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Total Synthesis and Absolute Stereochemistry of Pentenocin B, a Novel Interleukin-1β Converting Enzyme Inhibitor

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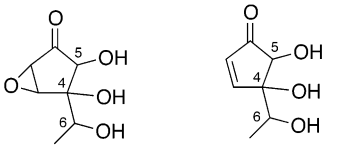
Abstract: Four possible diastereomers of pentenocin B were synthesized in a stereocontrolled manner, and the first total synthesis of a natural enantiomer of (+)-pentenocin B unequivocally established the absolute stereochemistry to be 4*S*,5*R*,6*R*.

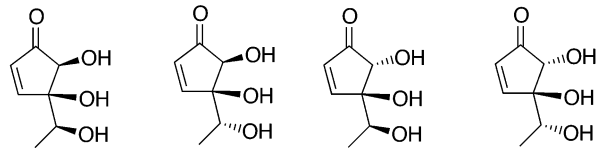
Interleukin-1β converting enzyme (ICE), also known as caspase-1, is a unique cystein protease that cleaves the inactive precursor of IL-1β into biologically active IL-1β, a key mediator in the pathogenesis of acute and chronic inflammation.[1] Evidence that ICE is an excellent target for therapeutic intervention has spurred much research interest directed toward discovery of novel small-molecule inhibitors.[2]

Pentenocins A (**1**) and B (**2**) were isolated by Ōmura and co-workers in 1999 from the culture broth of *Trichoderma hamatum* FO-6903 as the active agent against recombinant human ICE. The connectivity of novel, highly oxygenated cyclopentenones containing quaternary centers were determined by detailed NMR spectral analysis; however, the relative and absolute configurations of these cyclopentenones have not been elucidated.[3]



pentenocin A (**1**) pentenocin B (**2**)

In this paper, we report on the syntheses of the four possible racemic pentenocin B diastereomers **3**−**6** and the first synthesis of (+)-pentenocin B, as well as the determination of the relative and absolute configurations of natural pentenocin B. Because there are four possible diastereomers of pentenocin B but eight stereoisomers in total (including enantiomeric pairs) (Figure 1), we synthesized the four possible racemic pentenocin B diastereomers **3**−**6** to elucidate the relative configuration of pentenocin B using racemic ketodicyclopentadiene (KDP)[4] **7** as the common starting material.



3 or *ent*-**3** **4** or *ent*-**4** **5** or *ent*-**5** **6** or *ent*-**6**

FIGURE 1. Four possible diastereomers of pentenocin B.

Thus, the 1,4-addition of vinylmagnesium bromide to **7** from its convex face afforded the vinyl ketone **8** in 91% yield (Scheme 1). The vinyl ketone was transformed into 1,4-diketone by Wacker oxidation[5] and was then oxidized by DDQ[6] to afford **9** in 71% yield for the two steps. The reduction of **9** by DIBALH afforded the 1,4-diols **10a** and **10b** in 97% yield as an 86:14 mixture of diastereomers at the stereogenic center on the side-chain alcohol, which was fractionated by silica gel column chromatography.[7] The major alcohol **10a** was transformed into bromoether by NBS, followed by the protection of the remaining side-chain alcohol by MOMCl affording the MOM-ether **11a** in 63% yield for the two steps. The diastereoselective dihydroxylation of **11a** with OsO_4 from its convex face and the following treatment of the diols with 2,2-dimethoxypropane afforded the acetonide **12a** in 74% yield for the two steps. The treatment of **12a** with zinc restored olefin-alcohol functionalities. The subsequent oxidation of alcohol with PDC afforded the ketone **13a** in 74% yield for the two steps. The retro Diels−Alder reaction of **13a** was performed at 280 °C for 15 min in Ph_2O[8] to afford the cyclopentenone **14a** in 93% yield. Although hydrolytic removal of the acetonide moiety under conventional conditions, i.e., concentrated HCl in MeOH or 5 N HCl in THF, suffered from complex destructive reactions, the treatment of **14a** with 90% TFA[9] at 0 °C for 2 h allowed us to isolate (±)-pentenocin B diastereomer **3** in a yield of 30%.

The minor alcohol **10b** was transformed to (±)-pentenocin B diastereomer **4** by the same procedures as those for the major alcohol **10a** to (±)-pentenocin B diastereomer **3**.

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(1) (a) Thornberry, N. A.; Bull, H. G.; Calaycay, J. R.; Chapman, K. T.; Howard, A. D.; Kostura, M. J.; Miller, D. K.; Molineaux, S. M.; Weidner, J. R.; Aunins, J.; Elliston, K. O.; Ayala, J. M.; Casano, F. J.; Chin, J.; Ding, G. J.-F.; Egger, L. A.; Gaffney, E. P.; Limjuco, G.; Palyha, O. C.; Raju, S. M.; Ronando, A. M.; Salley, J. P.; Yamin, T.-T.; Lee, T. D.; Shively, J. E.; MacCross, M.; Mumford, R. A.; Schmidt, J. A.; Tocci, M. J. *Nature* **1992**, *356*, 768. (b) Dinarello, C. A.; Wolff, S. M. *N. Engl. J. Med*. **1993**, *328*, 6.

(2) (a) Koizumi, F.; Matsuda, Y.; Nakanishi, S. *J. Antibiot*. **2003**, *56*, 464. (b) Shahripour, A. B.; Plummer, M. S.; Lunney, E, A.; Sawyer, T. K.; Stankovic, C. J.; Connolly, M. K.; Rubin, J. R.; Walker, N. P. C.; Brady, K. D.; Allen, H. J.; Talanian, R. V.; Wong, W. W.; Humblet, C. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2779. (c) Tanaka, T.; Tsukuda, E.; Uosaki, Y.; Matsuda, Y. *J. Antibiot*. **1996**, *49*, 1085. (d) Tsukuda, E.; Tanaka, T.; Ochiai, K.; Kondo, H.; Yoshida, M.; Agatsuma, T.; Saitoh, Y.; Teshiba, S.; Matsuda, Y. *J. Antibiot*. **1996**, *49*, 333.

(3) (a) Matsumoto, T.; Ishiyama, A.; Yamaguchi, Y.; Masuma, R.; Ui, H.; Shiomi, K.; Yamada, H.; Ōmura, S. *J. Antibiot*. **1999**, *52*, 754; (b) **2003**, *56*, C2.

(4) Stork, G.; Nelson, G. L.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc*. **1971**, *93*, 3091.

(5) Tsuji, J. *Synthesis* **1984**, 369.

(6) Chai, K.-B.; Sampson, P. *J. Org. Chem*. **1993**, *58*, 6807.

(7) Although the stereochemistry of the side-chain alcohol of **10a** and **10b** generated by the DIBALH reduction of **9** was assigned tentatively as depicted in Scheme 1, the structure of the major alcohol **10a** was confirmed by applying the modified Mosher method[13] to the advanced chiral synthetic intermediate (+)-**22a** and X-ray structure of (+)-**12a**, as shown in Scheme 3.

(8) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett*. **1992**, *33*, 1909.

(9) (a) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. D. *Pure Appl. Chem*. **1978**, *50*, 1363. (b) Pohmakotr, M.; Popuang, S. *Tetrahedron Lett*. **1991**, *32*, 275.

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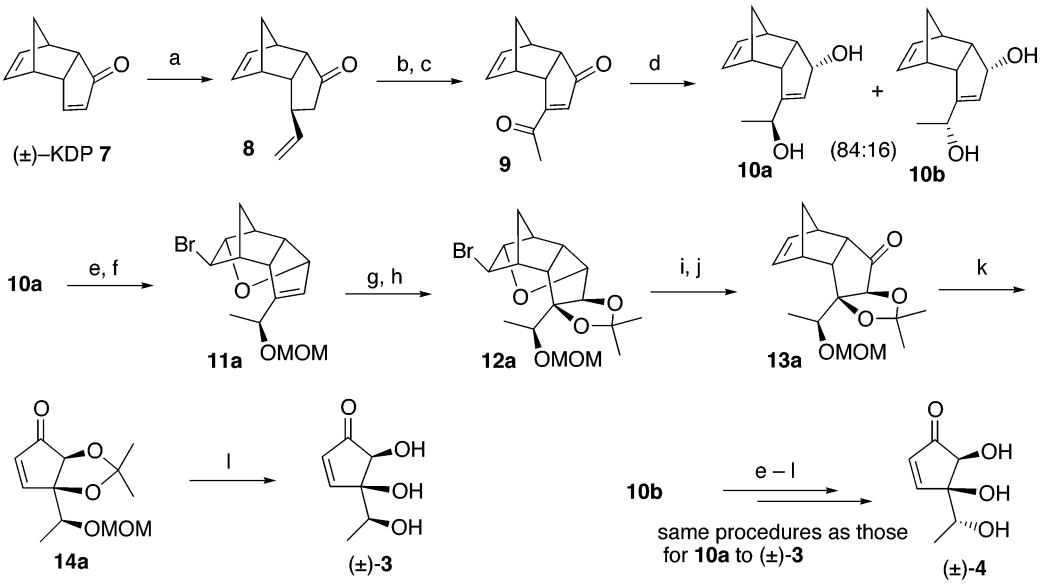
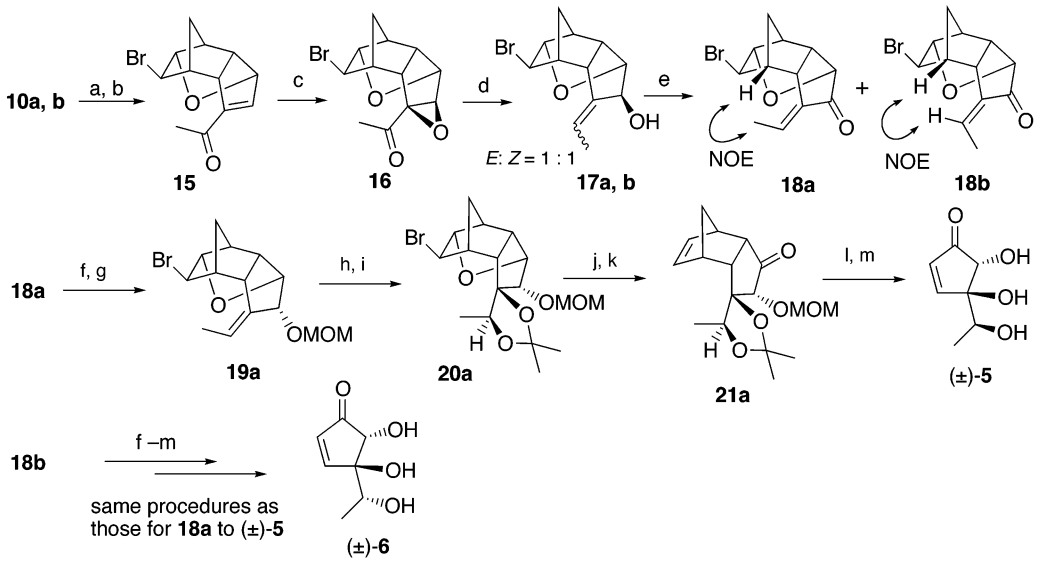
SCHEME 1[a]



[a] Reagents and conditions: (a) vinyl magnesium bromide, CuI, THF, −30 °C, 91%; (b) O_2, $PdCl_2$, CuCl, DMF−H_2O, 45 °C, 18 h, 97%; (c) DDQ, *p*-TsOH, dioxane, reflux, 73%; (d) DIBALH, THF, −78 °C, 97%; (e) NBS, THF, −15 °C, 76%; (f) MOMCl, *i*Pr_2NEt, CH_2Cl_2, rt, 83%; (g) OsO_4 (cat.), NMO, THF−H_2O, 80%; (h) 2,2-dimethoxypropane, *p*-TsOH (cat.), 92%; (i) Zn, MeOH−AcOH, 80 °C, quant; (j) PDC, CH_2Cl_2, 74%; (k) Ph_2O, 280 °C, 15 min, 93%; (l) 90% TFA, 0 °C, 2 h, 30%.

SCHEME 2[a]



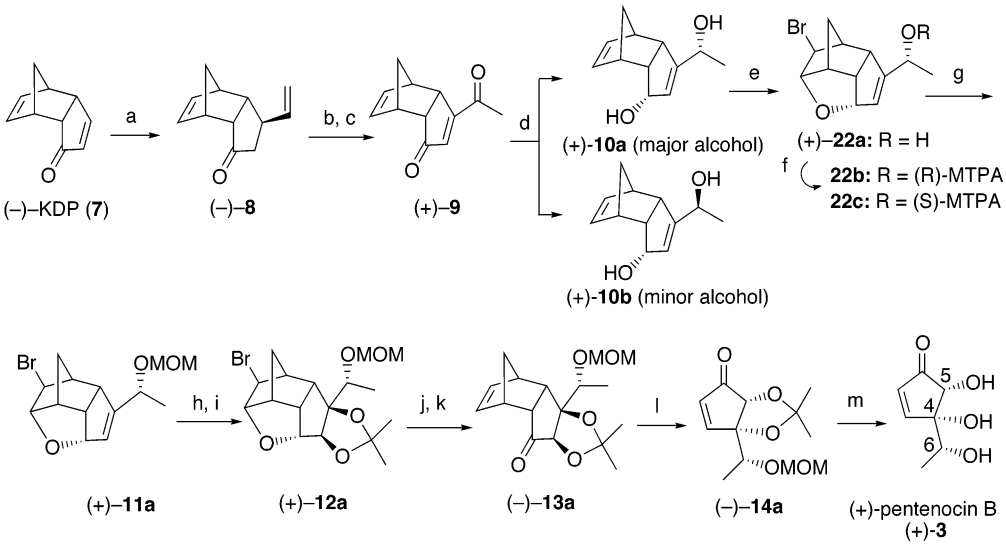
[a] Reagents and conditions: (a) NBS, THF, −15 °C; (b) MnO_2, CH_2Cl_2, 73% (2 steps); (c) 30% H_2O_2, 40% Triton B, MeOH, 0 °C, 97%; (d) NH_2NH_2·H_2O, THF−MeOH, reflux, 95%; (e) Dess−Martin periodinane, CH_2Cl_2, 81%; (f) DIBALH, THF, −78 °C, 94%; (g) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 91%; (h) OsO_4 (cat.), NMO, THF−H_2O, quant; (i) 2,2-dimethoxypropane, *p*-TsOH (cat.), 85%; (j) Zn, MeOH−AcOH, 50 °C, 87%; (k) PDC, CH_2Cl_2, 89%; (l) Ph_2O, 280 °C,15 min, quant; (m) 90% aqueous TFA, 0 °C, 3 h, 35%.

To synthesize (±)-pentenocin B diastereomer **5** or **6**, the mixture of the 1,4-diols **10a** and **10b** was treated with NBS. The subsequent oxidation of the remaining side-chain alcohol with MnO_2 afforded the α,*β*-unsaturated ketone **15** in 73% yield for the two steps (Scheme 2). The epoxidation of **15** was performed with 30% H_2O_2 and 40% Triton B from its convex face to afford the epoxy-ketone **16** in 97% yield, which was then transformed to an inseparable 1:1 *E*,*Z*-mixture of the allylic alcohols **17a** and **17b** with a Wharton rearrangement[10] in 95% yield. The Dess−Martin periodinane oxidation[11] of **17a** and **17b** afforded an *E*,*Z*-mixture of the α,*β*-unsaturated ketones **18a** and **18b** in 81% yield, respectively, which were separated by silica gel column chromatography. The stereochemistries of the *E*-olefin **18a** and the *Z*-olefin **18b** were determined by ^1H NMR analysis and NOE experiments. The reduction of **18a** by DIBALH from its convex face afforded an allylic alcohol, which was then protected as the MOM-ether **19a** in 86% yield for the two steps. The diastereoselective dihydroxylation of **19a** with OsO_4

(10) (a) Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636. (b) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6576.

(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

SCHEME 3[a]



[a] Reagents and conditions: (a) vinylmagnesium bromide, CuI, THF, −30 °C, 91%; (b) O_2, $PdCl_2$, CuCl, DMF−H_2O, 50 °C, 84%; (c) DDQ, *p*-TsOH, dioxane, reflux, 73%; (d) DIBALH, THF, −78 °C, 77%; (e) NBS, THF, −15 °C, 97%; (f) (*R*)- or (*S*)-MTPACl, Et_3N, DMAP, CH_2Cl_2; (g) MOMCl, $^iPr_2NEt$, CH_2Cl_2, rt, 91%; (h) OsO_4 (cat.), NMO, THF−H_2O, 61%; (i) 2,2-dimethoxypropane, *p*-TsOH (cat.), CH_2Cl_2, 75%; (j) Zn, MeOH−AcOH, 50°C, quant; (k) Swern oxidation, −78 °C to rt, 99%; (l) Ph_2O, 280 °C, 15 min, 98%; (m) 90% TFA, 0 °C, 2 h, 42%.

from its convex face and the subsequent protection of diols as the acetonide afforded **20a** in 85% yield for the two steps. The treatment of **20a** with zinc, followed by PDC oxidation of the regenerated alcohol, afforded the ketone **21a** in 77% yield for the two steps. The retro Diels−Alder reaction of the ketone **21a** at 280 °C in Ph_2O afforded the cyclopentenone in a quantitative yield, which was then treated with 90% TFA, affording (±)-pentenocin B diastereomer **5** in approximately 35% yield. The *Z*-isomer **18b** was transformed to (±)-pentenocin B **6** by the same procedures as those for **18a** to **5**.

All of the pentenocin B diastereomers **3**−**6** were found to have distinct ^1H and ^{13}C NMR spectra (see Supporting Information). Spectral data for one of the diastereomers, compound **3**, were confirmed to be identical with those of natural pentenocin B,[3] thereby establishing the relative configuration of pentenocin B as 4*R**,5*S**,6*S**.

Having clarified the diastereoselective route to pentenocin B diastereomers, we then conducted the enantioselective synthesis of such compounds to determine the absolute stereochemistry of natural pentenocin B. (−)-KDP (**7**)[12] was transformed to the major diol (+)-**10a**, $[\alpha]^{28}_D$ +154.2 (*c* 0.15, $CHCl_3$), and the minor diol (+)-**10b**, $[\alpha]^{26}_D$ +146.5 (*c* 0.14, $CHCl_3$), via (−)-**8** and (+)-**9** as shown in Scheme 3 with the same procedures as those described for the synthesis of the racemic pentenocin B **3**. The major diol (+)-**10a** was transformed to the bromoether (+)-**22a**, $[\alpha]^{27}_D$ +87.7 (*c* 0.59, $CHCl_3$), using NBS. The absolute configuration of the remaining secondary alcohol in **22a** was determined using the modified Mosher method.[13] Thus, **22a** was converted to both (*R*)- and (*S*)-MTPA esters **22b** and **22c**, respectively. Selected ^1H NMR spectral data (that of $CDCl_3$) indicated chemical shift differences consistent with the (*R*)-stereochemistry of the secondary alcohol of **22a**. **22a** was subsequently transformed into the protected trihydroxy bromoether (+)-**12a**, $[\alpha]^{27}_D$ +4.6 (*c* 1.02, $CHCl_3$), via the same three steps used in the conversion of (±)-**10a** to (±)-**12a** by the previous racemic synthesis. The X-ray crystal structure of (+)-**12a** confirmed that the absolute configuration of the side-chain alcohol was (*R*)-stereochemistry as determined by the modified Mosher method (see Supporting Information).

The treatment of (+)-**12a** with zinc, followed by the Swern oxidation of the regenerated alcohol, afforded the ketone (−)-**13a**, $[\alpha]^{27}_D$ −228.1 (*c* 0.56, $CHCl_3$). The retro Diels−Alder reaction of (−)-**13a**, followed by the deprotection of the resulting (−)-**14a**, afforded (+)-pentenocin B (**3**), $[\alpha]_D^{30}$ +101 (*c* 1.0, H_2O) (natural:[14] $[\alpha]_D$ +76 (*c* 1.0, H_2O).

In conclusion, we have realized the first enantiocontrolled synthesis of (+)-pentenocin B and determined its absolute stereochemistry to be 4*S*,5*R*,6*R* as shown by (+)-**3**. Synthetic studies of pentenocin A (**1**) are now under way and will be reported in due time.

Experimental Section

Compound (+)-22a. To a stirred solution of (+)-**10a** (201 mg, 1.05 mmol) in THF (5 mL) was added *N*-bromosuccinimide (280 mg, 1.57 mmol) at −15 °C. The reaction mixture was stirred at −15 °C under dark for 15 min, quenched by addition of saturated aqueous $Na_2S_2O_3$ solution, and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:2) to give (+)-**22a** (274 mg, 1.01 mmol, 97%) as a colorless oil: $[\alpha]^{27}_D$ +87.7 (*c* 0.59, $CHCl_3$); IR (neat) 3390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 4.68 (dd, 1H, *J* = 5.6, 2.4 Hz), 4.62 (d, 1H, *J* = 4.9 Hz), 4.36 (q, 1H, *J* = 6.6 Hz), 3.97 (d, 1H, *J* = 2.2 Hz), 3.13 (ddd, 1H, *J* = 8.8, 5.4, 5.3 Hz), 3.03 (dd, 1H, *J* = 8.8, 3.9 Hz), 2.72−2.69 (m, 1H), 2.50 (s, 1H), 2.40 (d, 1H, *J* = 11.0 Hz), 1.96 (d, 1H, *J* = 11.0 Hz), 1.33 (d, 3H,

(12) (a) Ogasawara, K. *Pure Appl. Chem.* **1994**, *66*, 2119. (b) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419 and references therein.

(13) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(14) Private communication with Professor S. Ōmura.

J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 127.9, 91.0, 84.9, 66.7, 55.0, 51.8, 50.3, 47.9, 47.2, 40.2, 22.0; MS (EI) m/z 191 (M^+ − Br), 43 (100%); HRMS (EI) m/z calcd for $C_{12}H_{15}O_2$ (M^+ − Br) 191.1071, found 191.1052.

Compound (+)-11a. To a stirred solution of (+)-**22a** (274 mg, 1.01 mmol) and ^{i}Pr$_2$NEt (0.88 mL, 5.05 mmol) in CH_2Cl_2 (5 mL) was added MOMCl (0.23 mL, 3.03 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 h and then poured into water and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:4) to give (+)-**11a** (290 mg, 0.92 mmol, 91%) as a colorless oil: (+)-**11a**: $[\alpha]^{30}_D$ +145.0 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, 1H, J = 2.2 Hz), 4.66 (dd, 1H, J = 5.9, 2.4 Hz), 4.62 (d, 1H, J = 4.9 Hz), 4.59 (s, 2H), 4.29 (q, 1H, J = 6.6 Hz), 3.96 (d, 1H, J = 2.2 Hz), 3.37 (s, 3H), 3.12 (ddd, 1H, J = 8.8, 5.6, 5.4 Hz), 3.01 (dd, 1H, J = 8.8, 3.9 Hz), 2.69 (ddd, 1H, J = 5.1, 5.1, 1.2 Hz), 2.50−2.49 (m, 1H), 2.44 (d, 1H, J = 10.7 Hz), 1.95 (dd, 1H, J = 10.7, 1.5 Hz), 1.29 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 130.3, 94.2, 91.0, 84.7, 70.5, 55.4, 55.0, 51.3, 50.3, 48.2, 47.1, 40.2, 19.6; MS (EI) m/z 314 (M^+), 45 (100%); HRMS (EI) m/z calcd for $C_{14}H_{19}BrO_3$ 314.0517, found 314.0529. Anal. Calcd for $C_{14}H_{19}BrO_3$: C, 53.35; H, 6.08; Br, 25.35. Found: C, 53.43; H, 6.12; Br, 25.42.

Compound (+)-12a. To a stirred solution of (+)-**11a** (70 mg, 0.223 mmol) and 4-methylmolpholine *N*-oxide (39 mg, 0.334 mmol) in THF (1.5 mL) and H_2O (0.5 mL) was added OsO_4 (0.197M in THF, 0.227 mL, 0.045 mmol) at room temperature. The mixture was stirred at room temperature for 4 days, quenched by addition of saturated aqueous $Na_2S_2O_3$ solution, and extracted with $CHCl_3$. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:1) to give the diol (47 mg, 0.135 mmol, 61%) as a colorless oil. A mixture of the diol (43 mg, 0.123 mmol) and anhydrous *p*-toluenesulfonic acid (2.3 mg, 0.013 mmol) in 2,2-dimethoxypropane (0.5 mL) was stirred at room temperature for 17 h. The reaction mixture was added to a saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:2) to give (+)-**12a** (36 mg, 0.093 mmol, 75%) as a colorless crystal: mp 93 °C (recrystallized from hexane); $[\alpha]^{27}_D$ +4.6 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, 1H, J = 6.8 Hz), 4.62 (d, 1H, J = 6.8 Hz), 4.57 (s, 1H), 4.56 (d, 1H, J = 6.1 Hz), 4.36 (d, 1H, J = 5.9 Hz), 3.68 (q, 1H, J = 6.3 Hz), 3.61 (d, 1H, J = 2.2 Hz), 3.35 (s, 3H), 3.16 (ddd, 1H, J = 9.3, 5.9, 5.4 Hz), 2.87−2.78 (m, 1H), 2.64 (dd, 1H, J = 9.5, 4.0 Hz), 2.32 (d, 1H, J = 3.2 Hz), 2.28 (d, 1H, J = 10.7 Hz), 1.71 (d, 1H, J = 11.7 Hz), 1.46 (s, 3H), 1.37 (s, 3H), 1.29 (d, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 95.4, 95.1, 92.2, 90.6, 89.2, 75.0, 56.3, 55.7, 55.0, 48.4, 47.8, 45.1, 37.6, 29.1, 27.2, 15.9; MS (EI) m/z 373 (M^+ − Me), 299 (100%); HRMS (EI) m/z calcd for $C_{16}H_{22}BrO_5$ (M^+ − Me) 373.0650, found 373.0626. Anal. Calcd for $C_{17}H_{25}BrO_5$ C, 52.45; H, 6.47; Br, 20.53. Found: C, 52.25; H, 6.47; Br, 20.81.

Compound (−)-13a. A mixture of (+)-**12a** (89 mg, 0.229 mmol) and activated Zn (375 mg, 5.73 mmol) in MeOH (2 mL) and AcOH (0.2 mL) was stirred at 50 °C for 1 h and then filtered through Celite. The filtrate was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:2) to give the alcohol (71 mg, 0.229 mmol, 100%) as a colorless crystal. To a stirring solution of oxalyl chloride (0.10 mL, 1.16 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.165 mL, 2.32 mmol) dropwise at −78 °C. After 10 min, the alcohol (60 mg, 0.194 mmol) in CH_2Cl_2 (1 mL) was added to the solution. The mixture was stirred at −78 °C for 30 min, and triethylamine (0.486 mL, 3.48 mmol) was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 10 min and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane 1:2) to give (−)-**13a** (59 mg, 0.192 mmol, 99%) as a colorless crystal: mp 79−80 °C (recrystallized from hexane); $[\alpha]^{27}_D$ −228.1 (c 0.56, $CHCl_3$); IR (Nujol) 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, 1H, J = 5.6, 2.9 Hz), 6.15 (dd, 1H, J = 5.6, 2.4 Hz), 4.72 (d, 1H, J = 7.1 Hz), 4.55 (d, 1H, J = 6.8 Hz), 3.85 (s, 1H), 3.75 (q, 1H, J = 6.3 Hz), 3.37 (s, 3H), 3.24 (brs, 1H), 3.20−3.17 (m, 1H), 3.04 (brs, 1H), 2.97 (dd, 1H, J = 8.5, 3.7 Hz), 1.62 (d, 1H, J = 8.3 Hz), 1.49 (d, 1H, J = 8.3 Hz), 1.47 (s, 3H), 1.37 (d, 3H, J = 6.3 Hz), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 138.4, 133.9, 111.1, 95.0, 90.2, 83.8, 74.8, 55.7, 53.2, 52.0, 48.9, 46.1, 45.0, 29.1, 26.6, 15.0; MS (EI) m/z 308 (M^+), 153 (100%); HRMS (EI) m/z calcd for $C_{17}H_{24}O_5$ 308.1622, found 308.1646. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.07; H, 7.70.

Compound (−)-14a. A mixture of (−)-**13a** (35 mg, 0.114 mmol) in Ph_2O (1 mL) was heated at reflux for 15 min. After cooling to room temperature, the reaction mixture was directly purified by silica gel column chromatography (EtOAc−hexane 1:4) to give (−)-**14a** (27 mg, 0.112 mmol, 98%) as a colorless oil: $[\alpha]^{26}_D$ −10.9 (c 0.90, $CHCl_3$); IR (neat) 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, J = 5.9 Hz), 6.27 (d, 1H, J = 6.1 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.63 (d, 1H, J = 7.1 Hz), 4.28 (s, 1H), 4.05 (q, 1H, J = 6.3 Hz), 3.35 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.23 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 161.8, 134.1, 115.6, 95.3, 90.9, 78.4, 73.9, 55.7, 28.3, 28.2, 15.8; MS (EI) m/z 227 (M^+ − Me), 45 (100%); HRMS (EI) m/z calcd for $C_{11}H_{15}O_5$ 227.0919, found 227.0917.

(+)-Pentenocin B (3). A mixture of (−)-**14a** (33 mg, 0.136 mmol), H_2O (0.02 mL), and trifluoroacetic acid (0.2 mL) was stirred at 0 °C for 2 h. The mixture was concentrated in vacuo and purified by silica gel column chromatography (EtOAc−MeOH 9:1) to give (+)-pentenocin B {**(+)-3**} (9.1 mg, 0.058 mmol, 42%) as a colorless resin: $[\alpha]^{30}_D$ +100.8 (c 1.0, H_2O) {lit.[14] $[\alpha]_D$ +76 (c 1.0, H_2O)}; IR (neat) 3386, 1678 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, 1H, J = 6.1 Hz), 6.15 (d, 1H, J = 6.1 Hz), 5.32 (d, 1H, J = 7.3 Hz), 4.90 (s, 1H), 4.83 (d, 1H, J = 5.1 Hz), 3.91 (d, 1H, J = 7.3 Hz), 3.69 (qd, 1H, J = 6.3, 5.6 Hz), 1.12 (d, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, DMSO- d_6) δ 208.1, 165.3, 131.6, 78.8, 70.7, 69.2, 18.0; MS (FAB) m/z 159 (MH^+).

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Supporting Information Available: Characterization data for all new compounds and experimental procedures, including ORTEP and crystallographic details for (+)-**12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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