Asymmetric synthesis of a seven carbon *anti*-3,5-diol building block. A polyacetate derivative with completely resolved C_2 symmetry

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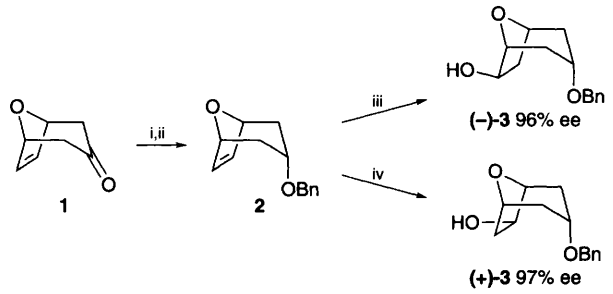
Methyl (3*R*,5*R*)-5-benzyloxy-7-([1,3]dithian-2-yl)-3-hydroxyheptanoate (+)-7 has been prepared from 8-oxabicyclo[3.2.1]oct-6-en-3-one 1 in 7 steps and 40% overall yield.

The construction of 1,3-diols, especially *anti*-1,3-diols of the polyacetate rather than the polypropionate type,[1,2] is a continuing synthetic challenge. The 1,3-diol functionality appears in a wide variety of biologically active compounds and macrolides, including the oxo polyenes[2] Mycoticin A[3] and Roxaticin.[4] In hidden form a functionalized *anti*-1,3,5-triol segment also appears in the Bryostatins[5] at carbon atoms C-3, C-5 and C-7. Recent approaches to these building blocks have also been reported by Masamune, Evans, Nicolaou, Paterson and other groups.[5,6]

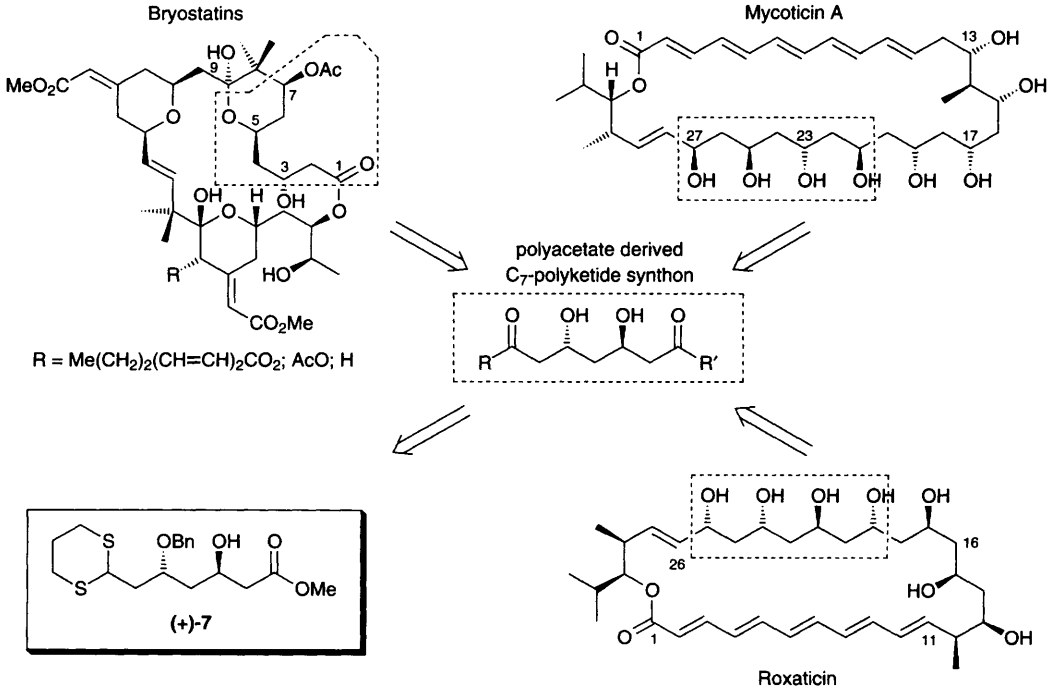
It occurred to us that the polyacetate derived oxygenation pattern of these natural products should be readily accessible from a terminally functionalized 3,5-dihydroxyheptanoic ester such as (+)-**7** (Scheme 1). In turn, the C_7 ester should be derivable from 8-oxabicyclo[3.2.1]oct-6-en-3-one[7] **1** by functionalization and twofold opening of the oxabicyclic skeleton.

Diastereoselective reduction of **1** with L-Selectride® afforded exclusively the axial alcohol, which was protected by benzylation (71% combined yield). Unsaturated *meso*-substrate **2** was desymmetrized by asymmetric hydroboration[8] to give, after oxidative work up, *exo* alcohol **3**. Either enantiomer (+)-**3** and (−)-**3** has been prepared in high yield and with excellent enantioselectivity. Absolute configuration and enantiomeric purity of the alcohols were determined by ^{1}H NMR of the corresponding Mosher esters[9] (prepared from *S*-MTPA-Cl, cat. 4-DMAP, pyridine, CH_2Cl_2, 0 °C to room temp.).

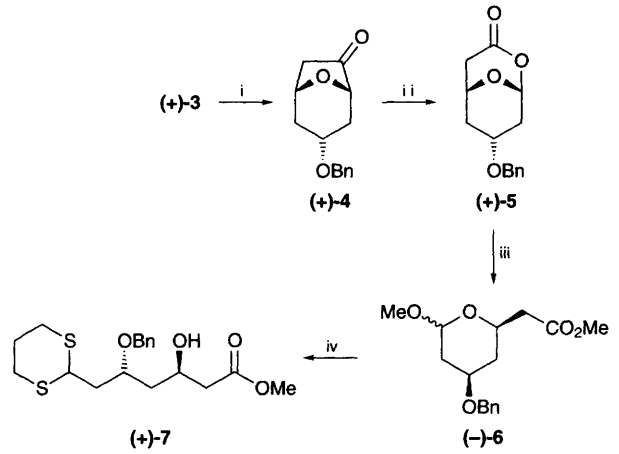
PCC oxidation of (+)-**3** was straightforward and gave bicyclic ketone (+)-**4** which was submitted to Baeyer–Villiger rearrangement with buffered M-CPBA.[10] Bicyclic lactone (+)-**5** was obtained as colourless crystals, mp 81.5–82.5 °C. Attempts to open the lactone under basic conditions were not successful.[11] However, acidic methanolysis opened the bicyclic ring system smoothly and provided the ester (−)-**6** in 98% yield as an anomeric mixture with the α-anomer predominating as expected (α : β = 7.5 : 1). Initial attempts to further open the six-membered methylacetal with an excess of 1,2-ethanediol and 2,2-dimethylpropane-1,3-diol under the influence of catalytic amounts of *p*-TsOH were not successful, but yielded only



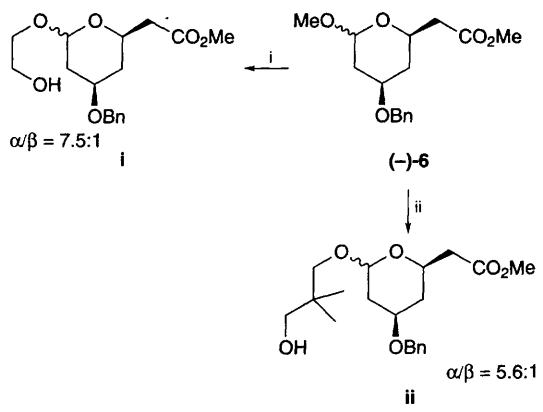
Scheme 2 *Reagents and conditions*: i, $LiBH(Bu^i)_3$, THF, −76 to 0 °C; ii, NaH, BnBr, THF, reflux, 71%; iii, $(-)\text{-}(Ipc)_2BH$, THF, 48 h, −15 to −10 °C, 70%; iv, $(+)\text{-}(Ipc)_2BH$, THF, 48 h, −15 to −10 °C, 80%



Scheme 1



Scheme 3 *Reagents and conditions*: i, PCC, CH_2Cl_2, room temp., 92%; *m*-CPBA, $NaHCO_3$, CH_2Cl_2, room temp., 88%; iii, cat. H_2SO_4, MeOH, room temp., 98%; iv, $BF_3{\cdot}Et_2O$, propane-1,3-dithiol, CH_2Cl_2, 0 °C to room temp., 89%



Scheme 4 *Reagents and conditions*: i, ethanediol, cat. *p*-TsOH, C_6H_6, reflux, 50%; ii, 2,2-dimethylpropane-1,3-diol, cat. *p*-TsOH, C_6H_6, reflux, 70%

products derived from simple alcohol interchange.‡ In contrast, Lewis acid mediated transthioacetalization[12] of acetal (−)-**6** afforded the desired C_7-polyketide (+)-**7** in high yield.

In conclusion, starting from the *meso*-configurated oxabicycle **1** we have developed an innovative approach to *anti*-configurated, skipped polyols with predictable stereochemistry. An *endo*-selective reduction of the carbonyl group is followed by a reagent controlled, asymmetric hydroboration. The remaining four steps are refunctionalizations involving oxidations and stepwise opening of the resulting bicyclic lactone (+)-**5**. The heptanoic ester (+)-**7** contains an *anti*-1,3-diol relationship (with one hydroxy group benzylated) and in fact all four functionalities are chemodifferentiated. The polyacetate-derived acyclic C_7-building block features completely resolved C_2-symmetry. It can be obtained in either enantiomeric form and has remarkable flexibility and synthetic potential. Applications in the total synthesis of macrolides are underway. Polyketide (+)-**7** has been prepared in 7 steps (40% overall yield) on a 5 g scale. All compounds gave satisfactory spectroscopic and analytical data.§

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Footnotes

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‡ Expulsion of methanol from (−)-**6** afforded compounds **i** and **ii** (Scheme 4).

§ *Analytical data*. For (+)-**3**; mp 58.5–59 °C. $[\alpha]_D^{22}$ + 4.7 (*c* 1, $CHCL_3$); ^1H NMR (200 MHz, $CDCl_3$, Me_4Si) δ 7.41–7.23 (m, 5 H), 4.72 (dt, ^3J 8, 2 Hz, 1 H), 4.56–4.43 (m, 1 H), 4.44 (s, 2 H), 4.15 (m, 1 H), 3.67 (m, 1 H), 2.86 (dd,^3J 13.5, 7.5 Hz, 1 H), 2.06 (d, ^3J 8 Hz, 1 H), 2.03–1.88 (m, 3 H) 1.84 (br s, 1 H), 1.81–1.69 (m, 1 H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 138.44 (+), 128.20 (−), 127.24 (−), 126.90 (−), 82.28 (−), 75.33 (−), 74.37 (−), 70.93 (−), 70.31 (+), 41.44 (+), 34.33 (+), 32.84 (+). For (+)-**5**; mp 81.5–82.5 °C; $[\alpha]_D^{21}$ +61.5 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2931, 2878, 1731, 1282, 1231, 1185, 1105, 1090, 1031, 920; ^1H NMR (200 MHz, $CDCl_3$, Me_4Si) δ 7.40–7.24 (m, 5 H), 5.76 (m, 1 H), 4.65 (d, ^2J 12 Hz, 2 H), 4.50–4.40 (m, 1 H), 3.92 (m, 1 H), 2.98 (ddd, ^2J 18, ^3J 8,^4J 1 Hz, 1 H), 2.66 (d, ^2J 18 Hz, 1 H), 2.43 (dq, ^2J 15, $^{3/4}J$ 2 Hz, 1 H), 2.22 (dt, ^2J 14.5, ^3J 4 Hz, 1 H), 2.01 (dq, ^2J 14.5, $^{3/4}J$ 2 Hz, 1 H), 1.86 (dt, ^2J 15, ^3J 3.5 Hz, 1 H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 166.37 (+) 137.37 (+), 128.29 (−), 127.76 (−), 127.58 (−), 96.71 (−), 70.13 (+), 68.22 (−), 65.62 (−), 35.62 (+), 33.38 (+), 31.35 (+); *m/z* (FAB) 249 (49%, M + 1), 247 (20, M − 1), 141 (100) (Calc. for $C_{14}H_{16}O_6$: C, 67.73; H, 6.50. Found, C, 67.64; H 6.49). For (+)-**7**; $[\alpha]_D^{22}$ +1.7, $[\alpha]_{365}^{22}$ +15.1 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3470, 3030, 2950, 2900, 1735, 1496, 1437, 1358, 1276, 1162, 1070, 1039, 909; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.39–7.28 (m, 5 H), 4.63 (d, ^2J 11.3 Hz, 2 H), 4.29 (m, 1 H), 4.11 (dd, ^3J 8.2, 6.2 Hz, 1 H), 4.05 (m, 1 H), 3.71 (s, 3 H), 3.25 (d, ^3J 3.5 Hz, 1 H), 2.87–2.79 (m, 4 H), 2.47 (d, ^3J 6.3, 2 H), 2.08–2.15 (m, 2 H), 1.94–1.89 (m, 2 H), 1.78 (ddd, ^2J 14, ^3J 10.0, 3.5 Hz, 1 H), 1.63 (ddd, ^2J 14, ^3J 8.0, 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, DEPT, $CDCl_3$) δ 172.81 (C-1), 138.14 (Ar-C), 128.41 (*meta* Ar-C), 128.06 (*ortho* Ar-C), 127.77 (*para* Ar-C), 73.33 (C-5), 72.20 (OCH_2Ph), 64.92 (C-3), 51.69 (OCH_3), 43.72 (C-7), 41.52/40.66 (C-2 and C-4), 40.24 (C-6), 30.76/30.16 (CH_2S), 25.83 (CH_2); *m/z* (110 °C) 370 (2.7%, M+), 339 (1.5), 262 (55.6), 170 (12.9), 159 (20.7), 145 (23.5), 133 (66.5), 119 (86.3), 107 (29.4), 91 (100) (Calc. for $C_{18}H_{26}O_4S_2$, 370.1273. Found, 370.1272).

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