# A Novel and Stereospecific Synthesis of Conduritol-A

**Yaşar Sütbeyaz, Hasan Seçen, and Metin Balcı***

*Department of Chemistry, Faculty of Science, Atatürk University, Erzurum, Turkey*

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 $KMnO_4$-oxidation followed by photo-oxygenation; suitable ring-opening reactions gave the desired conduritol-A.

Conduritols and aminoconduritols are interesting potential inhibitors for Glycosidases.[1] In 1908 Kubler[2] 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 $C_2$ and $C_3$ positions by $KMnO_4$-oxidation and the other two oxygen functionalities at the $C_1$ and $C_4$ positions by photo-oxygenation.[6]

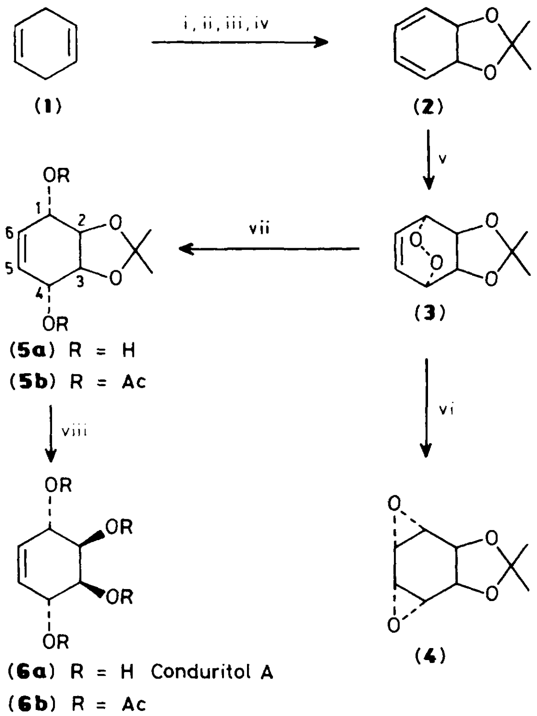
The key compound, (**2**), in the synthesis of conduritol-A was synthesized by bromination of cyclohexa-1,4-diene followed by $KMnO_4$-oxidation as described in the literature.[7] The resulting *cis*-diol was protected by ketal formation with 2,2-dimethoxypropane. Dehydrobromination with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) 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 $^{13}C$ n.m.r. spectra revealed suprisingly the formation of only one isomer. A six-line $^{13}C$ 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-*meso*-tetraphenylporphyrin (CoTPP) catalysed reaction.[8] We submitted 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 thiourea[9] 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 $^{13}C$ 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 ($H_5$ and $H_6$) resonate at δ 5.70 as a singlet. Since the bulky acetoxy groups will prefer the equatorial position, the adjacent protons ($H_1$ 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 tetra-acetate (**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, $CDCl_3$) δ 1.35 (s,3), 1.46 (s, 3), 3.12 (br. s, 2), 4.27 (br. s, 4), 5.85 (s, 2); $^{13}C$ n.m.r. (100 MHz, $CDCl_3$) 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, $CDCl_3$) 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); $^{13}C$ n.m.r. (100 MHz, $CDCl_3$) 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 $cm^{-1}$; $^1H$ n.m.r. (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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, $^1O_2$, $h\nu$, 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, $Ac_2O$, pyridine, r.t.

reported conduritol-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-1,4-diene.

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