A Study on the "Non-Chelation Controlled" Organometallic Addition to *trans* α,β-Epoxy Aldehydes − A Straightforward Stereoselective Synthesis of the Abbot Amino Dihydroxyethylene Dipeptide Isoster

Giuliana Righi,*[a] Silvia Ronconi,[a] and Carlo Bonini[b]

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A study of the organometallic addition to α,β-epoxy aldehydes in "non-chelation controlled" conditions is reported. The conditions able to give the best stereoselectivities are used to prepare the Abbott amino diol.

Introduction

The diastereoselective addition of organometallic compounds to α-alkoxy aldehydes has been extensively studied and, under chelation controlled conditions, this addition proceeds with a very high *syn* stereoselectivity, which can be explained by the cyclic chelate model.[1]

In some cases, particularly when an α-oxygen substituent is present within a ring, the addition of reagents able to suppress chelation (e.g. HMPA, TMEDA) causes a reversal in the stereoselectivity, yielding the *anti* diastereoisomer as the dominant product, in agreement with the Felkin−Ahn model.[2]

Organometallic addition to particular α,β-epoxy aldehydes has also been investigated (Figure 1), although not widely, and these studies have shown that the *anti* adduct often predominates;[3] once again the Felkin−Ahn model has been invoked to explain the stereoselectivity (Figure 2). In this case it can be assumed that the oxygen atom of the epoxide ring is the large group and the incoming nucleophile attacks antiperiplanar to it.

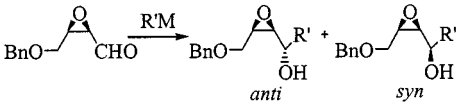


Figure 1. Organometallic addition to γ-alkoxy-α,β-epoxy aldehydes

Only two examples of good to excellent *syn* diastereoselectivity in the addition of dialkylzinc reagents to α,β-epoxy aldehydes have been reported by Sato et al.;[4] as usual the cyclic chelate model would account for this selectivity (Figure 3).

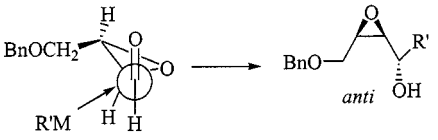


Figure 2. The Felkin−Ahn model

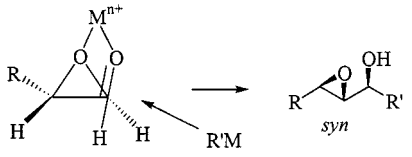
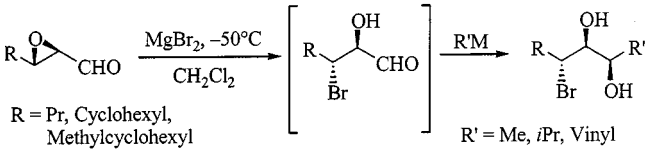


Figure 3. The cyclic chelate model

Recently, we have performed a general "one pot" ring-opening organometallic addition to *trans* α,β-epoxy aldehydes to afford *anti* or *syn* 3-bromo-1,2-diols *anti,syn* with a high stereoselectivity and chemical yield using $MgBr_2$ and then adding R′MgBr in the same reaction vessel (Scheme 1).[5]

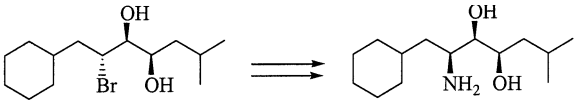


Scheme 1. "One pot" ring-opening organometallic addition

From the obtained results, we determined that Mg^{2+} initially controls the regiochemistry of the C-3 attack by chelation between the carbonyl and the epoxide oxygen (as already observed by us for epoxy alcohols[6] and esters[7]) and,

[a] Istituto di Chimica Biomolecolare − Sezione di Roma − Dipartimento di Chimica, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy
[b] Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

subsequently, the *syn* stereochemistry of the Grignard addition. Moreover, this methodology has proved to be a useful way to obtain *syn,syn* amino diols; the bromine, in fact, could be substituted, with inversion of configuration, by the azide ion, one of the most used precursors of the amino group. This sequence allowed us to synthesize the (2*S*,3*R*,4*R*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol, a diastereoisomer of the Abbott amino diol, which is a potent antihypertensive agent (Scheme 2).[8]



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

We were also intrigued by the possibility of reversing the stereochemistry of the diol system to obtain *syn,anti* 1-amino-2,3-diol fragments that are found, for example, in the Abbott compound. With this in mind we decided to investigate the stereochemistry of the organometallic addition to α,β-epoxy aldehydes; in particular, we thought that, as already mentioned for some α-alkoxy aldehydes, the use of reagents able to coordinate the metal of the organometallic nucleophile might enhance the formation of the *anti* diastereoisomer, in accordance with the Felkin−Ahn model.

Results and Discussions

In order to be able to understand all the factors involved in the reaction, we prepared substrates with various R groups and used different organometallic reagents to investigate the influence of the steric hindrance of the substituents on either the oxirane ring or the organometallic reagent.

The α,β-epoxy aldehydes were easily obtained from the corresponding 2,3-epoxy alcohols by oxidation with SO_3/pyridine, without any need for further purification. Our preliminary studies were restricted, for convenience, to racemic compounds, although the corresponding optically pure epoxy alcohols are easily obtainable from well-known procedures.[9]

To inhibit the chelation between metal, epoxide oxygen and carbonyl group we added HMPA, DMPU (less toxic) or EDTA in the case of Grignard reagents, while with organolithium compounds we added HMPA or TMEDA.

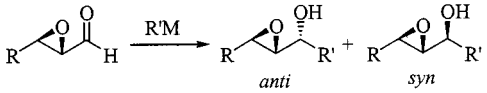
The best reaction conditions, optimized by studying the addition of MeMgBr or MeLi to *trans* 2,3-epoxy hexanal, are reported in Table 1.

Table 1. Optimal reaction conditions

R′M	Aldehyde:R′M	Solvent	Temp. (°C)
MeMgBr	1:1.5	CH_2Cl_2	room temp.
MeLi	1:3	CH_2Cl_2	−40/−20

Other solvents gave lower yields, while higher or lower temperatures led to a decrease in the regioselectivity or conversion, respectively. The degree of conversion also decreased when using a lower stoichiometric ratio of aldehyde and organometallic reagent.

All the diastereomeric α,β-epoxy alcohols prepared for our study are reported in Scheme 3.



1 R = Pr	R' = Me	**1a**	**1b**
	*i*Bu	**1c**	**1d**
	*i*Pr	**1e**	**1f**
2 R = CH_2-*c*-hexyl	Me	**2a**	**2b**
	*i*Bu	**2c**	**2d**
	*i*Pr	**2e**	**2f**
3 R = *c*-Hexyl	Me	**3a**	**3b**

Scheme 3. The diastereomeric α,β-epoxy alcohols prepared

Regarding the nucleophilic addition to compound **1**, with R = Pr, in every case we obtained a diastereomeric ratio of the products of approximately 50:50, both with the Grignard reagent alone and with Mg^{2+} coordinating agents (HMPA, EDTA,DMPU). However, when a sterically hindered substituent is present on the epoxide ring, the effect of the coordination of Mg^{2+} on the *anti*/*syn* ratio is more evident.

The addition of organolithium reagents alone affords a mixture of diastereoisomers, mainly *anti* when bulky substituents are present on the oxirane ring, but with a decrease in the chemical yield. Moreover, the employment of Li^+ coordinating agents not only does not improve the diastereomeric ratio, but it often inhibits the reaction completely, as does the use of bulkier organolithiums. Only **3a** was obtained with reasonable chemical yield and good diastereoselectivity in the presence of HMPA (48%, **3a**/**3b** = 80:20).

The most significant results obtained in the addition of different Grignard reagents to the *trans* α,β-epoxy aldehydes **2** and **3** are reported in Table 2 and 3.

Table 2. Organometallic addition to α,β-epoxy aldehyde **2** (R = CH_2-*c*-hexyl)

Entry	R′M	Yield (%)	*Anti*:*Syn*
1	MeMgBr	75	50:50 (**2a**:**2b**)
2	MeMgBr/HMPA or EDTA	60	71:29 (**2a**:**2b**)
3	MeMgBr/DMPU (1:3)	65	62:38 (**2a**:**2b**)
4	*i*BuMgBr	70	70:30 (**2c**:**2d**)
5	*i*BuMgBr/HMPA (1:3)	65	85:15 (**2c**:**2d**)
6	*i*BuMgBr/EDTA (1:1)	65	82:18 (**2c**:**2d**)
7	*i*PrMgBr	50	70:30 (**2e**:**2f**)
8	*i*PrMgBr/HMPA or EDTA	45	80:20 (**2e**:**2f**)

From the results shown in these tables we can conclude that the use of the Grignard reagent alone affords a diastereomeric ratio of the epoxy alcohols that depends on the steric bulk of the groups present both on the oxirane ring and in the Grignard reagent. However the employment of

Table 3. Organometallic addition to α,β-epoxy aldehyde **3** (R = *c*-Hexyl)

Entry	R′M	Yield (%)	*Anti*:*Syn*
9	MeMgBr	75	67:33 (**3a**:**3b**)
10	MeMgBr/HMPA (1:3)	78	82:18 (**3a**:**3b**)
11	MeMgBr/DMPU (1:3)	72	80:20 (**3a**:**3b**)
12	MeMgBr/EDTA (1:1)	60	92:8 (**3a**:**3b**)

Mg^{2+} coordinating agents causes an increase in the proportion of the *anti* diastereoisomer, at least with large substituents on the epoxide (entries 2−3 and 10−12). The increase in the *anti* diastereoisomer is also very evident when using bulky Grignard reagents; in fact the *anti*/*syn* ratio, already good in some cases (entries 4 and 7), improves only slightly upon addition of HMPA or EDTA (entries 5, 6 and 8). Moreover, with very bulky Grignard reagents the addition takes place with lower chemical yield: even with *t*BuMgBr the main reaction is the reduction of α,β-epoxy aldehyde to the corresponding α,β-epoxy alcohol, as expected for sterically hindered Grignard reagents with an H in α position.

In the light of these results we concluded that to obtain mainly the *anti* diastereoisomer it is necessary to carry out the nucleophilic addition with a Grignard reagent in the presence of HMPA or EDTA tetrasodium salt. We decided to follow this approach to synthesize (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol, commonly known as the Abbott amino diol, one of the most common and effective core units of peptide hydrolysis transition-state mimics of renin inhibitors.

A great number of inhibitors of the aspartic acid protease (such as renin and HIV-1 protease) have structures that incorporate a dihydroxyethylene dipeptide (DHED) isoster into the inhibitor molecule. The 1,2-diol moiety of the DHED isoster binds to the enzyme by forming tight hydrogen bonds to the aspartic acid residues that are present at the active site, miming a stable transition state. In this context, A-72517 (Figure 4), where the Abbott amino diol is recognizable, has proved to be a potent inhibitor of human renin.

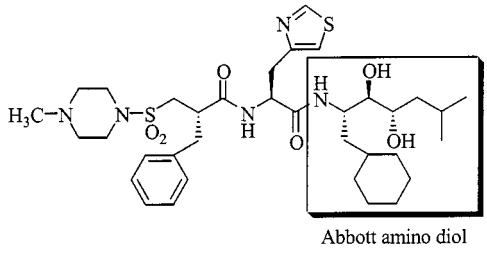
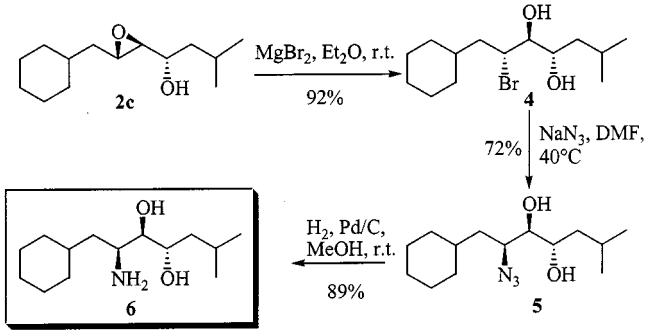


Figure 4. Renin inhibitor A-72517

As shown in Scheme 4, the key step of this synthesis is the reaction of the *i*BuMgBr/EDTA (1:1) system with the suitable chiral α,β-epoxy aldehyde **2**, easily obtained from the oxidation of the corresponding 2,3-epoxy alcohol.[7] The obtained *anti* epoxy alcohol **2c** was then treated with $MgBr_2$ to afford the *anti,anti* bromodiol **4** in high yield and in a totally regio- and stereoselective fashion. The subsequent substitution of the bromine with azide (**5**), followed by catalytic hydrogenation of the amino group, led to the desired compound **6** in only four steps and with a reasonable overall yield (31%).



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

Conclusion

The studies reported above allow to conclude that, first of all, organometallic addition to α,β-epoxy aldehydes gives a higher yield when employing Grignard reagents instead of alkyllithiums. Moreover, the presence in the reaction mixture of reagents able to suppress chelation causes the prevalence of the *anti* diastereoisomer, especially when bulky substituents are present on the oxirane ring. Finally, these results were applied in order to synthesize (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol, following a flexible approach that can be used for the synthesis of various analogs of related enzyme inhibitors.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 Hz, respectively, in $CDCl_3$ referenced to TMS. 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 were performed by the Servizio Microanalisi of the Dip. Chimica of the Università of Roma "La Sapienza"

(2*S**,3*R**)-2,3-Epoxyhexanal (**1**), (2*S**,3*R**)-3-cyclohexyl-2,3-epoxypropanal (**2**), and (2*S**,3*R**)-4-cyclohexyl-2,3-epoxybutanal **3** are know compounds.[5]

General Procedure for the Alkylation of α,β-Epoxy Aldehydes: The coordinating compound [HMPA (4.5 mmol, 0.75 mL); DMPU (4.5 mmol, 0.54 mL)] was added to a solution of α,β-epoxy aldehyde (1 mmol) in CH_2Cl_2 (10 mL) at room temperature. EDTA tetrasodium salt hydrate (1.5 mmol, 570 mg) was stirred with 4 Å molecular sieves (500 mg) in CH_2Cl_2 for 30 min and then the aldehyde was added. This solution was stirred for 10 min and then the

organometallic reagent was added [MeMgBr (1.5 mmol, 0.5 mL of 3 M solution in Et_2O; *i*PrMgCl, (1.5 mmol, 0.75 mL of 2 M solution in Et_2O); *i*BuMgBr (1.5 mmol, 0.75 mL of 2 M solution in Et_2O)]. After 2 h (TLC monitoring), the reaction was quenched with saturated NH_4Cl solution, diluted with Et_2O and the organic layers were dried over Na_2SO_4 and then evaporated to dryness in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 8:2).

(2*R,3*R**,4*R**)-3,4-Epoxyheptan-2-ol (1a) (*anti*):** According to the general procedure compound **1** afforded **1a** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3250, 2950, 1260, 840 cm^{-1}. ^1H NMR: δ = 3.9 (dq, *J* = 6.6, 2.9 Hz, 1 H, C*H*OH), 3.0 (dt, *J* = 2.9, 2.2 Hz, 1 H, CH_2CHO_{epox}), 2.7 (dd, *J* = 2.9, 2.7 Hz, 1 H, $CHO_{epox}CHOH$), 2.15 (br. s, 1 H, *OH*), 1.5 (m, 4 H, CH_2CH_2), 1.2 (d, *J* = 6.6 Hz, 3 H), 0.9 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR: δ = 64.6, 61.7, 54.9, 33.5, 19.2, 18.6, 13.8. $C_7H_{14}O_2$ (130.19): calcd. C 64.58, H 10.84; found C 64.7, H 11.1.

(2*S,3*R**,4*R**)-3,4-Epoxyheptan-2-ol (1b) (*syn*):** According to the general procedure compound **1** afforded **1b** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3250, 2950, 1260, 840 cm^{-1}. ^1H NMR: δ = 3.6 (quintet, *J* = 6.6 Hz, 1 H, C*H*OH), 2.9 (dt, *J* = 2.9, 5.1 Hz, 1 H, CH_2 *OH* O_{epox}), 2.7 (dd, *J* = 2.9, 2.2 Hz, 1 H, $CHO_{epox}CHOH$), 2.2−2.0 (br. s, 1 H, *OH*), 1.5 (m, 4 H, CH_2CH_2), 1.2 (d, *J* = 6.6 Hz, 3 H), 0.9 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR: δ = 67.6, 62.7, 56.7, 33.5, 19.5, 19.2, 13.8. $C_7H_{14}O_2$ (130.19): calcd. C 64.58, H 10.84; found C 64.8, H 11.3.

(4*R,5*R**,6*R**)-2-Methyl-5,6-epoxynonan-4-ol (1c) (*anti*):** According to the general procedure compound **1** afforded **1b** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3200, 2940, 1260, 1090, 840 cm^{-1}. ^1H NMR: δ = 3.9 (dt, *J* = 2.9, 8.1 Hz, 1 H, C*H*OH), 3.0 (dt, *J* = 2.9, 5.1 Hz, 1 H, CH_2CHO_{epox}), 2.75 (t, *J* = 2.9 Hz, 1 H, $CHO_{epox}CHOH$), 2.0−1.8 (m, 2 H, O*H*+ *OH*), 1.6−1.2 (m, 6 H, CH_2CH_2 + CH_2CH), 1.01 (d, *J* = 5.1 Hz, 3 H, $CHCH_3$), 1.01 (t, *J* = 7.3 Hz, 3 H, CH_3), 0.98 (d, *J* = 5.1 Hz, 3 H, $CHCH_3$). ^{13}C NMR: δ = 66.6, 61.2, 54.6, 42.4, 33.6, 24.4, 23.5, 21.9, 19.3, 13.9. $C_{10}H_{20}O_2$ (172.27): calcd. C 69.72, H 11.70; found C 69.9, H 12.1.

(4*S,5*R**,6*R**)-2-Methyl-5,6-epoxynonan-4-ol (1d) (*syn*):** According to the general procedure compound **1** afforded **1d** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3200, 2940, 1260, 1090, 840 cm^{-1}. ^1H NMR: δ = 3.55 (dt, *J* = 4.4, 8.7 Hz, 1 H, C*H*OH), 2.95 (dt, *J* = 2.2, 5.1 Hz, 1 H, CH_2CHO_{epox}), 2.7 (dd, *J* = 2.2, 4.4 Hz, 1 H, $CHO_{epox}CHOH$), 1.9−1.45 (m, 4 H), 1.4−1.15 (m, 2 H), 0.96 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.94 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.9 (t, *J* = 6.6 Hz, 3 H, CH_3). ^{13}C NMR: δ = 69.6, 60.4, 56.8, 43.2, 34.1, 24.3, 22.3, 13.9. $C_{10}H_{20}O_2$ (172.27): calcd. C 69.72, H 11.70; found C 70.1, H 12.2.

(3*R,4*R**,5*R**)-2-Methyl-5,6-epoxyoctan-3-ol (1e) (*anti*):** According to the general procedure compound **1** afforded **1e** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3250, 2940, 1260, 1090, 860 cm^{-1}. ^1H NMR: δ = 3.6 (dd, *J* = 2.9, 5.0 Hz, 1 H, C*H*OH), 3.05 (dt, *J* = 2.9, 5.1 Hz, 1 H, CH_2CHO_{epox}), 2.8 (t, *J* = 2.9 Hz, 1 H, $CHO_{epox}CHOH$), 1.9−1.7 (m, 1 H), 1.6−1.4 (m, 5 H), 1.05 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.02 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.98 (t, *J* = 6.6 Hz, 3 H, CH_3). ^{13}C NMR: δ = 72.7, 59.5, 54.7, 33.6, 31.6, 18.4, 17.8, 13.9. $C_9H_{18}O_2$ (158.24): calcd. C 68.31, H 11.47; found 68.6, H 11.7.

(3*S,4*R**,5*R**)-2-Methyl-5,6-epoxyoctan-3-ol (1f) (*syn*):** According to the general procedure compound **1** afforded **1f** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3250, 2940, 1260, 1090, 860 cm^{-1}. ^1H NMR: δ = 3.22 (dd, *J* = 5.1, 10.1 Hz, 1 H, C*H*OH), 2.95 (dt, *J* = 2.2, 5.8 Hz, 1 H, CH_2CHO_{epox}), 2.78 (dd, *J* = 2.2, 5.1 Hz, 1 H, $CHO_{epox}CHOH$), 1.9−1.7 (m, 2 H, *OH* + C*H*), 1.6−1.4 (m, 4 H), 1.1−0.8 (m, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.02 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.0 (t, *J* = 6.6 Hz, 3 H, CH_3). ^{13}C NMR: δ = 75.7, 58.3, 56.2, 34.7, 31.76, 19.5, 18.4, 17.8, 14.1. $C_9H_{18}O_2$ (158.24): calcd. C 68.31, H 11.47; found 68.5, H 11.8.

(2*R,3*R**,4*R**)-5-Cyclohexyl-3,4-epoxypentan-2-ol (2a) (*anti*):** According to the general procedure compound **2** afforded **2a** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3200, 2950, 1250, 1090, 830 cm^{-1}. ^1H NMR: δ = 3.95 (dq, *J* = 2.9, 6.6 Hz, 1 H, C*H*OH), 3.06 (dt, *J* = 2.2, 5.5 Hz, 1 H, CH_2CHO_{epox}), 2.74 (t, *J* = 2.9 Hz, 1 H, $CHO_{epox}CHOH$), 1.9−1.6 (m, 6 H), 1.6−1.3 (m, 3 H), 1.2 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.15−0.9 (m, 5 H). ^{13}C NMR: δ = 64.7, 61.8, 53.8, 39.4, 35.8, 33.6, 33.1, 26.3, 26.2, 26.1, 18.7. $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 71.9, H 11.2.

(2*S,3*R**,4*R**)-5-Cyclohexyl-3,4-epoxypentan-2-ol (2b) (*syn*):** According to the general procedure compound **2** afforded **2b** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3200, 2950, 1250, 1090, 830 cm^{-1}. ^1H NMR: δ = 3.61 (dq, *J* = 5.2, 6.6 Hz, 1 H, C*H*OH), 2.95 (dt, *J* = 2.2, 5.2 Hz, 1 H, CH_2CHO_{epox}), 2.7 (dd, *J* = 2.2, 5.2 Hz, 1 H, $CHO_{epox}CHOH$), 1.8−1.32 (m, 9 H), 1.28 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.25−0.9 (m, 5 H). ^{13}C NMR: δ = 67.2, 60.4, 57.1, 40.5, 34.1, 31.3, 26.4, 26.2, 25.9, 19.7, 18.7. $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 72.1, H 11.3.

(2*S*,3*S*,4*S*)-1-Cyclohexyl-6-methyl-2,3-epoxyheptan-4-ol (2c) (*anti*): According to the general procedure compound **2** (prepared in this case in an optically form[7]) afforded **2c** as a colorless oil. $[\alpha]_D^{25}$ = −11.0 (*c* = 0.7 $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3300, 2920, 1240, 1090, 840 cm^{-1}. ^1H NMR: δ = 3.88 (quintet, *J* = 4.4 Hz, 1 H, C*H*OH), 3.05 (dt, *J* = 2.5, 5.5 Hz, 1 H, CH_2CHO_{epox}), 2.7 (t, *J* = 2.5 Hz, 1 H, $CHO_{epox}CHOH$), 1.95−1.18 (m, 17 H), 0.97 (d, *J* = 5.5 Hz, 3 H, $CHCH_3$), 0.92 (d, *J* = 5.5 Hz, 3 H, $CHCH_3$). ^{13}C NMR: δ = 66.7, 61.3, 53.6, 42.4, 39.4, 35.8, 33.6, 33.0, 26.3, 26.2, 26.1, 24.4, 23.4, 21.9. $C_{14}H_{26}O_2$ (226.36): calcd. C 74.29, H 11.58; found C 74.5, H 11.8.

(2*R,3*R**,4*S**)-1-Cyclohexyl-6-methyl-2,3-epoxyheptan-4-ol (2d) (*syn*):** According to the general procedure compound **2** afforded **2d** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3290, 2940, 1230, 1090, 850 cm^{-1}. ^1H NMR: δ = 3.55 (sext., *J* = 4.4 Hz, 1 H, C*H*OH), 2.9 (dt, *J* = 2.2, 5.1 Hz, 1 H, CH_2CHO_{epox}), 2.61 (dd, *J* = 2.2, 4.4 Hz, 1 H, $CHO_{epox}CHOH$), 1.85−1.1 (m, 17 H), 0.88 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.86 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). ^{13}C NMR: δ = 69.3, 62.1, 55.7, 43.3, 39.4, 35.8, 33.6, 33.1, 26.3, 26.2, 26.1, 24.3, 23.3, 22.1. $C_{14}H_{26}O_2$ (226.36): calcd. C 74.29, H 11.58; found C 74.4, H 11.9.

(3*R,4*R**,5*R**)-6-Cyclohexyl-2-methyl-4,5-epoxyhexan-3-ol (2e) (*anti*):** According to the general procedure compound **2** afforded **2e** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3280, 2900, 1240, 1080, 850 cm^{-1}. ^1H NMR: δ = 3.55 (dd, *J* = 4.4, 5.5 Hz, 1 H, C*H*OH), 3.05 (dt, *J* = 2.5, 5.1 Hz, 1 H, CH_2CHO_{epox}), 2.78 (dd, *J* = 2.5, 5.5 Hz, 1 H, $CHO_{epox}CHOH$), 1.9−1.6 (m, 9 H), 1.6−1.1 (m, 6 H), 1.02 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$), 0.98 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$). ^{13}C NMR: δ = 65.9, 59.7, 53.8, 41.2, 36.0, 33.7, 33.3, 26.6, 26.5, 26.4, 26.3, 18.6, 18.0. $C_{13}H_{24}O_2$ (212.33): calcd. C 73.54, H 11.39; found C 73.7, H 11.8.

(3*S,4*R**,5*R**)-6-Cyclohexyl-2-methyl-4,5-epoxyhexan-3-ol (2f) (*syn*):** According to the general procedure compound **2** afforded **2f** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3280, 2900, 1240, 1080, 850 cm^{-1}. ^1H NMR: δ = 3.21 (dd, *J* = 4.4, 10.2 Hz, 1 H, C*H*OH), 2.95 (dt, *J* = 2.2, 6.6 Hz, 1 H, CH_2CHO_{epox}), 2.75 (dd, *J* = 2.2,

4.4 Hz, 1 H, C*H*O$_{epox}$CHOH), 1.85−1.60 (m, 7 H), 1.50−1.40 (m, 2 H), 1.35−1.15 (m, 2 H), 1.02 (d, J = 6.6 Hz, 3 H, CHC*H*$_3$), 0.93 (d, J = 6.6 Hz, 3 H, CHC*H*$_3$). ^{13}C NMR: δ = 75.5, 60.2, 55.5, 39.4, 35.8, 33.5, 33.2, 32.6, 26.3, 26.1, 18.4, 17.9. $C_{13}H_{24}O_2$ (212.33): calcd. C 73.54, H 11.39; found C 73.8, H 11.9.

(2*R,3*R**,5*R**)-4-Cyclohexyl-3,4-epoxybutan-2-ol (3a) (*anti*):** According to the general procedure compound **3** afforded **3a** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3280, 2900, 1240, 1080, 850 cm^{-1}. ^{1}H NMR: δ = 3.95 (dq, J = 4.4, 6.6 Hz, 1 H, C*H*OH), 2.85−2.76 (m, 2 H, C*H*$_2$O$_{epox}$), 1.9−1.45 (m, 7 H), 1.25 (d, J = 6.6 Hz, 3 H, C*H*$_3$), 1.4−1.02 (m, 5 H). ^{13}C NMR: δ = 64.6, 61.7, 59.0, 39.3, 29.4, 28.7, 26.01, 25.4, 25.3, 18.6. $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.9, H 10.9.

(2*R,3*R**,5*R**)-4-Cyclohexyl-3,4-epoxybutan-2-ol (3b) (*syn*):** According to the general procedure compound **3** afforded **3b** as a colorless oil. IR (liquid film): $\tilde{\nu}_{max}$ = 3280, 2900, 1240, 1080, 850 cm^{-1}. ^{1}H NMR: δ = 3.58 (sext, J = 5.1 Hz, 1 H, C*H*OH), 2.78 (dd, J = 2.1, 2.9 Hz, 1 H, CH C*H*O$_{epox}$), 2.65 (dd, J = 2.9, 5.1 Hz, 1 H, C*H*O$_{epox}$CHOH), 2.15 (d, J = 5.1 Hz, 1 H, O*H*), 1.95−1.45 (m, 7 H), 1.2 (d, J = 5.1 Hz, 3 H, C*H*$_3$), 1.43−0.97 (m, 4 H). ^{13}C NMR: δ = 67.8, 62.5, 57.1, 39.50, 29.7, 28.8, 26.1, 25.5, 25.3, 19.2. $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.8, H 10.8.

(2*R*,3*S*,4*S*)-2-Bromo-1-cyclohexyl-6-methylheptane-3,4-diol (4): $MgBr_2{\cdot}Et_2O$ (516.5 mg, 2 mmol) was added to a solution of **2c** (226.4 mg, 1 mmol) in dry Et_2O (10 mL). The solution was stirred at room temperature for 2 h (TLC monitoring), and was then filtered through a Celite pad and the solvents evaporated in vacuo. The residue was then chromatographed on silica gel (petroleum ether/EtOAc, 8:2) affording **4** (282.7 mg, 92%) as a pale oil. $[\alpha]_D^{25}$ = 13.1 (c = 0.34 $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3250, 2840, 1250, 1080, 550 cm^{-1}. ^{1}H NMR: δ = 4.37 [ddd, J = 0.9, 6.0, 7.2 Hz, 2 H, C*H*(*i*Bu)OH], 3.93 (ddd, J = 0.9, 5.2, 6.7 Hz, 1 H, C*H*Br), 3.78 (dd, J = 5.2, 6.0 Hz, 1 H, C*H*OH), 2.35 (br. s, 1 H, O*H*), 1.92−1.45 (m, 9 H), 1.42−0.85 (m, 8 H), 0.97 (d, J = 6.6 Hz, 3 H, C*H*$_3$), 0.93 (d, J = 6.6 Hz, 3 H, C*H*$_3$). ^{13}C NMR: δ = 78.2, 70.4, 57.7, 41.1, 40.3, 35.5, 34.1, 31.3, 26.5, 26.2, 25.9, 24.3, 23.9, 21.4. $C_{14}H_{27}BrO_2$ (307.27): calcd. C 54.72, H 8.86; found C 54.9, H 9.1.

(2*S*,3*R*,4*S*)-2-Azido-1-cyclohexyl-6-methylheptane-3,4-diol (5): A mixture of compound **4** (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 **5** (194.4 mg, 72%) as white solid (mp 95−96 °C). IR (liquid film): $\tilde{\nu}_{max}$ = 3280, 2900, 2235, 1260, 1090 cm^{-1}. ^{1}H NMR: δ = 3.75−3.58 [m, 1 H, C*H*-(*i*Bu)OH], 3.55−3.43 (m, 1 H, C*H*N$_3$), 3.38 (dd, J = 2.9, 5.8 Hz, 1 H, C*H*OH), 2.51 (br. s, 1 H, O*H*), 2.19 (br. s, 1 H, O*H*), 1.59−1.15 (m, 18 H), 0.93 (d, J = 5.9 Hz, 6 H, C*H*$_3$). ^{13}C NMR: δ = 76.1, 70.9, 59.9, 42.1, 37.3, 34.2, 33.6, 33.0, 26.3, 26.1, 26.2, 24.4, 23.8, 21.5. $C_{14}H_{27}N_3O_2$ (269.39): calcd. C 62.42, H 10.10, N 15.60; found C 62.7, H10.5, N 15.8.

(2*S*,3*R*,4*S*)-2-Amino-1-cyclohexyl-6-methylheptane-3,4-diol (6): A solution of **5** (269 mg, 1 mmol) was hydrogenated with 10% Pd/C (27 mg) in EtOAc (1 mL) under H_2 (50 psi) for 24 h. The mixture was then filtered through a celite pad and concentrated in vacuo. The crude residue was crystallized from EtOH affording **6** as a white solid. (216 mg, 89%). m.p. 106−109 °C. $[\alpha]_D^{25}$ = −28.7°.[8c] IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3280, 2900, 1580, 1240, 1080, 850 cm^{-1}. ^{1}H NMR: δ = 4.15−4 [m, 2 H, C*H*(*i*Bu)OH + C*H*NH$_2$], 3.44 (dd, J = 5.7, 2.6 Hz, 1 H, C*H*OH), 2.5 (br. s, 1 H,O*H*), 1.95 (br. s, 1 H, O*H*), 1.9−1.45 (m, 13 H), 1.4−1.15 (m, 5 H), 0.97 (d, J = 2.9 Hz, 3 H, CHC*H*$_3$), 0.93 (d, J = 2.9 Hz, 3 H, CHC*H*$_3$). ^{13}C NMR: δ = 68.3, 62.1, 42.9, 42.8, 40.8, 34.3, 31.6, 29.7, 26.5, 26.3, 25.9, 24.4, 23.3, 22.0. $C_{14}H_{29}NO_2$ (243.39): calcd. C 69.09, H 12.01, N 5.75; found C 69.3, H 12.4, N 5.6.

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