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Total Synthesis of (+)-Mupirocin H from D-Glucose†

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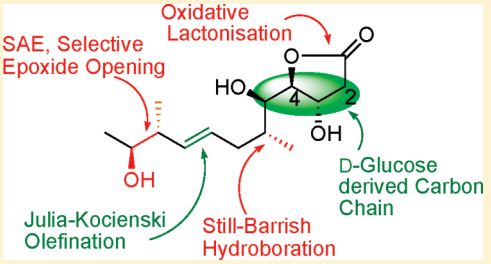
Supporting Information

ABSTRACT: Enantioselective total synthesis of mupirocin H is accomplished starting from D-glucose featuring strategic application of D-glucose derived chirality, diastereoselective Still−Barrish hydroboration, and further elaboration of carbon chain to furnish a phenyltetrazolyl sulfone intermediate, which on coupling with (2*S*,3*S*)-2-methyl-3-(triisopropylsilyloxy)butanal under Julia−Kocienski olefination conditions gave an advanced *E*-olefinic intermediate selectively. The *E*-olefin was transformed to the 4-hydroxynitrile, a prefinal substrate, which on acid-catalyzed oxidative lactonization furnished the target molecule mupirocin H in 19 steps from known compound **6** (longest linear sequence) with an overall yield of 4.96%.



Mupirocin, a naturally occurring metabolite isolated from *Pseudomonas fluorescens* (a soil isolate, NCIB 10586) proved highly efficient in treatment of skin infections and one of the most successful topical antibiotics for eradication of nasal *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Mupirocin is a mixture of pseudomonic acids[2] with principal constituent pseudomonic acid A accounting for 90%, and the other components present are pseudomonic acids B, C, and D shown in Figure 1. Structural complexity and important biological activities of these pseudomonic acids attracted synthetic organic chemists resulting in many total syntheses of these molecules.[3] Studies on biosynthesis of pseudomonic acids from *Pseudomonas fluorescens* and its biosynthetic gene cluster resulted in isolation of novel pseudomonic acid analogues mupirocin W[4] (**1**) and mupirocin H[5] (**2**), among which **1** has shown moderate bioactivity similar to those of earlier reported pseudomonic acids. Despite excellent antibiotic properties of mupirocin, it is associated with poor metabolic stability and poor bioavailability restricting it to be used as topical antibiotic. Moreover emerging resistance to mupirocin is also a matter of serious concern.[6] In this scenario, development of better alternatives to mupirocin is significant that led us to perform total synthesis of mupirocin H. The versatility of the present route lies in the fact that three out of its six chiral centers are derived from D-glucose followed by late-stage introduction of its *trans* double bond making this pathway useful for total synthesis of many other structurally similar molecules like pseudomonic acids and analogues, mupirocin W, antibiotic thiomarinols,[7] and their analogues for biological evaluations. The common core for all these molecules, shown in red in Figure 1, can be derived using the present strategy.

Our retrosynthetic analysis is illustrated in Scheme 1. We planned to generate the γ-lactone functionality in the final step of our synthesis by acid-catalyzed oxidative lactonization of 4-hydroxynitrile moiety **3**, whose *E*-olefinic linkage suggested

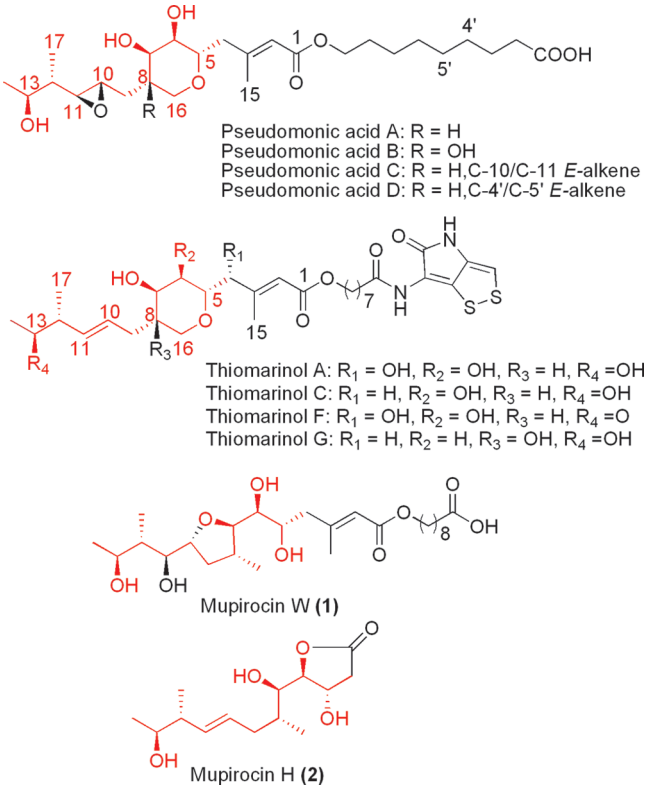


Figure 1. Chemical structures of pseudomonic acids, selected thiomarinols, and mupirocin W, H having a common core, shown in red, which could be derived using the present strategy.

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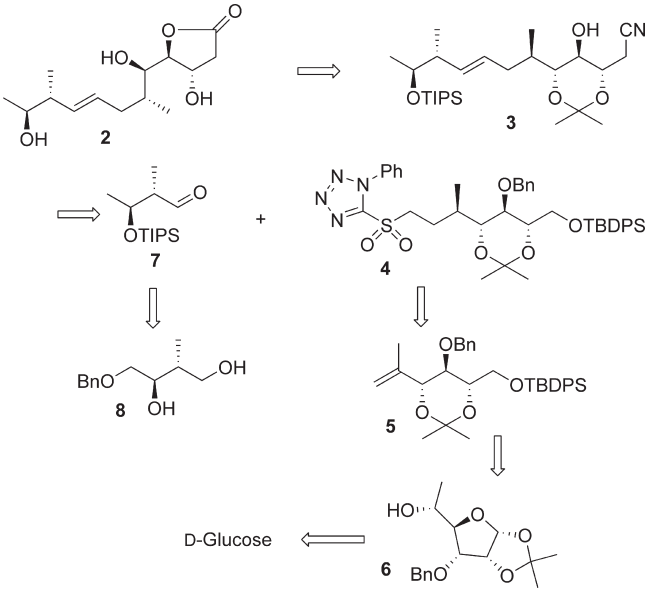
Scheme 1. Retrosynthetic Analysis of Mupirocin H (2)

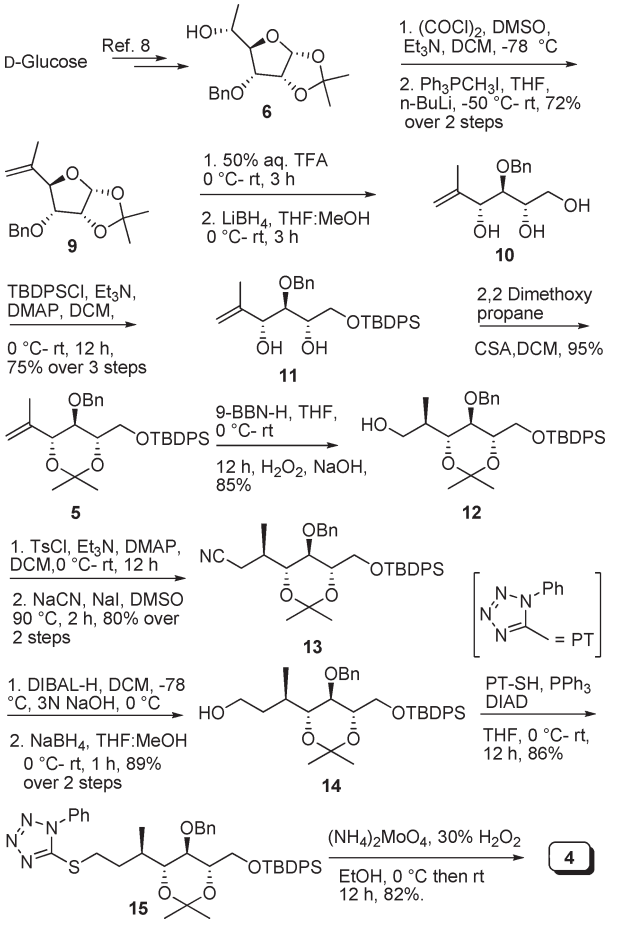


disconnection of double bond to Julia–Kocienski olefination precursors, sulfone **4**, and aldehyde **7**. Further simplification of **4** via Still–Barrish hydroboration, one-carbon homologation, Mitsunobu reaction, and peroxide oxidation resulted in terminal alkene precursor **5**, which could easily be resourced from D-glucose-derived known alcohol **6**. On the other hand, aldehyde **7** was planned to be derived from another known alcohol **8**.

To synthesize sulfone **4**, as depicted in Scheme 2, we began with D-glucose which was transformed into alcohol **6** using a known procedure.[8] This alcohol **6** was subjected to Swern oxidiation[9] conditions to give the corresponding keto intermediate which under one-carbon Wittig olefination[10] conditions afforded the olefin **9** in 72% yield. Treatment of **9** with 50% aqueous TFA followed by $LiBH_4$ reduction afforded triol **10**, which was subjected to selective TBDPS protection to give **11** in 75% yield over three steps. Compound **11** on treatment with 2,2-dimethoxypropane in presence of CSA (cat.) gave the terminal alkene **5**, the Still–Barrish hydroboration precursor, in 95% yield. Thus, **5** on treatment with 9-borabicyclononane (9-BBN) in dry THF at 0 °C followed by treatment with H_2O_2 and NaOH gave **12** as a single diastereomer in 85% yield.[11]

In the course of the above hydroboration reaction, steric bulkiness of the boron ligand in 9-BBN oriented the reagent to such a face of the alkene **5**, which ensured minimum interactions with allylic hydroxyl (here protected as its acetonide) group of alkene **5**, thereby imparting maximum stability to that transition state (*TS*). The above facial bias can be explained using the Houk[12] rationale for two possible *TS*s as depicted in Figure 2.[13] As seen in *TS-2*, the allylic acetonide protected hydroxyl group of alkene and the boron ligands are in eclipsed form generating steric repulsive strain which is destabilizing this *TS* making it nonfavored, whereas in *TS-1* the allylic acetonide-protected hydroxyl group of alkene and the boron ligands is in noneclipsed form, making this *TS* more stable and favored, ultimately resulting in the formation of single diastereomer **12** in this reaction. The diastereoselection observed in the Still–Barrish hydroboration is widely documented, and many examples of such hydroboration are reported.[14]

Scheme 2. Synthesis of Sulfone 4



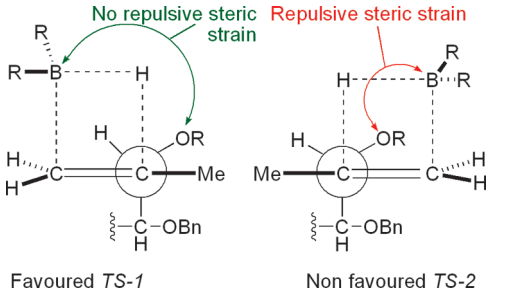


Figure 2. Transition states for hydroboration of alkene **5**.

The alcohol **12** was tosylated with TsCl and triethylamine to give a tosylate, which on heating with an excess of NaCN and catalytic amount of NaI in DMSO produced **13** in 80% yield. Intermediate **13** on reaction with DIBAL-H at −78 °C formed intermediate aldehyde,[15] which on reduction with $NaBH_4$ gave the alcohol **14** in 89% yield. Mitsunobu reaction of **14** and 1-phenyl-1-1*H*-tetrazole-5-thiol (PT-SH) formed sulfide **15** in 86% yield, which on oxidation with H_2O_2 and ammonium molybdate afforded the sulfone **4** in 82% yield.

Synthesis of the aldehyde **7**, depicted in Scheme 3, was started from the known compound **8**, which was prepared from (*E*)-4-(benzyloxy)but-2-en-1-ol by employing the Sharpless asymmetric epoxidation reaction, followed by dimethylcopper lithium

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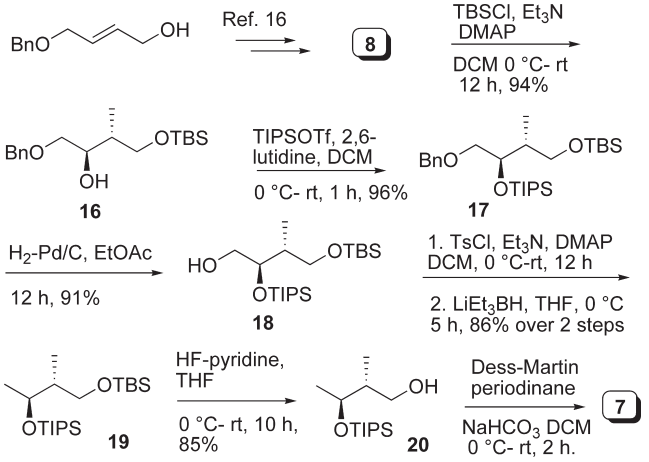
Scheme 3. Synthesis of Aldehyde 7

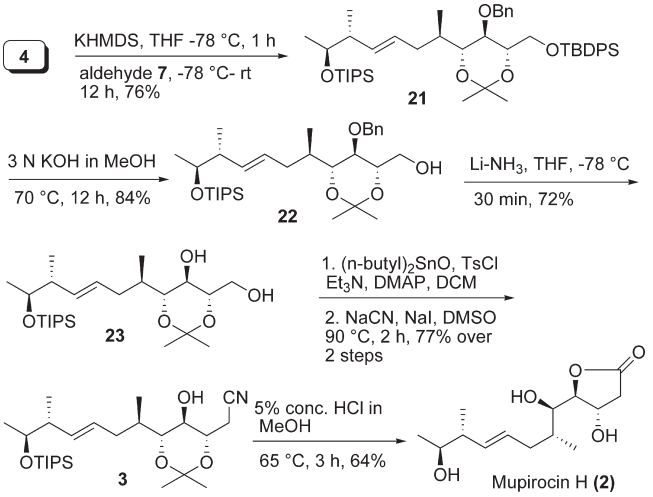


mediated regioselective epoxide opening.[16] The diol **8** on selective protection of a primary hydroxyl group as TBDMS ether followed by protection of secondary hydroxyl group as a TIPS ether gave the fully protected compound **17** in 90% overall yield in two steps. Compound **17** on hydrogenation in presence of Pd−C in ethyl acetate gave **18** in 91% yield. Here we sought the removal of the free hydroxyl group of **18**. Hence, it was converted to tosyl derivative, which on treatment with $LiEt_3BH$ (Superhydride) in dry THF gave **19** in 86% yield.[17] Compound **19** on treatment with HF−pyridine complex in THF gave the alcohol **20**, which on Dess−Martin periodinane oxidation[18] furnished aldehyde **7**.

With sulfone **4** and aldehyde **7** in hand, the stage was set for the crucial Julia−Kocienski olefination.[19] Accordingly, **4** was treated with KHMDS in dry THF at −78 °C, followed by slow addition of **7** over 10 min period, and the same temperature was maintained for 1.5 h. It was then warmed to rt and further stirred for 12 h to furnish the *E*-olefinic compound **21** in 76% yield (with trace amounts of *Z*-isomer which was separated by simple column chromatography). Compound **21** was then treated with 3 N KOH in MeOH solution under refluxing conditions to give the TBDPS-deprotected compound[20] **22** in 84% yield, which on Li−liquid ammonia mediated benzyl deprotection[21] afforded diol **23** in 72% yield. The diol on selective monotosylation[22] gave primary *O*-tosylate, which was heated with NaCN and catalytic amount of NaI in DMSO to give our prefinal substrate **3** in 77% yield. This compound with terminal 4-hydroxy-1-nitrile moiety was proven to be ideal for our end game. Thus, it was heated with 5% concd HCl in MeOH solution[23] generating the required γ-lactone functionality with concomitant removal of diacetonide and triisopropylsilyl (TIPS) protecting groups, all in one pot, to give our target molecule mupirocin H in 64% yield (Scheme 4). The ^1H and ^{13}C NMR spectra and specific rotation of synthetic mupirocin H (**2**) were found to be in good agreement with the reported values.[5]

In summary, we have achieved the total synthesis of mupirocin H using D-glucose as chiral pool material and Still−Barrish hydroboration and Julia−Kocienski olefination as key steps. Three chiral centers out of six were obtained from D-glucose. The convergent strategy developed here can be utilized in the total synthesis of other natural products of the same family like pseudomonic acids, mupirocin W, and thiomarinols. Currently we are working in this direction.

Scheme 4. Julia−Kocienski Coupling between Sulfone 4 and Aldehyde 7 and Completion of Synthesis



EXPERIMENTAL SECTION

(3a*R*,5*R*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-(prop-1-en-2-yl)tetrahydrofuro[2,3-*d*][1,3]dioxole (9). (*R*)-1-((3a*R*,5*R*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethanol (**6**) was prepared from D-glucose using a known procedure.[8] Alcohol **6** (8.0 g, 27.37 mmol) was subjected to Swern oxidation reaction using same procedure as described in our previous work[24] to give the corresponding ketone. The ketone (R_f = 0.60, 30% EtOAc in PE), thus obtained, was directly used after flash chromatography for the next reaction.

To a suspension of methyltriphenylphophonium iodide (22.13 g, 54.74 mmol) in dry THF (150 mL) at 0 °C was added *n*-BuLi (1.6 M in hexane, 34.21 mL, 54.74 mmol) slowly. After being stirred at the same temparature for 10 min, the mixture was warmed to rt rapidly, stirred for 25 min, and then cooled to −50 °C, and to this was added slowly the above ketone dissolved in dry THF (25 mL). The mixture was stirred at the same temperature for 1 h, then gradually warmed to rt, and stirred for 24 h. Water was added to the mixture, which was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 8% EtOAc in PE) yielded compound **9** as a colorless oil (5.72 g, 72%): R_f = 0.6 (SiO_2, 30% EtOAc in PE); $[\alpha]^{24}_D$ = +60.5 (*c* 2.62, $CHCl_3$); IR ν_{max} 2924, 2857, 1726, 1513, 1454 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.26 (m, 5H), 5.70 (d, *J* = 3.9 Hz, 1H), 5.12 (s, 1H), 4.94 (s, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.52 (dd, *J* = 3.9, 3.8 Hz, 1H), 4.39 (d, *J* = 8.7 Hz, 1H), 3.52 (dd, *J* = 8.7, 3.9 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 137.4, 128.2, 127.7, 114.2, 112.6, 103.5, 81.1, 79.7, 77.4, 71.8, 26.6, 26.4, 17.4; MS *m*/*z* 308 $[M + NH_4]^+$; HRMS calcd for $C_{17}H_{22}O_4Na$ $[M + Na]^+$ 313.1416, found 313.1422.

(2*S*,3*R*,4*R*)-3-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-5-methylhex-5-ene-2,4-diol (11). Aqueous TFA (50%, 18.25 mL, 1 mL/mmol) was added to compound **9** (5.30 g, 18.25 mmol) at 0 °C, and the resulting mixture was allowed to warm to rt and stirred for 3 h. Then TFA was removed in vacuo, and the residue was dissolved in DCM, washed with saturated aq $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The lactol (R_f = 0.60, 50% EtOAc in PE), thus obtained, was directly used after flash chromatography for next reaction.

The lactol obtained above was dissolved in THF/MeOH (1:1, 60 mL) and cooled to 0 °C, and $LiBH_4$ (0.795 g, 36.50 mmol) was slowly added. The reaction mixture was then allowed to warm to rt,

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stirred for 3 h, quenched slowly using saturated NH_4Cl solution, extracted with DCM, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The (2*S*,3*R*,4*R*)-3-(benzyloxy)-5-methylhex-5-ene-1,2,4-triol (**10**) (R_f = 0.30, 60% EtOAc in PE), thus obtained, was directly used after flash chromatography for next reaction.

Triol **10** was subjected to selective mono-TBDPS protection using the same procedure as described in our previous work.[25] Purification by column chromatography (SiO_2, 10% EtOAc in PE) afforded **11** as a colorless oil (6.72 g, 75% over three steps): R_f = 0.4 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = −6.44 (*c* 6.1, $CHCl_3$); IR ν_{max} 3565, 3421(br), 2929, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 5H), 7.46−7.33, (m, 6H), 7.28−7.23 (m, 2H), 7.17−7.14 (m, 2H), 5.10 (s, 1H), 4.97 (s, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 10.6 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 1H), 3.93−3.88 (m, 2H), 3.79 (dd, *J* = 11.3, 6.8 Hz, 1H), 3.63 (dd, *J* = 11.3, 5.3 Hz, 1H), 2.85 (bs, 1H), 1.80 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 137.8, 135.5, 133.0, 132.8, 129.8, 128.3, 127.9, 127.8, 113.1, 79.7, 76.2, 73.6, 73.1, 64.7, 26.8, 19.2, 19.0; MS *m*/*z* 513 $[M + Na]^+$; HRMS calcd for $C_{30}H_{38}O_4SiNa$ $[M + Na]^+$ 513.2437, found 513.2426.

(((4*S*,5*R*,6*R*)-5-(Benzyloxy)-2,2-dimethyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl)methoxy)(*tert*-butyl)diphenylsilane (5). Diol **11** (6.50 g, 13.25 mmol) was protected to give **5** using the same procedure as described in our previous work.[24] Purification by column chromatography (SiO_2, 2 to 5% EtOAc in PE) afforded compound **5** as a colorless oil (6.68 g, 95%): R_f = 0.4 (SiO_2, 10% EtOAc in PE); $[\alpha]^{24}_D$ = −41.0 (*c* 3.63, $CHCl_3$); IR ν_{max} 2932, 2859, 1462, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.70 (m, 5H), 7.44−7.33 (m, 6H), 7.31−7.20 (m, 4H), 5.24 (s, 1H), 5.08 (d, *J* = 1.5 Hz, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 4.50 (d, *J* = 9.8 Hz, 1H), 4.24 (d, *J* = 9.1 Hz, 1H), 3.98 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.84 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.78 (m, 1H), 3.69 (dd, *J* = 9.1, 9.1 Hz, 1H), 1.89 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 137.9, 135.9, 135.6, 134.0, 133.4, 129.5, 128.3, 128.0, 127.8, 127.6, 127.4, 115.7, 98.2, 77.4, 74.0, 73.6, 71.4, 63.5, 29.3, 26.8, 19.4, 17.7; MS *m*/*z* 548 $[M + NH_4]^+$; HRMS calcd for $C_{33}H_{42}O_4SiNa$ $[M + Na]^+$ 553.2750, found 553.2740.

(*R*)-2-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol (12). A solution of 9-BBN (0.5 M in THF, 67.8 mL, 33.9 mmol) was slowly added dropwise at 0 °C to a solution of alkene (**5**) (6.0 g, 11.3 mmol) in dry THF (30 mL). After the addition, the mixture was allowed to warm to rt, stirred for 12 h, and then treated with EtOH (21.1 mL), aqueous NaOH (3 N, 14 mL), and 30% aqueous H_2O_2 (14 mL) and stirred at rt for 2 h. The mixture was saturated with solid K_2CO_3 and extracted with Et_2O. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 10% EtOAc in PE) afforded compound **12** as colorless oil (5.27 g, 85%): R_f = 0.5 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = −4.4 (*c* 3.96, $CHCl_3$); IR ν_{max} 3530, 2931, 2865, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.70 (m, 5H), 7.45−7.22 (m, 10H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 3.98 (dt, *J* = 11.3, 3.0 Hz 1H) 3.91−3.77 (m, 4H) 3.72 (m, 1H), 3.55 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.64 (bs, 1H), 2.04 (m, 1H) 1.43 (s, 3H), 1.42 (s, 3H), 1.14 (d, *J* = 7.5 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 137.6, 135.9, 135.6, 133.8, 133.2, 129.5, 128.5, 127.9, 127.6, 127.4, 98.5, 77.6, 74.4, 74.3, 71.5, 64.2, 63.4, 34.5, 29.3, 26.8, 19.4, 18.9, 14.8; MS *m*/*z* 566 $[M + NH_4]^+$; HRMS calcd for $C_{33}H_{44}O_5SiNa$ $[M + Na]^+$: 571.2855, found 571.2850.

(*R*)-3-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)butanenitrile (13). To a solution of **12** (5.0 g, 9.11 mmol) in DCM (30 mL) was added Et_3N (3.81 mL, 27.33 mmol) followed by TsCl (2.084 g, 10.93 mmol) at 0 °C. After being stirred at the same temperature for 15 min, DMAP (0.111 g, 0.91 mmol) was added, and the reaction mixture was allowed to warm to rt, then stirred for 12 h followed by quenching with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The tosylate (R_f = 0.5, 10% EtOAc in PE), thus obtained, was directly used after flash chromatography for the next reaction.

To a solution of above tosylate in dry DMSO (30 mL) were added sodium cyanide (3.57 g, 72.88 mmol) followed by sodium iodide (0.136 g, 0.911 mmol), and the reaction mixture was stirred at 90 °C for 2 h. After being cooled to rt, the mixture was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 5% EtOAc in PE) afforded compound **13** as colorless oil (4.06 g, 80% over two steps): R_f = 0.6 (SiO_2, 10% EtOAc in PE); $[\alpha]^{24}_D$ = +13.34 (*c* 3.45, $CHCl_3$); IR ν_{max} 2953, 2864, 2362, 2324, 1695, 1516 cm^{-1}; ^1H NMR δ 7.79−7.70 (m, 5H), 7.45−7.24 (m, 10H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 10.6, Hz, 1H), 4.00 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.86 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.71−3.56 (m, 3H), 2.34−2.20 (m, 3H), 1.40 (s, 6H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.9, 135.6, 134.7, 133.7, 133.1, 129.6, 128.6 128.2, 128.1, 127.6, 127.4, 119.7, 98.3, 74.6, 74.1, 70.7, 63.3, 31.1, 29.0, 26.8, 19.4, 19.1, 18.2, 17.4; MS *m*/*z* 575 $[M + NH_4]^+$; HRMS calcd for $C_{34}H_{43}NO_4SiNa$ $[M + Na]^+$ 580.2984, found 580.2980.

(*R*)-3-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)butan-1-ol (14). Nitrile **13** (3.90 g, 6.99 mmol) was converted to alcohol **14** using a two-step protocol viz. DIBAL-H mediated conversion of nitrile to aldehyde, followed by $NaBH_4$ reduction using the same procedure as described in our previous work.[24] Purification by column chromatography (SiO_2, 18% EtOAc in PE) afforded compound **14** as a colorless oil (3.5 g, 89%): R_f = 0.4 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = −3.4 (*c* 0.35, $CHCl_3$); IR ν_{max} 3618, 2933, 2856, 1694, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.71 (m, 5H), 7.44−7.22 (m, 10H), 4.70 and 4.64 (ABq, *J* = 10.6 Hz, 2H), 3.98 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.86 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.80−3.68 (m, 4H), 3.58 (m, 1H), 2.43 (bs, 1H), 2.19 (m, 1H), 1.81−1.62 (m, 2H), 1.43 (s, 6H), 1.10 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 135.9, 135.6, 133.8, 133.3, 129.5, 128.4, 127.9, 127.8, 127.5, 127.4, 98.3, 76.5, 74.3, 74.2, 71.0, 63.5, 59.8, 32.7, 29.9, 29.0, 26.8, 19.3, 19.2, 16.6; MS *m*/*z* 585 $[M + Na]^+$; HRMS calcd for $C_{34}H_{46}O_5SiNa$ $[M + Na]^+$ 585.3012, found 585.3000.

5-((*R*)-3-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)butylthio)-1-phenyl-1*H*-tetrazole (15). Triphenylphosphine (3.84 g, 14.65 mmol), 1-phenyl-1-1*H*-tetrazole-5-thiol (1.57 g, 8.79 mmol), and the alcohol **14** (3.30 g 5.86 mmol) were dissolved in dry THF (18 mL). This solution was cooled to 0 °C, and diisopropyl azodicarboxylate (DIAD, 2.88 mL, 14.65 mmol) was slowly added and then the mixture allowed to warm to rt. After 12 h of stirring, the reaction mixture was directly concentrated in vacuo. Purification by column chromatography (SiO_2, 12% EtOAc in PE) afforded compound **15** as a colorless oil (3.64 g, 86%): R_f = 0.5 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = +31.0 (*c* 0.73, $CHCl_3$); IR ν_{max} 2930, 2858, 1795, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.61 (m, 5H), 7.44−7.38 (m, 5H), 7.35−7.23 (m, 5H), 7.22−7.11 (m, 5H), 4.58 and 4.52 (ABq, *J* = 10.9 Hz, 2H), 3.88 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.66−3.58 (m, 3H), 3.49 (m, 1H), 3.19 (m, 1H), 2.07−1.94 (m, 2H), 1.74 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 137.8, 135.9, 135.6, 133.8, 133.6, 133.3, 129.9, 129.6, 129.5, 128.4, 127.8, 127.6, 127.4, 123.7, 98.1, 76.4, 74.2, 70.8, 63.6, 32.2, 31.7, 29.4, 29.2, 26.8, 19.3, 19.2, 16.5; MS ESIMS (*m*/*z*) $C_{41}H_{50}N_4O_4SSiNa$ $[M + Na]^+$ 745; HRMS calcd for $C_{41}H_{50}N_4O_4SSiNa$ $[M + Na]^+$ 745.3219, found 745.3197.

5-((*R*)-3-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)butylsulfonyl)-1-phenyl-1*H*-tetrazole (4). To a solution of compound **15** (3.40 g,

4.70 mmol) in absolute EtOH (15 mL) at 0 °C was added a premixed solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.89 g, 7.05 mmol) in H_2O_2 (30% aq, 9.6 mL, 94 mmol) using a glass pipet. The resulting yellow solution was then removed from the ice bath and allowed to warm to rt. After 12 h, saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 15% EtOAc in PE) afforded compound **4** as colorless oil (2.91 g, 82%): R_f = 0.4 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = +20.3 (*c* 1.75, $CHCl_3$); IR ν_{max} 2991, 2933, 1462, 1384 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.57 (m, 6H), 7.56−7.46 (m, 4H), 7.36−7.16 (m, 10H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 3.89 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.83−3.73 (m, 2H), 3.66−3.56 (m, 3H), 3.48 (m, 1H), 2.07−1.95 (m, 2H), 1.88 (m, 1H), 1.33 (s, 6H), 0.99−1.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 137.8, 135.9,135.6, 133.8, 133.2, 131.3, 129.6, 129.5, 128.5, 128.0, 127.6, 127.4, 125.0, 98.3, 76.1, 74.3, 71.1, 63.5, 54.2, 31.6, 29.2, 26.8, 22.6, 19.4, 19.1, 16.5; MS *m*/*z* 777 $[M + Na]^+$; HRMS calcd for $C_{41}H_{54}N_5O_6SiS$ $[M + NH_4]^+$ 772.3564, found 772.3548.

(2*R*,3*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-ol (16). Compound **8** (5.50 g, 26.16 mmol), prepared using a known procedure,[16] was selectively protected as primary TBDMS ether using the same procedure as described in our previous work.[26] Purification by column chromatography (SiO_2, 10% EtOAc in PE) afforded pure compound **16** as colorless oil (7.96 g, 94%): R_f = 0.6 (SiO_2, 10% EtOAc in PE); $[\alpha]^{24}_D$ = −5.0 (*c* 2.28, $CHCl_3$); IR ν_{max} 3480 (br), 2929, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.17 (m, 5H), 4.52 and 4.46 (ABq, *J* = 12.1 Hz, 2H), 3.68−3.62 (m, 2H), 3.56−3.39 (m, 4H), 1.80 (m, 1H), 0.80−0.83 (m, 12H), −0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.3, 127.6, 127.5, 74.2, 73.3, 72.7, 66.7, 37.2, 25.7, 18.0, 13.3, −5.7; MS *m*/*z* 325 $[M + H]^+$; HRMS calcd for $C_{18}H_{33}O_3Si$ $[M + H]^+$ 325.2198, found 325.2206.

(6*R*,7*R*)-7-(Benzyloxymethyl)-9,9-diisopropyl-2,2,3,3,6,-10-hexamethyl-4,8-dioxa-3,9-disilaundecane (17). Compound **16** (7.0 g, 21.57 mmol) was converted to TIPS ether **17** using the same procedure as described in a previously published work[27] with TIPS-OTf and 2,6-lutidine. Purification by column chromatography (SiO_2, 1% EtOAc in PE) afforded compound **17** as a colorless liquid (9.95 g, 96%): R_f = 0.5 (SiO_2, in PE); $[\alpha]^{24}_D$ = −3.7 (*c* 0.9, $CHCl_3$); IR ν_{max} 2932, 2862, 1725, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.18 (m, 5H), 4.42 (s, 2H), 4.28 (m, 1H), 3.59 (m, 1H), 3.54−3.36 (m, 3H), 1.92 (m, 1H), 1.00−1.01 (m, 21H,), 0.81−0.86 (m, 12H), 0.03 to −0.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.1, 127.6, 127.3, 73.1, 73.0, 72.8, 64.9, 40.7, 25.9, 18.1, 12.7, 12.4, −5.5; MS *m*/*z* 481 $[M + H]^+$; HRMS calcd for $C_{27}H_{52}O_3Si_2Na$ $[M + Na]^+$ 503.3353, found 503.3365.

(2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-2-(triisopropylsilyloxy)butan-1-ol (18). To a stirred solution of **17** (8.0 g, 16.64 mmol) in EtOAc (50 mL) was added catalytic Pd−C (10%), and the mixture was hydrogenated overnight using a H_2-filled balloon. It was then filtered through a short pad of Celite, and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo. Purification by column chromatography (SiO_2, 6% EtOAc in PE) afforded compound **18** as a colorless liquid (5.91 g, 91%): R_f = 0.3 (SiO_2, 10% EtOAc in PE); $[\alpha]^{24}_D$ = +16.4 (*c* 2.77, $CHCl_3$); IR ν_{max} 3496 (br), 2935, 2864, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (m, 1H), 3.68−3.53 (m, 4H), 3.01 (bs, 1H), 2.02, (m, 1H), 1.09−1.03 (m, 21H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.3, 64.8, 63.5, 40.0, 25.8, 18.1, 12.6, 11.9, −5.58, −5.62; MS *m*/*z* 391 $[M + H]^+$; HRMS calcd for $C_{20}H_{46}O_3Si_2Na$ $[M + Na]^+$ 413.2883, found 413.2900.

(6*R*,7*S*)-9,9-Diisopropyl-2,2,3,3,6,7,10-heptamethyl-4,8-dioxa-3,9-disilaundecane (19). Compound **18** (5.50 g, 14.07 mmol) was subjected to tosylation following the same procedure as per the synthesis of compound **13**. The tosylate (R_f = 0.6, 10% EtOAc in PE), thus obtained, was directly used after flash chromatography for next reaction.

A solution of the above tosylate in dry THF (75 mL) at 0 °C was treated with lithium triethylborohydride (1.0 M in THF, 70.35 mL, 70.35 mmol) slowly. After being stirred for 5 h at the same temperature, the reaction mixture was quenched with methanol (24 mL) and 1 N NaOH (24 mL). The mixture was treated with 30% aqueous H_2O_2 (8 mL), stirred for 16 h at rt, and then concentrated in vacuo. The residue was taken up in saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 1% EtOAc in PE) afforded pure **19** (4.54 g, 86%) as a colorless oil: R_f = 0.6 (silica gel, 10% EtOAc in PE); $[\alpha]^{24}_D$ = +3.0 (*c* 1.79, $CHCl_3$); IR ν_{max} 2993, 2862, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (m, 1H), 4.52−4.42 (m, 2H), 1.86 (m, 1H), 1.07−1.06 (m, 24H), 0.88 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04−0.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.8, 65.6, 43.1, 25.9, 18.5, 18.2, 12.6, 10.8, −5.5, −5.4; MS *m*/*z* 375 $[M + H]^+$; HRMS calcd for $C_{20}H_{47}O_2Si_2$ $[M + H]^+$ 375.3114, found 375.3125.

(2*R*,3*S*)-2-Methyl-3-(triisopropylsilyloxy)butan-1-ol (20). Compound **20** was synthesized from compound **19** (4.20 g, 11.21 mmol), following the same procedure as described in our previous work.[24] Purification by column chromatography (SiO_2, 4% EtOAc in PE) afforded the pure alcohol **20** (2.48 g, 85%) as a colorless oil. Analytical data of **20** was matched with literature values.[28]

(((4*S*,5*R*,6*R*)-5-(Benzyloxy)-2,2-dimethyl-6-((2*R*,6*R*,7*S*,*E*)-6-methyl-7-(triisopropylsilyloxy)oct-4-en-2-yl)-1,3-dioxan-4-yl)methoxy)(*tert*-butyl)diphenylsilane (21). Alcohol **20** (1.12 g, 4.30 mmol) was subjected to Dess−Martin oxidation using the same procedure as described in our previous work.[24] The (2*S*,3*S*)-2-methyl-3-(triisopropylsilyloxy)butanal (**7**) (R_f = 0.6, 10% EtOAc in PE), thus obtained, was directly used after flash chromatography for next reaction.

A solution of sulfone **4** (2.70 g, 3.58 mmol) in dry THF (50 mL) at −78 °C was treated with dropwise addition of potassium bis-(trimethylsilyl)amide (KHMDS, 0.5 M in toluene, 14.32 mL, 7.16 mmol) under nitrogen. The resulting yellow solution was stirred at −78 °C for 1 h, and then a solution of aldehyde **7** in dry THF (20 mL) was slowly added via syringe over 10 min. The reaction mixture was stirred at −78 °C for 1.5 h and then at rt for overnight. The cloudy white reaction mixture was quenched with water, and extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 2% EtOAc in PE) afforded compound **21** as a colorless liquid (2.14 g, 76%): R_f = 0.3 (SiO_2, 5% EtOAc in PE); $[\alpha]^{24}_D$ = +9.43 (*c* 1.24, $CHCl_3$); IR ν_{max} 2935, 2865, 1712, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73−6.63 (m, 5H), 7.36−7.16 (m, 10H), 5.36−5.24 (m, 2H), 4.62 (d, *J* = 10.6 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 3.91 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.87−3.75 (m, 2H), 3.71−3.57 (m, 3H), 2.27−2.17 (m, 2H), 1.93−1.80 (m, 2H), 1.34 (s, 6H), 1.01−0.96 (m, 33H), 0.93−0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 136.0, 135.6, 134.0, 133.3, 129.5, 129.2, 128.4, 127.8, 127.7, 127.6, 127.4, 98.1, 76.2, 74.3, 71.9, 71.3, 63.6, 44.1, 33.7, 33.4, 29.3, 26.8, 19.4, 19.3, 19.1, 18.1, 16.8, 14.1, 12.5; MS *m*/*z* 810 $[M + Na]^+$; HRMS calcd for $C_{48}H_{78}NO_5Si_2$ $[M + NH_4]^+$ 804.5418, found 804.5445.

((4*S*,5*R*,6*R*)-5-(Benzyloxy)-2,2-dimethyl-6-((2*R*,6*R*,7*S*,*E*)-6-methyl-7-(triisopropylsilyloxy)oct-4-en-2-yl)-1,3-dioxan-4-yl)methanol (22). Compound **21** (500 mg, 0.63 mmol) was treated with 3 N KOH solution in MeOH (3 mL), and the resulting mixture was refluxed at 70 °C for 12 h. The reaction mixture was then diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 10% EtOAc in PE) afforded compound **22** as a colorless liquid (289.3 mg, 84%): R_f = 0.3 (SiO_2, 10% EtOAc in PE); $[\alpha]^{24}_D$ = +20.2

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(*c* 0.96, $CHCl_3$); IR ν_{max} 3619, 2931, 2866, 1741, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.42−5.28 (m, 2H), 4.61 (s, 2H), 3.90 (m, 1H), 3.83−3.65 (m, 4H), 3.48 (dd, *J* = 9.4, 9.3 Hz, 1H), 2.33−2.19 (m, 2H), 2.04 (m, 1H), 1.96−1.80 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.07−1.03 (m, 24H), 1.01−0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 134.1, 129.0, 128.5, 128.0, 98.4, 76.4, 74.5, 73.7, 71.8, 71.3, 62.3, 44.1, 33.4, 33.3, 29.3, 19.4, 19.1, 18.2, 16.9, 14.2, 12.5; MS *m*/*z* 571 $[M + Na]^+$; HRMS calcd for $C_{32}H_{56}O_5Si$ Na $[M + Na]^+$ 571.3794, found 571.3774.

(4*S*,5*R*,6*R*)-4-(Hydroxymethyl)-2,2-dimethyl-6-((2*R*,6*R*,7*S*,*E*)-6-methyl-7-(triisopropylsilyloxy)oct-4-en-2-yl)-1,3-dioxan-5-ol (23). A solution of lithium in liquid ammonia was prepared by stirring lithium (50 mg, 7.2 mmol, cleaned by successive dipping in hexane and ether, and cut into small pieces) and liquid ammonia (∼20 mL) at −78 °C for 0.5 h. To this dark blue Li−NH_3 solution was added compound **22** (200 mg, 0.36 mmol) in dry THF (3 mL) via cannula under nitrogen atmosphere. After being stirred at −78 °C for 0.5 h, the reaction was quenched by addition of excess solid NH_4Cl and diluted with ether, and ammonia was evaporated at rt. More ether was added, and the mixture was filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 20% EtOAc in PE) afforded compound **23** as a colorless liquid (120.3 mg, 72%): R_f = 0.3 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = +8.94 (*c* 2.13, $CHCl_3$); IR ν_{max} 3620, 3390, 2928, 2863, 1836, 1708, 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.43−5.33 (m, 2H), 3.90 (m, 1H), 3.78 (d, *J* = 3.5 Hz, 2H), 3.66 (m, 1H), 3.60−3.54 (m, 2H), 2.35−2.21 (m, 3H), 2.03 (m, 1H), 1.93−1.86 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.05−1.03 (m, 24H), 0.99−0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 129.0, 98.5, 76.4, 73.5, 71.9, 64.9, 63.1, 44.1, 34.0, 33.8, 29.3, 19.4, 19.2, 18.2, 18.1, 16.4, 14.2, 12.5; MS *m*/*z* 481 $[M + Na]^+$; HRMS calcd for $C_{25}H_{50}O_5Si$ Na $[M + Na]^+$ 481.3325, found 481.3348.

2-((4*S*,5*S*,6*R*)-5-Hydroxy-2,2-dimethyl-6-((2*R*,6*R*,7*S*,*E*)-6-methyl-7-(triisopropylsilyloxy)oct-4-en-2-yl)-1,3-dioxan-4-yl)acetonitrile (3). Compound **23** (100 mg, 0.22 mmol) was subjected to the tosylation following the same procedure as per the synthesis of compound **13**, except for the initial addition of di-*n*-butyltin oxide (5 mg, 0.02 mmol). The tosylate (R_f = 0.6, 20% EtOAc in PE), thus obtained, was directly used after flash chromatography for the next reaction.

The above tosylate was converted to nitrile **3** following the same procedure as per the synthesis of compound **13**. Purification by column chromatography (SiO_2, 12% EtOAc in PE) afforded compound **3** as a colorless oil (79.5 mg, 77%): R_f = 0.5 (SiO_2, 20% EtOAc in PE); $[\alpha]^{24}_D$ = +14.55 (*c* 1.45, $CHCl_3$); IR ν_{max} 3476 (br), 2935, 2866, 2263, 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46−5.33 (m, 2H), 3.90, (m, 1H), 3.81 (m, 1H), 3.55 (m, 1H), 3.41 (m, 1H), 2.77 (dd, *J* = 16.8, 3.8 Hz, 1H), 2.65 (dd, *J* = 16.8, 6.2 Hz, 1H), 2.30−2.22 (m, 2H), 1.97−1.87 (m, 2H), 1.65 (bs, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.10−1.04 (m, 24 H), 1.01−0.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 128.8, 117.3, 99.1, 76.6, 71.9, 70.1, 67.5, 44.1, 33.9, 33.7, 29.1, 21.6, 19.4, 19.2, 18.2, 16.6, 14.4, 12.6; MS *m*/*z* 490 $[M + Na]^+$; HRMS calcd for $C_{26}H_{49}NO_4Si$ Na $[M + Na]^+$ 490.3328, found 490.3323.

Mupirocin H (2). To the nitrile **3** (50 mg, 0.11 mmol) in methanol (5 mL) was added concd HCl (0.25 mL). The resulting solution was stirred at 65 °C for 3 h. After the reaction mixture was cooled to rt, 15 mL each of DCM and half-saturated aqueous NaCl solution were added. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 12% MeOH in chloroform) afforded mupirocin H (**2**) as a colorless oil (18.8 mg, 64%): R_f = 0.3 (SiO_2, 10% MeOH in chloroform); $[\alpha]^{24}_D$ = +25.8 (*c* 0.64, $CHCl_3$ (lit.[5] $[\alpha]^{20}_D$ = +30.5, *c* 1.3, $CHCl_3$)); IR ν_{max} 3375 (br), 2965, 2924, 1759, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.59 (ddd, *J* = 15.1, 8.3, 6.8 Hz, 1H), 5.37 (dd, *J* = 15.1, 8.3 Hz, 1H), 4.58 (m, 1H), 4.44 (dd, *J* = 5.3, 3.0 Hz, 1H), 3.57 (dd, *J* = 6.8, 6.0 Hz, 1H), 3.49 (m, 1H), 2.93 (dd, *J* = 18.1, 7.6 Hz, 1H), 2.50 (dd, *J* = 18.1, 3.8 Hz, 1H), 2.36−2.21 (m, 2H), 2.06 (m, 1H), 1.89 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 134.7, 129.6, 88.0, 75.1, 71.6, 68.4, 45.3, 38.3, 35.3, 34.6, 20.6, 17.0, 16.0; MS *m*/*z* 290 (100) $[M + NH_4]^+$; HRMS calcd for $C_{14}H_{24}O_5$ Na $[M + Na]^+$ 295.1521, found 295.1522.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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