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STEREOCONTROLLED CONVERGENT SYNTHESIS OF 1,3-POLYOL

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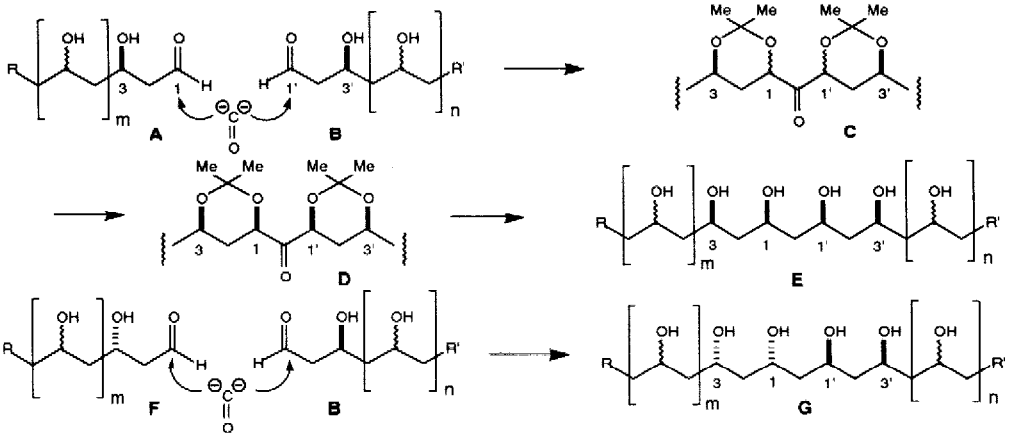
Abstract: Stereocontrolled convergent method for the synthesis of 1,3-polyol was developed.

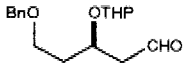
In connection with the synthetic studies of polyenemacrolide antibiotics, an importance of developing an effective method for the synthesis of a 1,3-polyol system has been widely recognized in recent years and a number of synthetic strategies has been reported so far.[1] However, for the purpose of constructing an extended 1,3-polyol chain, development of a technique to combine two polyol segments stereoselectively is highly desired. We now report a stereochemically well-controlled convergent method useful for the synthesis of a higher member of 1,3-polyols.

Coupling of two polyol segments **A** and **B** involving a β-hydroxy aldehyde moiety with a carbonyl dianion equivalent and the subsequent acetonization may afford the diacetonide **C** as an isomeric mixture at the C-1 and C-1' positions. The axial ketonic side chain at C-1 or C-1' with respect to the acetonide ring, if any, should be converted into the equatorial one on mild base treatment by an interaction with the gem-dimethyl group of the acetonide.[2] The same type of reaction sequence is expected to proceed with the epimeric hydroxy aldehyde **F**. Thus, in principle, both **E** involving 1,3-1,1'-1',3'-all-syn-tetraol and **G** involving 1,3,-syn-1,1'-anti-1',3'-syn-tetraol could be synthesized stereoselectively based on the present strategy.



To demonstrate an availability of the above strategy, we examined the synthesis of 3,5,7,9-all-syn-tetraol derivative **16** and 3,5-syn-5,7-anti-7,9-syn-tetraol derivative **18** having different functionality on the both side of the 1,3-polyol chains.

We chose three optically active aldehydes (R)-**1**,[3] (S)-**2**,[3] and (S)-**3**[3] as the starting materials corresponding to **A**, **B**, and **F**. Three alternative routes using t-butyl acetate (route A), nitromethane (route B), and 1,3-dithiane (route C) as the carbonyl dianion equivalent were undertaken.



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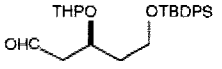

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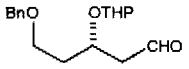

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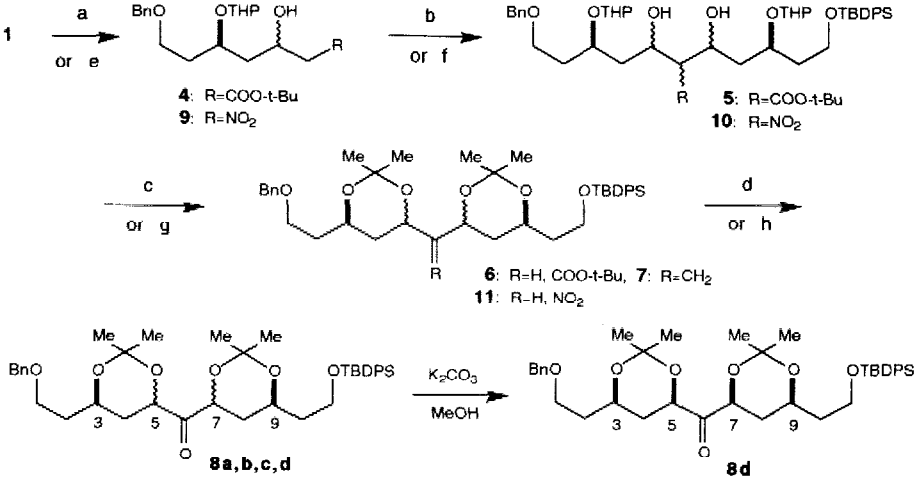
1) Route A: Aldol condensation of aldehyde **1** with lithium enolate of t-butyl acetate gave hydroxy ester **4** (89%), which after treatment with 2 equiv LDA was coupled with aldehyde **2** yielding dihydroxy ester **5** in 50% yield (76% based on the consumed **4**). Removal of the protecting THP group and the subsequent acetonization afforded diacetonide **6** in 73% yield. The diacetonide **6** was converted into olefin **7** in 3 step sequences; 1) DIBAH reduction (84%), 2) phenylselenation[4] (82%), 3) formation of double bond (100%). Ozonolysis of **7** gave a mixture of four ketones **8a~d**[5] (87%) due to the isomers at the C-5 and C-7 positions, which without separation was treated with K_2CO_3 in MeOH affording the single isomer **8d**[6] in 80% yield. The ketone **8d** proved to be 3,5,7,9-all-syn-compound having all-equatorial side chains based on the coupling constants of C-5 and C-7 protons: δ 4.67 (dd, J=12.0, 2.7 Hz), 4.75 (dd, J=12.0, 2.7 Hz). It should be noted that signals



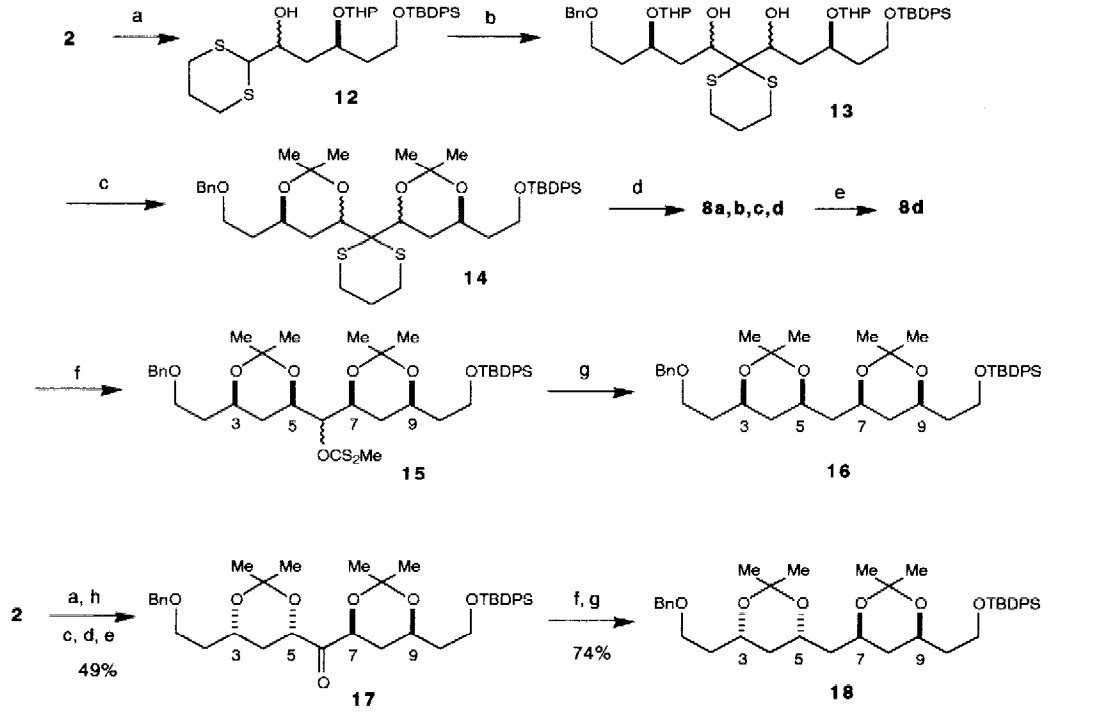
Route A: a) LDA/MeCOO-t-Bu/THF/-78°C, b) 2 equiv LDA/THF/-78°C/aldehyde **2**, c) aq AcOH; $Me_2C(OMe)_2$/TsOH/CH_2Cl_2; DIBAH/PhMe/-78°C~rt; PhSeCN/Ph_3P/THF; $NaIO_4$/MeOH; Et_3N/PhH/60°C, d) O_3/MeOH/-78°C/Me_2S
Route B: e) $MeNO_2$/Et_3N/rt, f) Et_3N/aldehyde **2**, g) aq AcOH; $Me_2C(OMe)_2$/CSA/CH_2Cl_2, h) t-BuONa/t-BuOH/$KMnO_4$

of protons at newly formed asymmetric centers adjacent to carbonyl groups appeared at lower field without overlapping with those of the other protons, which makes it possible to assign the stereochemistry of hydroxyl groups at C-5 and C-7 unequivocally.

In route A, several steps were required to yield **8d**, which obviously ascribed to the use of a two-carbon carbonyl dianion equivalent, t-butyl acetate. Thus, the routes, B and C, using one-carbon analogues were then undertaken. As was expected, the pathway to **8d** became much shorter and the overall yields were remarkably increased.

2) Route B: Condensation of aldehyde **1** with nitromethane in the presence of Et_3N gave nitro alcohol **9** (98%). The alcohol **9** was coupled with aldehyde **2** giving nitro diol **10** (74%) which, after deprotection of THP groups, was converted to diacetonide **11** in 68% yield. Treatment of **11** with t-BuONa and $KMnO_4$[7] gave a mixture of four ketones **8a~d** which on base treatment gave the single ketone **8d** in 52% yield.

3) Route C: Aldehyde **2** was treated with lithiated 1,3-dithiane producing alcohol **12** (97%), which after addition of 2 equiv n-BuLi was coupled with aldehyde **1** to give a mixture of diol **13** (76%). Deprotection of THP group followed by acetonization gave **14** in 75% yield. Deprotection of thioacetal **14** with NBS[8] produced a mixture of ketones **8a~d** which was epimerized to ketone **8d** in 72% yield.



Route C: a) n-BuLi/1,3-dithiane/THF/-78°C, b) 2 equiv n-BuLi/HMPA/THF/-78°C/aldehyde **1**, c) aq AcOH; $Me_2C(OMe)_2$/CSA/CH_2Cl_2, d) NBS/$AgNO_3$/2,6-lutidine/aq MeCN, e) K_2CO_3/MeOH, f) DIBAH/PhMe/-48°C; NaH/CS_2/MeI/THF, g) n-Bu_3SnH/AIBN/PhMe/reflux, h) 2 equiv n-BuLi/HMPA/THF/-78°C/aldehyde **3**

Reduction of the pure ketone **8d** with DIBAH gave two epimeric alcohols and the mixture was converted to xantate **15**. Reduction of **15** with n-Bu_3SnH in the presence of AIBN[9] produced the 3,5,7,9-all-syn-tetraol derivative **16**, $[\alpha]_D^{24}$ +4.9° (c 1.02, $CHCl_3$), in 90% yield (3 steps).

Starting from aldehyde **2** and **3**, the 3,5-syn-5,7-anti-7,9-syn-tetraol derivative **18**, $[\alpha]_D^{23}$ +1.6° (c 6.36, $CHCl_3$), was synthesized via ketone **17**[10] in the same way as described in the synthesis of **16** by route C.

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References and Notes

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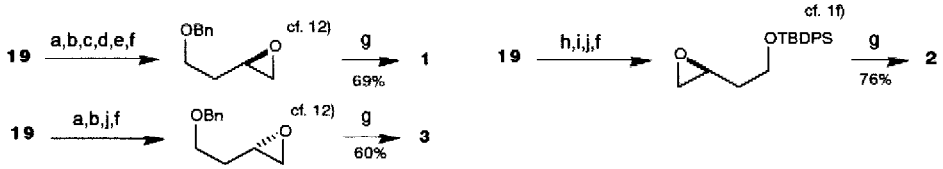
3) The aldehydes **1**, **2**, and **3** were prepared from (2S)-1,2-O-isopropylidene-1,2,4-butanetriol (**19**)[11] as shown below.



a) BnBr/NaH/n-Bu_4NI/THF, b) H_2SO_4/THF, c) t-$BuMe_2SiCl$/imidazole/DMF, d) MsCl/Py/CH_2Cl_2, e) aq AcOH, f) K_2CO_3/MeOH, g) n-BuLi/1,3-dithiane/THF; DHP/TsOH/CH_2Cl_2; HgO/$HgCl_2$/aq Acetone, h) t-$BuPh_2SiCl$/imidazole/DMF, i) aq AcOH, j) TsCl/Py/CH_2Cl_2

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5) These ketones are separable on silicagel column chromatography. 400MHz ^{1}H-NMR ($CDCl_3$) **8a**: δ 4.57 (dd, J=12.0, 2.7 Hz), 4.73 (dd, J=9.9, 7.0 HZ), **8b**: δ 4.59 (dd, J=12.0, 2.9 Hz), 4.71 (dd, J=9.8, 6.8 Hz), **8c**: δ 4.61 (dd, J=7.1, 2.0 Hz), 4.63 (dd, J=7.2, 2.3 Hz).

6) $[\alpha]_D^{24}$ +2.5° (c 1.06, $CHCl_3$).

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10) 400 MHz ^{1}H-NMR ($CDCl_3$) δ 4.67 (dd, J=11.9, 2.45 Hz), 4.71 (dd, J=11.9, 2.45 Hz); $[\alpha]_D^{18}$ -17.8° (c 1.10, $CHCl_3$).

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