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A CONVERGENT GENERAL SYNTHETIC PROTOCOL FOR SYN-1,3-POLYOLS

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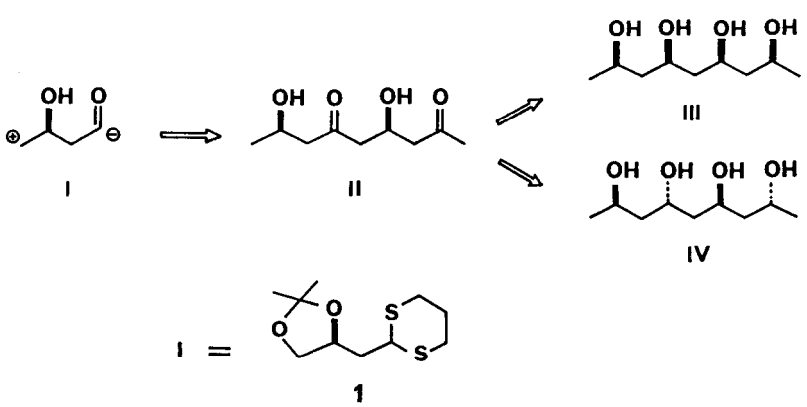
Abstract: A method for the stereoselective synthesis of syn-1,3-polyols using a chiral building block **1** is described. High syn-stereoselectivity in the reduction of β-hydroxy ketones was achieved using lithium aluminum hydride-lithium iodide.

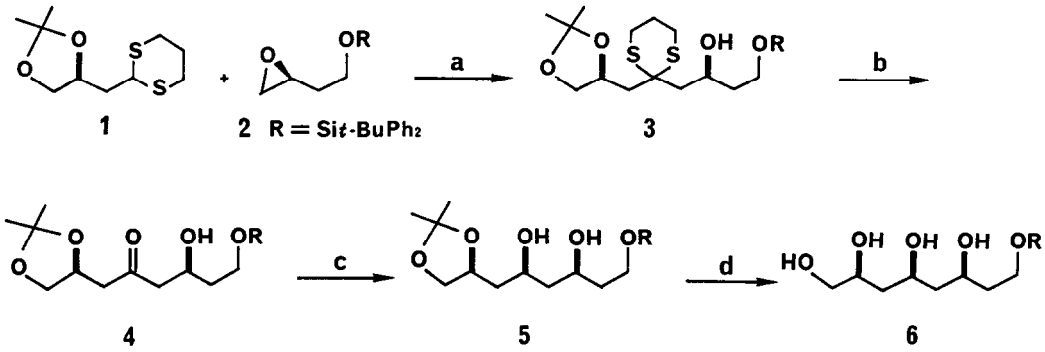
A great deal of attention has been paid to the stereocontrolled synthesis of polyhydroxylated acyclic compounds in recent years since they form the basic structure of polyene and polyol macrolide antibiotics.[1] A characteristic feature of the families is the presence of 1,3-polyol subunits. Despite their importance as antifungal agents, little is known about the stereochemistry of the macrolide antibiotics except for amphotericin B,[2] which is the only member of this family of known absolute configuration to have syn-1,3-diol units. In 1987 Schreiber *et al.* reported the absolute configurations of mycoticins A and B and demonstrated that the antibiotics contained both syn and anti-1,3-polyols.[3] The presence of an anti-1,3-polyol structure was also shown in the stereochemical study of lienomycin by Nakanishi *et al.*[4] Therefore the stereoselective synthesis of continuous 1,3-diol units is important.

In connection with our stereochemical study of sporaviridin,[5] a polyol macrolide, we needed efficient methods for preparing syn and anti-polyols.[6] In this letter we describe a convergent and general protocol for syn-1,3-polyol synthesis which is extendable to higher homologues of this series by repetition. The strategy for the polyol synthesis is presented in Scheme I.

Scheme I



A common precursor for syn and anti-polyols **III** and **IV** is considered to be the hydroxy ketone **II**, which could be obtained by coupling of the chiral synthon **1**, a synthetic equivalent of the C_4 unit **I**.

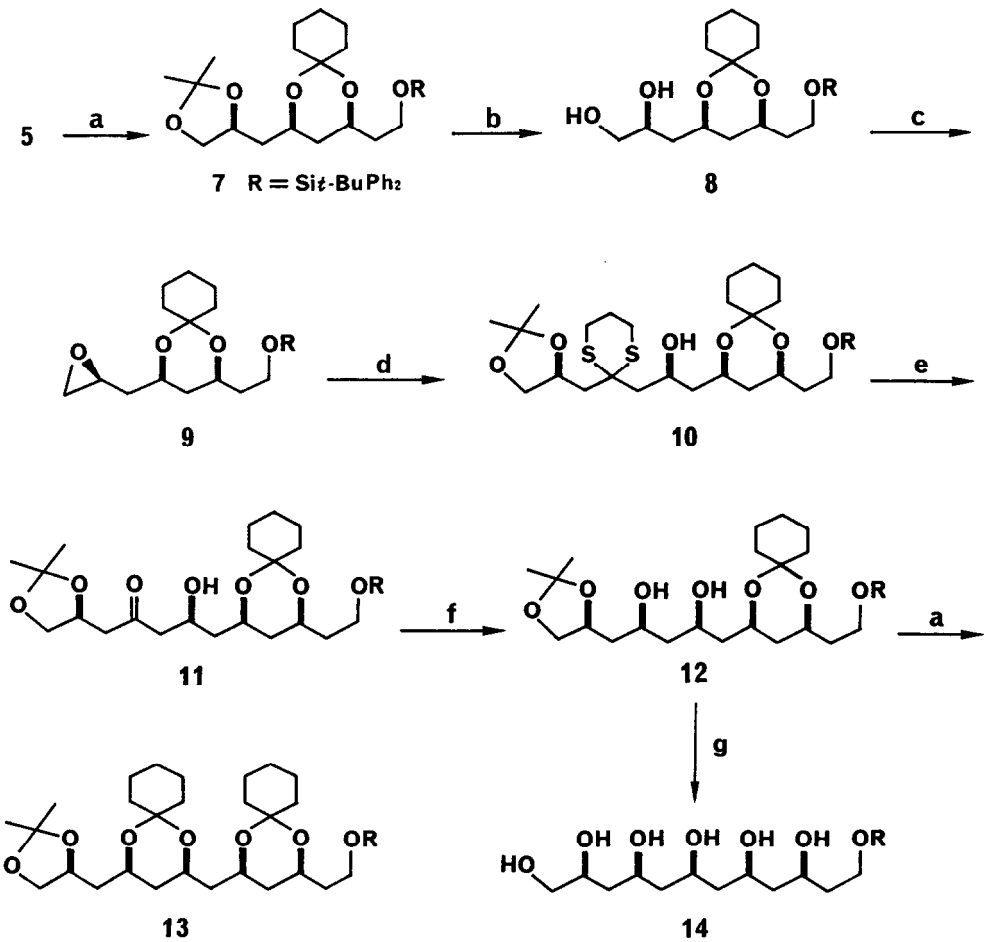


Scheme II (a) **1**, n-BuLi, THF, -20°C, 2h, then **2**, 17h; (b) 6.0 equiv. NBS, 6.3 equiv. $AgNO_3$, 12 equiv. 2,6-lutidine, 85% aq. CH_3CN 7 min; (c) 5.0 equiv. $LiAlH_4$, 5.0 equiv. LiI, ether, -100°C, 30 min; (d) PPTS, MeOH, 45°C, 2h.

Our synthesis (Scheme II) started with the coupling reaction of the anion generated from the chiral synthon **1**[7] ($[\alpha]_D^{23}$-9.05°($CHCl_3$)) with the chiral epoxide **2**[8] ($[\alpha]_D^{24}$-3.60°($CHCl_3$)) to give the dithiane **3** in 98% yield. Careful treatment of **3** with NBS-$AgNO_3$ in the presence of 2,6-lutidine in aq. CH_3CN for 7 min afforded the β-hydroxy ketone **4** (78% yield).[9] The next step was the stereoselective reduction of **4** to the syn-1,3-diol **5**. We have reported a lithium aluminum hydride-lithium iodide reduction as a promising new method for such purposes.[10] Thus, reduction of **4** with $LiAlH_4$ in the presence of LiI in ether at -100°C resulted in the formation of the syn-product **5** in 91% yield with exellent syn-selectivity (syn : anti = 95:5). A moderate selectivity (syn: anti = 79:21) was observed when the reduction was carried out without LiI at -78°C. It is worthy to note that the presence of the hydroxyl group in **4** is not important in this 1,3-asymmetric reduction.[10] Deprotection of **5** yielded all syn-pentol derivative **6** ($[\alpha]_D^{25}$+11.58°($CHCl_3$)) in 80% yield. The compounds **5** and **6** have a 1,2-diol structure which is a useful functional group for further elaboration of the molecules.

The stage was set to build higher homologues of 1,3-polyols (Scheme III). The syn-diol **5** was protected as a cyclohexylidene ketal **7** (93% yield). Selective deprotection of the acetonide was accomplished by the treatment of **7** with 80% AcOH-THF (9:1) at -10°C and the desired diol **8** was isolated in 42% yield along with **7** (89% yield based on the consumed starting material). This was converted to the epoxide **9** ($[\alpha]_D^{24}$-1.93°($CHCl_3$)) by routine synthetic operations in 78% overall yield.

A second coupling reaction was carried out by treatment of the epoxide **9** with the anion of the chiral dithiane **1** to afford the alcohol **10** in 93% yield, which was converted to the β-hydroxy ketone **11** (69% yield) under carefully controlled conditions. The highly syn-stereoselective reduction of **11** was again achieved using $LiAlH_4$-LiI in ether at -100°C to yield the syn-diol **12** in 86% yield. The diastereoselectivity of the reduction was syn: anti = 95:5. Protection of **12** with cyclohexylidene ketal gave **13** ($[\alpha]_D^{23}$+3.11°($CHCl_3$)) in 88% yield, which in principle could be homologated to higher members of all



Scheme III

(a) 1,1-dimethoxycyclohexane, PPTS, CH_2Cl_2, 7h; (b) 80% AcOH-THF (9:1), -10°C, 48h; (c) (i) 5 equiv. TsCl, pyridine, 0°C, 3h, (ii) KH, ether-MeOH (5:1), 0°C, 20 min; (d) **1**, n-BuLi, THF, -20°C, 2h, then **9**, 18h; (e) 6.0 equiv. NBS, 6.3 equiv. $AgNO_3$, 12 equiv. 2,6-lutidine, 85% aq. CH_3CN, 7 min; (f) 5.0 equiv. $LiAlH_4$, 5.0 equiv. LiI, ether, -100°C, 30 min; (g) PPTS, MeOH, 45°C, 5h.

syn-1,3-polyols. Finally the sequence was terminated by the acid treatment of **12** to give the heptol derivative **14** ($[\alpha]_D^{23}$+9.93°($CHCl_3$)) in 53% yield.

The success of the present convergent synthesis is particulary owed to developments of a new chiral building block **1** and a highly syn-selective $LiAlH_4$-LiI reduction method. Further investigation of this new methodology and its applications to the synthesis of polyhydroxylated natural products are in progress.

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7. Prepared from (3S)-3,4-dihydroxybutanal acetonide (propanedithiol, BF_3OEt_2, CH_2Cl_2, then 2,2-dimethoxypropane) in 76% yield.
8. Prepared from (2S)-butane-1,2,4-triol 1,2-acetonide in four steps: (a) Ph_2(t-Bu)SiCl, imidazole, DMF (98%), (b) PPTS, MeOH (88%), (c) TsCl, pyridine, (d) K_2CO_3, MeOH (87% yield in two steps).
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