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Asymmetric synthesis of (*S*)-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-butanol, a key intermediate for (1*S*,5*R*)-(−)-frontalin via asymmetric bromolactonization

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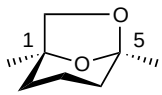
Abstract—A asymmetric synthesis of (*S*)-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-butanol, a key intermediate for (1*S*,5*R*)-(−)-frontalin, via asymmetric bromolactonization employing (*S*)-(−)-proline as a chiral auxiliary is described.

1. Introduction

(1*S*,5*R*)-(−)-Frontalin **1** is one of the aggregation pheromones secreted from the southern pine beetle (*Dendroctonus frontalis*), the western pine beetle (*Dendroctonus brevicomis*), and the Douglas-fir beetle (*Dendroctonus pseudotsugae*).[1] Since these beetles destroy large areas of pine forest each year, frontalin has been used to exterminate the harmful insects. In terms of environmental impact, the aggregation pheromone method is very desirable as compared to the use of general chemical pesticides. Studies on the biological activities of **1** revealed that of the two possible enantiomers, only the (1*S*,5*R*)-isomer shows aggregation activity. A number of enantioselective synthetic methods for **1** have been presented, employing chiral building blocks,[2] chiral auxiliaries,[3] chiral reagents,[4] and Sharpless asymmetric dihydroxylation.[5] Herein, we introduce a new, efficient enantioselective synthetic method for (1*S*,5*R*)-(−)-frontalin via bromolactonization,[6] using (*S*)-(−)-proline as a chiral auxiliary.



1

(1*S*,5*R*)-(-)-Frontalin

2. Results and discussion

Although (1*S*,5*R*)-(−)-frontalin contains two stereogenic centers, only the configuration at C(1) needs to be considered in the enantioselective synthesis because the stereochemistry at C(5) can be controlled in forming the ketal from the corresponding methyl ketone.

Based on the retrosynthetic analysis depicted in Scheme 1, we planned to prepare enantiomerically pure **2** by asymmetric bromolactonization, which can be converted to (1*S*,5*R*)-(−)-frontalin in four steps by a known method.[7,10] The α,β-unsaturated ester **7**, the substrate for asymmetric bromolactonization, was prepared from the commercially available 4-benzyloxybutylbromide **5** (Scheme 2). The successive alkylation of triethyl phosphonoacetate with **5** and Horner–Wadsworth–Emmons reaction[8] using formaldehyde, followed by alkaline hydrolysis gave **7**. Compound **7** was coupled with (*S*)-(−)-ethyl prolinate[9] using diethyl phosphorocyanidate (DEPC) in the presence of triethylamine to give the (*S*)-α,β-unsaturated acyl proline ethyl ester **8**, $[\alpha]_D^{20} = -41.3$ (*c* 2.40, $CHCl_3$), which was hydrolyzed to the (*S*)-α,β-unsaturated acyl proline **9**, $[\alpha]_D^{20} = -91.4$ (*c* 0.91, $CHCl_3$). Bromolactonization of **9** was performed with *N*-bromosuccinimide (NBS) in *N*,*N*-dimethylformamide (DMF) to give **10** with 99% e.e., $[\alpha]_D^{20} = -93.9$ (*c* 1.94, $CHCl_3$) (vide infra).

The bromolactone **10** was then debrominated with *n*-Bu_3SnH to give lactone **11**, $[\alpha]_D^{20} = -101.7$ (*c* 0.80,

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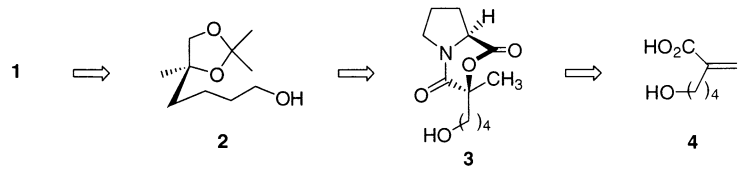
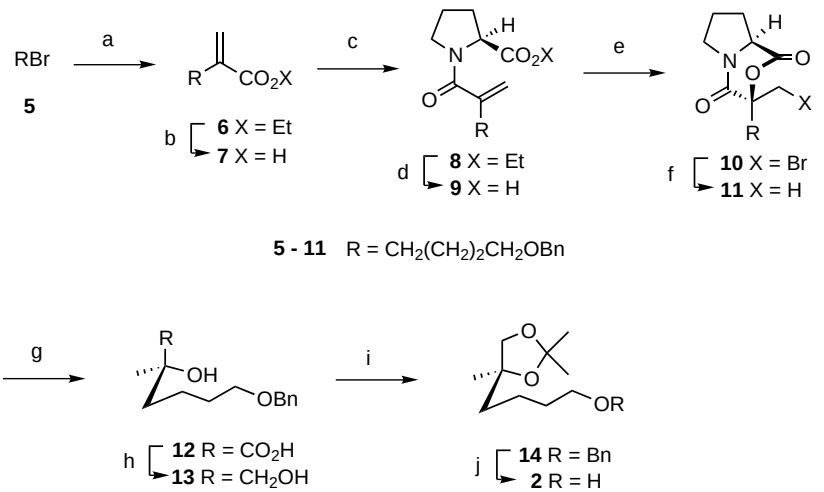


Scheme 1.



Scheme 2. *Reagents and conditions*: (a) triethyl phosphonoacetate, NaH, DME, reflux, 20 h; $(CH_2O)_n$, NaH, DME, rt, 4 h, 55%. (b) KOH, MeOH, H_2O, rt, 6 h, quant. (c) (*S*)-(−)-Ethyl prolinate, DEPC, Et_3N, DMF, rt, 2.5 h, 92%. (d) KOH, MeOH, H_2O, reflux, 4 h, quant. (e) NBS, DMF, 0°C to rt, 24 h, 60%. (f) *n*-Bu_3SnH, benzene, reflux, 2 h, 95%. (g) 2N aq. KOH, reflux, 24 h. (h) $BH_3{\cdot}SMe_2$, THF, 0°C, 24 h, 80% (two steps from **11**). (i) 2,2-Dimethoxypropane, PPTS, CH_2Cl_2, rt, 3 h, 95%. (j) H_2, 10% Pd/C, abs. EtOH, rt, 2 h, quant.

$CHCl_3$), which was hydrolyzed under basic conditions to produce the α-hydroxy acid **12**. Diol **13**, $[\alpha]_D^{20}=-5.3$ (*c* 0.92, $CHCl_3$), was prepared by reduction of **12** using borane. The diastereoselectivity of the bromolactonization step (**10**, 99% d.e.) was determined by HPLC (Chiralcel OD column) of **13**.[11] Protection of the diol **13** gave the acetonide **14**, $[\alpha]_D^{20}=-1.9$ (*c* 1.13, $CHCl_3$), and the subsequent removal of the benzyl group of **14** by hydrogenolysis provided **2**, $[\alpha]_D^{20}=-2.43$ (*c* 1.07, $CHCl_3$); lit.[10] $[\alpha]_D^{24}=-2.57$ (*c* 1.11, $CHCl_3$). The absolute configuration at C(1′) of **10** was assigned as *S* by chemical correlation with **2**. Compound **2** can be converted to (1*S*,5*R*)-(−)-frontalin in four steps by a known process.[7,10]

3. Conclusion

In summary, a new enantioselective synthetic method for (*S*)-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-butanol **2**, a key intermediate for (1*S*,5*R*)-(−)-frontalin, has been developed via asymmetric bromolactonization using (*S*)-proline as a chiral auxiliary from the α,β-unsaturated acid **7** in eight steps (40% overall yield, 99% e.e.). Due to the high enantioselectivity and the good chemical yield, we believe that this synthetic method can be easily applied in an industrial process.

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-1000 digital polarimeter. Infrared spectra were taken on a Perkin–Elmer 1710 FT-IR spectrometer. Mass spectra and high resolution mass spectra were obtained on an HP 5890 Series II. ^1H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300, a JEOL JNM-GCX 400 spectrometer using TMS as the internal standard. HPLC analysis was carried out on HITACHI L-7420, L-7100 chromatography with Chiralcel OD column from DAICEL. All reactions were carried out under a nitrogen atmosphere using anhydrous solvents except for those involving hydrolysis. Most reagents were obtained from commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone.

4.2. Ethyl 2-[4-(benzyloxy)butyl]acrylate 6

To a suspension of NaH (95%, 579 mg, 22.9 mmol) in 1,2-dimethoxyethane (15 mL) was added a solution of triethyl phosphonoacetate (4.13 mL, 20.8 mmol) in 1,2-dimethoxyethane (15 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred for 2 h then 4-benzyloxybutyl bromide (5.07 g, 20.8 mmol) was added. The mixture was heated under reflux for 20

h then cooled to room temperature. The reaction mixture was cooled to 0°C and NaH (95%, 579 mg, 22.9 mmol) was added. The resulting suspension was allowed to warm to room temperature, stirred for 1 h and treated with paraformaldehyde (95%, 697 mg, 22 mmol) and then stirred for 4 h. The excess solvent was then removed in vacuo and the residue was diluted with ethyl acetate (600 mL). The ethyl acetate solution was washed with water (2×30 mL) and brine (2×30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:30) to give **6** as a colorless oil (3.02 g, 55% yield). IR (neat): 2937, 1714, 1455, 1151 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.21 (m, 5H), 6.11 (s, 1H), 5.49 (s, 1H), 4.48 (s, 2H), 4.18 (q, 2H, J = 7.1 Hz), 3.47 (t, 2H, J = 6.3 Hz), 2.30 (t, 2H, J = 7.2 Hz), 1.68–1.49 (m, 4H), 1.28 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.31, 140.77, 138.62, 128.50, 128.20, 127.76, 127.64, 127.47, 127.36, 72.900, 70.141, 60.565, 31.595, 29.308, 25.007, 14.333. MS (EI): m/z 262 $[M]^+$. HRMS (CI): calcd for $C_{16}H_{23}O_3$, 263.1647 $[M+1]^+$; found: 263.1642.

4.3. 2-[4-(Benzyloxy)butyl]acrylic acid 7

A mixture of methanol–water (1:1, 60 mL), **6** (3 g, 11.5 mmol) and 85% potassium hydroxide (1.14 g, 17.2 mmol) was heated under reflux for 6 h. Excess methanol was removed in vacuo and the water mixture was acidified with a 5% aqueous HCl solution. The solution was extracted with ethyl acetate (3×150 mL). The combined ethyl acetate solution was washed with brine (2×20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give crude **7** as a colorless oil (2.68 g, 100% yield). IR (neat): 2921, 1696, 1445, 1103 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.21 (m, 5H), 6.25 (s, 1H), 5.61 (s, 1H), 4.49 (s, 2H), 3.47 (t, 2H, J = 6.3 Hz), 2.31 (t, 2H, J = 7.2 Hz), 1.69–1.51 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.71, 140.29, 138.97, 128.77, 128.06, 127.93, 127.53, 127.16, 122.90, 73.324, 70.465, 31.649, 29.677, 24.315. MS (EI): m/z 234 $[M]^+$. HRMS (CI): calcd for $C_{14}H_{19}O_3$, 235.1334 $[M+1]^+$; found: 235.1335.

4.4. Ethyl (2*S*)-1-2-[4-(benzyloxy)butyl]acryloyl-pyrrolidine-2-carboxylate 8

To a solution of **7** (2.66 g, 11.4 mmol) and (*S*)-(−)-ethyl prolinate (1.79 g, 12.5 mmol) in *N*,*N*-dimethylformamide (70 mL) was added diethyl phosphorocyanidate (1.9 mL, 12.5 mmol) and triethylamine (1.74 mL, 12.5 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2.5 h. The excess solvent was removed in vacuo and the residue was diluted with ethyl acetate (500 mL). The ethyl acetate solution was washed with a 1N aqueous HCl solution (2×20 mL), a saturated aqueous $NaHCO_3$ solution (2×20 mL), water (5×20 mL) and brine (2×20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:2) to give **8** as a colorless oil (3.75 g, 92% yield). $[\alpha]_D^{20}$ −41.3 (*c* 2.40, $CHCl_3$). IR (neat): 3479, 2935, 1746, 1651, 1186 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.21 (m, 5H), 5.24 (s, 1H), 5.21 (s, 1H), 4.41–4.57 (m, 3H), 4.16 (q, 2H, J = 7.1 Hz), 3.65–3.55 (m, 2H), 3.46 (t, 2H, J = 6.1 Hz), 2.31 (t, 2H, J = 7.1 Hz), 2.02–1.84 (m, 4H), 1.66–1.54 (m, 4H), 1.24 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.99, 170.78, 145.77, 139.02, 128.79, 128.67, 128.51, 128.29, 128.07, 115.95, 73.263, 70.462, 61.264, 59.368, 49.582, 33.934, 31.701, 29.760, 25.450, 24.553, 14.462. MS (EI): m/z 359 $[M]^+$. HRMS (CI): calcd for $C_{21}H_{30}NO_4$, 360.2175 $[M+1]^+$; found: 360.2178.

4.5. (2*S*)-1-2-[4-(Benzyloxy)butyl]acryloylpyrrolidine-2-carboxylic acid 9

A mixture of methanol–water (1:1, 75 mL), **8** (3.62 g, 10.1 mmol) and 85% potassium hydroxide (1.0 g, 15.1 mmol) was stirred at room temperature for 4 h. Excess methanol was removed in vacuo and the water mixture was acidified with 1N aqueous HCl solution and extracted with ethyl acetate (5×200 mL). The combined ethyl acetate solution was washed with water (2×25 mL) and brine (2×25 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo to give crude **9** as a colorless oil (3.35 g, 100% yield). $[\alpha]_D^{20}$ −91.4 (*c* 0.91, $CHCl_3$). IR (neat): 3444, 2924, 1732, 1645, 1455 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.19 (m, 5H), 5.28 (s, 1H), 5.18 (s, 1H), 4.56–4.54 (m, 1H), 4.43 (s, 2H), 3.59–3.46 (m, 2H), 3.42 (t, 2H, J = 6.3 Hz), 2.28 (t, 2H, J = 7.5 Hz), 2.05–1.76 (m, 4H), 1.61–1.45 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.89, 172.21, 144.58, 138.48, 128.31 (×2), 127.61 (×2), 127.49, 116.42, 72.849, 62.920, 59.257, 49.648, 33.344, 29.213, 28.254, 24.889, 24.127. MS (EI): m/z 331 $[M]^+$. HRMS (CI): calcd for $C_{19}H_{26}NO_4$, 332.1862 $[M+1]^+$; found: 332.1865.

4.6. Bromolactone 10

To a solution of **9** (0.390 g, 2.35 mmol) in *N*,*N*-dimethylformamide (4 mL) cooled at 0°C was added a solution of NBS (0.42 g, 4.70 mmol) in *N*,*N*-dimethylformamide (5 mL). The reaction mixture was stirred at 0°C for 2 h and then allowed to warm to room temperature and stirred for 24 h. The excess solvent was removed in vacuo and the residue was diluted with ethyl acetate (150 mL). The ethyl acetate solution was washed with a saturated aqueous $NaHCO_3$ solution (2×10 mL), water (5×10 mL), a 1N aqueous HCl solution (2×10 mL), brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 2:3) to give bromolactone **10** as a colorless oil (0.29 mg, 60% yield). $[\alpha]_D^{20}$ −93.9 (*c* 1.94, $CHCl_3$). IR (neat): 2921, 1748, 1682, 1455, 1104 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.26 (m, 5H), 4.52–4.49 (m, 1H), 4.47 (s, 2H), 3.74 (ABq, 2H, J = 11.2 Hz), 3.73–3.67 (m, 2H), 3.44 (t, 2H, J = 6.3 Hz), 2.50–2.46 (m, 2H), 2.24–1.75 (m, 4H), 1.63–1.45 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.34, 163.44, 138.42, 128.29 (×2), 127.56 (×2), 127.46, 88.586, 72.756, 69.580, 57.933, 44.971, 37.939, 37.599, 29.877, 29.224, 21.472, 20.584. MS (EI): m/z 409 $[M]^+$. HRMS (CI): calcd for $C_{19}H_{25}NO_4{}^{81}Br$, 412.0967 $[M+1]^+$; found: 412.0937.

4.7. (3*S*,8a*S*)-3-[4-(Benzyloxy)butyl]-3-methyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,4(3*H*)-dione 11

To a solution of **10** (144 mg, 0.35 mmol) in benzene (4 mL) was added *n*-Bu_3SnH (283 μL, 1.05 mmol). The reaction mixture was heated under reflux for 2 h. The excess solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:1) to give **11** as a white solid (110 mg, 95% yield). $[\alpha]_D^{20}$ −101.7 (*c* 0.80, $CHCl_3$). IR (neat): 2925, 1754, 1667, 1454, 1106 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.23 (m, 5H), 4.49 (s, 2H), 4.24–4.19 (m, 1H), 3.67–3.55 (m, 2H), 3.46 (t, 2H, J = 6.0 Hz), 2.51–2.42 (m, 2H), 2.19–2.03 (m, 4H), 1.97–1.62 (m, 4H), 1.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.21, 166.73, 138.63, 128.34 (×2), 127.64 (×2), 127.46, 86.30, 72.85, 70.13, 57.45, 45.39, 37.70, 37.55, 29.65, 23.92, 22.27, 20.23. MS (EI): *m*/*z* 331 $[M]^+$. HRMS (CI): calcd for $C_{19}H_{26}NO_4$, 332.1862 $[M+1]^+$; found: 332.1862.

4.8. (2*S*)-6-(Benzyloxy)-2-hydroxy-2-methylhexanoic acid 12

A solution of **11** (92.4 mg, 0.279 mmol) in a 3N aqueous KOH (2.5 mL) was heated under reflux for 24 h. The reaction mixture was acidified with a 1N aqueous HCl solution and extracted with ethyl acetate (5×10 mL). The combined ethyl acetate solution was washed with brine (2×5 mL), dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo to give the crude acid **12** as pale yellow oil (70 mg), which was not purified further.

4.9. (2*S*)-6-(Benzyloxy)-2-methyl-1,2-hexanediol 13

To a solution of **12** (847 mg, 3.36 mmol) in tetrahydrofuran (18 mL) was added $BH_3{\cdot}SMe_2$ (2.0 M solution in THF, 4.2 mL, 8.39 mmol). The reaction mixture was stirred for 24 h at 0°C then the reaction was quenched with a 5% aqueous AcOH solution (2–3 drops) and the excess solvent was removed in vacuo. The residue was diluted with ethyl acetate (100 mL) and the ethyl acetate solution was washed with a saturated aqueous $NaHCO_3$ solution (3×10 mL), water (5×10 mL), brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The excess solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:1) to give **13** as a colorless oil (400 mg, 80% yield). $[\alpha]_D^{20}$ −5.3 (*c* 0.92, $CHCl_3$). IR (neat): 2937, 1456, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.26 (m, 5H), 4.50 (s, 2H), 3.49 (t, 2H, J = 6.3 Hz), 3.43 (ABq, 2H, J = 10.7 Hz), 1.85 (br s, 2H), 1.69–1.42 (m, 6H), 1.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.51, 128.39, 127.77, 127.71, 127.66, 127.58, 72.96, 72.89, 70.16, 69.77, 38.33, 30.16, 23.21, 20.50. MS (EI): *m*/*z* 237 $[M-1]^+$. HRMS (CI): calcd for $C_{14}H_{23}O_3$, 239.1647 $[M+1]^+$; found: 239.1650.

4.10. Benzyl 4-[(4*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl]-butyl ether 14

To a solution of **13** in dichloromethane (6 mL) and pyridinium *p*-toluenesulfonate (182 mg, 0.73 mmol) was added 2,2-dimethoxypropane (0.54 mL, 4.36 mmol). The reaction mixture was stirred at room temperature for 3 h. The excess solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with a saturated aqueous $NaHCO_3$ solution (2×15 mL), water (2×15 mL), brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:9) to give **14** as a colorless oil (354 mg, 95% yield). $[\alpha]_D^{20}$ −1.9 (*c* 1.13, $CHCl_3$). IR (neat): 2936, 1455 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.26 (m, 5H), 4.50 (s, 2H), 3.73 (ABq, 2H, J = 8.3 Hz), 3.48 (t, 2H, J = 6.5 Hz), 1.65–1.42 (m, 6H), 1.39 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.63, 128.37, 127.65 (×2), 127.52 (×2), 109.00, 81.20, 73.99, 72.95, 70.19, 39.90, 30.22, 27.26, 27.13, 24.79, 21.22. MS (EI): *m*/*z* 277 $[M-1]^+$. HRMS (CI): calcd for $C_{17}H_{27}O_3$, 279.1960 $[M+1]^+$; found: 279.1954.

4.11. (*S*)-4-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-1-butanol 2

To a solution of **14** in absolute ethanol (7 mL) was added 10% Pd/C (972 mg). The reaction mixture was stirred at room temperature for 2 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. Then the residue was purified by column chromatography (SiO_2, ethyl acetate:*n*-hexane = 1:2) to give **2** as a colorless oil (180 mg, quant.). $[\alpha]_D^{20}$ −2.43 (*c* 1.07, $CHCl_3$) (lit.[10] −2.57 (*c* 1.11, $CHCl_3$)). IR (neat): 1117 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (ABq, 2H, J = 8.3 Hz), 3.66 (t, 2H, J = 6.3 Hz), 1.64–1.42 (m, 6H), 1.40 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.02, 81.15, 73.93, 62.62, 39.72, 33.06, 27.17, 27.07, 24.73, 20.67. MS (EI): *m*/*z* 189 $[M+1]^+$. HRMS (CI): calcd for $C_{10}H_{21}O_3$, 189.1490 $[M+1]^+$; found: 189.1494.

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11. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention time; *R* (minor) 15.8 min, *S* (major) 23.4 min, 99% ee).