Tetrahedron Letters,Vol.30,No.33,pp 4383-4386,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF 1,3-SYN-3,5-ANTI-TRIOLS USING A SYN-1,3-ASYMMETRIC REDUCTION: A NOVEL ROUTE TO ANTI-1,3-POLYOLS

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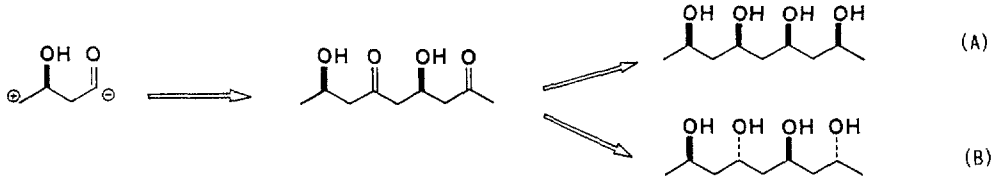
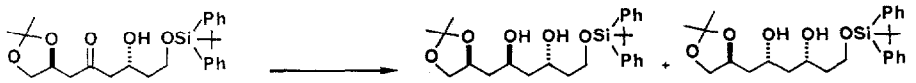
Summary: A method for the stereoselective synthesis of optically active anti-1,3-polyols containing a 1,3-syn-3,5-anti-triol unit has been developed using a chiral building block (1) and a highly syn-diastereoselective reduction with lithum tri-tert-butoxyaluminium hydride-lithium iodide.

Structural studies on polyene macrolide antibiotics have been extensively undertaken because of their importance in antifungal activity.[1] Despite widespread use in medicine, their stereochemistries remain unknown except for amphotericin B.[2] Recent stereochemical studies established the absolute configurations of mycoticins[3] and pentamycin[4], and portions of lienomycin[5] and nystatin.[6] These studies revealed the presence of both anti- and syn-1,3-diol units in a polyol chain. Therefore the stereoselective synthesis of continuous 1,3-diol units is of importance.[7]

We recently developed a general method for the stereoselective synthesis of syn-1,3-polyols[8] based on a $LiAlH_4$-LiI reduction[9] (route A). In this letter we report a 1,3-asymmetric reduction for the preparation of a 1,3-syn-3,5-anti-triol unit and its application to anti-1,3-polyol synthesis (route B).



Our initial experiments were designed to assay the stereoselectivity of the reduction of β-hydroxy ketone (I) (Table). Among the reagents employed, $LiAlH_4$ and $LiAlH_4$-LiI gave moderate anti:syn ratios in an opposite stereochemical sense, respectively. Sterically hindered $LiAlH(O^tBu)_3$ which has single hydride source showed good selectivity; the presence of LiI in the reaction medium remarkably enhanced the syn-selectivity to the alkoxy group of dioxolane ring, giving the anti-diol (II) (run 9). The β-alkoxy-induced high syn-selectivity of $LiAlH(O^tBu)_3$-LiI reduction can be rationalized by considering β-chelation of lithium cation between the ketone and the alkoxy group of the terminal acetonide; the α-oriented hydroxy group was protected as an aluminum alkoxide and then the second hydride attacked from less hindered α-side to give the anti-product (II). These results prompted us to develop a general protocol for anti-1,3-polyol synthesis using the



I anti-II syn-II

Table 1,3-Asymmetric Reduction of the β-Alkoxy β′-hydroxy Ketone (I)

	hydride	solvent	temp(℃)	anti:syn[1]	yield(%)
1	$LiAlH_4$	Et_2O	0	44 : 56	93
2	$LiAlH_4$	Et_2O	-78	36 : 64	98
3	$LiAlH_4$-LiI	Et_2O	0	72 : 28	95
4	$LiAlH_4$-LiI	Et_2O	-78	70 : 30	97
5	$LiAlH(O^tBu)_3$	Et_2O	22	80 : 20	96
6	$LiAlH(O^tBu)_3$	Et_2O	0	78 : 22	94
7	$LiAlH(O^tBu)_3$	Et_2O	-78	90 : 10	94
8	$LiAlH(O^tBu)_3$-LiI	Et_2O	22	92 : 8	97
9	$LiAlH(O^tBu)_3$-LiI	Et_2O	0	95 : 5	96
10	$LiAlH(O^tBu)_3$-LiI	Et_2O	-78	94 : 6	98

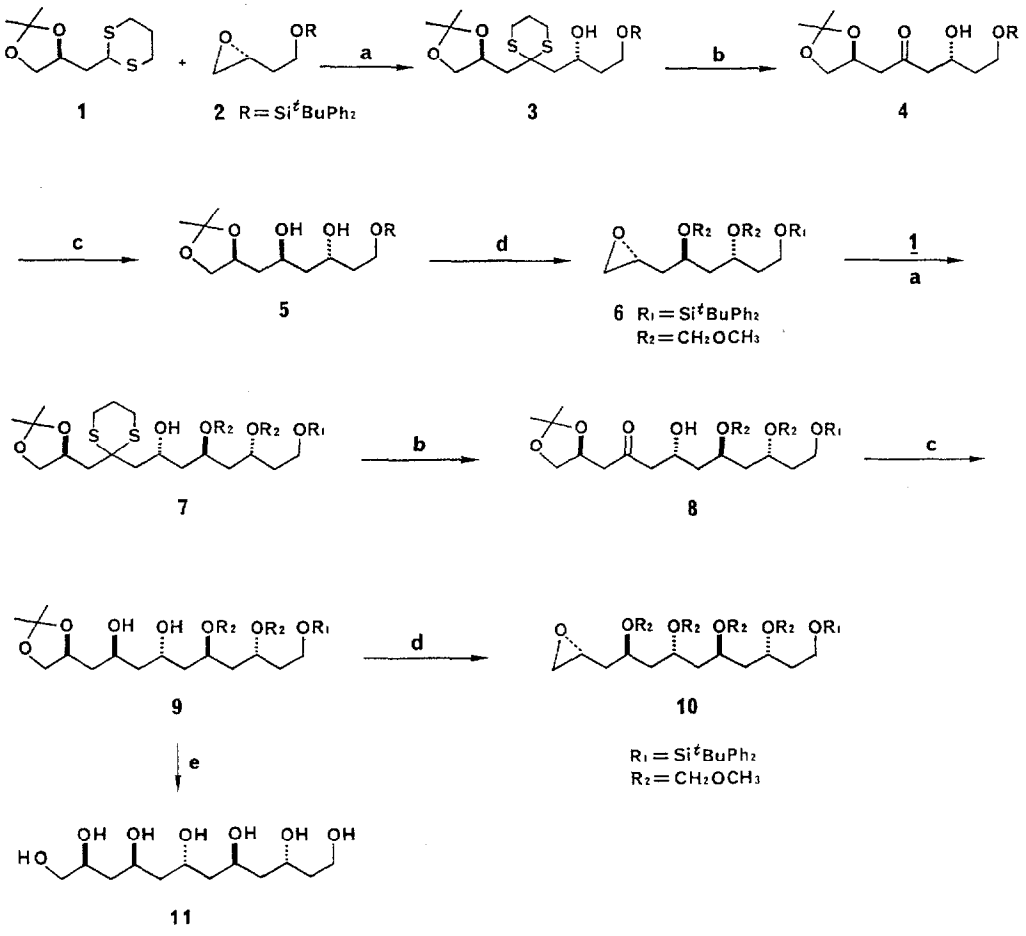
1) The anti:syn ratios were determined on the basis of the relative intensity of the acetonide methyl signals of two isomers by 400MHz ^{1}H-NMR (C_6D_6).

1,3-asymmetric reduction of $LiAlH(O^tBu)_3$-LiI as a key step.

Our synthesis started with the coupling reaction of the anion generated from the chiral dithiane (1) ($[\alpha]_D^{23}$ -9.05° ($CHCl_3$)) with the epoxide (2) ($[\alpha]_D^{25}$ +6.17° ($CHCl_3$)), both prepared from (S)-malic acid, to give the dithiane (3) ($[\alpha]_D^{24}$ -1.90° ($CHCl_3$)) in 93% yield. Deprotection of the dithioacetal group with MeI-$CaCO_3$ in aqueous acetonitrile yielded the β-hydroxy ketone (4), $[\alpha]_D^{24}$ -5.63° ($CHCl_3$), with anti-relationship of the alkoxy and hydroxy groups in 81% yield. The stereoselective reduction of 4 was accomplished using $LiAlH(O^tBu)_3$-LiI, giving the anti-diol (5), $[\alpha]_D^{25}$ -3.64° ($CHCl_3$), with excellent anti-selectivity (anti:syn=95:5). After protection of the anti-diol with methoxymethyl group the terminal acetonide group was converted to the epoxide (6), $[\alpha]_D^{24}$ -3.87° ($CHCl_3$), in 77% overall yield by routine synthetic operations; i) CH_3OCH_2Cl, ^{i}Pr$_2$EtN, ii) pyridinium p-toluenesulfonate, MeOH, iii) pivaloyl chloride, pyridine, iv) methanesulfonyl chloride, Et_3N, v) MeOK, MeOH.

The stage was set to prepare higher homologs of anti-1,3-polyols. Second coupling of the dithiane (1) and the epoxide (6) afforded the alcohol (7), $[\alpha]_D^{24}$ +3.13° ($CHCl_3$), (90% yield), which was transformed to the β-hydroxy ketone (8) ($[\alpha]_D^{24}$ +4.51° ($CHCl_3$)) in 90% yield. In the present synthesis the hydroxy groups on the chain were protected as methoxymethyl ethers, which offer many chelating sites with lithium cation and have possibility to affect the selectivity of 1,3-asymmetric reduction of a longer polyol chain. So we examined the effectiveness of the second reduction. The β-alkoxy-induced syn-stereoselective reduction (95%) was again achieved by $LiAlH(O^tBu)_3$-LiI in ether at -78℃ to give the anti-diol (9), $[\alpha]_D^{24}$ +6.82° ($CHCl_3$). The selectivity of the second reduction was anti:syn =96:4. Reduction of 8 at 0℃ decreased the anti:syn ratio to 89:11. The anti-diol (9) was converted to the epoxide (10), $[\alpha]_D^{25}$ -1.24° ($CHCl_3$) in 68%

overall yield by the reaction step d, and 10, in principle, could be homologated to higher members of anti-1,3-polyols. Finally the sequence was terminated by the acid treatment of 9 to give the heptol 11, $[\alpha]_D^{24}$ -6.58° (MeOH), in 96% yield.



Reagents: (a) n-BuLi, THF, -20℃; (b) MeI, $CaCO_3$, 80% aqueous MeCN; (c) LiAlH(O^{t}Bu)$_3$, LiI, Et_2O, 0 or -78℃.; (d) (i) CH_3OCH_2Cl, $^i Pr_2EtN$, CH_2Cl_2, 0 ℃ (ii) PPTS, MeOH, 45 ℃, (iii) ^{t}BuCOCl, pyridine, 0 ℃, (iv) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0℃, (v) KH, MeOH-Et_2O(1:1), 0℃, (e) 1% HCl, MeOH.

The stereochemical assignments of the reduction products (5) and (9) were accomplished by chemical transformation. As an example, acid treatment (PPTS, MeOH) of 9 gave a tetrol derivative, which was converted to a 3:1 mixture of the acetate (12) by periodide oxidation followed by acetylation. Analysis of ^{1}H-NMR spectrum of the major isomer (12β) showed that the C-1 and C-3 acetoxy groups were equatorial (H_1, dd, J=10.0, 2.2Hz; H_3, tt, J=11.5, 4.9Hz); thus, the stereochemistry of the diol of 9 was established unequivocally to have anti-relationship.

In conclusion a general synthetic protocol for anti-1,3-polyols containing a 1,3-syn-3,5-anti-triol unit has been estabilshed by the route that is iterative and stereochemically controlled.

9 $R_1 = Si^tBuPh_2$, $R_2 = CH_2OCH_3$ **12**

General procedure for $LiAlH(O^tBu)_3$-LiI reduction: To a stirred solution of a β-alkoxy ketone (1 mmol) in dry ether (35 ml) at room temperature was added LiI (5 mmol). The mixture was stirred at -78℃ for 5 min under nitrogen and then $LiAlH(O^tBu)_3$ (5 mmol) was added. The reaction mixture was stirred for 1h at the temperature and worked up in usual manner to give products. The anti and syn isomers were separated by flash chromatography on silica gel beads (30-50 μm).

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(Received in Japan 7 June 1989)