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Studies in Macrolide Synthesis: Stereocontrolled Synthesis of a C_1–C_{13} Segment of Concanamycin A.

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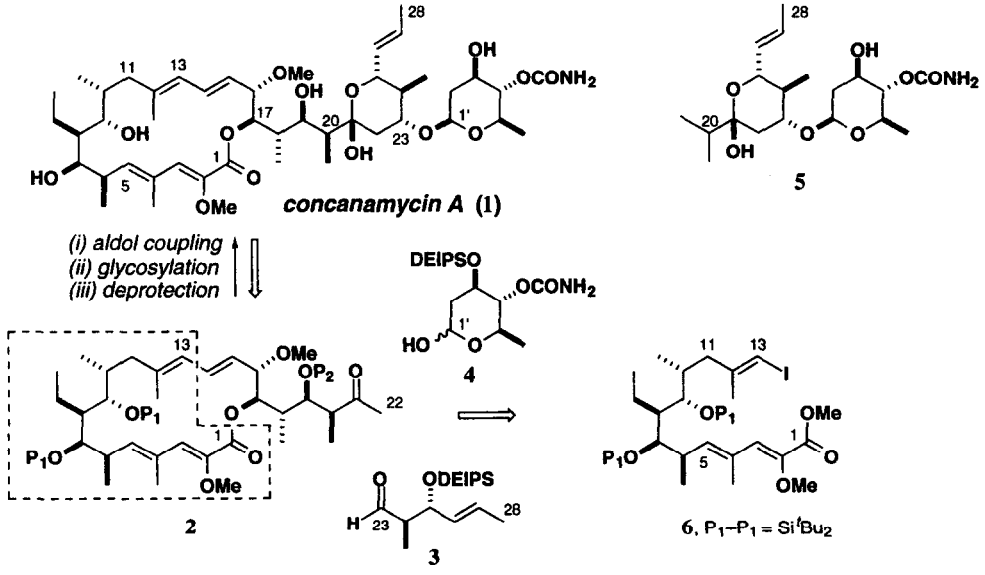
Abstract: The C_1–C_{13} segment **6** of concanamycin A (**1**) was prepared by a highly stereocontrolled route (87% overall ds) in 16 steps from the ester **9**. Key steps are the one-pot aldol/reduction, **8** → **12**, and the HWE reaction, **18** + **19** → **6**. © 1997 Elsevier Science Ltd.

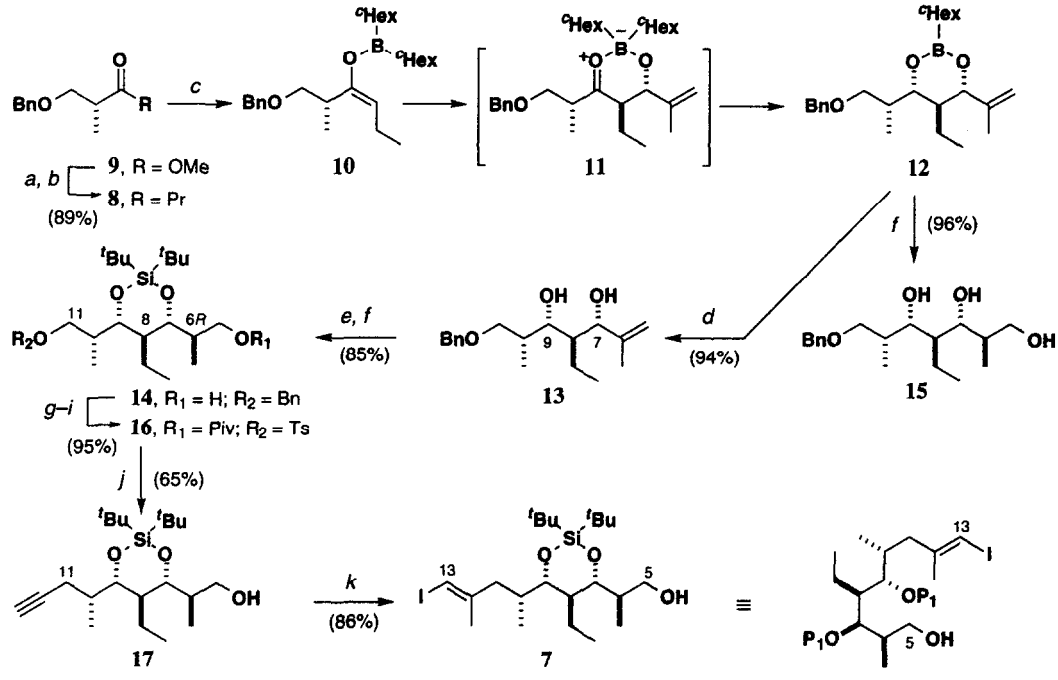
Concanamycin A (**1**)[2] is a potent and specific ATPases' inhibitor,[3] which belongs to a family of structurally related polyketide antibiotics including the bafilomycins[4] and hygrolidins.[5] The 18-membered macrolide structure in **1** features a polyoxygenated sidechain at C_{17}, incorporating 4'-*O*-carbamoyl-2'-deoxy-D-rhamnose linked β-glycosidically at C_{23} to a 6-membered hemiacetal ring. Central to our strategy for the synthesis[6,7] of concanamycin A (**Scheme 1**) is the late installation of this sidechain by the three-component coupling of the methyl ketone **2**, the aldehyde **3** and the 2-deoxysugar **4**. We recently described[6] the efficient assembly of **5**, by an aldol/glycosylation/deprotection sequence making use of **3** and **4**, as a model for the introduction of this sensitive C_{20}–C_{28} region. We now report an expedient, highly stereocontrolled synthesis of the C_1–C_{13} segment **6**, as an intermediate for subsequent elaboration into the macrocyclic methyl ketone **2**.



Scheme 1

The C_1–C_{13} segment **6** contains the five contiguous stereogenic centres spanning the C_5 to C_{11} region of concanamycin A. We have previously described a general aldol approach to the stereocontrolled synthesis of such stereopentads.[8a] As shown in **Scheme 2**, our synthesis of the precursor **7** is based on an extension of the one-pot aldol/reduction process first used in the synthesis of denticulatin A and B.[8b,c]

In this case, the required ketone (*R*)-**8** was prepared by a modification of our previous route[9] starting from the benzyl ether derivative **9** of methyl (*R*)-3-hydroxy-2-methylpropionate. We now recommend the use of the Merck conditions[10] for formation of the corresponding Weinreb amide, which involves the *in situ* generation of the magnesium amide, MeON(Me)MgCl, using ^{i}PrMgCl as base. This avoids the use of pyrophoric Me_3Al and gives an improved yield of the Weinreb amide (98%), which was converted into (*R*)-**8** (91%) by addition of ^{n}PrMgCl.[11] The *anti* aldol reaction[9a,b] of the corresponding (*E*)-dicyclohexylenol borinate **10** with methacrolein (Et_2O, –20 °C) was followed, on cooling to –78 °C, by axial attack[8] of $LiBH_4$ on the intermediate boron aldolate **11**. In the presence of excess Et_3N (as a trap for BH_3), this one-pot procedure proceeded smoothly, leading to isolation of the boronic ester **12**. Chromatographic purification and oxidative removal of boron from **12** gave the *syn* 1,3-diol **13** in 94% overall yield from **8** with 95% ds for the installation of the three new stereocentres.

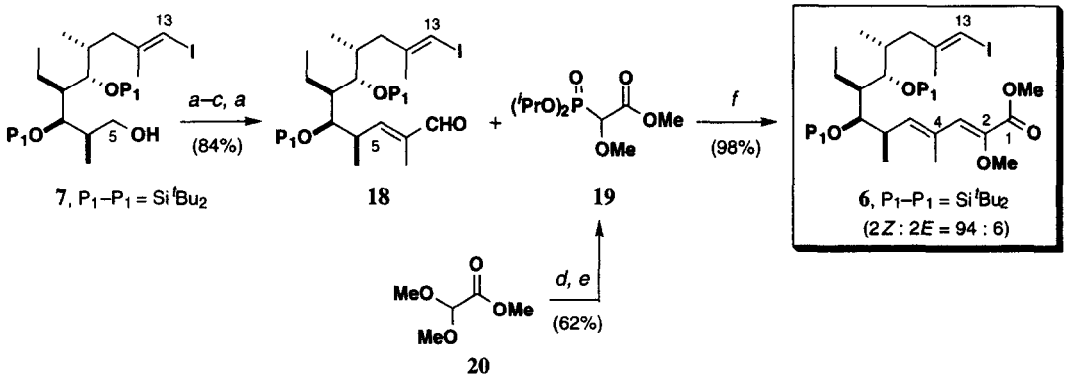


Scheme 2: (*a*) MeNHOMe•HCl, *i*-PrMgCl, THF, –15 °C, 50 min; (*b*) PrMgCl, THF, 0 °C, 1 h; (*c*) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C, 2 h; $H_2C{=}C(Me)CHO$, –20 °C, 1.5 h; Et_3N, $LiBH_4$, –78 °C, 1.5 h; NH_4Cl; (*d*) H_2O_2, NaOH, MeOH, 0 → 20 °C, 1 h; (*e*) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 0 → 20 °C, 2.5 h; (*f*) 9-BBN, THF, 0 → 20 °C, 3 h; H_2O_2, NaOH, MeOH, 1 h; (*g*) PivCl, DMAP, Et_3N, CH_2Cl_2, 18 h; (*h*) 10% Pd / C, H_2, THF, 3 h; (*i*) TsCl, py, 16 h; (*j*) HC≡CLi•en, HMPA, DMSO, 2.5 h; (*k*) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, 40 °C, 16 h; I_2, THF, –20 → 20 °C.

Examination of the X-ray crystal structure[2e] of concanamycin A suggested that the presence of a cyclic protecting group (P_1–P_1) across C_7 and C_9 would not perturb the preferred conformation of the macrolide ring. Accordingly, the required stereopentad sequence was completed from **13** by di-*tert*-butylsilylene formation and alkene hydroboration using 9-BBN, giving the alcohol **14** as a single isomer in 85% overall yield. At this stage, the expected[8b,c,12] (6*R*) configuration was confirmed by hydrogenolysis of the benzyl ether in **14** to give the corresponding diol, which had ^{1}H and ^{13}C NMR spectra and optical rotation in accord with the lack of symmetry about C_8. Alternatively, this same stereochemical relationship could be

achieved by hydroboration of the boronic ester **12** to give the triol **15** (96%; >95% ds) after oxidative work-up. Next, the alcohol **14** was converted in three straightforward steps (95%) into the tosylate **16**, followed by displacement at C_{11} with lithium acetylide-ethylenediamine complex,[13] and concomitant ester cleavage, to give the terminal alkyne **17** (65%). Next, the (*E*)-alkenyl iodide was installed by a Negishi carbometallation[14] of the alkyne and quenching the resulting organoalane with I_2 to give **7** in 86% yield.

A stepwise approach for the stereocontrolled introduction of the diene ester unit into alcohol **7** was adopted, as outlined in **Scheme 3**, to complete the synthesis of the C_1–C_{13} segment **6**. First, oxidation to the aldehyde and Wittig olefination ($Ph_3P{=}C(Me)CO_2Et$) gave the corresponding ester (*E* : *Z* = 97 : 3), which was converted into the enal **18** (84% overall) by a reduction/oxidation sequence. Introduction of the methoxy-bearing alkene proved to be more challenging. Previously, the use of MeO-substituted phosphonate reagents[15] for similar Horner-Wadsworth-Emmons transformations has been achieved with only modest levels of stereoselectivity.[7d] Therefore, studies to optimise the selectivity obtained for the step, **18** → **6**, were undertaken. Variables investigated included the size of the phosphonate alkyl group, the reaction temperature and the choice of counter ion.[16] This culminated in the use of the bulky, ^{i}Pr-substituted, phosphonate **19** (obtained from **20**) in conjunction with KHMDS and 18-crown-6,[17] as a minimally coordinating base, at 0 °C. These conditions gave the desired (2*Z*, 4*E*)-diene ester **6** in 98% yield,[11] as a 94 : 6 ratio of isomers which were seperable by HPLC.



Scheme 3: (*a*) SO_3•py, Et_3N, DMSO, CH_2Cl_2, 0 → 20 °C, 1 h; (*b*) $Ph_3P{=}C(Me)COOEt$, PhMe, 110 °C, 16 h; (*c*) DIBAL, CH_2Cl_2, –78 °C, 30 min; (*d*) PCl_5, 140 °C, 1 h; (*e*) (*i*-PrO)$_3$P, 150 °C, 4 h; (f) **19**, KHMDS, 18-crown-6, THF, 0 °C, 30 min; **18**, 4 h.

In summary, the foregoing sequence allows the efficient synthesis of the C_1–C_{13} segment **6** of concanamycin A (**1**) with a high level of stereocontrol (87% overall ds) and proceeds in 16 steps and 31% yield from the starting ester **9**. Studies toward the synthesis of the remaining C_{14}–C_{22} segment and its elaboration into concanamycin A by sequential coupling with the available subunits (*i.e.* **3**, **4** and **6**) are currently under investigation.

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11. All new compounds gave spectocopic data in agreement with the assigned structures. Ester **6** had $[\alpha]_D^{20}$ –28.6 (*c* 1.6, $CHCl_3$); ^1H NMR δ(500 MHz, $CDCl_3$) 6.58 (1H, s, 3-CH), 6.07 (1H, d, *J* = 9.6 Hz, 5-CH), 5.93 (1H, s, 13-CH), 3.98 (1H, dd, *J* = 10.2, 1.4 Hz, 7-CH), 3.87 (1H, d, *J* = 10.2 Hz, 9-CH), 3.80 (3H, s, COOMe), 3.66 (3H, s, OMe), 2.78 (1H, m, 6-CH), 2.45 (1H, dd, *J* = 13.4, 8.3 Hz, 11-CH_a), 2.17 (1H, dd, *J* = 13.4, 6.2 Hz, 11-CH_b), 2.00 (3H, s, 4-Me), 1.91 (1H, m, 10-CH), 1.83 (3H, s, 12-Me), 1.48 (1H, m, 8-CH), 1.35-1.19 (2H, m, $C\underline{H}_2Me$), 1.10 (3H, d, *J* = 6.8 Hz, 6-Me), 1.02 (9H, s, Si^tBu_a), 1.02 (9H, s, Si^tBu_b), 0.82 (3H, d, *J* = 6.7 Hz, 10-Me), 0.76 (3H, t, *J* = 7.6 Hz, $CH_2\underline{Me}$); ^{13}C NMR δ(50.3 MHz, $CDCl_3$) 165.5, 146.4, 142.7, 139.7, 130.9, 129.9, 79.7, 77.1, 76.4, 60.2, 51.9, 44.4, 43.1, 35.8, 32.8, 27.7, 27.4, 23.6, 23.2, 20.4, 19.1, 17.6, 14.6, 12.6, 8.7; HRMS (+CI, NH_3) calcd for $C_{29}H_{52}IO_5Si$ $[M+H]^+$ 635.2629, found 635.2630.
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16. In preliminary investigations of this HWE reaction, phosphonate **19** gave 82–87% selectivity with tiglic aldehyde for the desired (2*Z*, 3*E*)-diene ester. Use of the analogous $(MeO)_2POCH(OMe)CO_2Me$ gave considerably poorer selectivity. For both phosphonates, a modest dependence on counter ion and temperature was observed favouring the *Z*-alkene at low temperature and with non-coordinating counter ions.
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