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## Synthesis of chiral epoxyalkynes

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### Abstract

The synthesis of novel chiral propargylic epoxides ((*R*)-1-*t*-butyldimethylsilyl-3,4-epoxy-1-butyne, (3*S*,4*S*)-3,4-epoxy-1-octyne, (3*R*,4*S*)-1-*t*-butyldimethylsilyl-3,4-epoxy-1-pentyne) has been developed starting from the readily available tartaric acid derivative, (*S,S*)-(+)-2,3-O-isopropylidene-L-threitol. © 1998 Elsevier Science Ltd. All rights reserved.

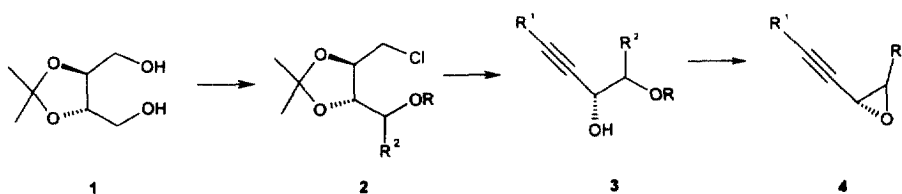
### 1. Introduction

Chiral  $\alpha$ -functionalised alkyne units are often essential fragments of naturally occurring molecules that show interesting and important biological (e.g. cytotoxic and antifungal)<sup>1,2</sup> activity. For the preparation of such compounds and many other complex chiral structures, enantiomerically pure  $\alpha$ -epoxyalkynes may serve as versatile building blocks. However, the synthesis of enantiomerically pure epoxyalkynes has received surprisingly little attention, if compared to the variety of methods for the synthesis of enantiomerically pure  $\alpha$ -epoxyalkenes and epoxyalkanes (Sharpless epoxidation,<sup>3</sup> direct asymmetric epoxidation with salen complexes,<sup>4,5</sup> hydrolytic kinetic resolution<sup>6</sup>). To date Grandjean<sup>7–9</sup> has described the only method for the asymmetric synthesis of these compounds. For this reason, the search for methods of the synthesis of acetylenic epoxides from readily available natural compounds is still of interest.

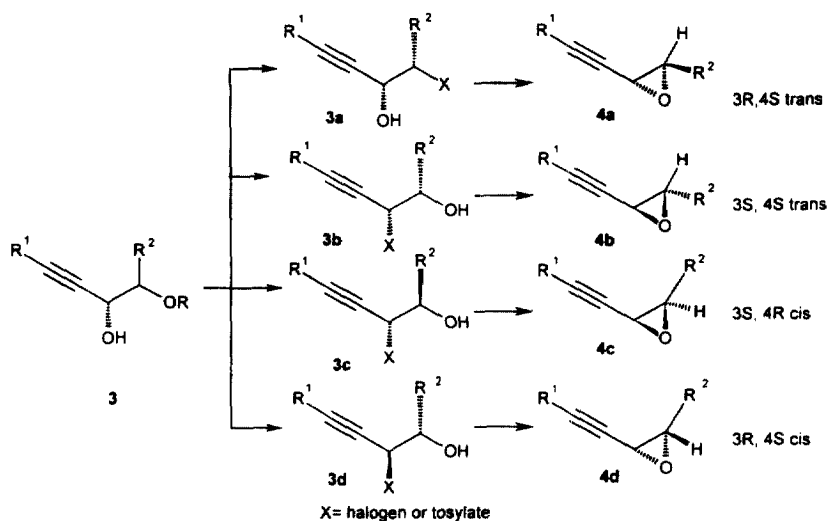
We have developed a general route for the synthesis of propargylic epoxides (terminal epoxides, disubstituted *cis*-epoxides and *trans*-epoxides)<sup>10,11</sup> starting from a readily available tartaric acid derivative — (*S,S*)-(+)-2,3-O-isopropylidene-L-threitol **1** (Scheme 1). The key reaction of the route is the stereospecific base-induced double elimination of the appropriately substituted and protected chloride **2** with LiNH<sub>2</sub> in liquid ammonia.<sup>12</sup> The obtained monoprotected propargylic diol **3** is converted selectively into one of the possible different halohydrins or monotosylates **3a**, **3b**, **3c** or **3d**, which have a strictly

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defined configuration of the substituents (Scheme 2). The absolute configuration at the propargylic centre may remain the same as in the starting monoprotected diol **3** in the case of **3a** and **3d**, (double  $S_N2$  reaction). An inversion of the configuration at C-3 takes place with compounds **3b** and **3c**. The geometry of the epoxide (*cis* or *trans*) is determined by the configuration of the alkyl substituent, and also by the choice of the OH group for the nucleophilic ring formation reaction (the  $\alpha$ -OH or the  $\beta$ -OH-group).



Scheme 1.



Scheme 2.

The main possibilities to obtain *cis*- and *trans*-epoxides of different configuration are presented in Scheme 2. The route is completely stereoconvergent, which means that epoxides with different absolute configuration and geometry may be obtained from one stereoisomeric propargylic diol.

The basic problems arising from the current route are: (a) the synthesis of the appropriately protected and substituted triol chlorides **2** with a strictly determined configuration of the alkyl group (*syn* or *anti* to the OH group(s)); (b) the appropriate manipulation of the OH groups in diol **3** before epoxidation (the selection of groups, one of which will act as a nucleophile and the other as a leaving group; inversion or retention of the configuration at the chiral centre with the leaving group before epoxidation).

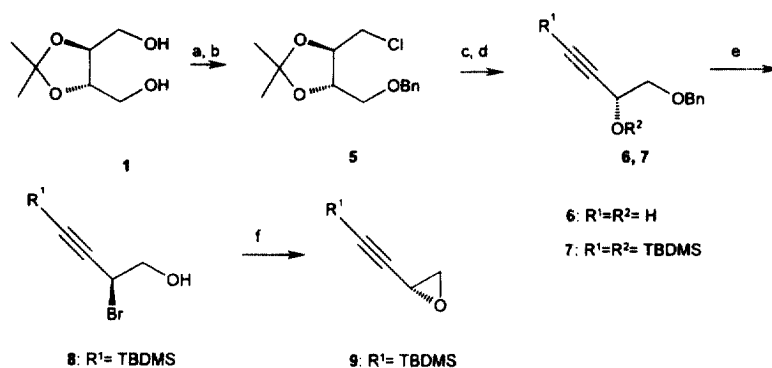
The possibilities of the route are presented below.

## 2. Results and discussion

### 2.1. Terminal propargylic epoxide

This is the least complicated case. The absolute configuration of the final epoxide is determined by the selection of a nucleophile and leaving group. The following is an example of how bromohydrin **8**

is made by means of the stereoselective conversion of the secondary OH-group into a bromide group (inversion of configuration). The primary OH-group acts in this case as a nucleophile in the oxirane formation reaction (case **3d** on Scheme 2,  $R^2=H$ ). The synthesis starts from selective monobenylation of tartaric acid derivative **1** followed by chlorination under non-acidic conditions<sup>13</sup> (Scheme 3). The obtained chloroacetal **5** is a key synthon for base-induced eliminations<sup>12</sup> with  $\text{LiNH}_2$  in liquid ammonia affording propargylic alcohol **6** in 70% yield. Although it has been stated that no epimerization takes place under these conditions,<sup>14</sup> we checked the enantiomeric excess of intermediate **6** prior to subsequent conversions. The corresponding ester from (*R*)- $\alpha$ -methoxy- $\alpha$ -trifluoro-methylphenylacetic acid did not reveal any traces of the other diastereomer by means of HPLC and NMR analyses. Also, in order to verify the absolute configuration, compound **6** was hydrogenated ( $\text{H}_2/\text{Pd}$  on C) to give (*R*)-1,2-butanediol ( $[\alpha]_{\text{D}}^{20}=+14.8$ , lit<sup>15</sup>  $[\alpha]_{\text{D}}^{20}=+12.6$ ).



Scheme 3. Reagents and conditions: (a)  $\text{NaH}$ ,  $\text{BnCl}$ , THF,  $0^\circ\text{C}$ , 1 h r.t., 86%; (b)  $\text{Ph}_3\text{P}$ ,  $\text{CCl}_4$ ,  $70^\circ\text{C}$ , 2 h, 95%; (c)  $\text{LiNH}_2$ , liq.  $\text{NH}_3$ ,  $-33^\circ\text{C}$ , 0.5 h, 70%; (d)  $\text{BuLi}$ , THF,  $-78^\circ\text{C}$  followed by *t*- $\text{BuMe}_2\text{SiCl}$ ,  $-20^\circ\text{C}$  to r.t., 6 h, 59%; (e)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-70^\circ\text{C}$ , 15 min, 85%; (f)  $\text{K}_2\text{CO}_3$ , acetone/ $\text{H}_2\text{O}$ , 30 min, r.t., 70%

The terminal triple bond and the OH group in compound **6** were silylated with  $\text{TBDMSCl}$ , affording propargylic alcohol **7**. The debenylation reaction of **7** with  $\text{BBr}_3$  occurred simultaneously with a highly stereoselective propargylic bromination (substitution of TBDMSO group) affording bromohydrin **8**. A similar conversion of alkyl, benzyl and adamantyl alcohols to the corresponding bromides with  $\text{BBr}_3$  is known from the literature.<sup>16,17</sup> However, our example is the first application of this reaction to propargylic silyl ethers. The bromination reaction is stereoselective (as can be seen from the enantiomeric excess of the target compound) and chemoselective (only the propargylic silyl ether is replaced by bromide, the primary OH function remains unchanged),<sup>†</sup> resulting in a high yield (85%) of bromohydrin **8**. The final step of the route is the conversion of bromohydrin **8** under the basic conditions into the target epoxide **9** (intramolecular  $\text{S}_{\text{N}}2$  reaction). The stereoconvergent synthesis that allows the synthesis of the other enantiomeric epoxide (where the propargylic OH-group is converted to a tosylate with retention of configuration) is demonstrated on the example of the substituted *trans*-epoxides.

## 2.2. Synthesis of substituted propargylic epoxides

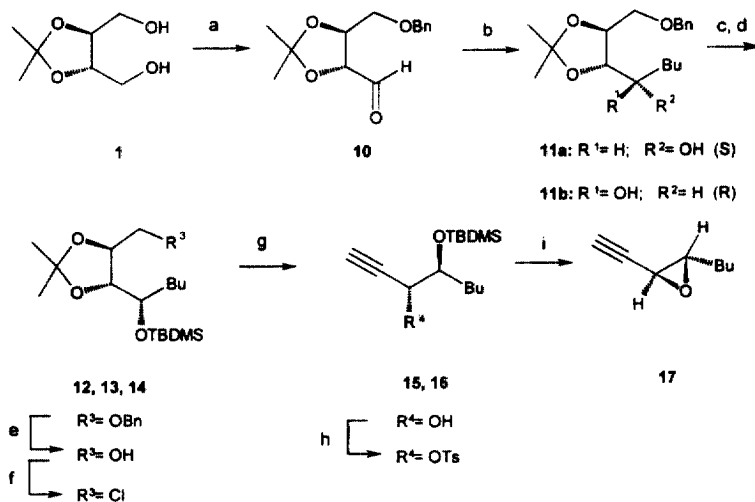
### 2.2.1. *trans*-Epoxides

In the synthesis of disubstituted epoxides, the key intermediate is the protected triol chloride **2**. The configuration of the stereogenic centre on the alkyl chain determines the configuration of the  $\beta$ -carbon

<sup>†</sup> Debonylation of unprotected alcohol **6** afforded but-3-yn-1,2-diol, no bromination was detected.

atom of the  $\alpha$ -epoxyalkyne. The geometry of the epoxide is determined by the relative configuration of the leaving group/nucleophilic group (see Scheme 2). Although the synthetic route is stereoconvergent as well as convergent in respect of the geometry of the epoxide function, the selectivity of the alkylation is of great importance for achieving the strictly defined stereochemistry of intermediate **3**. For that reason we tried to control (and direct) the selectivity of alkylation.

The alkyl chain is introduced *via* nucleophilic addition to aldehyde **10** (Scheme 4). The alkylation with different organometallic nucleophiles afforded a mixture of diastereomeric alcohols **11a** and **11b**, which are easily separable by column chromatography. The ratio of diastereomers was determined by HPLC and the results are presented in Table 1. The ratio of derived alcohols **11a**(*S*):**11b**(*R*) is dependent on the alkylation reagent. The highest excess of desired isomer **11a** was obtained with BuLi (entry 1). Various Lewis acid additives (ZnCl<sub>2</sub>, Ti(*i*-PrO)<sub>3</sub>Cl, BF<sub>3</sub>·Et<sub>2</sub>O, entries 2–4) increased the amount of the undesired isomer **11b**. Alkylation with BuMgBr and Bu<sub>2</sub>CuLi reagents gave an even lower ratio of isomers. Lewis acid additives did not change the ratio considerably (entries 5–11). It was assumed that four heteroatoms in the molecule of aldehyde **10** might form several chelates (the five-, six- or seven-membered ring, Scheme 5). These possible chelates may exist simultaneously in the reaction medium and direct the attack of the nucleophile in the opposite direction, which results in poor diastereoselection. Despite the fact that the ratio of diastereomeric alcohols was the highest in the case of BuLi, the reaction with BuMgBr gave a better isolated yield of product **11a** (40% after chromatographic purification) and, therefore, the preparative synthesis was carried out using the Grignard reagent.



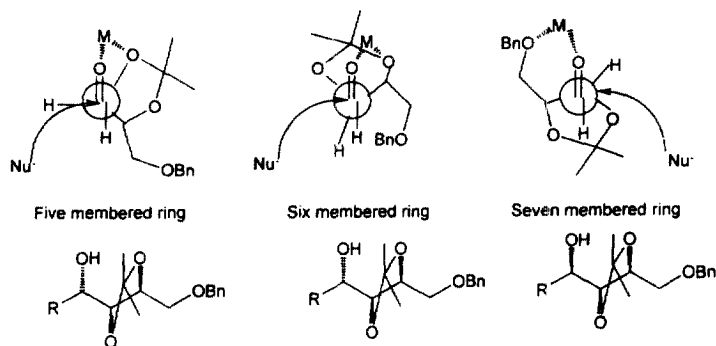
Scheme 4. Reagents and conditions: (a) *lit.*<sup>10,11</sup>; (b) BuMgBr, Et<sub>2</sub>O, r.t., 12 h; 61%; (c) separation of isomers on silica gel; (d) TBDMSCl, imidazole, DMF, 40°C, 38 h, 90%; (e) Na, liq. NH<sub>3</sub>, -33°C, 4 h, 80%; (f) PPh<sub>3</sub>, CCl<sub>4</sub>, 3 h, 78%; (g) LDA, THF, -78°C to r.t., 3 h, 72%; (h) TsCl, Py, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 24 h, 84%; (i) Bu<sub>4</sub>NF, THF, -78°C to 0°C, 2 h, 55%

The choice of benzyl as a protecting group for the primary alcohol group in compounds **10–12** enables its selective removal in compound **12** in the presence of acid sensitive silyl and acetal groups, affording intermediate **13**. This compound was chlorinated with PPh<sub>3</sub>/CCl<sub>4</sub> and transformed to propargylic alcohol **15** (3 equiv. of LDA in THF at -78°C) in good yield (72%).<sup>‡</sup> HPLC, <sup>1</sup>H and <sup>13</sup>C NMR analyses did not reveal any trace of the diastereomeric alcohol. Alcohol **15** was converted into tosylate **16** with tosyl chloride in 84% yield. This intermediate corresponds to compound **3b** in Scheme 2. The following

<sup>‡</sup> The same results were obtained when running the reaction in liq. NH<sub>3</sub> with NaNH<sub>2</sub>.

Table 1  
Alkylation of aldehyde **10** with organometallic reagents

Entry No.	Reagent	Additives	Solvent	Ratio <b>11a</b> : <b>11b</b>
1	BuLi	-	THF/hexane	6.3:1
2	BuLi	Ti(O- <i>i</i> Pr) <sub>3</sub> Cl	THF/hexane	3.6:1
3	BuLi	ZnCl <sub>2</sub>	THF/hexane	3.1:1
4	BuLi	BF <sub>3</sub> ·Et <sub>2</sub> O	THF/hexane	3.4:1
5	BuMgBr	-	Et <sub>2</sub> O	2.4:1
6	BuMgBr	Ti(O- <i>i</i> Pr) <sub>3</sub> Cl	Et <sub>2</sub> O	2.5:1
7	BuMgBr	ZnCl <sub>2</sub>	Et <sub>2</sub> O	2:1
8	Bu <sub>2</sub> CuLi	-	THF/hexane	1:1
9	Bu <sub>2</sub> CuLi	-	Et <sub>2</sub> O/hexane	1:1
10	Bu <sub>2</sub> CuLi	BF <sub>3</sub> ·Et <sub>2</sub> O	Et <sub>2</sub> O/hexane	1:1.3
11	Bu <sub>2</sub> CuLi	Ti(O- <i>i</i> Pr) <sub>3</sub> Cl	Et <sub>2</sub> O/hexane	1:1.2



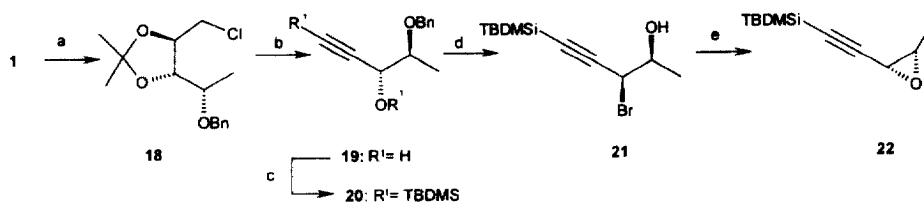
Scheme 5.

desilylation with Bu<sub>4</sub>NF led to the desired propargylic epoxide **17** in one step.<sup>18</sup> The *trans*-configuration at the oxirane ring was confirmed by the 2.0 Hz vicinal coupling constant.<sup>11</sup>

### 2.2.2. *cis*-Epoxides

The synthetic route to *cis*-epoxide **22** generally follows the same scheme. A *cis*-configuration of the target compound was achieved via *syn*-configuration in intermediate **21** (Scheme 6). Since the selection of the leaving group and the nucleophile is the same as in the case of terminal epoxide, the obtained target compound has the same absolute configuration at C-3. This process has been described in detail in our recent work<sup>11</sup> and now only the principles are presented.

Chloroacetal **18** (derived from diol **1**) was converted into monoprotected propargylic diol **19** in good yield (82%). Its disilylation followed by bromination results in bromohydrin **21** with an inverted



Scheme 6. Reagents and conditions: (a) lit.<sup>11</sup>; (b) LDA, THF,  $-78^{\circ}\text{C}$  to r.t., 1 h, 82%; (c) BuLi, THF,  $-78^{\circ}\text{C}$  followed by *t*-BuMe<sub>2</sub>SiCl,  $-20^{\circ}\text{C}$  to r.t., 4 h, 60%; (d) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>,  $-70^{\circ}\text{C}$ , 2 h, 91%; (f) K<sub>2</sub>CO<sub>3</sub>, acetone/H<sub>2</sub>O, 30 min, r.t., 92%

configuration at the propargylic carbon atom (it corresponds to the intermediate **3d** on Scheme 2). The synthesis was completed with a nucleophilic attack of the  $\beta$ -OH group affording *cis*-epoxide **22**.

### 2.3. Determination of the absolute configuration of $\alpha$ -epoxyalkynes

The absolute configuration of the target compounds was determined *via* products obtained by the epoxide opening reaction. Epoxide **9** was converted to oct-1-yn-3-ol with dibutylcuprate. The specific rotation ( $[\alpha]_{\text{D}}^{20} = -21$ , lit.<sup>14</sup>  $[\alpha]_{\text{D}}^{20} = -23$ ) corresponds to oct-1-yn-3-ol having an *S*-configuration. In addition, NMR analysis was performed with the use of 2D <sup>1</sup>H–<sup>1</sup>H and <sup>1</sup>H–<sup>13</sup>C COSY correlation diagrams from the esters made from the alcohol and (*R*)-(–)- $\alpha$ -methoxyphenylacetic acid and  $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid, as described earlier.<sup>19</sup> This method enables us to assign <sup>1</sup>H chemical shifts from the overlapping parts of the NMR spectra and in this way can be obtained a whole set of chemical shifts for the determination of the absolute configuration on the basis of ring current effects from the aromatic nucleus of chiral acid. The spectra of these esters confirm the *S*-configuration of oct-1-yn-3-ol, which, in turn, corresponds to the *R*-configuration of epoxide **9**. *trans*-Epoxide **17** was regioselectively reduced with LiAlH<sub>4</sub> to the homopropargylic alcohol.<sup>5</sup> The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the *O*-methyl mandelic acid ester of the derived octynol<sup>11</sup> showed a high enantiomeric purity of the compound (*ee* 98%) and 4*S* configuration at the stereogenic centre. This conclusion is drawn from the high field shifts of alkyl protons from H-6, H-7 and H-8 in the (*R*)-(–)- $\alpha$ -methoxyphenylacetic acid ester of 4-hydroxy-1-octyne, because in the 4*S*-enantiomer the phenyl ring is orientated towards the saturated side chain of this homopropargylic alcohol. The absolute configuration of *cis*-epoxide **22** was determined by its regioselective reduction to homopropargylic alcohol with LiAlH<sub>4</sub>. Its specific rotation ( $[\alpha]_{\text{D}}^{20} = -19.8$ ) confirms the 4*S* configuration in **22** ( $[\alpha]_{\text{D}}^{20} = -20.0$  for (*S*)-4-pentyn-2-ol<sup>20</sup>).

### 3. Conclusions

The proposed approach provides a simple route to the synthesis of various useful propargylic epoxides. As different protective groups and *syn*- or *anti*-substituted intermediates can be used, the method becomes enantioconvergent and stereoconvergent with respect to double bond geometry. Since the starting diol

<sup>5</sup> 4(*S*)-Hydroxy-1-octyne: <sup>13</sup>C NMR, CDCl<sub>3</sub>: 70.72 (C-1), 80.91 (C-2), 27.76 (C-3), 69.86 (C-4), 35.91 (C-5), 27.33 (C-6), 22.58 (C-7), 13.98 (C-8).

<sup>11</sup> (*R*)-(–)- $\alpha$ -Methoxyphenylacetic acid ester of 4(*S*)-hydroxy-1-octyne: <sup>1</sup>H NMR, CDCl<sub>3</sub>, chemical shifts, assigned by 2D <sup>1</sup>H–<sup>1</sup>H and <sup>1</sup>H–<sup>13</sup>C COSY correlation diagrams: 1.97 (H-1), 2.48 (H-3), 4.97 (H-4), 1.56 (H-5), 0.94 (H-6), 1.11 (H-7), 0.72 (H-8). <sup>13</sup>C NMR; CDCl<sub>3</sub>: 70.45 (C-1), 79.52 (C-2), 24.05 (C-3), 72.50 (C-4), 32.57 (C-5), 26.76 (C-6), 22.16 (C-7), 13.76 (C-8).

**1** is available in both enantiomeric forms, all stereoisomers of a certain propargylic epoxide could be synthesised.

## 4. Experimental

### 4.1. General data

$^{13}\text{C}$  NMR spectra were obtained on a Bruker AMX-500 spectrometer in  $\text{CDCl}_3$  solution. The chemical shifts are reported relative to the TMS signal. Mass spectra were recorded on a Hitachi M80B spectrometer at an ionizing potential of 70 eV. Optical rotations were obtained using a Polamat A polarimeter. HPLC analyses were performed using a LKB liquid chromatograph equipped with a UV spectrophotometric detector (206 nm, 254 nm, 278 nm, column Zorbax Sil 4.6×250 mm). Epoxide **22** was synthesised according to the literature procedure.<sup>11</sup>

### 4.2. (2R,3S)-4-Benzoyloxy-1-chloro-2,3-isopropylidenedioxybutane **5**

Diol **1** was converted into compound **5** via known methods. Selective monobenylation was carried out according to the literature<sup>21</sup> followed by nonacidic chlorination<sup>13</sup> affording chloro acetal **5** in 81% yield.

### 4.3. (R)-1-Benzoyloxy-but-3-yne-2-ol **6**

A solution of chloride **5** (2.06 g, 7.62 mmol) in THF (10 ml) was added to freshly prepared  $\text{LiNH}_2$  (1.05 g, 45.7 mmol) in liquid ammonia (300 ml). After 30 minutes, solid  $\text{NH}_4\text{Cl}$  (802 mg, 15 mmol) was added and ammonia was allowed to evaporate. Water was added to the residue and it was extracted with  $\text{Et}_2\text{O}$  (3×50 ml). The extracts were dried over  $\text{MgSO}_4$ , solvent was evaporated and the product was purified by flash chromatography on silica gel affording butynediol **6** (939 mg, yield 70%).  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=73.67$  (C-1), 81.67 (C-2), 61.49 (C-3), 73.47 (C-4), 73.37 ( $\text{CH}_2$ ), 137.48 (s), 127.78 (o), 128.47 (m), 127.91 (p).  $[\alpha]_{\text{D}}^{20}=-8.5$  (c 2.68,  $\text{CHCl}_3$ ).

### 4.4. (R)-1-Benzoyloxy-4-tert-butyl dimethylsilyl-2-tert-butyl dimethylsilyloxy-3-butyne **7**

A solution of  $\text{BuLi}$  in hexanes (1.6 M, 1.86 ml, 3.0 mmol) was added to a solution of butynediol **6** (250 mg, 1.4 mmol) in THF (4 ml) at  $-78^\circ\text{C}$  under an Ar atmosphere. The mixture was allowed to warm to  $-20^\circ\text{C}$  and *tert*-butyldimethylsilyl chloride (440 mg, 2.94 mmol) was added. The reaction mixture was stirred at room temperature overnight, and then quenched with saturated solution of  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$  (3×20 ml). Extracts were dried over  $\text{MgSO}_4$ , solvent was evaporated and the product was purified by flash chromatography on silica gel affording disilylated compound **7** (385 mg, yield 68%). MS:  $m/z=347$  ( $\text{M}^+-t\text{-Bu}$ ), 283, 241, 117, 91.  $[\alpha]_{\text{D}}^{20}=-28.8$  (c 5.63,  $\text{CHCl}_3$ ).

### 4.5. (S)-2-Bromo-4-tert-butyl dimethylsilyl-but-3-yne-1-ol **8**

Boron tribromide (0.91 ml, 9.85 mmol) was added dropwise to a solution of compound **7** (3.98 g, 9.85 mmol) in methylene chloride (20 ml) at  $-70^\circ\text{C}$  under an Ar atmosphere. The mixture was stirred at this temperature for 15 minutes and water (10 ml) was added. The mixture was allowed to warm up to room

temperature, layers were separated, the organic fraction was dried over  $\text{MgSO}_4$ , solvent was evaporated and product was purified by flash chromatography on silica gel affording bromohydrin **8** (2.20 g, 85%).  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=100.87$  (C-1), 92.87 (C-2), 39.53 (C-3), 67.00 (C-4),  $-4.90$  ( $\text{Me}_2\text{Si}$ ), 16.56, 25.89 (*t*-Bu).  $[\alpha]_{\text{D}}^{20}=-2.66$  (c 4.66,  $\text{CHCl}_3$ ).

#### 4.6. (R)-1-tert-Butyldimethylsilyl-3,4-epoxy-but-1-yne **9**

A solution of bromohydrin **8** (2.29 g, 8.7 mmol) and  $\text{K}_2\text{CO}_3$  (1.80 g, 13.1 mmol) in acetone:water (2:1, 15 ml) was stirred at room temperature for 30 minutes. Acetone was evaporated, the residue was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  ml). Extracts were dried over  $\text{MgSO}_4$ , solvent was evaporated and the product was purified by flash chromatography on silica gel (eluent: pentane/methylene chloride) affording target epoxide **9** (1.11 g, yield 70%).  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=102.53$  (C-1), 87.55 (C-2), 39.89 (C-3), 48.95 (C-4),  $-4.82$  ( $\text{Me}_2\text{Si}$ ), 16.43, 25.98 (*t*-Bu). MS:  $m/z=182$  ( $\text{M}^+$ ), 166, 125.  $[\alpha]_{\text{D}}^{20}=-72.3$  (c 5.63,  $\text{CH}_2\text{Cl}_2$ ).

#### 4.7. (2S,3S)-1-Benzylloxy-2,3-isopropylidenedioxy-4-octanol (mixture of 4S and 4R isomers) **11a** and **11b**

To stirred solution of  $\text{BuMgBr}$  (20 mmol) in  $\text{Et}_2\text{O}$  (40 ml) at  $-60^\circ\text{C}$  was added dropwise a solution of aldehyde **10**<sup>11</sup> (1.02 g, 4.1 mmol) in  $\text{Et}_2\text{O}$  (10 ml). The mixture was allowed to warm to  $0^\circ\text{C}$  and stirred for 3 hours, the temperature increased to room temperature and the mixture was stirred for a further 12 hours. After addition of a saturated solution of  $\text{NH}_4\text{Cl}$ , the layers were separated and the aqueous layer was extracted with  $\text{EtOAc}$  ( $3 \times 30$  ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and the solvent was evaporated. Isomers were separated by column chromatography on silica gel to give 544 mg of epimer **11a** and 227 mg of epimer **11b**. The total yield of isomers was 61%. MS:  $m/z=293$  ( $\text{M}^+-15$ ), 250, 221, 129, 91. **11a**:  $[\alpha]_{\text{D}}^{20}=-4.4$  (c 4.1,  $\text{CHCl}_3$ ). IR (film)  $\nu=3360, 2980, 1550, 1490, 1380, 1260, 1220, 1090$   $\text{cm}^{-1}$ .  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=13.98$  (C-1), 22.64 (C-2), 27.62 (C-3), 32.89 (C-4), 71.66 (C-5), 81.73 (C-6), 77.32 (C-7), 70.85 (C-8), 73.62 ( $\text{CH}_2\text{Ph}$ ), 137.43 (s), 127.81 (o), 128.42 (m), 127.83 (p), 26.83 and 26.94 ( $\text{Me}_2$ ), 108.85 (C-Me<sub>2</sub>).

#### 4.8. (2S,3S,4S)-1-Benzylloxy-4-tert-butyldimethylsiloxy-2,3-isopropylidenedioxyoctane **12**

To a solution of compound **11a** (392 mg, 1.27 mmol) in DMF (8 ml) *tert*-butyldimethylsilyl chloride (220 mg, 1.47 mmol) and imidazole (122 mg, 1.8 mmol) were added at room temperature. The mixture was stirred at  $40^\circ\text{C}$  for 38 hours, cooled to room temperature, poured into water and extracted with  $\text{EtOAc}$ . The extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. The residue was purified by flash chromatography on silica gel affording (90%) **12** in 90% yield (482 mg). MS:  $m/z=407$  ( $\text{M}^+-15$ ), 307, 221, 91.  $[\alpha]_{\text{D}}^{20}=-5.36$  (c 1.3,  $\text{CHCl}_3$ ). IR (film)  $\nu=3030, 2870, 1550, 1490, 1260, 1090, 840$   $\text{cm}^{-1}$ .

#### 4.9. (2S,3S,4S)-4-tert-Butyldimethylsiloxy-2,3-isopropylidenedioxy-1-octanol **13**

To a solution of compound **12** (1.30 g, 2.44 mmol) in liquid ammonia (30 ml), sodium (224 mg, 9.76 mmol) was added in pieces. The dispersion was stirred for 4 hours, solid  $\text{NH}_4\text{Cl}$  was added and  $\text{NH}_3$  was evaporated in the flow of Ar. The residue was dissolved in water and extracted with  $\text{EtOAc}$ . The organic layers were washed with water, dried ( $\text{MgSO}_4$ ) and evaporated. The residue was purified by flash chromatography on silica gel affording alcohol **13** (684 mg, yield 80%). MS:  $m/z=317$  ( $\text{M}^+-15$ ), 275, 201, 131, 75.  $[\alpha]_{\text{D}}^{20}=-1.92$  (c 3.1,  $\text{CHCl}_3$ ).



#### 4.10. (2R,3S,4S)-4-tert-Butyldimethylsiloxy-1-chloro-2,3-isopropylidenedioxyoctane 14

A solution of alcohol **13** (427 mg, 1.29 mmol) and  $\text{Ph}_3\text{P}$  (673 mg, 2.5 mmol) in anhydrous  $\text{CCl}_4$  (5 ml) was stirred at  $80^\circ\text{C}$  for 3 h. The mixture was allowed to cool to room temperature and the insoluble material was filtered off. The solvent was evaporated, the residue triturated with hexane ( $5 \times 4$  ml). The insoluble residue was filtered, the crude product concentrated and passed through a short column of silica gel affording chloride **14** (353 mg, yield 78%). MS:  $m/z=335$  ( $\text{M}^+ - 15$ ), 293, 149.  $[\alpha]_{\text{D}}^{20} = -3.19$  (c 2.16,  $\text{CHCl}_3$ ). IR (film)  $\nu=3030, 2980, 1490, 1380, 1260, 1090, 840 \text{ cm}^{-1}$ .

#### 4.11. (3R,4S)-4-tert-Butyldimethylsiloxy-1-octyn-3-ol 15

A solution of BuLi in hexanes (1.6 M, 2.94 ml) was added dropwise to a stirred solution of diisopropylamine (0.66 ml, 4.7 mmol) in THF (10 ml) at  $-40^\circ\text{C}$  under an Ar atmosphere and the mixture was stirred for 30 min. The solution was cooled to  $-78^\circ\text{C}$ , chloride **14** (326 mg, 0.93 mmol) was added in THF (2 ml) and the mixture was stirred at this temperature for 30 minutes. The mixture was warmed to  $0^\circ\text{C}$  over 3 hours and quenched with a saturated solution of  $\text{NH}_4\text{Cl}$ . The solution was extracted with  $\text{Et}_2\text{O}$ , dried ( $\text{MgSO}_4$ ) and the solvent was evaporated. Flash chromatography on silica gel afforded propargylic alcohol **15** (171 mg, yield 72%).  $[\alpha]_{\text{D}}^{20} = -9.56$  (c 10.1,  $\text{CHCl}_3$ ). IR (film)  $\nu=3360, 2890, 2240, 1490, 1380, 1260, 1090, 840 \text{ cm}^{-1}$ .  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=74.21$  (C-1), 81.65 (C-2), 65.84 (C-3), 74.69 (C-4), 31.97 (C-5), 27.52 (C-6), 22.73 (C-7), 13.96 (C-8), 25.76 and 18.06 (*t*-Bu),  $-4.40$  and  $-4.50$  ( $\text{Me}_2\text{Si}$ ).

#### 4.12. (3R,4S)-4-tert-Butyldimethylsiloxy-3-tosyloxy-1-octyne 16

A solution of tosyl chloride (200 mg, 1.05 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added slowly to a solution of propargylic alcohol **15** (230 mg, 0.90 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and pyridine (3 ml) at  $0^\circ\text{C}$ . The mixture was stirred at room temperature for 24 hours, poured into ice-water and extracted with EtOAc. The extract was washed with 0.1 M HCl, water, saturated solution of  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ) and evaporated. The residue was passed through a short column of silica gel to give 310 mg (84%) of tosylate **16**. MS:  $m/z=319$  ( $\text{M}^+ - 91$ ), 255, 171, 155.  $[\alpha]_{\text{D}}^{20} = -49.8$  (c 9.3,  $\text{CHCl}_3$ ). IR (film)  $\nu=3030, 2890, 2240, 1640, 1490, 1390, 1260, 1180, 970, 840 \text{ cm}^{-1}$ .  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=77.13$  (C-1), 76.81 (C-2), 74.05 (C-3), 73.72 (C-4), 32.76 (C-5), 27.14 (C-6), 22.52 (C-7), 13.90 (C-8), 25.77 and 18.11 (*t*-Bu),  $-4.50$  and  $-4.65$  ( $\text{Me}_2\text{Si}$ ), 144.75, 129.25, 128.07, 133.90, 21.62 (Tos).

#### 4.13. (3S,4S)-Epoxy-1-octyne 17

To a tosylate **16** (280 mg, 0.68 mmol) in THF (14 ml) at  $-78^\circ\text{C}$  under an Ar atmosphere was slowly added 1 M solution of  $\text{Bu}_4\text{NF}$  in THF (0.78 ml, 0.78 mmol). The mixture was allowed to warm to  $0^\circ\text{C}$  and stirred for 2 hours at this temperature. The reaction mixture was quenched with brine (10 ml) and extracted with  $\text{Et}_2\text{O}$ . The extracts were washed with water, dried ( $\text{MgSO}_4$ ) and evaporated. The crude product was passed through a short column of silica gel eluting with pentane: $\text{Et}_2\text{O}$  (100:2.5) to afford 46 mg (55%) of epoxide **17**. The yield of the target compound is relatively low because of its high volatility. MS: (CI)  $m/z=125$  ( $\text{M}^+ - 1$ ), 107, 95, 55.  $^1\text{H}$  NMR:  $\delta_{\text{H}}=0.889$  (t,  $J=7.1$  Hz, H-8), 1.386 (m, H-7), 1.446 (m, H-6), 1.564 (m, H-5), 2.143 (d,  $J=1.7$  Hz, H-1), 3.10 (m, H-3), 3.11 (m, H-4); the first order spectrum from oxirane ring protons was obtained by adding  $\text{C}_6\text{D}_6$ : 2.975 (t,  $J=2 \times 2.0$  Hz, H-3), 3.020 (d,  $J=2.0$  Hz, H-2 to H-3 and  $J=2 \times 5.5$  Hz, H-2 to H-4), a 2.0 Hz vicinal coupling constant of oxirane protons points to *trans*-substitution, in the *cis*-isomer it should be about 4 Hz.<sup>7</sup>  $^{13}\text{C}$  NMR:  $\delta_{\text{C}}=71.64$  (d,  $J=253$  Hz; d,

J=4.2 Hz; C-1), 80.59 (d, J=49.6 Hz; d, J=4.8 Hz; d, J=2.5 Hz; C-2), 44.84 (d, J=185 Hz, C-3), 60.37 (d, J=174 Hz, C-4), 31.33 (t, C-5), 27.66 (t, C-6), 22.38 (t, C-7), 13.89 (q, C-8).  $[\alpha]_D^{20} = -9.8$  (c 3.0, Et<sub>2</sub>O). IR (film)  $\nu = 2980, 2890, 2240, 1000, 850 \text{ cm}^{-1}$ .

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