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A NOVEL SYNTHESIS OF PSEUDO-α-L-ALTROPYRANOSE FROM D-GLUCOSE

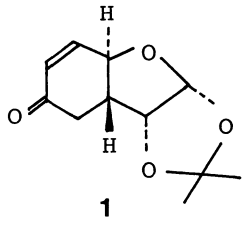
Tetsuo SUAMI,* Kin-ichi TADANO, Yoshihide UENO, and Chiyoko FUKABORI

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223

(1*R*,6*R*,8*R*,9*R*)-8,9-Isopropylidenedioxy-3-oxo-7-oxabicyclo[4.3.0]-non-4-ene, a highly functionalized bicyclic compound, has been synthesized from D-glucose employing an intramolecular aldol condensation as the key reaction, and a transformation of it into pseudo-α-L-altropyranose was achieved efficiently.

As reported in previous papers, two pseudo-sugars, namely, pseudo-α-D-glucopyranose and pseudo-β-L-altropyranose,[1] and methyl (-)-shikimate[2] have been synthesized employing L-arabinose or D-lyxose as a starting chiral material. As part of a chiral synthesis of carbocyclic compounds, we described herein a synthesis of (1*R*,6*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-3-oxo-7-oxabicyclo[4.3.0]non-4-ene (1) starting from 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (2). Compound 1 seems to be an important intermediate for a synthesis of optically active carbocyclic compounds, such as pseudo-hexopyranoses and pseuo-heptopyranoses. In fact, the utility was embodied in a synthesis of pseudo-α-L-altropyranose (17).

Wittig olefination of 2 with acetylmethylenetriphenylphosphorane gave the known 3-C-acetylmethylene-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranose (3) as a mixture of (*E*)- and (*Z*)-isomers in 96% yield.[3] Catalytic hydrogenation of 3 in the presence of Raney nickel and successive oxidation[4] with pyridinium chlorochromate (PCC) afforded 3-C-acetylmethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (4)[5] in 88% yield. The ^{1}H NMR spectrum of 4 (90 MHz, $CDCl_3$) revealed a triplet at δ 4.77 (1H, $J_{1,2}=J_{2,3}=4.5$ Hz), which was attributed to H-2 with a *cis* configuration with respect to H-2 and H-3 establishing the D-allo configuration.[6] Selective hydrolysis of the 5,6-O-isopropylidene group of 4 in 60% aqueous acetic acid at ambient temperature gave the compound (5)[5] in 95% yield. Glycol cleavage of 5 with sodium periodate in aqueous methanol gave the aldehyde (6)[5] in a quantitative yield. The crucial intramolecular aldol condensation of 6 was investigated under basic or acidic conditions.[7] When 6 was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry benzene under reflux for 35 h, and



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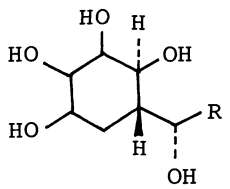
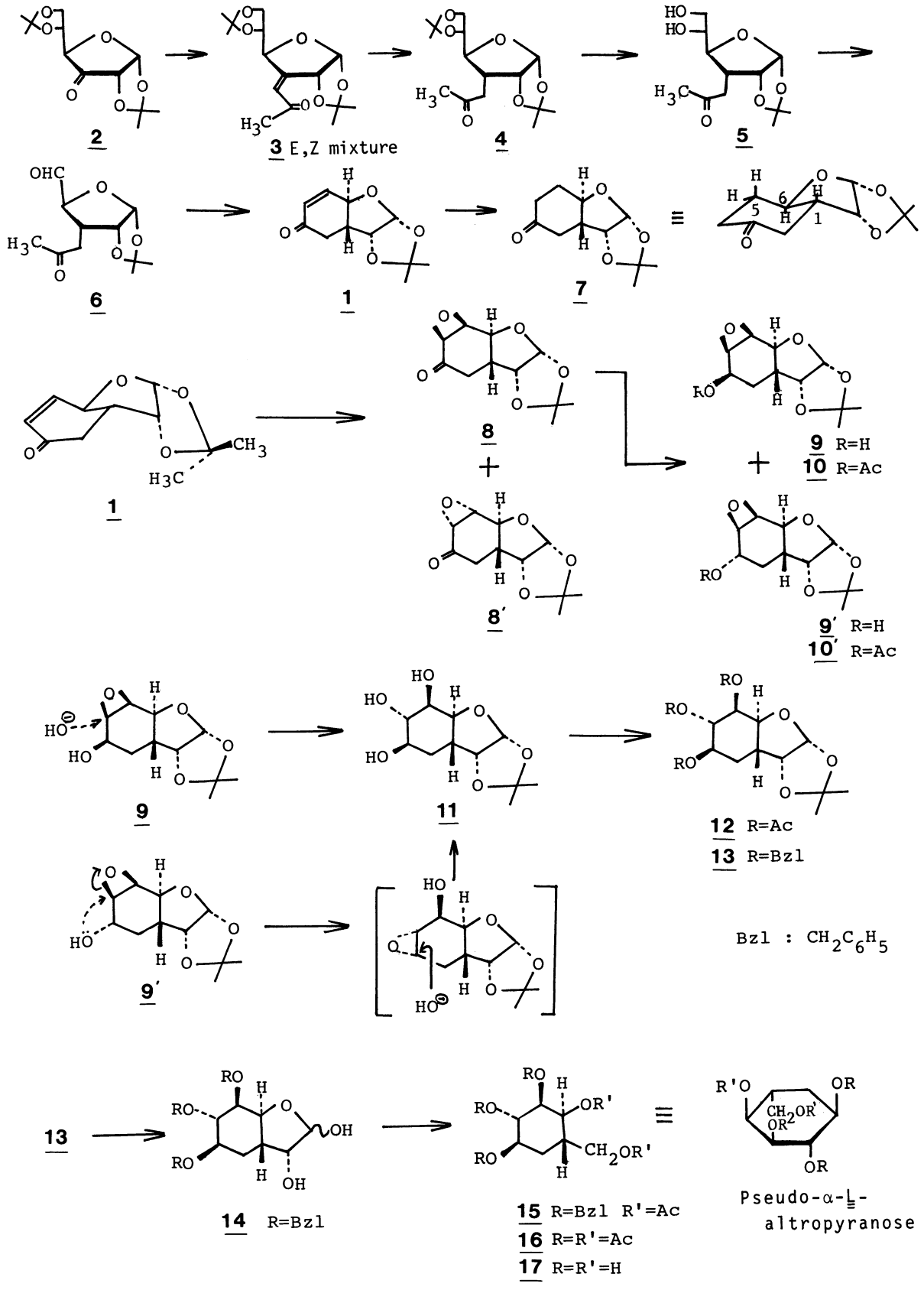


R=H Pseudo-hexopyranose

R=CH_2OH Pseudo-heptopyranose


2
3 E,Z mixture
4
5
6
1
7
8
8'
9 R=H
10 R=Ac
9' R=H
10' R=Ac
11
12 R=Ac
13 R=Bzl
Bzl : $CH_2C_6H_5$
14 R=Bzl
15 R=Bzl R'=Ac
16 R=R'=Ac
17 R=R'=H
Pseudo-α-L-altropyranose

then successively treated with acetic anhydride in pyridine, the desired compound 1[5] was obtained in 44% yield as crystals.

Catalytic hydrogenation of 1 in the presence of Raney nickel in ethanol and successive PCC oxidation[4] afforded (1*R*,6*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-3-oxo-7-oxabicyclo[4.3.0]nonane (7)[5] in 82% yield. The ^{1}H NMR spectrum of 7 showed a doublet of triplets at δ 4.10 (1H, $J_{1,6}=J_{5ax,6}=10.5$ Hz, $J_{5eq,6}=4.5$ Hz) which was attributed to H-6, and this fact may be explained by the *trans* relationship of H-1 and H-6 provided the molecule takes a chair conformation.

In order to introduce oxygen functionalities to the 2-cyclohexenone ring, epoxidation of 1 with 35% hydrogen peroxide in methanol in the presence of 1 mol dm^{-3} sodium hydroxide solution (pH 9) was carried out. The β-epoxide (8)[5] was obtained in 96% yield along with the α-epoxide (8')[5] in 3% yield. Dreiding model inspections show that the β-face of 1 is less hindered and the observed highly stereoselective epoxidation is reasonable. In the ^{1}H NMR spectrum of 8, the methine proton at C-1 was deshielded (δ 2.28-2.76) in comparison with that of 8' (δ 1.73-2.18).

Sodium borohydride reduction of the β-epoxide 8 gave a mixture of (9)[5] and (9')[5] (*ca.* 4 to 1 ratio), which was separable by silica gel chromatography, in a 84% combined yield. Acetylation of 9 and 9' in the usual manner gave the acetate (10)[5] and (10').[5] In the ^{1}H NMR spectrum of 10, a one-proton triplet at δ 5.11 was attributed to H-3 ($J_{2,3}=J_{2',3}=8.5$ Hz, $J_{3,4}=0$ Hz). Besides, H-3 of 10' was appeared at δ 5.25 as a quartet bearing $J_{2,3}=J_{2',3}=J_{3,4}=4$ Hz in its ^{1}H NMR spectrum.

Epoxide ring opening of 9 by hydroxy anion was accomplished by refluxing with sodium acetate in aqueous 2-methoxyethanol to give a diaxial opening product, (1*R*,3*R*,4*S*,5*S*,6*S*,8*R*,9*R*)-3,4,5-trihydroxy-8,9-isopropylidenedioxy-7-oxabicyclo[4.3.0]nonane (11)[5] exclusively (73% yield). The stereochemistry of the newly introduced hydroxyl groups was established by the ^{1}H NMR spectrum of the triacetate (12)[5] which was prepared by acetylation of 11. Nucleophilic ring opening of the epoxide 9' by hydroxy anion also gave 11 in 81% yield. The formation of 11 from 9' is rationalized by migration of the epoxide and a subsequent hydroxide ring opening in a diaxial manner.

Benzylation of 11 with benzyl bromide and sodium hydride afforded the tri-O-benzyl derivative (13)[5] in 91% yield. Compound 13 was converted into (1*S*,2*S*,3*S*,4*S*,5*R*)-2-acetoxy-1-acetoxymethyl-3,4,5-tribenzyloxycyclohexane (15)[5] in 52% overall yield by the sequential reactions as follows, 1) hydrolysis in 80% aqueous acetic acid under reflux (13 to 14), 2) sodium borohydride reduction, 3) periodate oxidation of the formed 7,8-diol, 4) sodium borohydride reduction of an aldehyde formed, and 5) acetylation. Compound 15 was converted into penta-O-acetyl-pseudo-α-L-altropyranose (16)[5] by reductive cleavage of the protecting groups with sodium in liquid ammonia followed by acetylation in 33% yield. The ^{1}H NMR spectrum of 16 ($CDCl_3$) was superimposable with that of the known pseudo-α-DL-altropyranose pentaacetate.[8] O-Deacetylation of 16 with sodium methoxide gave pseudo-α-L-altropyranose, (1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxy-1-hydroxymethylcyclohexane 17[5] in 81% yield.

Compound 1 seems to be a versatile chiral synthon for the synthesis of other pseudo-sugars.

References

1) T. Suami, K. Tadano, Y. Kameda, and Y. Iimura, *Chem. Lett.*, 1984, 1919.
2) T. Suami, K. Tadano, Y. Ueno, and Y. Iimura, *Chem. Lett.*, 1985, 37.
3) J. M. J. Tronchet, C. Cottet, B. Gentile, E. Mihaly, and J.-B. Zumwald, *Helv. Chim. Acta*, 56, 181 (1973).
4) In hydrogenation of 3 and 1 under these conditions, over-hydrogenation product, i.e. diastereomer mixtures of saturated alcohols were produced along with the desired saturated ketones.
5) All the new compounds were characterized by IR, ^{1}H NMR, mass spectra, and gave satisfactory elemental analyses or high resolution mass spectra. The physical and/or spectral data for the selected compounds are as follows. 4: mp 36.5-37 °C; $[\alpha]_D^{20}$+82.1° (*c* 1.35, $CHCl_3$). 5: mp 69-69.5 °C; $[\alpha]_D^{24}$+79.7° (*c* 1.82, $CHCl_3$). 1: mp 48-49 °C; $[\alpha]_D^{17}$-45.3° (*c* 0.92, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 1675, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35, 1.53 (3Hx2, each s, $C(CH_3)_2$), 1.90-2.35 (1H, m, H-1), 2.35-3.00 (2H, m, H-2,2'), 4.47-4.80 (2H, m, H-6,9), 5.73-6.10 (2H, m, H-4,8), 7.28 (1H, d, J=9 Hz, H-5); Found: C, 62.96; H, 6.80%. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%. 7: mp 98-99.5 °C; $[\alpha]_D^{22}$-33.7° (*c* 1.66, $CHCl_3$). 9: $[\alpha]_D^{27}$+26.1° (*c* 1.05, $CHCl_3$). 9': mp 141-143 °C; $[\alpha]_D^{27}$ +63.2° (*c* 0.89, $CHCl_3$). 10: $[\alpha]_D^{27}$+50.1° (*c* 0.77, $CHCl_3$). 10': mp 136-138 °C; $[\alpha]_D^{27}$+84.6° (*c* 1.04, $CHCl_3$). 11: mp 159-161 °C ; $[\alpha]_D^{25}$-6.6° (*c* 1.00, MeOH). 12: mp 55-58 °C; $[\alpha]_D^{26}$-7.8° (*c* 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32, 1.51 (3Hx2, each s, $C(CH_3)_2$), 2.05 (3H, s, $OCOCH_3$), 2.08 (6H, s, 2x$OCOCH_3$), 1.84-2.48 (3H, m, H-1,2,2'), 4.00 (1H, dd, $J_{1,6}$=11 Hz, $J_{5,6}$=3 Hz, H-6), 4.60 (1H, t, $J_{1,9}=J_{8,9}$=4 Hz, H-9), 5.00 (1H, q, $J_{2,3}=J_{2,3'}=J_{3,4}$=3 Hz, H-3), 5.12 (1H, t, $J_{4,5}=J_{5,6}$=3 Hz, H-5), 5.37 (1H, t, $J_{3,4}=J_{4,5}$=3 Hz, H-4), 5.83 (1H, d, $J_{8,9}$=4 Hz, H-8). 13: $[\alpha]_D^{27}$-0.8° (*c* 1.22, $CHCl_3$). 15: $[\alpha]_D^{26}$-25.7° (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.87 (2H, dd, J=5 and 6.5 Hz, H-6,6'), 2.00, 2.06 (3Hx2, each s, 2x$OCOCH_3$), 2.42 (1H, q, J=6 Hz, H-1), 3.47-3.82 (3H, m, H-3,4, 5), 4.00 (2H, dd, J=2.5 and 6.5 HZ, H-7,7'), 4.59 (4H, s, 2x$OCH_2C_6H_5$), 4.72 (2H, s, $OCH_2C_6H_5$), 5.28 (1H, dd, J=2.5 and 6 Hz, H-2), 7.30 (15 H, s, 3x $OCH_2C_6H_5$). 16: mp 84-85 °C; $[\alpha]_D^{26}$-13.7° (*c* 1.36, $CHCl_3$); high resolution mass calcd for $C_{17}H_{25}O_{10}$: *m/z* 389.1446, found: M+H, 389.1463. 17: $[\alpha]_D^{25}$ -43.6 ° (*c* 1.29, MeOH); high resolution mass calcd for $C_7H_{15}O_5$: *m/z* 179.0918, found: M+H, 179.0915.
6) A. Rosenthal and M. Spinzl, *Can. J. Chem.*, 47, 3941 (1969).
7) The following reaction conditions were attempted: 1) CH_3ONa in CH_3OH (none of 1), 2) 1 mol dm^{-3} aqueous NaOH (trace of 1), 3) Et_3N-PhH-reflux (none of 1), 4) LDA (-78 °C to 0 °C) (none of 1), 5) NaH-PhH-reflux (trace of 1), and 6) BF_3-Et_2O-CH_2Cl_2 (none of 1).
8) T. Suami, S. Ogawa, T. Ishibashi, and I. Kasahara, *Bull. Chem. Soc. Jpn.*, 49, 1388 (1976).

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