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From cyclooctatetraene to chiral polyfunctionalized C_8 building blocks—*meso*-persubstituted oxepanes and azepanes

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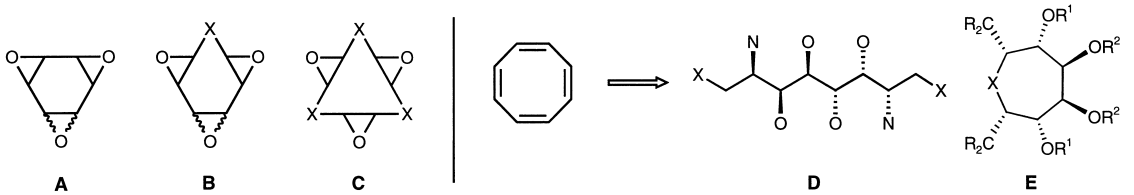
Abstract

Cyclooctatetraene—via its 1α,2α,5α,6α-diepoxy-3β,4β-diol (**4**)—is the basis for the construction of specifically polyfunctionalized C_8 building blocks. Whilst with monofunctional nucleophiles only mono-substitution and with 1,1-dinucleophiles neatly intramolecular cyclization to aza(oxa,thia)bicyclo[4.2.1]-nonenes occurred, the desired substitution pattern became, in principle, accessible with 1,2-disubstituted hydrazines. The usefulness of the 7-hetero[4.2.1]bicycles for the preparation of *meso*-persubstituted azepanes and oxepanes is exemplified.

Keywords: cyclooctatetraene-oxides; 7-heterobicyclo[4.2.1]nonenes; 7,8-diazabicyclo[4.2.2]decenes; azepanes; oxepanes.

In the context of mechanistic as well as synthetic studies the polyfunctionalization of bulk cycloolefins—such as polyepoxides **A**–**C** from benzene,[1] cycloheptatriene,[2] 1,4,7-cyclononatriene[3]—has been intensively investigated.[4] In this letter we report on a project based on cyclooctatetraene (COT), with the (still missing) all-*cis*-tetroxide **1** as an early target,[5] directed at the synthesis of enantiopure linear C_8 building blocks of type **D**[6] and *meso*-persubstituted oxepanes and azepanes **E**.[7] (Scheme 1).



Scheme 1.

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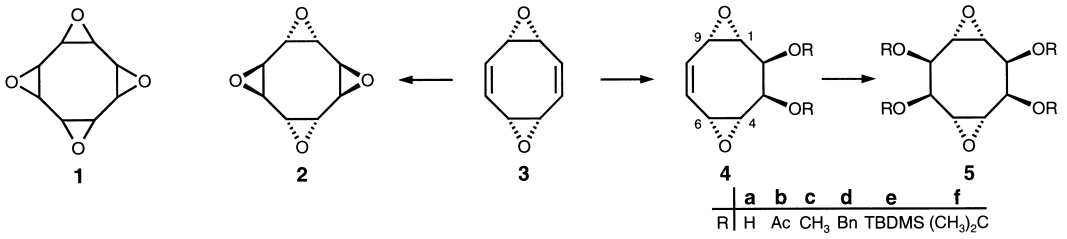
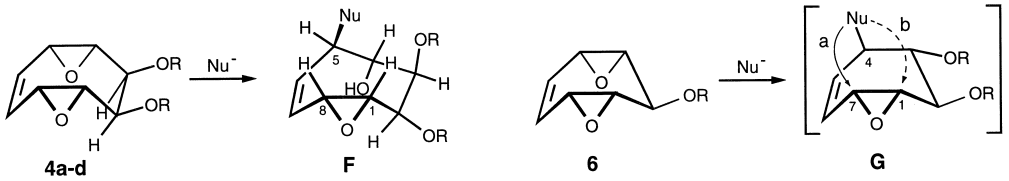
For the C_8 building blocks **D** featuring diaminopolyol-segments, offering the chance for biocatalytic routes to enantiopure products,[6] the diepoxy-cyclooctene-diol **4a** was chosen as starting material. To this end, conditions for the selective mono-*cis*-bishydroxylation of COT-s*yn*-l,5-dioxide **3**, though accessible only with moderate efficiency (CF_3CO_3H, ca. 50%;[8] the DMDO oxidation of **3** had not led even to traces of **1**, but instead to the all-*trans* tetroxide **2**[5] described since by Murray's group[9]),[10] were worked out: Along an optimized protocol crystalline **4a**, resulting from the *anti*-specific attack upon the boat-like conformation with quasi-*equatorial* epoxide rings, was obtained in 85–90% yield (2.5 mg [OsO_4]/mmol **3**:acetone:water 5.5:l:1.05 equiv. of NMO/room temperature/24 h/continuous extraction of **4a**[10,11]) (Scheme 2). From the significantly slower reaction of **4a** (3 equiv. of NMO/72 h) the crystalline, water-soluble diepoxy-tetrol **5a** was obtained in moderate, not optimized yield of ca. 50% after crystallization from methanol. Under standard conditions the derivatization of **4a** to **4b**–**4f**, in part effected to influence conformational flexibility and relative substitution rates, was in all cases straightforward (90–98%). At room temperature generally averaged boat conformations (C_s) with quasi all-*equatorial* substitution were established ($J_{1,2(3,4)} = 5.8$ Hz (**4b**), 4.0 Hz (**4c**, **d**, **e**), 3.9 Hz (**4f**); $J_{6,7(8,9)} < 1$ Hz).



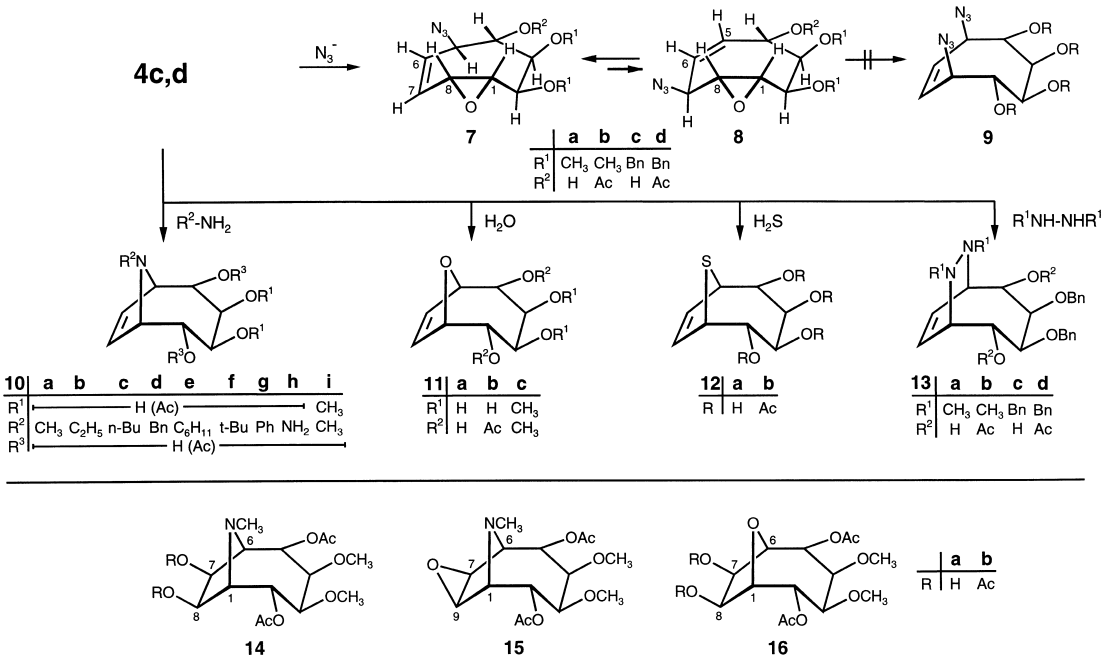
Scheme 2.

For the installation of *N*- and *O*-functionalities via allylic substitutions in diepoxides **4a**–**f**—as practiced before with the diepoxy-cycloheptenes **6**[12]—model considerations and force-field calculations signaled: (i) an energy barrier rapidly increasing with the conformational rigidity (from **4a** to **4f**); (ii) a very high barrier for the subsequent epoxide opening to give bisadducts; and (iii) with bifunctional nucleophiles favorable prerequisites for intramolecular cyclization (C-8) in the primary twisted boat conformations **F** hardly to be offset by steric manipulations (Nu, R) (Scheme 3). To recall, in the case of the cycloheptenes **6** the first addition of monofunctional nucleophiles to give the relatively flexible monoadducts **G** was much slower than the second one (only bisadducts were isolable), and with 1,1(1,2)-dinucleophiles the intramolecular allylic a-substitution (C-7) had to compete with the *b*-substitution (C-1).



Scheme 3.

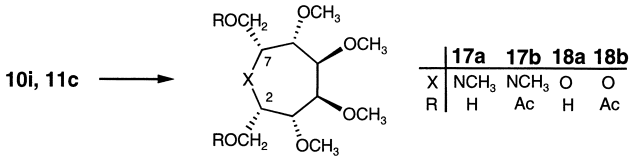
In practice, the response of **4a**–**f** to monofunctional (N_3^-), 1,1-(primary amines, water, 1,1-disubstituted hydrazines), and 1,2-difunctional nucleophiles (1,2-disubstituted hydrazines) lived up to expectation in that the rigidized **4e** and **4f** remained intact towards all nucleophiles tested. The reactions with N_3^- as exemplified with **4c**,**d**, performed at room temperature in order to restrict subsequent aza-Cope rearrangement and hence very slow (NaN_3, $MgSO_4$, 3 resp. 10 days), provided nevertheless mixtures of the monoazides **7a**,**c** and their Cope-isomers (S_N2'?) **8a**,**c** (together >95%; the ratios of 1.6:1 resp. 19:1 are practically the equilibrium compositions established at 60°C for the individual chromatographically separated triacetates) (Scheme 4). In line with the reluctance of the low-energy conformations of the rather immobile **7a**,**c** (**7b** ($CDCl_3$): $\delta_{1\text{-H}} = 3.49$, $\delta_{2\text{-H}} = 3.24$, $\delta_{3\text{-H}} = 3.57$, $\delta_{4\text{-H}} = 5.38$, $\delta_{5\text{-H}} = 4.10$, $\delta_{6\text{-H}} = 5.67$, $\delta_{7\text{-H}} = 5.97$, $\delta_{8\text{-H}} = 3.60$; $J_{1,2} = 8.3$, $J_{2,3} = 2.1$, $J_{3,4} = 6.7$, $J_{4,5} = 9.1$, $J_{5,6} = 5.4$, $J_{6,7} = 11.8$, $J_{7,8} = 1.1$, $J_{8,1} = 5.6$; $J_{1,7} = \approx J_{6,8} = \approx J_{5,8} = \approx 1.1$ Hz) and of the more flexible **8a**,**c** (**8b** ($CDCl_3$): $\delta_{1\text{-H}} = 3.14$, $\delta_{2\text{-H}} = 3.47$, $\delta_{3\text{-H}} = 3.82$, $\delta_{4\text{-H}} = 5.57$, $\delta_{5\text{-H}} = 5.88$, $\delta_{6\text{-H}} = 5.74$, $\delta_{7\text{-H}} = 4.25$, $\delta_{8\text{-H}} = 3.16$; $J_{1,2} = 8.0$, $J_{2,3} = 1.1$, $J_{3,4} = J_{4,5} = 7.5$, $J_{5,6} = 11.8$, $J_{6,7} = 7.5$, $J_{7,8} = 7.6$, $J_{8,1} = 5.2$, $J_{5,7} = 1.6$ Hz) to adjust to the necessary conformational changes, neither underwent further addition to a bisazide (e.g. desired **9**). Forcing, particularly S_N1 type protocols, led to complex product mixtures and decomposition. With several, sterically more or less demanding primary amines (R^2NH_2), **4a**,**c** reacted without a directive effect of the R^1/R^2 groups being noticed; in all cases the smoothly formed monoadducts **F** cyclized, too rapidly to be observable, via regiospecific attack at C-8, to the 7-azabicyclo[4.2.1]nonenes **10a**–**i** (derivatized as diacetates). Analogously, hydrazinolysis of **4a** (refluxing in 4 equivalents of deoxygenated 80% aq. N_2H_4), hydrolysis of **4a**,**c** ($H_2O/THF/BF_3/Et_2O$/rt/24 h) as well as the reaction of **4a** with Na_2S ($LiClO_4/CH_3OH/H_2O$, rt/24 h) uniformly (NMR, TLC) led to the respective 7-aza(oxa, thia)bicyclo[4.2.1]nonenes **10h**, **11a** and **12a**, isolated after acetylation as crystalline **10i**, **11b** and



Scheme 4.

12b (>90%). *Cis*-bishydroxylation as well as epoxidation of the 7-aza(oxa)bicyclo[4.2.1]octenes occurred expectedly only from the *exo*-sides to give, quantitatively, e.g. **14a**, **15a**, and **16a**, respectively ($J_{1,8(6,7)} = 0.5–2$; $J_{1,2(5,6)} = 4.5–6.5$; $J_{2,3(4,5)} = 5–6.5$ Hz). On the other hand, the substitution pattern not accessible through the azide addition (**9**), in principle, was realized when **4d**, with 1,2-disubstituted hydrazines (1,2-dimethyl-, 1,2-dibenzyl-, refluxing methanol/water), yielded highly selectively (up to 95%) the 7,8-diazabicyclo[4.2.2]decenes **13a**,**c** (derivatized as **13b**,**d**, invertomers). This pathway seemingly depends on the nature of the R groups in **4**(**F**); with $R = CH_3$ selectivity is not achieved.

For the oxidative transformation (ozonation) of the bicycles **10** and **11** into the *meso*-persubstituted azepanes and oxepanes of type **E**, in order to avoid complications potentially arising from neighboring groups at C-2(5), exploratory runs were performed with the tetrakis(methylethers) **10i** and **11c**. After reductive workup and acetylation *meso*-azepane **17** (at 110°C (DMSO) $J_{2,3(6,7)} = 3.5$, $J_{3,4(5,6)} = 6.3$ Hz) and *meso*-oxepane **18** ($J_{3,4(5,6)} = 6.1$ Hz) were isolated in 50–60% yield; at least within these limits no epimerization at the intermediate stages had occurred (Scheme 5).



Scheme 5.

Acknowledgements

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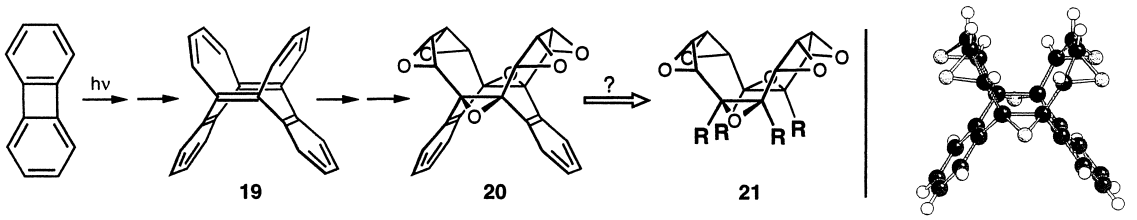
Centre, Cambridge, UK. Copies of the data can be obtained free of charge (e-mail: deposit@chemcrys.cam. ac.uk) on quoting the deposition number CCDC 144141.



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