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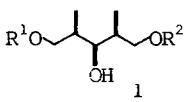
STEREOCONTROLLED SYNTHESIS OF CHIRAL SYNTHONS FOR POLYKETIDE-DERIVED NATURAL PRODUCTS

Yuji Oikawa,* Takao Nishi, Hiroyuki Itaya, and Osamu Yonemitsu
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Summary. Four chiral synthons having three consecutive asymmetric centers for the synthesis of macrolide and polyether antibiotics were synthesized form D-glucose via stereoselective hydroboration.

In connection with a project on the stereocontrolled synthesis of polyketide-derived natural products such as macrolide and polyether antibiotics from D-glucose as a chiral starting material, we required the appropriately protected four possible diastereomers, 1∿4, which are chiral synthons for many natural product syntheses. Selective deprotection of R^1 and R^2 in 1 will give enantiomeric primary alcohols, 5a and 5b, respectively. Similarly 2 can give an enantiomeric pair of primary alcohols.[1)]

There are some precedents for the synthesis of such chiral synthons. Kishi et al.[3)] reported an elegant synthesis of three consecutive asymmetric units corresponding to the antipodes of 1∿4 by Sharpless asymmetric epoxidation[4)] and MCPBA epoxidation followed by regioselective dimethylcuprate reaction of the epoxides. Lukacs et al.[5)] synthesized eight optically active diastereomers having four asymmetric centers from structurally related hexopyranosides, but a disadvantage of this method is the low stereoselectivity.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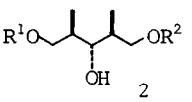
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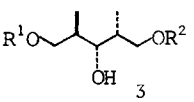
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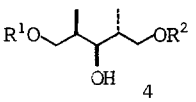
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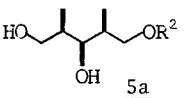
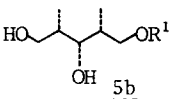
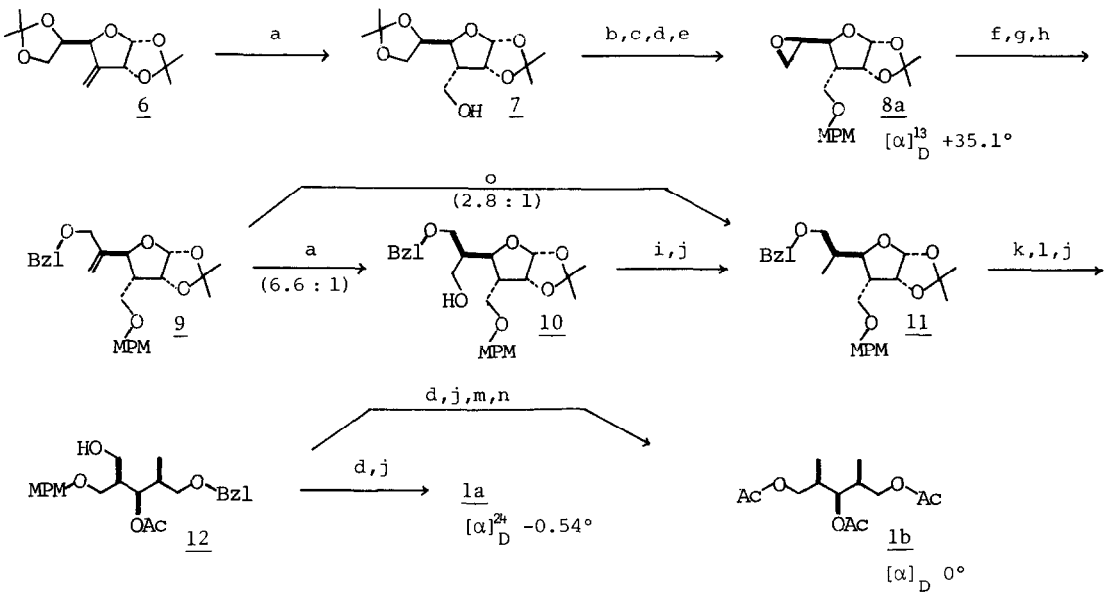

5a


5b

We report here a general and alternative stereoselective method for the conversion of 1,2:5,6-di-O-isopropylidene-3-C-methylene-α-D-ribo-hexofuranose (6), derived quite readily from D-glucose,[6)] to optically active four diastereomers, 1∿4, in which the two primary hydroxy groups are suitably differentiated from each other by the protection with different groups, R^1 and R^2. Primary alcohols selectively deprotected either R^1 and R^2 can be used for further elongation of the carbon chains at the respective side. A new protective group, MPM (p-methoxyphenylmethyl)[7)] other than usual BDMS (t-butyldimethylsilyl) and Bzl (benzyl) groups is shosen as R, and the MPM protection can be selectively removed by treatment with DDQ under the conditions not affecting



a: BH_3/THF, b: NaH/MPMCl, c: 2%H_2SO_4, d: TsCl/Py, e: K_2CO_3/MeOH, f: BzlONa/DMSO, g: PCC, h: $Ph_3P{=}CH_2$, i: TsCl/Et_3N, j: $LiAlH_4$, k: 4N-HCl/THF, l: $Pb(OAc)_4$, m: Na/liq.NH_3, n: Ac_2O, o: H_2/Rh-Al_2O_3

Scheme 1

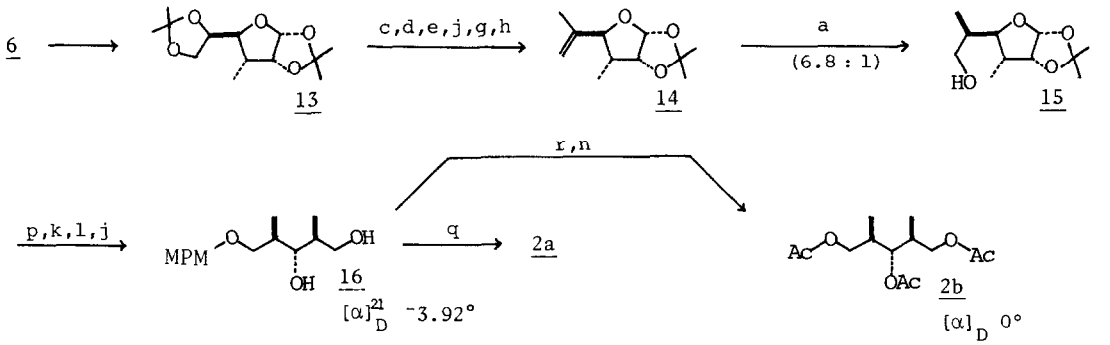
all of other usual protective groups.[7]

Compound 7[8] derived from 6[6] by hydroboration was treated with MPMCl[7] (p-methoxyphenylmethyl chloride)[7] to protect the primary hydroxy group followed by selective hydrolysis of the 5,6-isopropylidene group to give a diol, which was monotosylated and then converted to the epoxide (8a; 60%) in the usual way. Successive treatments of 8a with sodium benzyloxide, PCC (pyridinium chlorochromate), and then methylenetriphenylphosphorane afforded the olefin (9; 31%).

Hydroboration of 9 gave the expected alcohol (10; 67%) as a main product in the ratio of 6.6 : 1 with the stereoisomeric alcohol.[9] The alcohol (10) without purification was tosylated, followed by reduction with LAH (lithium aluminium hydride) to afford 11 (61%), which was also obtained more conveniently from 9 in quantitative yield by the direct catalytic hydrogenation over rhodium-alumina, though the stereoselectivity (2.8 : 1) was unsatisfactory. Three step conversion of 11, acid hydrolysis, lead tetraacetate oxidation, and LAH reduction, gave a crude diol (12), which was purified by silica-gel chromatography (45%). The primary alcohol of 12 was tosylated and then reduced with LAH to give a colorless oil of 1a (74%; R^1= MPM, R^2= Bzl).

The following sequence of reactions starting from 12, tosylation, LAH reduction, sodium-ammonia reduction, and acetylation, provided the meso-triacetate (1b; 55%) (Table). The structures of 1a and 1b were unequivocally determined by the correlation with the degradation products of erythronolide A corresponding to the C-1∿C-5 fragment of its seco acid.[10]

Compound 13[6] derived from 6 was converted to the olefin (14) in the sequence of reactions as shown in scheme 2. Hydroboration of 14 proceeded with 6.8 : 1 stereoselection to provide 15 (59%). Four step conversion from 15 afforded a colorless oil of 16 (64%) after purification through a



p: NaH/MPMCl, q: $Me_2(tBu)SiCl$, r: H_2/Pd-C

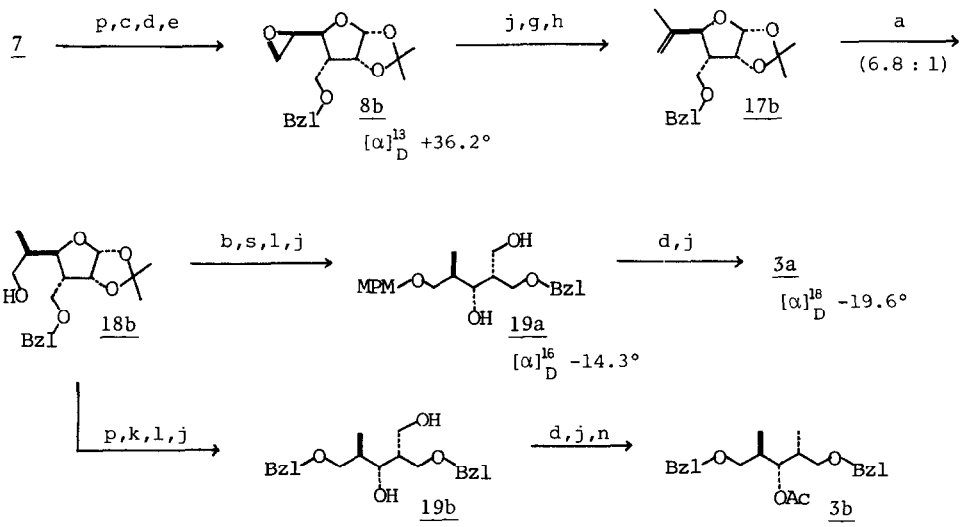
Scheme 2

Table. Chemical Shifts (ppm) in NMR Spectra

Compd	CH_3	CH-OAc
1b	0.96(6H,d)	5.04(1H,t)
16	0.96(3H,d), 0.99(3H,d)	
2b	1.01(6H,d)	4.92(1H,t)
3b	0.93(3H,d), 0.98(3H,d)	5.03(1H,dd)
1a	1.01, 1.03	
2a	0.94, 1.00	
3a	0.82, 0.92	
4	0.84, 0.92	

silica gel column. Treatment of 16 with t-butyldimethylsilyl chloride gave 2a (R^1= MPM; R^2 = t-Bu(Me)$_2$Si; 84%; colorless oil). In order to confirm the configuration of 2a, 16 was converted to the second meso-triacetate (2b; 93%) (Table).

Compound 7 was converted to the epoxide (8b; 68%) and then to the olefin (17b; 65%; mp 47∿49°C) in the multistep procedure (scheme 3). Hydroboration of 17b gave 18b (76%; 6.8 : 1 stereoselection), which was subjected to four successive reactions and then chromatographic

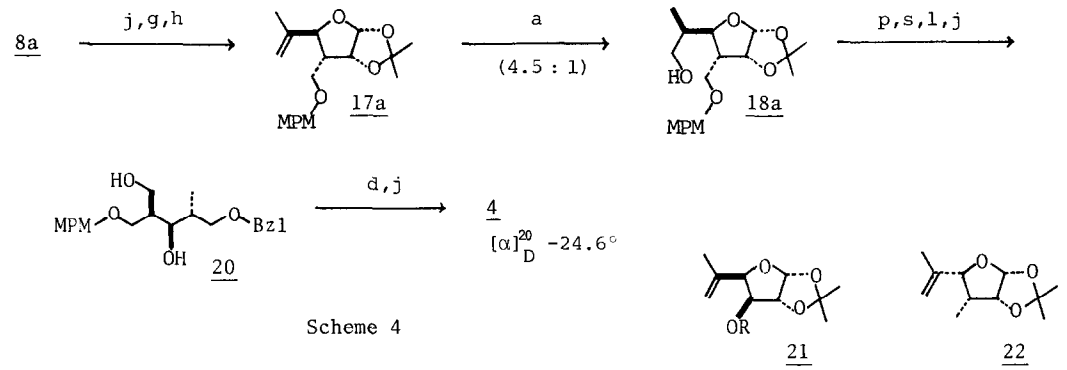


s: CF_3CO_2H/aq.THF

Scheme 3

purification to give 19a (31%). Reduction of the primary alcohol of 19a via a tosylate afforded 3a (R^1= MPM, R^2= Bzl; 69%; colorless oil). In order to confirm the structure of 3a, 18b was converted to the unsymmetrical dibenzylmonoacetate (3b) via 19b (Table).

In the same manner 8a was converted to the olefin (17a; 73%; mp 73∿74°C), which was hydroborated to give 18a (4.5 : 1 stereoselection). Several step conversion of 18a easily afforded 4 (R^1= MPM, R^2= Bzl; colorless oil) via 20.

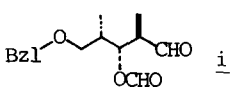


Scheme 4

Since almost no stereoselectivity was observed in the case of 21 and 22, it is difficult to explain unequivocally the stereoselectivity of the hydroborations presented here, though steric hinderance by the α-substituent at the 3-position is presumably responsible for it. Calculation seeking the most stable conformer of each starting material (9, 14, 17a, 17b) will give a solution.

REFERENCES AND NOTES

1) The primary alcohol deprotected R^1 in 3 is not antipodal with that deprotected R^2 in 4, but identical stereochemically. Antipodal compounds such as i have been synthesized with a good stereoselection of 24 : 1 in this laboratory.[2)]



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2) Y. Oikawa, unpublished results.

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4) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980); B. E. Rossiter, T. Katsuki, and K. B. Sharpless, ibid., 103, 464 (1981).

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7) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 23, 885 (1982).

8) A. Rosenthal and M. Sprinzl, Can. J. Chem., 47, 4477 (1969).

9) The ratio was determined by nmr spectroscopy.

10) Y. Oikawa and T. Nishi, unpublished results.

11) All $[\alpha]_D$ were measured in chloroform.

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