Turkish Journal of Chemistry

Volume 20 | Number 4 Article 12

1-1-1996

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Tr. J. of Chemistry
20 (1996) , 341 – 344.

A Novel and Stereospecific Synthesis of Conduritol-E *via* Cyclohexa-3,5-diene-1,2-diol

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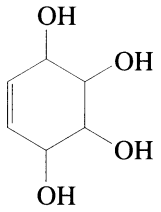
Received 3.9.1996

Conduritol-E was synthesized starting from cyclohexa-3,5-diene-1,2-diol **1a** in six steps. Acetylation of the diol **1a** followed by bromination gave ($2\alpha/1\beta$, 3β, 4β)-1,2-dibromo-2,3- diacetoxy- 5-cyclohexene **3** as main product. $KMnO_4$-hydoxylation of the dibromide **3** followed by acetylation, Zn-elimination and hydrolysis afforded conduritol-E **5a**.

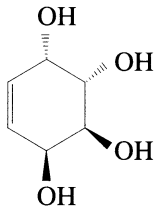
Key Words: cyclohexa-3,5-diene-1,2-diol, bromination, conduritol-E, conduritol-E tetraacetate.

Introduction

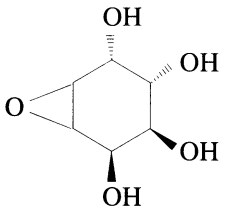
Conduritols are cyclohex-5-ene-1,2,3-tetrols of which there are six diastereoisomers. They have proven to be useful intermediates for the preparation of cyclitols[1]. Additionally, conduritol-epoxides and aminoconduritols act as inhibitors of D-glycosidases[2]. Up to the present all possible conduritol isomers have been synthesized by many different methods[3]. Substituted or nonsubstituted cyclohexa-3,5-diene-1,2-diols, prepared from benzene or its derivatives by using of *pseudomonas putida*, have been used for the preparation of many cyclitol derivatives[4]. At this stage, conduritol-E has been synthesized from trans-diacetoxybenzene[5], carbohydrates[6], cis-benzenediol[7] and p-benzoquinone[8].



Conduritol



Conduritol–E



Conduritol–E Epoxide

Furthermore, conduritol-E epoxide has been synthesized starting from 3-chloro- or bromo-cyclohexa-3,5-diene-1,2-diol[9]. Enantioselective synthesis of conduritol-E, was recently accomplished by asymmetric dihydroxylation of cyclohexa-3,5-diene-1,2-diol[10]. We here report the use of cyclohexa-3,5-diene-1,2-diol **1a** for a novel and stereospecific synthesis of conduritol-E.

Experimental Section

Acetylation of cyclohexa-3,5-diene-1,2-diol 1a. To a stirred solution of **1a**[11] (3g, 27 mmol) in 10 ml pyridine was added Ac_2O (8 .26 g, 81 mmol) at 0° C. The reaction mixture was stirred at the same temperature for 6 hours. The mixture was added to 50 mL of cold water, and extracted with ether (3x50 ml). The combined organic extracts were washed with $NaHCO_3$ solutions (3 × 15 mL) and then dried over M_gSO_4. Removal of the solvent under reduced pressure gave 1,2- diacetoxycyclohexa-3,5-diene **1b** (4.57 g, 87%, colorless liquid).

^{1}**H-NMR 1b**[12] (60 MHz, CCl_4, TMS) δ 6.02 (AA′BB′ system, 4H), 5.52 (m, 2H), 2.10 (s, 6H).

Bromination of 1,2-diacetoxy-cyclohexa-3,5-diene 1b. To a stirred solution of 1,2-diacetoxy-cyclohexa-3,5-diene **1b** (4 g, 20 mmol) in 20 ml of $CHCl_3$ was added dropwise a solution of bromine (3.2 g, 20 mmol) in 10 ml of $CHCl_3$ at −45° C over one hour. After addition was completed, the mixture was stirred for 30 minutes. The mixture was added to a solution of 20 ml of 20 % $Na_2S_2O_5$, organic phase separated and washed with 100 mL of 1N KOH solution. Drying of the organic solution over $MgSO_4$ and evaporation of the solvent under reduced pressure gave a dibromide mixture of **2** and **3** in a ratio of 2:98 determined by ^{1}H-NMR spectrum (6.17 g, total yield: 85%). Recrystallization of the mixture consisting of **2** and **3** from chloroform: hexane (80: 20) gave pure **3** (m.p: 105° C): The residual mixture was separated from the silica gel column (20 g) eluting with $CHCl_3$/ hexanes (3:7) to give pure **2** and **3**.

(2α/1β,3β,4β)-1,2-dibromo-2,3- diacetoxy- 5-cyclohexene 3 ^{1}**H-NMR** ($CDCl_3$, 200 MHz) δ 6.40 (A part of AB system, dd, 1H, J=9.98, 2.90), 5.76 (B part of AB system, ddd, 1H, J=9.98, 4.60, 1.70), 5.64 (dd, 1H, J=4.40, 4.02), 5.50 (dd, 1H, J=9.50, 4.02), 4.76 (A part of AB system, ddd, 1H, J=9.40, 2.92, 1.60), 4.46 (B part of AB system, dd, 1H, J=9.60, 6.10), 2.07 (s, 3H), 2.05 (s, 3H).

^{13}**C-NMR** ($CDCl_3$, 50 MHz) δ 170.29, 169.91, 132.42, 125.21, 70.20, 65.54, 50.20, 48.80, 21.29, 21.19.

IR (KBr, cm^{-1}) 3004, 2953, 2876, 1778, 1395, 1242, 1089, 1038, 936, 782.

(1α/2β,3β,4β)-1,2-dibromo-2,3- diacetoxy-5-cyclohexene 2 ^{1}**H-NMR** ($CDCl_3$, 200 MHz) δ 5. 93 (A part of AB system, dd, 1H, J=7.50, 2.55), 5.87 (B part of AB system, ddd, 1H, J=7.51, 3.76, 2.20), 5.53 (dd, 1H, J=4.40, 2.20), 5.30 (dd, 1H, J= 6.50, 2.20), 5.05 (dd, 1H, J=4.48, 2.27), 4.68 (dd, 1H, J=6.56, 3.70), 2.16(s, 3H), 2.11 (s,3H).

^{13}**C-NMR** ($CDCl_3$, 50 MHz) δ 175.61, 170.32, 129.14, 128.85, 73.72, 68.35, 52.84, 43.71, 21.22, 21.17.

IR (KBr, cm^{-1}) 2953, 2876, 1777, 1394, 1242, 1089, 1038, 936,

(1α,2β,3α,4α,5β,6β)-1,2- dibromo-3,4,5,6-tetraacetoxy-cyclohexane 4b. To a stirred EtOH solution (500 ml) of **3** (5g, 14 mmol) was added a solution of $KMnO_4$ (6.7 g, 14 mmol) in and $MgSO_4$ (5g, 14 mmol) water (200 ml) at −5° C for 5 hours. After the addition of bromine was completed, the reaction mixture was stirred for 15 hours at the given temperature and filtered. The precipitate was washed several times with hot water. The combined filtrates were concentrated to 50 ml using a rotary evaporator. The aqueous solution was extracted with ethyl acetate (3x100 ml) and the extracts were dried (Na_2SO_4). Evaporation of the solvent gave **4a** (55%).

To a stirred solution of **4a** (3g, 7.7 mmol) in 10 ml of pyridine was added Ac_2O (2.36 g, 23 mmol). The reaction mixture was stirred at room temperature for 8 hours. The mixture was cooled to 0° C and added to 60 ml of 4 N HCl solution, and extracted with ether (3x50 mL). The combined organic extracts were washed with $NaHCO_3$. Removal of the solvent under reduced pressure gave tetraacetate **4b**. (3.21 g, 88%, m.p 122° C).

^{1} **H-NMR of 4b** ($CDCl_3$, 200 MHz) δ 5.30 (m, 4H), 4.20 (m, 2H), 2.19 (s, 6H), 2.07 (s, 6H).

^{13} **C-NMR of 4b** ($CDCl_3$, 50 MHz) δ 169.17, 168.78, 71.03, 67.50, 51.50, 20.62, 20.50.

IR (KBr, cm^{-1}) 2998, 1745, 1425, 1365, 1230, 1125, 1075, 1045, 1000.

($1\alpha, 2\alpha, 3\beta, 4\beta$)-1,2,3,4-tetraacetoxy-5-ene (Conduritol-E tetraacetate) 5a. To a solution of **4b** (4.5g, 25 mmol) in 5 ml of acetic acid and 20 ml of ether was added 2g of Zn dust. The mixture was refluxed for 1 hour. After addition of 5 ml of water, the mixture was stirred for 5 minutes. After filtering of the precipitate, the organic phase was separated and the aqueous phase was extracted with ether (3x20 mL). The combined organic phases were washed with $NaHCO_3$ solution (3x15 mL) and then dried over Na_2SO_4. Removal of the solvent gave conduritol-E tetraacetate **5a** (2.2 g, 74 %, m.p. 150- 151 °C, recystallized from chloroform: hexane).

^{1}**H-NMR** ($CDCl_3$, 200 MHz) δ 5.93 (m, 2H), 5.70 (m, 2H), 5.45 (m, 2H), 2.09 (s, 6H), 2.05 (s, 6H).

^{13}**C-NMR** ($CDCl_3$, 50 MHz) δ 170.09, 169.81, 128.11, 66.56, 66.06, 20.69, 20.58.

IR (KBr, cm^{-1}) 2995, 1744, 1363, 1222, 1068, 1025.

($1\alpha, 2\alpha, 3\beta, 4\beta$)-1,2,3,4-tetrahydoxy-cyclohex-5-ene (conduritol-E) 5b. **5a** (200 mg, 0.88 mmol) was dissolved in 5 ml of 0.5 N H_2SO_4 and the resulting mixture was stirred at room temperature for 3 hours. The acid was neutralized with $BaCO_3$. After filtration of the precipitate, evaporation of the solvent under reduced pressure gave conduritol-E **5b**. (77%, m.p[8]. 176-177 °C, recrystallized from MeOH/hexane).

^{1}**H-NMR** (DMSO-d_6, 200 MHz) δ 5.50 (m, 2H), 4.07 (m, 2H), 3.75 (m,2H).

^{13}**C-NMR** (DMSO-d_6, 50 MHz) δ 129.52, 70.29, 65.31.

IR (KBr, cm^{-1}) 3550, 2990, 1438, 1226, 1098, 1030, 902.

Results and Discussion

Synthesis of conduritol-E started from 1,2-benzenediol and protection of hydroxyl group by acetylation using pyridine-acetic anhydride at 0° C. The resulting diacetate **1b** was reacted with bromine at −45° C to form sterically hidered dibromides able to control the approach of $KMnO_4$. We isolated two isomeric dibromides **2** and **3** in a ratio of 2:98 formed by 1.2-addition. Compound **3** was easily separated by recrystallisation of the mixture. Compound **3** has the same configuration as conduritol-F. The structural assignment was easily made by comparison of the NMR-spectrum with those of conduritol- F[13]. $KMnO_4$-oxidation of **3** gave **4a** the known compound[8] as a sole product. Careful examination of the reaction mixture did not reveal the formation of any other isomer (conduritol-D derivative on which all hydroxyl groups have cis-configuration). Therefore, we assume that the approach of MnO_4^- anion to double bond of **3** takes place exclusively in anti fashion to give **4a**. Zn-Elimination of **4b** followed by acidic hydrolysis afforded conduritol-E **5b**.

This methodology provides us entry to high-scale and stereoselective synthesis of conduritol-E. Application of asymmetric dihydroxylation should result in enantioselective synthesis of conduritol-E.

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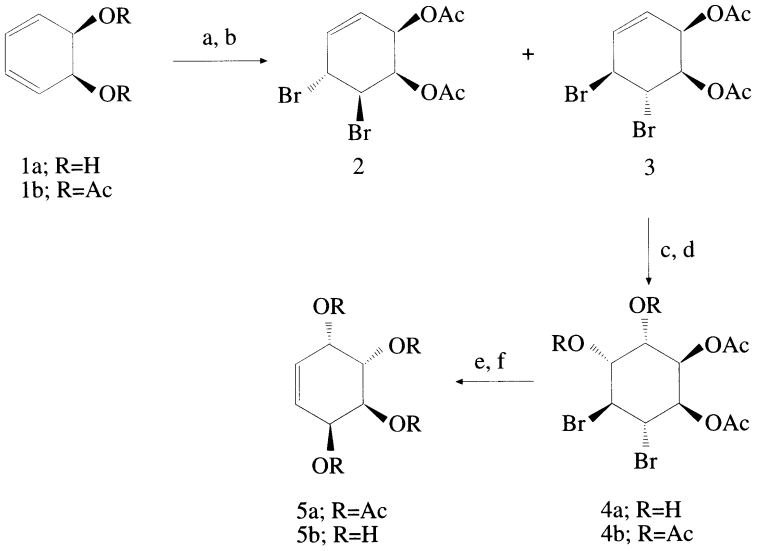
Acknowledgment

We thank the Department of Chemistry (Atatürk University) for financial support of this work and the State Planning Organisation (DPT) of Turkey for purchasing a 200 MHz NMR.



Reagents and Conditions: **a)** Ac_2O-Pyridine, 0° C, 6 h; **b)** Br_2, CCl_4, −45° C, 1h; **c)** $KMnO_4$-$MgSO_4$, EtOH, −15° C, 20 h **d)** Ac_2O, Pyridine, r.t., 8h, **e)** Zn, AcOH-Ether, reflux, 30 min, **f)** 0.5 N H_2SO_4, r.t., 3 h.

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