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INTRODUCTION OF *gem*-DIALKYL GROUP TO HEXOFURANOSE BY ORTHO ESTER CLAISEN REARRANGEMENT

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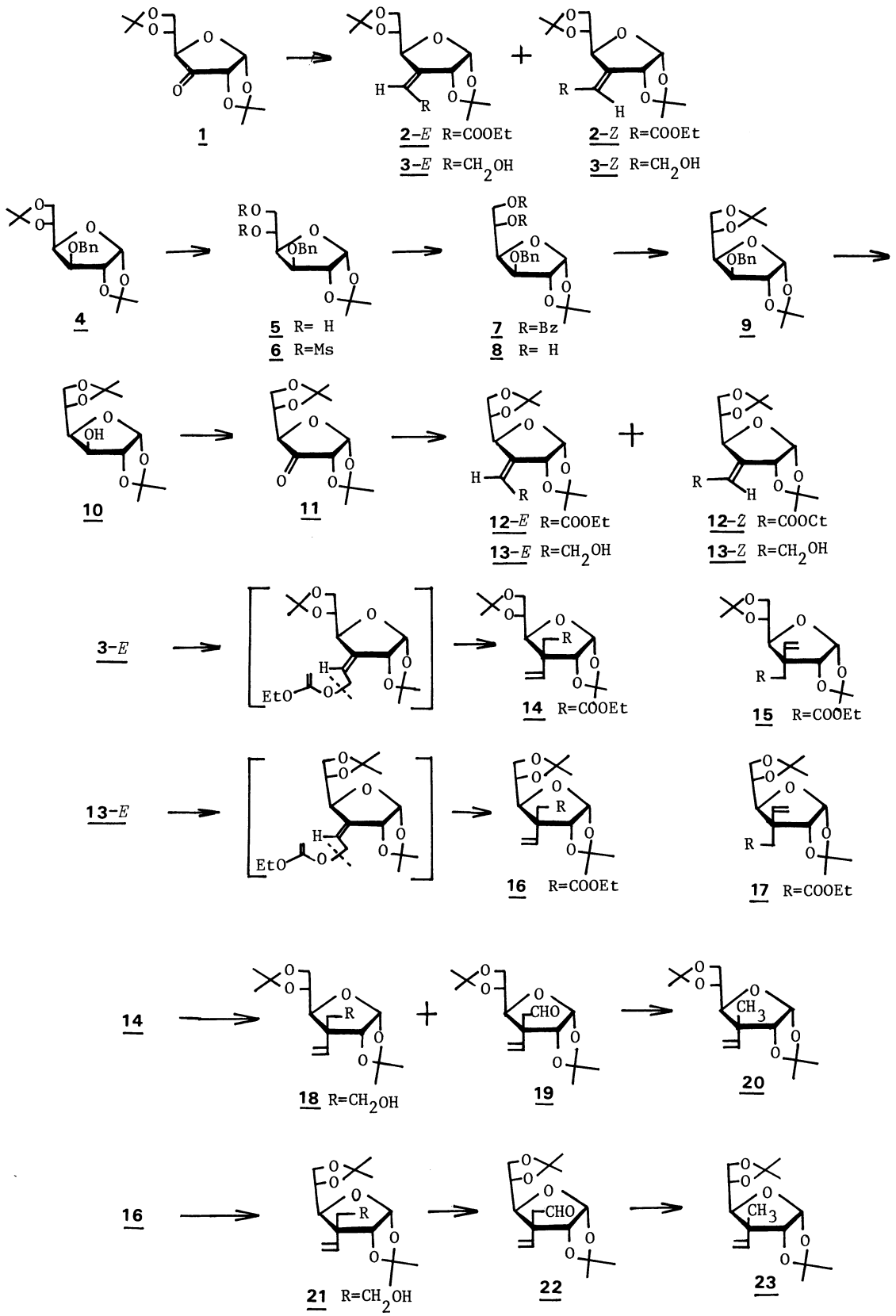
The ortho ester Claisen rearrangement of D-*ribo*- or L-*lyxo*-hexofuranose derivative which possesses an allyl alcohol functionality on C-3, proceeds stereoselectively to give a 3-C-dialkylated product. The stereochemistry of a newly introduced quaternary center of the product was unambiguously established by a chemical modification.

Construction of quaternary center(s) on the carbon framework is a challenging subject in the chemical synthesis of natural products, and several sophisticated approaches have been developed.[1] The usage of the ortho ester Claisen rearrangement for this purpose is one of the most promissing approaches,[2] however, it has never been well explored so far in the carbohydrate field. We wish to describe herein a successful construction of the quaternary center by the ortho ester Claisen rearrangement of (*E*)-3-deoxy-3-C-(hydroxymethyl)methylene-1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranose (3-*E*) and (*E*)-3-deoxy-3-C-(hydroxymethyl)methylene-1,2:5,6-di-O-isopropylidene-β-L-*lyxo*-hexofuranose (13-*E*).[3]

Wittig olefination of 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) with ethoxycarbonylmethylenetriphenylphosphorane afforded a mixture of 3-C-(ethoxycarbonyl)methylene derivatives, (2-*E*) and (2-*Z*), which was separable by silica gel chromatography in 60 and 22% yield, respectively.[4] Treatment of 2-*E* or 2-*Z* with diisobutylaluminium hydride (Dibal-H) in dichloromethane (-30 °C) gave 3-*E*[5] (86% yield) or (3-*Z*)[5] (92% yield).

Mesylation of known 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose[6] (5) gave the 5,6-di-O-mesyl derivative (6). Nucleophilic displacement of 6 with sodium benzoate, followed by deacylation afforded 3-O-benzyl-1,2-O-isopropylidene-β-L-idofuranose[5] (8) in 41% yield from 5. O-Isopropylidenation of 8 with 2,2-dimethoxypropane in the presence of camphorsulfonic acid gave the 1,2:5,6-di-O-isopropylidene derivative (9). Catalytic debenzylation of 9 in ethanol in the presence of Raney nickel afforded 1,2:5,6-di-O-isopropylidene-β-L-idofuranose[5] (10) in 71% yield from 8. Pyridinium chlorochromate (PCC) oxidation of 10 gave the 3-ulose[5] (11) in 95% yield. Wittig olefination of 11 followed by treatment with Dibal-H as described in the preparation of 3-*E* and 3-*Z* from 1 gave 13-*E*[5] and (13-*Z*)[5] in 65% (12-*E*, 75%) and 16% (12-*Z*, 18%) yield, respectively.

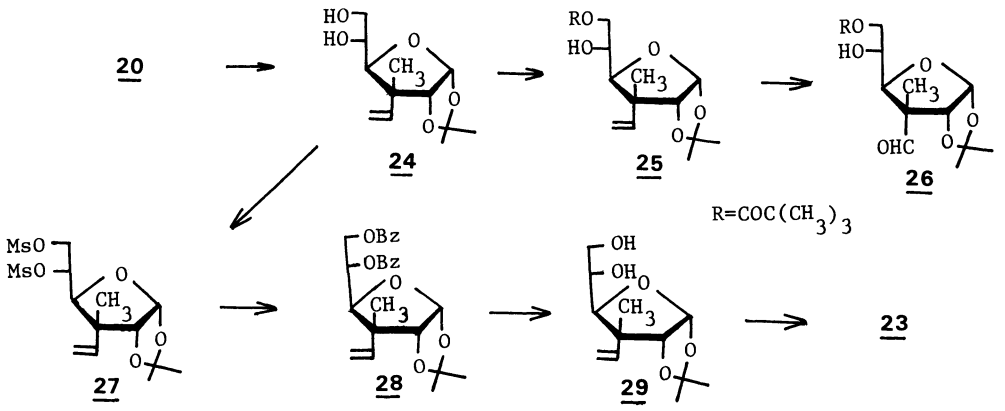
The ortho ester Claisen rearrangement took place by heating 3-*E* in triethyl-


1
2-E R=COOEt
3-E R=CH2OH
2-Z R=COOEt
3-Z R=CH2OH
4
5 R= H
6 R=Ms
7 R=Bz
8 R= H
9
10
11
12-E R=COOEt
13-E R=CH2OH
12-Z R=COOCt
13-Z R=CH2OH
3-E
14 R=COOEt
15 R=COOEt
13-E
16 R=COOEt
17 R=COOEt
14
18 R=CH2OH
19
20
16
21 R=CH2OH
22
23

orthoacetate (1.45 mmol/mL) in the presence of a catalytic amount of propionic acid at 135 °C under removal of ethanol[7] formed to give 3-deoxy-3-C-(ethoxycarbonyl)-methyl-1,2:5,6-di-O-isopropylidene-3-C-vinyl-α-D-allofuranose[5,8] (14) as a sole product in a fairly good yield (64%, 84% based on the consumed 3-*E*). Under analogous conditions, the ortho ester Claisen rearrangement of 13-*E* proceeded smoothly to afford 3-deoxy-3-C-(ethoxycarbonyl)methyl-1,2:5,6-di-O-isopropylidene-3-C-vinyl-β-L-talofuranose[5,8] (16) in 55% yield (79% yield based on the compound 13-*E*). Besides, 3-*Z* underwent the ortho ester Claisen rearrangement slowly and gave a mixture of 14 and the 3-epimer (15) (approximately 3:2 ratio based on ^{1}H NMR) in 16% yield. Also, 13-*Z* gave a mixture of 16 and its 3-epimer (17) (approximately 3:1 ratio) in 6% yield (79% of 13-*Z* was recovered). In the cases of 3-*Z* and 13-*Z*, the steric hindrance of the 5,6-O-isopropylidene groups seems to be unexpectedly large in the transition state of the rearrangement.

The stereochemistry of the newly introduced quaternary center (C-3) in 14 has been established as follows. Compound 14 was first converted to 3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-3-C-vinyl-α-D-allofuranose[5,8] (20) in 71% overall yield by the known procedure,[9] [1) Dibal-H reduction to a mixture of (18)[5] and (19), 2) PCC oxidation to 19,[5] and 3) thermal decarbonylation by refluxing in benzonitrile in the presence of 10% palladium on charcoal]. Similarly, 16 was converted to 3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-3-C-vinyl-β-L-talofuranose[5,8] (23) *via* compounds (21)[5] and (22)[5] in 40% overall yield. Hydrolysis of 20 in 50% aqueous acetic acid gave the 5,6-O-deisopropylidene derivative (24)[5] in 93% yield. The primary hydroxyl group in 24 was selectively protected as the trimethylacetyl ester (25)[5] in 83% yield. Ozonolysis of 25 and successive treatment with triphenylphosphine afforded 3-deoxy-3-C-formyl-1,2-O-isopropylidene-3-C-methyl-6-O-trimethylacetyl-α-D-allofuranose[5,8] (26) in 91% yield. The fact that no lactol formation was occurred between the 3-C-formyl group and the 5-hydroxyl group in 26 clarified the stereochemistry at C-3 as depicted, and therefore the structure of 14 was established undoubtedly.[10]

On the other hand, 24 was converted to 3-deoxy-1,2-O-isopropylidene-3-C-methyl-3-C-vinyl-β-L-talofuranose[5,8] (29) *via* compounds (27)[5] and (28)[5] by the analogous reaction sequence from 5 to 8 in 71% overall yield. O-Isopropylidenation of 29 afforded 23, which was identical with the compound derived from 16 in all respects, and the stereochemistry of the quaternary center of 16 was



established.

The carbon-carbon bond formation in the ortho ester Claisen rearrangement of 3-*E* and 13-*E* occurred stereoselectively from the upper side of the furanose ring (β-attack), and the configuration of the 1,2-O-isopropylidene group seems to be a stereocontrolling factor.

References

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5) All the new compounds were characterized by IR, ^{1}H NMR and mass spectra, and gave satisfactory high resolution mass spectral data. The physical and spectral data for the selected compounds are as follows. 14: $[\alpha]_D^{28}$+18.9° (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7.5 Hz), 1.38 (6H, s), 1.43, 1.58 (3Hx2, each s), 2.60 (2H, ABq, J=15 Hz), 3.91-4.26 (4H, m), 4.19 (2H, q, J=4.5 Hz), 5.08 (1H, d, J=4.5 Hz), 5.18-5.48 (2H, m), 5.82 (1H, d, J=4.5 Hz), 6.13 (1H, dd, J=11 and 18.5 Hz); high resolution mass spectrum, calcd for $C_{18}H_{29}O_7$: *m/z* 357.1910, found: M+H, 357.1900. 16: $[\alpha]_D^{26}$+20.1° (*c* 1.45, $CHCl_3$); ^{1}H NMR δ 1.25 (3H, t, J=7.5 Hz), 1.31, 1.35, 1.39, 1.51 (3Hx4, each s), 2.57 (2H, ABq, J=15.5 Hz), 3.74 (1H, q, J=8.5 Hz), 3.88-4.31 (3H, m), 4.13 (2H, q, J=7.5 Hz), 4.97 (1H, d, J=4 Hz), 5.09-5.40 (2H, m), 5.89 (1H, d, J=4 Hz), 6.07 (1H, dd, J=10.5 and 18 Hz); high resolution mass spectrum, calcd for $C_{18}H_{28}O_7$: *m/z* 356.1833, found: M, 356.1809. 20: $[\alpha]_D^{26}$+67.5° (*c* 1.28, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, s), 1.29 (6H, s), 1.37, 1.52 (3Hx2, each s), 3.88-4.10 (4H, br s), 4.14 (1H, d, J=4.5 Hz), 5.06-5.38 (2H, m), 5.76 (1H, d, J=4.5 Hz), 6.04 (1H, dd, J=10.5 and 18 Hz). 23: mp 87-88.5 °C; $[\alpha]_D^{26}$ +54.8° (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.30, 1.35, 1.40, 1.55 (3Hx4, each s), 3.38-3.64, 3.72-4.20 (4H, m), 4.10 (1H, d, J=4 Hz), 5.04-5.38 (2H, m), 5.87 (1H, d, J=4 Hz), 6.06 (1H, dd, J=11 and 18 Hz). 26: $[\alpha]_D^{24}$+80.8° (*c* 1.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, s), 1.27 (6H, s), 1.30, 1.55 (3Hx2, each s), 2.65-3.04 (1H, br s), 3.68-3.95 (1H, m), 4.08 (3H, m), 4.50 (1H, d, J=4 Hz), 5.88 (1H, d, J=4 Hz), 9.75 (1H, s).
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10) For the lactol formation of the analogous quaternized carbohydrate models, see Ref. 3b.

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