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Asymmetric Amino-Hydroxylation of Dienylsilanes. An Efficient Route to Amino-Cyclitols.

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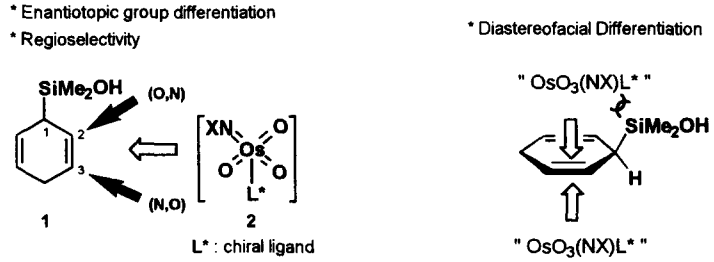
Abstract: Sharpless asymmetric amino-hydroxylation of a silyl-2,5-cyclohexadiene occurs with complete regio- and diastereocontrol. An enantioselectivity of up to 68% e.e. was also observed. An application of the methodology to the synthesis of relevant examples of amino-cyclitols is described.

We recently reported the synthesis of optically active cyclitols using the desymmetrization of silyl-2,5-cyclohexadienes such as **1**[1] through the Sharpless asymmetric dihydroxylation (AD)[2] (Scheme 1). This approach afforded an easy and stereocontrolled access to this important class of potent inhibitors of glycosidases. Extension of such a methodology to the closely related amino-hydroxylation (AA) would provide a rapid entry to amino-cyclitols which also possess important biological activity.[3] The recent discovery by Sharpless[4] that amino-hydroxylation could be carried out in an enantioselective fashion, using conditions which parallel those employed for the dihydroxylation, prompted us to apply this useful reaction to our substrates. However, as illustrated in Scheme 1, such an approach would give rise to several stereochemical problems. The putative asymmetric osmium reagent **2** will not only have to differentiate between the two enantiotopic double bonds[5] but also both faces of the π-system, approaching either *syn* or *anti* relative to the bulky silicon group.[6] In addition, one could predict a problem of regioselectivity since the nitrogen (NX) and the oxygen groups can attack at both C-2 or/and C-3 positions. As a useful element of comparison, the asymmetric dihydroxylation was found to afford the desired 1,2-diol with complete diastereocontrol (*anti*) and good enantioselectivity.[1] We could anticipate a similar outcome with reagent **2** but no information was available at the time concerning the regioselectivity of the amino-hydroxylation of allylsilanes.[7] We report here that complete regio- and diastereocontrol, as well as a good enantiocontrol is achieved during Sharpless amino-hydroxylation of dienylsilane **1**. An application of the methodology to the synthesis of relevant examples of amino-cyclitols is also described and serves to demonstrate the versatility of our approach.



Scheme 1

Amino-hydroxylation of **1** was initially carried out using the first generation of amino-hydroxylation reagent reported by Sharpless,[4] *i.e.* using chloramine T (TsNClNa) as oxidant-nitrogen source. Unfortunately, this system was found unreactive in our case leading to recovered starting material. However, replacing TsNClNa with the sterically less demanding $EtO_2CNClNa$[8] afforded the desired hydroxy-carbamate **3** in good yield and more importantly ***with complete diastereo- and regioselectivity*** (in the limit of detection of ^1H NMR)(Scheme 2). The relative stereochemistry of **3** was unambiguously assigned by X-ray structure determination of the corresponding alcohol **4** (Fig.-1), prepared through oxidation of the C-Si bond, with retention of configuration,[9] and protection of the hydroxy-carbamate. It is noteworthy that the protection is also regioselective involving only those groups which are *cis* to each other.[10] The preference of the carbamate group for the slightly more hindered C-2 position suggests that electronic directing effects might operate during the AA process. This parallels Sharpless' observations that on amino-hydroxylation of α,β-unsaturated esters, the tosyl-amino group prefers the β-position, away from the electron-withdrawing ester group.[4] However, these preliminary results are yet unconclusive and more experimental data will be required to draw more definite conclusions concerning the factors governing regioselectivity.[11] Finally, an enantiomeric excess of 68%, measured from the Mosher's ester of **4** (^{19}F NMR),[12] was obtained using $(DHQ)_2PYR$ as chiral ligand, which is very similar to the e.e. obtained during dihydroxylation using the same ligand.[1] Interestingly, the absolute configuration of **3**[13] is the same as that of the diol obtained through AD of **1**, indicating that the rule set up for AD also applies to AA.[2,4]

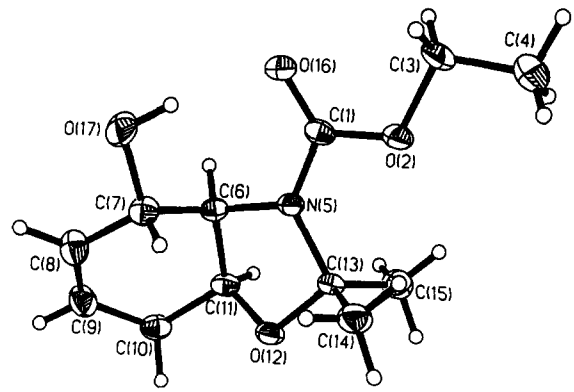
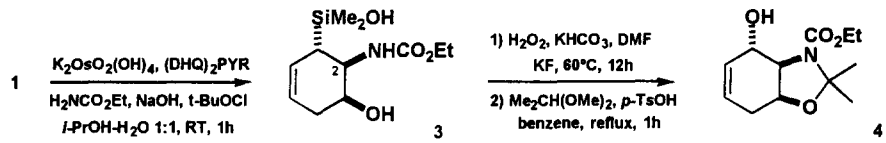
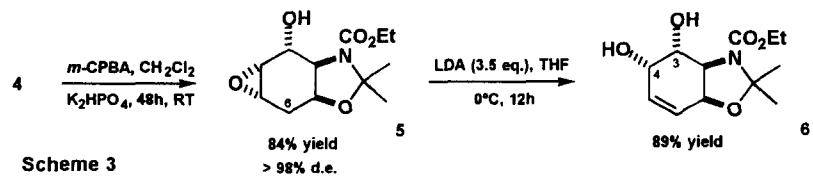


Fig.-1. X- Ray structure of **4**.



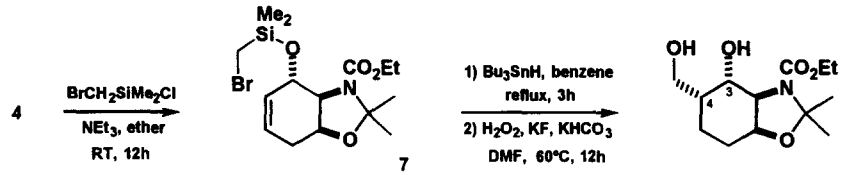
Scheme 2

It is worthy of note that this moderate enantiomeric purity can be easily ***raised to > 99% through a single crystallization of synthon*** **4**. Further functionalizations of optically pure **4** were carried out as shown below and demonstrate the versatility of such a synthon for the preparation of homochiral amino-cyclitols. Functionalization of the remaining double bond and the methylene group at C-6 was carried out by *m*-CPBA epoxidation[14] followed by the base-induced epoxide ring opening to afford the unusual conduramine **6** in 75% overall yield from **4** (Scheme 3). The exclusive *cis*- relative stereochemistry between OH at C-3 and C-4 indicates that the *m*-CPBA epoxidation was directed by the allylic alcohol group.[15] Interestingly, **6** should be useful as an advanced intermediate in the synthesis of fortamine, the aglycon moiety of antibiotic *fortimicins*.[16]



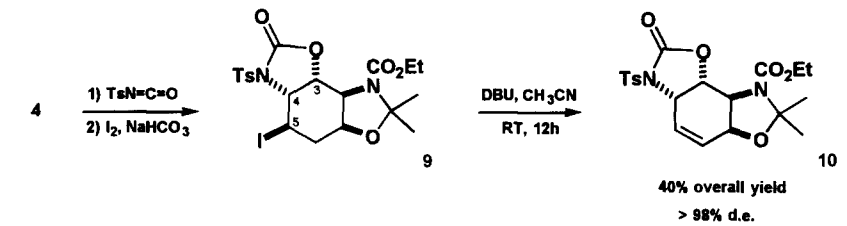
Scheme 3

The intermediate **4** was also transformed in a straightforward manner into a new class of amino-carbasugars through the temporary silicon connection strategy depicted in scheme 4.[17] The CH_2OH moiety of the sugar analogue was easily introduced *via* radical cyclisation of the silyl ether **7**, followed by oxidation of the C-Si bond of the cyclic siloxane intermediate (Scheme 4). Amino-cyclitol **8** was thus obtained in 74% from **4**, with complete diastereocontrol. Only the *cis*-stereomer (C-3-C-4) was obtained, in good agreement with recent reports on carbasugar analogues.[17]



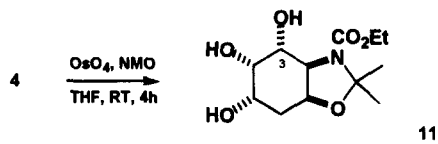
Scheme 4

The 1,3-diamino moiety found in aminocyclitol aglycons of *streptomycin* antibiotics,[18] can also be set up from chiron **4** via a *5-exo-trig* iodocarbamation.[19] Thus, treatment of **4** with tosyl-isocyanate afforded the carbamate intermediate which was directly cyclized under kinetic conditions (5% $NaHCO_3$). **9** was thus obtained as the sole diastereomer, having the *cis-trans* (C-3-C-4-C-5) relative stereochemistry shown in Scheme 5. Elimination of HI and formation of the double bond was then easily accomplished using DBU, leading to **10** having two 1,2-amino-alcohol moieties protected with chemically differentiated carbamates.



Scheme 5

Finally, we found that simple dihydroxylation of **4** afforded the triol **11** in good yield as a single diastereomer (Scheme 6). Interestingly, the osmylation took place *syn* relative to the hydroxy group. Similar topicity was observed with an analogous, oxygenated allylsilane (Si at C-3). It is reasonable to assume that the steric hindrance induced by the oxazolidine ring prevents the osmylation occurring from the top face.



Scheme 6

In summary, we have shown that complete functionalization of an arene by a *Birch reduction-asymmetric-amino-hydroxylation* sequence, followed by manipulation of the remaining double bond, provide efficient access to a biologically relevant class of amino-cyclitols. It is noteworthy that the diastereofacial selectivity in this type of cyclohexenyl skeleton is always very high, a trend which we have already observed in the polyoxygenated series.[1]

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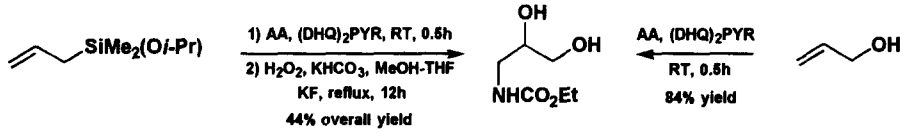
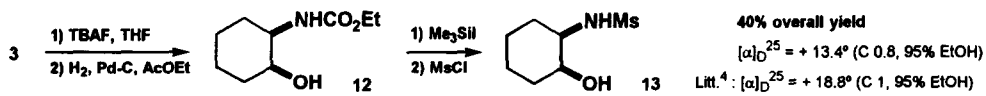
10. ^{13}C NMR in $CDCl_3$ at room temperature indicates that **4** is in fact a 9:1 mixture of two conformations. Variable temperature experiments indeed support the occurrence of a dynamic equilibrium between *cis* and *trans* carbamate rotamers appearing during the formation of the oxazolidine ring. For similar observations, see: Garner, P.; Park, J.M. *J. Org. Chem.*, **1987**, *52*, 2361-2364.
11. Interestingly, we have observed that with mono-substituted olefins, the carbamate prefers to attack the less substituted carbon centre (>98% regioselectivity), away from the allylic group and irrespective of the electronic nature of the latter (SiR_3 or OH).



12. ^{19}F NMR of Mosher's ester of **4** in d^8-toluene produced 4 signals at room temperature due to the occurrence of two conformations. Upon raising the temperature to 80°C, these signals finally coalesced into one signal for each diastereomer.
13. The absolute configuration of **3** was determined through its conversion into the known mesylate **13**,[4,8] using the following sequence :



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