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A New and Stereospecific Synthesis of Conduritol-F and Conduritol-B

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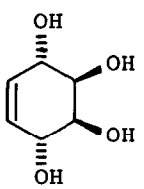
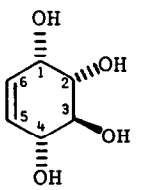
Summary: *A new and stereospecific synthesis for conduritol-F has been developed starting from trans-benzenediacetate **5** and oxepine-benzeneoxide **8** where the oxygen functionalities were introduced in both cases by photooxygenation; suitable ring opening reactions gave the desired conduritol-F. Acid-catalyzed ring opening reaction of **11** in aceticanhydride gave conduritol-F and conduritol-B in a ratio of 2:1.*

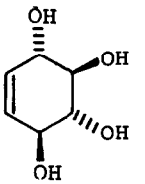
Conduritols are 1,2,3,4-cyclohexenetetrol isomers and interesting potential inhibitors for glycosidases[1]. Theoretically, six conduritol diastereoisomers are possible. To avoid ambiguity, the diastereoisomers have been called with letters A,B,C,D,E, and F[2]. In the nature the occurrence of only two conduritols, namely Conduritol-A and conduritol-F has been established.



1 Conduritol-A



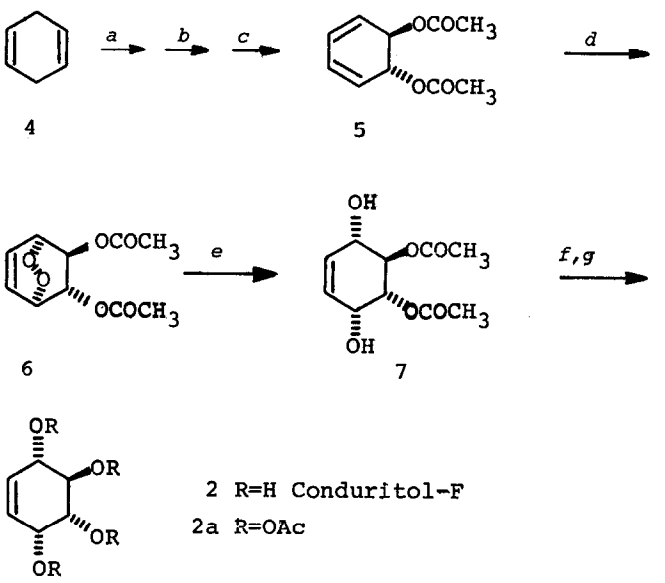
2 Conduritol-F



3 Conduritol-B

Conduritol-A[3] was dicovered by Kübler from the bark of the vine *Marsdenia condurango* in 1908. In 1962 Plouvier[4] discovered a new optically active cyclitol-isomer from *Crysanthemum Leucanthemitol* which was isomer with Conduritol-A and he named this new conduritol isomer as L-Leucanthemitol (Conduritol-F). This very restricted distribution of conduritol-A is in contrast to that of its isomer, Conduritol-F which at least in traces can be detected in almost green plants. In the mean-time all possible Conduritol isomers have been synthesized by many different synthetic sequences[5].Recently, we developed a new synthetic methodology leading to saturated cyclohexane tetrols[6] and conduritol-A[7,8]. In this communication, we wish to present a new and stereospecific synthesis for conduritol-F by two different approach and conduritol-B.

For the first approach we used the known trans-benzenediacetate **5** which was synthesized as described in the literature[9]. Tetraphenylporpyrine sensitized photooxygenation of **5** in carbontetrachloride solution at 0 °C followed by silica gel chromatography afforded the endoperoxide **6** in a yield of 56%.



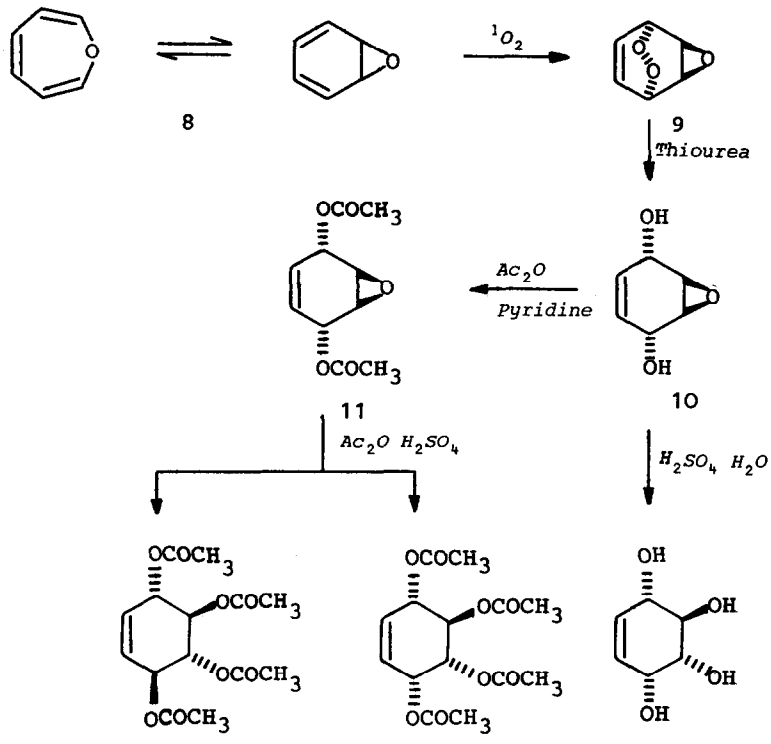
Scheme 1

a) Br_2, -40 °C, b) m-ClPBA, Ac_2O, H_2SO_4 c) LiCl, Li_2CO_3, HMPA d) $^1O_2$, TPP, CCl_4 hv e) MeOH, Thiourea f) Ac_2O, Pyridine g) NH_3, MeOH

At this step we introduced all possible oxygen functionalities in correct configuration as desired in conduritol-F. The structure of the endoperoxide **6**[10] was determined on the basis of ^{1}H-NMR data and chemical transformations. Selective reduction of the peroxide linkage was performed with thiourea[11] under very mild conditions to give **7**. Since only the oxygen-oxygen bond breaks in this reaction, it preserves the configuration at all four carbon atoms. The diacetate **7** was converted into the corresponding tetraacetate **2a**. The 360 MHz ^{1}H-NMR and 90 MHz ^{13}C-NMR spectra are in full agreement with the proposed structure. The complete analysis of the ^{1}H-NMR spectrum indicates that the three acetoxy groups at C_1, C_2, and C_3 prefer the equatorial position the last one at C_4 the axial position. Deacetylation of **2a** was carried out with ammonia in methanol to give conduritol-F which was identical with those reported in the literature[4,12].

In the second approach, we started from oxepine-benzenoxide[13] **8**. Foster and Berchtold reported that reaction of oxepine-benzeneoxide with singlet oxygen afforded the unsaturated anti epoxyendoperoxide[14] **9**. The peroxide linkage in **9** was reduced by thiourea in methanol to give epoxydiol **10**. Acid catalyzed ring-opening of **10** afforded conduritol-F which was identical with the compound obtained from the first sequence.

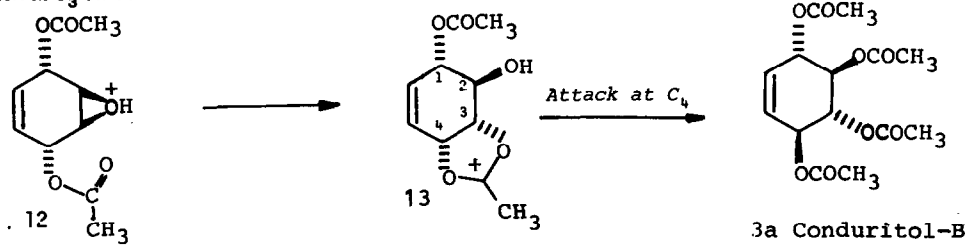
In another reaction we converted epoxydiol **10** into the corresponding epoxydiacetate **11**. Epoxydiacetate **11** was submitted to acid-catalyzed ring-opening reaction in aceticanhydride. Analysis of the reaction mixture has revealed that the product was consisting from two isomers. Column chromatography on silica gel afforded the tetraacetates of Conduritol-F and Conduritol-B in a ratio of 2:1 (Total yield 67%). Deacetylation of 3a with ammonia in methanol afforded conduritol-B (80%) which was identical with those reported in the literature[2,12a,15,16].



Scheme 2

3a Conduritol-B 2a Conduritol-F 2 Conduritol-F

Conduritol-F was the expected product in this reaction. The formation of conduritol-B has a likely explanation on the basis of the involving of the neighboring acetoxy group on the course of the epoxide ring-opening. We assume preliminary formed oxonium ion **12** by an axial attack of the carbonyl oxygen at the adjacent acetoxy group to give a 2-methyl-1,3-dioxolen-2-ylium ion **13** paired with acetate anion. This cation can undergo nuchleophilic displacement by the anion at either of the uncharged dioxolenium carbons C_3 and C_4 to give conduritol-A and conduritol-B, respectively. Since this displacement takes place with inversion of configuration, the next result is the formation of conduritol-B. The fact that we observe only formation of conduritol-B indicates that the neighboring hydroxy (or acetoxy) group prevents any attack at C_3 carbon.



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10) **2** : ^{1}H-NMR (360 MHz, CD_3OD): 5.77 (ddd, H_5, J_{56}= 9.82; J_{45}= 4.8; J_{15}= 1.88), 5.70 (dd, H_6, J_{16}= 1.91), 4.15 (t, H_4, J_{34}= 4.1), 3.92 (br. d, H_1, J_{12}= 7.60), 3.61 (dd, H_2, J_{23}= 10.1), 3.41 (dd, H_3).-^{13}C-NMR (90 MHz): 133.84 (C_6), 128.07 (C_5), 74.04 (C_1), 73.89 (C_2), 72.68 (C_3), 68.05 (C_4).

2a :^{1}H-NMR (360 MHz, $CDCl_3$), 5.91 (ddd, H_5, J_{56}= 9.99; J_{45}= 4.80; J_{15}= 1.56), 5.84 (dd, H_6, J_{16}= 1.93), 5.62 (t, H_4, J_{34}= 3.97), 5.57-5.49 (m, H_1 and H_2), 5.13 (dd, H_3, J_{23}= 10.01), 2.11 (s, CH_3), 2.08 (s, CH_3), 2.05 (s, CH_3), 2.02 (s, CH_3).-^{13}C-NMR (90 MHz, $CDCl_3$): 170.15 (2x C=O), 169.95 (C=O), 169.72 (C=O), 130.71 (C_6), 125.21 (C_5), 71.67 (C_1), 68.98 (C_2), 68.34 (C_3), 65.72 (C_4), 20.79 (2x CH_3), 20.68 (CH_3), 20.51 (CH_3).

6 :^{1}H-NMR (60 MHz, $CDCl_3$): 6.40-6.90 (m, olefinic), 4.20-5.00 (m, 4H), 2.15 (s, CH_3), 2.00 (s, CH_3).

10 :^{1}H-NMR (60 MHz, CD_3COCD_3): 5.55 (br. s, olefinic), 4.20 (br. s, H_1, and H_4), 3.10 (br. s, H_2, and H_3).

11 :^{1}H-NMR (60 MHz, CCl_4): 5.68 (br. s, olefinic), 5.33 (br. s, -CHOAc), 3.10 (br. s, epoxide), 2.05 (s, 6H).-IR (CCl_4): v= 1740 (carbonyl), 1000 (epoxide).

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