The Efficient Synthesis of the Optically Active β-Hydroxyl-γ-butyrolactone Derivatives

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The optically active β-hydroxyl-γ-butyrolactones were synthesized from nonchiral starting material by employing reductive cleavage reaction, sharpless asymmetric epoxidation and dihydroxylation, and Lewis acid-catalysed cyclization as key steps. This strategy can be used to prepare many chiral β-hydroxyl-γ-butyrolactone analogues.

Keywords: Asymmetric synthesis; β-Hydroxy-γ-butyrolactone; Reductive cleavage reaction; Sharpless epoxidation and dihydroxylation; Cyclization.

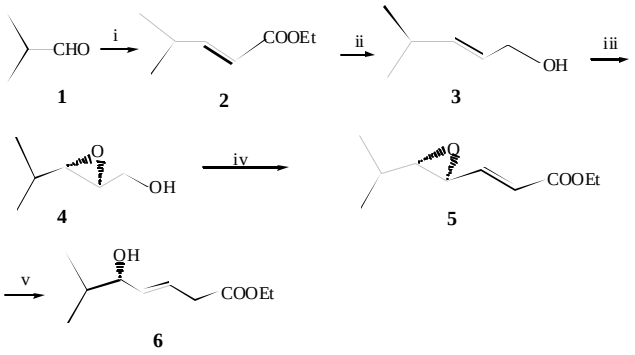
INTRODUCTION

Chiral γ-butyrolactones have attracted substantial interest in recent years due to their presence in many strongly active natural products having antitumor, fungicidal, anti-inflammatory activity,[1,2,3] and their use as important precursors in natural product synthesis.[4] Presently the asymmetric synthesis of β-hydroxy-γ-butyrolactones have been a target for organic synthesis in various laboratories. In the course of the total synthesis of the natural product Tuxpanolide[5] and its analogues,[6] we prepared the various optically active β-hydroxyl-γ-butyrolactones derivatives as needed key intermediates, finding a practical strategy for building chiral β-hydroxy-γ-butyrolactones. In this paper, we present our results on the efficient stereocontrolled synthesis of β-hydroxyl-γ-butyrolactone derivatives from cheap and nonchiral starting material.

RESULTS AND DISCUSSION

The starting material isobutyaldehyde **1** was subjected to the wittig reaction followed by the reduction with $LiAlH_4$-$AlCl_3$ in dry ether to give the allylic alcohol **3**. Sharpless asymmetric epoxidation[7] of the allyl alcohol **3** with (+)-DET, Ti(*i*-OPr)$_4$, TBHP led to the epoxy alcohol (+)-**4** in 71% yield[8] and 90%ee as determined by ^{1}H NMR analysis of the corresponding Moster's ester.[9] Coupling reaction of aldehyde obtained by swern oxidation of **4** and triphenyphosphorane afforded (+)-**5** (41% for two steps). After the synthesis of four steps, by simply applying the reductive cleavage reaction of α,β-unsaturated ester **5** by magnesium in methanol,[10] we luckily accessed the sole product (+)-**6** in 72% yield (Scheme I).

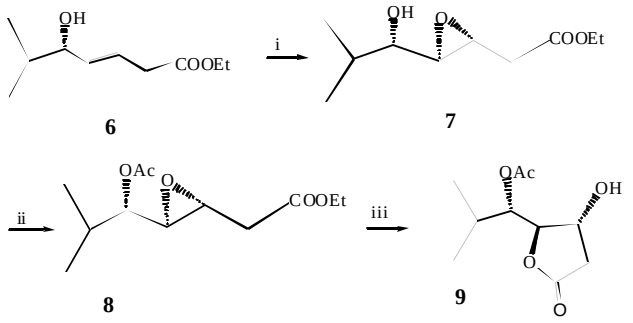
Scheme I



(i) Ph_3P=CHCOOEt, CH_2Cl_2, 0 °C-r.t.; (ii) $LiAlH_4$:$AlCl_3$ = 3:1, Et_2O, -78 °C; (iii) Ti(O-*i*-Pr)$_4$, (+)-DET, TBHP, CH_2Cl_2, -20 °C; (iv) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (b) Ph_3P=CHCOOEt, CH_2Cl_2, r.t.; (v) Mg, MeOH, -23°C.

Subsequent treatment of **6** with *t*-BuOOH-VO(acac)$_2$ catalyst system in dry benzene gave a 7.5:1 mixture (determined by GLC, 88%de) of the desired α-epoxyalcohol (+)-**7** and its β-isomers in 61% yield. After the protection of a secondary hydroxy of **7**, the (+)-**8** was obtained in 73% yield. Finally with the treatment of **8** with camphosulfonic acid (CSA) catalysed cyclization,[11] we proceeded to construct a chiral butyrolactone (+)-**9** in 63% yield, 98%de determined by GLC, and 95%ee in accordance with the ^{1}H NMR analysis of the corresponding Moster esters[9] (Scheme II). This route successfully employed the sharpless catalytic asymmetric epoxidation reaction, which allowed the two chiral centers of the intermediate **3** to remain S in a highly predictable way. Moreover, the configurations of C_3, C_4 in the compound **7** were determined by the fact that the vanadium-catalyzed epoxidation exhibited the cis stereoselectivity.[12] It provided

Scheme II

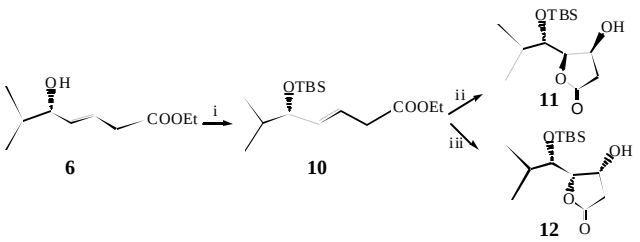


(i) *t*-BuOOH, $VO(acac)_2$, benzene, 5 °C-r.t. (ii) Ac_2O, DMAP, Py, r.t.; (iii) CSA, CH_2Cl_2, 0 °C-r.t.

the ef fi cient stereocontrolled syn thetic ap proach for build ing the trans β-hydroxy-γ-butyrolactone blocks.

The Sharpless asym met ric dihydroxylation (ADs) of olefine is an in dis pens able tool for con tem po rary or ganic syn the sis. In Scheme III, the key in ter me di ate **6** was al lowed to re act with *tert*-butyldimethylchlorosilane (1.2 eq) and imidazole (3.0 eq) in an hy drous DMF. Af ter 6 hours, **10** was ob tained in 82% yield. Then ADs of **10** (in ac cor dance with the lit er a ture pre ce dence[13]) pro vided lactonized dihydroxyla tion prod ucts **11** (ee 73%) and **12** (ee 78%), re spec tively, in 45% and 51% yield. Thus, the cis β-hydroxyl-γ-butyrolactones **11** and **12** were suc cess fully ob tained by this econom i cal and ef fi cient method. Re mark ably, if **6** was pro tected with an acetyl, the AD re ac tion did not hap pen.

Scheme III



(i) TBDMCl, Et_3N, DMAP, DMF, r.t; (ii) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH-H_2O, r.t.; (iii) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH-H_2O, r.t.

Here we re port the asym met ric syn the sis of the op tically ac tive β-hydroxyl-γ-butyrolactone deriviatives **9**, **11**, **12**. With the above Lewis acid cat a lyzed cyclization and ADs lactonization, the var i ous chiral β-hydroxyl-γ-butyrolactones can be con structed gen er ally and prac ti cally via the key in ter me di ate **6** and its de riv a tives.

EXPERIMENTAL SECTION

General Methods

IR spec tra were re corded on an FT-170SX spec trom e ter. ^1H NMR and ^{13}C NMR spec tra were re corded on Bruker AM-200 or AM-400 MHz in stru ments us ing tetramethylsilane (TMS) as the in ter nal stan dard. Mass spec tra were record on VG ZAB-HS or VG-7070 (70 ev) spectrameters. GLC anal y ses were car ried out on a Shimadzu GC-9AM instrument. Optical rotations were measured with a Perkin Elmer 341 in stru ment.

(*E*)-4-Methyl-2-pentenoate (2)

To a stirred so lu tion of (ethoxycarbonylmethylene) triphenylphosphorane (20 g, 57.4 mmol) in dry CH_2Cl_2 (50 mL) was added isobutyaldehyde (4.14 g, 57.5 mmol) un der an Ar at mo sphere. The re ac tion mix ture was stirred for 2 h at room tem per a ture and the sol vent was evap o rated. The crude res i due was pu ri fied by col umn chro ma tog ra phy (pe tro leum) to fur nish **2** as a col or less liq uid (6.5 g, 80%). IR (film): ν = 2982, 1708, 1651, 1514, 1436, 1314, 1290, 1207, 1150, 981 cm^{-1}. ^1H NMR (200 M, $CDCl_3$): δ 1.05 (d, *J* = 7.0 Hz, 6H), 1,23 (t, *J* = 7.2 Hz, 3H), 2.38-2.42 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.72 (d, *J* = 15.8 Hz, 1H), 6.90 (dd, *J* = 15.8 , 6.6 Hz, 1H). The data matched those re ported in the lit er a ture.[14]

(*E*)-4-Methyl-2-penten-1-ol (3)

To a stirred and precooled (-78 °C) so lu tion of $LiAlH_4$ (294 mg, 7.75 mmol) and $AlCl_3$ (344 mg, 2.58 mmol) in dry ether (25 mL) was added dropwise com pound **2** (366 mg, 2.58 mmol). The re ac tion was stirred for 1.5 h at -78 °C and then H_2O was added slowly to quench the unreacted $LiAlH_4$. The mix ture was fil tered and the ether so lu tion was washed by wa ter and brine. The ethe real layer was dried over $MgSO_4$. Re moval of sol vent by ro tary evap o ra tion yielded a col or less liq uid **3** (237 mg, 92%). IR (film): ν = 3350, 2934, 2889, 1117, 1465, 1382, 1205, 980 cm^{-1}. ^1H NMR (200 M, $CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 6H), 2.22-2.27 (m, 1H), 2.43 (brs, OH), 4.01 (d, *J* = 5.6 Hz, 2H), 5.48-5.55 (m, 1H), 5.6 (dd, *J* = 15.7 Hz, 6.0 Hz, 1H). EIMS: *m/e* 101, 81, 55, 43. The data were con sis tent with those re ported in the lit er a ture.[15]

(+)-(4*S*,5*S*)-6-Methyl-4,5-epoxy-2-heptenoate (5)

To a stirred so lu tion of oxalyl chlo ride (0.23 mL, 2.6 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added dropwise DMSO (0.37 mL, 5.2 mmol). Upon com plete ad di tion, **4** (150 mg, 1.3 mmol) dis solved in CH_2Cl_2 (0.5 mL) was added dropwise. The initially clear solution became white and cloudy af ter stir ring for 1.5 h. Triethylamine (657 mg, 6.5

mmol) was then added dropwise at -78 °C. Then the reaction mixture was warmed slowly to -10 °C for 2 h and quenched by addition of water (0.3 mL). The organic layer was separated and washed with water and brine; the combined aqueous washes were extracted with CH_2Cl_2. The organic phases were combined and dried over $MgSO_4$. After the removal of solvent, buff oil (100 mg) was obtained. To a stirred solution of (ethoxycarbonylmethylene) triphenylphosphorane (306 mg, 0.89 mmol) in dry CH_2Cl_2 (10 mL) was added to the buff oil (100 mg) under an Ar atmosphere. The reaction mixture was stirred for 2 h at room temperature and the solvent was evaporated. The crude residue was purified by column chromatography (petroleum:EtOAc, 32:1) to furnish **5** as a buff oil (110 mg, two steps 41%). $[\alpha]_D^{27}$ 10.6° (*c* 1.4 CH_2Cl_2). IR (film): ν = 2962, 1725, 1661, 1593, 1439, 1307, 1275, 1192, 978, 857 cm^{-1}. ^1H NMR (200 M , $CDCl_3$): δ 0.96 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.56-1.64 (m, 1H), 2.67 (dd, *J* = 1.8, 6.6 Hz, 1H), 3.25 (dd, *J* = 6.8, 1.9 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 6.11 (d, *J* = 15.6 Hz, 1H), 6.69 (dd, *J* = 15.6, 6.7 Hz, 1H). ^{13}C NMR (50 M, $CDCl_3$): δ 14.07, 18.04, 18.74, 30.41, 55.09, 60.38, 66.50, 123.26, 144.79, 165.55. EIMS: *m/e* 185, 139, 111, 98, 83, 56, 45, 43, 41.

(+)-(5*S*)-6-Methyl-5-hydroxy-3-heptenoate (6)

The substrate **5** (160 mg, 0.87 mmol) in dry methanol (5 mL) was cooled at -23 °C before magnesium powder (63 mg, 2.61 mmol) was added. The reaction mixture was stirred for 2 h under Ar atmosphere. To the gray solution was added an equal volume of diethyl ether, the whole mixture was filtered through a silica gel pad and concentrated in vacuo, and crude product was purified by flash chromatography (SiO_2) (petroleum:EtOAc, 8:1) to obtain a color less oil **6** (11 mg, 72%). $[\alpha]_D^{26}$ +12.1° (*c* 1.8 CH_2Cl_2). IR (film): ν = 3410, 2922, 1733, 1626, 1405, 1381, 1158, 1072, 1023 cm^{-1}. ^1H NMR (200 M, $CDCl_3$): δ 0.87 (d, *J* = 2.4 Hz, 3H), 0.90 (d, *J* = 2.4 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.63-1.70 (m, 1H), 3.05 (brd, 2H), 3.88 (t, *J* = 6.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.55 (dd, *J* = 7.2, 15.4 Hz, 1H), 5.73 (dt, *J* = 7.5, 15.4 Hz, 1H). ^{13}C NMR (50 M, $CDCl_3$): δ 14.11, 17.88, 18.10, 33.64, 37.69, 60.63, 72.33, 123.80, 135.30, 171.65. EIMS: *m/e* 143, 130, 97, 73, 43. HRMS ($M+NH_4$) calcd for $C_{10}H_{22}O_3N$ 204.1594, found 204.1597.

(+)-(3*R*,4*S*,5*S*)-6-Methyl-5-hydroxy-3,4-epoxy-heptanoate (7)

To a stirred solution of **6** (136 mg, 0.73 mmol) in anhydrous benzene (5 mL at 5°C under Ar atmosphere, was added $VO(acac)_2$ 10 mg (0.04 mmol). After the reaction mixture was stirred for 10 minutes at 5 °C, *tert*-butylhydroperoxide 0.5 mL (1.46 mmol) was added dropwise and the resulting mixture was stirred for 12 h at the room temperature. The quenching was made by adding a saturated solution of $NaHCO_3$, followed by extraction with benzene. Then the organic layer was washed with saturated solution of $Na_2S_2O_3$, water and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (petroleum:EtOAc, 4:1) to give a 7.5:1 mixture of α-epoxide **7** (79 mg, 54%, 88%de) and β-epoxides (11 mg, 7%, 12%de) as a color less oil. Compound **7**: $[\alpha]_D^{26}$ +8.0° (*c* 2.0 CH_2Cl_2). IR (film): ν = 414, 2971, 1733, 1467, 1373, 1235, 1026 cm^{-1}. ^1H NMR (200 M, $CDCl_3$): δ 0.96 (d, *J* = 2.4 Hz, 3H), 1.01 (d, *J* = 2.4 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.60-1.71 (m, 1H), 2.52 (dd, *J* = 5.6, 10.3 Hz, 1H), 2.63 (dd, *J* = 5.8, 10.4 Hz, 1H), 2.89 (dd, *J* = 2.2, 5.0 Hz, 1H), 3.30 (ddd, *J* = 2.2, 6.0, 11.0 Hz, 1H), 3.74 (dd, *J* = 5.0, 6.6 Hz, 1H), 4.20 (q, *J* = 7.6 Hz, 2H). ^{13}C NMR (50 M, $CDCl_3$): δ 14.14, 18.28, 19.55, 29.91, 32.37, 37.04, 52.18, 60.47, 71.23, 169.53. EIMS: *m/e* 159, 131, 117, 85, 71, 43. HRMS ($M+NH_4$) calcd for $C_{10}H_{22}O_4N$ 220.1543, found 220.1539.

(+)-(3*R*,4*S*,5*S*)-6-Methyl-5-acetoxy-3,4-epoxy-heptanoate (8)

To a solution of **7** (83 mg, 0.41 mmol) in pyridine (1 mL) was added acid anhydride (63 mg, 0.62 mmol) and DMAP (3 mg, 0.02 mmol); the reaction mixture was stirred for 12 h at room temperature. The mixture was extracted with EtOAc and then the organic layer was washed with aqueous 10% NaOH, 5% HCl, H_2O and brine, respectively, then dried over $MgSO_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography (petrolum: EtOAc, 8:1) to finish **8** (74 mg, 73%) as a buff oil. $[\alpha]_D^{26}$ +11.2° (*c* 1.1 CH_2Cl_2). IR (film): ν = 2971, 2925, 1739, 1467, 1373, 1235, 1183, 1026 cm^{-1}. ^1H NMR (400 M, $CDCl_3$): δ 0.96 (d, *J* = 4.7 Hz, 3H), 0.98 (d, *J* = 4.7 Hz, 3H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.96-2.02 (m, 1H), 2.09 (s, 3H), 2.52 (dd, *J* = 5.3, 10.3 Hz, 1H), 2.63 (dd, *J* = 5.8, 11.0 Hz, 1H), 2.94 (dd, *J* = 1.8, 6.5 Hz, 1H), 3.21 (ddd, *J* = 1.8, 6.0, 11.0 Hz, 1H), 4.17 (q, *J* = 7.4 Hz, 2H), 4.53 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 M, $CDCl_3$): δ 14.06, 18.25, 18.60, 20.80, 28.96, 37.08, 52.53, 57.83, 60.88, 75.95, 169.73, 170.22. EIMS: *m/e* 201, 159, 131, 117, 85, 71, 43.

(+)-(3*R*,4*R*,5*S*)-4-(1-acetoxy-isopropyl)-3-Hydroxy-butyrolactone (9)

To a stirred solution of **8** (109 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0°C under Ar atmosphere, was added camphosulfic acid (11 mg, 0.045 mmol). The reaction mix-

ture was stirred for 24 h at room tem per a ture. The quench ing was made by add ing a sat u rated so lu tion of $NaHCO_3$, followed by ex trac tion with CH_2Cl_2, dried over $MgSO_4$ and concen trated to give the crude prod uct pu ri fied by sil ica gel column chro ma tog ra phy (pe tro leum:EtOAc, 4:1), yielded a colorless gum **9** (56 mg, 63%, 99%de). $[\alpha]_D^{26}$ +5.6° (*c* 0.7 CH_2Cl_2). IR (film): ν = 3414, 2964, 1783, 1743, 1378, 1235, 1178, 1073 cm^{-1}. ^1H NMR (400 M, $CDCl_3$) : δ 97 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.70-1.95 (m, 1H), 2.11 (s, 3H), 2.49 (dd, *J* = 1.6, 18.6 Hz, 1H), 3.07 (dd, *J* = 7.2, 18.5 Hz, 1H), 3.51 (dd, *J* = 3.7, 8.0 Hz, 1H), 4.58 (dd, *J* = 1.7, 3.7 Hz, 1H), 5.45 (dd, *J* = 1.6, 7.2 Hz). ^{13}C NMR (100 M, $CDCl_3$): δ 18.16, 18.87, 29.92, 35.92, 70.34, 85.84, 170.19,175.17. EIMS: *m/e* 173, 155, 1 43, 84, 43. HRMS (M+NH_4) calcd for $C_{10}H_{22}O_5N$ 234.1336, found 234.1336.

(+)-(5*S*)-6-Methyl-5-*tert*-butyldimethyl-siloxy-3-heptenoate (10)

To a so lu tion of **6** (350 mg, 1.88 mmol) in an hy drous DMF (3 mL) at r.t. un der Ar at mo sphere, were added Et_3N (1.44 mL), TBDMCl (340 mg, 2.26 mmol) and DMAP (12 mg, 0.094 mmol). The mix ture was stirred 6 hours at r.t., quenched with a sat u rated so lu tion of NH_4Cl (1.5 mL) and diluted with Et_2O. The or ganic layer was washed with H_2O and brine, dried over $MgSO_4$ and con cen trated to give the crude prod uct pu ri fied by sil ica gel col umn chro ma tog ra phy (pe tro leum:EtOAc, 16:1), yielded a col or less oil **10** (463 mg, 82%). $[\alpha]_D^{20}$ +9.6° (*c* 1.7 CH_2Cl_2). IR (film): ν = 2922, 1733, 1626, 1405, 1381, 1158, 1072, 1023 cm^{-1}. ^1H NMR (200 M, $CDCl_3$): δ 0.04 (s, 3H), 0.08 (s, 3H), 0.83 (brs, 3H), 0.86 (brs, 3H), 090 (s, 12H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.63-1.70 (m, 1H), 3.04-3.09 (m, 2H), 3.80 (t, *J* = 6.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.54-5.62 (m, 2H). EIMS: *m/e* 243, 213, 185, 143, 130, 117, 97, 73, 43.

(+)-(3*S*,4*R*,5*S*)-4-(1-*tert*-butyldimethylsiloxy-isopropyl)-3-hydroxy-butyrolactone (11)

To com pound **10** (208 mg, 0.68 mmol) was added a mix ture of t-BuOH (3.5 mL), H_2O (3.5 mL), AD-mix β (966 mg, 0.69 mmol), and methanesulfonyl am ide (66 mg, 0.69 mmol). The so lu tion was stirred for 72 hours at 0 °C. Af ter the ad di tion of sat u rated Na_2SO_3 (1.0 g, 0.69 mmol), the mixture was stirred for 40 min utes and di luted with EtOAc. The or ganic layer was washed with H_2O and brine, dried over $MgSO_4$ and con cen trated to give the crude prod uct pu ri fied by sil ica gel col umn chro ma tog ra phy (pe tro leum:EtOAc, 4:1), yielded a col or less fis sile crys tal **11** (82 mg, 45%). $[\alpha]_D^{20}$ +7.0° (*c* 1.9 CH_2Cl_2). IR (film): ν = 3467, 2956, 2930, 2856, 1770, 1754, 1469, 1389, 1252, 1128, 1065, 841 cm^{-1}. ^1H NMR (400 M, $CDCl_3$): δ 0.14 (s, 3H), 0.20 (s, 3H), 0.91(s, 12H), 1.04 (d, *J* = 4.2 Hz, 3H), 1.06 (d, *J* = 4.2 Hz, 3H), 2.03-2.08 (m, 1H), 2.59 (brd, 1H), 2.69 (dd, *J* = 4 .8, 17.4 Hz, 1H), 4.07 (dd, *J* = 1.9, 7.0 Hz, 1H), 4.33-4.35 (m, 1H), 4.71 (dd, *J* = 1.8, 7.7 Hz, 1H), 4.97 (d, *J* = 3.2 Hz, OH). ^{13}C NMR (100 M, $CDCl_3$): δ 18.10, 19.02, 19.19, 25.82, 31.48, 40.48, 69.99, 81.31, 175.33. EIMS: *m/e* 287, 245, 231, 201, 187, 171, 159, 147, 129, 117, 113, 101, 25, 43. HRMS (M+NH_4) calcd for $C_{14}H_{32}O_4NSi$ 306.2095, found 306.2099.

(-)-(3*R*,4*S*,5*S*)-4-(1-*tert*-butyldimethylsiloxy-isopropyl)-3-hydroxy-butyrolactone (12)

Com pound **12** was pre pared in the same method as **11**, ob tained a col or less fis sile crys tal in yield 51%. $[\alpha]_D^{20}$ -14.0° (*c* 1.0 CH_2Cl_2). ^1H NMR (200 M, $CDCl_3$): δ 0.13 (s, 3H), 0.19 (s, 3H), 0.90 (s, 12H), 1.04 (d, *J* = 4.2 Hz, 3H), 1.06 (d, *J* = 4.2 Hz, 3H), 1.99-2.10 (m, 1H), 2.61-2.69 (m, 2H), 4.07 (dd, *J* = 3.0, 7.0 Hz, 1H), 4.31-4.35 (m, 1H), 4.69-4.71 (m, 1H), 4.96 (d, *J* = 3.2 Hz, OH). ^{13}C NMR (50 M, $CDCl_3$): δ 18.10, 19.02, 19.22, 25.82, 31.49, 40.48, 70.01, 81.29, 175.33. IR, EIMS and HRMS were same as com pound **11**.

ACKNOWLEDGMENT

We thank the Natural Sci ence Foun da tion of China (20272020) and Spe cial Re search Grant for Doc tor Sites in Chinese University.

Received January 2, 2003.

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