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), substitutted 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 syntheses3,4 or starting from cis-CHD through inversion of configuration,5 they have been relatively rarely used in natural product synthesis.

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).

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.

(2S,3S)-trans-Dihydroxy-2,3-dihydrobenzoic acid7 (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 Enantipure 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-C4,5,7 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-
Compounds 8 and 9 possess already the core structure of epi-senepoxide and iso-crotepoxide. Benzoylation and subsequent cleavage of the siloxy groups with tetrabutylammonium 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.  

In summary, we developed a short and efficient synthesis of numerous other cyclitols and carbohydrate mimics. M. N. thanks DAAD for financial support.

Notes and references

10. Crystallographic data for 3: C$_5$H$_5$OM, M = 186.2, T = 123 K, monocyclic, space group P2$_1$(No.4), a = 8.6140(2), b = 4.5655(1), c = 11.0991(4) \(\AA\), \(\beta\) = 112.512(2)\(^\text{\circ}\), \(V\) = 403.23 \(\text{\AA}^3\), \(Z\) = 2, \(D\) = 1.53 g cm$^{-3}$, F(000) = 196, \(\mu\) (Mo-K\(\alpha\)) = 0.11 mm$^{-1}$, 8907 reflections measured, 1418 unique which were used in all calculations, wR2(F2) = 0.078 (all data), R1 = 0.029 (I > 2\(\sigma\)(I)), Flack parameter x = 0.5(10). CCDC 174631. See http://www.rsc.org/suppdata/cc/b1/b110420a/ for crystallographic files in cif format.
16. Crystallographic data for 4: C$_4$H$_4$O$_6$, M$_p$ = 278.3, T = 123 K, orthorhombic, space group P2$_1$2$_1$2$_1$ (No.19), a = 8.8687(2), b = 11.7119(2), c = 12.0177(3) \(\text{\AA}\), \(V\) = 1250.80 \(\text{\AA}^3\), \(Z\) = 4, F(000) = 584, D, = 1.48 g cm$^{-3}$, \(\mu\) (Mo-K\(\alpha\)) = 0.12 mm$^{-1}$, 24670 reflections measured, 2206 unique which were used in all calculations, wR2(F2) = 0.056 (all data), R1 = 0.022 [I > 2\(\sigma\)(I)], Flack parameter x = -0.016(6). CCDC 174632.