Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2063–2066

TETRAHEDRON

A new and stereospecific synthesis of an inositol analogue: bis-homoinositol

Yunus Kara[a] and Metin Balci[b,*]

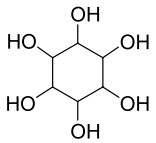
[a]*Department of Chemistry, Atatürk University, 25240 Erzurum, Turkey*
[b]*Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey*

Received 8 November 2002; revised 13 January 2003; accepted 7 February 2003

Abstract—The photooxygenation of *trans*-8-(acetyloxy)bicyclo[4.2.0]octa-2,4-dien-7-yl acetate afforded the bicyclic endoperoxide. Reduction of the endoperoxide with thiourea followed by acetylation gave the corresponding tetraacetate. The $KMnO_4$ oxidation of the tetraacetate followed by acetylation gave dihydroxytetraacetate Ammonolysis of tetraacetate afforded the bis-homoinositol, bicyclo[4.2.0]-octane-2,3,4,5,7,8-hexol.

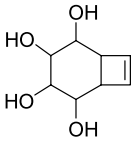
1. Introduction

The polyhydroxy cyclohexanes have been an interest to those concerned with carbohydrates.[1] In 1850, Scherer[2] isolated the first cyclohexanehexol from meat, which was an optically inactive *myo*-inositol isomer. 'Inositol' **1** has been assigned as the generic term for cyclohexanehexols. Nine stereoisomers are predicted for inositol. All nine isomers are known and three are commercially available. There are many reported methods for the synthesis of the inositols.[3] The biological activities of inositols and their phosphate derivatives (especially in their role in intracellular communication), have been studied.[4] Inositols have been prepared from halobenzenes,[5] benzene,[6] hexahydroxybenzene,[7] sugars,[8] tetrahyroxyquinone,[9] inositol,[10] and transformation of conduritol.[11] Especially, the cyclohexa-3,5-diene-1,2-diol derived from aromatics precursors by microbial oxidation have been extensively used in the synthesis of inositols and most of the inositols have been synthesized from these metabolites.[12] Recently we successfully used cyclooctatetraene for the stereospesific synthesis of bis-homoconduritol-D and bis-homo-conduritol-F.[13]



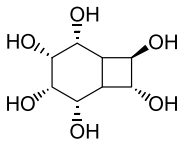
1

Inositol



2

Bis-homoconduritol



3

Bis-homoinositol

In this paper we report the first synthesis and characterization of a new inositol analogue, bis-homoinositol **3** from commercially available cyclooctatetraene **4**.

2. Results and discussions

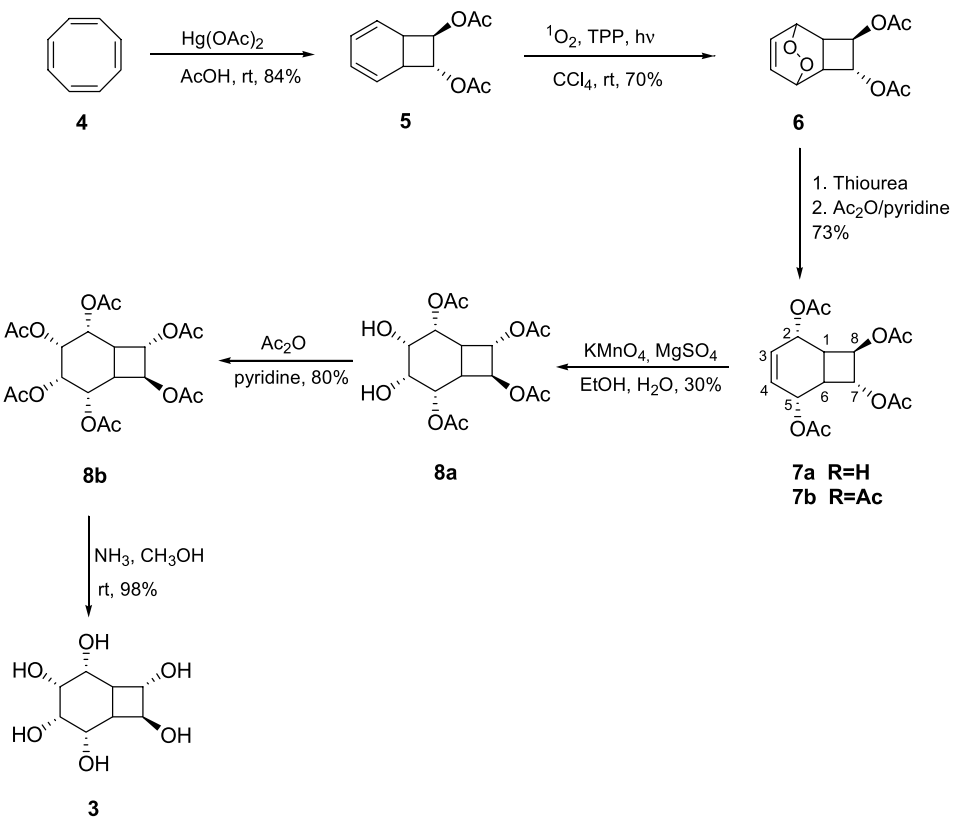
Diacetoxydiene **5** was synthesized from cyclooctateraene **4** by addition of mercury (II)acetate to cyclooctatetraene in 84% yield.[14] *meso*-Tetraphenylporphyrine (TPP) sensitized photooxygenation of diacetoxydiene **5** in carbon tetrachloride solution at room temperature afforded the endoperoxide **6** in a yield of 70% (Scheme 1).

Since the diacetoxydiene **5** has no plane of symmetry, singlet oxygen is quite sensitive to steric consideration and approaches the substrate predominantly, if not exclusively, from the less congested side.[15] Thus, we assume that the singlet oxygen approaches the diene unit in **5** from the less hindered face of the molecule due to the cyclobutane ring.

The structure of the endoperoxide **6** was determined on the basis of ^1H, ^{13}C NMR spectroscopic data and by comparison with related systems reported in the literature.[16] Reduction of the peroxide **6** linkage was performed with thiourea under very mild conditions to give diol **7a**. (Scheme 2). Since only the oxygen-oxygen bond is cleaved in this reaction, the configuration of the carbon atoms is preserved. For further structure proof, **7a** was converted into the corresponding acetate **7b** was fully characterized by spectroscopic methods. The 200 MHz ^1H NMR spectrum displayed a broad singlet at δ 5.93, which was assigned to the olefinic protons. Acetoxy protons H_5 and H_2 resonate as a broad singlet (δ 5.55), and doublet (δ 5.21), respectively. Inspection of Dreiding models indicates that the dihedral

Keywords: cyclitols; peroxides; bicyclic aliphatic compounds; oxidation.
* Corresponding author. Tel.: +90-312-210-5140; fax: +90-312-210-1280; e-mail: mbalci@metu.edu.tr

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00209-6

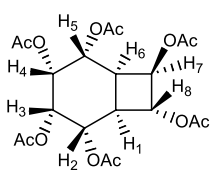


Scheme 1.

angle between H_2 and H_1 as well as H_2 and H_3 is near 80–90°, whereas the dihedral angle between H_6 and H_5 is near 130°. This conformation is responsible for the doublet resonance of H_2 and singlet resonance of H_1 proton. The triplet splitting of the H_1 proton can be also explained with this conformation.

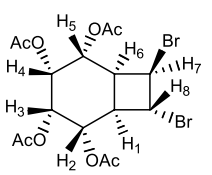
cis-Hydroxylation of **7b** with $KMnO_4$ at −10°C gave the corresponding diol **8a** which was converted into the hexaacetate **8b** by treatment with acetic anhydride in pyridine (Scheme 1). The spectral data confirmed the hydroxylation of the double bond. The stereochemical course of the hydroxylation may be *syn* or *anti*. In our previous studies, we found out that hydroxylation of **9** proceeded in a stereoselective manner affording *syn* **10**[13] whose correct structure was determined by single crystal X-ray analysis (Scheme 2).

Table 1. The vicinal coupling constants of **8b** and **10**



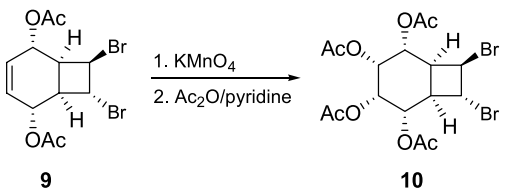
8b

J_{12}=9.7 Hz
J_{23}=2.4 Hz
J_{45}=4.4 Hz
J_{35}=2.1 Hz
J_{67}=9.2 Hz
J_{78}=7.2 Hz
J_{18}=7.2 Hz
J_{16}=9.8 Hz



10

J_{12}=9.2 Hz
J_{23}=2.2 Hz
J_{45}=4.7 Hz
J_{35}=undetermined
J_{67}=8.9 Hz
J_{78}=8.9 Hz
J_{18}=9.2 Hz
J_{16}=9.2 Hz



Scheme 2.

The stereoselective *syn*-addition of MnO_4^- to **9** was explained by the fact that the *endo*-bromine atom blocked the double bond in the six membered ring. Compound **7b** is also structurally quite similar to **9**. Therefore, we assume that MnO_4^- ion basically attacks **7b** from the *syn*-face, since the endo-acetate group normally blocks the double bond, which results in the formation of **8a**. Then, the formed tetraacetoxydiol **8a** was converted into the acetate derivative **8b** for further characterization.

The structure of **8b** has been elucidated on the basis of ^1H and ^{13}C NMR spectroscopic data and extensive double resonance experiments by the comparison of the H–H coupling constants with those obtained for **10**. Very similar coupling constants, extracted from the ^1H NMR spectra of **8b** and **10** indicates clearly that these compounds are likely to have the same configuration (Table 1).

Deacetylation of **8b** with ammonia was carried out in methanol to give the free hexol **3** in nearly quantitative yield (Scheme 1).

In summary, a short, simple and stereocontrolled method for the preparation of bis-homoinositol **3**, the parent member of a new class of compounds, has been accomplished starting from cyclooctatetraene. Further studies starting from **7a** concerning the synthesis of bis-homoaminoinositol are currently in progress.

3. Experimental

3.1. General

Melting points were determined on a melting apparatus. Infrared spectra were obtained from KBr pellets on an infrared spectrophotometer. ^{1}H NMR spectra were recorded on 200 MHz spectrometer and reported in (units with $SiMe_4$ as internal standard. All column chromatography was performed on silica gel (60 mesh, Merck).

3.1.1. 1*S*(*R*),6*R*(*S*),7*S*(*R*),8*S*(*R*)-8-(Acetyloxy)bicyclo-[4.2.0]octa-2,4-dien-7-yl acetate (5). The title compound was prepared in 84% yield as described in the literature.[14]

3.1.2. 1*S*(*R*),2*S*(*R*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*S*(*R*)-4-(Acetyl-oxy)-7,8-dioxatricyclo[4.2.2.0^{2,5}] dec-9-en-3-yl acetate (6). A sample of 2.0 g (9 mmol) of the diacetate **5** and 20 mg of *meso*-tetraphenylporphyrine in 30 mL of carbon-tetrachloride were photolyzed for 5 h at room temperature with a 150 W projection lamp while a slow stream of oxygen gas was passed through the solution. After removal of the solvent (25°C, 20 mm-Hg), the mixture was chromatographed on silica gel (40 g) by elution with hexane/Et_2O (2:1) to afford **6** as colorless crystals from hexan/$CHCl_3$ (1.6 g (70%), mp 59–60°C; Found: 56.45; H, 5.71. $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.55%; ν_{max}(KBr) 3070, 2973, 1739, 1438, 1380, 1234, 1160, 1118, 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.66 (2H, m, C=C*H*), 5.02 (1H, dd, *J*=9.1, 5.1 Hz, H_3), 4.85 (1H, m, H_1 or H_6), 4.63 (1H, m, H_1 or H_6), 4.57 (1H, t, *J*=5.1 Hz, H_4), 3.32 (1H, dt, *J*=8.8, 5.1 Hz, H_5), 2.75 (dt, *J*=8.8, 5.1 Hz, H_2), 1.98 (3H, s, OCH_3), 1.96 (3H, s, OCH_3). δ_C (50 NMR, $CDCl_3$); 171.5, 171.0, 135.2, 133.4, 76.8, 73.5, 72.5, 71.8, 37.6, 36.9, 22.5, 22.4.

3.1.3. 1*S*(*R*),2*S*(*R*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*S*(*R*)-2,5,8-Tris-(acetyloxy)bicyclo[4.2.0]oct-3-en-7-yl acetate (7b). To a magnetically stirred slurry of 0.44 g (5.9 mmol) of thiourea in 30 mL of methanol was added a solution of 1.50 g (5.9 mmol) of endoperoxide **6** in 50 mL of CH_2Cl_2/CH_3OH (1:9) at 25°C. After complete of addition (ca 10 min) the mixture was stirred for 1 h and the solid was removed by filtration. Evaporation of solvent gave crude the diol **7a**, which was dissolved 10 mL of pyridine, and to this magnetically stirred solution was added 1.6 g (15.2 mmol) of acetic anhyride. The reaction mixture was stirred at room temperature for 12 h. The mixture was cooled to 0°C and 80 mL of 4 M HCl solution was added. The mixture was extracted with ether (3×50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (10 mL) and water (45 mL) and then dried (Na_2SO_4). Removal of the solvent under reduced pressure (25°C, 20 mm-Hg) gave tetraacetate **7b** (1.5 g, 73%) as colourless crystals from Et_2O/hexane, mp 108–109°C; Found: 56.39; H, 5.81. $C_{16}H_{20}O_8$ requires C, 56.47; H, 5.92%; ν_{max}(KBr) 2930, 1730, 1480, 1290, 1220, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.93 (2H, bs, =C*H*), 5.55 (1H, d, *J*=4.0 Hz, H_5), 5.21 (1H, bs, H_2), 5.15 (1H, dd, *J*=7.6, 4.4 Hz, H_7 or H_8), 4.90 (1H, dd, *J*=7.6, 4.4 Hz, H_7 or H_8), 2.8 (1H, m, H_6), 2.40 (1H, t, *J*=7.5 Hz, H_1), 2.21 (6H, s, OCH_3), 2.05 (6H, s, OCH_3); δ_H (50 MHz, $CDCl_3$) 170.5 (2C), 170.4 (2C), 131.1, 127.9, 73.7, 70.4, 65.9, 63.8, 38.2, 33.5, 21.5, 21.4, 21.1, 21.0.

3.1.4. 1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*S*(*R*)-2,3,4,5,8-Pentakis-(acetyloxy)bicyclo[4.2.0]octanyl acet-ate (8b). To a stirred solution of 1.25 g (3.67 mmol) tetraacetate **7b** in EtOH (60 mL) was added a solution of $KMnO_4$ (0.6 g, 3.7 mmol) and $MgSO_4$ (0.52 g, 3.7 mmol) in water (40 mL) at −5°C over a period of 5 h. After the addition was completed, the reaction mixture was stirred for an additional 15 h at −5°C and then filtered. The precipitate was washed several times with hot water. The combined filtrates were concentrated to 15 mL by rotary evaporotion. The aqueous solution was extracted with ethyl acetate (3×50 mL) and the extracts were dried (Na_2SO_4). Evapor-ation of the solvent gave diol tetraacetate **8a** (0.35 g, 30%) which was submitted to acetylation as previously described to give hexaacetate **8b** (0.26 g, 80%), white crystals from EtOH, mp 89–90°C; Found: 52.43; H, 5.72. $C_{20}H_{26}O_{12}$ requires C, 52.40; H, 5.72%; ν_{max}(KBr) 2930, 1700, 1420, 1220, 1100 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.43 (2H, m, H_3 and H_5), 5.26 (1H, dd, *J*=9.7, 2.4 Hz, H_2), 5.12 (1H, dd, *J*=4.4, 2.1 Hz, H_4), 5.02 (1H, dd, *J*=9.2, 7.2 Hz, H_7), 4.95 (1H, t, *J*=7.2 Hz, H_6), 2.89 (1H, ddd, *J*=9.8, 9.7, 7.2 Hz, H_1), 2.46 (1H, dd, *J*=9.8, 9.2 Hz, H_6), 2.17 (3H, s, OCH_3), 2.13 (6H, s, OCH_3), 1.97 (6H, s, OCH_3), 1.92 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 170.4, 170.23, 170.19, 170.1, 169.7, 169.6, 72.1, 69.6, 68.7, 68.0, 67.5, 65.8, 39.1, 32.6, 21.2, 21.1, 20.9 (2C), 20.84, 20.78.

3.1.5. 1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*S*(*R*)-Bicyclo[4.2.0]octane-2,3,4,5,7,8-hexol (3). 0.1 g (0.3 mmol) of hexaacetate **8b** was dissolved in 20 mL of absolute methanol. While being passed dry NH_3 through the solution the mixture was stirred for 2 h at room temperature. Evaporation of methanol and formed acetamide gave bis-homoinositol **3** in nearly quantitative yield (50 mg, 98%), colorless powder from $CHCl_3$/MeOH, mp 185–188°C; Found: 46.39; H, 6.75. $C_8H_{14}O_6$ requires C, 46.60; H, 6.84%; ν_{max}(KBr) 3448, 3286, 2923, 2545, 2460, 1427, 1365, 1311, 1211, 1164, 1079, 1033, 987 cm^{-1}; δ_H ^{1}H NMR (200 MHz, D_2O) 4.7 (6H, s, O*H*), 3.99 (1H, t, *J*=7.2 Hz, H_6), 3.90 (2H, m, C*H*OH), 3.76 (1H, dd, *J*=9.2, 2.3 Hz, H_2), 3.64 (2H, m, C*H*OH), 2.33 (1H, q, *J*=9.2 Hz, H_1), 2.08 (1H, t, *J*=9.4 Hz, H_6); δ_C (50 MHz, D_2O) 79.3, 78.6, 76.0, 73.34, 72.7, 72.5, 46.7, 38.6.

Acknowledgements

The authors are indebted to the Department of Chemistry (Atatürk University) and Turkish Academy of Sciences (TUBA) for financial support of this work and the State Planning Organization of Turkey (DPT) for purchasing a 200 MHz NMR and liquid nitrogen cryogenerator.

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