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TOTAL SYNTHESIS OF PYRIDOMYCIN#

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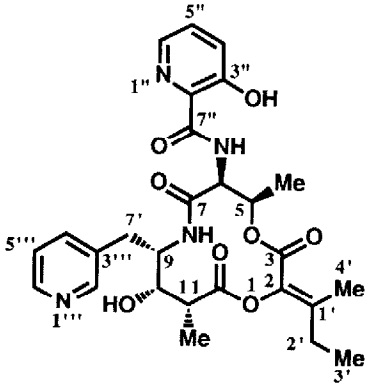
Summary: The first total synthesis of pyridomycin is described including the stereocontrolled construction of the exocyclic (*Z*)-*s*-butylidene moiety in the 12-membered ring system.

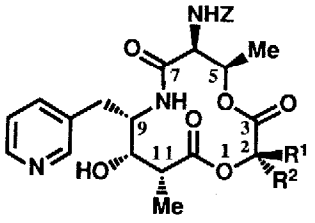
An antimycobacterial antibiotic, pyridomycin (**1**), was discovered in 1953 by Umezawa et al.[1,2] and the structure was determined by X-ray crystallography[3] and chemical degradation.[4] The characteristic structure is a novel heterocyclododecane system with unique exocyclic (*Z*)-*s*-butylidene and 3-pyridylmethyl side chains. Recently, Kinoshita and Mori[5] described the syntheses of the cyclic intermediates, **2a**, **2b**, and **2c**, which were designed for the construction of the intact 12-membered ring compound **3a**. Unfortunately, their attempts to convert these cyclic intermediates into **3a** by the usual β-elimination reaction procedures were unsuccessful, because the H-2 hydrogens in these cyclic compounds were kinetically less acidic probably due to the stereoelectronically unfavorable conformational effects[6] in comparison with the corresponding hydrogens in the acyclic model compounds.[5] We now wish to describe here the first total synthesis of pyridomycin (**1**) *via* a new cyclic intermediate **5** whose H-2 hydrogen is activated by the C-2 propionyl side chain.

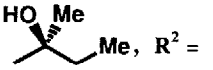
Our new strategy to construct the exocyclic (*Z*)-*s*-butylidene structure in **3a** consists in the first application of Weiler's method[7] for a transformation of α-acyloxy-β-keto ester **5** into α-acyloxy-β-alkyl-α,β-unsaturated ester **3a**. Encouraged at the success of model studies[8] using methyl 2-benzoyloxy-3-oxopentanoate (**11**), the intermediate **5** was reasonably considered to give the (*E*)-enol phosphate **4**, which would be methylated with lithium dimethylcuprate to afford **3a** with complete retention of the configuration. As a synthetic precursor of **5** , we chose the compound **6**, which was prepared by a convergent combination of the three segments, **8**, **9**,[5] and **10**,[9] according to the procedure described for the synthesis of **2a**.[5]

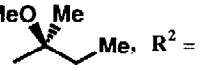
Starting with (*S*)-(-)-1-O-benzyl-3-O-tritylglycerol (**12**),[10] the new segment **8** [mp 80 - 81°C, $[\alpha]_D^{26}$ +16.7° (c 1.15, MeOH)] was prepared in 35% overall yield by 10-step transformation. Ester condensation of **8** and **9** with DCC/DMAP afforded **15** in 83% yield. Sequential treatments of **15** with 90% TFA and diphenyldiazomethane gave the benzhydryl ester **16** in 80% yield. Condensation of **10** and **16** with DCC/DMAP provided the ester **17**, which was sequentially deprotected with 2% HCl in 50% aqueous dioxane and 90% TFA to afford the azido acid **18** in 62% overall yield from **16**. Selective hydrogenolysis of the azido group with Raney Ni W-4 followed by cyclisation of the resulting seco-amino acid with DCC (20 equiv) and HOBt (5 equiv)



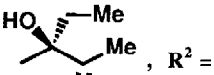
1: pyridomycin

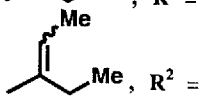


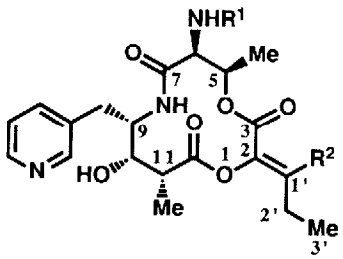
2a: R^1 =  , R^2 = H

2b: R^1 =  , R^2 = H

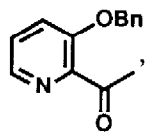
2c: R^1 = H, R^2 = 

6: R^1 =  , R^2 = H

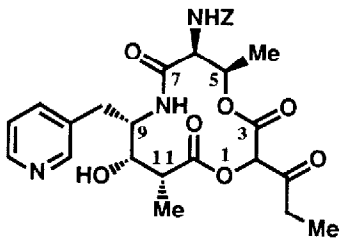
7: R^1 =  , R^2 = H



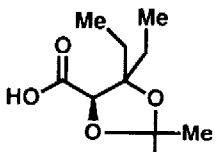
3a: R^1 = Z, R^2 = Me

3b: R^1 =  , R^2 = Me

4: R^1 = Z, R^2 = $OP(O)(OEt)_2$



5



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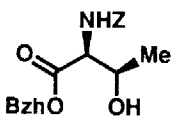

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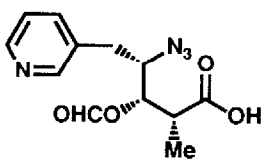

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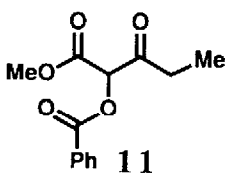
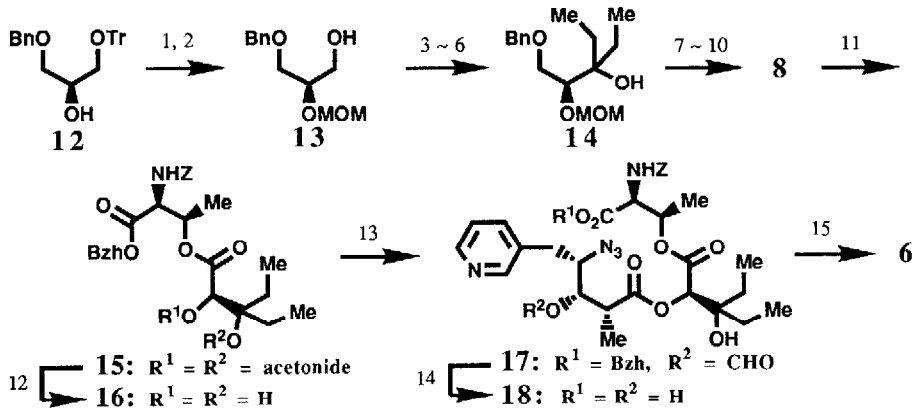


11

Bn = $PhCH_2$, Z = BnOCO, Bzh = Ph_2CH



1) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 38h. 2) 0.1% HCl-MeOH, rt, 2h. 3) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -72°C ~ 0°C, 40 min. 4) EtMgBr, Et_2O, rt, 1.5h. 5) PCC, MS3AP, CH_2Cl_2, rt, 0.5h. 6) EtMgBr, Et_2O, rt, 1.5h. 7) 1:1 1.5M aq HCl-dioxane, 50°C, 3h. 8) DMP, cat. H_2SO_4, acetone, rt, 2h. 9) H_2, $Pd(OH)_2$, MeOH, rt, 1h. 10) $RuCl_3$, $NaIO_4$, 2:2:3 CCl_4-CH_3CN-H_2O, rt, 1h. 11) **9**, DCC, DMAP, EtOAc, rt, 2h. 12) i) 90% aq TFA, rt, 1h; ii) diphenyldiazomethane, EtOAc-pet.ether, rt, 2.5h. 13) **10**, DCC, DMAP, EtOAc, rt, 2.5h. 14) i) 2% HCl in 50% aq dioxane, 35°C, 12h; ii) 90% aq TFA, rt, 20 min. 15) i) H_2, Raney Ni W-4, MeOH, 35°C, 40 min. ii) DCC, HOBt, 10^{-3}M DMF, 2°C, 68h.

in DMF[5,11] gave the cyclisation product **6**[12] in 48% yield. Dehydration of **6** with $SOCl_2$ in pyridine proceeded smoothly (-30°C, 1h) to generate exclusively the desired regioisomeric olefinic product **7** as a mixture of (*E*)- and (*Z*)-isomers in 95 % yield. Ozonolysis of **7** (O_3/O_2, CH_2Cl_2, -78°C, 15 sec, then Me_2S work-up) afforded the α-acyloxy-β-keto ester **5**[13] in 84% yield. Sequential treatment of **5** with NaH (2 equiv) in THF at 0°C for 15 min and with diethyl chlorophosphate (1 equiv) at 0°C for 1h gave the (*E*)-enol phosphate **4**[12] in 83 % yield. Methylation of **4** in THF with 4.0 equiv of an etherial lithium dimethylcuprate solution (-70 ~ -30°C, 3h) gave a crude substance containing **3a** and decomposed materials, which was readily purified by PLC (Merck Kiesel gel 60F-254) to provide **3a**[12] as a sole product in 25% yield.

De-N-benzyloxycarbonylation of **3a** (H_2, Pd-black, MeOH, rt, 0.5h) followed by N-acylation with N-(3-benzyloxypicolynoyloxy)succinimide[14] afforded 3-benzyloxypicolinamide derivative **3b**[12] in 50% yield. Hydrogenolysis (Pd-black, MeOH) of the benzyl group gave a sample of synthetic pyridomycin (**1**)[12] in 95% yield, which proved to be identical with natural pyridomycin (**1**) by spectroscopic means and mixture melting point measurement.

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8. **11** was prepared from the segment **8**. According to Weiler's procedure,[7] the sequential treatments of **11** with NaH and diethyl chlorophosphate in THF afforded the (*E*)-enol phosphate in 80% yield, which was then treated with Me_2CuLi in ether at -60°C for 1h gave methyl 2-benzoyloxy-2-[(*Z*)-*s*-butylidene]acetate **5** (54% isolated yield) as a sole product.
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11. K. Nakajima, T. Tanaka, M. Neya, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **55**, 3237 (1982).
12. **6:** $[\alpha]_D^{36}$ = -16.8° (c 1.69, $CHCl_3$); IR (KBr) 1742, 1722, 1667 cm^{-1}; ^1H NMR [270 MHz, δ($CDCl_3$, TMS), J(Hz)] 0.87 (3H, t, 3xH-3', J=7.3), 0.88 (3H, t, 3xH-3', J=7.3), 1.30 (3H, d, 5-Me, J=6.4), 1.40 (3H, d, 11-Me, J=7.8), 2.52 (1H, dq, H-11, J=1.0, 7.8), 3.60 (1H, br s, H-10), 4.05 (1H, br dt, H-9, J=0, 9.0, 9.0), 4.35 (1H, dd, H-6, J=6.4, 8.8), 4.30~4.60 (1H, br, 10-OH), 5.11 (1H, s, H-2), 5.35 (1H, dq, H-5, J=6.4, 6.4), 5.55 (1H, br d, 6-NH, J=8.8), 6.37 (1H, br d, NH(8), J=9.0); HRMS calcd for $C_{30}H_{38}N_3O_9$ (M^+-1) 584.2605, found 584.2591. **4:** ^1H NMR [400 MHz, δ($CDCl_3$, TMS), J(Hz)] 1.17 (3H, t, 3xH-3', J=7.5), 1.27 (3H, d, 5-Me, J=6.2), 1.34-1.40 (6H, m, 2xOCH_2Me), 1.46 (3H, d, 11-Me, J=7.4), 2.30~2.55 (2H, m, 2xH-2'), 2.61 (1H, br, H-11), 3.61 (1H, br, H-10), 4.04 (1H, br, H-9), 4.10~4.35 (6H, m, H-6, 10-OH, 2xOCH_2Me), 5.32 (1H, br, H-5), 5.45 (1H, br, 6-NH), 6.08 (1H, br, NH(8)). **3a:** $[\alpha]_D^{38}$ = -17.5° (c 0.56, $CHCl_3$); IR ($CHCl_3$) 1726, 1679 cm^{-1}; ^1H NMR [270MHz, δ($CDCl_3$, TMS), J(Hz)] 1.02 (3H, t, 3xH-3', J=7.8), 1.26 (3H, d, 5-Me, J=6.0), 1.48 (3H, d, 11-Me, J=7.8), 2.27 (3H, s, 3xH-4'), 2.59 (1H, br q, H-11, J=0, 7.8), 3.58 (1H, br d, H-10, J=0, 8.0), 4.03 (1H, br dt, H-9, J=0, 8.0, 8.0), 4.28 (1H, br dd, H-6, J=6.0, 6.0), 4.35 (1H, br d, 10-OH, J=8.0), 5.31 (1H, dq, H-5, J=6.0, 6.0), 5.45 (1H, br d, 6-NH, J=6.0), 6.03 (1H, br d, NH(8), J=8.0); HRMS calcd for $C_{29}H_{35}N_3O_8$ (M^+) 553.2421, found 553.2402. **3b:** $[\alpha]_D^{33}$ -45.0° (c 0.32, $CHCl_3$); IR ($CHCl_3$) 1724, 1669 cm^{-1}; ^1H NMR [270 MHz, δ($CDCl_3$, TMS), J(Hz)] 1.03 (3H, t, 3xH-3', J=7.8), 1.24 (3H, d, 5-Me, J=6.0), 1.48 (3H, d, 11-Me, J=7.8), 2.27 (3H, s, 3xH-4'), 2.61 (1H, q, H-11, J= 0, 7.8), 3.56 (1H, br d, H-10, J=0, 9.4), 4.06 (1H, br dt, H-9, J=0, 8.2, 8.2), 4.39 (1H, d, 10-OH, J=9.4), 4.78 (1H, dd, H-6, J=6.0, 8.2), 5.39 (1H, dq, H-5, J=6.0, 6.0), 6.11 (1H, br d, NH(8), J=8.2); MS 630 (M^+). **1:** $[\alpha]_D^{34}$ -66.1° (c 0.26, 2:1 dioxane-H_2O) [lit,[4] $[\alpha]_D^{21}$ -62.0° (c 1.0, 2:1 dioxane-H_2O)]; mp 230~232°C (dec), mix. mp 230~232°C (dec) [lit,[4] mp 231-233°C (dec)]; UV (EtOH) λ_{max} nm (log ε) 262 (3.79), 266 (3.76), 270 (3.74), 304 (4.06) [lit,[4] UV (EtOH) λ_{max} nm ($E_{1cm}^{1\%}$) 264 (92), 270 (80), 305 (177); IR (KBr) 1731, 1684, 1651 cm^{-1} [lit,[4] IR (KBr) 1735 cm^{-1}]; ^1H NMR [270MHz, δ($CDCl_3$, TMS), J(Hz)] 1.04 (3H, t, 3xH-3', J=7.6), 1.37 (3H, d, 5-Me, J=6.4), 1.50 (3H, d, 11-Me, J=7.8), 2.00~2.25 (2H, m, 2xH-2'), 2.28 (3H, s, 3xH-4'), 2.65 (1H, br q, H-11, J=0, 7.8), 3.01 (2H, d-like, 2xH-7', J=7.6), 3.60 (1H, br d, H-10, J=0, 9.6), 4.10 (1H, br dt, H-9, J=0, 7.6, 7.6), 4.41 (1H, br d, 10-OH, J=9.6), 4.64 (1H, dd, H-6, J=6.4, 8.4), 5.43 (1H, dq, H-5, J=6.4, 6.4), 6.24 (1H, br d, NH(8), J=7.6), 7.17 (1H, dd, H-5''', J=5.0, 8.0), 7.33 (1H, dd, H-4'', J=2.0, 8.4), 7.38 (1H,dd, H-5'', J=4.2, 8.4), 7.64 (1H, ddd, H-4''', J=2.0, 2.0, 8.0), 8.12 (1H, dd, H-6'', J=2.0, 4.2), 8.39 (1H, dd, H-6''', J=2.0, 5.0), 8.53 (1H, d, H-2''', J=2.0), 8.56 (1H, d, 6-NH, J=8.4).
13. The inspection of **5** by ^1H NMR spectroscopy revealed that **5** was present largely in keto form as a mixture of (2*R*)- and (2*S*)-epimers. The active H-2 hydrogen (δ 5.13 and 5.53) of these epimers easily disappeared by D_2O exchange like the 10-OH hydrogen (δ 4.27).
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