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Formal Total Synthesis of (−)-Saliniketals

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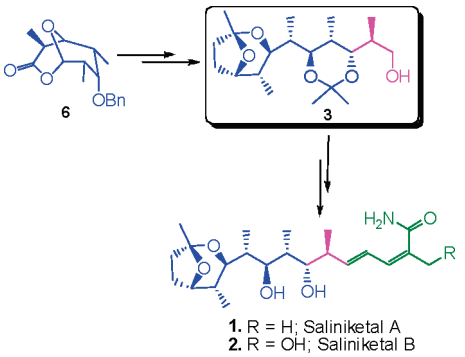


A highly stereoselective formal total synthesis of the ornithine decarboxylase inhibitors (−)-saliniketals A and B is described. The salient features of the synthesis are the utilization of a desymmetrization technique to create six contiguous chiral centers from a single bicyclic precursor as well as substrate-controlled Grignard reaction, intramolecular Wacker-type oxidation, and antialdol reaction following Pirrung−Heathcock conditions.

Saliniketals A (**1**) and B (**2**), unusual bicyclic polyketides, constitute a novel class of bioactive marine natural products that were isolated in 2007 by Fenical and co-workers from actinomycete *Salinispora arenicola* (Figure 1).[1] They inhibit ornithine decarboxylase (ODC) induction, which is used as a marker of tumorigenesis and is often seen in epithelial tumors of the colon, skin, prostate, and stomach.[2] Thus, the inhibition of ODC activity decreases the cellular concentration of polyamines and this may provide an effective strategy to prevent carcinogenesis.[3]

The saliniketals A and B possess a 1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane ring featuring an elaborate side chain at C11 that terminates in an unsaturated primary amide. The structures were assigned mainly by 2D NMR spectroscopic methods. The absolute stereochemistry was assigned by modified Mosher's method.[4] The total synthesis of **1** and **2** was considered of interest, as part of our ongoing research activities in the total syntheses of complex biologically active natural and designed molecules,[5] by a desymmetrization strategy to create contiguous chiral centers from a single bicyclic precursor. We report herein a highly stereoselective formal total synthesis of saliniketals A (**1**) and B (**2**). To date only two total syntheses of these have been reported by Paterson et al. and De Brabander et al.[6]

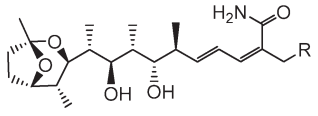
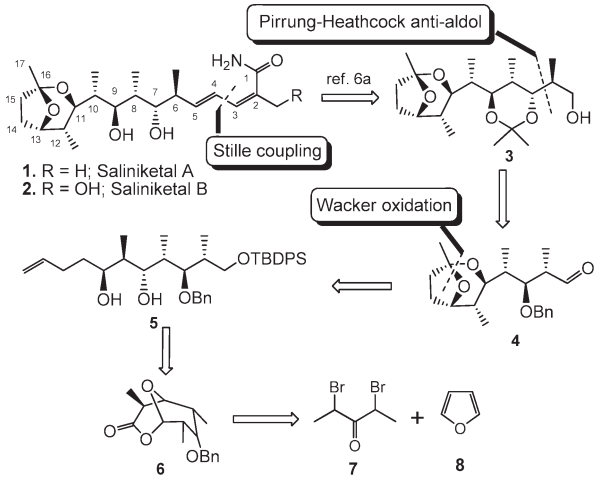


FIGURE 1. Structures of (−)-saliniketals A and B.

The details of our approach toward the synthesis of saliniketals A and B are depicted in Scheme 1, which illustrates that they could be constructed by Stille coupling[7] through a common advanced intermediate **3**, which in turn could be obtained from **4**. The aldehyde **4** could be prepared from **5**, which in turn could be accessed from **6**. Compund **6** would be obtained by utilizing a desymmetrization technique to create six contiguous centers.

SCHEME 1. Retrosynthetic Analysis of (−)-Saliniketals A and B



The *exo*-alkylated lactone **6**[8] was obtained by the following sequence, Zn−Cu couple mediated (−10 °C) [4+3]

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(1) Williams, P. G.; Asolkar, R. N.; Kondratyuk, T.; Pezzuto, J. M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 83.

(2) (a) Saunders, L. R.; Verdin, E. *Mol. Cancer Ther.* **2006**, *5*, 2777. (b) Thomas, T.; Thomas, T. J. *Cell Mol. Life Sci.* **2001**, *58*, 244.

(3) (a) Basuroy, U. K.; Gerner, E. W. *J. Biochem.* **2006**, *139*, 27. (b) Gerner, E. W., Jr. *Nat. Rev. Cancer* **2004**, *4*, 781.

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

(5) Yadav, J. S.; Srinivas Rao, C.; Chandrasekhar, S.; Rama Rao, A. V. *Tetrahedron Lett.* **1995**, *36*, 7717.

(6) (a) Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295. (b) Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562.

(7) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442 and references cited therein.

(8) (a) Kindly see the Supporting Information. (b) Rama Rao, A. V.; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55.

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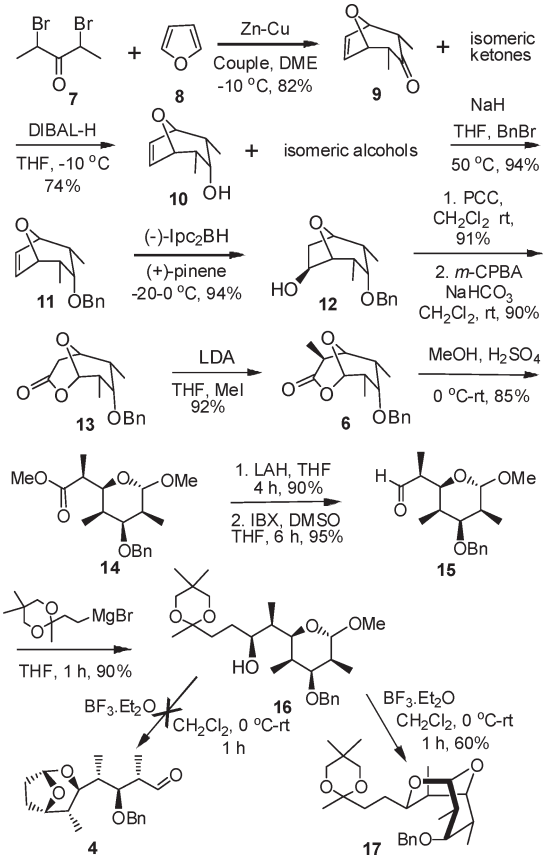
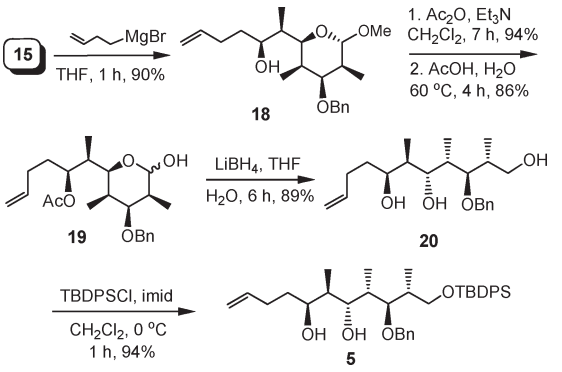
SCHEME 2. Initial Attempt To Synthesize the Fragment 4



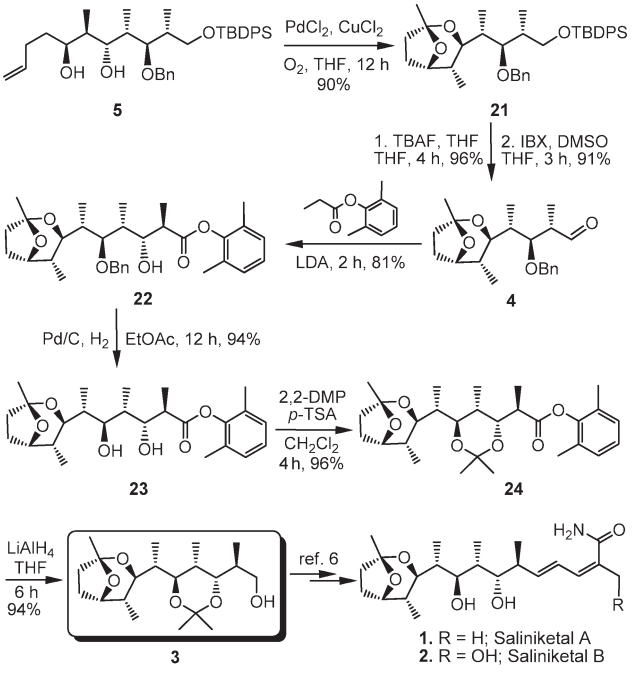
cycloaddition between 2,4-dibromopentan-3-one (**7**) and furan to form 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene-3-ones,[9] DIBAL-H reduction, benzyl protection, asymmetric hydroboration, PCC mediated oxidation, Bayer−Villiger reaction,[10] and alkylation. Acid-catalyzed methanolysis[11] of the bicyclic lactone **6** proceeded smoothly to furnish ester **14** in 85% yield. Lithium aluminum hydride mediated reduction of the ester afforded the primary alcohol in 90% yield, which was subsequently oxidized to aldehyde **15** with IBX[12] in DMSO. Our initial approach for a substrate-controlled Grignard reaction[13] with protected bromoketone[14] in THF afforded the alcohol **16** with good stereoselectivity (86:14 by HPLC) in high yield (Scheme 2). Compound **16** on treatment with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 0 °C afforded a new product **17** instead of **4**, which was assigned based on ^1H NMR spectroscopy and mass analysis. Even treatment with aqueous acetic acid at 80 °C afforded compound **17** as the sole product.

To avoid the protecting group manipulation, Grignard reaction with 1-butenylmagnesium bromide[15] in THF afforded the alcohol **18** with excellent stereoselectivity (96:4 by HPLC) in high yield. The absolute stereochemistry of the newly introduced chiral center was confirmed at a later stage of the synthesis. The hydroxyl group was protected as its acetate derivative, and upon further treatment with aq acetic acid (60%) at 60 °C afforded the lactol **19** in 86% yield. Treatment of compound **19** with $LiBH_4$ gave the triol **20**. The TBDPS ether derivative **5** was obtained in 94% yield by treating **20** with TBDPSCl and imidazole (Scheme 3).

SCHEME 3. Synthesis of the Fragment 5



SCHEME 4. Synthesis of the Advanced Intermediate 3



At this stage, we utilized the intramolecular Wacker oxidation reaction as followed by Paterson et al. for the total synthesis of saliniketals A and B. An intramolecular Wacker-type cyclization[16] of the 1,3-diol **5** with a catalytic amount of $PdCl_2$ and $CuCl_2$ in THF under oxygen at 0 °C afforded the desired [3.2.1]-dioxabicycle **21** (Scheme 4). The ^1H and ^{13}C

(9) Hoffmann, H. M. R. *Angew Chem., Int. Ed.* **1984**, *23*, 1.
(10) Corey, E. J.; Weinshenker, N. M.; Schoff, T. F.; Hubber, W. J. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
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(14) Stowell, J. C.; Keith, D. R.; King, B. T. *Org. Synth.* **1984**, *62*, 140.
(15) Walkup, R. D.; Kim, Y. S. *Tetrahedron Lett.* **1995**, *36*, 3091.
(16) (a) Ploysuk, C.; Kongkathip, B.; Kongkathip, N. *Synth. Commun.* **2007**, *37*, 1463. (b) Bulman Page, P. C.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535. (c) Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3429. (d) Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175.

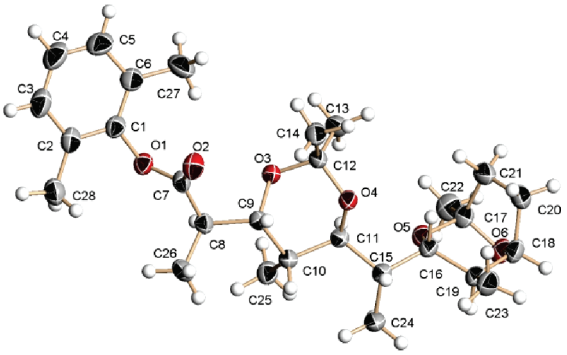

FIGURE 2. ORTEP diagram of compound **24**.

NMR data for the bicyclic acetal **21** were in good agreement with the corresponding region of saliniketals A and B.[17]

Deprotection of the TBDPS group with a 1 M solution of TBAF in THF at room temperature afforded the primary alcohol, which was oxidized with IBX to obtain the aldehyde intermediate **4** in 91% yield. The resulting aldehyde **4** on antialdol reaction following Pirung−Heathcock[18] protocol (lithium enolate of 2,6-dimethylphenyl propionate) gave the required compound **22** in 96:4 ratio (by HPLC). Catalytic hydrogenation of compound **22** followed by acetonide protection afforded compound **24**, whose nOe correlation provided the information about its *anti*-geometry. The value at 100.6 ppm in ^{13}C NMR also supported the *anti*-geometry between C7 and C9.[19] In addition, the single crystal X-ray crystallographic analysis unambiguously confirmed its relative and absolute stereochemistry (Figure 2). The absolute configuration of the molecule was further confirmed by converting the ester **24** to an advanced common intermediate **3**. The spectral and analytical data of **3** {$[\alpha]^{25}_D$ +6.1 (*c* 1.24, $CHCl_3$); lit.[6a] $[\alpha]^{25}_D$ +6.2 (*c* 0.81, $CHCl_3$)} were in good agreement with the reported values by Paterson et al.

In conclusion, we have achieved the formal total synthesis of saliniketals A and B following our own protocol of desymmetrization approach to create six contiguous asymmetric centers from a bicyclic lactone and following a 19-step synthetic sequence with 18% overall yield starting from a known intermediate **11**.

Experimental Section

(3*S*,4*R*)-4-((2*R*,3*R*,4*S*,5*S*,6*S*)-4-Benzyloxy)-6-methoxy-3,5-dimethyltetrahydro-2*H*-pyran-2yl)-1-(2,5,5-trimethyl-1,3-dioxan-2-yl)pentan-3-ol (16). To a mixture of magnesium (1.083 g, 44.56 mmol) in 1,2-dibromoethane (0.01 mL) in THF (20 mL) was added a solution of 2,5,5-trimethyl-2-(bromoethyl)-1,3-dioxan (7.014 g, 29.72 mmol) in THF (30 mL) under argon at a rate to maintain the internal temperature of the reaction below 25 °C. The solution was stirred for an additional 2 h at room temperature before being cooled to −40 °C. A solution of aldehyde **15** (0.9 g, 2.97 mmol) in THF (15 mL) was added to the reaction mixture, which was stirred for another 1 h at the same temperature. After completion of reaction, the reaction mixture was quenched with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, and purified by silica gel chromatography, utilizing ethyl acetate and hexane (1:7) as mobile phase, to afford **16** as a colorless oil (1.24 g, 90%). $[\alpha]^{27}_D$ +36.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.22 (m, 5H), 4.56 (s, 1H), 4.51 (s, 2H), 3.97−3.82 (m, 3H), 3.57 (dd, *J* = 2.8, 11.5 Hz, 2H), 3.53−3.35 (m, 3H), 3.40 (s, 3H), 2.29−1.46 (m, 7H), 1.39 (s, 3H), 1.07 (d, *J* = 7.5 Hz, 3H), 1.04 (s, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ESIMS for $C_{27}H_{44}O_6$ *m*/*z* 487 $[M + Na]^+$.

(1*S*,3*R*,4*S*,5*R*,6*S*,7*R*,8*R*)-4,6,7,8-Tetramethyl-3-(2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl)-2,9-dioxabicyclo[3.3.1]nonane (17). Compound **16** (100 mg, 0.22 mmol) was taken in CH_2Cl_2 (4 mL) under N_2 atmosphere and cooled to 0 °C. To this solution was added $BF_3 \cdot Et_2O$ (0.01 mL), then the mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction mixture was quenched with a saturated solution of NH_4Cl and the organic layer was separated and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness in vacuo, and purified by silica gel chromatography, using 3% ethyl acetate in hexane as the mobile phase to obtain compound **17** as a colorless liquid (56 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 4.59 (dd, *J* = 12.4, 13.2 Hz, 2H), 4.52 (d, *J* = 5.3 Hz, 1H), 4.18 (dd, *J* = 3.6, 5.8 Hz, 1H), 3.76 (m, 1H), 3.64−3.53 (m, 2H), 3.43−3.33 (m, 3H), 2.11−1.65 (m, 7H), 1.50 (s, 3H), 1.25 (s, 6H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 8.7 Hz, 3H); ESIMS for $C_{26}H_{40}O_5$ *m*/*z* 455 $[M + Na]^+$.

(2*R*′,3*S*′)-2-((2*R*,3*R*,4*S*,5*S*)-4-(Benzyloxy)-6-methoxy-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)hept-6-en-3-ol (18). To a stirred solution of aldehyde **15** (3.8 g, 12.45 mmol) in dry THF (50 mL) under nitrogen atmosphere was added butenyl magnesium bromide in THF [prepared from magnesium (0.76 g, 31.37 mmol) and butenyl bromide (2.54 mL, 25.09 mmol) in THF (25 mL)] at −78 °C, then stirring was continued for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution at −78 °C and allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography with ethyl acetate and hexane (1:9) as eluent to afford alcohol **18** (4.06 g, 90%) as a colorless liquid. $[\alpha]^{27}_D$ +31.2 (*c* 1.4, $CHCl_3$); IR (neat) ν 3492, 3068, 3030, 2974, 2916, 1639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 4.5 Hz, 4H), 7.24 (m, 1H), 5.80 (ddt, *J* = 16.6, 9.8, 6.8 Hz, 1H), 5.03 (dd, *J* = 16.6, 1.5 Hz, 1H), 4.95 (dd, *J* = 9.8, 1.5 Hz, 1H), 4.51 (s, 1H), 4.49 (s, 2H), 3.91 (m, 1H), 3.81 (m, 1H), 3.35 (s, 3H), 2.36−1.99 (m, 4H), 1.96−1.77 (m, 2H), 1.67−1.39 (m, 3H), 1.06 (d, *J* = 7.6 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.6, 128.2, 127.2, 127.1, 114.5, 104.7, 75.2, 71.8, 71.0, 69.3, 55.4, 38.5, 36.4, 33.4, 33.1, 30.8, 13.2, 9.7, 7.6; HRMS calcd for $C_{22}H_{34}O_4$ $[M + Na]^+$ 385.2354, found 385.2344.

(2*R*,3*R*,4*R*)-3-(Benzyloxy)-4-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-2-(methylpentyloxy)(*tert*-butyl)-diphenylsilane (21). To a stirred solution of diol compound **5** (500 mg, 0.85 mmol) in dry THF (10 mL) at 0 °C was added $CuCl_2$ (22.8 mg, 0.17 mmol) and $PdCl_2$ (30 mg, 0.17 mmol). The reaction mixture was flushed with O_2 twice at 0 °C and stirring was continued for 12 h at the same temperature under O_2 atmosphere. The reaction mixture was quenched with Et_2O (10 mL) and filtered through a pad of a 1:1 mixture of $MgSO_4$:SiO_2 and washed with Et_2O. The combined organic layer was concentrated to dryness under reduced pressure and the resulting oil was purified by silica gel chromatography with ethyl acetate and hexane (1:19) as the mobile phase to obtain compound **21** (448 mg, 90%) as a colorless oil. $[\alpha]^{27}_D$ −22.3 (*c*

(17) Kindly see the Supporting Information.
(18) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.
(19) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

3.05, $CHCl_3$); IR (neat) ν 3451, 3067, 2958, 2932, 2859, 1725, 1631, 1463, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 4H), 7.40−7.21 (m, 11H), 4.58 (dd, J = 18.1, 11.3 Hz, 2H), 4.11 (m, 1H), 3.81 (dd, J = 9.8, 6.0 Hz, 1H), 3.70 (dd, J = 10.5, 1.5 Hz, 1H), 3.51 (dd, J = 10.5, 7.5 Hz, 1H), 3.34 (dd, J = 9.8, 1.5 Hz, 1H), 1.94−1.76 (m, 2H), 1.75−1.61 (m, 3H), 1.41 (s, 3H), 1.42−1.34 (m, 2H), 1.08−1.01 (m, 12H), 0.78 (d, J = 7.5 Hz, 3H), 0.56 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 135.6, 133.9, 133.8, 129.5, 128.2, 127.5, 127.1, 126.9, 104.7, 83.2, 80.1, 74.9, 73.0, 64.9, 38.2, 36.4, 34.2, 33.8, 29.7, 26.8, 24.2, 23.9, 19.2, 16.2, 12.7, 10.0; HRMS calcd for $C_{37}H_{50}O_4NaSi$ $[M + Na]^+$ 609.3376, found 609.3367.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2,6-Dimethylphenyl-5-(benzyloxy)-6-((1*S*,3*R*,4*R*,5*S*)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-3-hydroxy-2,4-dimethylheptanoate (22). *n*-Butyl lithium (3.6 mL, 1.6 M in hexane, 5.88 mmol) was added dropwise to an ice-cooled solution of diisopropylamine (0.82 mL, 5.88 mmol) in dry THF (10 mL) and the mixture was stirred for 20 min. The reaction mixture was then cooled to −78 °C and propionate ester (671 mg, 6.53 mmol) in dry THF (10 mL) was added slowly to the in situ generated LDA solution with stirring for an additional 45 min. Aldehyde **4** (452 mg, 1.31 mmol) in dry THF (10 mL) was added to the reaction mixture, which was stirred another 1 h at −78 °C. The reaction mixture was quenched with aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography, using ethyl acetate and hexane (1:9) as the mobile phase, to afford aldol adduct **22** (555 mg, 81%) as a colorless oil. $[\alpha]^{27}_D$ −37.0 (*c* 2.1, $CHCl_3$); IR (neat) ν 3486, 2971, 2882, 1755, 1636, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 7.02 (s, 3H), 4.72 (dd, J = 38.1, 11.3 Hz, 2H), 4.31 (d, J = 10.0 Hz, 1H), 4.23 (dd, J = 6.4, 3.5 Hz, 1H), 3.91 (s, 1H), 3.82 (dd, J = 10.5, 1.3 Hz, 1H), 3.65 (dd, J = 10.1, 1.7 Hz, 1H), 2.88 (qd, J = 10.0, 6.9 Hz, 1H), 2.17 (s, 6H), 2.11−1.95 (m, 3H), 1.92−1.64 (m, 4H), 1.48 (s, 3H), 1.25 (d, J = 7.1 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 148.1, 138.0, 130.4, 128.7, 128.5, 128.3, 127.7, 126.9, 125.5, 104.8, 86.8, 80.0, 76.1, 72.9, 72.1, 44.0, 36.3, 34.3, 33.8, 33.7, 24.1, 23.8, 16.3, 16.2, 13.9, 12.8, 11.5, 9.9; HRMS calcd for $C_{32}H_{44}O_6$ $[M + Na]^+$ 547.3030, found 547.3042.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2,6-Dimethylphenyl-6-((1*S*,3*S*,4*R*,5*S*)-1,4-dimethyl-2,8-dioxa-bicyclo[3.2.1]octan-3-yl)-3,5-dihydroxy-2,4-dimethylheptanoate (23). To a solution of compound **22** (200 mg, 0.38 mmol) in ethyl acetate (6 mL) was added a catalytic amount Pd−C (10%) under H_2 balloon pressure with stirring at room temperature for 12 h. The reaction mixture was filtered on a small pad of Celite, concentrated to dryness under reduced pressure, and purified by silica gel chromatography, using ethyl acetate and hexane (1:6), to obtain compound **23** (155 mg, 94%) as a colorless liquid. $[\alpha]^{27}_D$ −9.6 (*c* 2.5, $CHCl_3$); IR (neat) ν 3449, 2968, 1752, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 3H), 4.38 (dt, J = 9.8, 2.4 Hz, 1H), 4.24 (m, 1H), 3.86 (dd, J = 10.3, 1.8 Hz, 1H), 3.61 (dd, J = 12.8, 6.6 Hz, 1H), 3.36 (m, 2H), 2.96 (qd, J = 10.0, 7.1 Hz, 1H), 2.18 (s, 6H), 2.09 (m, 1H), 2.01−1.77 (m, 6H), 1.46 (s, 3H), 1.31 (d, J = 7.1 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 148.0, 130.2, 128.5, 125.7, 105.0, 80.0, 77.7, 77.2, 74.8, 72.3, 43.9, 35.5, 35.0, 34.4, 33.7, 23.9, 16.4, 14.1, 12.6, 11.1, 10.4; HRMS calcd for $C_{25}H_{38}O_6$ $[M + 1]^+$ 435.2741, found 435.2740.

(*R*)-2,6-Dimethyl-2-((4*R*,5*S*,6*S*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (24). To a stirred solution of compound **23** (150 mg, 0.35 mmol) in dry dichloromethne (4 mL) was added 2,2-dimethoxypropane (0.4 mL, 3.4 mmol) followed by a catalytic amount of *p*-TSA at °C. The reaction mixture was stirred for 4 h at room temperature and quenched with H_2O (2 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, and purified by silica gel chromatography to afford compound **24** (157 mg, 96%) as a crystalline solid. Mp 145 °C; $[\alpha]^{27}_D$ −1.5 (*c* 1.2, $CHCl_3$); IR (neat) ν 2927, 2855, 1757, 1656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 3H), 4.21 (m, 1H), 4.07 (dd, J = 10.9, 3.7 Hz, 1H), 3.75 (dd, J = 10.5, 1.8 Hz 1H), 3.34 (dd, J = 9.1, 6.4 Hz, 1H), 2.90 (qd, J = 10.9, 6.9 Hz, 1H), 2.17 (s, 6H), 2.03−1.66 (m, 7H), 1.44 (s, 3H), 1.28 (d, J = 3.7 Hz, 6H), 1.25 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 148.1, 130.2, 128.4, 125.6, 104.8, 100.6, 80.2, 74.4, 72.7, 70.9, 40.6, 38.8, 35.2, 34.1, 33.7, 25.5, 24.1, 23.9, 23.4, 16.3, 13.7, 12.7, 12.4, 7.9; HRMS calcd for $C_{28}H_{42}O_6$ $[M + Na]^+$ 497.2874, found 497.2872.

(*S*)-2-((4*S*,5*R*,6*R*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propan-1-ol (3). To an ice-cooled suspension of LAH (16 mg, 0.42 mmol) in dry THF (4 mL) was added a solution of compound **24** (100 mg, 0.21 mmol) in dry THF (3 mL) under N_2 atmosphere with stirring for 4 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with aqueous ammonium chloride solution and the formed precipitate was filtered on a small pad of Celite and washed with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography, using ethyl acetate and hexane (1:5) as the mobile phase, to obtain alcohol **3** (70 mg, 94%) as a colorless liquid. $[\alpha]^{27}_D$ +6.1 (*c* 1.24, $CHCl_3$); IR (neat) ν 3457, 2922, 1640, 1462, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, J = 6.1, 3.9 Hz, 1H), 3.72 (dd, J = 10.3, 3.9 Hz, 1H), 3.67 (dd, J = 10.3, 3.9 Hz, 1H), 3.63−3.49 (m, 2H), 3.34 (m, 2H), 2.03−1.60 (m, 8H), 1.43 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.76 (d, J = 7.1 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.8, 100.5, 80.2, 76.3, 74.5, 72.7, 69.4, 38.8, 36.4, 34.7, 34.2, 33.7, 25.9, 24.2, 23.9, 23.4, 12.9, 12.6, 12.5, 7.8; HRMS calc for $C_{20}H_{36}O_5$ $[M+1]^+$ 357.2636, found 357.2635.

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Supporting Information Available: Experimental procedures and spectroscopic data, copies of ^1H and ^{13}C NMR spectra for new compounds, NOE spectrum of **18**, **24**, and a CIF file of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.