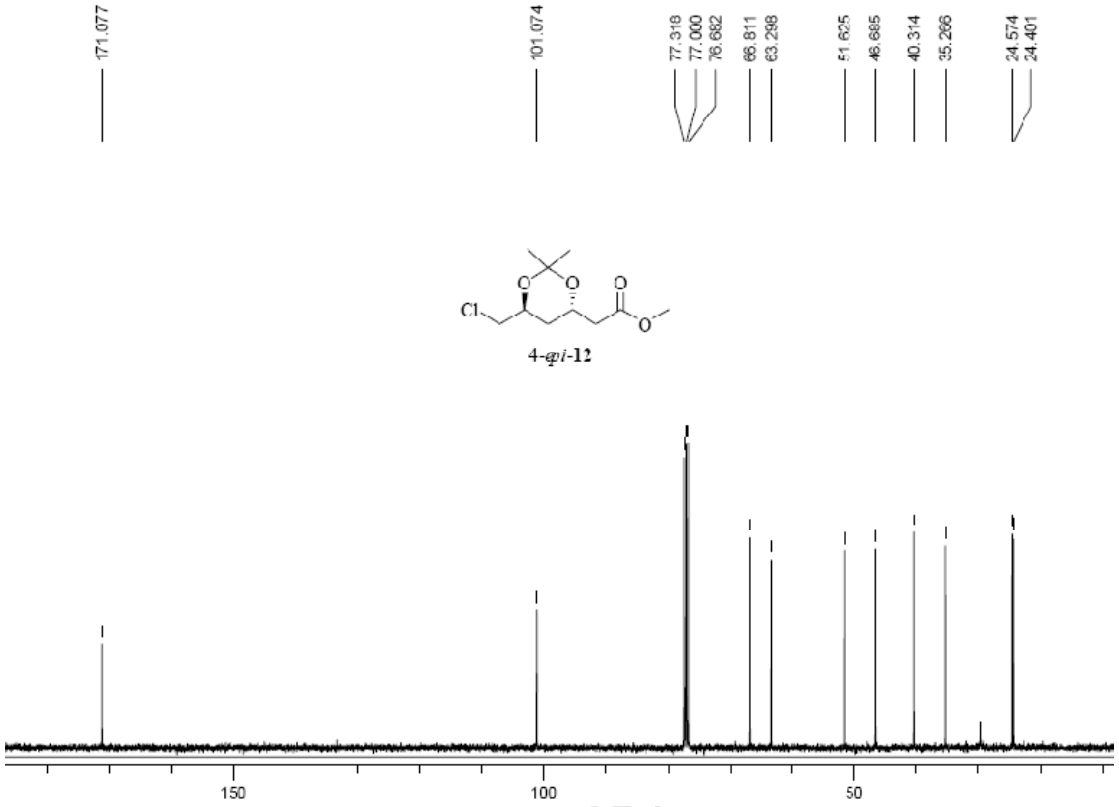
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O
O
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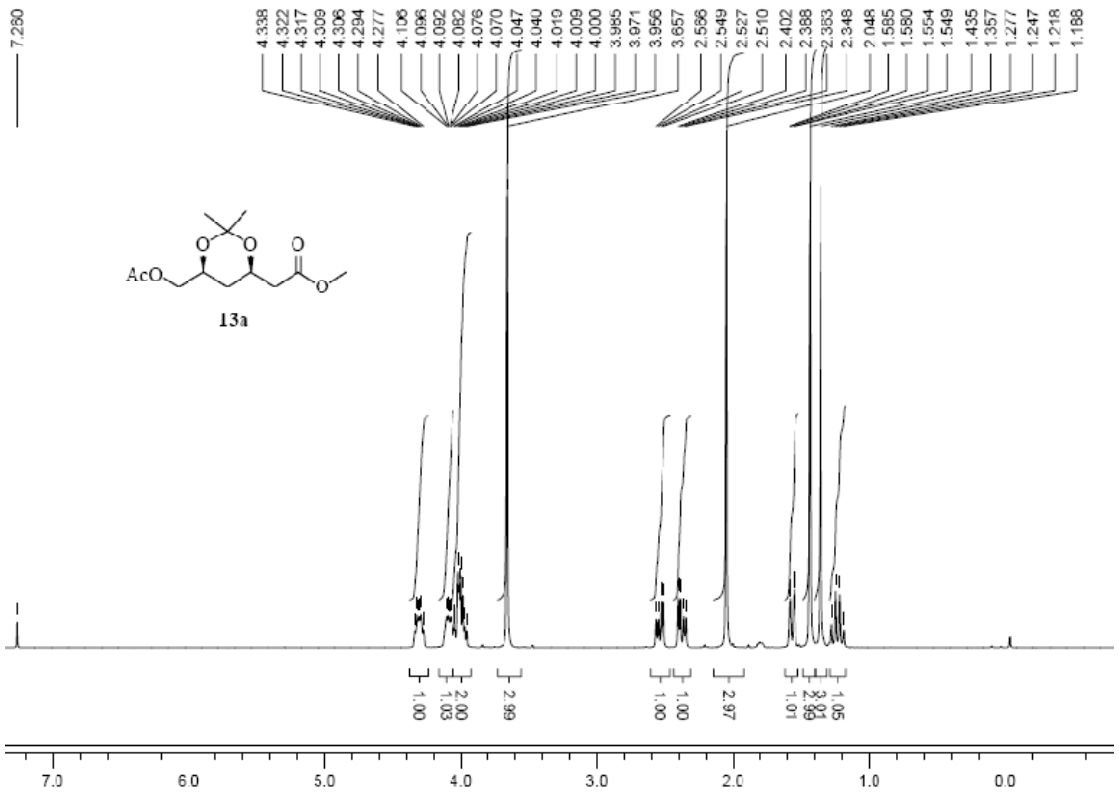
100
50

4-*epi*-**12**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4.076
4.070
4.047
4.040
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4.009
4.000
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3.971
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3.657
2.596
2.549
2.527
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2.402
2.388
2.353
2.348
2.048
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1.580
1.554
1.549
1.435
1.357
1.277
1.247
1.218
1.188
AcO
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O
O
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2.00
2.99
1.00
1.00
2.97
1.07
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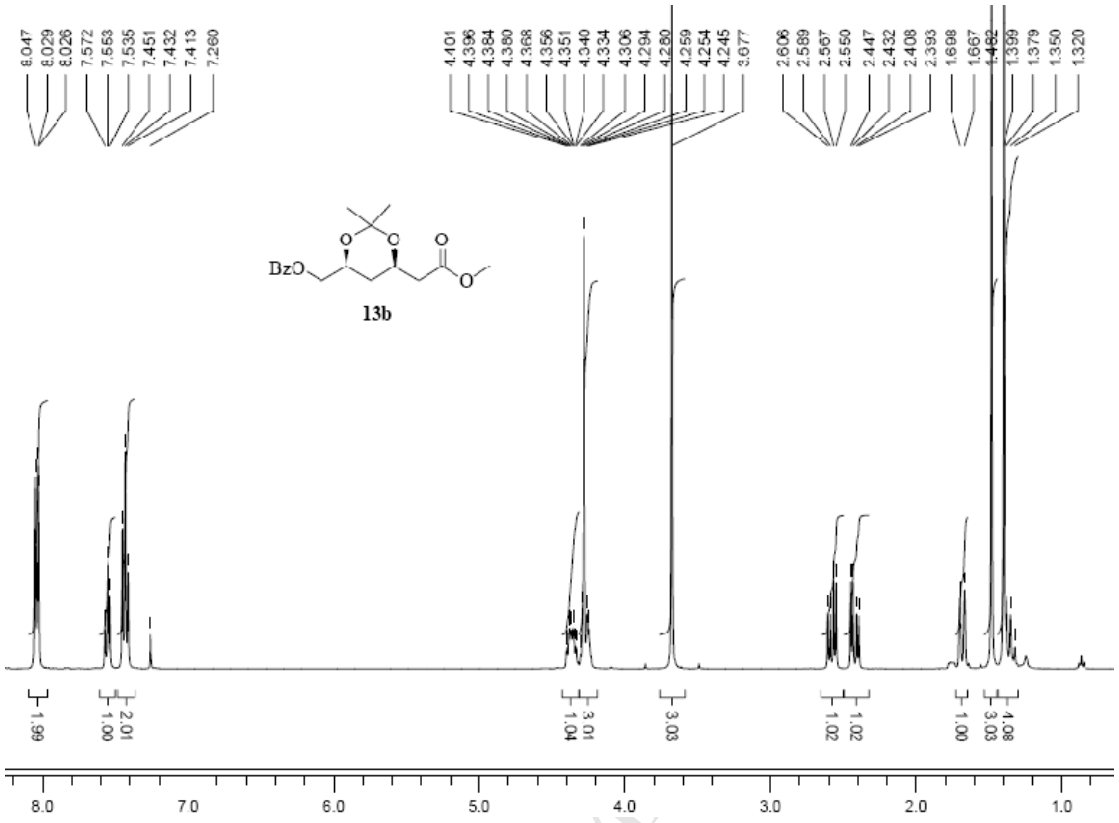
13a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4.356
4.351
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4.245
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2.567
2.550
2.447
2.432
2.408
2.393
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1.667
1.482
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1.379
1.350
1.320
BzO
O
O
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13b
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1.00
1.01
1.04
3.03
1.02
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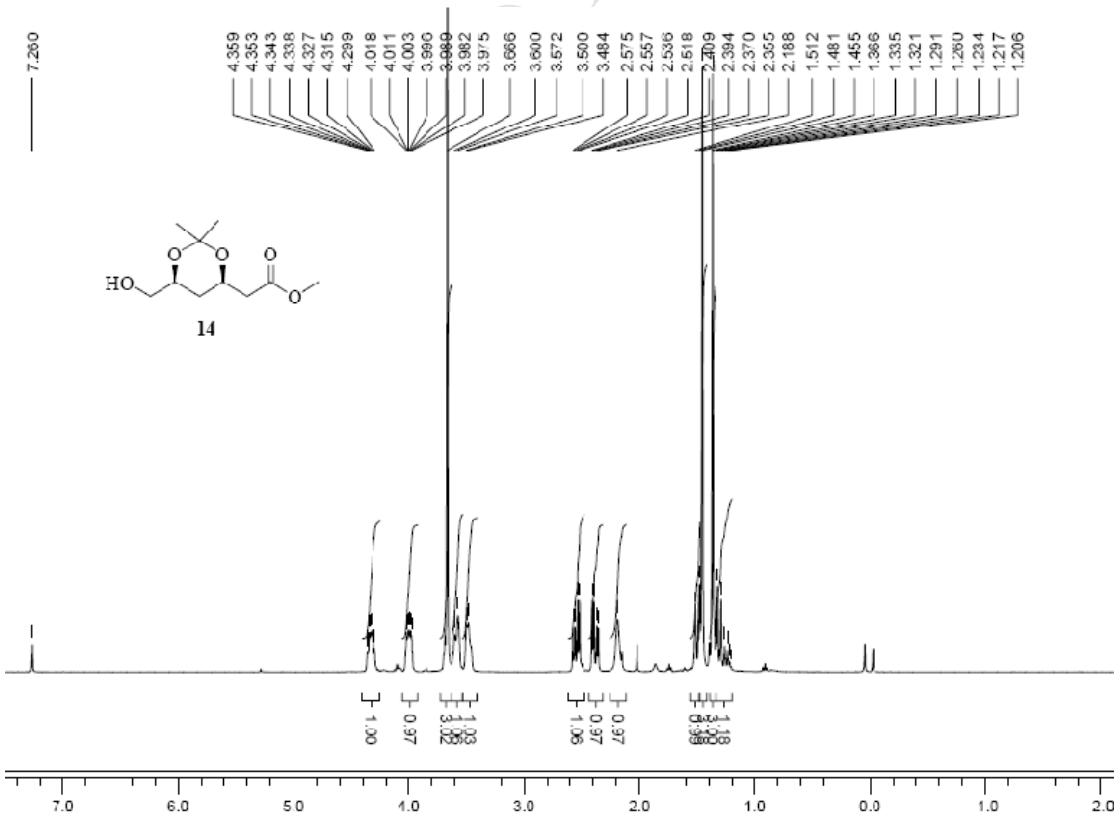
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2.557
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2.518
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2.370
2.355
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1.206
HO
O
O
O
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0.97
3.02
1.03
1.06
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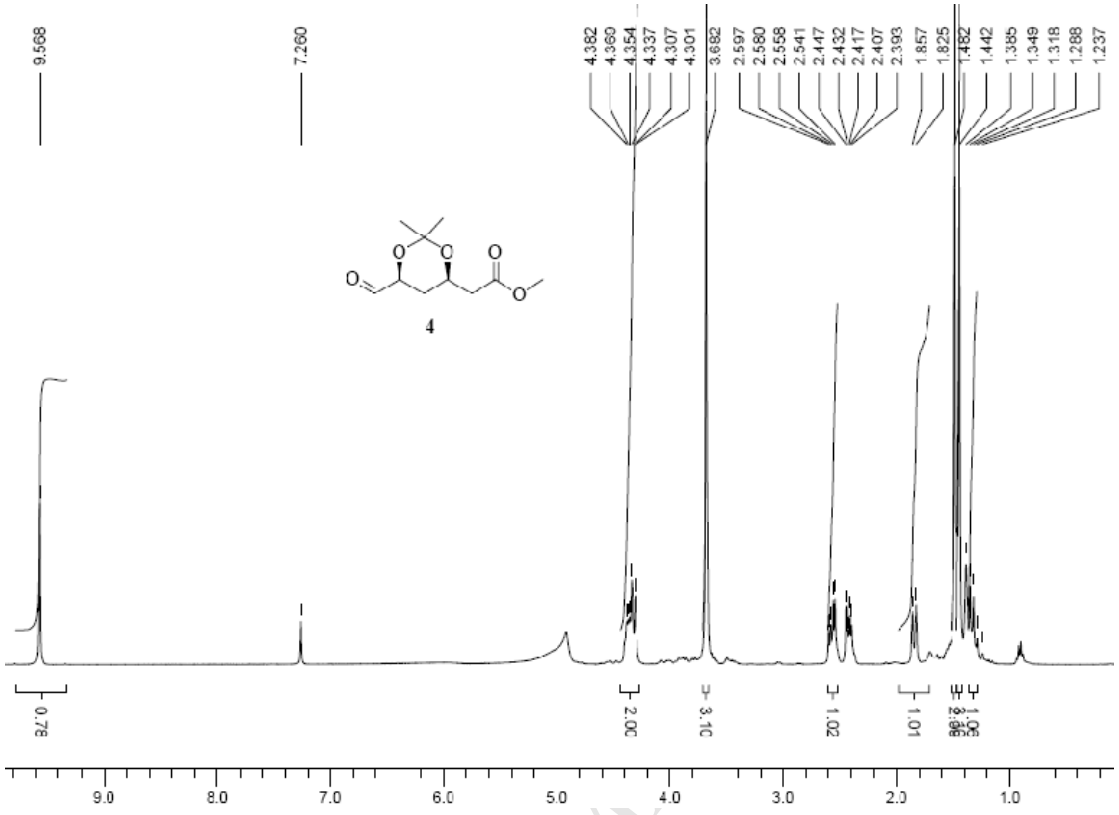
2.0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2.432
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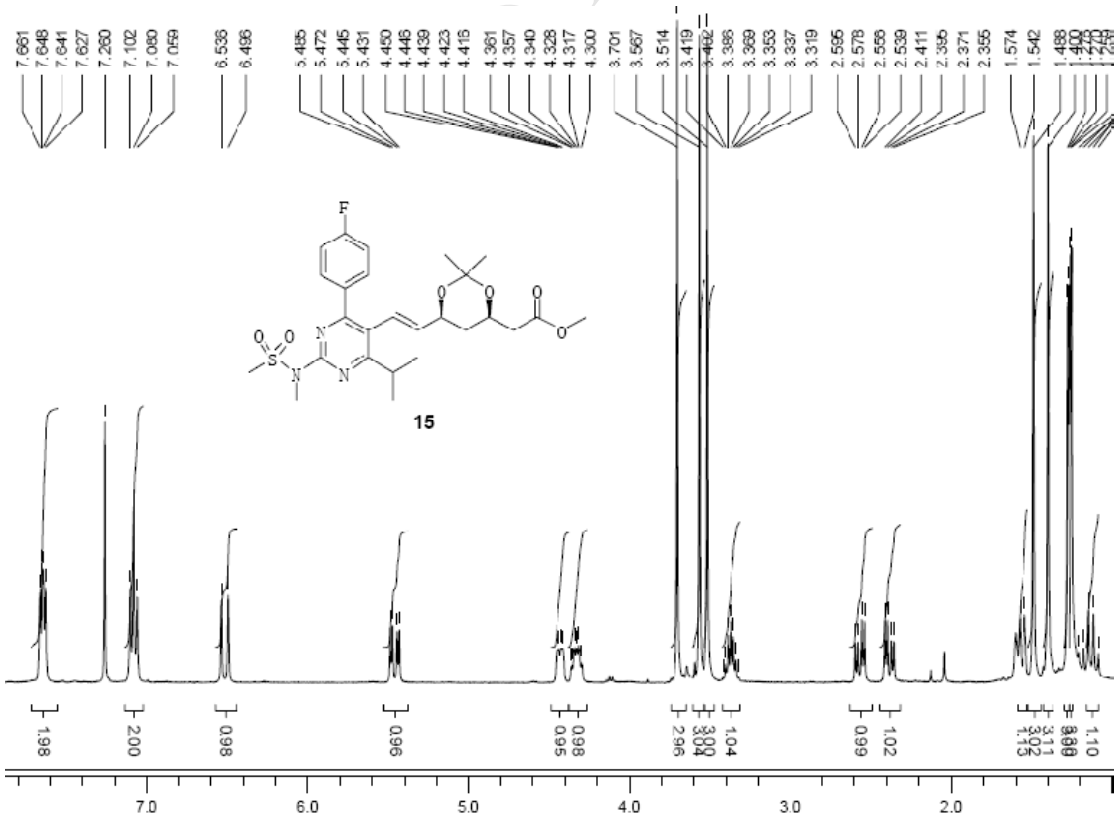
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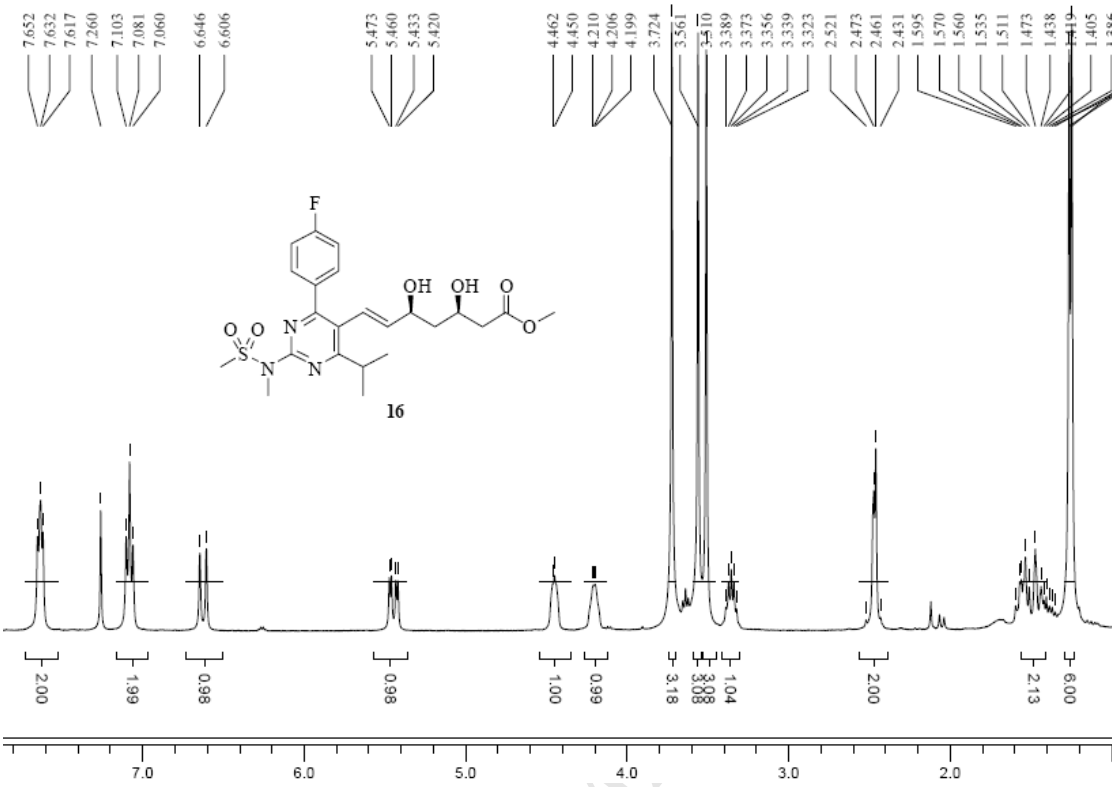
2.0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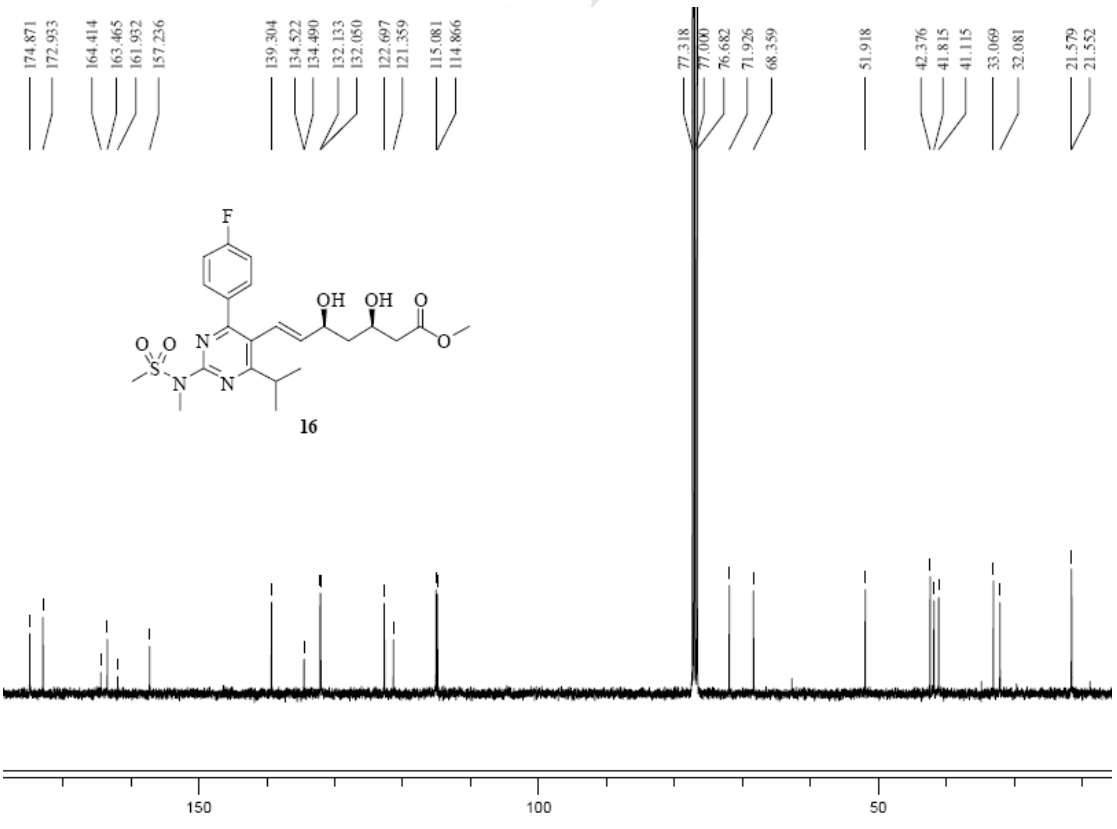
2.0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51.918
42.376
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21.552
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OH
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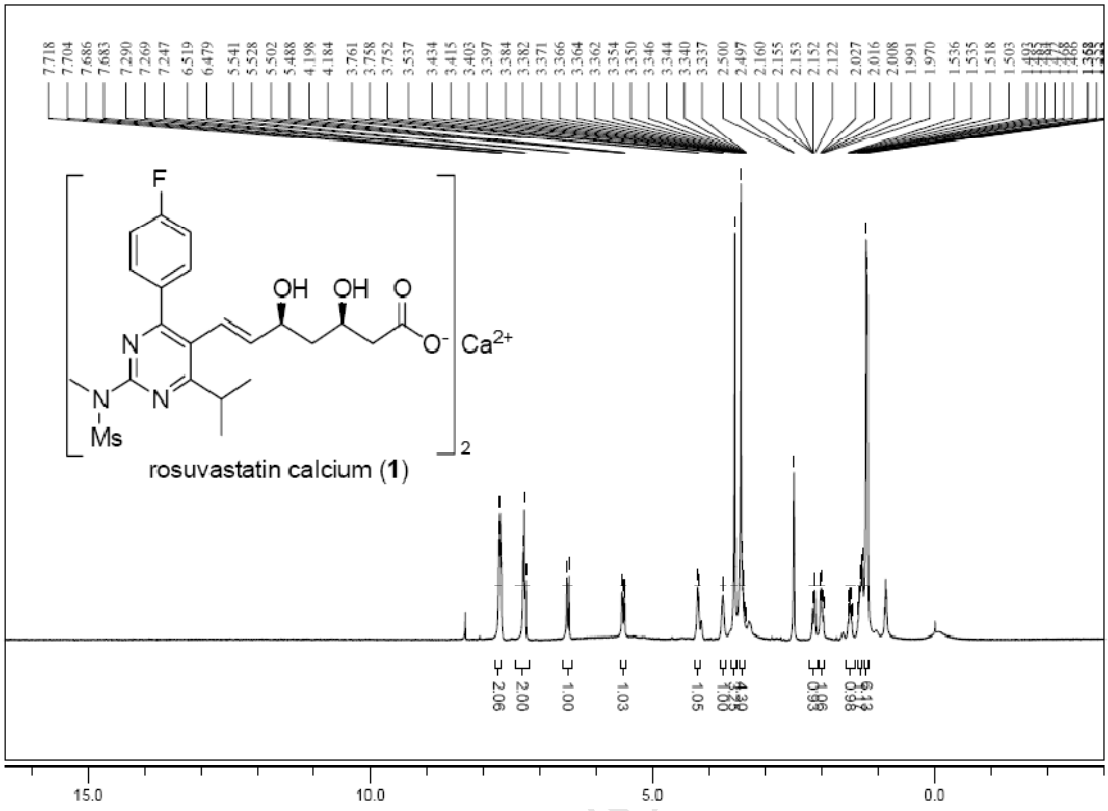
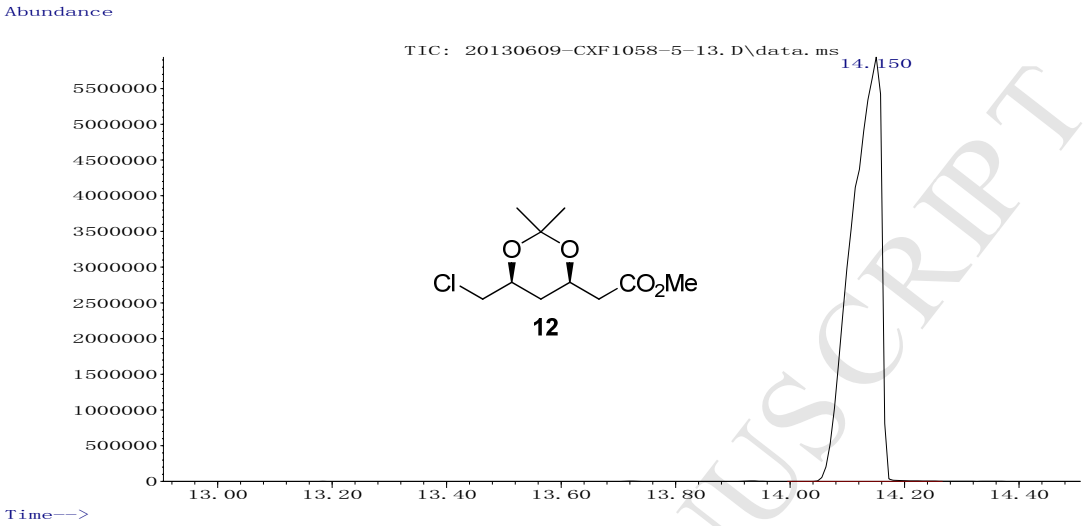
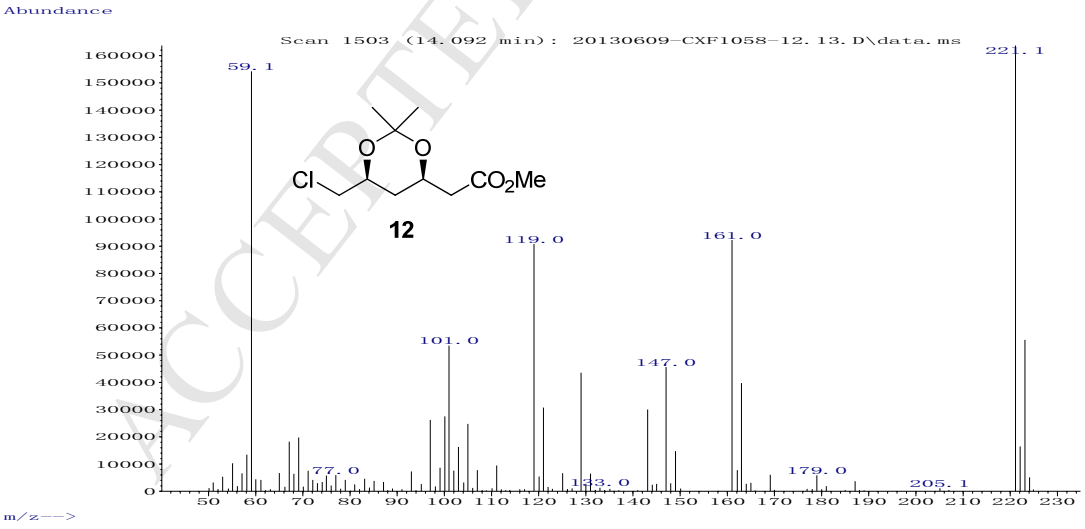


ACCEPTED MANUSCRIPT

Copies of GC-MS spectra



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	14.150	1490	1511	1527	M	5949513	215342880	100.00%	100.000%



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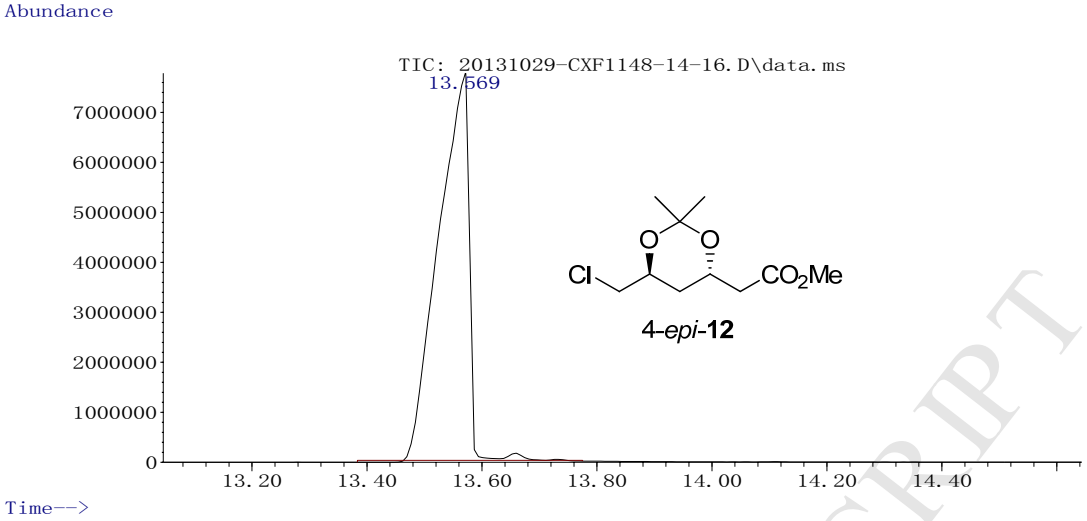
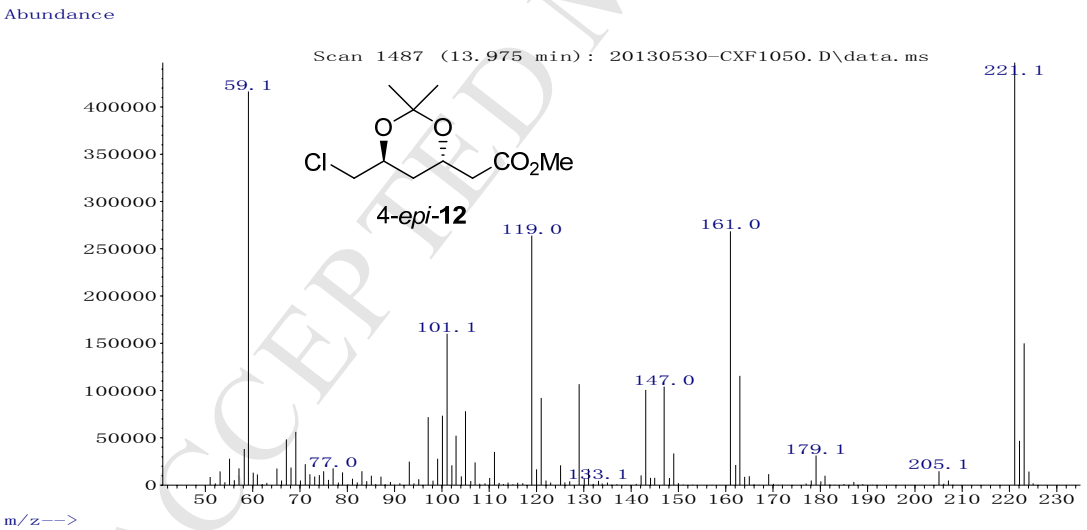
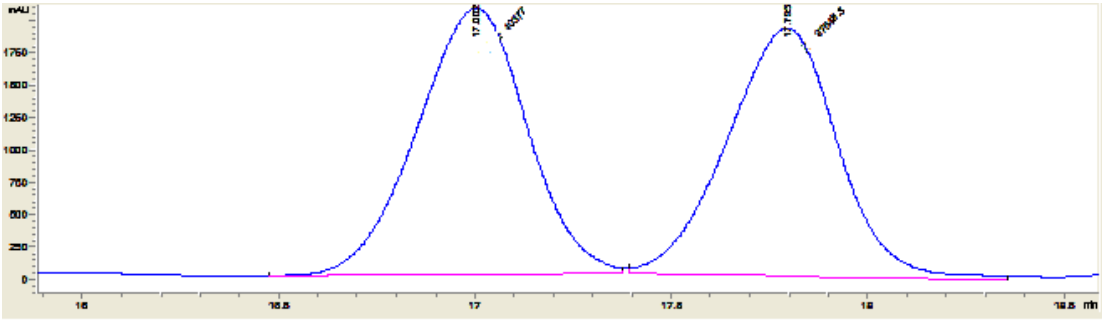


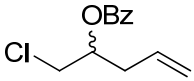
peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	13.569	1406	1432	1460	M	8161895	285438057	100.00%	100.000%



ACCEPTED MANUSCRIPT

Copies of HPLC spectra





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Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
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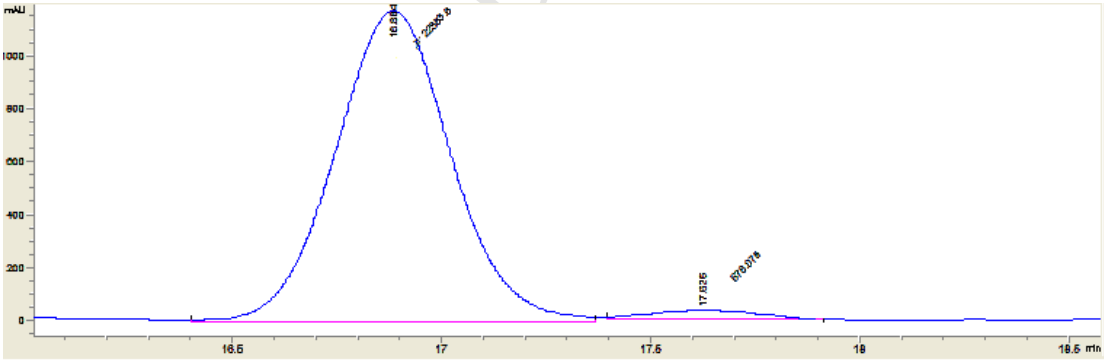
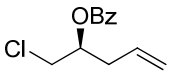
2	17.795	37648	1915.5	0.3276	48.9





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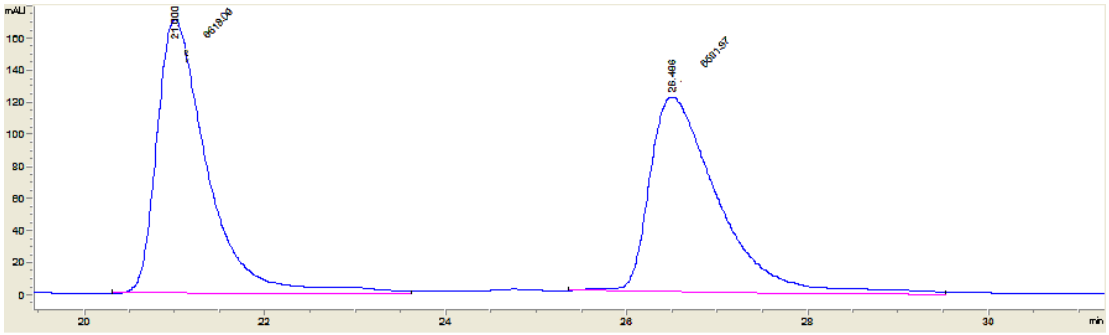
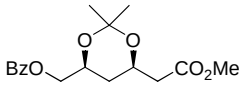
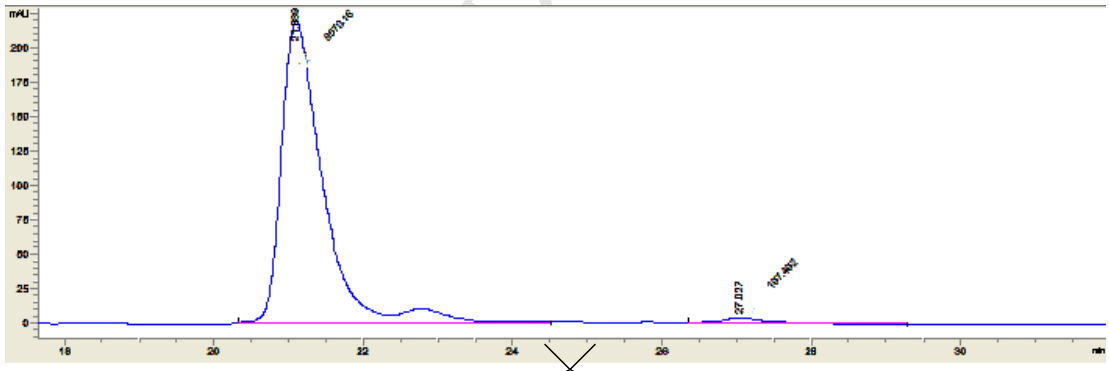
Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
1	16.884	22553.6	1172.6	0.3206	97.081
2	17.626	678.1	36.5	0.3093	2.919

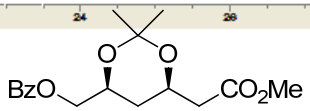




rac-**13b**

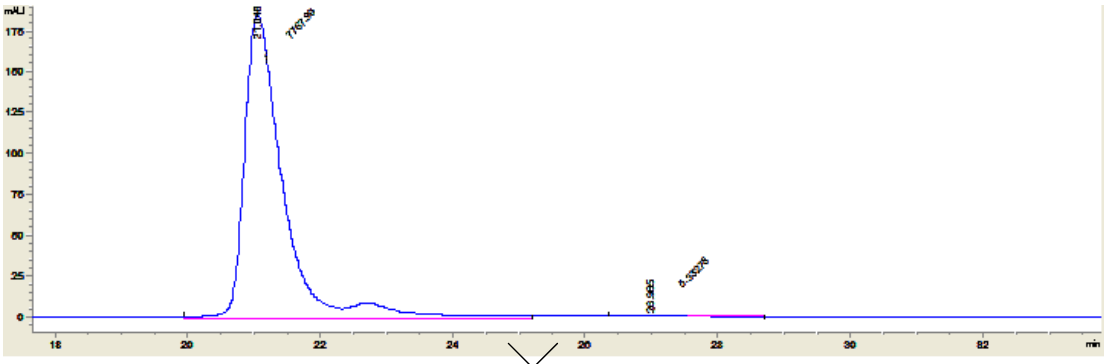
Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
1	21.000	6618.1	170.6	0.6466	50.443
2	26.496	6502	121.9	0.8892	49.557

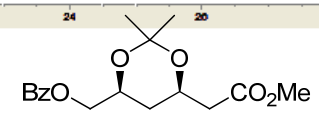




13b (no recrystallization)

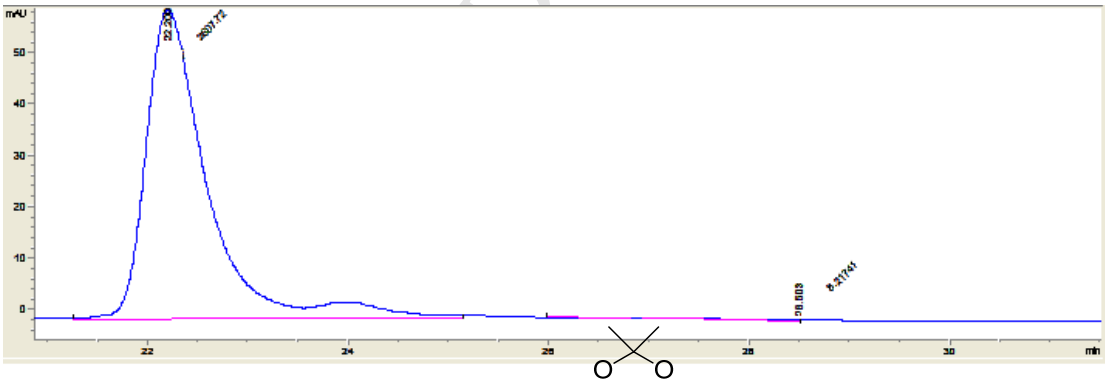
Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
1	21.089	8570.2	219.2	0.6517	97.747
2	27.027	197.5	3.6	0.9068	2.253

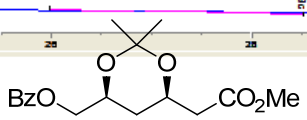




13b (recrystallization)

Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
1	21.048	7768	186.4	0.6946	99.931
2	26.958	5.3	0.12	0.7614	0.069





13b (derived from **13a**)
(recrystallization)

Peak No.	Ret. Time (min)	Area	Peak Height	Peak Width	Area (%)
1	22.000	2607.7	60.3	0.7208	99.686
2	28.503	8.2	0.18	0.7548	0.314