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Stereoselective Total Syntheses of Conduritols-F and -A from Tricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3,6-dione

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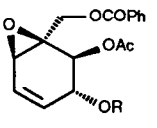
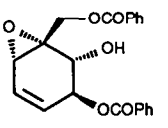
Abstract: Effective syntheses of conduritols-F and A have been accomplished starting from cyclopentadiene/benzoquinone adduct 6. Key intermediates are tricyclic acetates 9 and 15 which, when subjected to flash vacuum thermolysis, afford epoxycyclohexene diacetate 10 and cyclohexadiene diacetate 17, respectively. Conduritol-F is obtained from 10 by hydrolysis while conduritol-A is produced from 17 by osmylation. In both cases the final step involves removal of the acetate groups by amidation with ammonia.

Highly oxygenated monocyclic cyclohexene compounds occur widely in nature and usually possess a wide variety of interesting biological activities. Typical examples are cyclohexene epoxides such as (+)-β-senepoxide 1, (+)-pandoxide 2 and (-)-pipoxide 3[1,2] and the conduritols 4[3]. As part of our continuing studies on the exploitation of the rich arsenal of medicinal plants in Tanzania as a source for new pharmaceutical products, we sought a general synthesis to this class of natural products.



1 R= Ac
2 R= Me



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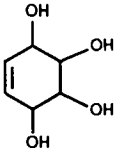

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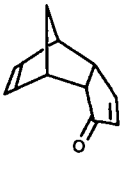

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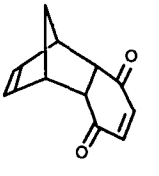


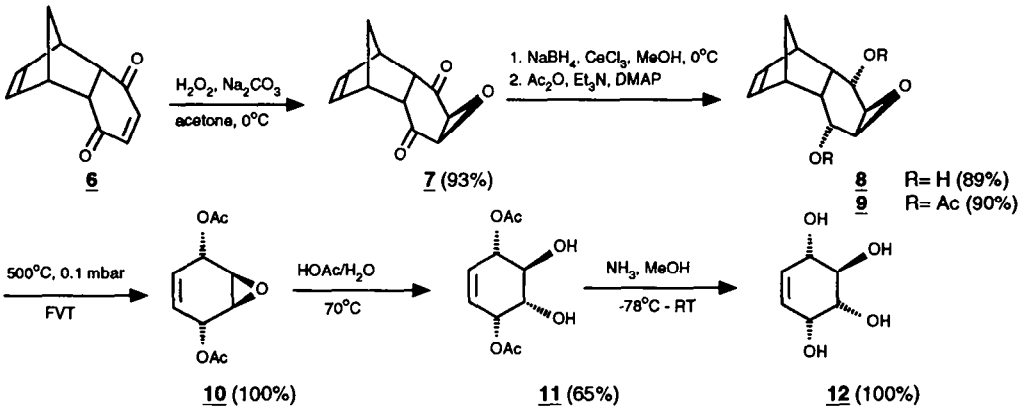
6

In recent years, we and others have demonstrated that tricyclodecadienone 5 is an extremely useful synthon for oxygenated cyclopentenones[4]. Key steps in this approach to cyclopentenoids are (i) the stereo- and regioselective functionalization of the enone system in 5 followed by (ii) thermal [4+2]cycloreversion utilizing the technique of flash vacuum thermolysis (FVT). In a similar way tricyclo[6.2.1.0^{2,7}]undecadiene-dione 6, which is essentially the Diels-Alder adduct of cyclopentadiene and benzoquinone, may be used for the stereoselective synthesis of oxygenated cyclohexene derivatives[5]. In this paper we wish to report an efficient stereoselective synthesis of some novel oxygenated cyclohexa-1,3-dienes, *e.g.* 10 and 17, which may serve as synthons for a variety of interesting cyclohexanoids. Their applicability in natural product synthesis is demonstrated by their conversion in conduritol-F and conduritol-A, respectively[7].

endo-Tricycloundecadiene-dione 6 is readily and stereoselectively epoxidized to *exo*-4,5-epoxydione 7

with hydrogen peroxide under mild alkaline conditions[8] (Scheme I). Treatment of this epoxide with sodium

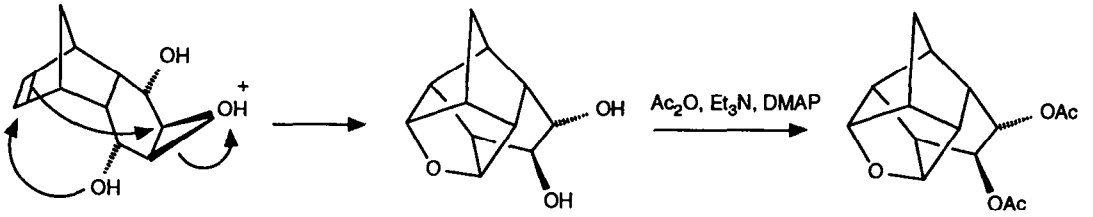
Scheme I



6 7 (93%) 8 9 10 (100%) 11 (65%) 12 (100%)

borohydride in the presence of ceriumtrichloride[9] afforded in a completely stereoselective reduction step *meso*-3,6-diol epoxide **8** as a crystalline solid (m.p.130-131 °C) in excellent yield of 89%. This result can, however, only be attained when the reduction is carried out in methanol at 0 °C and worked up under alkaline conditions (1M sodium hydroxide solution). Normal aqueous work up of the reduction mixture led to a mixture of products, the major one being tetracyclic ether **13** isolated as its diacetate **14** (m.p. 90-91 °C) (Scheme II). The formation of product **13** is readily explained by a synchronous addition/substitution process involving intramolecular alcohol addition to the C_9-C_{10} ethylenic double bond and nucleophilic epoxide ring opening by the nucleophilic center at C_{10}. This unusual cage forming reaction is most likely triggered by initial protonation of the epoxide oxygen atom which causes considerable electron deficiency at C_4[10].

Scheme II



13 14

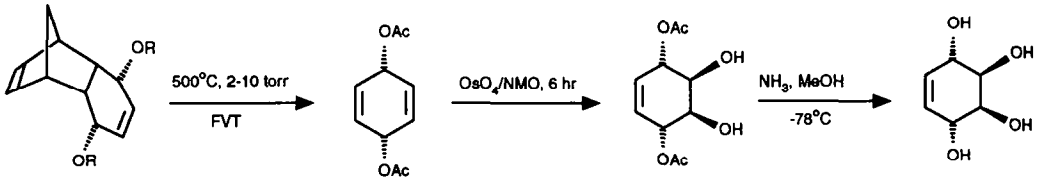
Formation of **13** was also observed when an attempt was made to purify **8** by chromatography on silica gel. Attempted reduction of **7** using zinc borohydride or sodium borohydride in the absence of ceric chloride did not meet with success. The *endo*-stereochemistry of both alcohol functions in **8** could unmistakably be deduced from its ^{1}H NMR-spectrum. The exclusive formation of **8** proves that steric control of this hydride reduction of **7** is primarily exerted by the norbornene C_9-C_{10} ethylene bridge despite the presence of an adjacent *exo*-epoxide function. Double acylation of **8** was conveniently carried out with acetic anhydride in the presence of dimethylaminopyridine to give diacetate **9** (m.p. 84-85 °C) in 90% yield. The thermal cycloreversion of **9** applying the technique of flash vacuum thermolysis (500 °C, 10^{-2} torr) smoothly led to

quantitative formation of diacetoxycyclohexene epoxide **10** (m.p. 85-86 °C). Both with respect to efficiency and convenience this route to **10** is far superior to that reported by Prinzbach *et al.* which starts from cyclohexa-1,4-diene and uses allylic bromination with N-bromosuccinimide as the key step[11].

A completely stereoselective epoxide ring opening of **10** to give diacetoxydiol **11** was achieved by treating **10** with a solution of 80% acetic acid in water. Under these conditions no hydrolysis of the acetate functions was observed. At this stage of the synthesis such a hydrolysis should be avoided as isolation of the resulting tetrol **12** turned out to be quite troublesome due to its excellent solubility in water. Deacylation of **11** was readily accomplished by amidation of the acetate functions with ammonia in methanol, starting at -78 °C and slowly increasing the temperature to room temperature. The formed acetamide was conveniently removed by sublimation to give crude conduritol-F **12** in nearly quantitative yield. Recrystallization from ethanol afforded pure **12** (m.p. 102-104 °C). Both melting point and spectral data of **12** were entirely consistent with those reported for conduritol-F[12].

A short and particularly efficient synthesis of conduritol-A was realized starting from *meso*-tricyclo[6.2.1.$0^{2,7}$]undecadien-3,6-diol **15** which is readily obtained from **6** in almost quantitative yield by stereoselective reduction with sodium borohydride in the presence of ceric chloride[13] (Scheme III).

Scheme III



15 R= H
16 R= Ac

17

18

19

Acylation of **15** with acetic anhydride gave the corresponding diacetate **16**, which then was subjected to flash vacuum thermolysis at 500 °C (10^{-1} torr) to give the hithertho unknown 1,4-diacetoxy-cyclohexa-1,4-diene **17** together with some phenyl acetate which is the result of aromatization of **17**. It was impossible to remove this byproduct by chromatography over silica gel because of partial aromatization of **17** on the column. However, its presence did not interfere with the subsequent bis-hydroxylation reaction. Stereoselective bishydroxylation of one of the olefinic bonds in **17** with a catalytic amount of osmium tetroxide in the presence of morpholine N-oxide using standard conditions gave the expected diol **18**. Using again the mild amidation procedure as described above, applying ammonia in methanol, the acetate functions were effectively removed to give conduritol-A **19** (m.p. 139-140 °C after recrystallization from ethanol) in quantitative yield. Its spectral and physical data corresponded in all respects to those reported[14,15].

In conclusion, we have realized effective syntheses of both naturally occurring conduritols-A and -F from the readily available benzoquinone/cyclopentadiene adduct **6**. Moreover, we showed that the technique of flash vacuum thermolysis uniquely allows the efficient and stereoselective synthesis of sensitive compounds such as diacetoxycyclohexene epoxide **10** and cyclohexa-1,4-diene diacetate **17**. The absence of the latter in the literature hitherto is most likely due to its rapid aromatization under expulsion of an acetoxy group under more conventional chemical conditions. Recently, benzoquinone adducts of anthracenes have been applied for the synthesis of conduritol A following a similar strategy[15]. However, the use of **6** has

considerable advantage over these anthracene adducts as thermal cycloreversion of derivatives of **6** allows easy isolation of the desired cyclohexenoids without the necessity of a separation from cyclopentadiene because of the high volatility of this accompanying product. Thermolysis of anthracene adducts always leads to mixtures of anthracene and product which must be separated. Especially for highly reactive compounds, such as **10** and **17**, this separation step may be troublesome if possible at all. As demonstrated in this paper these compounds have great potential as synthons in natural product synthesis, *e.g* for the synthesis of oxygenated cyclohexanes. Currently, we are exploring these promising synthons in our laboratory.

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