Pergamon

Tetrahedron Letters 39 (1998) 4393–4396

TETRAHEDRON LETTERS

First Synthesis of (±)-1α,2α,4β-Trihydroxycyclohex-5-ene. Anchimeric Assistance in Conduritol Syntheses.

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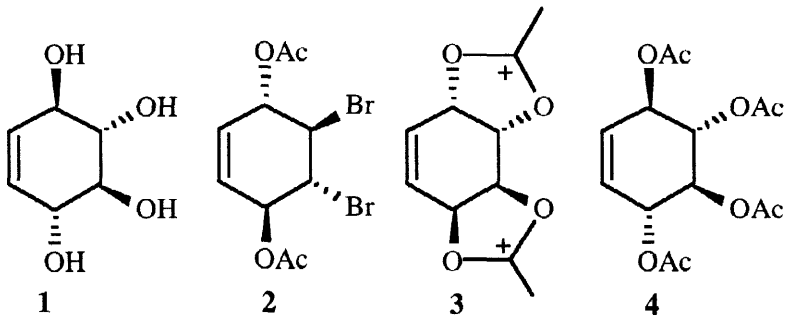
Received 3 March 1998; accepted 7 April 1998

Abstract: The deoxy-conduritol (1α,2α,4β)-1,2,4-trihydroxycyclohex-5-ene (**6**) has been prepared in racemic form from 1,4-benzoquinone in a six-step sequence, the key reaction involving a monohalide displacement by anchimeric assistance in the diacetoxy-dibromo compound previously employed for a synthesis of conduritol-B. Evidence for the mechanism of the double halide displacement in the latter synthesis has been obtained. © 1998 Elsevier Science Ltd. All rights reserved.

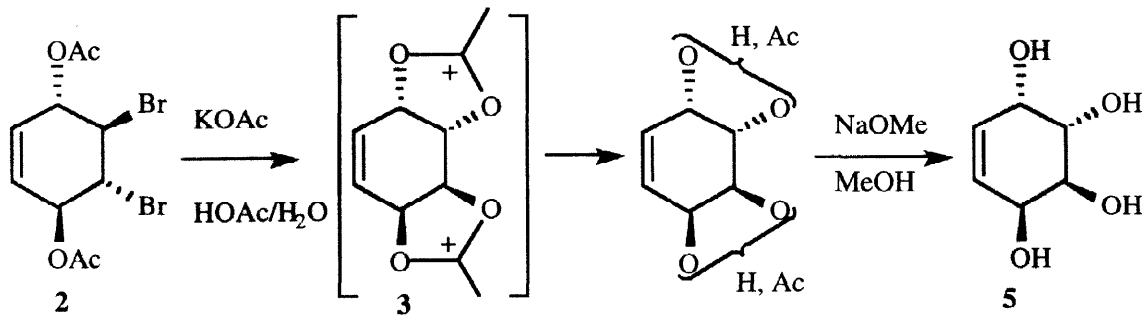
The stereocontrolled synthesis of conduritols and related derivatives is a continuing challenge in view of the biological activity of many representatives of this class of compounds.[1] Especially attractive are syntheses from simple, commercially available starting materials. We have reported[2] an improved synthesis of racemic conduritol-B, (1α,2β,3α,4β)-1,2,3,4-tetrahydroxycyclohex-5-ene (**1**), based on an earlier method[3], from 1,4-benzoquinone which presumably involves neighbouring group participation in (1α,2β,3α,4β)-1,4-diacetoxy-2,3-dibromocyclohex-5-ene (**2**) to afford the diacetoxonium species **3** which undergoes ring opening through attack by acetate anion, most likely at the allylic centres, to give the tetraacetate of conduritol-B (**4**).



1 **2** **3** **4**

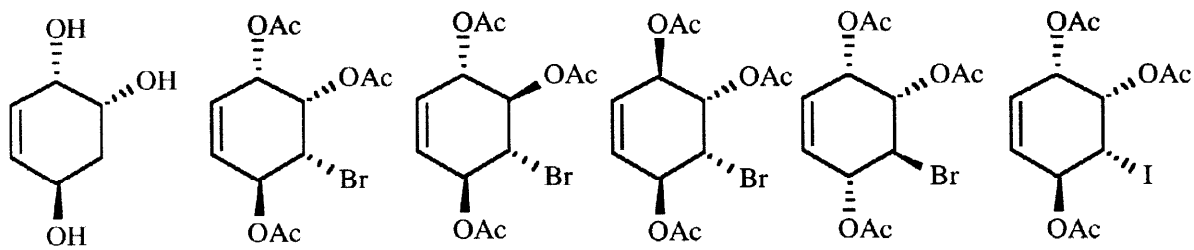
Involvement of such acetoxonium ions in this reaction is reminiscent of intermediates in the Prévost reaction for the *trans*-hydroxylation of alkenes[4,5] and raised the question whether, by performing the reaction in the presence of sufficient water to trap the diacetoxonium intermediate, it might be possible to direct the reaction to produce conduritol-E (**5**), in a manner related to the Woodward procedure for the *cis*-hydroxylation of alkenes[5,6] (Scheme). This letter reports surprising results from our investigation into this type of synthesis, their bearing on the possible course and mechanism of the conduritol-B synthesis, and the first synthesis of the 1α,2α,4β-stereoisomer, compound **6**, of 1,2,4-trihydroxycyclohex-5-ene.[7] Surprisingly, only the 1α,2α,4α- and 1α,2β,4α-stereoisomers of 1,2,4-trihydroxycyclohex-5-ene have been reported previously[8,9] although the 1,2-di-*tert*-butyldimethylsilyl ether of the 1α,2α,4β–isomer reported here has been described[10] as a mixture of enantiomers in which the (1*S*,4*R*,5*S*)-isomer predominated with an ee of 76%.

PII: S0040-4039(98)00745-X



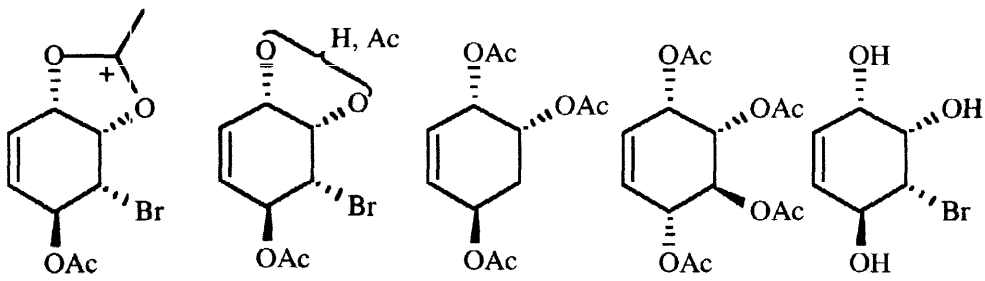
Scheme

Heating the 1,4-diacetoxy-2,3-dibromocyclohex-5-ene (**2**) in acetic acid containing 0.1% water and potassium acetate under reflux for 24 hours gave a multicomponent mixture according to TLC. However, evaporation of the solvent and treatment of the residue with acetic anhydride followed by product isolation by column chromatography gave a crystalline major product which analysed for $C_{12}H_{15}BrO_6$. Six signals for ring carbon atoms in its ^{13}C NMR spectrum indicated the product lacked symmetry and its ^1H NMR spectrum supported the structure **7**, which would be predicted on mechanistic considerations (orthoester type intermediate or direct displacement of one halide ion), although structures **8** and **9** require consideration if the presumed intermediate acetoxonium ion had been opened in a *trans*-manner by acetate attack rather than reacting with water to give an intermediate orthoacid and thus *cis*-1,2-stereochemistry. A comparison of spectral data established non-identity with the recently reported stereoisomer **10**[11], and comparison of spectral data with that for (1α,2α,3α,4β)-1,2,4-triacetoxy-3-iodocyclohex-5-ene (**11**)[12,13] clearly established the compound to be (1α,2α,3α,4β)-1,2,4-triacetoxy-3-bromocyclohex-5-ene (**7**).[14] The overall yield of **7** from **2** was 38%.



Most surprising is the completely different course of the reaction undergone by **2** in the presence of a small proportion of water ($HOAc/H_2O/KOAc$) compared to that under anhydrous conditions ($HOAc/Ac_2O/KOAc$). Significantly, when the bromotriacetate **7** was subjected to the anhydrous conditions which lead to displacement of both halide substituents in **2**, it was recovered unchanged. We interpret this result to indicate that the formation of tetraacetate **4** proceeds sequentially via a monoacetoxonium species **12** and then the diacetoxonium species **3**, the formation of the latter being aided by a favourable stereoelectronic alignment of acetoxy and bromo substituents in the intermediate monoacetoxonium ion **12**. In the presence of water, ion **12** is trapped immediately and the orthoacid intermediate collapses to give a mixture of two alcohols **13**; the actual reaction mixture may be further complicated by partial hydrolysis of ester groups in this mixture but is simplified on final acetylation of the mixed products.

Reduction of bromotriacetate **7** with tributyltin hydride in refluxing benzene in the presence of AIBN afforded (1α,2α,4β)-1,2,4-triacetoxycyclohex-5-ene (**14**)[15] in 71% yield, de-*O*-acetylation of which on



12 **13** **14** **15** **16**

treatment with a catalytic amount of sodium in methanol gave (1α,2α,4β)-1,2,4-trihydroxycyclohex-5-ene (**6**)[16] as a syrup in 81% yield. The NMR spectral properties of **14** and **6** clearly distinguished them from the corresponding 1α,2α,4α- and 1α,2β,4α-stereoisomers recently reported.[8,9]

Bromide displacement on bromotriacetate **7** could be achieved under more forcing conditions on heating under reflux in acetic acid/acetic anhydride in the presence of silver acetate rather than potassium acetate. After 3 days starting material and a new component in approximately equal proportions were detected by TLC and the latter was isolated by column chromatography. That this material consisted of a major and a minor component in an approximate ratio of 5:1 was shown by TLC with repeated development in a solvent of low polarity. ^{13}C NMR spectroscopy and a comparison of δ_C values of the major peaks with values for all of the conduritol tetraacetates[17] suggested the major component was conduritol-F tetraacetate (**15**), an assignment confirmed by comparison of the ^1H NMR spectrum of the major component, isolated pure but in low yield by re-chromatography of the mixture, with reported data.[18,19] This product sterochemistry suggests that halide displacement in **7** occurs with anchimeric assistance of the neighbouring acetoxy group followed by acetate attack at the allylic position in the so-formed acetoxonium ion.

The identity of the minor product (or products) has not been established but conduritol-C tetraacetate, the other isomer likely to arise from an intermediate acetoxonium ion, can be ruled out on the basis of ^{13}C shift values.[17,20] The four ring-C resonances (66.32, 66.82, 68.35, and 69.50 ppm) and two alkene-C resonances (127.93 and 128.46 ppm) observed in the spectrum of the minor product or products could arise from the presence of *two* symmetrical conduritol tetraacetates (A, B, D, or E). Although one set of resonances is compatible with conduritol-E tetraacetate, the remaining three resonances taken together do not correspond to any one of the remaining symmetrical isomers.

Bromotriacetate **7** could be de-*O*-acetylated (NaOMe/MeOH) to give the corresponding bromotriol **16**[21] as a crystalline solid in 75% yield. The utility of compounds **7** and **16** for the preparation of novel thio and amino analogues of the conduritols, and their conversion into the corresponding diol epoxide, a potential glycosidase inhibitor, is under active investigation.

We thank A. W. R. Saunders for microanalysis, and the Mass Spectrometry Service Centre at Swansea for high resolution mass spectra. A. S. H. K. and J. R. K. thank the EPSRC and MRC, respectively, for funding.

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13. Selected data for **11** (oil) quoted in ref 12: δ_H (270 MHz, $CDCl_3$) 2.03, 2.145, 2.18 (3 x 3 H, 3 x s, 3 x MeCO), 4.30 (1 H, dd, $J_{2,3}$ 1.8, $J_{3,4}$ 9.3, 3-H), 5.63-5.78 (5 H, complex, 1,2,4,5,6-H); δ_C (75 MHz, $CDCl_3$) 20.69, 20.71, 20.97, (3 x *Me*CO), 23.82 (CHI), 67.04, 73.27, 73.65, (3 x *C*HOAc), 126.64, 128.51 (2 x -CH=), 170.59, 170.71, 170.88 (3 x CO).
14. Selected data for **7** (m.p. 71-73 °C): δ_H (270 MHz, $CDCl_3$) 2.04, 2.14, 2.17 (3 x 3 H, 3 x s, 3 x MeCO), 4.23 (1 H, dd, $J_{2,3}$ 2.0, $J_{3,4}$ 8.9, 3-H), 5.58-5.86 (5 H, complex, 1,2,4,5,6-H); δ_C (67.9 MHz, $CDCl_3$) 20.58, 20.65, 20.86 (3 x *Me*CO), 47.28 (CHBr), 67.78, 72.20, 72.26 (3 x *C*HOAc), 126.70, 128.43 (2 x -CH=), 169.88, 170.08, 170.19 (3 x CO).
15. Selected data for **14** (oil): δ_H (270 MHz, $CDCl_3$) 1.90 (1 H, ddd, $J_{3,4}$ 3, $J_{2,3}$ 4.95, $J_{3,3'}$ -14, 3-H), 2.33 (1 H, ddd, $J_{2,3'}$ 5.3, $J_{3',4}$ 9.9, 3'-H), 5.38 (1 H, ddd, $J_{4,5}$ 3.3, 4-H), 5.44-5.54 (2 H, complex, 1,2-H), 5.85 (1 H, dd, $J_{1,6}$ 4, $J_{5,6}$ 10.1, 6-H), 5.99 (1 H, dd, 5-H); δ_C (67.9 MHz, $CDCl_3$) 20.91, 20.99, 21.17 (3 x *Me*CO), 29.87 (CH_2), 66.01, 67.08, 67.30 (3 x *C*HOAc), 127.92, 130.29 (2 x -CH=), 170.54, 170.61, 170.75 (3 x CO).
16. Selected data for **6** (oil): δ_H (270 MHz, CD_3OD) 1.64 (1 H, ddd, *J* 2.6, 6.3, $J_{3,3'}$ -13.5, 3-H), 2.16 (1 H, ddd, $J_{2,3'}$ 5.3, $J_{3',4}$ 8.6, 3'-H), 3.97-4.11 (2 H, complex), 4.27-4.38 (1 H, m), 5.70 (1 H, dddd, *J* 1.0, 1.0, 3.5, $J_{5,6}$ 10.3, -CH=), 5.81 (1 H, dd, *J* 2.5, -CH=); δ_C (67.94 MHz, CD_3OD) 36.82 (CH_2), 65.35, 67.80, 68.50 (3 x CHOH), 130.27, 133.06 (2 x -CH=).
17. ^{13}C NMR data on tetraacetates of the conduritols are contained in the following references: (a) conduritol-A, Sütbeyaz, Y; Seçen, H; Balci, M. *J. Chem. Soc., Chem. Commun.*, **1988**, 1330. (b) conduritol-B, ref. 18. (c) conduritol-C, Seçen, H; Maras, A; Sütbeyaz, Y.; Balci, M. *Synth. Commun.*, **1992**, *22*, 2613. (d) conduritol-D, ref. 12. (e) conduritol-E, ref. 17(c). (f) conduritol-F, ref. 18.
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20. The authors thank Dr. H. A. J. Carless of the Department of Chemistry, Birkbeck College, University of London for providing ^1H and ^{13}C NMR spectra of the tetraacetate of conduritol-C.
21. Selected data for **16** (m.p. 168-171 °C): δ_H (270 MHz, CD_3OD) 4.04 (1 H, dd, $J_{2,3}$ 1.7, $J_{3,4}$ 8.9, 3-H), 4.20-4.25 (1 H, m), 4.27-4.33 (1 H, m), 4.42 (1 H, dddd, *J* 2.5, 2.5, 2.5, 4-H), 5.58 (1 H, dddd, *J* 1.8, 1.8, 1.8, $J_{5,6}$ 10.2, 6-H), 5.68 (1 H, ddd, *J* 2.2, 2.2, 5-H); δ_C (67.9 MHz, CD_3OD) 59.56 (CHBr), 69.46, 71.00, 75.91 (3 x CHOH), 130.29, 131.21 (2 x -CH=).