Desymmetrization of a Silyl-2,5-cyclohexadiene. Synthesis of (+)-Conduritol E and (−)-2-Deoxy-*allo*-inositol

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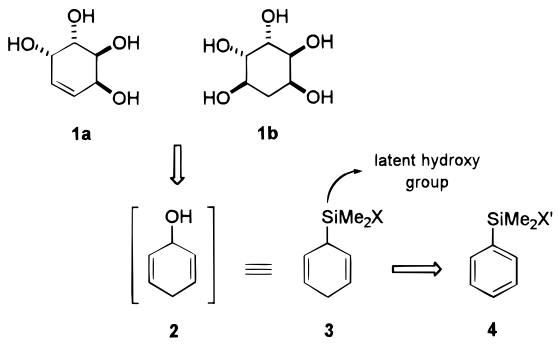
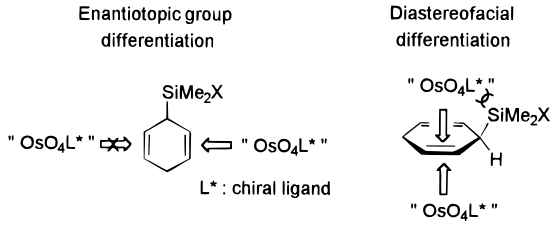
Desymmetrization of *meso* compounds[1] or symmetrical bifunctional substrates[2] is a very attractive method, allowing the transformation of easily available symmetrical precursors into asymmetric synthons of high value in a limited number of steps. While this approach has been very successful and is well documented in acyclic series, it has never been applied to cyclic systems such as **2**. Such an approach would be particularly significant in the context of developing the potential of polyhydroxylated cyclohexanes such as cyclitols **1a**,**b**[3] as inhibitors of glycosidases. Their ability to inhibit oligosaccharide-processing enzymes provides a wide range of possible applications in chemotherapy for these compounds, since glycoproteins are involved in numerous biochemical processes.[4] This has stimulated enormous synthetic efforts recently, and several asymmetric approaches to these substrates have been proposed,[5] among the most efficient of which is the microbial oxidation of aromatic precursors.[6] We propose here a general strategy directed toward the synthesis of polyhydroxylated cyclohexanes through desymmetrization of silyl-2,5-cyclohexadienes using Sharpless asymmetric dihydroxylation.[7] Surprisingly, the functionalization of such precursors has never been addressed so far.[8] The silylated analogue of **2** (i.e., **3**) possesses a silicon group that can be regarded as a hydroxy equivalent[9] and is easily accessible via a Birch reduction[10] of the corresponding arylsilane **4** (Scheme 1). Further elaboration of the resulting synthons was anticipated to give access to the necessary homochiral intermediates. As a demonstration of the utility and the versatility of our methodology, we also undertook the asymmetric syntheses of both conduritol E (**1a**) and 2-deoxy-*allo*-inositol (**1b**).

Scheme 1



Scheme 2



We speculated that the commercially available Sharpless dihydroxylation reagent[7] (*i.e.*, AD-mix) would be able to differentiate the two enantiotopic double bonds and that the silicon moiety would control the diastereofacial selectivity by forcing the attack of the incoming electrophile in an *anti* fashion (*1,2-stereocontrol*)[11] (Scheme 2). The carbon−silicon group would then be oxidized with retention of configuration using the classical Tamao−Kumada−Fleming procedure, finally revealing the OH group.[9]

2,5-Cyclohexadienylsilanol **3a** was readily prepared in 70% yield[12] using the Birch reduction (Li/NH_3) of commercially available $PhMe_2SiCl$[13] **4a** (Scheme 3). This result contrasts with the studies of Eaborn et al.[10b,c] on Birch reduction of $PhSiMe_3$, where only 20% of dienylsilane was formed along with recovered starting material. It is likely that, in our case, the reaction takes place on a more reactive aminosilane intermediate (formed by aminolysis[14] of **4a**), which would then produce the silanol **3a** after hydrolysis. Dihydroxylation of **3a** using various

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(10) (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1. (b) Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 470. (c) Eaborn, C.; Jackson, R. A.; Pearce, R. *Ibid.* **1975**, 2055. (d) Taber, D. F.; Bhamidipati, R. S.; Yet, L. *J. Org. Chem.* **1995**, *60*, 5537.

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(12) Ten to 20% of the corresponding siloxane is sometimes produced during the workup but is easily removed by distillation. The amount of siloxane can be reduced by diluting the reaction mixture prior to aqueous workup.

(13) Available from Aldrich (no. 11,337-9). $PhMe_2SiCl$ is also conveniently prepared on a 200 g scale from bromobenzene and Me_2SiCl_2: Andrianov, K. A.; Delazari, N. V. *Dok. Akad. Nauk. SSSR* **1958**, *122*, 393; *Chem. Abst.* **1959**, *53*, 2133.

S0022-3263(96)00814-6 CCC: $12.00

Scheme 3

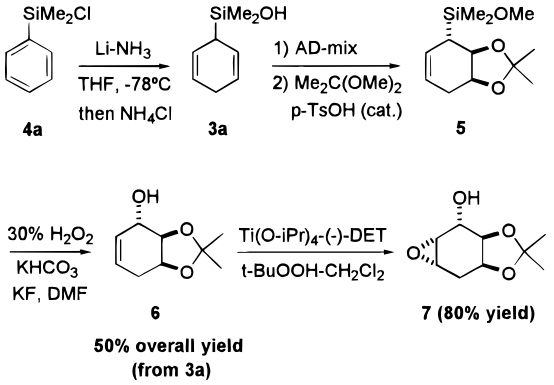


Table 1. Influence of the Nature of the Ligands in AD-mix on the Asymmetric Dihydroxylation of 3a (Scheme 3)

ligand[a]	ee[b]	ent[c]
$(DHQD)_2PHAL$	44	(−)
DHQD-IND	40	(−)
$(DHQD)_2PYR$	52	(−)
$(DHQ)_2PYR$	65	(+)

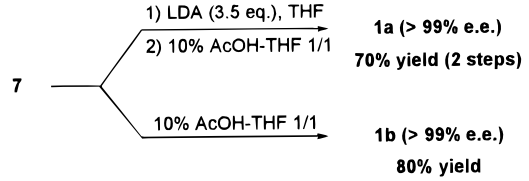
[a] DHQ:dihydroquinine; DHQD:dihydroquinidine; PHAL:phthalazine; PYR:diphenylpyrimidine; IND:indole. [b] Enantiomeric excess measured using ^1H NMR ($Eu(hfc)_3$) or capillary GC. [c] Enantiomer formed.

AD-mix formulations (Table 1) afforded the desired 1,2-diol,[15] which was directly protected as the acetonide **5**. Interestingly, the silanol was converted into the silylmethyl ether during the diol protection. Examination of the ^1H NMR of **5** revealed that only one diasteroisomer was formed under these conditions and that according to our expectations (as proved by difference NOE experiments), dihydroxylation *anti* relative to the bulky silicon group had occurred in a highly selective manner. The carbon−silicon bond was then oxidized[16] to afford the allylic alcohol **6**, diastereoisomerically pure and with 65% ee.[17]

This moderate enantioselectivity was not surprising if one considers the observations of Sharpless and coworkers,[7] who mentioned that *Z*-olefins and cyclic olefins usually give poor results using the commercially available AD-mix ($(DHQD)_2PHAL$). Different AD-mixes were prepared by varying the chiral ligands and the spacers as described by these authors.[7] Our results summarized in Table 1 indicate that the best enantioselectivity was obtained using $(DHQ)_2PYR$, which correlates with the observations made during asymmetric dihydroxylations on closely related substrates.

With enantiomerically enriched **6** in hand, we proceeded to examine the functionalization of the remaining double bond. Several routes were envisaged, and Sharpless epoxidation was retained due to the known efficiency of this kinetic resolution process.[18] Therefore, epoxidation using the standard conditions ((−)-DET) gave the expected *syn* epoxide **7** in a completely diastereoselective fashion and 90% ee (Scheme 3). At the same time, by

Scheme 4



repeating the reaction with (+)-DET we obtained the same diol after 4 days at −20 °C in a much lower yield, indicating a remarkable rate difference between "matched" and "mismatched" pairs.

The total synthesis of (+)-conduritol E was completed using LDA-mediated opening[19] of the epoxide ring of **7** followed by removal of the acetonide, leading to optically pure **1a** (after one recrystallization) in 20% overall yield from $PhMe_2SiCl$ (Scheme 4). It is worth mentioning that such a transformation allows the functionalization of the methylene C-4 center and, hence, functionalization of each carbon centre of the cyclohexadiene **3a**. Alternatively, the treatment of epoxide **7** with a 10% AcOH−THF mixture afforded, with complete regioselectivity, optically pure (−)-2-deoxy-*allo*-inositol (**1b**) (after one recrystallization) in a 30% overall yield from $PhMe_2SiCl$. The ring epoxide opening follows as expected a *trans*-diaxial mode obeying the Fürst−Plattner rule.[20] Base-catalyzed epoxide opening ($PhCO_2Na$ (cat.), H_2O) likewise afforded the regioisomer **1b** in good agreement with Hudlicky's recent observations.[3b] We also noticed that opening of the epoxide is slower than the deprotection of the acetonide since quenching the reaction mixture after only 24 h under reflux furnished a mixture of **1b** and the epoxy triol intermediate in a 1:1 ratio.

In summary, we have demonstrated that the desymmetrization of a readily available silyl-2,5-cyclohexadiene using asymmetric dihydroxylation affords an efficient and rapid entry into cyclohexane skeletons having four or five stereogenic centers in a stereocontrolled manner. This strategy is competitive in terms of cost, efficiency, and versatility with other approaches to similar substrates.[3,5,6] The chlorosilane precursor **4a** is inexpensive, and both enantiomers are theoretically accessible. Further manipulation of intermediates such as **6** or **7** should also provide the means to access other cyclitols and related analogues. Finally, it is worth mentioning that we have only reported the desymmetrization of **3a** using asymmetric electrophilic processes. Other asymmetric non-electrophilic functionalizations of these dienes may, however, be envisioned and are now under study in our laboratory. In addition, the conversion of the *syn*-1,2-diol moiety into useful functions such as 1,2-amino alcohols[7,21] or 1,2-thio alcohols[22] has now been reported and could well broaden the scope of our methodology.

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Supporting Information Available: Experimental procedures and spectral data for compounds **3a**, **5**, **6**, **7**, **1a**, and **1b** (3 pages).

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(14) On addition of the chlorosilane to the reaction mixture (NH_3−THF), one could observe the immediate formation of a heavy precipitate, presumably NH_4Cl.

(15) The reaction between **3a** and AD-mix was complete after 12 h at 0 °C and led after careful extraction to the desired 1,2-diol in 65−75% crude yield. The presence of more polar, intractable tetrols in the aqueous phase cannot, however, be excluded.

(16) DMF was used instead of the standard THF−MeOH mixture, which led to incomplete oxidation.

(17) Enantiomeric excesses were determined either by capillary GC (Cyclodex-B), ^1H NMR with $Eu(hfc)_3$, or ^1H NMR of Mosher's esters.

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