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New Simple and Inexpensive Synthetic Route, Mediated by Sulfur, to Enantiopure (–)-Conduritol E Derivative from D-mannitol.

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Abstract: We have synthesized a (-)-Conduritol E derivative, enantiomerically pure, using as starting material D-mannitol. This latter, possessing already the same configuration of the expected product at the four chiral carbon atoms, was subjected to reaction to form a cyclic unsaturated polyhydroxylated compound, preserving the configuration at all chiral carbon atoms of the sugar. © 1997 Elsevier Science Ltd.

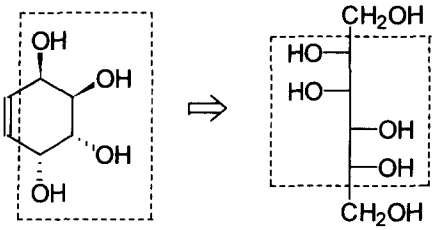
The conduritols, related epoxides and polyhydroxylated cyclohexanes are a prominent class of biologically active compounds of interest as inhibitors of glycosidases.[1] Wide application of these compounds is easily predictable in chemotherapy due to their property of inhibiting oligosaccharide-processing enzymes.[2] Moreover, the conduritols continue to attract the attention of organic chemists also as synthetic intermediates in the preparation of cyclitols and pseudo-sugars.

Many syntheses of conduritols produce racemic mixtures because the starting materials, as optically pure compounds, are not easily available. Other syntheses starting from enantiopure unsaturated cyclic *cis*-diols, obtained by microbial oxidation of halobenzenes, use enantiocontrolled procedures to introduce new hydroxy groups.[3] Recently was reported the "naked sugar" approach of Vogel,[4] a Samarium diiodide-mediated carbocyclization from D-mannitol[5] and a synthesis by asymmetrization of *meso*-symmetric cyclic dienes.[6]

Nevertheless, several of these synthetic approaches, even when they proceed with good enantiomeric excess, require a chemical or enzymatic resolution step to obtain enantiomerically pure compounds.

These synthetic challenges, dealing with compounds of proven biological activity, stimulated us to engage a new synthetic route for this target. By means of sulfur we have obtained an easy access to this kind of product, starting from a very trivial sugar.

Having envisaged in the structure of (-)-Conduritol E[7] the skeleton of D-mannitol we have projected a synthetic strategy which, starting from this sugar-alcohol, through some steps performed under mild conditions, preserves the configuration at all four chiral carbon atoms of the sugar (Scheme 1).



Scheme 1

Moreover, the two terminal hydroxy groups of D-mannitol can be used to synthesize an unsaturated 6-membered ring; this can be realized by intramolecular thiacyclization to a tetrahydroxy thiepane derivative,[8] followed by oxidation to the sulfone and subsequent expulsion of SO_2, exploiting a Ramberg-Bäcklund reaction, to form a new double bond (Scheme 2).

In fact the Ramberg-Bäcklund reaction has presented a broad application for the preparation of olefins which it would be difficult to achieve with other methods. In the present case, the base induced rearrangement of α-halosulfones could offer an attractive opportunity for a facile synthesis of conduritols.

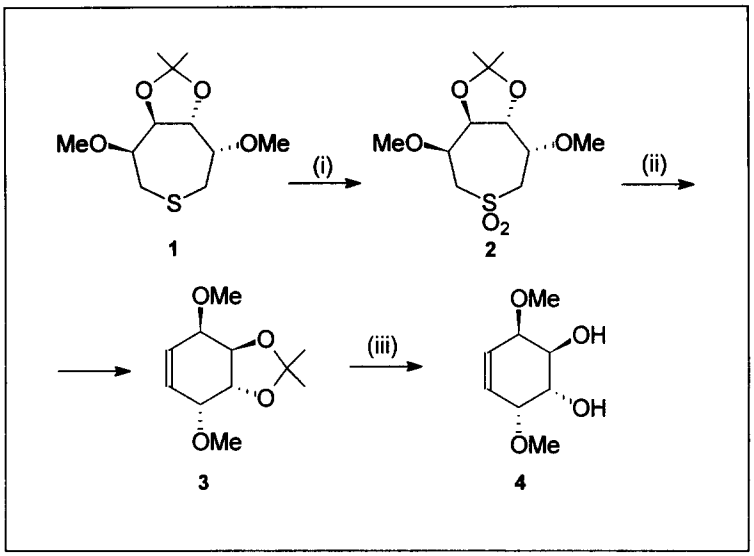
In practice, from D-mannitol the (1S,2S,6S,7S)-(−)-2,6-dimethoxy-9,9-dimethyl-8,10-dioxa-4-thia bicyclo[5.3.0]decane (**1**) can be easily prepared, on multigram scale, following well known procedures.[9]

This compound (**1**) was quantitatively oxidised to the corresponding sulfone **2**[10] (Scheme 2) and subjected to Ramberg-Bäcklund reaction.[8] The treatment of **2** with KOH/CCl_4 at rt for 1.5h resulted in a complete conversion to (1R,2R,3R,4R)-(−)-1,4-dimethoxy-2,3-isopropylidenecyclohex-5-ene (**3**)[11] which, by acid treatment, gave the enantiopure (−)-Conduritol E derivative **4**.[12]

In conclusion this new procedure, mediated by sulfur, is a goal of great interest because it is predictable that, starting from different sugar-alcohols, the route could be used also for the synthesis of many enantiopure conduritols.

We have accomplished the synthesis of (−)-Conduritol E derivative **4** in three steps only, without needing any further purification and in overall yield of 86% from **1**.

Our new and simple synthetic approach would be greatly enlarged by applying it to synthesis of conduritols and aminoconduritols which are also important intermediates for the synthesis of inositols and aminoinositols respectively, compounds of interest as inhibitors for different glycosidases.[1,13]



(i) $KHSO_5$, MeOH/H_2O, rt 1.5h, 98%; (ii) KOH, t-BuOH, CCl_4, H_2O, rt 2h, 94%; (iii) H_2SO_4 0.1N, 2h at 90°C, 94%.

Scheme 2

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10. Selected physical data of **2** - The product was purified by flash chromatography (CH_2Cl_2/ MeOH; 99/1), to give a crystalline product, mp 161-162°C. ^1H NMR ($CDCl_3$) δ: 4.43

(m, 2H, CHO), 3.85 (m, 2H, CHO), 3.48 (s, 6H, $2OCH_3$), 3.35 (m, 4H, $2CH_2S$), 1.40 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 109.64 (C), 76.48 (2CHO), 72.51 (2CHO), 59.84 ($2OCH_3$), 57.15 ($2CH_2S$), 26.58 ($2CH_3$). $[\alpha]_D^{27} = -90.84$ ($CHCl_3$; c = 1.54).

11. In order to obtain **3** pure, caution should be used in the reaction work-up. Neutralization of the reaction mixture must be carried out carefully because acid conditions could lead to a mixture of **3** and **4**. Selected physical data of **3** - The product was purified by flash chromatography (light petroleum/Et_2O; 2/1). ^1H NMR ($CDCl_3$) δ: 5.92 (dd, 2H, 2CH=, J=2.91 Hz, J=1.36 Hz), 4.05 (m, 2H, 2CHO, irradiation at δ 5.92 resolved the multiplet into doublet J=1.18 Hz), 4.01 (m, 2H, 2CHO, irradiation at δ 5.92 resolved the multiplet into doublet J=1.20 Hz), 3.50 (s, 6H, $2OCH_3$), 1.43 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 129.28 (2CH=), 109.87 (C), 74.52 (2CHO), 73.96 (2CHO), 59.34 ($2CH_3O$), 26.76 ($2CH_3$). $[\alpha]_D^{27} = -249.39$ ($CHCl_3$; c = 1.81). m/z: 214, 199, 184, 139, 127, 124, 114, 97, 73.
12. Selected physical data of **4** - The product, purified by flash chromatography (Et_2O), give a white crystalline product, mp 66-67°C. ^1H NMR (C_6D_6) δ: 5.90 (m very sharp, 2H, 2CH=, irradiation at δ 4.62 resolved the multiplet into doublet J=0.82 Hz), 4.62 (m very sharp, 2H, 2CHO), 4.19 (m very sharp, 2H, 2CHO), 3.30 (s, 6H, $2CH_3$), 3.15 (s broad, 2H, 2OH). ^{13}C NMR ($CDCl_3$) δ: 127.44 (2CH=), 75.21 (2CHO), 68.59 (2CHO), 57.34 ($2CH_3O$). $[\alpha]_D^{27} = -234.04$ ($CHCl_3$, c = 1.00).
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