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Enantioselective synthesis of (*S*)-*N*,*N*-diethyl-2-formyl-2-(methoxymethoxy)butyramide, a key intermediate for 20(*S*)-camptothecin analogues, via asymmetric bromolactonization

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Abstract

A new enantioselective synthetic method for enantiomerically pure (*S*)-*N*,*N*-diethyl-2-formyl-2-(methoxymethoxy)butyramide **5**, a versatile key intermediate has been developed employing asymmetric bromolactonization using (*S*)-proline as the chiral auxiliary. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Camptothecin **1**, a pentacyclic alkaloid with potent antitumor activity, has a peculiar mode of action trapping a cleavable complex between topoisomerase I and DNA.[1] Several camptothecin derivatives such as **2** (CKD 602),[2] **3** (lurtotecan),[3] and **4** (DX8951f)[4] developed through recent SAR studies have been highlighted as potential candidates for anticancer agents. As only the 20(*S*)-enantiomer shows biological activity, efficient enantioselective synthetic methods have been extensively studied. So far a few enantioselective syntheses of 20(*S*)-camptothecin have been reported by employing chemical[5] or enzymatic resolution,[6] asymmetric alkylation[7] with chiral enolates, and catalytic asymmetric dihydroxylation[8] as key reactions. Among them, Ciufolini's 3-cyanopyridone protocol[6b,d,9] providing the best enantioselectivity is one of the most attractive synthetic methods for 20(*S*)-camptothecin. (*S*)-Aldehyde **5** was the key synthetic intermediate which was prepared by enzymatic (pig liver esterase) resolution.[6b,d]

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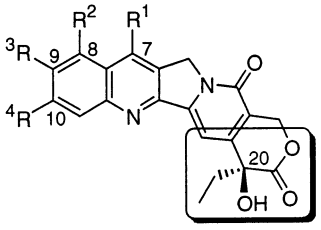
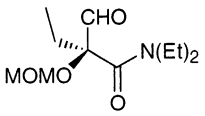




5

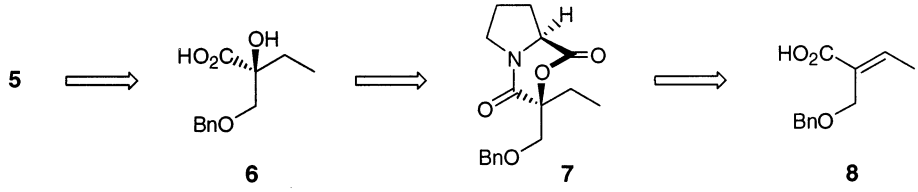
1 R^1, R^2, R^3, R^4 = H

2 R^1 = $CH_2CH_2NHCH(CH_3)_2$, R^2, R^3, R^4 = H

3 R^1 = $CH_2N(CH_2CH_2)_2NCH_3$, R^3 and R^4= OCH_2CH_2O, R^2= H

4 R^1 and R^2 = $(CH_2)_2$ (*S*) $CHNH_2$, R^3, R^4 = H

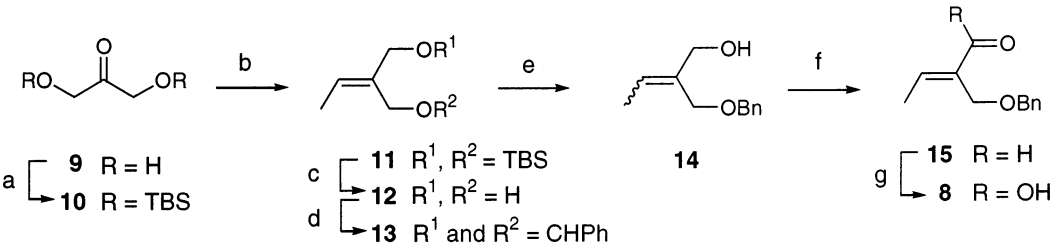
In connection with our development of an efficient synthetic process for CKD 602 **2** in phase II clinical trials, it was envisaged that the (*S*)-aldehyde **5** could be obtained from (*S*)-α,α-disubstituted-α-hydroxy acid **6** which would be accessible from α,β-unsaturated acid **8** by employing an asymmetric bromolactonization[10] as shown by retrosynthetic analysis (Scheme 1). In this paper, a highly enantioselective synthetic method for **5** using asymmetric bromolactonization is described.



Scheme 1.

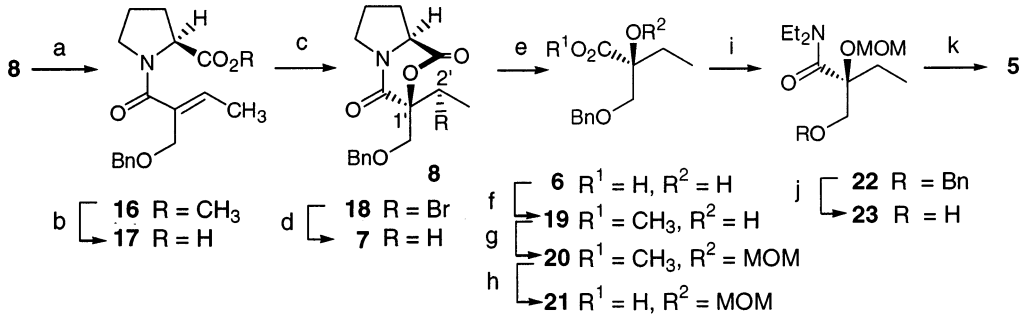
2. Results and discussion

α,β-Unsaturated acid **8**, the substrate for asymmetric bromolactonization, was prepared from dihydroxyacetone **9**. Conversion of **9** to *tert*-butyldimethylsilyl ether **10** using *tert*-butyldimethylsilyl chloride (TBSCl) followed by a Wittig reaction with (ethyl)triphenylphosphonium iodide and *n*-butyllithium gave di-*tert*-butyldimethyloxyalkene **11** in 83% from **9**. Deprotection of the TBS group of **11** with tetrabutylammonium fluoride, followed by acetal formation using benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid and subsequent reduction with DIBALH afforded benzyloxyallylalcohol **14** as a mixture (*E*:*Z*=1:1) in 93% yield. Swern oxidation of **14** gave (*E*)-α,β-unsaturated aldehyde **15** exclusively, which was converted to the corresponding acid **8** using $NaClO_2$ in the presence of excess 2-methyl-2-butene in 80% from **14** (Scheme 2).



Scheme 2. Reagents and conditions: (a) TBSCl, TEA, CH_2Cl_2, rt; (b) Ph_3PEtI, *n*-BuLi, THF, 0°C to rt; (c) *n*-Bu_4NF, THF, rt; (d) $C_6H_5CH(OCH_3)_2$, PTSA, CH_2Cl_2, reflux; (e) DIBALH, CH_2Cl_2, −78 to 0°C; (f) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 to 0°C; (g) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, rt

The (*S*)-aldehyde **5** was obtained from the α,β-unsaturated acid **8** by asymmetric bromolactonization using (*S*)-proline as the chiral auxiliary (Scheme 3). Compound **8** was coupled with (*S*)-proline methyl ester using diethyl phosphorocyanidate in the presence of triethylamine to give (*S*)-α,β-unsaturated acyl proline methyl ester **16**, $[\alpha]_D^{20}=-54$ (*c* 1.0, $CHCl_3$), which was hydrolyzed to (*S*)-α,β-unsaturated acyl proline **17**, $[\alpha]_D^{20}=-97$ (*c* 1.0, $CHCl_3$) in 90% from **8**. Bromolactonization of **17** was performed with *n*-butyllithium and *N*-bromosuccinimide in dimethylformamide to give enantiomerically pure bromolcatone **18**, $[\alpha]_D^{20}=-29$ (*c* 4.2, $CHCl_3$) (51%) (vide infra). The bromolactone **18** was debrominated with n-Bu_3SnH to provide lactone **7**, $[\alpha]_D^{20}=-65$ (*c* 1.4, $CHCl_3$) in 95%. The hydrolysis of both the lactone and lactam groups under basic condition gave (*S*)-α-hydroxy acid **6**, $[\alpha]_D^{20}=+12$ (*c* 1.0, $CHCl_3$), in 73% yield. Esterification of **6** with excess CH_2N_2 gave (*S*)-α-hydroxy acid methylester **19**, $[\alpha]_D^{20}=-3.1$ (*c* 0.78, $CHCl_3$), which was treated with MOMCl to afford (*S*)-α-MOMoxy methyl ester **20**, $[\alpha]_D^{20}=+29$ (*c* 1.0, $CHCl_3$) in 94% from **6**. The methyl ester **20** was hydrolyzed to (*S*)-α-methoxymethoxy acid **21**, $[\alpha]_D^{20}=+18$ (*c* 1.0, $CHCl_3$) in 94% yield. Coupling of **21** and diethylamine using 2-chloro-1-methylpyridinium iodide afforded (*S*)-α-methoxymethoxy amide **22**, $[\alpha]_D^{20}=+33$ (*c* 1.0, $CHCl_3$) in 92% yield. Removal of benzyl group of the (*S*)-amide **22** by hydrogenolysis led to (*S*)-α-hydroxymethyl amide **23**, $[\alpha]_D^{20}=+33$ (*c* 1.4, $CHCl_3$). The diastereoselectivity of the asymmetric bromolactonization step (**18**, >99% ee) was determined by HPLC (Chiral OD column) of **23**, which showed no detectable *R* enantiomer. Swern oxidation of **23** provided the enantiomerically pure (*S*)-aldehyde **5**,[11] $[\alpha]_D^{20}=-55$ (*c* 8.0, $CHCl_3$); lit.[6a] $[\alpha]_D^{20}=-40.8$ (*c* 10.25, $CHCl_3$) in 95%. The absolute configuration of C(1′) of **18** was assigned as *S* by chemical correlation with **5**.



Scheme 3. Reagents and conditions: (a) (*S*)-proline methyl ester, DEPC, TEA, DMF, 0°C–rt; (b) KOH, MeOH–H_2O=1:1, rt; (c) NBS, *n*-BuLi, DMF, 0°C–rt; (d) n-Bu_3SnH, AIBN, benzene, reflux; (e) 3N KOH, reflux; (f) CH_2N_2, ether, 0°C–rt; (g) MOMCl, NaH, THF, 0–60°C; (h) KOH, MeOH:H_2O=1:1, rt; (i) Et_2NH, TEA, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 0°C–rt; (j) Pd/C, H_2, EtOH, rt; (k) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78°C to rt

3. Conclusion

In summary, a new enantioselective synthetic method for enantiomerically pure (*S*)-*N*,*N*-diethyl-2-formyl-2-(methoxymethoxy)butyramide **5** has been developed via asymmetric bromolactonization using (*S*)-proline as the chiral auxiliary from α,β-unsaturated acid **8** in 11 steps (25%, >99% ee). Because of high enantioselectivity, we believe that this new synthetic method can be applied to prepare various potential 20(*S*)-camptothecin derivatives **2**, **3**, and **4** in enantiomerically pure form.

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 FTIR spectrometer. Mass spectra were obtained on a VG Trio-2 GC–MS instrument; high-resolution mass spectra were obtained on a HP 5890 Series II spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300, a JEOL JNM-GCX 400, or a Bruker AMX-500 spectrometer using TMS as the internal standard. All reactions were carried out under an argon 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^0 and benzophenone, and methylene chloride from CaH_2.

4.2. 1,3-Bis-(tert-butyl-dimethyl-silanyloxy)-propan-2-one **10**

To a methylenechloride solution (100 mL) of dihydroxy acetone (5 g, 55.51 mmol) and TBSCl (18.5 g, 122.12 mmol) was added triethylamine (17 mL, 55.51 mmol) at 0°C. The reaction solution was stirred at room temperature (24 h) and diluted with ethyl acetate (500 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2×100 mL), water (2×100 mL), and brine (100 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (30:1)) to give **10** as a colorless oil (16.84 g, 95% yield): IR (neat) 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.42 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.80, 67.88, 25.71, 18.37; MS (EI) m/e 319 [M^++1], HRMS (EI) calcd for $C_{15}H_{34}O_3Si_2$ [M^++1] 319.2125, found 319.2115.

4.3. 1-(tert-Butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-but-2-ene **11**

To a tetrahydrofuran solution (200 ml) of ethyltriphenylphosphonium iodide (42.09, 100.62 mmol) was added *n*-BuLi (1.6 M in hexane, 63 mL, 100.8 mmol) at −78°C under nitrogen. The solution was allowed to warm to room temperature and stirred for 20 min, after which it was recooled to −78°C, and tetrahydrofuran solution of **10** (16 g, 50.31 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature over 1 h and quenched with water (100 mL) and extracted with pentane (3×100 mL). The organic layer was washed with water (2×50 mL), and brine (100 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (30:1)) to give **11** as a colorless oil (14.85 g, 89% yield): IR (neat) 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (q, J=6.8 Hz, 1H), 4.21 (s, 2H), 4.16 (s, 2H), 1.67 (d, J=6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.26, 121.25, 64.86, 58.22, 25.71, 18.40, 12.83; MS (EI) m/e 330 [M^+], HRMS (EI) calcd for $C_{17}H_{38}O_2Si_2$ [M^+] 330.2411, found 330.2434.

4.4. 2-Ethylidene-propane-1,3-diol **12**

To the tetrahydrofuran (200 mL) solution of **11** (14 g, 42.42 mmol) was added TBAF (1 M in THF, 84.84 mL, 84.84 mmol) dropwise at 0°C. The dark reaction mixture was stirred for 1 h at room temperature. 1N aq. HCl (100 mL) and EtOAc (600 mL) were added to the reaction

mixture and the organic layer was washed with water (2×50 mL) and brine (100 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, EtOAc) to give **12** as a brown oil (4.33 g, 100% yield): IR (neat) 3333 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.65 (q, $J=6.8$ Hz, 1H), 4.33 (s, 2H), 4.20 (s, 2H), 2.01 (br s, 2H), 1.70 (d, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.79, 124.94, 66.12, 58.32, 13.39; MS (EI) m/e 102 [M^+], HRMS (EI) calcd for $C_5H_{10}O_2$ [M^+] 102.0681, found 102.0676.

4.5. 5-Ethylidene-2-phenyl-[1,3]dioxane **13**

A methylene chloride solution of **12** (4 g, 39.2 mmol), benzaldehydedimethylacetal (11.77 mL, 78.43 mmol), and catalytic amount of *p*-toluenesulfonic acid was refluxed for 3 h under nitrogen. The reaction solution was washed with sat. aq. $NaHCO_3$ (2×20 mL), water (20 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (10:1)) to give **13** as a colorless oil (7.30 g, 98% yield): IR (neat) 1558 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.30 (m, 5H), 5.64 (s, 1H), 4.90 (AB q, $J=12.7$ Hz, 1H), 4.54–4.34 (m, 3H), 1.67 (dt, $J=6.8$ Hz, $J=1.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.18, 133.62, 130.10, 128.41, 126.04, 101.61, 72.41, 65.96, 12.24; MS (EI) m/e 190 [M^+], HRMS (EI) calcd for $C_{12}H_{14}O_2$ [M^+] 190.0994, found 190.0985.

4.6. 2-Benzyloxymethyl-but-2-en-1-ol **14**

To a methylene chloride solution (150 mL) of **13** (7 g, 36.84 mmol) was added DIBAL (1 M in CH_2Cl_2, 184 mL, 184 mmol) dropwise at −78°C. It was allowed to warm to 0°C, and stirred for 2 h. The reaction mixture was quenched with Rochell solution (150 mL) and stirred for 1 h at room temperature, then poured into EtOAc (300 mL). The organic layer was washed with water (50 mL) and brine (50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (3:1)) to give **14** as a mixture of isomers (6.72 g, 95% yield): IR (neat) 3443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.28 (m, 5H), 5.76–5.63 (m, 1H), 4.71, 4.50, 4,28 (3d, 2H, $J=6.0$ Hz, $J=6.0$ Hz, $J=5.9$ Hz, 2H), 4.54, 4.52 (2s, 1H), 4.19, 4.09 (2s, 2H), 2.19, 2.09 (2t, $J=5.9$ Hz, 6.0 Hz, 1H), 1.73, 1.67 (2d, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.87, 135.52, 128.51, 127.61, 127.17, 126.45, 74.78, 72.22, 67.10, 66.59, 59.54, 13.28; MS (EI) m/e 192 [M^+], HRMS (EI) calcd for $C_{12}H_{16}O_2$ [M^+] 192.1150, found 195.1133.

4.7. 2-Benzyloxymethyl-but-2-enal **15**

To a methylene chloride (150 mL) solution of oxalyl chloride (9.13 mL, 104.69 mmol) was added Me_2SO (14.86 mL, 209.38 mmol) at −78°C. After 30 min, the CH_2Cl_2 (60 mL) solution of alcohol **14** (6.7 g, 34.9 mmol) was added at −78°C and stirred for 1 h. Et_3N (48.64 mL, 349 mmol) was added and the reation mixture was allowed to warm to room temperture over 1 h. After the reaction was complete, the methylene chloride was removed in vacuo and the residue was diluted with EtOAc (400 mL). The organic solution was washed with water (50 mL) and brine (50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (5:1)) to give **15** as a

yellow oil (5.55 g, 80% yield): IR (neat) 1693, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.42 (s, 1H), 7.38–7.28 (m, 5H), 6.85 (q, $J=7.1$ Hz, 1H), 4.53 (s, 2H), 4.25 (2, 2H), 2.09 (d, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.74, 154.86, 140.96, 138.02, 128.34, 127.82, 126.92, 72.81, 60.72, 15.27; MS (EI) m/e 191 [M^++1], HRMS (EI) calcd for $C_{12}H_{14}O_2$ [M^++1] 191.1072, found 191.1092.

4.8. 1-(2-Benzyloxymethyl-but-2-enoyl)-pyrrolidine-2-carboxylic acid methyl ester **16**

To the *tert*-butanol (300 mL) and 2-methyl-2-butene (58.8 mL, 555.0 mmol) solution of aldehyde **15** (5.3 g, 27.75 mmol) was added an aqueous solution of sodium chlorite (22.59 g, 249.75 mmol) and sodium dihydrogen phosphate (30.30 g, 194.25 mmol) dropwise over 10 min. The pale yellow reaction mixture was stirred at room temperature for 1 h. After the solvent was removed in vacuo, the residue was dissolved in water (100 mL) and extracted with two 20 mL portions of hexane. The aqueous layer was acidified to pH 3 with 1N aq. HCl and extracted with ether (3×100 mL). The combined ether layers were washed with water (30 mL), brine (30 mL), dried and concentrated to give **8** as a colorless oil (5.75 g), which was not purified further. To an *N*,*N*-dimethylformamide solution (60 mL) of the crude acid **8** (5.7 g, 27.54 mmol) and (*S*)-(−)-methyl prolinate (3.91 g, 30.29 mmol) were added diethyl phosphorocyanidate (4.60 mL, 30.29 mmol) and triethylamine (4.22 mL, 30.29 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 h. The reaction solution was diluted with ethyl acetate (200 mL) and the ethyl acetate solution was washed with 5% aq. HCl (30 mL), sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (2:1)) to give **16** as a colorless oil (7.88 g, 90% yield): $[\alpha]_D^{20}$ −54 (*c* 1.0, $CHCl_3$); IR (neat) 1746, 1621 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.42 (s, 1H), 7.36–7.24 (m, 5H), 6.08 (q, $J=6.9$ Hz, 1H), 4.59–4.54 (m, 3H), 4.29 (s, 2H), 3.78–3.56 (m, 5H), 2.30–1.70 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.79, 170.33, 138.31, 134.69, 131.63, 128.34, 128.23, 127.46, 72.64, 63.54, 58.58, 52.05, 49.17, 29.33, 25.12, 16.08; MS (EI) m/e 318 [M^++1], HRMS (EI) calcd for $C_{18}H_{23}NO_4$ [M^++1] 318.1706, found 318.1703.

4.9. 1-(2-Benzyloxymethyl-but-2-enoyl)-pyrrolidine-2-carboxylic acid **17**

The methanol–water (1:1, 160 mL) solution of **16** (7.8 g, 24.61 mmol) and 85% potassium hydroxide (3.25 g, 49.22 mmol) was stirred at room temperature for 3 h. After the methanol was removed in vacuo, the water layer was acidified to pH 4 with 5% aq. HCl solution (60 mL) and extracted with ethyl acetate (3×200 mL). The combined ethyl acetate solution was washed with water (50 mL) and brine (50 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo to give crude **17** as a colorless oil (7.46 g, 100% yield): $[\alpha]_D^{20}$ −97 (*c* 1.0, $CHCl_3$); IR (neat) 1731, 1586 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.28 (m, 5H), 6.01 (q, $J=7.1$ Hz, 1H), 4.64 (m, 1H), 4.53 (s, 2H), 4.28 (s, 2H), 3.69–3.52 (m, 2H), 2.51–2.45 (m, 1H), 2.11–1.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.18, 174.23, 137.97, 134.46, 128.95, 128.32, 127.73, 72.80, 64.96, 60.42, 49.65, 29.50, 24.91, 14.12; MS (EI) m/e 304 [M^++1], HRMS (EI) calcd for $C_{17}H_{21}NO_4$ [M^++1] 304.1549, found 304.1539.

4.10. 3-Benzyloxymethyl-3-(1-bromo-ethyl)-tetrahydro-pyrrolo[2,1-c][1,4]oxazine-1,4-dione **18**

To an *N*,*N*-dimethylformamide solution (30 mL) of **17** (5 g, 16.50 mmol) was added *n*-BuLi (1.6 M in hexane, 10.3 mL, 16.5 mmol) dropwise at 0°C and then an *N*,*N*-dimethylformamide solution (30 mL) of NBS (11.75 g, 66 mmol) was added. The reaction mixture was stirred at 0°C for 2 h and room temperature for 24 h. The reaction mixture was quenched with water (5 mL) and diluted with ethyl acetate (500 mL) and the organic layer was washed with sat. aq. $NaHCO_3$ (2×50 mL), water (5×50 mL), and brine (100 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (2:1)) to give **18** as a yellow oil (3.21 g, 51% yield): $[\alpha]_D^{20}$ −29 (*c* 4.2, $CHCl_3$); IR (neat) 1723, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.18 (m, 5H), 4.49–4.42 (m, 3H), 4.31–4.25 (m, 1H), 3.92 (AB q, $J=9.3$ Hz, 1H), 3.79–3.70 (m, 2H), 3.43–3.35 (m, 1H), 2.30–2.26 (m, 1H), 1.85–1.59 (m, 7H), other diastereomer was not detected; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.76, 162.09, 137.14, 128.31, 127.84, 127.69, 90.38, 74.26, 73.79, 58.04, 50.00, 45.47, 29.58, 21.41; MS (EI) *m*/*e* 381 [M^+], HRMS (EI) calcd for $C_{17}H_{20}{}^{79}BrNO_4$ [M^+] 381.0573, found 381.0571.

4.11. 3-Benzyloxymethyl-3-ethyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazine-1,4-dione **7**

To a benzene solution (100 mL) of **18** (5 g, 10.09 mmol) was added *n*-Bu_3SnH (10.6 mL, 39.28 mmol) and the reaction mixture was refluxed for 3 h. After the benzene was removed in vacuo, the crude residue was purified by column chromatography (SiO_2, hexane–EtOAc (1:1)) to give **7** as a yellow oil (3.77 g, 95% yield): $[\alpha]_D^{20}$ −65 (*c* 1.0, $CHCl_3$); IR (neat) 1755, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (m, 5H), 4.59–4.42 (m, 2H), 4.23–4.09 (m, 1H), 3.94 (AB q, $J=9.8$ Hz, 1H), 3.87–3.31 (m, 3H), 2.41–2.27 (m, 1H), 2.17–1.60 (m, 5H), 0.98 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.04, 164.83, 137.60, 128.27, 128.09, 127.65, 89.90, 73.64, 73.54, 57.79, 45.31, 29.58, 27.27, 21.76, 7.66; MS (EI) *m*/*e* 303 [M^+], HRMS (EI) calcd for $C_{17}H_{21}NO_4$ [M^+] 303.1471, found 303.1497.

4.12. 2-Benzyloxymethyl-2-hydroxy-butyric acid methyl ester **19**

A mixture of 3N aq. KOH solution (80 mL) and **7** (3.7 g, 12.21 mmol) was refluxed for 1 day. The reaction solution was acidified to pH 4 with 1N aq. HCl (250 mL) and extracted with ethyl acetate (3×300 mL). The combined ethyl acetate solution was washed with water (100 mL) and brine (100 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo to give **6** as a yellow oil (2.00 g), which was not purified further. To an ether solution (20 mL) of the crude acid **6** (1.9 g, 8.48 mmol) was added the ether solution of excess diazomethane at 0°C. The excess solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (3:1)) to give **19** as a colorless oil (1.98 g, 70% yield): $[\alpha]_D^{20}$ −3.1 (*c* 0.78, $CHCl_3$); IR (neat) 3519, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.21 (m, 5H), 4.56, 4.46 (AB q, $J=12.2$ Hz, 2H), 3.73 (s, 3H), 3.65, 3.43 (AB q, $J=9.3$ Hz, 2H), 3.35 (s, 1H), 1.72–1.51 (m, 2H), 0.83 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.10, 137.79, 128.32, 127.65, 127.50, 78.51, 75.23, 73.41, 52.61, 28.00, 7.38; MS (EI) *m*/*e* 238 [M^+], HRMS (EI) calcd for $C_{13}H_{18}O_4$ [M^+] 238.1205, found 238.1211.

4.13. 2-Benzyloxymethyl-2-methoxymethoxy-butyric acid methyl ester **20**

To a tetrahydrofuran suspension (40 mL) of 95% NaH (403 mg, 15.96 mmol) was added a tetrahydrofuran solution (10 mL) of **19** (1.9 g, 7.98 mmol) and MOMCl (1.82 mL, 23.94 mmol) at 0°C. The reaction mixture was refluxed for 4 h. After the solvent was removed in vacuo, the residue was diluted with ethyl acetate (200 mL). The ethyl acetate solution was washed with water (20 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (2:1)) to give **10** as a colorless oil (2.16 g, 96% yield): $[\alpha]_D^{20}$ +29 (*c* 1.0, $CHCl_3$); IR (neat) 1747, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.24 (m, 5H), 4.88, 4.77 (AB q, $J=7.1$ Hz, 2H), 4.54, 4.49 (AB q, $J=12.2$ Hz, 2H), 3.72 (s, 2H), 3.71 (s, 3H), 3.39 (s, 3H), 1.88–1.81 (m, 2H), 0.84 (t, $J=7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.74, 137.89, 128.27, 127.57, 127.54, 92.93, 82.41, 73.35, 71.53, 56.06, 52.00, 26.79, 7.58; MS (EI) *m*/*e* 282 [M^+], HRMS (EI) calcd for $C_{15}H_{22}O_5$ [M^+] 282.1467, found 282.1459.

4.14. 2-Benzyloxymethyl-N,N-diethyl-2-methoxymethoxy-butyramide **22**

A methanol–water (1:1, 40 mL) solution of **20** (2 g, 7.09 mmol) and 85% KOH (936 mg, 13.18 mmol) was stirred at 50°C for 3 h. After the methanol was removed in vacuo, the water layer was acidified to pH 4 with 1N aq. HCl (20 mL) and extracted with ethyl acetate (3×100 mL). The combined ethyl acetate solution was washed with water (20 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed in vacuo to give **21** as a colorless oil (1.9 g), which was not purified further. To the methylene chloride (40 mL) solution of the crude acid **21** (1.8 g, 6.72 mmol), Et_2NH (1.39 mL, 13.43 mmol), and Et_3N (3.75 mL, 26.88 mmol) was added 2-chloro-*N*-methylpyridinium iodide (2.58 g, 10.08 mmol) at 0°C. The reaction solution was stirred for 5 h. After the addition of sat. aq. $NaHCO_3$ (20 mL), the solution was extracted with EtOAc (3×50 mL). The combined ethyl acetate was washed with water (20 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (2:1)) to give **22** as a colorless oil (2.0 g, 92% yield): $[\alpha]_D^{20}$ +33 (*c* 1.0, $CHCl_3$); IR (neat) 1622, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.19 (m, 5H), 4.68, 4.63 (AB q, $J=6.8$ Hz, 2H), 4.52, 4.43 (AB q, $J=12$ Hz, 2H), 3.75 (s, 2H), 3.45–3.17 (m, 7H), 2.16–2.04 (m, 1H), 1.70–1.58 (m, 1H), 1.12–1.02 (m, 6H), 0.74 (t, $J=7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.30, 138.43, 128.19, 127.54, 127.38, 92.69, 85.01, 73.10, 69.99, 56.38, 41.44, 41.24, 26.30, 14.14, 12.48, 8.07; MS (EI) *m*/*e* 324 [M^++1], HRMS (EI) calcd for $C_{18}H_{29}NO_4$ [M^++1] 324.2176, found 324.2148.

4.15. N,N-Diethyl-2-hydroxymethyl-2-methoxymethoxy-butyramide **23**

An ethanol (60 mL) suspension of Pd/C (10%, 8.83 g) and **22** (1.9 g, 5.88 mmol) was stirred under hydrogen (1 atm) for 2 h. After filtration through celite, the solvent was removed in vacuo to give **23** as a colorless oil (1.36 g, 99% yield): $[\alpha]_D^{20}$ +33 (*c* 1.4, $CHCl_3$,); IR (neat) 3444, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.75, 4.66 (AB q, $J=6.6$ Hz, 2H), 3.92–3.76 (m, 3H), 3.67–3.60 (m, 1H), 3.40–3.30 (m, 4H), 3.24–3.19 (m, 1H), 1.99–1.74 (m, 2H), 1.18–1.09 (m, 6H), 0.91 (t, $J=7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.62, 93.24, 85.59, 64.16, 56.09, 41.08, 40.71, 26.73, 14.09, 12.54, 8.27; MS (EI) *m*/*e* 234 [M^++1], HRMS (EI) calcd for $C_{11}H_{23}NO_4$ [M^+] 233.1628, found 233.1651; enantiopurity was determined by HPLC analysis using a chiral

column (Daicel Chiralcel OD) with *n*-hexane:*i*-propanol (98:2)(1 mL/min) at 254 nm. It was established by analysis of racemic that the enantiomers were fully resolved (*S*, 17.4; *R*, 19.8 min). Chiral HPLC analysis showed no detectable *R* enantiomer.

4.16. N,N-*Diethyl-2-formyl-2-methoxymethoxy-butyramide* ***5***

To a methylene chloride solution (20 mL) of oxalyl chloride (1.35 mL, 15.52 mmol was added Me_2SO (2.2 mL, 31.04 mmol)) at −78°C. After 30 min, a methylene chloride solution (10 mL) of alcohol **23** (600 mg, 32.59 mmol) was added at −78°C. After 1 h, Et_3N (7.2 mL, 51.72 mmol) was added and the reaction solution was allowed to warm to room temperature for 1 h. After the reaction was complete, the methylene chloride was removed in vacuo and the residue was dissolved with EtOAc (100 mL). The organic solution was washed with water (20 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane–EtOAc (3:1)) to give **5** as a yellow oil (574 mg, 96% yield): $[\alpha]_D^{20}$ −55 (*c* 8.0, $CHCl_3$); IR (neat) 1715, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.66 (s, 1H), 4.75, 4.70 (AB q, $J=6.8$ Hz, 2H), 3.59–3.23 (m, 7H), 2.28–2.23 (m, 1H), 1.16–1.09 (m, 6H), 0.88 (t, $J=7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.97, 167.34, 92.80, 86.80, 56.10, 40.57, 40.14, 24.67, 13.45, 12.09, 7.63; MS (EI) *m*/*e* 231 [M^+], HRMS (EI) calcd for $C_{11}H_{21}NO_4$ [M^++1] 232.1549, found 232.1546.

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11. Enantiomeric excess of **5** was determined by chiral HPLC of the intermediate compound **23** (Chiral OD column). Chiral HPLC analysis showed no detectable *R* enantiomer. *n*-Hexane:*i*-propanol (98:2),1 mL/min, 254 nm (*S*) 17.4 min, (*R*) 19.8 min.