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Asymmetric Dihydroxylation Affords Enantiomerically Pure C_{12} Building Blocks from *trans,trans,cis*-1,5,9-Cyclododecatriene

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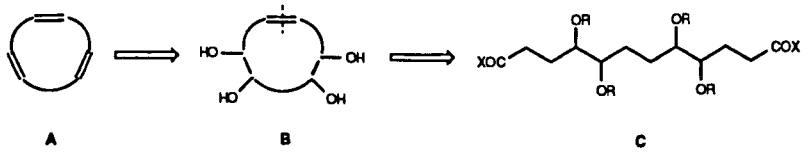
Abstract: Through sequential catalytic asymmetric dihydroxylation (AD), t,t,c-1,5,9-cyclododecatriene is transformed into functionalized cyclic cis-olefins with high enantio- and diastereocontrol. To demonstrate their synthetic utility as sources for open chain C_{12} building blocks, one such intermediate is converted into an α,ω-diester in which the chain ends are differentiated.

Multiply unsaturated cyclic hydrocarbons can be regarded as sources for cyclic, as well as linear, building blocks with the potential to be starting materials in asymmetric synthesis. In a preceding paper[1] we reported on the asymmetric dihydroxylation (AD)[2] of polyenes, including three of the four possible 1,5,9-cyclododecatrienes (the *t,t,t*-, *t,t,c*-, and *t,c,c*-isomers). Using the pyrimidine ligand $(DHQD)_2PYR$[3] at low conversions, the ee's of the diol products resulting from dihydroxylation of one *trans*-double bond are 95%, 88%, and 89%, respectively. More importantly, better ee's were achieved at higher conversions, indicating that a kinetic resolution process was operative. For the *t,t,t*-isomer the stereochemical outcome of the second dihydroxylation step depends not only on the choice of ligand, but also on the nature of the protecting group chosen to mask the established diol moiety. We report here on asymmetric dihydroxylations in the *t,t,c*-series as well as a method for transforming the products into acyclic building blocks.

Our strategy for using 1,5,9-cyclododecatrienes as starting materials for the preparation of linear C_{12} synthetic intermediates is based on sequential asymmetric dihydroxylation of two of the three double bonds of the cyclic trienes followed by cleavage of the remaining double bond to release a functionalized carbon chain (Scheme 1).

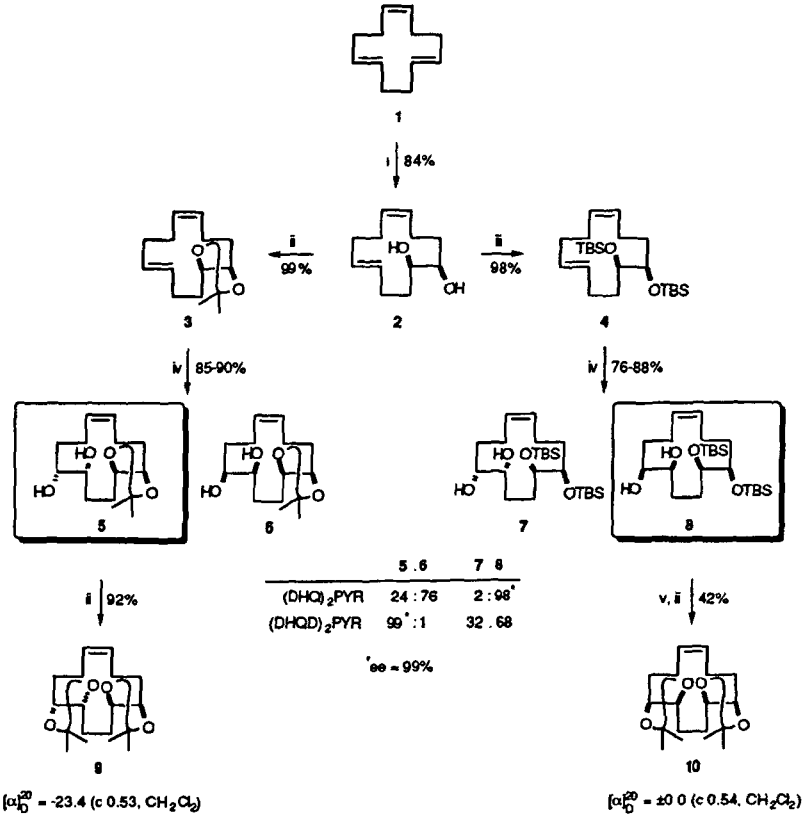


Scheme 1. General strategy for the preparation of open chain C_{12} building blocks from 1,5,9-cyclododecatrienes.

The differentiation[4] of the chain ends can then be addressed by exploiting one of the previously introduced hydroxyl groups. Since it is known that *trans*-double bonds are dihydroxylated much faster than *cis*-double bonds,[5] it was obvious that *t,t,c*-1,5,9-cyclododecatriene would best serve our requirements.

The previously described diol **2**[1] was obtained from triene **1** in 84% yield and 94% ee by standard

asymmetric dihydroxylation using $(DHQD)_2PYR$ as ligand. The reaction was allowed to reach completion to achieve the highest level of enantioselectivity.[6] Although **2** is a highly crystalline compound, recrystallization failed to enhance the ee. Two protected derivatives of diol **2** were prepared, acetonide **3** and bis-TBS-ether **4**. The AD of these derivatives was carried out using both of the "pseudoenantiomeric" ligands $(DHQ)_2PYR$ and $(DHQD)_2PYR$ (Scheme 2).

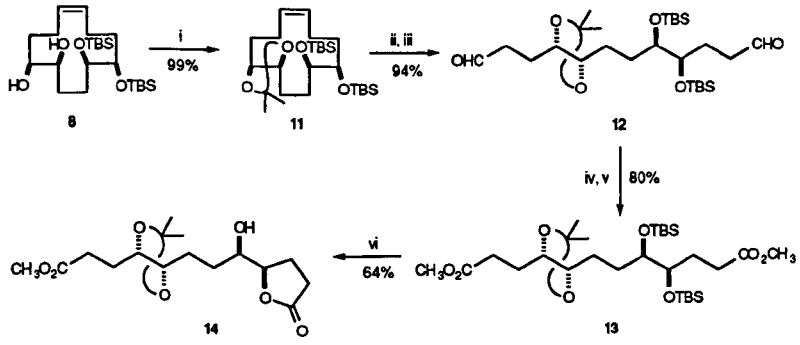


Scheme 2. i) $K_2OsO_2(OH)_4$, $(DHQD)_2PYR$, K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH/H_2O 1:1, 0°C; *ii*) DMP, *p*-TsOH; iii) TBSCl, imidazole, DMF; *iv*) $K_2OsO_2(OH)_4$, $(DHQ)_2PYR$ or $(DHQD)_2PYR$, K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH/H_2O 1:1, 0°C; v) TBAF, THF.

Using $(DHQ)_2PYR$, both **3** and **4** were transformed predominantly into the "*syn*"-products **6** and **8**. Interestingly, in the TBS series the intrinsic bias in favor of *syn*-attack could not be overcome by switching from the DHQ- to the DHQD-based ligand. The AD using $(DHQD)_2PYR$ favored the formation of the "*anti*"-product **5** from **3** but gave the "*syn*"-isomer **8** as the major product from **4**. In other words, synthetically useful levels of diastereoselection (98% *anti* and 96% *syn*) were only obtained after appropriate protection of the diol (i.e. acetonide for *anti* and TBS for *syn*). Again, in these cases, kinetic resolution plays a beneficial role since the ee climbs from 94% in the starting material to 99% in the products. The assignment of product

stereochemistry is based on the presence or absence of optical rotation after transformation of **5** and **8** into the bis-acetonides **9** (C_2-symmetric) and **10** (*meso*), respectively (Scheme 2).

Ozonolysis of **5** followed by dimethyl sulfide treatment proceeded smoothly to give a mixture of 5- and 6-membered cyclic hemiacetals. To avoid such product mixtures we decided to focus primarily on the ring opening of fully protected derivatives such as **11** (Scheme 3). In our hands the ring cleavage of **11** to give **12** was best achieved by sequential dihydroxylation-glycol cleavage. It is worth noting that dihydroxylation of the *cis* double bond in **11** using the Upjohn-procedure[7] took place with very high diastereoselection[8], but the configuration of the resulting diol has not yet been determined. Sodium periodate supported on silica gel[9] proved to be the most convenient reagent to achieve glycol cleavage. Oxidation of dialdehyde **12** followed by esterification furnished the fully protected diester **13**. TBAF-induced desilylation completed this sequence, resulting in spontaneous cyclization to yield γ-lactone **14**.[10] The overall reaction sequence represents a practical route to enantiomerically pure C_{12} building blocks which are closely related to intermediates that have previously been used in the context of acetogenin total synthesis.[4c,d]



Scheme 3. i) DMP, *p*-TsOH; ii) OsO_4, NMO, acetone/H_2O 8:1; iii) $NaIO_4$, silica gel, CH_2Cl_2; iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O 4:1; v) *N,N'*-diisopropyl-*O*-methylisourea, toluene, 100°C; vi) TBAF, THF.

In conclusion, we have demonstrated that cyclic polyunsaturated hydrocarbons such as *t,t,c*-1,5,9-cyclododecatriene can serve as a rich source of oxygenated building blocks when processed by consecutive asymmetric dihydroxylations in conjunction with a suitable protecting group strategy. The enantiomeric series of compounds would be accessible by using the respective complementary ligand in each step, e.g. $(DHQD)_2PYR$ instead of $(DHQ)_2PYR$ and *vice versa*. With compounds like **5** and **8** in hand, a maze of possible transformations unfolds and all from a triene that costs less than one dollar a pound.

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