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Concise Formal Synthesis of (−)-Salinosporamide A (Marizomib) Using a Regio- and Stereoselective Epoxidation and Reductive Oxirane Ring-Opening Strategy

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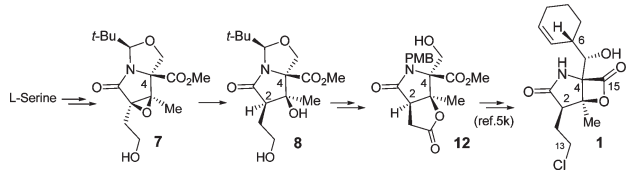

Expedient access to a highly functionalized 2-pyrrolidinone (**8**), the γ-lactam core of 20S proteasome inhibitor (−)-salinosporamide A (marizomib; NPI-0052; **1**), using a regio- and stereoselective epoxide formation/reductive oxirane ring-opening strategy is presented. Notably, the sequential construction of the C-4, C-3, and C-2 stereocenters of **1** in a completely stereocontrolled fashion is a key feature of streamlining the synthesis of intermediate **12**. A related strategy is also discussed.

Salinosporamide A (**1**; marizomib) is a highly potent and selective 20S proteasome inhibitor that is currently in phase I clinical trials for the treatment of cancer.[1,2a−c] First isolated as a secondary metabolite of the marine actinomycete *Salinispora tropica* by Fenical and co-workers in 2003,[1] **1** is structurally related to the natural products cinnabaramide A[3] and omuralide,[4a−f] sharing the unique fused γ-lactam-β-lactone bicyclic core. The global structural complexity and impressive biological profile of **1** have attracted intensive efforts from the synthetic community. In fact, numerous synthetic studies toward **1** have been reported,[5a−o] including our own.[5d] Herein, we present a new strategy based upon a regio- and stereoselective epoxide formation/reductive oxirane ring-opening sequence, and demonstrate its synthetic advantage in terms of providing expedient access to the highly functionalized 2-pyrrolidinone **8**, leading to an efficient formal synthesis of **1** (Scheme 1).

Recently, synthetic tactics directly targeting key intermediates **19** (Corey's intermediate[5a]) and **12** (Lam's intermediate[5k]) have been disclosed.[5j−l] The reported chemistry includes *N*-methylnitrone 1,3-dipolar cycloaddition,[5j] nickel-catalyzed reductive aldol cyclization-lactonization,[5k] and *N*-heterocyclic carbene-catalyzed intramolecular cyclization-lactonization,[5l] each featuring construction of C-2 and C-3 stereocenters guided by the C-4 stereocenter. However, the reported diastereoselective ratios (dr) of these methods[5j−l] range from poor to moderate; thus, further improvement is the focus of our current effort. Based upon our previous total synthesis of **1**,[5d] we envisioned using Seebach's self-regeneration of stereocenters (SRS) principle[6] followed by a regio- and stereoselective epoxide formation/reductive oxirane ring-opening sequence to sequentially construct the required C-4, C-3, and C-2 stereocenters of advanced intermediate **8** or **17** (Scheme 1). If successful, the desired C-2 and C-3 stereocenters would be constructed simultaneously or in a stepwise manner with high diastereoselectivity guided by the previously installed C-4 stereocenter inherited from L-serine (and maintained under SRS principle).[5d] Notably, the newly generated C-3 hydroxyl group would be *syn* to the C-4 methyl ester group, which would facilitate the required β-lactone formation. This new strategy would provide expedient access to the fused γ-lactam-γ-lactone bicyclic core (**12**) of **1**. As shown in our retrosynthetic analysis (Scheme 1), we recognized a fused oxazolidine pyrrolinone bicyclic ring system such as **6** or **14** that could potentially serve as a chiral template upon which a strategic epoxide functionality would be stereoselectively installed to generate α,β-epoxy amide **7** or **16**, followed by regio- and stereoselective reductive

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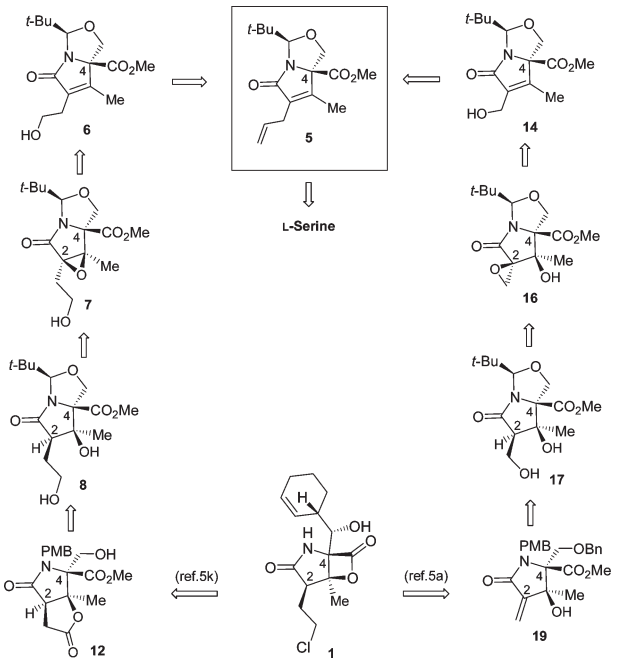
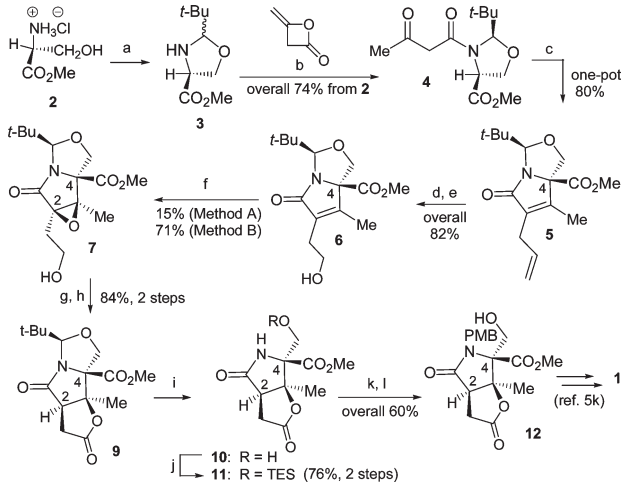
SCHEME 1. Retrosynthetic Analysis for the Formal Synthesis of 1



oxirane ring cleavage to generate the highly functionalized 2-pyrrolidinone (γ-lactam) core, i.e., tertiary β-hydroxy amide **8** or **17**. Finally, known intermediate **12**[5k] or an immediate precursor to Corey's intermediate **19**[5a] could be generated after simple protecting group maneuvers to complete the enantioselective formal synthesis of (−)-salinosporamide A (**1**).

First, we developed a streamlined synthesis of the key intermediate **5** from **2** (Scheme 2) using the strategy based upon the self-regeneration of stereocenters (SRS) principle developed by Seebach.[6] This approach was applied in our previous total synthesis of **1**, during which *ent*-**5** was observed as a minor dehydration product.[5d] Recognizing **5** as a suitable precursor for the epoxidation strategy, we developed an efficient method for its production. L-Serine methylester hydrochloride **2** was condensed with pivaldehyde to afford oxazolidine **3**, which was directly coupled with diketene to afford β-keto amide **4** with 74% overall yield, which was used in the next step without purification. In a one-pot operation, cyclization of β-keto amide **4** in the presence of allylbromide and K_2CO_3, followed by dehydration promoted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) afforded the desired intermediate **5** with 80% yield. Ozonolysis of **5** followed by $NaBH_4$ reduction afforded alcohol **6**, which was subjected to

SCHEME 2. Streamline Synthesis of Key Intermediate 5, 6, and 12 and Formal Synthesis of 1 from 2[a]



[a]Reagents and conditions: (a) pivaldehyde, Et_3N, pentane, 50 °C, 15 h. (b) Diketene, pyridine, benzene, 60 °C, 18 h, 74% overall yield from **2** (two steps). (c) Allylbromide, K_2CO_3, DMF, 25 °C, 16 h; then DBU, toluene, 110 °C, 15 h, one pot, 80% overall yield. (d) Ozonolysis, THF, −80 °C, 30 min. (e) $NaBH_4$, MeOH, −80 to 25 °C, 30 min, 82% overall yield for **6**. (f) Method A: Triton B (80 wt % in methanol), *t*-BuOOH solution (5−6 M solution in decane), THF, 25 °C, 10 min; then **6**, THF, 25 °C 18 h, 15% yield (with 43% recovered **6**). Method B: Triton B (80 wt % in methanol), concentrated *t*-BuOOH solution (the original 5−6 M solution in decane was concentrated 10-fold by volume using a stream of nitrogen at room temperature and **adopting appropriate personal safety precautions**), THF, 25 °C, 10 min; then **6**, THF, 25 °C, 40 h, 71% yield. (g) SmI_2, THF/MeOH (1:1), −80 °C, 30 min, quant. (h) PCC, dry 4 Å molecular sieves, CH_2Cl_2, 25 °C, 16 h, 84% yield. (i) 1,3-Propanedithiol, 12N HCl (cat.), CF_3CH_2OH, 60 °C, 1 h, 83% yield. (j) Imidazole, TESCl, CH_2Cl_2, 25 °C, 15 h, 92% yield. (k) NaH, dry DMF, 0 °C, 15 min; then PMBBr, 0 °C, 1 h; then 25 °C, 15 h. (l) DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), CH_2Cl_2/H_2O (20:1, v/v), 25 °C, 6 h, 60% overall yield (two steps).

various epoxidation conditions in order to generate epoxide **7**. The fused oxazolidine pyrrolinone bicyclic ring system **6** could potentially provide a unique chiral environment, one in which epoxidation is expected to occur from the less hindered *exo* face of the bicyclic concave system, thus providing the desired stereo outcome. Due to the challenging steric hindrance and electronic deficiency of **6**, several initial epoxidation conditions were unsuccessful (H_2O_2/NaOH(aq), mCPBA, *t*-BuOOH/Sm(O-*i*-Pr)$_3$/Ph_3As=O, DMDO, *t*-BuOOH/V(O)(acac)$_2$[7a−e] (note: a similar failed attempt was reported[8]). Gratifyingly, we found that epoxidation of **6** promoted by Triton B (benzyltrimethyl ammonium hydroxide) in concentrated *t*-BuOOH (*tert*-butyl hydroperoxide) solution[7f,g] provided the best results. The desired epoxide **7** was isolated as the sole product, and its relative stereochemistry was confirmed by NOESY (see Supporting Information), indicating that the bulky *tert*-butyl hydroperoxy anion indeed attacked only from the less hindered *exo* face of the fused oxazolidine pyrrolinone bicyclic ring system of **6**.

The strategic α,β-epoxy amide **7** was then subjected to SmI_2 (samarium(II) iodide) promoted regio- and stereoselective reductive oxirane ring cleavage[9a,b] to generate the

(7) Epoxidation conditions. H_2O_2/NaOH: (a) Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 2784–2793. *m*CPBA: (b) Camps, F.; Coll, J.; Messeguer, A.; Pujol, F. *J. Org. Chem.* **1982**, *47*, 5402–5404. *t*BuOOH/Sm(O-*i*Pr)$_3$/Ph_3As=O: (c) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544–14545. DMDO: (d) Meng, D.; Su, D. S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y. H.; Chou, T. C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734. *t*-BuOOH/V(O)(acac)$_2$: (e) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137. *t*-BuOOH/Triton B: (f) Jao, E.; Bogen, S.; Saksena, A. K.; Girijavallabhan, V. *Synthesis* **2003**, 2643–2646. (g) Triton B (benzyltrimethyl ammonium hydroxide, 80 wt % in methanol) was added to the concentrated tert-butyl hydroperoxide solution (the original 5−6 M solution in decane was concentrated 10-fold by volume using a stream of nitrogen at room temperature adopting appropriate personal safety precautions; the molarity of the final concentrated solution was not determined).

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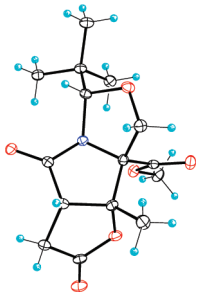
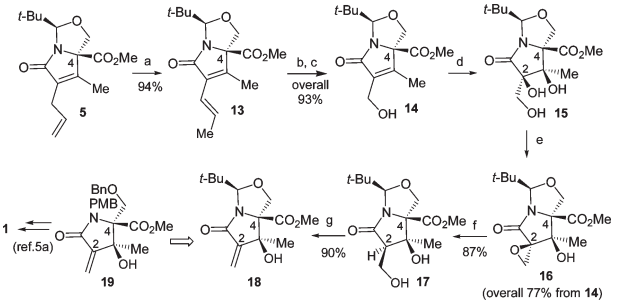


FIGURE 1. ORTEP plot of the X-ray crystal structure of *ent*-**9** depicting the absolute stereochemistry.[13]

desired thermodynamically favored tertiary β-hydroxy amide **8**, which represents the highly functionalized 2-pyrrolidinone (γ-lactam) core structure of **1**. In this case, the desired C-2 and C-3 stereocenters were constructed simultaneously, affording exclusively the desired diastereomer. The stereoselectivity is guided by the previously installed C-4 stereocenter: protonation of the enolate produced the thermodynamically favored product to minimize 1,2 interactions between the C-2 side chain and C-3 methyl group. The diol **8** was then oxidized to γ-lactam-γ-lactone **9** promoted by PCC (pyridinium chlorochromate); X-ray crystallographic analysis of *ent*-**9** (Figure 1) further confirmed the relative stereochemical assignments of diol **8**. The γ-lactam-γ-lactone **9** was subsequently converted to the known intermediate **12**[5k] by several simple protecting group manipulations, thereby completing the formal stereoselective total synthesis of **1**.

Encouraged by the above observations, we also developed a streamlined synthesis of highly functionalized α-methylene-γ-lactam **18** (an immediate precursor to Corey's intermediate **19**[5a]) from allylic alcohol **14**. As shown in Scheme 3, **14** can be easily generated from key intermediate **5**. The allyl group of **5** was subjected to olefin isomerization catalyzed by rhodium(III) chloride[10] to afford the conjugated diene **13**. Then, oxidative olefin cleavage of diene **13** by ozonolysis, followed by $NaBH_4$ reduction, afforded the allylic alcohol **14** with 93% overall yield. In the following operation, allylic alcohol **14** was converted to epoxide **16**. First, allylic alcohol **14** was subjected to modified Sharpless dihydroxylation conditions[11] in citric acid media, in the presence of NMO (4-methylmorpholine *N*-oxide) and $K_2OsO_4 \cdot 2H_2O$ (potassium osmate(VI) dihydrate) to afford the crude triol **15**. The newly generated C-3 tertiary hydroxyl group was strategically *syn* to the C-4 methyl ester group, indicating that Sharpless dihydroxylation occurred preferentially from the less hindered *exo* face of the fused oxazolidine pyrrolinone bicyclic ring system of allylic alcohol **14**. This secured the C-3 stereocenter, which was later confirmed by further transformation to **17**. Triol **15** was then treated with TsCl (*p*-toluenesulfonyl chloride) in the presence of Et_3N to afford epoxide **16** with high overall yield. Epoxide **16** was then subjected to SmI_2 promoted regio- and stereoselective reductive oxirane ring cleavage[9a,b] to generate the desired thermodynamically favored tertiary β-hydroxy amide **17**, which represents the highly functionalized pyrrolidinone γ-lactam core structure of **1**. The relative stereochemical

SCHEME 3. Synthesis of Key Intermediates 17 and 18 from 5[a]



[a]Reagents and conditions: (a) $RhCl_3$ (cat.), MeOH, 70 °C, 10 h, 94% yield. (b) Ozonolysis, THF, −80 °C, 30 min. (c) $NaBH_4$, MeOH, −80 to 25 °C, 30 min, 93% overall yield for **14** (two steps). (d) Citric acid, NMO, $K_2OsO_4 \cdot 2H_2O$, THF/H_2O (1:1), 25 °C, 15 h. (e) Et_3N, TsCl, dry CH_2Cl_2, 25 °C, 3 h, 77% overall yield (two steps). (f) SmI_2, THF/MeOH (1:1), −80 °C, 2 h, 87% yield. (g) PPh_3, imidazole, I_2, benzene, 80 °C, 1 h, 90% yield.

assignment of diol **17** was confirmed by NOESY (see Supporting Information). In this case, the desired C-2, C-3 stereocenters were constructed stepwise, giving rise to exclusively the desired diastereoisomer guided by the previously installed C-4 stereocenter. Although one-carbon homologation of diol **17** is necessary to generate either diol **8** or γ-lactam-γ-lactone **9**, diol **17** was easily converted to α-methylene-lactam **18** with 90% yield: dehydration was promoted by iodinization[12] and driven by formation of the conjugated α,β-unsaturated lactam moiety. The α-methylene-γ-lactam **18** now serves as an immediate precursor to Corey's intermediate **19**.[5a]

Conclusions

We have developed a new strategy based upon the Seebach principle (SRS), regio- and stereoselective epoxide formation, and reductive oxirane ring-opening reactions to sequentially construct the desired C-4, C-3, and C-2 stereocenters of **1** in highly stereocontrolled fashion. Notably, the newly generated C-3 tertiary hydroxyl group is *syn* to the C-4 methyl ester group; this desired strategic relative stereochemistry was observed as thermodynamically disfavored in our previous intramolecular aldol cyclization studies.[5d] Our improved synthesis therefore provides expedient access to the desired fused γ-lactam-γ-lactone bicyclic advanced intermediate en route to **1** and promises to further facilitate structure−activity relationship studies of its analogues.

Experimental Section

Synthesis of Compound 7. Method B: **Using appropriate personal safety precautions**, a 5−6 M *tert*-butyl hydroperoxide solution was concentrated 10-fold by volume using a stream of nitrogen at room temperature; the molarity of the final concentrated solution was not determined. Triton B (benzyltrimethyl ammonium hydroxide, 80 wt % in methanol, 15 mg, 0.18 mmol) was added to 400 μL of the concentrated *tert*-butyl hydroperoxide solution, and the reaction mixture was stirred for 5 min at rt.

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(13) The X-ray crystal data for *ent*-**9** has been deposited at the Cambridge Crystallographic Data Center with deposition no. CCDC-764363 and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.

Compound **6** (30 mg, 0.10 mmol) in THF (0.1 mL) was added to the above reaction mixture and stirred at 25 °C for 40 h. The reaction mixture was concentrated directly under reduced pressure to obtain a crude residue, which was purified by silica flash chromatography (EtOAc/hexanes 10% to 50%) to afford compound **7** (22 mg, 0.071 mmol, 71% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.63 (d, J = 8.55 Hz, 1H), 3.98−3.88 (m, 1H), 3.85−3.75 (m, 4H), 3.37 (d, J = 8.55 Hz, 1H), 2.14 (s, 1H), 2.07−2.0 (m, 2H), 1.48 (s, 3H), 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ178.6, 168.9, 99.9, 73.8, 70.3, 69.8, 65.3, 58.6, 53.0, 34.8, 30.8, 27.9, 24.9, 12.4 ppm. HRMS (ESI-TOF): calcd for $C_{15}H_{23}NO_6$ [M + H$^+$] 314.1598, found 314.1590. The relative stereochemistry was confirmed by NOESY data on its enantiomer (*ent*-**7**, see spectrum in Supporting Information).

Synthesis of Compound 9. To a solution of compound **7** (80 mg, 0.26 mmol) in THF/MeOH (1:1, 2.0 mL) was added samarium(II) iodide (0.1 M in THF, 7.6 mL, 0.76 mmol) at −80 °C, and the reaction mixture was stirred at this temperature for 30 min. The reaction was then quenched with aqueous $NaHCO_3$ (10 mL), $Na_2S_2O_3$ (10 mL) at −80 °C and extracted with EtOAc (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude diol **8**, which was filtered through a short silica plug, concentrated under high vacuum, and directly subjected to the next step without further purification. To a solution of compound **8** (47 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) with dried 4 Å molecular sieves (0.10 g) was added PCC (96 mg, 0.45 mmol). The reaction mixture was stirred at 25 °C for 16 h and concentrated under reduced pressure, and the resulting crude product was then purified by silica flash chromatography (50% EtOAc/hexanes) to afford **9** (29 mg, 0.125 mmol, 84% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.77 (d, J = 8.95 Hz, 1H), 3.76 (s, 3H), 3.56 (d, J = 8.90 Hz, 1H), 3.12−3.09 (m, 1H), 3.01 (s, 1H), 2.99 (s, 1H), 1.58 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 173.2, 168.9, 98.4, 85.3,79.4, 69.9, 52.9, 51.8, 35.4, 32.7, 30.9, 25.0, 24.7, 23.2. HRMS (ESI-TOF): calcd for $C_{15}H_{21}NO_6$ [M + H$^+$] 312.1442, found 312.1440. The ^{1}H and ^{13}C NMR spectra of compound **9** were identical to its enantiomer, *ent*-**9**, which was confirmed by X-ray crystal structure (Figure 1).

Synthesis of Compound 16. To a solution of allylic alcohol **14** (21.0 mg, 0.074 mmol) in THF/H_2O (1:1, 5.0 mL) was added citric acid (62.0 mg, 0.296 mmol) followed by NMO (26.0 mg, 0.222 mmol) and potassium osmate(VI) dihydrate ($K_2OsO_4\cdot 2H_2O$, 5.5 mg, 0.015 mmol). The resulting mixture was stirred at 25 °C for 15 h. The above reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (2 × 10 mL) followed by CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and dried under high vacuum to afford the crude product triol **15**. HRMS (ESI-TOF): calcd for $C_{14}H_{23}NO_7$ [M + H$^+$] 318.1547, found 318.1541. [^{1}H and ^{13}C NMR spectra confirmed the structure]. Then, the crude triol **15** was redissolved in dry CH_2Cl_2 (5.0 mL), and Et_3N (0.021 mL, 0.148 mmol) was added followed by *p*-toluenesulfonyl chloride (TsCl, 17.0 mg, 0.089 mmol); the reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL), the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude residue was purified by silica flash chromatography (EtOAc/hexanes, 10% to 50%) to afford the epoxide **16** (17.0 mg, 0.057 mmol, 77% overall yield for two steps) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.82 (d, J = 9.30 Hz, 1H), 3.83 (d, J = 9.25 Hz, 1H), 3.79 (s, 3H), 3.41 (d, J = 4.80 Hz, 1H), 2.92 (bs, 1H), 2.89 (d, J = 4.75 Hz, 1H), 1.37 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.4, 96.8, 78.5, 71.4, 68.7, 66.3, 52.9, 47.1, 36.2, 24.8, 22.4 ppm; HRMS (ESI-TOF): calcd for $C_{14}H_{21}NO_6$ [M + H$^+$] 300.1442, found 300.1446.

Synthesis of Compound 17. To a solution of the epoxide **16** (16.0 mg, 0.053 mmol) in THF/MeOH (1:1, 4.0 mL) was added samarium(II) iodide (0.1 M in THF, 1.60 mL, 0.16 mmol) at −80 °C, and the reaction mixture was stirred at this temperature for 2 h. The reaction was then quenched with aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL), and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica flash chromatography (50% EtOAc/hexanes) to afford the diol **17** (13.9 mg, 0.046 mmol, 87% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.66 (d, J = 8.85 Hz, 1H), 4.30−4.20 (m, 2H), 4.0−3.95 (m, 1H), 3.76 (s, 3H), 3.50 (d, J = 8.90 Hz, 1H), 3.04 (t, J = 6.0 Hz, 1H), 2.64 (dd, J = 3.70, 6.35 Hz, 1H), 1.43 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 170.8, 98.8, 80.9, 75.1, 70.2, 59.9, 58.5, 52.4, 35.3, 30.9, 26.5, 25.3, 24.9. HRMS (ESI-TOF): calcd for $C_{14}H_{23}NO_6$ [M + H$^+$] 302.1598, found 302.1603. The stereochemistry was confirmed by NOESY (see Supporting Information).

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Supporting Information Available: General experimental procedures, compound characterization data, and access to CIF file for *ent*-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.