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A NEW TRANSFORMATION OF ALDOSE DERIVED SYNTHONS TO PSEUDO-HEXOPYRANOSE OR PSEUDO-PENTOFURANOSE DERIVATIVES

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The D-ribose or D-erythrose derived acyclic synthon, which possesses a 2-malonyl carbon chain at C-1 position, was cyclized stereoselectively to a six- or five-membered carbocycle. Those carbocycles were converted into pseudo-β-L-mannopyranose derivatives or pseudo-β-L-arabinofuranose derivatives efficeintly.

In the previous papers, we demonstrated the transformation of carbohydrate derived synthons to optically pure carbocyclic compounds (i.e. some pseudo-hexopyranoses[1,2] and methyl (-)-shikimate[3]). Although the carbon-carbon bond formation between both terminal carbons of the aldopentose derived acyclic synthons and malonate gave the desired six-membered carbocyclic compounds, an undesired side reaction (so-called *C*-glycosides formation) was accompanied in the previous approach.[1,3] From this point of view, a more sophisticated approach is still desirable. So, we investigated a cyclization reaction of carbohydrate derived synthons which equipped 2-malonyl carbon units at C-1 positions to avoid a formation of the undesired *C*-glycosides (a stepwise carbon-carbon bond formation approach). Along this idea, we could achieve an improved access of optically pure carbocycles from readily available carbohydrates. In this letter, we wish to describe syntheses of pseudo-β-L-mannopyranose derivatives (11-12) and hitherto unknown pseudo-β-L-arabinofuranose derivatives (23-25) from D-ribose and D-erythrose, respectively. A worthy to special mention is the new synthetic approach toward optically pure highly oxidized five-membered carbocycles developed in this work.[4]

D-Ribose diethyl dithioacetal (1), which was prepared according to the reported procedure,[5] was converted to 2,3,4-tri-O-benzyl-5-O-(*t*-butyldiphenylsilyl)-D-ribose diethyl dithioacetal (3)[6] *via* compound 2 in 55% overall yield [1) TrCl/DMAP/pyr., 2) BnBr/NaH/DMF, 3) TsOH/MeOH-AcOEt, and 4) *tert*-butyldiphenylchlorosilane/imidazole/DMF] (Fig.1). Dethioacetalization of 3 with mercury (II) chloride in aqueous acetonitrile gave an acyclic aldehyde (4) which was subjected to the next reaction directly. The condensation of 4 with dimethyl malonate was best done by stirring a solution of 4 in a mixture of pyridine and acetic anhydride (v/v, 2:1) in the presence of 10 molar equivalents of malonate at ambient temperature for 2 days. Under this mild condition, an

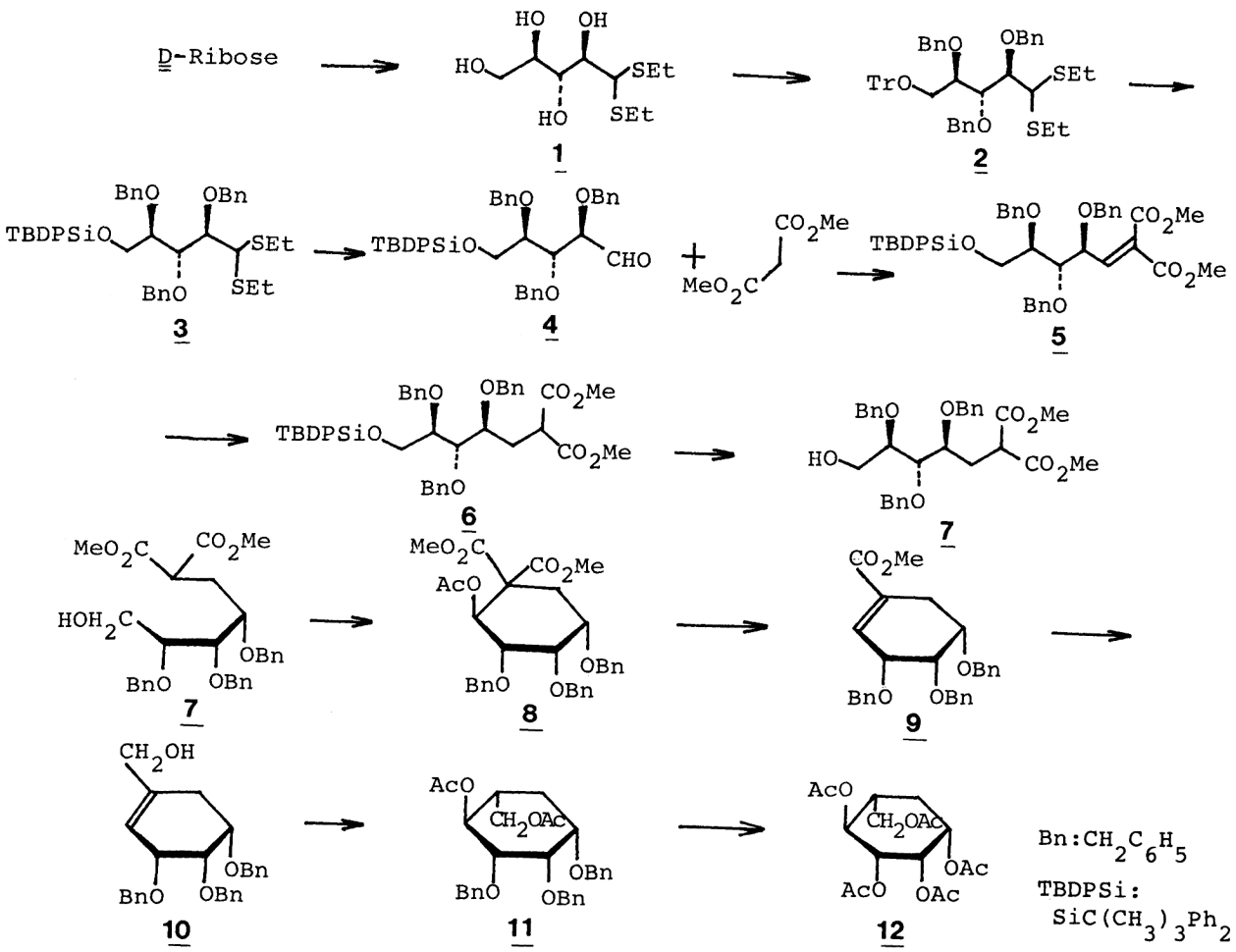
D-Ribose
1
2
3
4
5
6
7
7
8
9
10
11
12
Bn:CH2C6H5
TBDPSi:
SiC(CH3)3Ph2

Fig. 1.

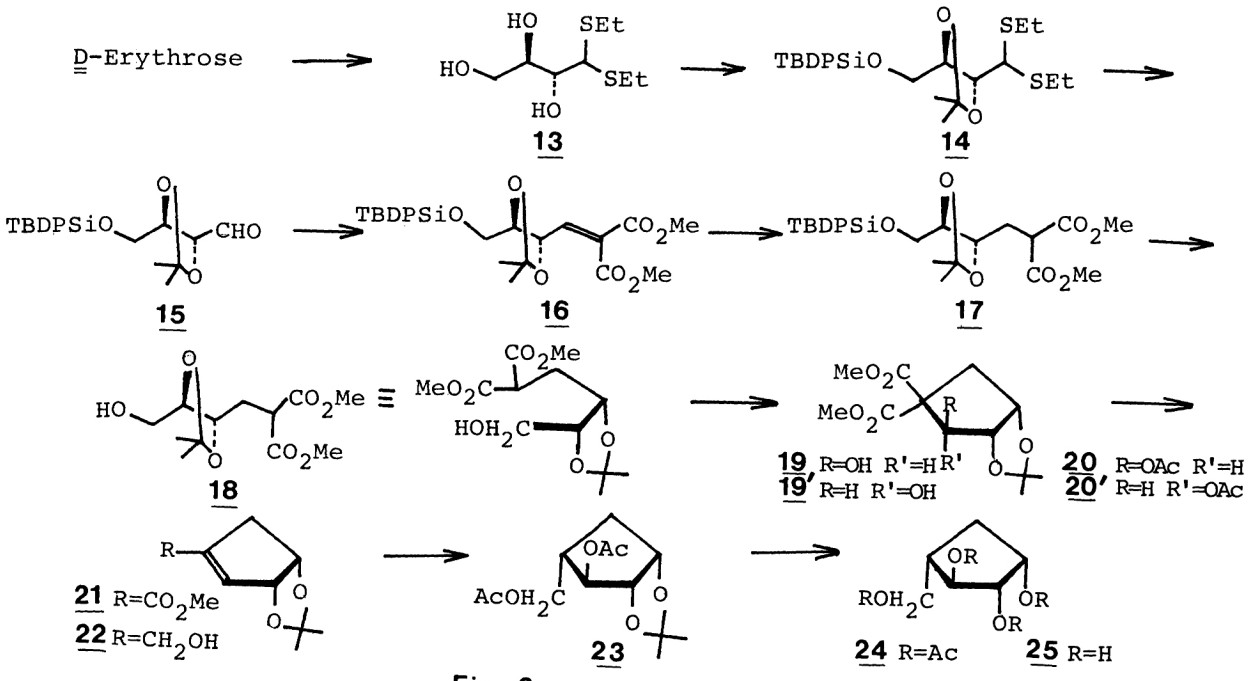
D-Erythrose
13
14
15
16
17
18
19, R=OH R'=H
19' R=H R'=OH
20, R=OAc R'=H
20' R=H R'=OAc
21 R=CO2Me
22 R=CH2OH
23
24 R=Ac
25 R=H

Fig. 2.

α,β-unsaturated diester (5) was obtained in 85% yield. In the absence of acetic anhydride, a hydroxy adduct was detected in the reaction mixture. However, isolation of the hydroxy adduct was difficult for a retro-aldol reaction of the adduct to compound 4. Hydrogenation of 5 in the presence of Raney nickel [5 to 6], and successive O-desilylation of 6 with tetrabutylammonium fluoride gave a synthon (7)[6] in a fairly good yield (48% overall yield from 3 in a 5 g scale experiment). Oxidation of 7 with PCC in dry CH_2Cl_2 for conversion of the hydroxyl group to an aldehyde group, and passing the reaction mixture through SiO_2 column, furnished a 1:1 inseparable mixture of the aldehyde compound and a cyclized compound. Acetylation of the mixture with acetic anhydride in pyridine gave a diastereomerically pure cyclohexane derivative (8)[6] in 69% yield. Under the acetylation condition, the aldehyde compound was smoothly cyclized and then acetylated to afford 8. On the ^1H NMR spectrum of 8, a proton on carbon bearing acetoxyl group appeared at δ 5.77 as a doublet with J=10.5 Hz. This fact leads a conclusion that the acetoxyl group is oriented equatorially in a stable *1C* conformation. Thermal decarbomethoxylation of 8 in aqueous DMSO in the presence of NaCl (110-170 °C) accompanied with β-elimination gave the unsaturated ester (9)[6] in 70% yield. Reduction of 9 with $LiAlH_4$ in THF (-15 °C) afforded the allyl alcohol (10)[6] in 88% yield. Hydroboration of 10 with BH_3-THF at ambient temperature, successive oxidative treatment (aq. NaOH/35% H_2O_2), and acetylation gave a derivative of pseudo-β-L-mannopyranose (11)[6] in 66% yield. No other stereoisomer was detected, so the hydroboration proceeded stereoselectively from the less hindered opposite side to three benzyloxy groups. Compound 11 was O-debenzylated by hydrogenolysis (Pd-black), then fully acetylated to afford the pentaacetate (12)[6] in 57% yield. The ^1H NMR spectrum of 12 coincided with that of the known DL-12.[7] The optical rotation value of 12 [$[\alpha]_D$-1.1°(*c* 1.1, $CHCl_3$)] matched with that of the known D-12[8] [$[\alpha]_D$+2.9°(*c* 1.28, $CHCl_3$)].

Next our attempt was turned to a construction of the five-membered carbocyclic compound by the cyclization of a D-erythrose derived acyclic compound (18) as a key reaction (Fig.2). 4,6-O-Ethylidene-D-glucose was converted to D-erythrose diethyl dithioacetal (13) according to the reported procedure.[9] The primary hydroxyl group in 13 was selectively protected as a *tert*-butyldiphenylsilyl ether, then the secondary hydroxyl groups were isopropylidenated (2,2-dimethoxypropane, acetone, TsOH) to give a fully protected compound (14)[6] in 68% yield. Compound 14 was converted to a carbon extended synthon 18,[6] *via* compounds 15 ,[6] 16 ,[6] and 17 ,[6] in 54% overall yield by the analogous reaction conditions as described in preparation of 7 from 3.[10] PCC oxidation of compound 18 followed by acetylation gave an inseparable diastereomers mixture of cyclopentane derivatives (20 and 20') in 71% combined yield. The ratio of 20 and 20' was estimated to be approximately 4 to 1 based on the ratio of the cyclized compounds (19 [6] and 19')[6] which were cleanly separated by SiO_2 chromatography of the oxidation mixture in a small scale. Acetylation of pure 19 and 19' gave 20[6] and 20'.[6] The stereochemistries of the acetoxyl groups in 20 and 20' were established as depicted based on their ^1H NMR. Thermal decarbomethoxylation of the mixture, 20 and 20', gave an α,β-unsaturated diester (21),[6] and DIBAL-H reduction of 21 (-78 °C) afforded the allyl alcohol (22)[6] in 61% overall yield.

Hydroboration of compound 22 with BH_3-THF, oxidative treatment (aq. NaOH/35% H_2O_2), and acetylation of the product gave compound 23 [6] in 70% yield. On the ^1H NMR spectrum of 23, a methine proton on carbon bearing the secondary acetoxyl group appeared at δ 5.07 as a double-doublet with J=2 Hz and 1 Hz. This fact leads that the secondary acetoxyl group is *trans* (*S*-configuration) to the O-isopropylidene group and the acetoxymethyl group. Therefore, the hydroboration proceeded stereoselectively from the less hindered side. Deblocking of the hydroboration product (90% acetic acid, reflux) followed by acetylation afforded compound 24 [6] in 64% overall yield from 22. O-Deacetylation of 24 (CH_3ONa) gave pseudo-β-L-arabinofuranose, [(1*S*,2*S*,3*S*,4*S*)-1,2,3-trihydroxy-4-hydroxymethyl-cyclopentane] (25),[6] in 97% yield.

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4) Some recent works on carbohydrate-mediated synthetic approaches toward cyclopentanoids: 1) M-I. Lim and V. E. Marquez, *Tetrahedron Lett.*, 1983, 4054; 2) R. J. Ferrier and P. Prasit, *Pure and Appl. Chem.*, 55, 565 (1983); 3) S. Achab, J-P. Cosson, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1984, 1040; 4) C. S. Wilcox and L. M. Thomasco, *J. Org. Chem.*, 50, 546 (1985).
5) G. W. Kenner, H. J. Rodda, and A. R. Todd, *J. Chem. Soc.*, 1949, 1613.
6) All new compounds were fully characterized by the IR, ^1H NMR, and mass spectra, and gave satisfactory elemental analyses and/or high resolution mass spectra. The physical [$CHCl_3$ for [α]] and spectral data ($CDCl_3$ for ^1H NMR) of the selected compounds are as follows. 5: $[\alpha]_D^{29}$-5.6° (*c* 0.78), 6: $[\alpha]_D^{29}$-27.6° (*c* 1.08), 7: $[\alpha]_D^{29}$-7.2° (*c* 1.00), 8: mp 134-137 °C; ^1H NMR δ 1.92 (3H), 2.20-2.73 (2H, m), 3.64 (6H), 5.77 (1H, d, J=12 Hz), 9: $[\alpha]_D^{29}$ -53.3° (*c* 1.11), 10: $[\alpha]_D^{28}$-49.8° (*c* 1.23), 11: $[\alpha]_D^{16}$+6.3° (*c* 1.08), 14: $[\alpha]_D^{26}$-12.7° (*c* 1.35), 16: $[\alpha]_D^{26}$+18.5° (*c* 0.94), 18: $[\alpha]_D^{27}$-5.2° (*c* 1.07), 19: mp 94.5-96 °C; $[\alpha]_D^{27}$-15.4° (*c* 1.31), 19': mp 90.5-92 °C; $[\alpha]_D^{21}$+39.9° (*c* 1.57), 20: $[\alpha]_D^{28}$-36.8° (*c* 1.12); ^1H NMR δ 1.24, 1.36 (3Hx2), 2.01 (3H), 3.67, 3.77 (3Hx2), 5.85 (1H, s), 20': mp 74.5-75.5 °C; $[\alpha]_D^{19}$+105.8° (*c* 1.44), 22: $[\alpha]_D^{21}$-16.9° (*c* 1.09), 23: $[\alpha]_D^{14}$+5.6° (*c* 0.64), 24: $[\alpha]_D^{23}$+4.1° (*c* 1.07), 25: mp 103-104 °C; $[\alpha]_D^{14}$-19.2° (*c* 1.00, MeOH).
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9) C. E. Ballou, H. O. L. Fischer, and D. L. MacDonald, *J. Am. Chem. Soc.*, 77, 5967 (1955).
10) Hydrogenation of 16 was rather slow. Sodium borohydride treatment of 16, however, gave compound 17 more efficiently in a 1,4-hydride addition fashion.

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