Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 23 Sep 2006

To cite this article: Hasan Seçen, Ahmet Maraş, Yaşar Sütbeyaz & Metin Balci (1992): A Novel Synthesis of Conduritol-C and Conduritol-E via p-Benzoquinone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:18, 2613-2619

To link to this article: http://dx.doi.org/10.1080/00397919208021660

SYNTHETIC COMMUNICATIONS, 22(18), 2613-2619 (1992)

A Novel Synthesis of Conduritol-C and Conduritol-E via p-Benzoquinone

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SUMMARY: A new and stereospecific synthesis for Conduritol-C **8** and Conduritol-E **13a** has been developed starting from p-benzoquinone **1**. 1,4-oxygen functionalities were introduced in both synthesis by the reduction of dibromo p-benzoquinone **2** with $NaBH_4$. 2,3-oxygen functionalities were introduced by $KMnO_4$ oxidation of **4** for Conduritol C **8**. Oxidation of **3** with m-chloroperbenzoic acid gave **9**. Acid-catalyzed ring opening reaction of **9** gave **10a** which leads to Conduritol-E.

Conduritols[1] are 1,2,3,4-cyclohexenetetrol isomers and interesting inhibitors for glycosidases[2]. A number of conduritol derivatives have been found to possess antifeedant[3], antibiotic, antileukemic, and growth-regulating[1] activity. Theoretically, six conduritol diasteroisomers are possible. The occurence in the nature of only two conduritols namely conduritol-A[4] and conduritol-F[5] has been established. Previously conduritols have been synthesized from carbohydrates, from microbial oxidation products of substituted benzenes and by deoxygenation of chiral inositols[1,6]. In this paper we describe a new synthetic methodology leading to conduritol-C **8** and conduritol-E **13a** starting from p-benzoquinone **1**.

The first synthesis of conduritol-C **8** was carried out by McCasland and Reeves[7] from epiinositol. Yurev and Zefirov[8] have described a short synthetic way to conduritol-C **8** starting from cycloaddition product of furan and ethylene carbonate.

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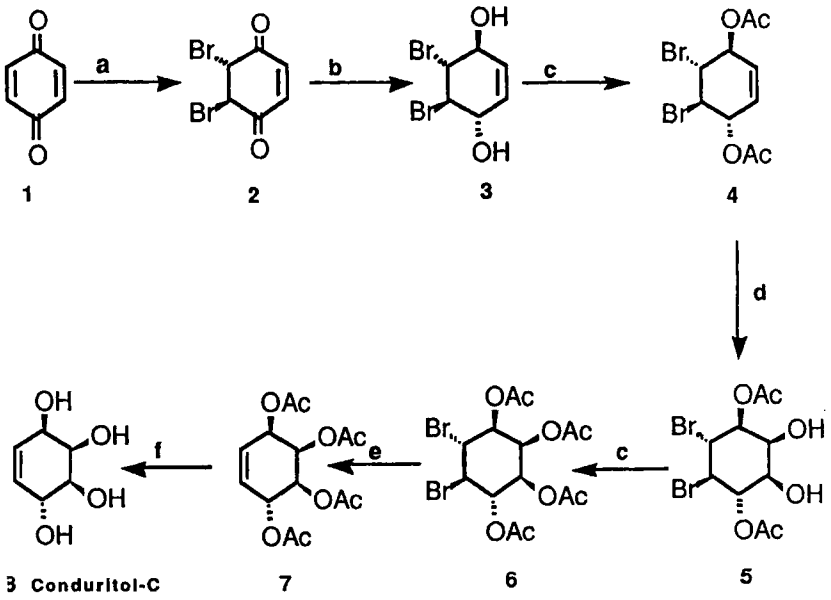


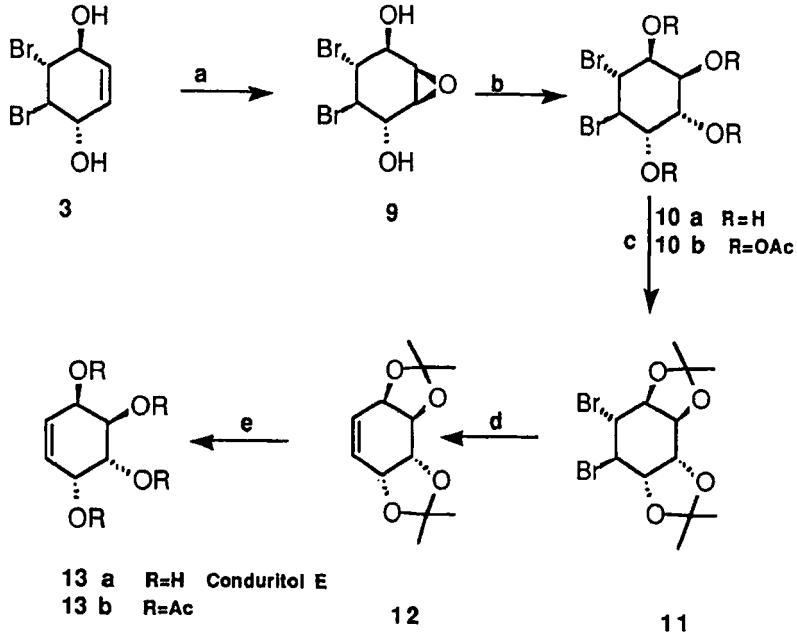
Reagents and Conditions:

a) Br_2, CCl_4, 0 °C, 2h **b)** $NaBH_4$, water, ether, 0 °C **c)** Aceticanhydride, pyridine, r.t, 12h **d)** $KMnO_4$, -15 °C, 20h **e)** Zn, DMSO, 95 °C, 12 h **f)** NH_3, MeOH, r.t, 24 h

Scheme 1

Bromination and following reduction of p-benzoquinone gave the known compound **3**[9] with definitive configuration. Subsequent to the protection of the alcohol functions as diacetates, cis-hydroxylation led to **4** as the sole isomer **5** which was characterized as the tetraacetate derivative **6**. This tetraacetate **6** on reaction with zinc-acetic acid gives **7** from which the free tetrol **8** was obtained by ammonylosis. The configuration was established by spectral data and by comparison with those reported in the literature.

The first synthesis of conduritol-E was described by Nakajima et al.[10] in 1957 which was not stereospecific and not useful. A stereospecific synthesis for conduritol-E was described by Angyal and Gilham[11] and later also again by Nakajima[12]. We used by our synthesis, again p-benzoquinone **1** as the



Reagents and Conditions:

a) 3-Chloro-perbenzoic acid (m-CPBA), ether, reflux, 12h b) 0.5 N H_2SO_4, reflux, 4 h c) 2,2-dimetoxy- propane, p-toluenesulphonic acid, benzene, 3 h d) Zn, DMSO, 95 ^{o}C, 12 h e) 0.5 N H_2SO_4 , reflux, 4 h.

Scheme 2

starting material. Oxidation of **3** with m-chloroperbenzoic acid (m-CPBA) gives the epoxy compound **9**[9]. In the trans epoxide ring opening by addition of water in classic substitution mechanism, **9** should give two different opening products. However, we obtained only **10a** which is the precursor of the Conduritol-E **13a**. The other precursor of Conduritol-B was not observed. The product was characterized as its tetraacetates **10b** by spectroscopic methods. For further reaction we converted the tetrol **10a** into the readily obtained di-O-isopropylidene derivative **11**. This cyclic ketal **11** reacted smoothly with zinc-DMSO and gave Conduritol-E as its diispropylidene derivative **12**. Hydrolysis of **12** gave Conduritol-E **13a** which was also converted to their tetraacetate **13b** for further structural proof.

EXPERIMENTAL:

(1α,2β,3α,4β)-1,4-diacetoxy-2,3-dibromo-cyclohex-5-ene 4. To a stirred solution of **3** (8g, 22.5 mmol) in 10 ml of pyridine was added Ac_2O (10.5g, 103 mmol). The reaction mixture was stirred at room temperature for 8 hours. The mixture was cooled to 0 °C and added 60 ml 4N HCl solution, and extracted with ether (3X50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (3X15 mL) and water (3X15 mL) than dried ($MgSO_4$). Removing of the solvent under reduced pressure gave **4** (76 %, m.p. 91-92 °C, recrystallized from $CHCl_3$/hexane).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 2 H), 5.70 (AA' part of AA'BB' systeme, 2H), 4.29 (BB' part of AA'BB' systeme, 2H), 2.17 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.63, 128.17, 73.33, 52.70, 20.70.

IR (KBr) 2980, 1750, 1370, 1215, 1120, 1030.

(1α,2β,3α,4β,5β,6β)-1,2-dibromo-3,4,5,6-tetraacetoxy-cyclo-hexane 6. To a stirred EtOH solution (500mL) of **4** (16g, 45 mmol) was added a solution of $KMnO_4$ (7.10 g, 45mmol) and $MgSO_4$ (5.4g, 45mmol) in water (200mL) at -5 °C for 5 hours. After the addition was completed, the reaction mixture was stirred for 15 hours at the given temperature then 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 AcOEt (3X100 mL) and the extracts were dried (Na_2SO_4) . Evaporation of the solvent gave **5** (8.88 g, 51 %).

6 was synthesized by acetylization of **5** as described by the synthesis of 4 above (77 %, mp 140-141 °C, recrystallized from $CHCl_3$/hexane).

^{1}H-NMR (200MHz, $CDCl_3$) δ 5.56 (m, 2H), 5.16 (dd, 1H), 5.03 (dd, 1H), 4.32 (dd, 1H), 4.05 (dd, 1H) , 2.20 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H).

^{13}C-NMR (50MHz, $CDCl_3$) δ 169.18, 168.95, 71.27, 69.31, 68.56, 52.28, 51.22, 20.63, 20.44.

IR (KBr) 2995, 1755, 1430, 1365, 1226, 1055, 920.

(1α,2β,3β,4β)-1,2,3,4-tetraacetoxy-cyclohex-5-ene 7. [Conduritol-C tetraacetate]. To a solution of **6** (5 g, 10.5 mmol) in 10 mL of DMSO was added 2g (30 mmol) of zinc dust and 50 mg of iodine .The mixture was stirred magnetically at 95 °C for 12 hours. After cooling to room

temperature was added 50 mL of water and 50 mL of ether. The aqueous phase was extracted with ether (2X50 mL), and the combined organic extracts were dried (Na_2SO_4) . Evaporation of the solvent gave conduritol-C tetraacetate 7 (61 %, m.p. 90-91 ^oC, recrystallization from $CHCl_3$ /hexane).

^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.71 (m, 5H), 5.21 (br.d, 1H), 2.13 (s,3H), 2.08 (s,3H), 2.05 (s,3H), 2.04 (s,3H).

^{13}C-NMR (50MHz, $CDCl_3$) δ 170.45, 169.99, 127.49, 127.03, 70.51, 69.75, 69.45, 67.58, 20.93, 20.71.

IR (KBr) 2995 , 1755, 1430 , 1365, 1226, 1055, 920.

(1α,2β,3β,4β)-1,2,3,4-tetrahydroxy-cyclohex-5-ene 8 [Conduritol-C]. 500 mg (1.59 mmol) of Conduritol-C tetraacetate 7 was dissolved in 20 mL of absolute methanol. While dry NH_3 is being passed through solution, the mixture was stirred for 24 hours at room temparature. Evaporation of methanol and acetamide, gave Conduritol-C **8** (80 %, m.p. 151-152 ^oC, recrystallized from absolute EtOH).

^{1}H-NMR (200 MHz, CD_3OD) δ 5.61 (m, 2H), 4.24 (m, 2H), 4.03 (m, 1H), 3.54 (m,1H).

^{13}C-NMR (50 MHz, CD_3OD) δ 130.78, 130.07, 76.09, 73.99, 70.59, 69.43.

IR (KBr) 3440, 2990, 1410, 1140, 1050, 1020, 840.

(1α,5α,6β,10β,11α,12β)-2,4,7,9-tetraoxa-3,3,8,8-tetra-methyl-11,12-dibromo-tricyclo[8.2.0$^{1.5}$.0$^{6.10}$]dodecan 11. Epoxide **9** (1g, 3.47mmol) was dissolved in 10 mL of 0.5 N H_2SO_4 and the resulting solution was refluxed at 90^o C for 6 hours. After cooling to room temparature, the acid was neutralized with $BaCO_3$. After filtration of the precipitate, removing the solvent under reduced pressure gave **10 a** (61 %) .

To a solution of **10 a** (500 mg , 1.63 mmol) in 250 mL of dry benzene was added 2,2-dimethoxy propane (430 mg, 4.13 mmol) and 20 mg of p-toluenesulphonic acid . The resulting mixture was refluxed for 3 hours. Evaporation of the solvent gave **11** (88 %, m.p. 162-163 ^oC, recrystallized from ethylacetate/hexane) .

^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.50 (m, 2H), 4.42 (m, 2H), 3.92 (m, 2H), 1.52 (s, 6H),1.40 (s, 6H).

^{13}C-NMR (63MHz, $CDCl_3$)δ 109.32, 79.46, 74.72, 55.30, 27.99, 25.42.

IR (KBr) 2998, 1465, 1400, 1230, 1145, 1065, 830.

(1α,2β,3α,4α,5β,6β)-1,2dibromo-3,4,5,6-tetraacetoxy-cyclo-hexane 10b. The tetraacetate **10b** was synthesized by acetylization of **10a** as described above by the synthesis of **4** (76 %, m.p. 140-141 °C).
^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.30 (m, 4H), 4.20 (m, 2H), 2.19 (s, 6H), 2.07 (s, 6H).
^{13}C-NMR (50 MHz, $CDCl_3$) δ 169.17, 168.78, 71.03, 67.50, 51.50, 20.62, 20.50.
IR (KBr) 2998, 1745, 1425, 1365, 1230, 1125, 1075, 1045, 1000.

(1α,5α,6β,10β)-2,4,7,9-tetraoxa-3,3,8,8-tetramethyl-tricyclo[8.2. $0^{1.5}.0^{6.10}$]dodec-11-ene 12. **12** was synthesized by debromination of **11** as described by the synthesis of Conduritol-C tetraacetate 7 (74 %, m.p. 53-54 °C, recrystallized from $CHCl_3$/ hexane) .
^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.72 (m, 2H), 4.55 (m, 4H), 1.38 (s, 6H), 1.37 (s, 6H).
^{13}C-NMR (63 MHz, $CDCl_3$) δ 126.91, 109.11, 73.21, 70.21, 27.81, 26.43.
IR (KBr) 2998, 1460, 1380, 1300, 1280, 1230, 1165, 1120, 1100, 1060.

(1α,2α,3β,4β)-1,2,3,4-tetrahydroxy-cyclohex-5-ene 13a [Conduritol-E]. **12** (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. (77 %, m.p. 176-177 °C, recrystallized from MeOH /hexane).
^{1}H-NMR (250 MHz, DMSO) δ 5.50 (s, 2H), 4.07 (m, 2H), 3.75 (m, 2H)
^{13}C-NMR (63 MHz, DMSO) δ 129.52, 70.29, 65.31.
IR (KBr) 3350, 2990, 1438, 1226, 1098, 1030, 902.

(1α,2α,3β,4β)-1,2,3,4-tetraacetoxycyclohex-5-ene 13b [Conduritol-E tetraacetate]. **13b** was synthesized by acetilization of **13a** as described above by the synthesis of **4.** (60 %, m.p. 150-151 °C, recrystallized from $CHCl_3$ / hexane).
^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.93 (m,2H), 5.70 (m, 2H), 5.45 (m, 2H), 2.09 (s, 6H), 2.05 (s, 6H).
^{13}C-NMR(50 MHz, $CDCl_3$) δ 170.09, 169.81, 128.11, 66.56, 66.06, 20.69 20.58.
IR (KBr) 2995, 1744, 1363, 1222, 1068, 1025.

ACKNOWLEDGEMENT: We thank Turkish Scientific and Technical Research Council (TUBITAK- Grant No. TBAG/1063) and Department of Chemistry (Atatürk University) for their financial support, and Prof. Dr. Waldemar Adam (University of Würzburg/ Germany) for High Resolution NMR Spectra.

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(Received in UK 6 May, 1992)