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Enantioselective synthesis of (*R*)-(−)-mevalonolactone via cyclic sulfate methodology†

Rodney A. Fernandes and Pradeep Kumar *

Division of Organic Chemistry: Technology National Chemical Laboratory, Pune-411008, India

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Abstract

An asymmetric synthesis of (*R*)-(−)-mevalonolactone is described using the Sharpless asymmetric dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfate as key steps.

1. Introduction

Mevalonic acid or mevalonolactone is the biosynthetic precursor of most terpenoids, steroids, carotenoids, isoprenoids and pentanoids,[1] and therefore, it has been a synthetic target of considerable interest. In connection with our studies on the synthesis of some naturally occurring lactones,[2] mainly by stereoselective transformation of diols via cyclic sulfates, we became interested in developing a simple and concise route to (*R*)-(−)-mevalonolactone.

Mevalonolactone was first discovered and synthesized via resolution by Folkers and co-workers.[3] Since then a number of asymmetric syntheses of this molecule has been published, the most popular of which involves the enantioselective synthesis provided by the Sharpless epoxidation of a suitable allylic alcohol.[4] The chiral pool materials such as linalool,[5] quinic acid,[6] 2-methyl-2-hydroxy-γ-butyrolactone,[7] and more recently a chiral equivalent of cyclohexa-2,5-dienone,[8] and the chiral template 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuran-3-ulose[9] were reported to be the best sources for the preparation of mevalonolactone. Other interesting synthetic methodologies involve the use of chiral sulfoxides,[10] 1,3-oxathianes[11] and axially dissymmetric binaphthyldiamines.[12] In addition, several enzymatic syntheses starting from achiral precursors have been known in the literature.[13] However, some of these methods suffer either from poor enantiomeric purity[10,12] or low chemical yield,[14] and therefore, an expeditious synthesis of the target molecule is highly desirable. Herein we report a new and enantiocontrolled five

* Corresponding author. E-mail: tripathi@dalton.ncl.res.in

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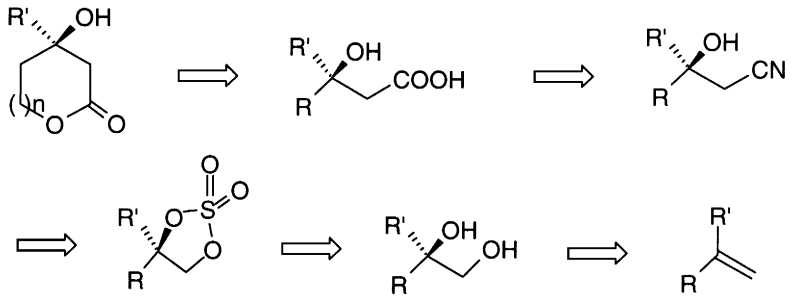
step strategy for the synthesis of (*R*)-(−)-mevalonolactone **6**. The Sharpless asymmetric dihydroxylation of an appropriate olefin **2** and the regioselective nucleophilic opening of a cyclic sulfate **4** were employed as key steps in the synthesis.

2. Results and discussion

Our synthetic strategy for the synthesis of (*R*)-(−)-mevalonolactone was envisioned through the retrosynthetic route as shown in Scheme 1. The β-hydroxy acid was visualized as an ultimate precursor for the target molecule which in turn could be obtained from the cyanide opening of the corresponding cyclic sulfate and subsequent hydrolysis. Thus, the essential feature of our retro-analysis was the presumption that the nucleophilic opening of the cyclic sulfate would occur in a regioselective manner at the terminal carbon. Another feature of this synthetic strategy was the formation of the cyclic sulfate with an acid sensitive group present and the chemoselective hydrolysis of the sulfate ester in order to furnish the desired β-hydroxy acid.

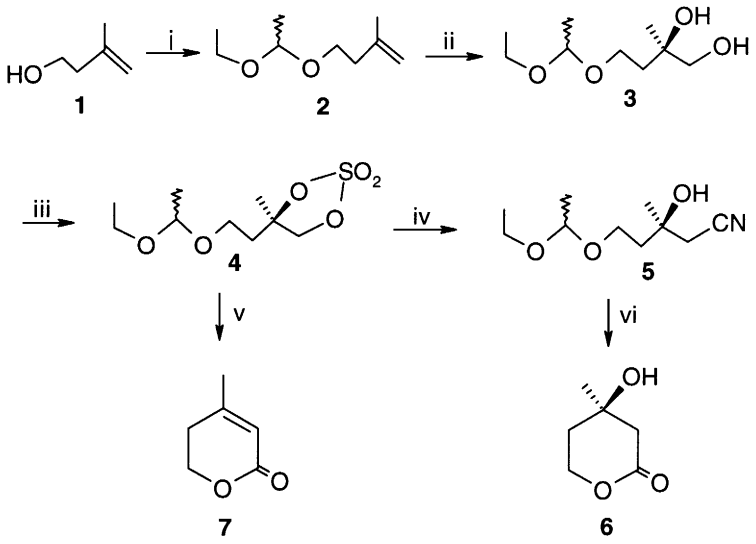


R′ = H, CH_3, alkyl, etc.
R = -CH_2OH, -CH_2CH_2OH, alkyl, etc.
n = 0, 1, 2, etc.

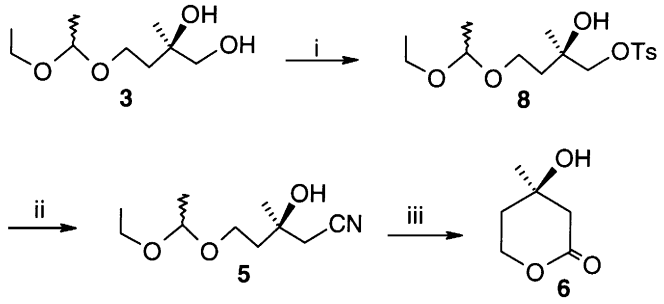
Scheme 1.

The detailed information regarding the reagents, solvents and reaction conditions followed by usual work up is provided in Schemes 2 and 3 and in the Experimental. Our synthesis of target molecule **6** started from 3-methyl-3-butene-1-ol **1**, a readily available starting material.[15] Thus, treatment of **1** with ethyl vinyl ether in the presence of a catalytic amount of *p*-toluenesulfonic acid gave **2** in 93% yield. The dihydroxylation of olefin **2** using the Sharpless asymmetric dihydroxylation procedure[16] gave the diol **3**,[17] $[\alpha]_D^{20}$ +1.95 (c 1, $CHCl_3$), in 97% yield. Diol **3** was then treated with thionyl chloride and triethylamine to obtain the cyclic sulfite which was further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate[18] **4** in 92% yield. The cyclic sulfate **4** on reaction with sodium cyanide followed by chemoselective hydrolysis of sulfate ester under mild conditions[19] furnished the desired compound **5** in 85% yield.

Alternatively, **5** could be obtained from the diol **3** following a sequence of reactions as depicted in Scheme 3. The diol **3** on treatment with *p*-toluenesulfonyl chloride in the presence of pyridine at room temperature afforded **8** in 96% yield. The nucleophilic displacement of tosylate with sodium



Scheme 2. (i) Ethyl vinyl ether, PTSA (cat.), 0°C, 1 h (93%); (ii) $(DHQD)_2$-PHAL, OsO_4 (cat.), $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0°C, 24 h (97%); (iii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 20 min; (b) $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O (1:1:1.5), 0°C, 2 h (92%); (iv) NaCN, DMF, 80°C, 8 h, then THF, concd H_2SO_4:H_2O (2:1), rt, 6 h (85%); (v) NaCN, DMF, 80°C, 8 h, then concd H_2SO_4 (2 equiv.), EtOH:H_2O (1:2), reflux, 18 h (60%); (vi) 3N NaOH, 70°C, 3 h, then MeOH, pH 2 (concd HCl), acetone, PTSA (cat.), rt, 8 h (70%)



Scheme 3. (i) TsCl, pyridine, rt, 18 h (96%); (ii) NaCN, EtOH:H_2O (3:2), rt, 18 h (97%); (iii) 3N NaOH, 70°C, 3 h, then MeOH, pH 2 (concd HCl), acetone, PTSA (cat.), rt, 8 h (70%)

cyanide in aqueous ethanol furnished the desired compound **5** in essentially quantitative yield. The physical and spectroscopic data for this compound exactly matched the one prepared from the cyclic sulfate. The enantiomeric excess of **5** was determined by converting it into the (+)-MTPA ester.[20] The diastereomeric excess (89%) as determined by ^1H NMR spectroscopy of the resulting (+)-MTPA ester is based on the integration of the characteristic methylene resonance α to the cyano group (doublet in the 2.59–2.61 ppm region) due to the MTPA ester portion. The cyano compound **5** on treatment with aqueous sodium hydroxide furnished the corresponding β-hydroxy acid which without any further isolation and purification was subsequently lactonized with *p*-toluenesulfonic acid to afford the target molecule **6** in 70% yield having $[\alpha]_D^{20}$ –19.1 (c 0.4, EtOH) [lit. $[\alpha]_D^{20}$ –21.6 (c 1.565, 95% EtOH),[21] $[\alpha]_D^{25}$ –19.0 (c 2.15, $CHCl_3$)[13b]].

However, attempts to achieve the one-pot cyclic sulfate opening, hydrolysis of the sulfate ester and cyano group hydrolysis to the corresponding acid followed by deprotection of the hydroxyl and subsequent lactonization to the target molecule **6** in strongly acidic media[22] failed. Thus, when the cyclic sulfate **4** was heated with sodium cyanide in dimethylformamide at 80°C followed by solvent removal

and treatment of the residual sulfate ester with aqueous ethanolic solution of concd sulfuric acid [concd H_2SO_4 (2 equiv.), EtOH:H_2O, 1:2] under reflux, it gave only the anhydromevalonolactone **7**, presumably by facile dehydration of the β-hydroxy group (Scheme 2). Compound **7** was fully characterized by its spectroscopic data which were found to be in full agreement with the literature data.[2a,23]

3. Conclusion

In conclusion, an asymmetric synthesis of (*R*)-mevalonolactone has been realized using the Sharpless asymmetric dihydroxylation as the source of chirality for the first time. Thus, the results described herein constitute a short and efficient synthesis of natural isomer of mevalonolactone. The unnatural enantiomer can be synthesized via α-dihydroxylation of **2** and following the reaction sequence as shown in Schemes 2 and 3. The synthetic strategy (retrosynthetic analysis, Scheme 1) described here has significant potential of further extension to chiral substituted β-hydroxy acids[24] which serve as important synthons for several naturally occurring and biologically active molecules.

4. Experimental

4.1. General information

The solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80°C was used. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on an ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL 300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by ^{1}H NMR spectra and by Chirasil-Val-D gas chromatograph.

*4.2. 4-(1-Ethoxyethoxy)-2-methyl-1-butene **2***

To a stirred solution of ethyl vinyl ether (30 mL) containing *p*-toluenesulfonic acid (60 mg) was added 3-methyl-3-butene-1-ol **1** (8.6 g, 100 mmol) dropwise at 0°C. After stirring for 1 h, the reaction mixture was warmed to room temperature and diluted with petroleum ether (100 mL). Filtration through a short pad of neutral alumina and removal of solvent gave a yellowish liquid which was distilled in vacuo to give **2** (14.65 g, 93%) as a colorless liquid, bp 60°C/10 torr: TLC (silica gel, petroleum ether:EtOAc, 1:1): R_f=0.89; IR (neat) 3025, 2976, 1648, 1399, 1132, 1096, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, *J*=7 Hz, 3H), 1.30 (d, *J*=6.5 Hz, 3H), 1.73 (s, 3H), 2.27 (t, *J*=6.5 Hz, 2H), 3.3–3.65 (m, 4H), 4.69 (q, *J*=6.5 Hz, 1H), 4.76 (d, *J*=3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.78. 19.27, 22.14, 37.64, 60.10, 63.18, 99.06, 110.9, 142.31; MS (EI), *m/z* (%) 158 [M^+] (0.8), 143 (3.8), 129 (4.3), 113 (40.6), 103 (32.5), 89 (22.7), 73 (97.4), 69 (100), 53 (29.5). Anal. calcd for $C_9H_{18}O_2$ (158.23): C, 68.31; H, 11.47. Found: C, 68.26; H, 11.62.

4.3. 4-(1-Ethoxyethoxy)-2-methyl-(2R)-butane-1,2-diol **3**

To a mixture of $K_3Fe(CN)_6$ (4.8 g, 14.6 mmol), K_2CO_3 (2.02 g, 14.6 mmol) and $(DHQD)_2$-PHAL (38 mg, 48.8 μmol) in *t*-BuOH–H_2O (1:1, 30 mL) cooled at 0°C was added osmium tetroxide (100 μL, 0.1 M solution in toluene). After stirring for 5 min at 0°C, the olefin **2** (0.75 g, 4.74 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (7 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3×20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **3** (0.884 g, 97%) as a colorless liquid: TLC (silica gel, EtOAc): R_f=0.62; $[\alpha]_D^{20}$ +1.95 (c 1, $CHCl_3$); IR (neat) 3430, 2977, 2931, 1451, 1381, 1343, 1132, 1089, 1054, 938 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, *J*=7 Hz, 3H), 1.28 (s, 3H), 1.30 (d, *J*=6.5 Hz, 3H), 1.72 (m, 1H), 1.87 (m, 1H), 2.17 (br s, 1H), 2.97 (br s, 1H), 3.43 (m, 2H), 3.5–3.8 (m, 4H), 4.67 (q, *J*=6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.00, 19.65, 23.86, 37.70, 61.09, 61.70, 69.70, 72.16, 99.78; MS (EI), *m/z* (%) 147 [$M^+ - OCH_2CH_3$] (6), 115 (69), 103 (16.7), 89 (29), 85 (86.3), 73 (100), 57 (37). Anal. calcd for $C_9H_{20}O_4$ (192.25): C, 56.22; H, 10.48. Found: C, 56.19; H, 10.46.

4.4. 5-(1-Ethoxyethoxy) ethyl-5-methyl-(5R)-1,3,2-dioxathiolane-2-dioxide **4**

To a stirred solution of the diol **3** (0.3 g, 1.56 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0°C were added Et_3N (0.436 g, 0.6 mL, 4.3 mmol) and a solution of $SOCl_2$ (0.278 g, 0.17 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) over a period of 10 min. Stirring was continued for 20 min at 0°C and then the solution was quenched by addition of water (5 mL) followed by addition of CH_2Cl_2 (30 mL). The organic layer was separated, washed with cold water (2×10 mL) and brine (20 mL), dried (Na_2SO_4) and filtered through a pad of silica gel. The filtrate was concentrated to give a yellow liquid. To this was added a cold solution of CCl_4 (3 mL) and CH_3CN (3 mL). The reaction flask was cooled in an ice bath and cold water (4.5 mL) was added. $RuCl_3 \cdot H_2O$ (4.5 mg, 0.021 mmol) and $NaIO_4$ (0.535 g, 2.5 mmol) were added at once and the reaction mixture was stirred vigorously at 0°C. The progress of reaction was monitored by TLC. After 2 h, ether (20 mL) was added and the layers were separated. The aqueous layer was extracted with ether (3×10 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and passed through a silica gel column. The filtrate was concentrated and the crude product was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **4** (0.365 g, 92%) as a yellow liquid: TLC (silica gel, petroleum ether:EtOAc, 4:1): R_f=0.51; $[\alpha]_D^{20}$ –1.3 (c 0.3, MeOH); IR (neat) 3027, 2979, 1447, 1399, 1207, 1131, 1091, 1059, 955, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, *J*=7 Hz, 3H), 1.26 (d, *J*=6.5 Hz, 3H), 1.39 (s, 3H), 1.92 (m, 1H), 2.21 (m, 1H), 3.4–3.8 (m, 4H), 4.4–4.6 (m, 2H), 4.65 (q, *J*=6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.07, 19.68, 24.93, 38.87, 60.45, 60.76, 74.48, 87.1, 99.72; MS (EI), *m/z* (%) 208 [$M^+ - HOCH_2CH_3$] (0.3), 165 (1), 100 (3), 85 (67), 73 (100), 55 (4). Anal. calcd for $C_9H_{18}O_6S$ (254.29): C, 42.51; H, 7.14; S, 12.61. Found: C, 42.60; H, 7.20; S, 12.58.

4.5. 4-(1-Ethoxyethoxy)-2-hydroxy-2-methyl-(2S)-butylcyanide **5**

To a solution of cyclic sulfate **4** (0.25 g, 0.983 mmol) in dry DMF (8 mL) was added NaCN (0.08 g, 1.63 mmol) and stirred under argon for 8 h at 80°C. The solvent was removed under reduced pressure. The residue was suspended in dry THF (5 mL) and concd H_2SO_4 (0.05 mL) and water (0.025 mL) were added to the stirred suspension. The hydrolysis was monitored by TLC. After 6 h, excess $NaHCO_3$ was added and stirred for 15 min. Filtration through Celite and concentration of the filtrate under reduced pressure gave the crude product which was purified by silica gel column chromatography using petroleum

ether:EtOAc (3:2) as eluent to give **5** (0.168 g, 85%) as a colorless oil: TLC (silica gel, EtOAc): R_f=0.825; $[\alpha]_D^{20}$ +1.3 (c 0.8, EtOH); IR (neat) 3470, 2979, 2933, 2250, 1451, 1382, 1345, 1131, 1092, 1058, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, *J*=7 Hz, 3H), 1.32 (d, *J*=6.5 Hz, 3H), 1.40 (s, 3H), 1.92 (m, 2H), 2.58 (d, *J*=2 Hz, 2H), 3.4–3.65 (m, 2H), 3.65–3.9 (m, 3H), 4.69 (dq, *J*=3, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.01, 19.62, 26.76, 31.13, 39.55, 61.24, 61.39, 70.32, 99.62, 117.54; MS (EI), *m/z* (%) 186 [M^+-15] (5.34), 156 [$M^+-OCH_2CH_3$] (13.24), 115 (13.9), 112 (21.36), 94 (27.35), 73 (100), 71 (53.84), 55 (3.84). Anal. calcd for $C_{10}H_{19}NO_3$ (201.25): C, 59.68; H, 9.52; N, 6.96. Found: C, 59.62; H, 9.56; N, 6.95.

*4.6. (*R*)-(−)–Mevalonolactone **6***

To the cyano compound **5** (100 mg, 0.497 mmol) was added an aqueous solution of NaOH (3N, 1.2 mL) and the mixture was stirred at 70°C for 3 h. The suspension was cooled in an ice bath followed by addition of MeOH (4 mL). The solution was acidified to pH 2 with concd HCl. MeOH was stripped off and the residue was dissolved in acetone (5 mL). To this was added *p*-toluenesulfonic acid (100 mg) and the mixture stirred at room temperature for 8 h. Et_3N was added and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether:EtOAc (1:4) as eluent to give **6** (45 mg, 70%) as a pale yellow oil; TLC (silica gel, EtOAc): R_f=0.29; $[\alpha]_D^{20}$ –19.1 (c 0.4, EtOH) [lit. $[\alpha]_D^{20}$ –21.6 (c 1.565, 95% EtOH),[21] $[\alpha]_D^{25}$ –19.0 (c 2.15, $CHCl_3$)[13b]]; IR (neat) 3400, 3018, 2976, 1732, 1265, 1215, 1190, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.91 (m, 2H), 2.5 (d, *J*=18 Hz, 1H), 2.6 (br s, 1H), 2.7 (d, *J*=18 Hz, 1H), 4.36 (m, 1H), 4.62 (m, 1H); MS (EI), *m/z* (%) 131 [M^++1] (4.48), 130 [M^+] (2.56), 115 (4.9), 85 (14.95), 71 (100), 58 (16.66).

*4.7. Anhydromevalonolactone **7***

To a solution of cyclic sulfate **4** (0.225 g, 0.885 mmol) in dry DMF (8 mL) was added NaCN (0.087 g, 1.77 mmol) and stirred under argon for 8 h at 80°C. The reaction mixture was cooled to room temperature, washed with brine and extracted with ether (3×15 mL). The ether layer was dried (Na_2SO_4) and concentrated. To this was added an aqueous ethanolic solution of concd H_2SO_4 [concd H_2SO_4 (0.1 mL, 2 equiv.), EtOH (1 mL) and water (2 mL)] and refluxed for 18 h. The reaction mixture was cooled, neutralised ($NaHCO_3$) and extracted with CH_2Cl_2 (3×15 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using petroleum ether:EtOAc (1:1) as eluent gave **7** (0.06 g, 60%) as a colorless oil. TLC (silica gel, petroleum ether:EtOAc, 1:1): R_f=0.57; IR (neat) 2978, 2923, 1721, 1647, 1397, 1267, 1150, 1063, 998 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.33 (t, *J*=6.5 Hz, 2H), 4.39 (t, *J*=6.5 Hz, 2H), 5.79 (s, 1H); MS (EI), *m/z* (%) 112 [M^+] (38.1), 99 (2.38), 82 (60.7), 67 (17.26), 54 (100).

*4.8. 4-(1-Ethoxyethoxy)-2-hydroxy-2-methyl-(2*R*)-butyl 4-methyl-1-benzenesulfonate **8***

To a solution of diol **3** (0.25 g, 1.3 mmol) in dry pyridine (8 mL) was added *p*-toluenesulfonyl chloride (0.324 g, 1.7 mmol) at room temperature and stirred for 18 h. Then aqueous $CuSO_4$ solution (20%, w/v, 10 mL) and EtOAc (15 mL) were added and stirring was continued for 45 min. The aqueous layer was extracted with EtOAc (4×20 mL) and combined organic layers were washed with water, brine and dried (Na_2SO_4). Removal of solvent gave a pale green liquid which was purified by silica gel column chromatography using petroleum ether:EtOAc (7:3) as eluent to give **8** (0.432 g, 96%) as a colorless oil: TLC (silica gel, EtOAc): R_f=0.92; $[\alpha]_D^{20}$ –0.8 (c 0.8, EtOH); IR (neat) 3474, 2979, 2931, 1605, 1359, 1179, 1130, 1094, 1056, 979, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, *J*=7 Hz, 3H), 1.26 (d, *J*=6.5 Hz,

3H), 1.28 (s, 3H), 1.82 (m, 2H), 2.45 (s, 3H), 3.4–3.6 (m, 4H), 3.65–3.9 (m, 3H), 4.64 (dq, *J*=3, 6.5 Hz, 1H), 7.36 (d, *J*=8 Hz, 2H), 7.80 (d, *J*=8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.07, 19.62, 21.33, 24.41, 37.04, 61.24, 61.40, 70.74, 75.37, 99.78, 127.77, 129.72, 132.92, 144.71; MS (EI), *m/z* (%) 257 [M^+-89] (0.2), 172 (8.1), 155 (40), 115 (100), 107 (12.5), 91 (90.2), 71 (69.6), 65 (17.85), 57 (3.6). Anal. calcd for $C_{16}H_{26}O_6S$ (346.43): C, 55.47; H, 7.57; S, 9.25. Found: C, 55.48; H, 7.61; S, 9.23.

*4.9. Compound **5** via tosyl displacement*

To a stirred solution of the tosylate **8** (0.35 g, 1.01 mmol) in EtOH:H_2O (3:2 v/v, 5 mL), cooled at 0°C, was added NaCN (0.174 g, 3.55 mmol). The mixture was slowly allowed to warm to room temperature. After stirring for 18 h, it was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine and water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (7:3) gave **5** (198 mg, 97%) as a colorless oil: $[\alpha]_D^{20}$ +1.25 (c 0.7, EtOH). The spectroscopic data were in full agreement with those of the one prepared by the opening of cyclic sulfate **4** via step iv.

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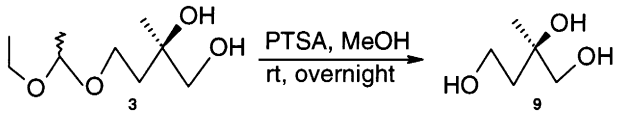

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