Synthesis of a Model for C7-C13 of Lankamycin.

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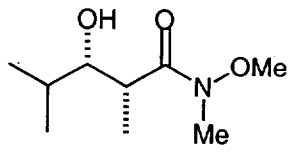
Supporting Information

(2*R*,3*S*)-*N*-Methoxy,*N*-methyl (3-hydroxy-2,4-dimethyl)-pentanamide (4). To imide **3** (1.70 g, 7.27 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added Et_3N (1.2 mL, 8.63 mmol) and Bu_2BOTf (2.0 mL, 8.0 mmol). After 20 min the enolate was cooled to -78 °C and freshly-distilled isobutyraldehyde (1.1 mL, 12.1 mmol) was added slowly. The reaction mixture was warmed to 0 °C after 10 min, stirred at 0 °C for 1.5 h, and then was slowly quenched with a 3:1 MeOH–30% H_2O_2 solution. The mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 x) and the combined organic layers were extracted with saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2.4 g of a yellow oil which was used in the next reaction without additional purification: R_F 0.55 (66:34-hexane:ethyl acetate).



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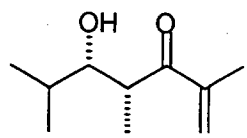
To a 0 °C suspension of HCl·HN(OMe)Me (2.23 g , 22.8 mmol) in THF (22 mL) was added slowly $AlMe_3$ (2.0 M in toluene, 11.4 mL, 22.8 mmol). The mixture was warmed to rt, stirred for 30 min, and then cooled to 0 °C. To this solution was added*via* cannula a 0 °C solution of the crude aldol adduct (2.4 g) in THF (22 mL). The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was slowly quenched at 0 °C with 1 N HCl, stirred for 30 min, and the layers were separated. The aqueous layer was extracted with ether (2 x) and the organic layer was extracted with 1 N HCl and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2.5 g of a yellow slurry. Purification by flash chromatography, eluting with 67:33-hexanes:ethyl acetate, provided 1.04 g (76% over two steps) of **4** as a colorless oil: R_F 0.20 (66:34-hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3, J=6.8), 1.03 (d, 3, J=6.6), 1.14 (d, 3, J=7.0), 1.67-1.76 (m, 1), 3.09 (s, 1), 3.19 (s, 1), 3.42 (dd, 1, J=8.5, 2.5), 3.65 (s, 1), 3.70 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.85, 18.81, 18.99, 30.24, 31.79, 35.69, 61.37, 76.79; IR (neat) 3464, 2962, 1639, 1462 cm^{-1}; $[\alpha]_D$ -9.16 (c=1.2, $CHCl_3$).

(4*S*,5*S*)-5-Hydroxy-2,4,6-trimethylhept-1-en-3-one (5). To a -78 °C solution of freshly distilled 2-bromopropene (1.65 mL, 18.5 mmol) in ether (30 mL) was added dropwise *t*-BuLi (1.75 M in pentane, 18.85 mL, 33.0 mmol) over 15 min. After 30 min amide **4** (1.03 g, 5.45 mmol) in ether (30 mL) was added *via* cannula. The mixture was stirred for 75 min and then quenched with saturated aqueous NH_4Cl. The layers were separated, the aqueous layer was extracted with ether, and the organic layer was extracted with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil (1.05 g). Purification by flash chromatography, eluting with 83:17-hexanes:ether, provided 0.70 g (76%) of **5** as a colorless oil: R_F 0.45 (75:25-hexane:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, 3, J=6.8), 0.99 (d, 3, J=6.6), 1.12 (d, 3, J=7.1), 1.64-1.70 (m, 1), 1.87 (dd, 3, J=1.4, 0.8), 3.41 (dq, 1, J=7.1, 3.1), 3.47 (dd, 1, J=8.0, 3.1), 5.85-5.83 (m, 1), 5.95



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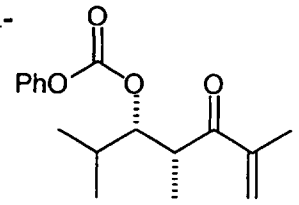
(s, 1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.20, 17.57, 18.47, 19.04, 30.59, 40.79, 76.74, 125.13, 143.43, 207.31; IR (neat) 3507, 2962, 2876, 1666, 1629, 1457 cm^{-1}.

(4*R*,5*S*)-2,4,6-Trimethyl-5-(phenoxy)carbonyloxyhept-1-en-3-one (6). To a 0 °C solution of alcohol **5** (305 mg, 1.79 mmol) in CH_2Cl_2 (4 mL) was added pyridine (1.5 mL, 18.6 mmol) and phenyl chloroformate (0.5 mL, 4.0 mmol). The reaction mixture was warmed to room temperature, stirred 30 min, and quenched with saturated aqueous $NaHCO_3$. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x), and the organic layer was extracted with 0.3 N NaOH (2 x), 0.5 N HCl (2 x), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a faint yellow solid (750 mg). Purification by flash chromatography, eluting with 95:5-hexanes:ethyl acetate, provided 464 mg (89%) of **6** as a colorless oil: R_F 0.75 (75:25-hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, 3, J=6.7), 1.00 (d, 3, J=6.8), 1.18 (d, 3, J=6.9), 1.88 (dd, 1, J=1.2, 0.8), 1.88-1.94 (m, 1), 3.65 (quin, 1, J=6.7), 4.99 (t, 1, J=6.2), 5.83 (d, 1, J=1.4), 5.94 (s, 1), 7.15-7.39 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.77, 17.21, 17.83, 19.26, 30.02, 41.13, 84.22, 120.93, 124.20, 125.78, 129.30, 143.92, 151.18, 153.68, 202.83; IR (neat) 2969, 2879, 1759, 1677, 1494 cm^{-1}.



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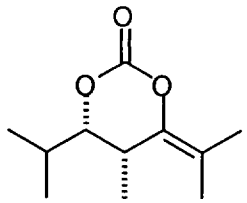
(4*R*,5*S*)-3,5-Carbonyldioxy-2,4,6-trimethylhept-2-ene (7). To a solution of enone **6** (103 mg, 0.36 mmol) in benzene (5 mL) was added triphenylphosphinecopper(I) hydride hexamer (0.043 M in benzene, 2 mL, 0.085 mmol). After 30 min a second aliquot of the copper hydride reagent (1 mL, 0.043 mmol) was added and the mixture was allowed to stir for an additional 45 min. The solution was opened to the atmosphere, diluted with hexanes (7 mL), and stirred for 45 min. The layers were separated, the aqueous layer was extracted with ether (2 x), and the organic layer was extracted with 0.25 N NaOH, 1 N HCl, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 200 mg of a solid. Purification by flash chromatography, eluting with 100% hexanes → 95:5 → 90:10-hexanes:ethyl acetate, provided 64 mg (91%) of 174: RF 0.40 (86:14-hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, 3, J=6.8), 1.07 (d, 3, J=7.1), 1.11 (d, 3, J=6.4), 1.66 (s, 3), 1.74 (s, 3), 1.84-1.94 (m), 3.00 (dq, 1, J=7.1, 2.4), 3.86 (dd, 1, J=10.2, 2.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.02, 16.21, 17.38, 17.57, 19.14, 27.99, 28.91, 85.50, 110.36, 143.78, 147.48; IR (neat) 2928, 1755, 1701 cm^{-1}.



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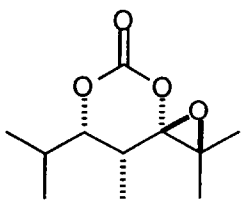
(3*S*,4*R*,5*S*)-3,5-Carbonyldioxy-2,3-epoxy-2,4,6-trimethylheptane (8). To a solution of enol carbonate **7** (60 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added freshly prepared dimethyldioxirane (~0.1 M in acetone, 6 mL, 0.6 mmol). When the reaction was complete by TLC analysis, the mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was extracted with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 60 mg of crude epoxide **8** which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3, J=6.8), 1.09 (d, 3, J=7.2), 1.13 (d, 3, J=6.4), 1.39 (s, 3), 1.52 (s, 3), 1.89-1.97 (m, 1), 2.01 (qd, 1, J=7.2, 2.5), 4.22 (dd, 1, J=10.2, 2.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.52, 17.38, 18.89, 19.05, 19.40, 28.89, 30.97, 65.43, 83.89, 92.78, 147.75; IR (neat) 1749 cm^{-1}.



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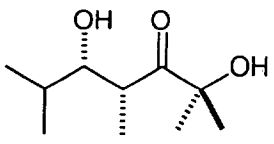
(4*R*,5*S*)-2,5-Dihydroxy-2,4,6-trimethylheptan-3-one (2). To a solution of epoxide **8** in 6:1 THF-H_2O (3.5 mL) was added LiOH•H_2O (50 mg, 1.2 mmol). After 30 min the solution was partitioned between ether and 1 N $NaHSO_4$, the aqueous layer was extracted with ether (3 x), and the organic layer was extracted with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 65 mg of a yellow oil. Purification by flash chromatography, eluting with 72:25-hexanes:ethyl acetate, provided 44 mg of keto-diol **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3, J=6.8), 1.01 (d, 3, J=6.6), 1.13 (d, 3, J=7.0), 1.40 (s, 3), 1.42 (s, 3), 1.65-1.72 (m, 1), 2.91 (s, 1), 3.24 (qd, 1, J=7.0, 2.7), 3.35 (d, 1, J=7.9), 3.53 (s, 1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.73, 18.83, 19.15, 26.25, 26.49, 30.58, 40.50, 76.48, 76.84, 220.00; IR (neat) 3430, 1697 cm^{-1}.



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