Chelation Control in the Ring Opening and Organometallic Addition of α,β-Epoxy Aldehydes: a New Entry to Amino Dihydroxyethylene Dipeptide Isostere Subunits

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Keywords: Asymmetric synthesis / Aldehydes / Grignard reactions / Amino alcohols

Selective ring opening and subsequent organometallic addition to α,β-epoxy aldehydes is found to afford *anti-syn* 3-bromo-1,2-diols in high stereo and chemical yield. This sequence is utilized for the enantioselective synthesis of (2*S*,3*R*,4*R*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol (an isomer of the Abbott amino diol).

Introduction

Epoxy alcohols and derivatives (acids, esters, amides or aldehydes) have been the subject of several studies on their regio- and stereocontrolled ring opening with various nucleophiles.[1] Since standard procedures allow their preparation in an optically active form, these promising functionalized compounds appear very attractive in the synthesis of highly functionalized structures.

The chelation control has been largely used to direct the opening of the oxirane ring at the C-3 position through an intermolecular attack of an external nucleophile[2] (Figure 1, **A** and **B**). On the other hand, ring opening at the C-2 position is presumed to be due to an intramolecular nucleophilic attack,[3] at least in the case of epoxy alcohols (Figure 1, **C**).

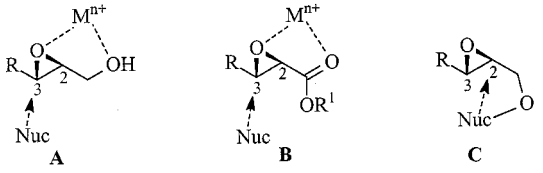


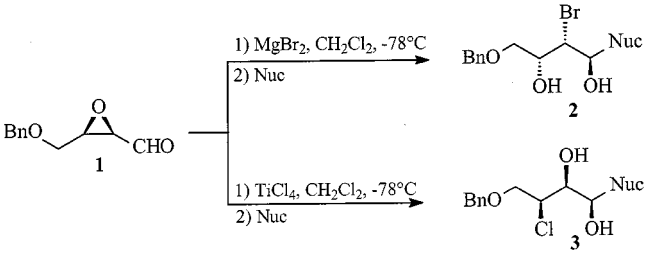
Figure 1. Inter- and intramolecular nucleophilic attack at C-2 functionalized epoxides

In particular cases a good to fair C-2 regioselectivity can be obtained in "non-chelating conditions" such as in some cases of epoxy esters and amides.[4]

During our studies on ring opening with metal halides of epoxy alcohols and esters,[5] we found nearly no examples of nucleophilic opening of α,β-epoxy aldehydes, probably due to the reactivity of the carbonyl group.

α,β-Epoxy aldehydes, easily obtained in an optically active form by the oxidation of the corresponding chiral epoxy alcohols,[6] could represent very useful substrates in organic synthesis. In fact, their controlled ring opening and subsequent organometallic addition to the carbonyl group could allow the elongation of the chain with the introduction of three contiguous stereogenic centers.

Only in a particular case[7] has the bifunctionalized epoxy aldehyde **1** (see Scheme 1) been opened to the corresponding halodiols **2** and **3** employing $MgBr_2$ or $TiCl_4$. Since there was a reverse in the regioselectivity on passing from $TiCl_4$ to $MgBr_2$, the authors suggested that $MgBr_2$, as opposed to $TiCl_4$, is unable to coordinate to the carbonyl group, thus leading to an unusual C-2 attack of the bromide.

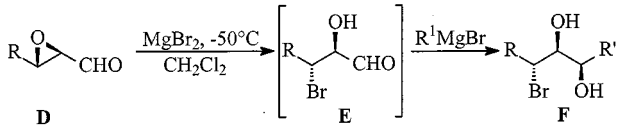


Scheme 1. Ring opening of α,β-epoxyaldehyde **1**

The authors also reported, however, that the situation was not so simple, since the ability of MgI_2 and $MgBr_2$ to control the chelation in the ring opening of α,β-epoxy esters and epoxy alcohols is well-known.[5]

Results and Discussion

In light of this intriguing problem, we decided to study the ring opening in the general case of the aliphatic, optically active α,β-epoxy aldehydes of type **D**, (see Scheme 2) with $MgBr_2$. The already reported difficulties in the isolation of **E** prompted us to add a Grignard reagent "in situ", thus obtaining directly the corresponding 3-bromo-1,2 *syn* diols of type **F**.



Scheme 2. Ring opening and organometallic addition to α,β-epoxy aldehydes

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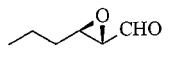
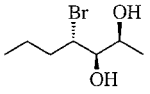
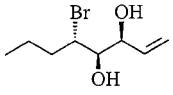
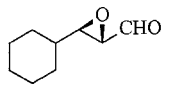
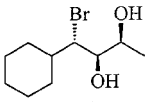
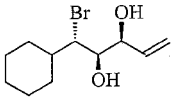
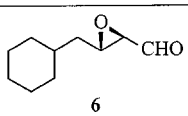
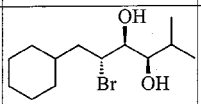
The best results were obtained with CH_2Cl_2 as solvent (Et_2O and THF gave lower yields) and carrying out the reaction at −50 °C (with higher or lower temperatures the regioselectivity or the conversion decrease).

Table 1. One-pot ring opening/organometallic addition of α,β-epoxy aldehydes

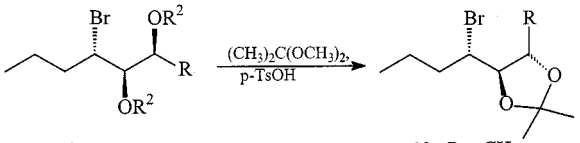
α,β-Epoxy aldehyde	R^1= -CH_3	R^1= -CH=CH_2
 **4**	 **7** 67%	 **10** 58%
 **5**	 **8** 62%	 **11** 55%
Chiral α,β-epoxy aldehyde	R^1 = -$CH(CH_3)_2$	
 **6**	 **9** 57%	

The reaction was performed on some substrates employing different Grignard reagents. As shown in Table 1, the sequence works well also when bulky groups are present either at the C-3 position of the α,β-epoxy aldehyde (compound **5**) or in the organometallic reagent (compound **9**). However, in all the cases reported of this remarkable two-step, one-pot transformation we observed:

1. The oxirane opening occurred regioselectively at the C-3 position to afford the corresponding bromohydrins, which are normally not isolated.

2. The subsequent carbon nucleophile addition afforded the final *syn* diols, in a totally controlled stereoselective fashion (see below), with an overall yield of 55−67%.

The regiochemistry of the bromine opening was established from NMR spectroscopy, by employing a spin-spin decoupling technique, on the acetyl derivative **14** and the acetonides **12** and **13** (Scheme 3). Regarding the stereochemistry of the diol system, in all cases the coupling constant values are in accordance with a *syn* stereochemistry ($J \approx 6$ Hz).

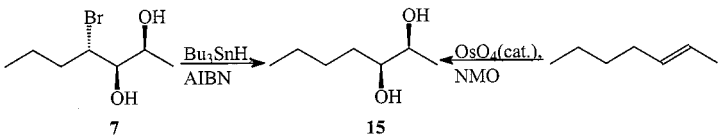


7 R^2 = H R = CH_3
10 R^2 = H R = $CHCH_2$
14 R^2 = Ac R = CH_3

12 R = CH_3
13 R = $CHCH_2$

Scheme 3. Derivatization of 3-bromo-1,2-diols

However, for a definitive confirmation of the stereochemistry, we reduced compound **7** with Bu_3SnH to the 2,3 heptenediol **15**, the same compound provided by the *cis*-dihydroxylation of (*E*)-2-heptene (see Scheme 4).

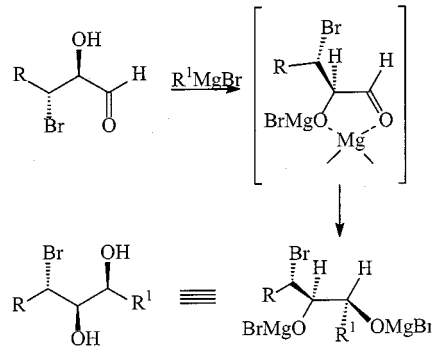


7 **15**

Scheme 4. Convergent preparation of *syn*-2,3-heptanediol

From these results we can assert that Mg^{2+} firstly controls the regiochemistry of the C-3 attack by chelation between the carbonyl and the epoxide oxygen (as already observed in the case of epoxy esters and epoxy amides) and, subsequently, the stereocontrolled Grignard addition.

The stereocontrolled addition of Grignard reagent to the α-hydroxycarbonyl intermediate can be assumed to occur via a cyclic chelate transition state (Scheme 5), which is always invoked when an α-substituent capable of coordination is present.[8]



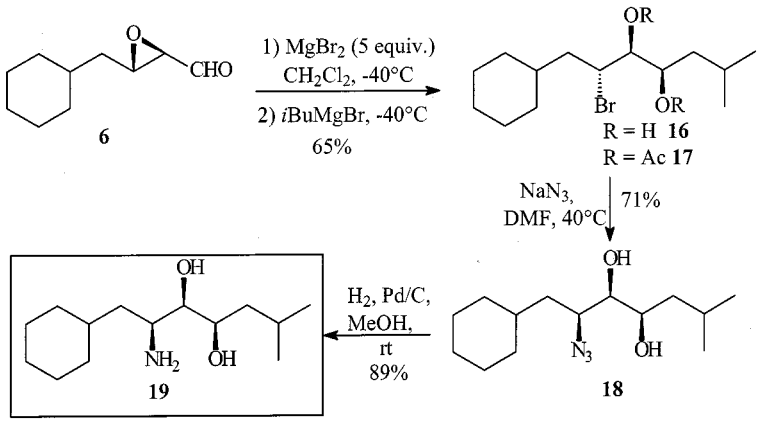
Scheme 5. Cyclic chelate transition-state model for the addition of Grignard reagents

From these results, it appears that the previously reported regioselective opening of the aldehyde[7] may be explained by the preference of $MgBr_2$ to coordinate the epoxide oxygen and hydroxyl group instead the epoxide oxygen and carbonyl group. The possibility that the chelation control of $MgBr_2$ between different functionalizations could be selective, has prompted us to perform further studies on several different bifunctionalized epoxides (Figure 2), whose results will be reported in due course.

$R^1 = CH_2OR^2$
R = CH_2OH, CHO, COOMe

Figure 2. Bifunctionalized epoxides

The methodology described above, which allowed us to prepare a compound with three contiguous stereogenic carbons, could be a useful way to obtain *syn,syn*-amino diols. The bromine, in fact, can be substituted, with inversion of configuration, by the azide ion, one of the most used precursors of amino function, as we have recently reported for similar halohydrins.[5c,9]



Scheme 6. Stereoselective synthesis of (2*S*,3*R*,4*R*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol **(19)**

To demonstrate the usefulness of our sequence we have synthesized one of the *syn* isomers of the Abbott amino diol, the (2*S*,3*R*,4*R*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol **(19)**. Since it was reported that the (2*S*,3*R*,4*S*) isomer, when incorporated into specific protected dipeptides, is a potent inhibitor of the renin-angiotensin system, the stereocontrolled synthesis of dihydroxyethylene dipeptide isostere subunits has received a great deal of attention.[10]

As shown in Scheme 6, the key step of this expeditious synthesis is the direct opening-alkylation of the appropriate chiral α,β-epoxy aldehyde, easily obtained from the oxidation of the corresponding 2,3-epoxy alcohol.[5c] The expected structure of compound **16** was also confirmed by ^{1}H NMR spectroscopy of its acetyl derivative **17**. Subsequent substitution of the bromine with azide, followed by catalytic hydrogenation to the amino group, leads to the desired compound in only three steps and with an overall yield of 41%.

Conclusion

In conclusion we have developed a new and general one-pot, stereocontrolled ring opening/organometallic addition of α,β-epoxy aldehydes, which allowed us to prepare *syn-syn*-1,2,3-aminodiols with various substitution patterns on the amino-diol framework. This strategy represents a general route to this important class of compounds as demonstrated by the straightforward stereoselective synthesis of (2*S*,3*R*,4*R*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol in only three steps with reasonable overall yield.

Studies on the possibility of reversing the stereocontrol of Grignard addition to obtain *syn-anti*-1,2,3-aminodiols are currently under investigation.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.3 Hz, respectively, in $CDCl_3$. Reactions were monitored by TLC using Merck silica gel 60 F-254 plates with UV indicator and/or visualized with phosphomolybdic acid (10% solution in EtOH). Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. All solvents were purified before use with standard drying procedures, unless otherwise specified. Elemental analyses for C, H and N are in agreement with the theoretical data, except for compounds containing halogens, where combustion analysis could not be performed.

General Preparation of α,β-Epoxy Aldehydes: Representative Procedure for the Preparation of (2*S,3*R**)-2,3-Epoxyhexanal (4):** [Bis(acetoxy)iodo]benzene (BAIB) (354 mg, 1.1 mmol) was added to a solution of 2,3-epoxyhexan-1-ol (116 mg, 1 mmol) and 2,2,6,6,-tetramethyl-1-piperidinyloxyl (TEMPO) (15 mg, 0.1 mmol) in 1 mL of CH_2Cl_2. The reaction mixture was stirred until the alcohol was no longer detectable (TLC monitoring), and was then diluted with CH_2Cl_2 (5 mL). The mixture was washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) affording **4** (80 mg, 70%). − ^{1}H NMR: δ = 8.92 (d, ^3J = 5.4 Hz, 1 H, C*H*O), 3.21−3.1 (m, 1 H, CH_2CHO), 3.05 (dd, ^3J = 5.4 and 0.2 Hz, 1 H, C*H*OCHO), 1.65−1.32 (m, 4 H, CH_2CH_2,), 0.90 (t, ^3J = 6.2 Hz, 3 H, CH_3). − ^{13}C NMR: δ = 198.7 (*C*HO), 58.9 [*C*HO(epox)], 56.4 [*C*HO(epox)], 32.9 (CH_2CHO), 18.8 (CH_2CH_2), 13.4 (CH_3). − $C_6H_{10}O_2$ (114): C 63.14, H 8.83; found C 63.2, H 8.7.

(2*S,3*R**)-3-Cyclohexyl-2,3-epoxypropanal (5):** According to the general procedure, 3-cyclohexyl-2,3-epoxypropan-1-ol afforded pure compound **5** (110 mg, 72%). − ^{1}H NMR: δ = 8.95 (d, ^3J = 6.3 Hz, 1 H, C*H*O), 3.16 (dd, ^3J = 6.3 and 1.9 Hz, 1 H, CH_2CHO), 3.12 (dd, ^3J = 6.5 and 1.8 Hz, 1 H, C*H*OCHO), 1.88−1.61 (m, 5 H, CH_2CHCH_2), 1.42−1.0 (m, 6 H, $CH_2CH_2CH_2$). − ^{13}C NMR: δ = 198.6 (*C*HO), 60.8 [*C*HO(epox)], 58.1 [*C*HO(epox)], 39.3 (CH_2CHCH_2), 29.4 (CH_2), 28.7 (CH_2), 26.01 (CH_2), 25.4 (CH_2), 25.3 (CH_2). − $C_9H_{14}O_2$ (154): C 70.10, H 9.15; found C 70.2, H 8.9.

(2*R*,3*S*)-4-Cyclohexyl-2,3-epoxybutanal (6): According to the general procedure, (2*S*,3*S*)-4-cyclohexyl-2,3-epoxybutan-1-ol afforded pure compound **6** (126 mg, 75%). − $[\alpha]_D^{25}$ = 23.3. − ^{1}H NMR: δ = 8.98 (d, ^3J = 6.3 Hz, 1 H, C*H*O), 3.27−3.14 (m, 1 H, CH_2CHO), 3.05 (dd, ^3J = 6.1 and 1.9 Hz, 1 H, C*H*OCHO), 1.82−0.8 [m, 13 H, (CH_2)$_6$C*H*]. − ^{13}C NMR: δ = 198.6 (*C*HO), 58.9 [*C*HO(epox)], 55.2 [*C*HO(epox)], 38.5 (CH_2CHCH_2), 35.5 (CH_2CHO), 28.7 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 25.7 (CH_2), 25.6 (CH_2). − $C_{10}H_{16}O_2$ (168): C 71.39, H 9.59; found C 71.5, H 9.7.

General One-pot Opening-Alkylation of α,β-Epoxy Aldehydes: Representative Procedure for the Preparation of (2*S,3*R**,4*S**)-4-Bromo-2,3-heptanediol (7):** To a solution of compound **4** (114 mg, 1 mmol) in CH_2Cl_2 (10 mL) at −50 °C was added $MgBr_2{\cdot}Et_2O$ (645.6 mg, 5 equiv.). The solution was stirred for 12 h (TLC monitoring), then MeMgBr (2 M in THF, 0.75 mL) was added. After 12 h (TLC monitoring), the reaction was quenched with a saturated solution of NH_4Cl, diluted with Et_2O and the organic layers were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 8:2) to afford **7** (141.4 mg, 67%). − ^{1}H NMR: δ = 4.22−4.08 [m, 2 H, C*H*Br + C*H*(OH)CH_3], 3.52 [ddd, ^3J = 6.89, 6.13 and 3.69 Hz, 1 H, C*H*(OH)], 2.82 (bd, ^3J = 6.89 Hz, 1 H, O*H*), 2.53 (bd, ^3J = 2.93 Hz, 1 H, OH), 1.95−1.78 (m, 2 H, CH_2CHBr), 1.73−1.58 (m, 1 H, C*H*CH_3), 1.49−1.36 [m, 1 H, C*H*(OH)CH_3], 1.23 [d, ^3J = 6.5 Hz, 3 H, CH(OH)CH_3], 0.94 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3). − ^{13}C NMR: δ = 78.3 [*C*H(OH)], 67.2 [*C*H(OH)], 58.9 (*C*HBr), 35.4 (CH_2), 20.8 (*C*H_2), 19.9 (*C*H_3), 13.4 (*C*H_3).

(3*S,4*R**,5*S**)-5-Bromo-oct-1-en-3,4-diol (10):** According to the general procedure, compound **4** afforded pure compound **10** (130 mg, 58%). − ^{1}H NMR: δ = 6.0−5.8 (m, 1 H, CH_2=C*H*), 5.45−5.24 (m, 2 H, CH_2=CH), 4.58−4.47 [m, 1 H, C*H*(OH)CH=CH_2], 4.21−4.07 (m, 1 H, C*H*Br), 3.74−3.64 [m, 1 H, CHBrC*H*(OH)CHOH], 2.54 (d, ^3J = 6.35 Hz, 1 H, O*H*), 2.32 (d, ^3J = 4.11 Hz, 1 H, O*H*), 2.05−1.25 (m, 4 H, CH_2CH_2), 0.93 (t, ^3J = 7.16 Hz, 3 H,CH_2CH_3). − ^{13}C NMR: δ = 137.3 (*C*H=CH_2), 117.7 (CH=*C*H_2), 77.06 (*C*HOH), 72.54 (*C*HOH), 57.7 (*C*HBr), 35.2 (CHBr*C*H2), 20.5 (CH_2CH_3), 13.1 (CH_2CH_3).

(1*S,2*R**,3*S**)-1-Bromo-1-cyclohexyl-2,3-butanediol (8):** According to the general procedure, compound **5** afforded pure compound **8** (156 mg, 62%). − ^{1}H NMR: δ = 4.35 [dq, ^3J = 6.4 and 0.43 Hz, 1 H, C*H*(OH)CH_3], 4.03 (dd, ^3J = 9.33 and 2.61 Hz, 1 H, C*H*Br), 3.56 [dd, ^3J = 9.33 and 0.43 Hz, 1 H, CHBrC*H*(OH)], 2.71 (br. s, 1 H, O*H*,), 2.42 (br. s, 1 H, O*H*,), 2.01−0.93 [m, 11 H, (CH_2)$_5$C*H*], 1.38 (d, ^3J = 6.4 Hz, 3 H, CH_3). − ^{13}C NMR: δ = 74.7 [*C*H(OH)], 67.05 [*C*H(OH)], 65.01 (*C*HBr), 38.8 (*C*HCHBr), 32.3 (*C*H_2), 27.2 (*C*H_2), 26.3 (*C*H_2), 25.9 (*C*H_2), 20.5 (*C*H_2).

(1*S,2*R**,3*S**)-1-Bromo-1-cyclohexylpent-4-ene-2,3-diol 11:** According to the general procedure, compound **5** afforded pure compound **11** (145 mg, 55%). − ^{1}H NMR: δ = 6.0−5.8 (m, 1 H, CH_2=C*H*), 5.45−5.24 (m, 2 H, CH_2=CH), 4.75−4.68 [m, 1 H, C*H*(OH)CH=CH_2], 4.12 (dd, ^3J = 9.39 and 2.6 Hz, 1 H, C*H*Br), 3.75 [dd, ^3J = 9.35 and 11.3 Hz, 1 H, CHBrC*H*(OH)CHOH], 2.26 (d, ^3J = 11.3 Hz, 1 H, OH), 1.94 (d, ^3J = 7.5 Hz, 1 H, OH), 2.01−0.93 (m, 11 H). − ^{13}C NMR: δ = 138.2 (*C*H=CH_2), 116.6 (CH=*C*H_2), 73.7 (*C*HOH), 72.4 (*C*HOH), 63.9 (*C*HBr), 38.4 (CHBr*C*H), 32.09 (*C*H_2), 26.7 (*C*H_2), 26.1 (*C*H_2), 25.5 (*C*H_2).

(2*R*,3*S*,4*R*)-2-Bromo-1-cyclohexyl-5-methylhexane-3,4-diol (9): According to the general procedure, compound **6** afforded pure compound **9** (167 mg, 57%). − ^{1}H NMR: δ = 4.25−4.1 [m, 1 H, C*H*(OH)*i*Pr], 3.75−3.6 [m, 2 H, C*H*(OH) + C*H*Br], 2.66 (d, ^3J = 7.7 Hz, 1 H, OH), 2.27 (d, ^3J = 3.9 Hz, 1 H, OH), 1.85−1.55 [m, 8 H, C*H*$(CH_3)_2$ + C*H*(CH_2)$_6$], 1.38−1.1 [m, 6 H, (CH_2)$_3$], 0.94 [t, ^3J = 6.7 Hz, 6 H, CH(CH_3)$_2$]. − ^{13}C NMR: δ = 75.4 (*C*HOH), 74.3 (*C*HOH), 57.9 (*C*HBr), 41.2 [*C*H(CH_2)$_5$], 35.3 [*C*H$(CH_3)_2$], 33.9 (*C*H_2), 31.3 (*C*H_2), 30.9 (*C*H_2), 26.3 (*C*H_2), 26.1 (*C*H_2), 25.7 (*C*H_2), 18.8 (*C*H_3), 17.8 (*C*H_3).

(2*R*,3*S*,4*R*)-2-Bromo-1-cyclohexyl-6-methylheptane-3,4-diol (16): According to the general procedure, compound **6** afforded pure compound **16** (200 mg, 65%). $[\alpha]_D^{25}$ = 31.6. − ^{1}H NMR: δ = 4.26−4.15 [(m, 1 H, C*H*(*i*Bu)OH], 4.08 (ddd, ^3J = 9.29 and 4.39, 3.29 Hz, 1 H, C*H*Br), 3.54 (dd, ^3J = 6.05 and 3.15 Hz, 1 H, C*H*OH), 2.7 (br. s, 1 H, OH), 2.25 (br. s, 1 H, OH), 1.9−1.14 (m, 11 H), 1.35−1.05 (m, 5 H), 0.95 (d, ^3J = 3.5 Hz, 3 H, CHCH_3), 0.92 (d, ^3J = 3.5 Hz, 3 H, CHCH_3). − ^{13}C NMR: δ = 77.38 (*C*HOH), 68.9 (*C*HOH), 57.2 (*C*HBr), 42.9 (*C*H_2CHBr), 40.9 (*C*H_2CHOH), 35.4 [*C*H$(CH_3)_2$], 34.1 [*C*H(CH_2)$_5$], 31.4 (*C*H_2), 26.5 (*C*H_2), 26.2 (*C*H_2), 25.9 (*C*H_2), 24.3 (*C*H_2), 23.3 (*C*H_3), 21.9 (*C*H_3).

(2*R*,3*S*,4*R*)-3,4-Acetoxy-2-bromo-1-cyclohexyl-6-methylheptane (17): Acetylation of **16** was performed in the usual manner (Ac_2O/Py) in nearly quantitative yield. − ^{1}H NMR: δ = 5.54−5.44 [m, 1 H,C*H*(iPr)OAc], 5.2 (dd, ^3J = 4.03 and 6.9 Hz, 1 H, C*H*OAc), 4.08 (ddd, J = 11.4 and 6.8 and 2.6 Hz, 1 H, C*H*Br), 2.14 (s, 3 H, CH_3CO), 2.07 (s, 3 H, CH_3CO), 1.85−1.35 (m, 10 H), 1.35−1.02 (m, 6 H), 0.94 (d, ^3J = 4.36 Hz, 3 H, CHCH_3), 0.9 (d, ^3J = 4.36 Hz, 3 H, CHCH_3).

(2*S*,3*R*,4*R*)-2-Azido-1-cyclohexyl-6-methylheptane-3,4-diol (18): A mixture of compound **16** (307 mg, 1 mmol) and NaN_3 (260 mg, 4 mmol) in DMF (1 mL) was stirred at 40 °C for 24 h. The reaction was diluted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 8:2) affording **18** (191.4 mg, 71%). $[\alpha]_D^{25}$ = −8. − ^{1}H NMR: δ = 3.52 [m, 1 H, C*H*(iBu)OH], 2.96 (dt, ^3J = 5.3 and 2.2 Hz, 1 H, C*H*N_3), 2.68 (dd, ^3J = 5.05 and 2.2 Hz, 1 H, C*H*OH), 1.59−1.15 (m, 18 H), 0.95 (d, ^3J = 3.7 Hz, 3 H, CHCH_3), 0.92 (d, ^3J = 3.7 Hz, 3 H, CHCH_3). − ^{13}C NMR: δ = 69.3 (*C*HOH), 62.2 (*C*HOH), 55.8 (*C*HN_3), 43.3 (*C*H_2CHN_3), 39.4 (*C*H_2CHOH), 35.8 [*C*H$(CH_3)_2$], 33.6 [*C*H(CH_2)$_5$], 33.2 (*C*H_2), 26.4 (*C*H_2), 26.2 (*C*H_2), 26.17 (*C*H_2), 24.3 (*C*H_2), 23.3 (*C*H_3), 22.1 (*C*H_3). − $C_{14}H_{27}N_3O_2$ (269): C 62.42, H 10.10, N 15.60; found C 62.5, H 10.2, N 15.8.

(2*S*,3*R*,4*R*)-2-Amino-1-cyclohexyl-6-methylheptane-3,4-diol (19): A mixture of **18** (269 mg, 1 mmol) in EtOAc (1 mL) was hydrogenated with 10% Pd/C (27 mg) under H_2 (50 psi) for 24 h. The solution was then filtered and concentrated in vacuo. The crude residue was crystallized (EtOH/H_2O 3:2) affording **19** (216 mg, 89%). $[\alpha]_D^{25}$ = −32.4. − ^{1}H NMR: δ = 4.15−4 [m, 2 H, C*H*(*i*Bu)OH + C*H*NH_2], 3.44 (dd, ^3J = 5.7 and 2.6 Hz, 1 H, C*H*OH), 2.5 (br. s, 1 H, OH), 1.95 (br. s, 1 H, OH), 1.9−1.45 (m, 13 H), 1.4−1.15 (m, 5 H), 0.97 (d, ^3J = 2.9 Hz, 3 H, CHCH_3), 0.93 (d, ^3J = 2.9 Hz, 3 H, CHCH_3). − ^{13}C NMR: δ = 68.3 (*C*HOH), 62.1 (*C*HOH), 42.9 (*C*HNH_2), 42.8 (*C*H_2CHOH), 40.8 (*C*H_2CHNH_2), 34.3 [*C*H$(CH_3)_2$], 31.6 [*C*H(CH_2)$_5$], 29.7 (*C*H_2), 26.5 (*C*H_2), 26.3 (*C*H_2), 25.9 (*C*H_2), 24.4 (*C*H_2), 23.3 (*C*H_3), 22.0 (*C*H_3). − $C_{14}H_{29}NO_2$ (243): C 69.09, H 12.01, N 5.75; found C 69.0, H 12.2, N 5.6.

(2*S,3*R**,4*S**)-2,3-Diacetoxy-4-bromo-heptane (14):** Acetylation of **7** was performed in the usual manner (Ac_2O/Py) in nearly quantitative yield. − ^{1}H NMR: δ = 5.42 [dq, ^3J = 6.51 and 3.47 Hz, 1 H, C*H*(OAc)CH_3], 5.18 (dd, ^3J = 8.19 and 3.42 Hz, 1 H, C*H*OAc), 4.01 (dt, ^3J = 6.46 and 3.47 Hz, 1 H, C*H*Br), 2.14 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 1.73−1.56 (m, 3 H), 1.45−1.32 (m, 1 H), 1.18 [d, ^3J = 6.51 Hz, 3 H, CH(OAc)CH_3], 0.9 (t, ^3J = 7.27 Hz, 3 H, CH_3). − ^{13}C NMR: δ = 169.9 (*C*O), 76.5 (*C*HOAc), 69.4 (*C*HOAc), 51.9 (*C*HBr), 35.8 (*C*H_2), 21.02 (*C*H_3CO), 20.6 (*C*H_3CO), 20.5 (*C*H_2), 16.6 (*C*H_3), 13.3 (*C*H_3).

(2*S,3*R**,4*S**)-4-Bromo-2,3-*O*-isopropylideneheptane-2,3-diol (12):** The reaction was performed on **7** in the usual manner (2,2-dimethoxypropane/*p*-TsOH) in nearly quantitative yield. − ^{1}H NMR: δ = 4.08 [quint, ^3J = 6.4 Hz, 1 H, C*H*(O)CH_3], 3.9 (dt, ^3J = 8.3 and 2.48 Hz, 1 H, C*H*Br), 3.79 (dd, ^3J = 8.3 and 6.6 Hz, 1 H, C*H*O), 2.1−1.92 (m, 1 H), 1.85−1.52 (m, 3 H), 1.44 (s, 3 H, CH_3), 1.4 (s, 3 H, CH_3), 1.37 (d, ^3J = 6.4, 3 H, CHCH_3), 0.92 (t, J =

7.3 Hz, 3 H, CH_3). – ^{13}C NMR: δ = 108.8 [$C(CH_3)_2$], 84.7 (*C*HO), 77 (*C*HO), 56.4 (*C*HBr), 37.1 (CH_2), 27.4 (CH_2), 26.8 (CH_3), 20.4 (CH_3), 20.01 (CH_3), 13.1 (CH_3).

(3*S,4*R**,5*S**)-5-Bromo-3,4-*O*-isopropylidene-1-octene-3,4-diol (13):** The reaction was performed on **10** in the usual manner (2,2-dimethoxypropane/*p*-TsOH) in nearly quantitative yield. – ^{1}H NMR: δ = 5.95 (ddd, ^3J = 17.1 and 10.3 and 6.6 Hz, 1 H, C*H*=CH_2), 5.41 (dt, ^3J = 17.1 and 1.2 Hz, 1 H, CH=CH_2), 5.24 (dt, ^3J = 10.3 and 1.2 Hz, 1 H, CH=CH_2), 4.43 [tt, ^3J = 6.6 and 1.2 Hz, 1 H, CH(O)CH=CH_2], 4 (ddd, ^3J = 9.5 and 7.1 and 3.3 Hz, 1 H, C*H*Br), 3.88 [dd, ^3J = 7.1 and 6.4 Hz, 1 H, CH(O)], 2.02–1.55 (m, 4 H), 1.42 (s, 3 H, CH_3), 1.4 (s, 3 H, CH_3), 0.91 (t, ^3J = 7.2 Hz, 3 H, CH_3). – ^{13}C NMR: δ = 136.7 (CH=*C*H_2), 118.4 (*C*H=CH_2), 109.9 [$C(CH_3)_2$], 83.3 (*C*HO), 81.3 (*C*HO), 56.1 (*C*HBr), 36.8 (CH_2), 27.16 (CH_2), 27.04 (CH_3), 20.23 (CH_3), 13.10 (CH_3).

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