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Preparation of enantioenriched tetraols and triolamines from a common epoxide

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ABSTRACT

We identify a silylcyclopentene oxide that is amenable to several distinct asymmetric catalytic transformations providing access to enantio-enriched tetraol and triol-amines. The sequence employed allows for selective protection of one amine or alcohol from the four heteroatoms that are introduced into the carbon scaffold.

Enantioenriched polyols and polyol amines make up important classes of building blocks for the preparation of biologically important natural products. Of recent interest has been work toward polyketides (and polyketide-like) macrolides where small polyol fragments have proven versatile.[1,2] Selectively protected benzyl ether polyols have been incorporated into the total syntheses of antitumor antibiotics azinothricin and kettapeptin.[3] Polyol amines such as 2-amino-1,3,4-butantriol are central to one preparation of the HIV-Protease Inhibitor Nelfinavir.[4] These small building blocks have many other applications including as hypoxic cell radiosensitizers,[5] in large macrolactams that demonstrate beta-secretase 1 (BACE-1) inhibition,[6] as a building block for phytosphingosines,[7] and as synthons for azasugars.[8] Applications where selective functionalization of the amine group as an amide[9] or triazole[10] have biological significance.

In identifying a common building block for these diverse applications we turned our attention to the highly innovative strategy of desymmetrizing meso epoxide **1** with chiral amide base to give alcohol **2** in high ee (Fig. 1).[11] Alcohol **2** was further elaborated and the silicon center upon oxidation yielded diverse alkyl substituted chiral tetraols **3** in greater than 70% yield (where R = butyl, isopropyl, allyl, Ph, and H). This strategy had immediate applications and advantages to the preparation of (−)-pinolidoxin.[1]

We began an examination to determine if other high-impact transformations were possible for substrate **1**. We identified a few racemic reactions that would be suitable for diversifying this epoxide, most notable was azide addition.[12,13] In parallel we became interested in asymmetric azide addition to cycloalkane oxides.[14] We began our work at the confluence of these reports.

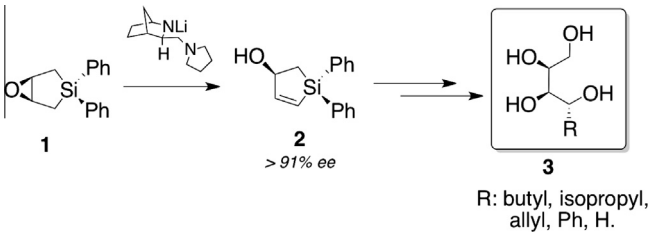

Figure 1. Desymmetrization of **1** and preparation of alkyl and aryl substituted polyols **3**.[11]

The highly effective salen catalyst developed by Jacobsen has been used very effectively for the asymmetric ring opening of epoxides[15] including cyclopentaneoxide and cyclohexaneoxide. Nucleophiles such as azide,[14] acetate, and benzoate[16] have been utilized in these reactions. Jacobsen identified Cr catalyst **4** as widely applicable for enantioselective ring opening with azide to cyclohexaneoxide, cyclopentaneoxide, tetrahydrofuranoxide, and pyrollidineoxide.[14] We began our investigation with *meso* silylcyclopenteneoxide **1** with the expectation that silicon removal would ultimately afford polyol azides or polyol amines.[14]

Treatment of **1** with 2 mol % of Cr catalyst (*R*,*R*)-**4** (Fig. 2) at elevated temperature resulted in formation of both the desired alcohol **5** as well as TMS ether **6** in a total of 80% isolated yield

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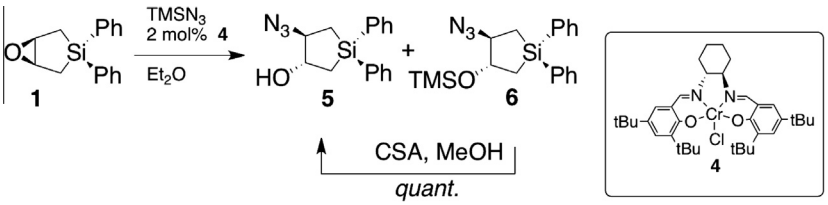

Figure 2. Enantioselective ring opening of epoxide **1** with azide and Jacobsen's catalyst **4** (see Table 1).

Table 1
Reaction outcome and conditions for the asymmetric ring opening of epoxide **1** with TMS azide and catalyst **4** (see Table 1)

Entry	Catalyst loading	*T* (°C)	Time	Alcohol **5** (yield)[a]	% ee[b] of **5**	TMS ether **6** (yield)[c]
1	2	50	11 h	58%	16	22%
2	2	22	12 h	97%[d]	68	—
3	15	−70	5 d	59%[e]	84	—

[a] Isolated yield after column chromatography.
[b] Determined by Mosher ester analysis.[17]
[c] Isolated yield after column chromatography, a brief workup with camphorsulfonic acid in methanol quantitatively converts TMS ether **6** into alcohol **5** without loss of ee.
[d] TMS ether hydrolyzed to alcohol prior to column chromatography.
[e] Corrected isolated yield after recovery of 57% of starting material **1**, trans chloro alcohol was isolated in 15% yield in addition to the desired alcohol **5**, no TMS ether was isolated (see ESI for complete details).

and low ee (Table 1, entry 1). The TMS ether **6** can be readily hydrolyzed with camphorsulfonic acid in methanol as part of the work up procedure to produce alcohol **5** quantitatvely.[14] The reaction was slightly slower at room temperature, but on 0.5 g scale the desired azido alcohol was isolated in 97% yield (entry 2) after hydrolysis of TMS, with 68% ee by Mosher ester analysis (see ESI for full details). At −15 °C the reaction slowed with only modest increase in ee (not shown), at −70 significant starting material remained after 4 days and a trans chloro alcohol (see ESI) was isolated in 15% yield. The chloro alcohol product likely arises from the chloride ligand of **4** attacking the epoxide. Despite these issues, an increase to 84% ee was achieved with a yield of the desired alcohol in 59% after accounting for recovered starting material. We determined absolute stereochemistry at the alcohol stereocenter to be (*R*) by a method described below (Fig. 3).

Having demonstrated the preparation of enantioenriched trans azido alcohol **5** we were eager to attempt oxidation and removal of the silicon core. We attempted the Woerpel[18] oxidation conditions as used by Kozmin[11] for the preparation of tetraols **3**, and instead of desired triol azide **7** we isolated exclusively the chiral allylic diol **8** (Fig. 3). It seems under these conditions azide presents a facile leaving group for elimination.

The unexpected alcohol **8** is a useful building block for a variety of synthetic applications.[19] The isolation of **8** allowed us to readily assign absolute stereochemistry at the alcohol stereocenter as introduced in the asymmetric step (Fig. 2). The literature optical rotation[20] for (*S*)-**8** is −44° and we found our sample to have +20.6°, which proves (*R*) stereochemistry at the alcohol center with an ee of 47%. This result is consistent with ee of the starting azide **5** (58% in this case) as determined by Mosher ester analysis. Precise

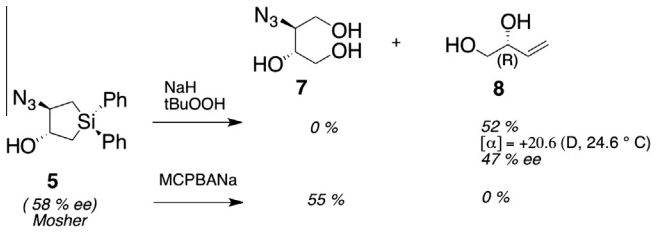

Figure 3. Oxidation of **5** to produce azido triol **7** and unexpected allylic diol **8**.

optical rotation data for this alcohol were particularly sensitive to experimental conditions, thus our confidence in ee lies with Mosher analysis.

We tried several oxidation procedures to overcome the elimination of azide, including KF with hydrogen peroxide, but these gave significant amounts of **8**. Treatment of **5** with MCPBA[21] under basic conditions however effected the desired transformation to **7** in 55% yield without unwanted elimination. A complete mechanistic explanation for conversion of **5** into **8** has not been explored, but it is likely oxidation to pentacoordinate silicon precedes elimination as alkenylsilanes treated with HOOH, KF, and $KHCO_3$ give carbonyl compounds.[22] Thus if **5** underwent E2 elimination to give a silylalkene, subsequent oxidation should give products that we have not observed.[23] Alternatively there may be two different outcomes depending on selection of oxidant. In the case of *t*-$BuOO^-$, carbon silicon bond breaking and elimination of azide would rationalize the alkene present in **8**.[24] In the case of $MCPBA^-$, the standard oxygen insertion reaction could account for the terminal alcohol.[21] The differential behavior could be the result of either the leaving group ability of *t*-BuO^- versus 3-chlorobenozate$^-$, or the inherent nucleophilicity difference between the two peroxy species.

Azide **7**'s diastereomers have previously been prepared from D or L-diethyltartrate and used toward the preparation of azasugars.[8] At this stage we explored modifications to the azide group of **5** to expand the utility of this transformation and to uncover oxidation conditions that avoid unwanted eliminations. Azide alcohol **5** readily underwent tin chloride reduction in HCl[25] to give the corresponding amine that was acylated with benzoyl chloride to give amide **9** in good yield. Oxidation with Na *t*-butylperoxide gave the desired amide triol **10** in acceptable yield (Fig. 4). Alternatively, triazole formation[26] with 1-hexyne and oxidation gave **11** and **12** in high yields, respectively. These two nitrogen triols (**10** and **12**) have direct application to medicinal chemistry.[9,10] Reduction of **5** with tin chloride gave the amine **13** in 75% yield, subsequent oxidation cleanly gave the expected amino triol **14** (TLC and crude NMR analysis), but challenges with isolation have as of yet only provided this compound in small quantities (Fig. 5). The methyl carbamate of **13** was also prepared (results not shown).

In addition to azide, we explored the use of acetate toward functionalizing epoxide **1** using asymmetric ring opening catalysis.[16] As previously reported, the use of Co(III) salen complex was

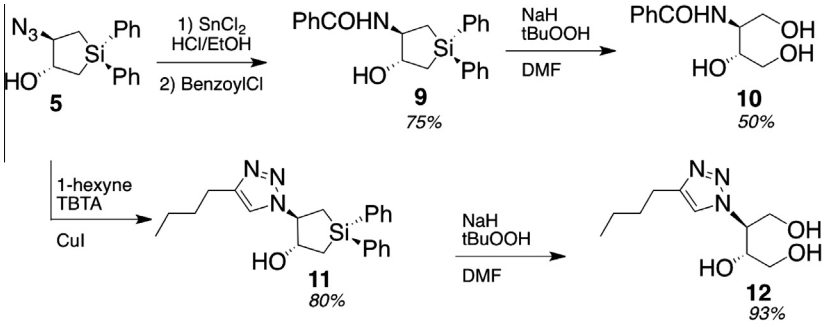

Figure 4. Preparation of 2-amide and 2-triazole 1,3,4-butantriols **10** and **12**.

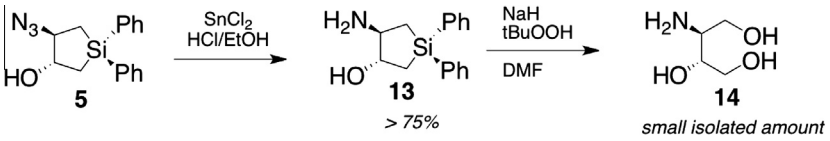

Figure 5. Access to 2-amino-1,3,4-butantriol **14**.

Table 2
Reaction outcome and conditions for the asymmetric ring opening of epoxide **1** with acetate and catalyst **10** (see Fig. 6)

Entry	Catalyst loading	*T* (°C)	Time	Alcohol **16** (yield)[a]	% ee[b] of **16**	Recovered **1** (yield)
1	10	0	12 h	71%	48	—
2	10	−20	3 d	73%	62	—
3	10	−70	6 d	16%[c]	65	79%

[a] Isolated yield after column chromatography.
[b] Determined by Mosher ester analysis.[17]
[c] Uncorrected isolated yield after recovery of 79% of starting material **1**.

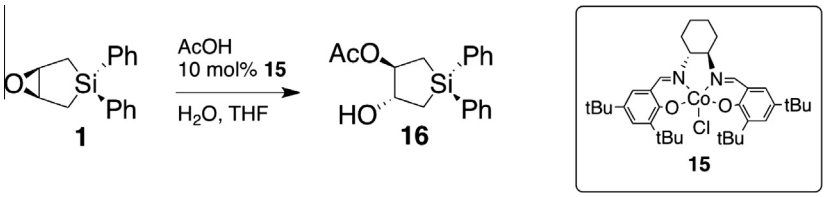

Figure 6. Enantioselective ring opening of epoxide **1** with acetate and Jacobsen's Co catalyst **15** (See Table 2).

most efficacious. Epoxide **1** was treated with 10 mol % catalyst (*R*,*R*)-**15** at 0 °C for 12 h, acetate alcohol **16** was isolated in 71% yield (Table 2, entry 1). The ee at the newly introduced stereocenter was determined to be 48% under these conditions. Lowering the temperature of the reaction resulted in minor improvement in ee (Table 2, entries 2 and 3). At −70 °C the reaction rate slowed drastically.

Despite the disappointing ee of this reaction we decided to test a few strategies toward developing useful chiral building blocks. Our attempt to isolate mono-acetate triol from treatment of **16** with Na *t*-butylperoxide failed to yield the desired triol, instead giving the elimination product allylic diol **8** (Fig. 7). Optical rotation confirmed (*R*) stereochemistry as was observed in Figure 3. Alternatively we benzylated the free alcohol using a silver(I) mediated alkylation giving benzyl ether **17** in 86% yield.[27] Hydrolysis of acetate **17** in methanol gave the free alcohol **18** in 78% yield. This ether was far more robust, surviving oxidation with tBuOONa to give 2-*O*-benzyl-D-threitol **19**[28] in 30% yield. This particular building block has applications for the total synthesis of (+)-azinothricin and (+)-kettapeptin.[3] In addition to **19** we isolated monobenzylether diol **20** in 27% yield. The oxidation at one carbon and hydrogen insertion at the second carbon center attached to silicon have been previously observed for the strained dimetylsilacyclobutane.[29] In that report, oxidation with hydrogen peroxide, KF, and $KHCO_3$ gave 1,3-propanediol and 1-propanol in a 1.5:1 ratio. The regio chemistry of **20** was determined by comparison to a literature report[30] as well as through acetonide formation; the acetonide product of **20** is consistent with a vicinal diol, not the alternative 1,3-diol (see ESI for full details).

The preparation of enantiopure building blocks remains a fundamental area of importance for synthetic chemistry. In many applications of asymmetric catalysis, feedstocks derived from simple petroleum products are converted into materials with very diverse properties. We started from a common building block, meso silylcylic epoxide **1** and demonstrated the application of two different asymmetric addition reactions. Further elaboration demonstrated that a variety of selective protection strategies could be employed before the final oxidation and removal of the silicon core. This first report demonstrates a variety of distinct chemical species with moderate ee and good yield. One major variable that remains untested for substrate **1** is the role of solvent in both the addition of azide (Fig. 2) and acetate (Fig. 6). This is one area we

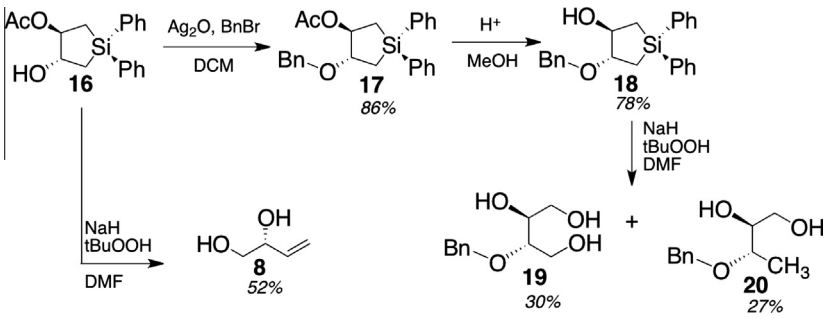

Figure 7. Preparation of 2-*O*-benzyl-D-threitol **19** and benzylether diol **20**.

are currently exploring. The other variable that might appear to be significant is the role of the spectator phenyl groups on epoxide **1**. We have some initial evidence that the role of these groups will have little consequence in the desymmetrization reactions reported herein. Additionally, they played no discernable role in the desymmetrization of **1** by chiral amide base as demonstrated in Figure 1.[11] We believe that the variety of chiral polyol and polyol amine building blocks reported herein are just the beginning and the results of our continued exploration will be reported in a sequel.

Acknowledgment

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Supplementary data

Supplementary data associated (Complete experimental procedures with tabulated ^{1}H, ^{13}C, and MS data are included for all new compounds. ^{1}H, ^{13}C, and DEPT-135 spectra are included for all new compounds. Ee calculation by Mosher analysis and absolute stereochemical determination are included.) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.001.

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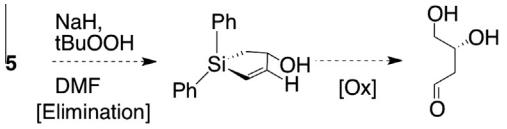
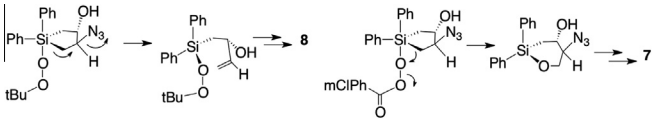


24. Possible mechanisms for differential oxidation outcomes.



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