A Novel and Stereospecific Synthesis of Conduritol-A

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A new and stereospecific synthesis for conduritol-A has been developed starting from cyclohexa-1,4-diene where hydroxy groups have been introduced by classical KMnO₄-oxidation followed by photo-oxygenation; suitable ring-opening reactions gave the desired conduritol-A.

Conduction of a minoconduction of the second conduction of the second c inhibitors for Glycosidases.¹ In 1908 Kubler² isolated from the bark of the vine Marsdenia condurango the first known cyclohexenetetrol which was named as conduritol.† The correct configuration of this isomer was later established by Dangschat and Fischer.³ The first successful and non-stereospecific synthesis of conduritol-A was carried out by Nakajima et al.⁴ starting from *trans*-benzenediol. More recently, Knapp et al.⁵ described a stereospecific synthesis of the naturally occurring conduritol-A using p-benzoquinone in a multistep sequence. Herewith, we describe a novel, efficient and stereospecific synthesis of conduritol-A starting from the readily available cyclohexa-1,4-diene. Our synthetic strategy is based on the introduction of two oxygen functionalities at the C₂ and C₃ positions by KMnO₄-oxidation and the other two oxygen functionalities at the C_1 and C_4 positions by photo-oxygenation.⁶

The key compound, (2), in the synthesis of conducitol-A was synthesized by bromination of cyclohexa-1,4-diene followed by KMnO₄-oxidation as described in the literature.⁷ The resulting cis-diol was protected by ketal formation with 2,2-dimethoxypropane. Dehydrobromination with DBU (1,8diazabicyclo (5.4.0) undec-7-ene) provided (2) in high yield. Photo-oxygenation of (2) in CCl_4 (150 W, projection lamp) at room temperature using tetraphenylporphyrin as the sensitiser, followed by silica gel chromatography afforded (3) in a yield of 95%. ¹H and ¹³C n.m.r. spectra revealed suprisingly the formation of only one isomer. A six-line ¹³C n.m.r. spectrum is in good agreement with the structure (3), which possesses a symmetry element. On the basis of the spectral data we were not able to predict the exact configuration of the molecule. We assume that singlet oxygen approaches the diene unit from the sterically less crowded face of the molecule to form the anti-adduct. The exact configuration was determined at the final step. For additional structural proof we have relied on chemical transformations such as the cobalt-mesotetraphenylporphyrin (CoTPP) catalysed reaction.⁸ We sub-

mitted the endoperoxide (3) to CoTPP-catalysed reaction and obtained the desired diepoxide (4) in high yield. Selective reduction of the peroxide linkage was performed with thiourea⁹ under very mild conditions to give (5a); in 80% yield. Since only the oxygen-oxygen bond breaks in this reaction, it preserves the configuration at all four carbon atoms. The ¹H and ¹³C n.m.r. spectra of the diol (5a) support the symmetrical structure in which a plane of symmetry bisects the ethylene unit and ketal-ring and is consistent only with a symmetrical diol structure. For further structural proof, the diol (5a) was converted into the corresponding diacetate (5b).[‡] The ¹H n.m.r. spectrum of (5b) is in full agreement with the proposed structure. Alkoxy protons $(H_1, H_2, H_3, and H_4)$ give rise to an AA'BB' system at δ 4.25 and 5.25 where the double bond protons (H₅ and H₆) resonate at δ 5.70 as a singlet. Since the bulky acetoxy groups will prefer the equatorial position, the adjacent protons $(H_1 \text{ and } H_4)$ will be in the axial position. Inspection of Dreiding models indicates that the dihedral angle between the protons H_1 and H_2 (and H_3 and H_4) in (5b) is nearly 160–170° where the dihedral angle between H_1 and H_6 (and H_4 and H_5) is nearly 90°. Therefore, we observe in the ¹H n.m.r. spectrum of (5b) a coupling only between the alkoxy protons $(H_1, H_2, H_3, and$ H_4). Deketelisation of (5a) was carried out in acidified methanol solution quantitatively. All analytical methods indicate the presence of only one cyclohexenetetrol (6a). The spectroscopic properties of (6a) and the corresponding tetraacetate (6b)[‡] compared well with those of the previously

[†] There are six possible conduritol isomers. To avoid ambiguity, this diastereoisomer was named conduritol-A.

[‡] Selected spectral data for (**5a**): i.r. (KBr): 3400, 2990, 1390, 1080 cm⁻¹; ¹H n.m.r. (400 MHz, CDCl₃) δ 1.35 (s,3), 1.46 (s, 3), 3.12 (br. s, 2), 4.27 (br. s, 4), 5.85 (s, 2); ¹³C n.m.r. (100 MHz, CDCl₃) δ 24.52, 26.77, 69.96, 79.28, 109.42, 131.07.

⁽⁵b): i.r. (KBr): 3000, 2945, 1755, 1375, 1220, 1060 cm⁻¹; ¹H n.m.r. (400 MHz, CDCl₃) δ 1.35 (s, 3), 1.47 (s, 3), 2.09 (s, 6), 4.25 (m, 2), 5.25 (m, 2), 5.70 (s, 2); ¹³C n.m.r. (100 MHz, CDCl₃) δ 21.08, 25.09, 27.09, 71.63, 75.36, 105.65, 128.22, 170.18.

⁽⁶b): i.r. (neat): 2950, 1750, 1375, 1225, 1060, 1030 cm⁻¹; 1 H n.m.r. (400 MHz, CDCl₃) δ 2.03, (s, 3), 2.06 (s, 3), 5.31 (d, 2), 5.40 (dd, 2), 5.85 (s, 2); 13 C n.m.r. (100 MHz, CDCl₃) δ 20.61, 20.91, 69.17, 69.31, 127.68, 169.67, 170.03.



Scheme 1. Reagents and conditions: i, Br_2 , $CHCl_3$, -40 °C; ii, $KMnO_4$, EtOH, H_2O , -10 °C; iii, 2,2-dimethoxypropane, H_2SO_4 , CH_2Cl_2 , r.t.; iv, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene, reflux; v, ${}^{1}O_2$, hv, tetraphenylporphyrin (TPP), CCl_4 , r.t.; vi, CoTPP, CH_2Cl_2 , 0 °C; vii, thiourea, MeOH, r.t.; viii, HCl, MeOH, 45 °C; ix, acetylation conditions, Ac₂O, pyridine, r.t.

reported conductiol-A. $^{+2.10}$ The melting point (140–141 °C) of (6a) is also in agreement with those reported in the literature (142–143 °C).²

In summary, with relatively little synthetic effort we have achieved the stereospecific synthesis of naturally occurring conduritol-A starting from readily available cyclohexa-1,4diene.

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