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Studies on the preparation of protomycinolide IV: Enantioselective synthesis of the C3–C9 segment

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Abstract

The C3–C9 segment, (−)-**16**, of the polyene macrolide antibiotic protomycinolide IV (**1a**) was prepared in optically pure form from commercially available methyl (S)-2-methyl-3-hydroxypropionate in 12 steps giving 17% yield.

1. Introduction

Protomycinolide IV and mycinolide IV (**1a** and **1b**) are 16-membered polyene macrolides isolated from the culture broth of *Micromonospora griseorubida* sp. nov.[1a] The configuration of **1b** was determined by X-ray diffraction analysis[1b] Conversion of **1b** into **1a** (tosylation of the 1° alcohol followed by reduction) demonstrated their structural association. While protomycinolide does not possess notable antibacterial activity, it has been shown to be a biosynthetic intermediate for the mycinamycin family of antibiotics which display significant activity against Gram-positive bacteria.[1c] Structural correlation between protomycinolide IV and other 16-membered macrolides (e.g. chalcomycin,[2a] rosaramicin[2b] and tylosin[2c]) has recently led to a proposed biosynthetic pathway for their formation.[2a] In support of this mechanism, methyl mycinoate II (**2a**) and dicarboxymycinonic acid III (**2b**) have been isolated from the culture broth of a mutant of *Micromonospora griseorubida* which is unable to produce **1a**.[1d] The total syntheses of **1a**,[3] **2a** and **b**[4] have been reported.

We recently described a synthetic strategy for the preparation of dienolide **1** which relies on the ability of an $Fe(CO)_3$ moiety to control C–C bond formation adjacent and remote to a coordinated diene (Scheme 1).[5] To this end, we have reported the preparation of the C10–C17 segment **3** from (methyl 3,5-hexadienoate)$Fe(CO)_3$ in a highly diastereoselective fashion, as well as model studies for generation of the C9–C10 dienone bond via Friedel–Crafts acylation. The synthesis of **1a** by this methodology

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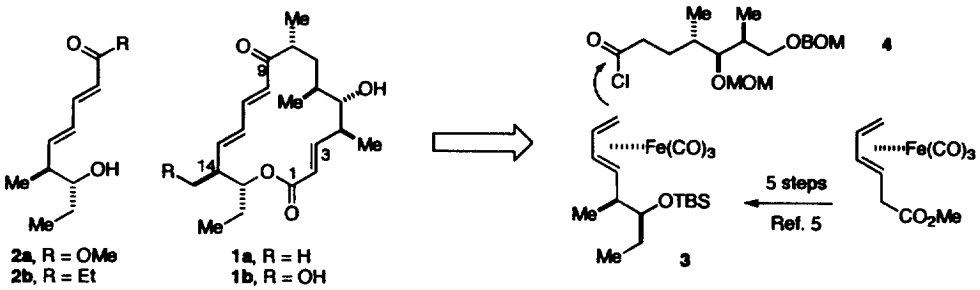
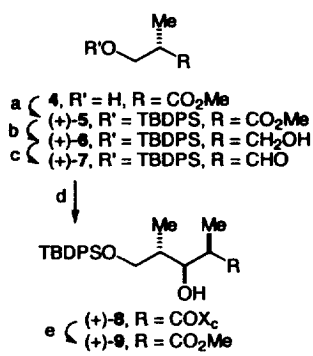
requires the functionalized acyl halide **4**. We herein report the preparation of the C3–C9 segment in an enantioselective fashion.



Scheme 1.

1.1. Enantioselective preparation of the C3–C9 segment

The preparation of **17**, in optically pure form, initially required preparation of the C4–C6 segment. There are many possibilities for generation of this stereotriad[6] and a double diastereoselective aldol condensation was chosen as our point of inception. Aldehyde (+)-**7** was prepared from commercially available methyl (S)-2-methyl-3-hydroxypropionate by protection, reduction[7] and oxidation[7] (70% yield, 3 steps, Scheme 2). Aldol condensation of (+)-**7** with *N*-propionyl-4(R)-methyl-5(S)-phenyloxazolidin-2-one[8] was effected by the use of dibutylboron triflate/NEt_2iPr. The proton NMR spectrum of the crude product revealed one major diastereomer and a trace amount of at least one other diastereomer; however, the quantity of this very minor diastereomer was insufficient to determine its relative configuration or to determine a diastereomeric ratio. Chromatographic purification gave pure (+)-**8** as a crystalline product (89%). The 'anti-Felkin–syn-aldol' stereochemistry, which was expected on the basis of literature precedents,[9] was confirmed by X-ray diffraction analysis (Fig. 1).[10]



Scheme 2. Reagents: (a) TBDPSCl/imidazole (93%); (b) DIBAL/THF (83%); (c) DMSO/$(COCl)_2$/NEt_3 (88%); (d) (*N*)-propyl-4(R)-methyl-5(S)-phenyloxazolidinone/nBu_2BOTf (89%); (e) NaOMe/MeOH (78%)

Treatment of (+)-**8** with NaOMe/MeOH gave the methyl ester (+)-**9** (78%) along with the recovered chiral auxilary (75%, Scheme 2). Protection of the secondary alcohol with methoxymethyl chloride gave the ether (+)-**10** (95%, Scheme 3). Reduction of ester (+)-**10** with DIBAL (THF/toluene) gave the alcohol (+)-**11** (92%), which was protected as its benzyloxymethyl ether (+)-**12** (69%). Removal of the silyl protecting group with TBAF (83%) followed by Swern oxidation (84%) gave the aldehyde (−)-**14**. Horner–Emmons olefination of (−)-**14** with triethyl phosphonoacetate gave the unsaturated ester **15** (88%) which contains all of the carbons of the C3–C9 segment of **1**. Brief (1 h) catalytic hydrogenation

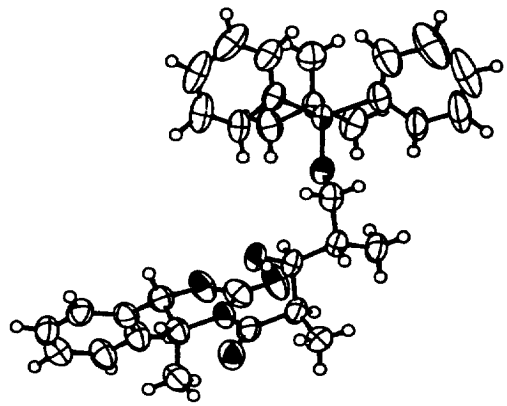
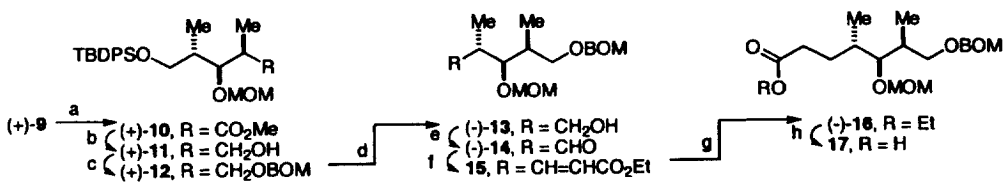


Fig. 1. ORTEP view of (+)-**8**

of **15** resulted in saturation of the C6–C7 olefin without removal of the BOM protecting group (79%). Hydrolysis of (−)-**16** gave the carboxylic acid **17** (51%). The use of this segment in the synthesis of **1** will be reported in due course.



Scheme 3. Reagents: (a) MOMCl/iPr_2NEt (95%); (b) DIBAL (92%); (c) BOMCl/iPr_2NH (69%); (d) TBAF/THF (83%); (e) DMSO/$(COCl)_2$/NEt_3 (84%); (f) $(EtO)_2P(O)CH_2CO_2Et$/NaH (88%); (g) H_2/10% Pd–C (79%); (h) KOH/H_2O/EtOH (51%)

2. Experimental section

2.1. General data

Spectrograde solvents were used without purification with the exception of tetrahydrofuran which was distilled from the sodium benzophenone ketyl. Aldrich sure-seal dichloromethane and DMSO were used without further purification. Methyl (S)-3-hydroxy-2-methylpropionate and 4(R)-methyl-5(S)-phenyloxazolidin-2-one were purchased from the Aldrich Chemical Company, Inc. Column chromatography was performed on silica gel 60 (0.04–0.063 mm, E. Merck or 60–200 mesh, Aldrich) and 'flash' chromatography was performed on silica gel 60 (230–400 mesh). Thin layer chromatography was performed on Merck (Kieselgel 60 F254) or Kodak Chromagram (silica gel without fluorescent indicator).

All ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were obtained from Robertson Microlit Laboratories, Inc., Madison, NJ and high resolution mass spectra (EI) were obtained from the Washington University Resource for Mass Spectrometry.

2.2. *Methyl (S)-3-(tert-butyldiphenylsilyloxy)-2-methylpropionate ((+)-5)*

This was prepared from (S)-3-hydroxy-2-methylpropionate in a fashion similar to the procedure of Ley et al.[7] (93%) and was identified by comparison to the literature ^{1}H NMR spectral data: $[\alpha]_D$ +17 (c 2.5, $CHCl_3$), (lit.[7] $[\alpha]_D$ +23 (c 7.8, CH_3OH)); R_f 0.38 (hexane:ethyl acetate=15:1).

2.3. *(R)-3-(tert-Butyldiphenylsilyloxy)-2-methyl-1-propanol ((+)-6)*

This was prepared by the reduction of (+)-**5** with DIBAL in a fashion similar to the procedure of Ley et al.[7] (83%) and was identified by comparison to the literature ^{1}H NMR spectral data: $[\alpha]_D$ +6.1 (c 2.5, $CHCl_3$), (lit.[7] $[\alpha]_D$ +6.3 (c 1.0, $CHCl_3$)); R_f 0.27 (CH_2Cl_2).

2.4. *(S)-3-(tert-Butyldiphenylsilyloxy)-2-methylpropanal ((+)-7)*

This was prepared by oxidation of (+)-**6** with DMSO/$(COCl)_2$ in a fashion similar to the procedure of Roush et al.[7] The crude product was passed through a 3.5 inch bed of SiO_2 (CH_2Cl_2) to give (+)-**7** as a waxy solid (88%) which was identified by comparison to the literature ^{1}H NMR spectral data: mp 61–63°C (lit.[7a] mp 51–61°C); $[\alpha]_D$ +22 (c 1.0, $CHCl_3$); R_f 0.20 (hexanes:CH_2Cl_2=2:1).

2.5. *Chiral aldol product ((+)-8)*

To a solution of *N*-propionyl-4(R)-methyl-5(S)-phenyloxazolidin-2-one (36.6 g, 157 mmol) in CH_2Cl_2 (315 mL) cooled to 0°C was added dropwise freshly distilled dibutylboron triflate (47.3 g, 173 mmol) followed immediately by diisopropylethylamine (32.8 mL, 188 mmol). The mixture was stirred for 30 min, then cooled to −78°C whereupon a solution of (+)-**7** in CH_2Cl_2 (157 mL) was added to the reaction mixture via a cannula transfer. The mixture was stirred for 30 min, warmed to rt, and stirred for an additional 90 min. The mixture was cooled to 0°C and pH 7 buffer (225 mL), methanol (600 mL) and 30% H_2O_2:methanol (1:1, 225 mL) were added in succession. The mixture was warmed to rt and stirred for 30 min, after which the phases separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=12:1 to 8:1 gradient) to give (+)-**8** as a colorless solid (78.4 g, 89%): mp 102–103°C; $[\alpha]_D$ +22 (c 1.2, $CHCl_3$); R_f 0.18 (hexanes:ethyl acetate=6:1); ^{1}H NMR ($CDCl_3/D_2O$) δ 7.70–7.66 (m, 4H), 7.44–7.37 (m, 9H), 7.33–7.30 (m, 2H), 5.68 (d, *J*=7.0 Hz, 1H), 4.78 (dq, 7.0, 6.6 Hz, 1H), 4.00–3.93 (m, 2H), 3.82 (dd, *J*=4.4, 9.9 Hz, 1H), 3.73 (d, *J*=6.6, 9.9 Hz, 1H), 1.90–1.80 (m, 1H), 1.25 (d, *J*=6.6 Hz, 3H), 1.06 (s, 9H), 0.93 (d, *J*=7.0 Hz, 3H), 0.91 (d, *J*=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.1, 152.6, 135.5, 133.2, 132.9, 132.8, 129.7, 128.6, 127.7, 125.5, 78.8, 75.1, 68.4, 55.0, 40.7, 37.5, 26.7, 19.1, 14.2, 13.2, 9.1; EI-HRMS *m/z* 560.2828 (calcd for $C_{33}H_{42}NO_5Si$ $(M+H)^+$ 560.2832); Anal. Calcd for $C_{33}H_{41}NO_5Si$: C, 70.81; H, 7.38; N, 2.50. Found: C, 70.54; H, 7.35; N, 2.45. A sample suitable for X-ray diffraction analysis[10] was obtained by recrystallization from hot methanol.

2.6. *Methyl (2R,3S,4S)-5-t-butyldiphenylsilyloxy-3-hydroxy-2,4-dimethylpentanoate ((+)-9)*

To a freshly prepared solution of methanolic sodium methoxide (1.9 g Na/350 mL MeOH) at 0°C was slowly added a solution of (+)-**8** (45.8 g, 81.8 mmol) in THF (250 mL). When **8** was no longer observed by TLC monitoring (ca. 15 min), saturated aqueous NH_4Cl was added and the heterogenous mixture

was partitioned between CH_2Cl_2/H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. All of the CH_2Cl_2 phases were combined, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=10:1) to give (+)-**9** as a viscous oil (26.4 g, 78%): $[\alpha]_D$ +6.8 (c 1.0, $CHCl_3$); R_f 0.5 (hexanes:ethyl acetate=4:1); ^1H NMR ($CDCl_3/D_2O$) δ 7.69–7.65 (m, 4H), 7.44–7.36 (m, 6H), 3.96 (dd, *J*=3.7, 8.4 Hz, 1H), 3.83 (d, *J*=4.2, 10.3 Hz, 1H), 3.70 (d, *J*=6.3, 10.3 Hz, 1H), 3.70 (s, 3H), 2.63 (dq, *J*=7.0, 3.7 Hz, 1H), 1.83–1.73 (m, 1H), 1.21 (d, *J*=7.0 Hz, 3H), 1.05 (s, 9H), 0.86 (d, *J*=7.0 Hz, 3H); MS (CI/NH_3) *m/z* 415 $(M+H)^+$, 432 $(M+NH_4)^+$.

2.7. *Methyl (2R,3S,4S)-5-t-butyldiphenylsilyloxy-3-[methoxy(methoxy)]-2,4-dimethylpentanoate ((+)-**10**)*

To a solution of (+)-**9** (26.1 g, 62.9 mmol) in freshly distilled diisopropylethylamine (125 mL) at 0°C was slowly added, via a syringe, chloromethyl methyl ether (24.0 mL, 315 mmol). The reaction mixture was warmed to rt, and then heated at 38°C for 18 h. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 and washed with 0.25 N HCl (2×160 mL), followed by saturated aqueous $NaHCO_3$, and brine:H_2O (1:1), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=10:1) to give (+)-**10** as a colorless oil which solidified upon storing in the freezer (27.5 g, 95%): mp 54.5–55.5°C; $[\alpha]_D$ +4 (c 0.9, $CHCl_3$); R_f 0.60 (hexanes:ethyl acetate=4:1); ^1H NMR ($CDCl_3$) δ 7.67–7.64 (m, 4H), 7.44–7.34 (m, 6H), 4.53 (d, *J*=6.6 Hz, 1H), 4.45 (d, *J*=6.6 Hz, 1H), 3.93 (dd, *J*=3.7, 7.8 Hz, 1H), 3.73 (d, *J*=4.2, 10.3 Hz, 1H), 3.66 (s, 3H), 3.61 (dd, *J*=6.0, 10.0 Hz, 1H), 3.19 (s, 3H), 2.70 (dq, *J*=7.0, 3.7 Hz, 1H), 1.90–1.80 (m, 1H), 1.14 (d, *J*=7.0 Hz, 3H), 1.07 (s, 9H), 0.99 (d, *J*=7.0 Hz, 3H); MS (FAB) *m/z* 497 $(M+K)^+$; Anal. Calcd for $C_{26}H_{38}O_5Si$: C, 68.08; H, 8.35. Found: C, 67.93; H, 8.24.

2.8. *(2S,3R,4S)-5-t-Butyldiphenylsilyloxy-3[(methoxy)methoxy]-2,4-dimethyl-1-pentanol ((+)-**11**)*

To a solution of (+)-**10** (26.7 g, 58.3 mmol) in THF (120 mL) at −78°C was added dropwise a solution of DIBAL (128 mL, 1.0 M in toluene, 128 mmol). The mixture was stirred for 15 min, and then methanol was cautiously added until gas evolution ceased. The mixture was warmed to rt and partitioned between ethyl acetate and 1 M potassium sodium tartrate. The separated organic layer was washed with fresh 1 M potassium sodium tartrate, and the combined aqueous phases were extracted with CH_2Cl_2. All of the organic phases were combined, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=8:1 to 4:1 gradient) to give (+)-**11** as a viscous oil (23.0 g, 92%): $[\alpha]_D$ +54 (c 1.0, $CHCl_3$); R_f 0.25 (hexanes:ethyl acetate=4:1); ^1H NMR ($CDCl_3/D_2O$) δ 7.66–7.62 (m, 4H), 7.45–7.34 (m, 6H), 4.68 (d, *J*=6.6 Hz, 1H), 4.43 (d, *J*=6.6 Hz, 1H), 3.75–3.67 (m, 3H), 3.61 (d, *J*=7.7 Hz, 1H), 3.34 (s, 3H), 1.96–1.87 (m, 1H), 1.87–1.77 (m, 1H), 1.08 (s, 9H), 0.94 (d, *J*=7.0 Hz, 3H), 0.76 (d, *J*=7.0 Hz, 3H); HRMS (CI) *m/z* 431.2603 (calcd for $C_{25}H_{39}O_4Si$ $(M+H)^+$ 431.2618; Anal. Calcd for $C_{25}H_{38}O_4Si$: C, 69.26; H, 8.90. Found: C, 69.72; H, 8.89.

2.9. *(2S,3R,4S)-1-[(Benzyloxy)methoxy]-5-t-butyldiphenylsilyloxy-3[(methoxy)methoxy]-2,4-dimethyl-1-pentane ((+)-**12**)*

To a solution of (+)-**11** (3.34 g, 7.76 mmol) in diisopropylamine (31 mL) at 0°C was added dropwise benzyloxymethyl chloride (8.0 mL, 46.6 mmol). The reaction mixture was gradually warmed to rt and stirred for 18 h. The mixture was then heated at a gentle reflux for 24 h. The mixture was cooled and 2 N aqueous HCl was carefully added. The mixture was extracted with ethyl acetate and the combined

extracts washed with 2 N aqueous HCl, brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=20:1) to give (+)-**12** as an oil (2.95 g, 69%): $[\alpha]_D$ +3.5 (c 1.4, $CHCl_3$); R_f 0.17 (hexanes:ethyl acetate=15:1); ^1H NMR ($CDCl_3$) δ 7.67–7.63 (m, 4H), 7.43–7.27 (m, 11H), 4.97–4.49 (m, 6H), 3.74 (dd, *J*=3.9, 9.7 Hz, 1H), 3.64–3.44 (m, 4H), 3.20 (s, 3H), 2.30–1.84 (m, 2H), 1.07 (s, 9H), 0.98 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=7.0 Hz, 3H); MS (CI/NH_3) *m/z* 568 $(M+NH_4)^+$; Anal. Calcd for $C_{33}H_{46}O_5Si$: C, 71.96; H, 8.42. Found: C, 71.83; H, 8.26.

2.10. (2S,3S,4S)-5-[(Benzyloxy)methoxy]-3-[(methoxy)methoxy]-2,4-dimethyl-1-pentanol ((−)-13)

To a solution of (+)-**12** (2.50 g, 4.65 mmol) in THF (18.5 mL) at 0°C was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 4.9 mL, 4.9 mmol). Thr reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into water and extracted with ether, the combined extracts dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=4:1) to give (−)-**13** as an oil (1.21 g, 83%): $[\alpha]_D$ −42 (c 1.2, $CHCl_3$); R_f 0.33 (hexanes:ethyl acetate=2:1); ^1H NMR ($CDCl_3$) δ 7.36–7.27 (m, 5H), 4.79–4.61 (m, 6H), 3.88–3.81 (m, 1H), 3.65 (dd, *J*=2.2, 9.2 Hz, 1H), 3.56–3.47 (m, 3H), 3.43 (s, 3H), 2.93 (t, *J*=6.8 Hz, OH), 2.07–1.97 (m, 1H), 1.88–1.79 (m, 1H), 0.96 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=7.0 Hz, 3H); MS (CI/NH_3) *m/z* 330 $(M+NH_4)^+$; Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.17; H, 9.08.

2.11. (2R,3R,4S)-5-[(Benzyloxy)methoxy]-3-[(methoxy)methoxy]-2,4-dimethylpentanal ((−)-14)

To a solution of oxalyl chloride (1.4 mL, 16.5 mmol) in CH_2Cl_2 (25 mL) cooled to −78°C was added DMSO (2.1 mL, 30 mmol), followed by dropwise addition of a solution of (−)-**13** (4.7 g, 15 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 15 min and then triethylamine (6.3 mL, 45 mmol) was added. The reaction mixture was stirred at −78°C for 15 min, warmed to rt, and a solution of 1 N HCl was added. The phases were separated, and the organic phase washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=8:1) to give (−)-**14** as an oil (3.93 g, 84%): $[\alpha]_D$ −27 (c 0.9, $CHCl_3$); R_f 0.17 (hexanes:ethyl acetate=8:1); ^1H NMR ($CDCl_3$) δ 9.72 (d, *J*=2.9 Hz, 1H), 7.42–7.26 (m, 5H), 4.75 (s, 2H), 4.69 (d, *J*=6.8 Hz, 1H), 4.60 (d, *J*=6.8 Hz, 1H), 4.60 (m, 2H), 3.94 (dd, *J*=3.3, 7.4 Hz, 1H), 3.50 (d, *J*=7.0 Hz, 2H), 3.33 (s, 3H), 2.70–2.60 (m, 1H), 2.04–1.97 (m, 1H), 1.07 (d, *J*=7.0 Hz, 3H), 0.94 (d, *J*=7.0 Hz, 3H); MS (CI/NH_3) *m/z* 328 $(M+NH_4)^+$.

2.12. Ethyl (2E,4S,5S,6S)-7-[(benzyloxy)methoxy]-5-[(methoxy)methoxy]-4,6-dimethyl-2-heptenoate (15)

To a slurry of NaH (415 mg, 13.8 mmol, 80% dispersion in mineral oil) in THF (25 mL) was added dropwise triethyl phosphonoacetate (2.7 mL, 13.8 mmol). After 15 min, a solution of (−)-**14** (3.9 g, 12.6 mmol) in THF (25 mL) was added. The reaction mixture was stirred for 18 h and then carefully quenched with 1 N aqueous HCl (140 mL). The phases were separated, and the aqueous phase extracted with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=12:1) to give **15** as an oil (4.2 g, 88%): R_f 0.42 (hexanes:ethyl acetate=4:1); ^1H NMR ($CDCl_3$) δ 7.40–7.26 (m, 5H), 7.03 (dd, *J*=8.5, 15.5 Hz, 1H), 5.85 (d, *J*=15.5 Hz, 1H), 4.75 (s, 2H), 4.64 (d, *J*=6.7 Hz, 1H), 4.60 (s, 2H), 4.58 (d, *J*=6.7 Hz, 1H), 4.18 (q, *J*=7.0 Hz, 2H), 3.60–3.46 (m, 3H), 3.36 (s, 3H), 2.66–2.53 (m, 1H), 2.20–1.92 (m, 1H), 1.28 (t, *J*=7.0 Hz, 3H), 1.07 (s, 3H), 0.94 (d, *J*=7.0 Hz, 3H); MS (CI/NH_3) *m/z* 398 $(M+NH_4)^+$.

2.13. Ethyl (4S,5S,6S)-7-[(benzyloxy)methoxy]-5-[(methoxy)methoxy]-4,6-dimethylheptanoate ((−)-16)

A solution of **15** (4.2 g, 11 mmol) and 10% Pd/C (360 mg) in ethyl acetate (22 mL) was stirred under an atmosphere of H_2 (1 atm) for 14 h. The reaction mixture was filtered and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate=15:1) to give **16** as an oil (3.3 g, 79%): $[\alpha]_D$ −9.2 (c 1.0, $CHCl_3$); R_f 0.42 (hexanes:ethyl acetate=4:1); ^1H NMR ($CDCl_3$) δ 7.38–7.26 (m, 5H), 4.76 (s, 2H), 4.68 (d, *J*=6.6 Hz, 1H), 4.63 (d, *J*=6.6 Hz, 1H), 4.60 (s, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 3.51–3.38 (m, 3H), 3.39 (s, 3H), 2.41 (ddd, *J*=5.5, 10.3, 15.6 Hz, 1H), 2.26 (ddd, *J*=6.4, 9.7, 15.6 Hz, 1H), 2.04–1.89 (m, 2H), 1.76–1.64 (m, 1H), 1.51–1.39 (m, H), 1.25 (t, *J*=7.0 Hz, 3H), 0.92 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.9, 137.9, 128.4, 127.8, 127.6, 98.4, 94.8, 83.4, 71.1, 69.4, 60.2, 56.0, 35.4, 35.2, 32.2, 27.8, 16.0, 14.2, 11.3; MS (CI/NH_3) *m/z* 400 $(M+NH_4)^+$; EI-HRMS *m/z* 321.2057 (calcd for $C_{19}H_{29}O_4$ $(M-OCH_2OCH_3)^+$ 321.2066).

2.14. (4S,5S,6S)-7-[(Benzyloxy)methoxy]-5-[(methoxy)methoxy]-4,6-dimethylheptanoic acid (17)

A solution of KOH (245 mg, 4.3 mmol) in water (3 mL) and ethanol (9 mL) was added to **16** (1.38 g, 3.6 mmol). The reaction mixture was stirred for 5 h. The mixture was acidified with excess 2 N HCl and extracted with CH_2Cl_2. All of the organic phases were combined, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography ($CHCl_3$:MeOH=98:2) to give **17** as an oil (650 mg, 51%): ^1H NMR ($CDCl_3$) δ 7.36–7.26 (m, 5H), 4.76 (s, 2H), 4.68 (d, *J*=6.6 Hz, 1H), 4.63 (d, *J*=6.6 Hz, 1H), 4.61 (s, 2H), 3.52–3.38 (m, 3H), 3.39 (s, 3H), 2.45 (ddd, *J*=5.5, 10.3, 16.0 Hz, 1H), 2.36 (ddd, *J*=6.9, 9.9, 16.0 Hz, 1H), 2.05–1.91 (m, 2H), 1.78–1.68 (m, 1H), 1.52–1.41 (m, H), 0.92 (d, *J*=6.7 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.7, 137.8, 128.4, 127.8, 127.6, 98.3, 94.8, 83.4, 71.0, 69.4, 65.8, 56.0, 35.2, 31.8, 27.5, 15.9, 15.2; MS (CI/NH_3) *m/z* 372 $(M+NH_4)^+$; Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 63.90; H, 8.49.

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References

1. (a) Hayashi, M.; Ohara, H.; Ohno, M.; Sakakibara, H.; Satoi, S.; Harada, K.; Suzuki, M. *J. Antibiotics* **1981**, *34*, 1075–7; (b) Hayashi, M.; Kinoshita, K.; Satoi, S.; Nakatsu, K. *J. Antibiotics* **1982**, *35*, 1243–4; (c) Suzuki, H.; Takenaka, S.; Kinoshita, K.; Morohoshi, T. *J. Antibiotics* **1990**, *43*, 1508–11; (d) Kinoshita, K.; Takenaka, S.; Hayashi, M. *J. Chem. Soc., Chem. Commun.* **1988**, 943–5.
2. (a) Woo, P. W. K.; Rubin, J. R. *Tetrahedron* **1996**, *52*, 3857–72; (b) Ganguly, A. K.; Liu, Y. T.; Sarre, O.; Jaret, R. S.; McPhail, A. T.; Onan, K. K. *Tetrahedron Lett.* **1980**, *21*, 4699–4702; (c) Omura, S.; Matsubara, H.; Nakagawa, A.; Furusaki, A.; Matsumoto, T. *J. Antibiotics* **1980**, *33*, 915–7.
3. (a) Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857–60; (b) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221–29.
4. (a) Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett.* **1989**, *30*, 4001–2; (b) Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Heterocycles* **1992**, *33*, 713–42.

5. Wasicak, J. T.; Craig, R. A.; Henry, R.; Dasgupta, B.; Li, H.; Donaldson, W. A. *Tetrahedron* **1997**, *53*, 4185–98.
6. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.
7. (a) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Brice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161–94; (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095–2105; (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–59.
8. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.
9. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111; Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–7. This stereotriad has been previously prepared by aldol condensation of (S)-3-benzyloxy-2-methylpropanal with *N*-propionyl-4(R)-isopropyloxazolidin-2-one: Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Lawson, K.; Sutter, M. A.; Thaisrivongs, S.; Zimmerman, J. *J. Am. Chem. Soc.* **1985**, *107*, 5292–3.
10. Crystal data for (+)-**8**: MW=559.8, $C_{33}H_{41}NO_5Si$, crystal dimensions 0.700×0.700×0.100 mm, monoclinic, $P2_1$ (#4), a=13.836(3), b=7.2965(6), c=16.358(3) Å, β=108.14(2)°, V=1569.5(5) Å^3, Z=2, D_{calc}=1.184 g cm^{-3}. Crystallographic data were collected with a Rigaku AFC5R diffractometer using Cu Kα radiation (λ=1.54178 Å). Refinement of the structure using full matrix least squares refinement of 360 parameters on 2363 reflections with $I>3.00\sigma(I)$ gave R=0.053, R_w=0.064(15). We thank Mr Rodger Henry, Abbott Laboratories, for performing this X-ray diffraction analysis.