Cyclohexadiene-*trans*-diols as versatile starting material in natural product synthesis: short and efficient synthesis of *iso*-crotepoxide and *ent*-senepoxide

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A new synthesis of *ent*-senepoxide and *iso*-crotepoxide starting from microbially produced (+)-*trans*-2,3-dihydroxy-2,3-dihydrobenzoic acid *via* regio- and stereoselective epoxidation is described.

Highly functionalized cyclohexane derivatives like conduritols and cyclitols have attracted considerable attention because of their useful biological activity.[1] Cyclohexadiene-*cis*-diols (*cis*-CHD), substituted at the diene unit, have been established as valuable chiral building blocks in the synthesis of such substances, in particular because of their good accessibility.[2] Functionalized cyclohexadiene diols possessing a *trans*-configuration of the two hydroxy groups (*trans*-CHD) have not been established as chiral building blocks in syntheses in the same way so far. Due to the difficult access to enantiomerically enriched *trans*-CHD by multistep syntheses[3,4] or starting from *cis*-CHD through inversion of configuration,[5] they have been relatively rarely used in natural product synthesis.


cis-CHD   *trans*-CHD

Recently, we have shown that *trans*-CHD are also available in multigram scale by cultivation of recombinant *Escherichia coli* cells.[6] This offers the possibility of establishing new short and efficient synthetic strategies to biologically active and pharmaceutically interesting compounds.

In order to demonstrate the potential of *trans*-CHD as versatile chiral building blocks, we present investigations towards regio- and stereoselective epoxidation of either one or both olefinic double bonds and the usage of this reaction in the synthesis of *ent*-senepoxide **12** and *iso*-crotepoxide **15** (1,2,3,4-tetra-*epi*-crotepoxide).

(2S,3S)-*trans*-Dihydroxy-2,3-dihydrobenzoic acid† (2,3-*trans*-CHD; **1**) occurs in *E. coli* as a metabolite derived from the shikimate–chorismate pathway. Using techniques of metabolic engineering microbial producer of **1** could be obtained.[6] Enantiopure compound **1** was isolated from the cultivation broth by ion exchange chromatography in high yield and was used as the starting material for the following reaction steps.

The syntheses started with an esterification of the carboxylic group of **1** (Scheme 1). Due to the electron withdrawing effect of the ester group, epoxidation of diol **2** and TBS-protected diol **4** using *meta*-chloroperoxybenzoic acid (*m*-CPBA) took place exclusively at double bond C3-C4.[3,7] The stereochemistry of the peroxide attack and the configuration of the resulting epoxide is directed by the functionality at C2. In the case of an allylic hydroxyl group, *m*-CPBA coordinates *via* hydrogen bonds and forces the C2-C3 *cis*-configuration of **3**.[8]

Applying the same conditions to the protected diol **4** the bulky 2-siloxy group shields the α-face of the cyclohexadiene plane hence the attack of the peracid takes place regiose-
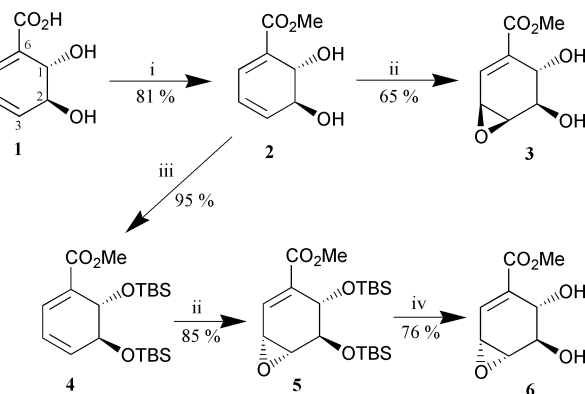
Scheme 1 *Reagents and conditions*: i, trimethylsilyl diazomethane (2 M in hexane), MeOH, rt, 6 h; ii, *m*-CPBA, NaHCO₃, CH₂Cl₂, rt, 3 h; iii, TBS-OTf, NEt₃, CH₂Cl₂, rt, 2 h; iv, aqueous HF (40%), acetonitrile, rt, 2 h.

lectively from the β-face. Compound **5** was obtained as a single diastereomer in 85% yield.[3] The relative configuration of the oxirane ring in **3** and **5** with regard to the substituent at C2 was confirmed by ¹H-NMR experiments. A coupling constant of $J_{1,2}$ = 7.9 Hz in **3** indicates the two hydroxy groups are in a diequatorial position due to the favoured twist conformation. On the other hand a $J_{1,2}$ coupling of 2.1 Hz shows the diaxial position of the protected hydroxy groups in **5**. In addition, the relative configuration of **3** was proven by X-ray structure analysis (Fig. 1).[9] Deprotection of **5** could be achieved by using hydrogen fluoride to give **6** in 76% yield.

The reduction of the ester group of **4** to the corresponding alcohol **7** was performed with diisobutylaluminium hydride (DIBAL-H) in 88% yield.[10] Epoxidation of **7** with equimolar amounts of *m*-CPBA at low temperatures led to **8** in 91% yield.[11] Reaction of **7** as well as **8** with an excess of the oxidizing agent at higher temperatures and prolonged reaction
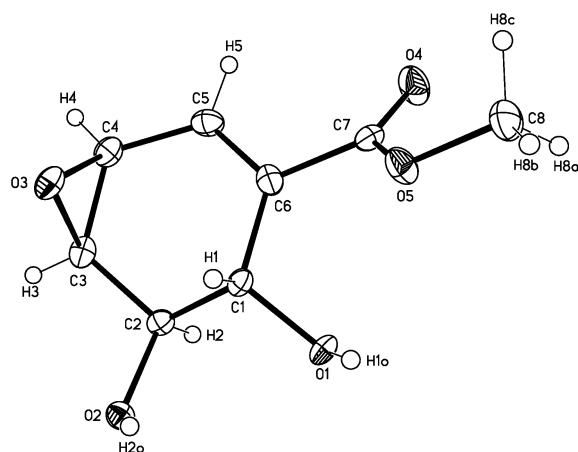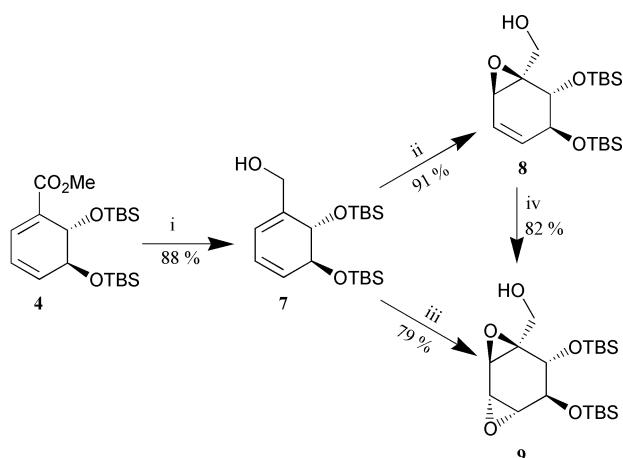

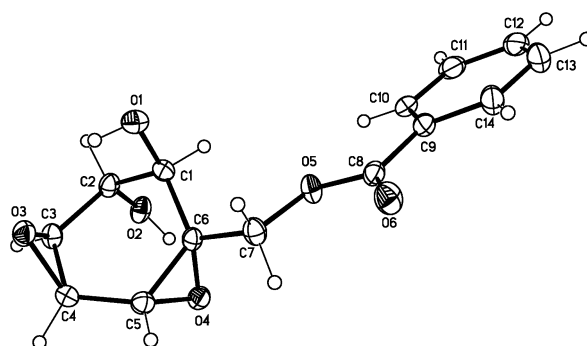**Fig. 1** Molecular structure of epoxide **3** showing the C2–C3 *cis*-configuration.

Fig. 2 Molecular structure of bisepoxide **14**. The epoxide moieties are arranged in a *trans*-configuration to each other.

Scheme 2 *Reagents and conditions*: i, DIBAL-H, hexane, 0 °C, 3 h; ii, 1 eq. *m*-CPBA, NaHCO₃, CH₂Cl₂, rt, 3 h; iii, 2.5 eq. *m*-CPBA, NaHCO₃, CH₂Cl₂, 50 °C, 16 h; iv, 1.5 eq. *m*-CPBA, NaHCO₃, CH₂Cl₂, 50 °C, 16 h.

time resulted in the formation of bisepoxide **9** in high yields (Scheme 2).[12]

Compounds **8** and **9** possess already the core structure of *ent*-senepoxide **12** and *iso*-crotepoxide **15**. Benzoylation and subsequent cleavage of the siloxy groups with tetrabutyl-ammonium fluoride (TBAF) led to **11** and **14**, respectively. Acetylation of **11** and **14** quantitatively gave the stereoisomers of the natural products (Scheme 3). The yield over seven steps starting from **1** is 26% for *ent*-senepoxide **12** and 24 % for *iso*-crotepoxide (1,2,3,4-tetra-*epi*-crotepoxide) **15**. In comparison, Shing *et al.* synthesized senepoxide starting from quinic acid in 17 steps.[13]
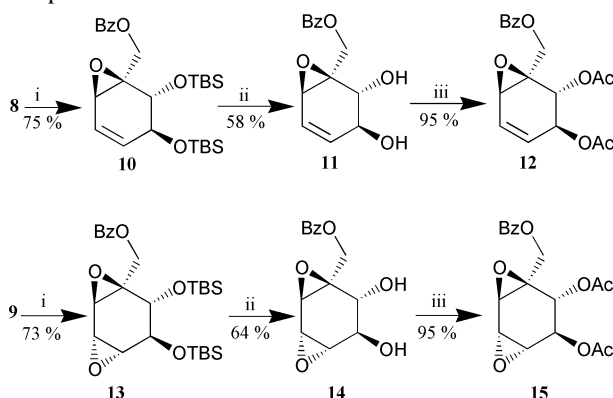
Scheme 3 *Reagents and conditions*: i, benzoyl chloride, pyridine, −5 °C, 6 h; ii, 2.5 eq. TBAF, THF, −78 °C → rt, 2 h; iii, acetic anhydride, pyridine, 0 °C → rt, 1 h.

Analytical data of *ent*-senepoxide **12** were identical with the literature data of Shing.[13] Analytical data we found for 1,2,3,4-tetra-*epi*-crotepoxide **15** are identical with those White and coworkers reported for 3,4,5,6-tetra-*epi*-crotepoxide.[14,15] However, evidence of the relative stereochemistry was given by X-ray structure analysis of **14** that revealed the C2–C3 *trans*-configuration (Fig. 2).[16]

In summary, we developed a short and efficient synthesis of stereoisomers of the biologically active cyclohexane epoxides senepoxide and crotepoxide. The synthetic approach is based on the regio- and stereoselective epoxidation of microbially produced enantiopure **1**. By choosing appropriate conditions and reasonable protecting groups it is possible to selectively introduce the oxirane moiety in senepoxide directly *via* peracid oxidation, contrary to other statements.[13]

All epoxides shown in this contribution, especially **3**, **6**, **8** and **9**, might also be ideal starting materials in the preparation of numerous other cyclitols and carbohydrate mimics.

Notes and references

† The numbering scheme of the ring atoms here is deduced from the traditional view of cyclohexadienes as derivatives of aromatic compounds. This scheme is different to that used in the equations and molecular structures.

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9 *Crystallographic data* for **3**: C₈H₁₀O₅, *M* = 186.2, *T* = 123 K, monoclinic, space group *P*2₁ (No.4), *a* = 8.6140(2), *b* = 4.5655(1), *c* = 11.0991(4) Å, *β* = 112.512(2)°, *V* = 403.23 Å³, *Z* = 2, *D*c 1.53 g cm⁻³, *F*(000) = 196, *μ*(Mo-Kα) = 0.13 mm⁻¹, 8907 reflections measured, 1418 unique which were used in all calculations, *wR2*(*F*²) = 0.078 (all data), *R1* = 0.029 [*I* > 2σ(*I*)], flack parameter *x* = 0.5(10). CCDC 174631. See http://www.rsc.org/suppdata/cc/b1/b110420a/ for crystallographic files in .cif format.

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15 ¹H-NMR data of **15**: δ (CDCl₃) 2.11 (3H, s), 2.16 (3H, s), 3.28 (1H, s), 3.62 (1H, s), 3.66 (1H, s), 4.11 (1H, d, *J* 12.5 Hz), 4.73 (1H, d, *J* 2.5 Hz), 5.18 (1H, s), 5.42 (1H, s), 7.47 (2H, t, *J* 7.6 Hz), 7.59 (1H, t, *J* = 6.8 Hz), 8.03 (2H, d, *J* = 7.4 Hz). The ¹H-NMR data Shing *et al.* [Lit. 13] published for 3,4,5,6-tetra-*epi*-crotepoxide show significant differences to the data of **15** resp. White's 3,4,5,6-tetra-*epi*-crotepoxide.

16 *Crystallographic data* for **14**: C₁₄H₁₄O₆, *M* = 278.3, *T* = 123 K orthorhombic, space group *P*2₁2₁2₁ (No.19), *a* = 8.8867(2), *b* = 11.7119(2), *c* = 12.0177(3) Å, *V* = 1250.80 Å³, *Z* = 4, *F*(000) = 584, *D*c 1.48 g cm⁻³, *μ*(Mo-Kα) = 0.12 mm⁻¹, 24670 reflections measured, 2206 unique which were used in all calculations, *wR2*(*F*²) = 0.056 (all data), *R1* = 0.022 [*I* > 2σ(*I*)], flack parameter *x* = −0.1(6). CCDC 174632.