Carbohydrate Research, 184 (1988) 271–275
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Synthesis of (1*S*,3*R*,4*R*,5*R*)-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-2-oxaspiro[4.4]non-6-en-8-one from D-glucose

KIN-ICHI TADANO*, SATOSHI KANAZAWA, HIROHIKO YAMADA, AND SEIICHIRO OGAWA

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223 (Japan)

(Received December 18th, 1987; accepted for publication in revised form, June 5th, 1988)

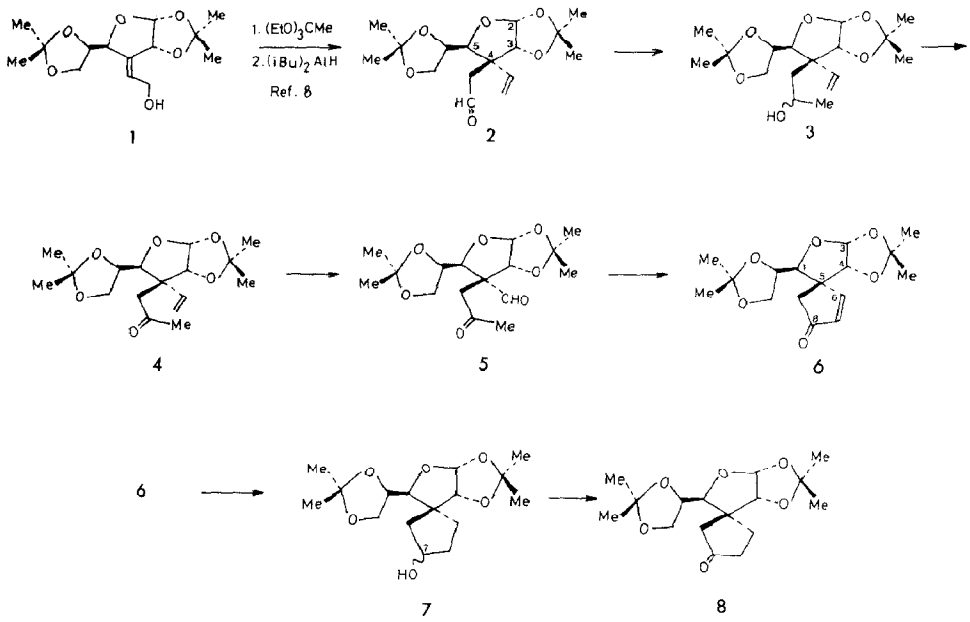
For the synthesis of carbocyclic spiro compounds, a challenging subject in organic synthesis, a number of approaches have recently been devised. The following procedures have been reviewed: (1) intramolecular alkylation[1], (2) rearrangement[2], and (3) cycloaddition[3]. In connection with the spiro type of sesquiterpenoid synthesis, several new methodologies have been developed[4,5]. Meanwhile, achieving access to the carbocyclic, spiro skeleton in an enantiomerically pure form constitutes an indispensable problem for the enantioselective total synthesis of natural products represented by the spirovativane sesquiterpenes. In relation to our synthetic interests in enantiomerically pure building-blocks for natural products synthesis[6,7], we now report a carbohydrate-mediated construction of the 2-oxaspiro[4.4]non-6-en-8-one skeleton. As a synthetic target, we selected the 2-oxaspiro[4.4]non-6-en-8-one **6**, which should serve as a synthetic precursor of carbocyclic spiro compounds.

It had previously[8] been demonstrated that the introduction of a quaternary carbon atom on the hexofuranose ring can be accomplished *via* ortho ester Claisen rearrangement of some 3-*C*-(hydroxymethyl)methylene derivatives of aldohexofuranoses. When **1**, prepared from D-glucose in a four-step sequence, was heated with triethyl orthoacetate, the ortho ester Claisen rearrangement proceeded stereoselectively to provide in high yield (2*R*,3*R*,4*R*,5*S*)-4-[(ethoxycarbonyl)methyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-vinyltetrahydrofuran†, which, on hydride reduction of this rearranged product, gave the *C*-(formylmethyl) derivative[8] **2**. When subjected to Grignard addition of methylmagnesium

*To whom correspondence should be addressed.

†Compounds described herein are derivatives of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose; however, we have named compounds **3**–**5** as derivatives of tetrahydrofuran, and compounds **6**–**8** as derivatives of 2-oxaspiro[4.4]nonane, in order to avoid an ambiguity that might occur by employing carbohydrate nomenclature.

0008-6215/88/$ 03.50



bromide in tetrahydrofuran (THF), compound **2** afforded an inseparable mixture of the adducts **3** (diastereomers) in 70% yield.

Oxidation[9] of **3** with pyridinium chlorochromate gave the ketone **4** (93.5%), and ozonolysis of its vinyl group of **4**, and treatment of the product with triphenylphosphine provided aldehyde **5**. Intramolecular aldol cyclization of **5** for cyclopentenone formation was best achieved by refluxing in 10% aqueous NaOH in methanol, to afford **6** in 84% yield from **4** after chromatographic purification on silica gel. The ^{1}H-n.m.r. spectrum of **6** revealed two alkenic protons, at δ 7.58 (for H-6) and 6.22 (for H-7), with a coupling constant of 6 Hz. Compound **6** possesses a quaternary carbon atom with an established stereochemistry [(*R*) configuration], and modification of the furanose ring would generate a variety of carbocyclic spiro compounds.

Hydrogenation of **6** in the presence of Raney nickel gave a diastereomeric mixture of the cyclopentanols **7**. Under these conditions, the carbonyl group was also reduced, presumably in a 1,4-addition fashion. The hydroxyl groups in the mixture **7** were oxidized with pyridinium chlorochromate, to afford the cyclopentanone **8** in 86% yield from **6**. Both **6** and **8** are considered to be versatile, chiral building-blocks for the synthesis of carbocyclic spiro compounds.

EXPERIMENTAL

General methods. — Dichloromethane (CH_2Cl_2) was dried over CaH_2 and distilled. Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and then over Na-benzophenone. Reactions were carried out at room temperature unless otherwise

stated. Reaction mixtures, combined extracts, and fractions from chromatography were evaporated under diminished pressure. Optical rotations were measured with a Jasco DIP-4 polarimeter for $CHCl_3$ solutions in a 10-mm cell. Column chromatography was performed with silica gel 60 (Katayama Chemicals, K070), and thin-layer chromatography (t.l.c.) on a glass plate coated with Kieselgel 60 GF_{254} (Merck), followed by detection with u.v. light or charring with sulfuric acid. I.r. spectra were recorded with a Jasco IR-810 spectrometer. ^{1}H-n.m.r. spectra were recorded with a Varian EM-390 (390 MHz) spectrometer for solutions in $CDCl_3$, with an internal standard of tetramethylsilane.

Diastereomeric mixture of (2R,3R,4R,5S)-4-[(2RS)-2-hydroxypropyl]-2,3-(isopropylidenedioxy)-5-[(1R)-1,2-(isopropylidenedioxy)ethyl]-4-vinyltetrahydrofuran (**3**). — To a solution of[8] **2** (1.01 g, 3.22 mmol) in THF (20 mL) was added methylmagnesium bromide (2.5M solution in THF; 2.5 mL, 6.25 mmol) under an argon atmosphere. The mixture was stirred for 2.5 h, more of the Grignard reagent (0.9 mL) was added, and the mixture was stirred for 1.5 h, treated with saturated, aqueous NH_4Cl solution (15 mL), diluted with water (80 mL), and extracted with ethyl acetate (3 × 50 mL). The extracts were combined, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (40 g) with 1:10 ethyl acetate–hexane, and the fraction having R_F 0.33 (1:2 ethyl acetate–hexane) was evaporated, to give inseparable mixture **3** (0.74 g, 70%) as a colorless syrup; ν_{max}^{neat} 3500, 2990, 2940, 2890, 1640, 1455, 1380, 1250, and 1220 cm^{-}; ^{1}H-n.m.r.: δ 1.20 [t, 3 H, *J* 3 Hz, C*H*$_3$CH(OH)CH$_2$–], 1.31, 1.36, 1.50 [each s, 6 H, 3 H, 3 H, 2 C(CH$_3$)$_2$], 1.55–2.04 [m, 4 H, CH$_3$C*H*(O*H*)C*H*$_2$–], 3.84–4.23 (m, 4 H, H-5, H-1,2,2′ of the C-5 side chain), 4.57, 5.03 (each d, total 1 H, each *J* 3.5 Hz, H-3), 5.13–5.51 (m, 2 H, CH=C*H*$_2$), 5.75 (d, 1 H, *J* 3.5 Hz, H-2), 5.97, and 6.19 (each dd, total 1 H, each, *J* 7 and 12 Hz, C*H*=CH$_2$).

Anal. Calc. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.43; H, 8.46.

(2R,3R,4R,5S)-2,3-(Isopropylidenedioxy)-5-[(1R)-1,2-(isopropylidenedioxy)-ethyl]-4-(2-oxopropyl)-4-vinyltetrahydrofuran (**4**). — To a stirred solution of **3** (1.75 g, 5.33 mmol) in CH_2Cl_2 (20 mL) were added pyridinium chlorochromate (2.64 g, 12.3 mmol) and powdered molecular sieves 4A (2.72 g). The mixture was stirred for 1.5 h, ether (5 mL) was added, the suspension was placed on a silica-gel column (30 g), and the column was eluted with ether. The fraction having R_F 0.56 (1:2 ethyl acetate–hexane) was evaporated, to give **4** (1.63 g, 93%) as a colorless syrup; $[\alpha]_D^{21}$ +36.8° (*c* 1.24, $CHCl_3$); ν_{max}^{neat} 2990, 2940, 2890, 1715, 1380, 1370, 1250, 1160, and 1070 cm^{-1}; ^{1}H-n.m.r.: δ 1.32, 1.37, 1.54 [each s, 6 H, 3 H, 3 H, 2 C(CH$_3$)$_2$], 2.20 (s, 3 H, CH$_3$C=O), 2.37, 2.96 (AB, each 1 H, *J* 18 Hz, CH$_3$COC*H*$_2$–), 3.88–4.26 (m, 4 H, H-5, H-1,2,2′ of the C-5 side chain), 4.99 (d, 1 H, *J* 3.5 Hz, H-3), 5.19 (d, 1 H, *J* 18 Hz, C*H*$_2$=CH), 5.22 (d, 1 H, *J* 11 Hz, C*H*$_2$=CH), 5.71 (d, 1 H, *J* 3.5 Hz, H-2), and 6.09 (dd, 1 H, *J* 11 and 18 Hz, CH$_2$=C*H*).

Anal. Calc. for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.36; H, 7.79.

(1S,3R,4R,5R)-3,4-(Isopropylidenedioxy)-1-[(1R)-1,2-(isopropylidenedioxy)-ethyl]-2-oxaspiro[4.4]non-6-en-8-one (**6**). — Into a solution of **4** (1.63 g, 4.98 mmol)

in CH_2Cl_2 (20 mL) was bubbled a stream of ozone (~3% v/v in O_2) for 2 h at −70°. To the solution was added a solution of triphenylphosphine (1.40 g, 5.34 mmol) in CH_2Cl_2 (10 mL) at −70°, and the mixture was gradually warmed to room temperature while triphenylphosphine (each 0.7 g) was added after 2, 4, and 5 h. The mixture was evaporated, and the residue was chromatographed on a silica-gel column (135 g, 1:7 ethyl acetate–hexane). Fractions having R_F 0.46 (1:2 ethyl acetate–hexane) were combined and evaporated, to give (2*R*,3*R*,4*R*,5*S*)-4-formyl-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-(2-oxopropyl)tetrahydrofuran (**5**) (1.44 g, 88%) as a colorless syrup which was directly subjected to the next step.

Compound **5**: ^{1}H-n.m.r.: δ 1.30, 1.33, 1.60 [each s, 3 H, 6 H, 3 H, 2 C(CH_3)$_2$], 2.31 (s, 3 H, CH_3CO), 2.21, 3.13 (AB, each 1 H, *J* 18 Hz, CH_3COCH_2–), 3.93–4.16 (m, 3 H, H-1,2,2′ of the C-5 side chain), 4.46 (d, 1 H, *J* 12 Hz, H-5), 5.26 (d, 1 H, *J* 3.5 Hz, H-3), 5.81 (d, 1 H, *J* 3.5 Hz, H-2), and 9.72 (s, 1 H, CHO).

A solution of **5** (1.44 g) in a mixture of aqueous NaOH (10 wt%, 7.5 mL) and methanol (30 mL) was refluxed for 135 min, and cooled, the base neutralized by addition of 6M aqueous HCl, the methanol evaporated, and the solution diluted with water (80 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were combined, dried (Na_2SO_4), and evaporated, the residue chromatographed on a silica-gel column (50 g, 1:7 ethyl acetate–hexane), and the fraction having R_F 0.51 (1:2 ethyl acetate–hexane) evaporated, to give **6** (1.30 g; 84% from **4**) as a colorless syrup; $[\alpha]_D^{21}$ +97.3° (*c* 1.06, $CHCl_3$); ν_{max}^{neat} 2990, 2940, 2980, 1720, 1670, 1580, 1380, 1370, 1250, and 1215 cm^{-1}; ^{1}H-n.m.r.: δ 1.22, 1.31, 1.56 [each s, 3 H, 6 H, 3 H, 2 C(CH_3)$_2$], 1.94, 2.68 (AB, each 1 H, *J* 8 Hz, H-9,9′), 3.87–4.19 (m, 4 H, H-1, H-1,2,2′ of the C-1 side chain), 4.31 (d, 1 H, *J* 3.5 Hz, H-4), 5.78 (d, 1 H, *J* 3.5 Hz, H-3), 6.22 (d, 1 H, *J* 6 Hz, H-7), and 7.58 (d, 1 H, *J* 6 Hz, H-6).

Anal. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.84; H, 7.08.

(1S,3R,4R,5R)-3,4-(Isopropylidenedioxy)-1-[(1R)-1,2-(isopropylidenedioxy)-ethyl]-2-oxaspiro[4.4]nonan-7-one (**8**). — A solution of **6** (520 mg, 1.68 mmol) in ethanol (20 mL) was hydrogenated in the presence of Raney nickel[10] T-4 under hydrogen at atmospheric pressure for 2.5 d. The catalyst was removed by filtration through a Celite pad, and washed with ethanol. The filtrate and washings were combined, and evaporated. The residue was chromatographed on a silica-gel column (45 g, 1:50 ethanol–toluene), and fractions having R_F 0.44 and 0.46 (1:8 ethanol–toluene) were combined and evaporated, to give a diasteromeric mixture of (1*S*,3*R*,4*R*,5*S*,7*RS*)-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-2-oxaspiro[4.4]nonan-7-ols (**7**) (427 mg) as a colorless syrup, which was directly oxidized.

Compound **7**: ν_{max}^{neat} 3520, 3020, 2970, 2910, 1400, 1385, 1260, 1235, and 1180 cm^{-1}; ^{1}H-n.m.r.: δ 1.31, 1.35, 1.43, 1.51 [each s, each 3 H, 2 C(CH_3)$_2$], 1.67–2.26 (m, 6 H, H-6,8,9,6′,8′,9′), 3.80–4.56 (m, 7 H, H-1,4,7, OH, H-1,2,2′ of the C-1 side chain), and 5.63 (d, 1 H, *J* 3.5 Hz, H-3).

To a stirred solution of the mixture **7** in CH_2Cl_2 (10 mL) were added pyridinium chlorochromate (1.13 g, 5.26 mmol) and powdered molecular sieves 4A (1.20 g). The mixture was stirred for 15 h, and then placed on a silica-gel column (16 g) that was eluted with ether, and the ethereal fraction having R_F 0.68 (1:8 ethanol–toluene) was evaporated, to give **8** (451 mg, 86%) as a colorless syrup; $[\alpha]_D^{28}$ +73.7° (*c* 1.26, $CHCl_3$); ν_{max}^{neat} 2980, 2935, 1740, 1450, 1400, 1370, 1250, 1160, and 1070 cm^{-1}; ^{1}H-n.m.r.: δ 1.32, 1.46, 1.53 [each s, 6 H, 3 H, 3 H, 2 $C(CH_3)_2$], 1.78–2.58 (m, H-8,9,8′,9′), 1.88, 2.49 (AB, each 1 H, *J* 18 Hz, H-6,6′), 3.77–4.20 (m, 4 H, H-1, H-1,2,2′ of the C-1 side chain), 4.22 (d, 1 H, *J* 3.5 Hz, H-4), and 5.71 (d, 1 H, *J* 3.5 Hz, H-3).

Anal. Calc. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.23; H, 7.58.

ACKNOWLEDGMENT

We thank Mr. Akio Takahashi of this University for performing the elemental analyses.

REFERENCES

1 A. P. KRAPCHO, *Synthesis,* (1974) 383–419.
2 A. P. KRAPCHO, *Synthesis,* (1976) 425–444.
3 A. P. KRAPCHO, *Synthesis,* (1978) 77–126.
4 J. A. MARSHALL, S. F. BRADY, AND N. H. ANDERSEN, *Fortschr. Chem. Org. Naturst.*, 31 (1974) 283–376.
5 M. VANDEWALLE AND P. DE CLERCQ, *Tetrahedron,* 41 (1985) 1767–1831.
6 T. SUAMI, K. TADANO, Y. IIMURA, AND H. YOKOO, *J. Carbohydr. Chem.*, 5 (1986) 1–10.
7 K. TADANO, Y. IIMURA, AND T. SUAMI, *J. Carbohydr. Chem.*, 5 (1986) 411–422.
8 K. TADANO, Y. IDOGAKI, H. YAMADA, AND T. SUAMI, *Chem. Lett.*, (1985) 1925–1928; *J. Org. Chem.*, 52 (1987) 1201–1210.
9 E. J. COREY AND J. W. SUGGS, *Tetrahedron Lett.*, (1975) 2647–2650.
10 S. NISHIMURA, *Bull. Chem. Soc. Jpn.*, 32 (1959) 61–64.