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Stereocontrolled 'one pot' organometallic addition–ring opening reaction of α,β-aziridine aldehydes. A new entry to *syn* 1,2-amino alcohols

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Abstract—'One pot' organometallic addition and subsequent ring opening of α,β-aziridine aldehydes is reported to afford *anti–syn* 3-bromo-1,2-amino alcohols in high chemical yield and stereoselectivity. The sequence allows the stereoselective preparation of *syn* 1,2-amino alcohols. © 2001 Elsevier Science Ltd. All rights reserved.

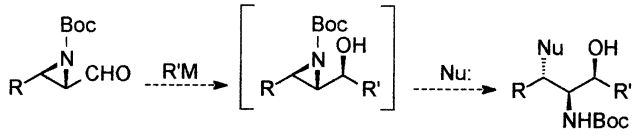
1. Introduction

1,2-Amino alcohols are characteristic structural features of many natural products and drugs,[1] and they are often utilized in the synthesis of biologically active molecules such as protease inhibitors,[2] glycosphingolipids[3] or polyhydroxylated nitrogen heterocycles.[4] Moreover, they play an important role as auxiliaries to control a range of asymmetric transformations by forming a 5-membered chelate in the presence of a metal counter-ion.[5]

In the last years, a great number of methods to prepare 1,2-amino alcohols stereoselectively have been reported;[6] among these methods, we have specifically studied an approach involving metal halide opening of epoxy alcohols[7] and esters[8] to the corresponding halohydrins, easily transformed into the corresponding amino alcohols derivatives. Also, the nucleophilic opening of α,β-aziridino alcohols proved to be a very efficient route to 2-amino-1-alkanols,[9] as demonstrated by our results.[10]

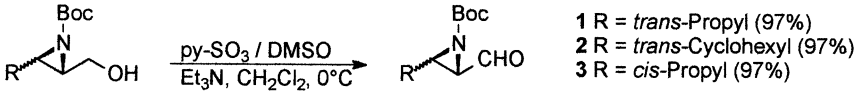
2. Results and discussions

Based on our results on the regioselective opening of epoxy or aziridine rings, we sought the possibility of obtaining general access to internal 1,2-amino alcohols also possessing, when necessary, a third stereogenic center; to this end, we exploited firstly the possibility of controlling the diastereoselectivity in the organometallic addition to the carbonyl group of α,β-aziridino aldehydes[11] and then the regioselectivity in the nucleophilic opening of the obtained secondary α,β-aziridino alcohols (Scheme 1).



Scheme 1.

Since we had previously used the more reactive and more easily purified *N*-Boc-2-functionalized-aziridines, the starting α,β-aziridino aldehydes were prepared by oxidation with pyridine–SO_3 complex of the corresponding *N*-Boc-α,β-aziridino alcohol (Scheme 2).[12] Our preliminary studies were restricted, for convenience, to racemic compounds, but the corresponding optically pure aziridino alcohols are easily obtainable by a known procedure.[9]



Scheme 2.

Keywords: asymmetric synthesis; α,β-aziridine aldehydes; Grignard reagent; 1,2-amino alcohols.

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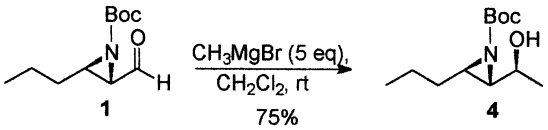
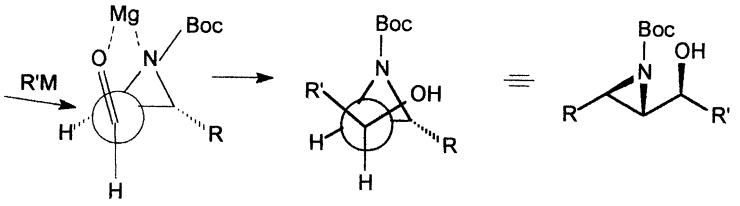


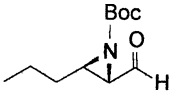
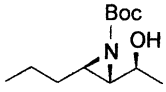
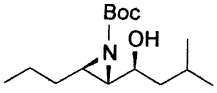
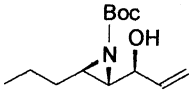
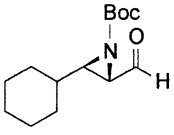
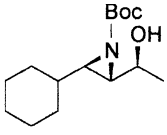
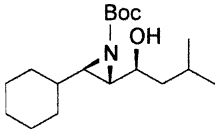
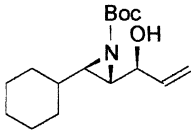
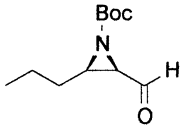
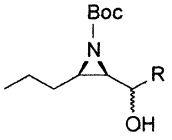
Scheme 3.

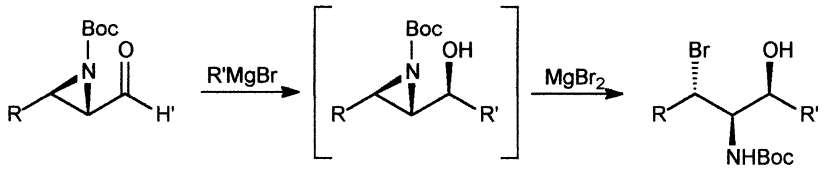
The reaction conditions were optimized studying the addition of methylmagnesium bromide to the *trans*-2-formyl-3-propyl-1-*t*-butoxycarbonyl aziridine **1**; the best results were obtained using CH_2Cl_2 as solvent (Et_2O and THF gave lower yields) and carrying out the reaction at room temperature with 5 equiv. of MeMgBr (at lower



Scheme 4.

Table 1. Grignard addition to α,β-aziridino aldehydes

α,β-Aziridino aldehyde	Grignard reagent	Main product	Yield (%)
 **1**	MeMgBr	 **4**	75
	i-BuMgBr	 **5**	70
	VinylMgBr	 **6**	55
 **2**	MeMgBr	 **7**	80
	i-BuMgBr	 **8**	80
	VinylMgBr	 **9**	60
 **3**	MeMgBr or *i*-BuMgBr	 mixture of diastereoisomers (1:1)	70



Scheme 5.

temperature or with less Grignard reagent the conversion decreased).

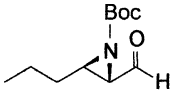
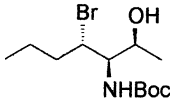
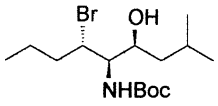
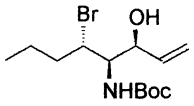
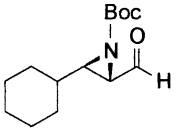
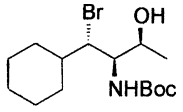
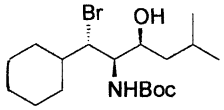
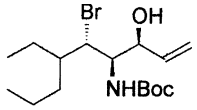
Under these conditions, the *syn* aziridino alcohol **4** was obtained in quite good yield with an excellent diastereomeric ratio (the *anti* diastereoisomer was never detected in the ^{1}H NMR spectra of the reaction mixture) (Scheme 3). The *syn* stereochemistry was proved by further elaboration into a compound synthesized by a different route, as discussed later.

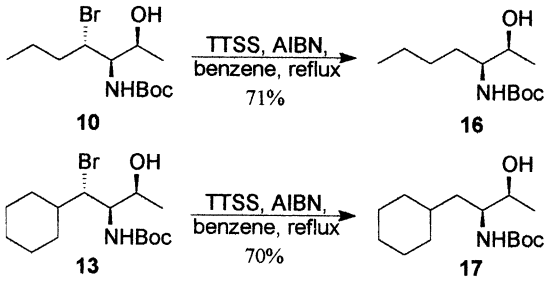
The stereoselectivity can be explained by invoking the 'cyclic chelate model' (Scheme 4).[13] In fact, the *syn* selectivity can be ascribed to the formation of a chelate between the magnesium atom, the carbonyl oxygen and the aziridine nitrogen; addition then occurs from the least-hindered face of the carbonyl affording the final *syn* aziridino alcohol (Scheme 4).

The applicability of the methodology was tested on *trans*-3-cyclohexyl-2-formyl-1-*t*-butoxycarbonyl aziridine **2** and on *cis*-2-formyl-3-propyl-1-*t*-butoxycarbonyl aziridine **3** as well as on compound **1** employing different Grignard reagents. As shown in Table 1, the reaction worked well also when a bulky group is present on C-3 position (compounds **4**, **5**, **6**), while the diastereoselectivity was completely lost in the *cis* stereoisomer. Probably, in this case, the hypothesized chelate is formed with greater difficulty.

The aziridino alcohol, easily obtained by the described conditions, can be used for further transformations. In this

Table 2. One pot organometallic addition–ring opening reaction

α,β-Aziridino aldehyde	Reagents	Main product	Yield (%)
 **1**	MeMgBr, then $MgBr_2$	 **10**	65
	i-BuMgBr, then $MgBr_2$	 **11**	60
	VinylMgBr, then $MgBr_2$	 **12**	55
 **2**	MeMgBr, then $MgBr_2$	 **13**	68
	i-BuMgBr, then $MgBr_2$	 **14**	65
	VinylMgBr, then $MgBr_2$	 **15**	52



Scheme 6.

regard, as already reported, we have extensively employed $MgBr_2$ to open α,β-aziridino alcohols and esters in regio- and stereocontrolled fashion; consequently we thought to add $MgBr_2$ 'in situ' after the reaction with the Grignard reagent was run (TLC monitoring), thus directly obtaining the corresponding *anti*, *syn* 3-bromo-1,2-amino alcohols (Scheme 5).

This 'one pot' reaction was performed at room temperature on the same two substrates examined before and it furnished the expected bromo-derivatives as single regio- and stereoisomers, independently by the substitution present in C-3 position (Table 2). As shown, the overall chemical yields (with different Grignard reagents) were reasonably good for a two-step procedure. The regiochemistry of the bromine opening was established from NMR spectroscopy, by employing a spin–spin decoupling technique.

Furthermore, the high reactivity of the halide can be conveniently utilized for further elaboration: at first, the easy radical reduction of this functional group allows the preparation of 1,2-amino alcohols with many substituents. To this end, compounds **10** and **13** were reduced with tris-(trimethyl silyl)silane[14] to give the corresponding *syn* 1,2-amino alcohols **16** and **17** in good yields (Scheme 6). Moreover, the substitution of the bromine atom with azide would lead to the synthesis of *syn*, *syn* 1,2-diamino alcohols, subunits present in some biologically active natural and synthetic compounds;[15] studies in this regard are currently underway.

The synthesis of **16** from **10** also allowed the *syn* amino alcohol stereochemistry to be established. As shown in Scheme 7, the synthesis of **16** (*syn* stereochemistry) and its diastereoisomer **20** (*anti* stereochemistry) were completed. The ^1H and ^{13}C NMR spectra of **16** prepared from **10**, were compared with those of **16** and **20**, prepared respectively in several steps from *cis* and *trans* 2-heptene; they resulted in identical spectral data of the diastereoisomer with *syn* configuration.

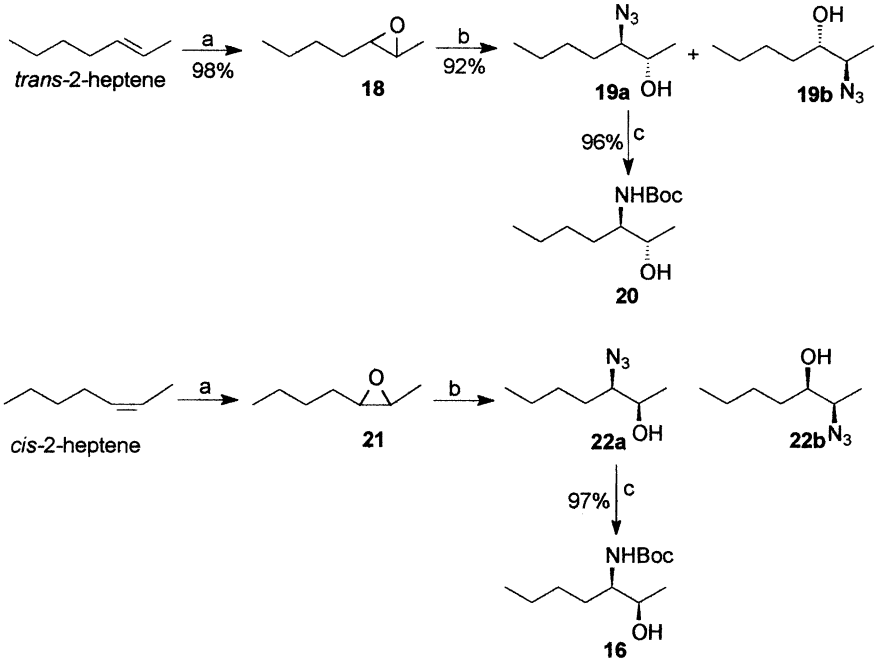
3. Conclusion

In conclusion, we have developed a new and general one pot stereocontrolled organometallic addition–ring opening reaction of *trans* α,β-aziridino aldehydes, which allows us to prepare *anti*, *syn* 1-bromo-2,3-amino alcohols. In view of the simple and mild reaction conditions used and of the large range of compatible substituents, the method appears to be of general application for the preparation of *syn* 1,2-amino alcohols and related compounds.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 Hz, respectively. 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



Scheme 7. a: oxone, $NaHCO_3$, $H_2O/(CH_3)_2O$, rt; b: NaN_3, NH_4Cl, MeOH, reflux; c: Pd/C, EtOH, $(t\text{-BuCO})_2O$.

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 were performed by the Servizio Microanalisi of the Dipartimento di Chimica, Università 'La Sapienza'.

4.2. General preparation of α,β-aziridino aldehydes

4.2.1. Representative procedure for the preparation of *trans*-2-formyl-3-propyl-1-*t*-butoxycarbonyl aziridine 1. To a stirred solution of *trans*-2-hydroxymethyl-3-propyl-1-*t*-butoxycarbonyl aziridine (215 mg, 1 mmol, prepared according to Ref. 6) in dry CH_2Cl_2 (7.5 mL) at 0°C, Et_3N (0.56 mL, 4 mmol) and a DMSO solution of SO_3–pyridine complex (477 mg, 3 mmol in 3 mL of DMSO) were added. Stirring was continued for ~30 min (TLC monitoring), then the reaction mixture was diluted with Et_2O (20 mL) and hexane (41 mL), washed with saturated $NaHCO_3$ solution (19 mL) and the organic layer separated. The aqueous phase was re-extracted with Et_2O (2 mL) and hexane (6 mL); the combined organic layer was washed with NaH_2PO_4 (39 mL of sol. 1 M), dried on Na_2SO_4 and concentrated in vacuo. The crude product did not need any purification affording **1** (207 mg, 97%) as a colorless oil. ν_{max} (liquid film): 2950, 1720, 1380, 1230 cm^{-1}. ^1H NMR: δ 9.1 (1H, d, J=4.8 Hz, C*H*O), 2.9 (1H, dd, J=4.8, 2.9 Hz, C*H*CHO), 2.8 (1H, m, C*H*CHCHO), 1.9–0.6 (4H, m, CH_2CH_2), 1.5 (9H, s, $C(CH_3)_3$), 0.95 (3H, t, J=6.9 Hz, CH_3). ^{13}C NMR: δ 195.6, 158.7, 82.3, 46.9, 43.4, 32.8, 27.8, 20.01, 13.4. $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found C 62.1, H 9.2, N 6.8.

4.2.2. *trans*-2-Formyl-3-cyclohexyl-1-*t*-butoxycarbonyl aziridine 2. According to the general procedure, *trans*-2-hydroxymethyl-3-cyclohexyl-1-*t*-butoxycarbonyl aziridine (255 mg, 1 mmol) gave **2** (245 mg, 97%) as a colorless oil. ν_{max} (liquid film): 2950, 1725, 1370, 1160 cm^{-1}. ^1H NMR: δ 9.1 (1H, d, J=5.05 Hz, C*H*O), 3.0 (1H, dd, J=5.05, 2.7 Hz, C*H*CHO), 2.65 (1H, m, C*H*CHCHO), 2.2–1.5 (5H, m, cyclohex.), 1.46 (9H, s, $C(CH_3)_3$), 1.2 (6H, m, cyclohex.). ^{13}C NMR: δ 195.9, 159.4, 82.8, 49.2, 46.3, 39.8, 30.7, 30.2, 28.3, 26.8, 25.9, 25.9. $C_{14}H_{23}NO_3$ (253.34): C 66.37, H 9.15, N 5.53; found C 66.6, H 9.4, N 5.8.

4.2.3. *cis*-2-Formyl-3-propyl-1-*t*-butoxycarbonyl aziridine 3. According to the general procedure, *cis*-2-hydroxymethyl-3-propyl-1-*t*-butoxycarbonyl aziridine (215 mg, 1 mmol) gave **3** (207 mg, 97%) as a colorless oil. ν_{max} (liquid film): 2950, 1720, 1385, 1310 cm^{-1}. ^1H NMR: δ 9.3 (1H, d, J=5.2 Hz, C*H*O), 2.9 (1H, dd, J=5.2, 6.8 Hz, C*H*CHO), 2.7 (1H, m, C*H*CHCHO), 1.6–1.1 (4H, m, CH_2CH_2), 1.4 (9H, s, $C(CH_3)_3$), 0.95 (3H, t, J=6.9 Hz, CH_3). ^{13}C NMR: δ 198.1, 160.4, 82.1, 45.5, 44.4, 30.5, 27.7, 20.5, 13.3. $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found C 62.2, H 9.3, N 6.8.

4.3. General procedure for the alkylation of α,β-aziridine aldehydes

To a solution of α,β-aziridine aldehyde (1 mmol) in CH_2Cl_2 (36 mL) at room temperature, Grignard reagent (5 mmol) was added. The solution was stirred for ~2 h (TLC monitoring), then the reaction was quenched with saturated NH_4Cl solution (10 mL), the organic layer dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 8:2).

4.3.1. (1′*S,2*S**,3*R**)-2-(1′-Hydroxyethyl)-3-propyl-1-*t*-butoxycarbonyl aziridine 4.** According to the general procedure, **1** (213 mg, 1 mmol) gave **4** as a pale oil (172 mg, 75%). ν_{max} (liquid film): 3250, 2950, 1310, 1260, 1370, 1090 cm^{-1}. ^1H NMR: δ 3.36 (1H, quintet, J=6.6 Hz, C*H*OH), 2.05 (1H, bs, O*H*), 2.21 (2H, m, C*H*NC*H*), 1.8–1.0 (4H, m, CH_2CH_2), 1.42 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, J=6.6 Hz, CHOHCH_3), 0.9 (3H, t, J=6.6 Hz, CH_3). ^{13}C NMR: δ 161.5, 81.6, 68.9, 49.15, 41.3, 33.0, 27.8, 20.1, 13.6. $C_{12}H_{23}NO_3$ (229.32): C 62.85, H 10.11, N 6.11; C 62.9, H 10.3, N 6.3.

4.3.2. (1′*S,2*S**,3*R**)-2-(1′-Hydroxy-3′-methyl-butyl)-3-propyl-1-*t*-butoxycarbonyl aziridine 5.** According to the general procedure, **1** (213 mg, 1 mmol) gave **5** as a pale oil (190 mg, 70%). ν_{max} (liquid film): 3230, 2955, 1360, 1270, 1160, 1090 cm^{-1}. ^1H NMR: δ 3.4–3.18 (1H, m, C*H*OH), 2.28 (2H, m, C*H*NC*H*), 1.92–1.2 (8H, m, CH_2CH_2+CH_2CH+O*H*), 1.5 (9H, s, $C(CH_3)_3$), 1.02–0.84 (9H, m, $CH(CH_3)_2$+CH_3). ^{13}C NMR: δ 161.5, 81.7, 70.6, 48.7, 43.8, 41.4, 33.1, 27.9, 24.1, 23.3, 22.04, 20.2, 13.7. $C_{15}H_{29}NO_3$ (271.40): C 66.38, H 10.77, N 5.16; found C 66.5, H 10.9, N 5.3.

4.3.3. (1′*S,2*S**,3*R**)-2-(1′-Hydroxy-allyl)-3-propyl-1-*t*-butoxycarbonyl aziridine 6.** According to the general procedure, **1** (213 mg, 1 mmol) gave **6** as a pale oil (132.5 mg, 55%). ν_{max} (liquid film): 3200, 2952, 1350, 1260, 1090, 995 cm^{-1}. ^1H NMR: δ 5.95 (1H, ddd, J=17.2, 10.6, 5.2 Hz, C*H*=CH_2), 5.4 (1H, dt, J=17.2, 1.6 Hz, CH=CH_aCH_b), 5.22 (1H, dt, J=10.6, 1.6 Hz, CH=CH_aCH_b), 3.72 (1H, ddt, J=8.2, 5.2, 1.6 Hz, C*H*OH), 2.32 (2H, m, C*H*NC*H*), 1.48 (9H, s, $C(CH_3)_3$), 1.92–1.1 (5H, m, CH_2CH_2+O*H*), 0.95 (3H, t, J=6.8 Hz, CH_3). ^{13}C NMR: δ 161.4, 136.3, 116.44, 81.9, 73.4, 47.5, 41.4, 32.9, 27.9, 20.1, 13.6. $C_{13}H_{23}NO_3$ (241.33); C 64.70, H 9.61, N 5.80; found C 64.9, H 9.8, N 6.1.

4.3.4. (1′*S,2*S**,3*R**))-3-Cyclohexyl-2-(1′-hydroxy-ethyl)-1-*t*-butoxycarbonyl aziridine 7.** According to the general procedure, **2** (253 mg, 1 mmol) gave **7** as a pale oil (216 mg, 80%). ν_{max} (liquid film): 3200, 2948, 1310, 1265, 1088 cm^{-1}. ^1H NMR: δ 3.34 (1H, dq, J=6.3, 8.3 Hz, C*H*OH), 2.3 (1H, dd, J=3.3, 8.3 Hz, C*H*CHOH), 2.05–1.95 (1H, m, C*H*NCH), 1.93 (1H, bs, O*H*), 1.82–1.55 (11H, m, cyclohexyl), 1.47 (9H, s, $C(CH_3)_3$), 1.29 (3H, d, J=6.3 Hz, CH_3). ^{13}C NMR: δ 160.6, 81.8, 69.7, 48.4, 46.7, 39.5, 30.5, 29.7, 27.9, 26.1, 25.6, 25.4, 19.9. $C_{15}H_{27}NO_3$ (269.38): C 66.88, H 10.10, N 5.20; found C 67.2, H 10.4, N 5.5.

4.3.5. (1′*S,2*S**,3*R**)-3-Cyclohexyl-2-(1′-hydroxy-3′-methyl-butyl)-1-*t*-butoxycarbonyl aziridine 8.** According to the general procedure **2** (253 mg, 1 mmol) gave **8** as a pale oil (249 mg, 80%). ν_{max} (liquid film): 3250, 2952, 1315, 1260, 1160, 1092 cm^{-1}. ^1H NMR: δ 3.22 (1H, dt,

J=8.9, 4.3 Hz, C*H*OH), 2.32 (1H, dd, J=8.9, 3.4 Hz, C*H*CHOH), 2.15 (1H, bs, O*H*), 2.09–1.98 (1H, m, C*H*NCH), 1.95–1.51 (7H, m), 1.47 (9H, s, C(CH_3)$_3$), 1.35–0.97 (7H, m), 0.92 (3H, d, J=7.4 Hz, CHCH_3), 0.88 (3H, d, J=7.4 Hz, CHCH_3). ^{13}C NMR: δ 161.8, 81.8, 71.4, 47.9, 46.7, 43.5, 39.6, 30.5, 29.9, 27.9, 26.1, 25.6, 25.5, 24.1, 23.4, 21.9. $C_{18}H_{33}NO_3$ (311.46): C 69.41, H 10.68, N 4.50; found C 69.7, 10.9, 4.7.

4.3.6. (1′*S,2*S**,3*R**)-3-Cyclohexyl-2-(1′-hydroxy-allyl)-1-*t*-butoxycarbonyl aziridine 9.** According to the general procedure, **2** (253 mg, 1 mmol) gave **9** as a pale oil (169 mg, 60%). ν_{max} (liquid film): 3270, 2890, 1310, 1260, 1092, 990 cm^{-1}. ^{1}H NMR: δ 5.95 (1H, ddd, J=17.2, 10.6, 5.2 Hz, C*H*=CH$_2$), 5.39 (1H, dt, J=17.2, 1.6 Hz, CH=CH_aCH$_b$), 5.22 (1H, dt, J=10.6, 1.6 Hz, CH=CH$_a$CH_b), 3.8 (1H, d, J=2.6 Hz, O*H*), 3.71(1H, m, C*H*OH), 2.38 (1H, dd, J=8.2, 3.3 Hz, C*H*CHOH), 2.13 (1H, dd, J=5.7, 3.3 Hz, C*H*NCH), 1.95–1.85 (1H, m, C*H*), 1.85–1.52 (5H, m, cyclohexyl), 1.48 (9H, s, C(CH_3)$_3$), 1.41–1.12 (5H, m, cyclohexyl). ^{13}C NMR: δ 161.7, 136.0, 116.4, 81.9, 74.3, 46.8, 46.7, 39.4, 30.5, 29.8, 27.9, 26.1, 25.6, 25.4. $C_{16}H_{27}NO_3$ (281.40): C 68.29, H 9.67, N 4.98; found C 68.5, H 9.9, N 5.2.

4.4. General procedure for the one pot alkylation–ring opening of α,β-aziridine aldehydes

To a solution of α,β-aziridine aldehyde (1 mmol) in CH_2Cl_2 (36 mL) at room temperature, Grignard reagent (5 mmol) was added. The solution was stirred for ~2 h (TLC monitoring), then $MgBr_2$ (517 mg, 1 mmol) was added. After ~2 h (TLC monitoring), the reaction was quenched with saturated NH_4Cl solution (10 mL), the organic layer dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 8:2).

4.4.1. (2*S,3*R**,4*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-4-bromo-heptan-2-ol 10.** According to the general procedure **1** (213 mg, 1 mmol) gave **10** as a yellow oil (202 mg, 65%). ν_{max} (liquid film): 3300, 2950, 1630, 1260, 1090, 550 cm^{-1}. ^{1}H NMR: δ 5.13 (1H, bd, J=9.3 Hz, N*H*), 4.46 (1H, dq, J=6.4, 1.3 Hz, C*H*OHCH$_3$), 4.12 (1H, dd, J=8.7, 6.6 Hz, C*H*Br), 3.55 (1H, ddd, J=9.3, 8.7, 1.3 Hz, C*H*NHBoc), 2.05 (1H, bs, O*H*), 1.97–1.6 (4H, m, CH_2CH_2), 1.48 (9H, s, C(CH_3)$_3$), 1.21 (3H, t, J=6.4 Hz, CHOHCH_3), 0.93 (3H, t, J=7.3 Hz, CH_3). ^{13}C NMR: δ 155.9, 79.8, 66.3, 58.7, 58.6, 37.3, 28.3, 20.8, 20.7, 13.4. $C_{12}H_{24}BrNO_3$ (310.23): C 46.46, H 7.80, N 4.51; found C 46.8, H 9.1, N 4.8.

4.4.2. (4*S,5*R**,6*S**)-5-(*N*-*t*-Butoxycarbonyl)amino-6-bromo-2-methyl-nonan-4-ol 11.** According to the general procedure **1** (213 mg, 1 mmol) gave **10** as a yellow oil (210 mg, 60%). ν_{max} (liquid film): 3250, 2865, 1520, 1265, 1165, 1090, 560 cm^{-1}. ^{1}H NMR: δ 5.12 (1H, bd, J=9.3 Hz, N*H*), 4.31 (1H, dq, J=5.6, 1.1 Hz, C*H*OHCH$_3$), 4.15–4.1 (1H, m, C*H*Br), 3.65 (1H, ddd, J=9.3, 8.2, 1.1 Hz, C*H*NHBoc), 2.05 (1H, bs, O*H*), 1.92–1.55 (5H, m, CH_2+CH_2C*H*), 1.48 (9H, s, C(CH_3)$_3$), 1.32–1.12 (2H, m, CH_2), 0.92 (6H, m, CH_3+CHC*H*3), 0.88 (3H, d, J=7.3 Hz, CHCH_3). ^{13}C NMR: δ 155.8, 79.7, 68.4, 58.8, 57.8, 43.5, 37.2, 28.3, 24.3, 22.9, 22.4, 20.8, 13.4. $C_{15}H_{30}BrNO$ (352.31): C 51.14, H 8.58, N 3.98; found C 51.4, H 8.8, N 4.2.

4.4.3. (3*S,4*R**,5*S**)-4-(*N*-*t*-Butoxycarbonyl)amino-5-bromo-2-octen-3-ol 12.** According to the general procedure **1** (213 mg, 1 mmol) gave **6** as a yellow oil (177.5 mg, 55%). ν_{max} (liquid film): 3250, 2930, 1670, 1255, 1080, 990, 500 cm^{-1}. ^{1}H NMR: δ 5.75 (1H, ddd, J=16.8, 10.2, 7.5 Hz, C*H*=CH$_2$), 5.12 (1H, bd, J=9.3 Hz, N*H*), 5.01 (1H, dt, J=16.8, 1.4 Hz, CH=CH_aCH$_b$), 4.92 (1H, dt, J=10.2, 1.4 Hz, CH=CH$_a$CH_b), 4.21–4.1 (1H, m, C*H*Br), 3.95–3.75 (1H, m, C*H*NHBoc), 3.62 (1H, t, J=7.5 Hz, C*H*OH), 2.35 (1H, bs, O*H*), 1.95–1.32 (4H, m, CH_2CH_2), 1.45 (9H, s, C(CH_3)$_3$), 0.92 (3H, t, J=7.2 Hz, CH_3). ^{13}C NMR: δ 155.5, 137.8, 116.0, 80.2, 71.3, 58.3, 57.2, 36.9, 28.9, 20.7, 13.4. $C_{13}H_{24}BrNO_3$ (322.24): C 48.46, H 7.51, N 4.35; found C 48.7, H 7.8, N 4.7.

4.4.4. (2*S,3*R**,4*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-4-bromo-4-cyclohexyl-butan-2-ol 13.** According to the general procedure **2** (253 mg, 1 mmol) gave **13** as a yellow oil (238 mg, 68%). ν_{max} (liquid film): 3300, 2950, 1680, 1260, 1090, 550 cm^{-1}. ^{1}H NMR: δ 5.02 (1H, bd, J=9.5 Hz, N*H*), 4.5 (1H, q, J=6.3 Hz, C*H*OH), 4.01 (1H, dd, J=8.9, 3.6 Hz, C*H*Br), 3.81 (1H, dd, J=8.9, 9.5 Hz, C*H*NHBoc), 2.12 (1H, bs, O*H*), 2–1.21 (11H, m, cyclohexyl), 1.45 (9H, s, C(CH_3)$_3$), 1.22 (3H, d, J=6.3 Hz, CH_3). ^{13}C NMR: δ 155.6, 79.6, 66.7, 65.4, 55.9, 40.2, 32.2, 29.7, 28.3, 26.3, 26.2, 25.9, 20.5. $C_{15}H_{28}BrNO_3$ (350.30): C 51.43, H 8.06, N 4.00; found C 51.7, H 8.5, N 4.3.

4.4.5. (1*S,2*R**,3*S**)-2-(*N*-*t*-Butoxycarbonyl)amino-1-bromo-1-cyclohexyl-5-methyl-hexan-3-ol 14.** According to the general procedure, **2** (253 mg, 1 mmol) gave **14** as a yellow oil (255 mg, 65%). ν_{max} (liquid film): 3250, 2860, 1530, 1260, 1160, 1090, 560 cm^{-1}. ^{1}H NMR: δ 5.12 (1H, bd, J=9.9 Hz, N*H*), 4.38 (1H, t, J=5.7 Hz, C*H*OH), 4.02 (1H, dd, J=9.4, 3.1 Hz, C*H*Br), 3.91–3.74 (1H, m, C*H*NHBoc), 2.26 (1H, bs, O*H*), 2.01–1.87 (1H, m, C*H*), 1.85–1.55 (6H, m,), 1.44 (9H, s, C(CH_3)$_3$), 1.43–1.05 (7H, m), 0.95 (3H, d, J=6.6 Hz, CHCH_3), 0.94 (3H, d, J=6.6 Hz, CHCH_3). ^{13}C NMR: δ 155.5, 79.5, 68.7, 65.2, 54.9, 43.3, 39.9, 32.3, 28.2, 26.3, 26.2, 25.8, 24.4, 22.9, 22.4. $C_{18}H_{34}BrNO_3$ (392.38): C 55.10, H 8.73, N 3.57; found C 55.4, H 8.9, N 3.8.

4.4.6. (1*S,2*R**,3*S**)-2-(*N*-*t*-Butoxycarbonyl)amino-1-bromo-1-cyclohexyl-4-penten-3-ol 15.** According to the general procedure **2** (253 mg, 1 mmol) gave **15** as a yellow oil (189 mg, 52%). ν_{max} (liquid film): 3252, 2865, 1530, 1265, 1090, 990, 560 cm^{-1}. ^{1}H NMR: δ 5.9 (1H, ddd, J=17.2, 10.5, 5 Hz, C*H*=CH$_2$), 5.36 (1H, dt, J=17.2, 1.4 Hz, CH=CH_aCH$_b$), 5.22 (1H, dt, J=10.4, 1.4 Hz, CH=CH$_a$CH_b), 4.95 (1H, bd, J=9.1 Hz, N*H*), 4.86 (1H, dd, J=5, 1.5 Hz, C*H*OH), 4.09 (1H, dd, J=9.8, 2.7 Hz, C*H*Br), 3.95 (1H, ddd, J=9.8, 9.1, 1.5 Hz, C*H*NHBoc), 2.22 (1H, bs, O*H*), 2.01–1.87 (1H, m, C*H*), 1.85–1.50 (4H, m), 1.42 (9H, s, C(CH_3)$_3$), 1.43–1.05 (6H, m). ^{13}C NMR: δ 155.3, 137.8, 115.9, 79.9, 64.3, 55.3, 39.9, 32.3, 28.3, 27.8, 26.3, 26.2, 25.9. $C_{16}H_{28}BrNO_3$ (362.31): C 53.04, H 7.79, N 3.87; found C 53.4, H 8.1, N 4.1.

4.5. General procedure for the preparation of 1,2-amino alcohols

To a solution of the bromo derivative (1 mmol) in benzene (10 mL), tris(trimethyl silyl) silane (0.31 mL, 1 mmol) and catalytic amount of AIBN were added. The solution was refluxed for ~5 h (TLC monitoring), then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 9:1).

4.5.1. (2*S,3*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-heptan-2-ol 16.** According to the general procedure **10** (310 mg, 1 mmol) gave **16** as a colorless oil (164 mg, 71%). ν_{max} (liquid film): 3250, 2860, 1630, 1265 cm^{-1}. ^1H NMR: δ 4.64 (1H, bd, J=9.5 Hz, N*H*), 3.78 (1H, dq, J=6.6, 2.9 Hz, C*H*OH), 3.45–3.31 (1H, m, C*H*NHBoc), 2.35 (1H, bs, O*H*), 1.48 (9H, s, C(CH_3)$_3$), 1.38–1.05 (6H, m, CH_2 CH_2 CH_2), 1.18 (3H, d, J=6.6 Hz, CHOHCH_3), 0.88 (3H, t, J=6.5 Hz, CH_3). ^{13}C NMR: δ 156.6, 85.1, 69.4, 55.8, 32.0, 28.3, 27.4, 22.5, 20.4, 13.9. $C_{12}H_{25}NO_3$ (231.34): C 62.30, H 10.89, N 6.05; found C 62.5, H 11.2, N 6.3.

4.5.2. (2*S,3*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-3-(methyl-cyclohexyl)-propan-2-ol 17.** According to the general procedure **13** (350 mg, 1 mmol) gave **17** as a colorless oil (190 mg, 70%). ν_{max} (liquid film): 3250, 2860, 1630, 1265 cm^{-1}. ^1H NMR: δ 4.62 (1H, bd, J=9.3 Hz, N*H*), 3.81 (1H, dq, J=6.7, 3.1 Hz, C*H*OH), 3.35–3.48 (1H, m, C*H*NHBoc), 2.47 (1H, bs, O*H*), 1.85–1.50 (6H, m), 1.42 (9H, s, C(CH_3)$_3$), 1.45–1.05 (7H, m), 1.21 (3H, d, J=6.7 Hz, CHOHCH_3). ^{13}C NMR: δ 156.6, 85.1, 69.4, 55.8, 32.2, 32.3, 28.3, 27.8, 26.3, 26.2, 25.9. $C_{15}H_{29}NO_3$ (271.40): C 66.38, H 10.77, N 5.16; found C 66.6, H 10.9, N 5.3.

Epoxides **18** and **21**, prepared according to Ref. 16, are known compounds.[17]

4.6. General procedure for the preparation of 1,2-azido alcohols

A solution of epoxide (114 mg, 1 mmol), NaN_3 (202 mg, 3.1 mmol) and NH_4Cl (166 mg, 3.1 mmol) in MeOH (3.5 mL) was refluxed for 5 h (TLC monitoring). After evaporation of the solvent, the residue was diluted with Et_2O and washed with brine; the organic layer were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 8:1).

The regioisomeric 1,2-azido alcohols were identified from NMR spectroscopy, by employing a spin–spin decoupling technique.

4.6.1. (2*S,3*R**)-3-Azido-heptan-2-ol 19a.** According to the general procedure **18** (114 mg, 1 mmol) gave **19a** as a pale oil (72 mg, 46%). ν_{max} (liquid film): 3250, 2960, 2235, 1265 cm^{-1}. ^1H NMR: δ 3.82 (1H, dq, J=6.5, 3.9 Hz, C*H*OH), 3.41–3.32 (1H, m, C*H*N_3), 1.92 (1H, bs, O*H*), 1.65–1.22 (6H, m, CH_2 CH_2 CH_2), 1.18 (3H, d, J=6.5 Hz, CHOHCH_3), 0.88 (3H, t, J=6.3 Hz, CH_3). ^{13}C NMR: δ 69.8, 68.2, 31.5, 29.9, 22.4, 18.1, 13.9. $C_7H_{15}N_3O$ (157.22): C 53.48, H 9.62, N 26.73; found C 53.7, H 9.9, N 26.9.

4.6.2. (2*R,3*S**)-2-Azido-heptan-3-ol 19b.** According to the general procedure, **18** (114 mg, 1 mmol) gave **19b** as a pale oil (72 mg, 46%). ν_{max} (liquid film): 3250, 2960, 2235, 1265 cm^{-1}. ^1H NMR: δ 3.67–3.47 (2H, m, C*H*OH+C*H*N_3), 1.8 (1H, bs, O*H*), 1.51–1.21 (6H, m, $CH_2CH_2CH_2$), 1.23 (3H, d, J=6.6 Hz, CHOHCH_3), 0.88 (3H, t, J=6.4 Hz, CH_3). ^{13}C NMR: δ 73.9, 61.8, 32.5, 31.6, 23.5, 22.5, 13.1. $C_7H_{15}N_3O$ (157.22) C 53.48, H 9.62, N 26.73; found C 53.8, H 9.8, N 26.8.

4.6.3. (2*R,3*R**)-3-Azido-heptan-2-ol 22a.** According to the general procedure **18** (114 mg, 1 mmol) gave **22a** as a pale oil (72 mg, 46%). ν_{max} (liquid film): 3250, 2960, 2235, 1265 cm^{-1}. ^1H NMR: δ 3.72 (1H, q, J=6.35 Hz, C*H*OH), 3.21–3.07 (1H, m, C*H*N_3), 2.02 (1H, bs, O*H*), 1.65–1.28 (6H, m, CH_2 CH_2 CH_2), 1.22 (3H, d, J=6.35 Hz, CHOHCH_3), 0.88 (3H, t, J=6.8 Hz, CH_3). ^{13}C NMR: δ 69.6, 68.8, 30.5, 28.2, 22.5, 20.0, 13.9. $C_7H_{15}N_3O$ (157.22): C 53.48, H 9.62, N 26.73; found C 53.6, H 9.9, N 26.8.

4.6.4. (2*R,3*R**)-2-Azido-heptan-3-ol 22b.** According to the general procedure, **18** (114 mg, 1 mmol) gave **22b** as a pale oil (72 mg, 46%). ν_{max} (liquid film): 3250, 2960, 2230, 1265 cm^{-1}. ^1H NMR: δ 3.58–3.35 (2H, m, C*H*OH+C*H*N_3), 2.8 (1H, bs, O*H*), 1.48–1.15 (6H, m, CH_2 CH_2 CH_2), 1.21 (3H, d, J=6.6 Hz, CHOHCH_3), 0.92 (3H, t, J=6.4 Hz, CH_3). ^{13}C NMR: δ 73.6, 62.4, 31.5, 30.0, 28.5, 23.5, 13.1. C 53.48, H 9.62, N 26.73; found C 53.9, H 9.9, N 26.8.

4.7. General procedure for the preparation of 3-(*N*-*t*-butoxycarbonyl)amino-heptan-2-ol

A suspension of 10% Pd/C (16 mg) in EtOAc (2.2 mL) was vigorously stirred under hydrogen atmosphere for 30 min. Then, the azido alcohol (157 mg, 1 mmol) and $(Boc)_2O$ (259 mg, 1.2 mmol) were added and the resulting solution was stirred under hydrogen at room temperature until disappearance of azido alcohol (TLC monitoring). The mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The crude product was characterized without any purification.

4.7.1. (2*S,3*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-heptan-2-ol 16.** According to the general procedure, **22a** (157 mg, 1 mmol) gave **16** as a colorless oil (153 mg, 97%).

4.7.2. (2*R,3*S**)-3-(*N*-*t*-Butoxycarbonyl)amino-heptan-2-ol 20.** According to the general procedure, **19a** (157 mg, 1 mmol) gave **20** as a colorless oil (150 mg, 96%). ν_{max} (liquid film): 3250, 2860, 1630, 1265 cm^{-1}. ^1H NMR: δ 4.58 (1H, bd, J=8.0 Hz, N*H*), 3.82 (1H, dq, J=6.6, 2.9 Hz, C*H*OH), 3.65–3.51 (1H, m, C*H*NHBoc), 2.21 (1H, bs, O*H*), 1.48 (9H, s, C(CH_3)$_3$), 1.35–1.15 (6H, m, $CH_2CH_2CH_2$), 1.18 (3H, d, J=6.6 Hz, CHOHCH_3), 0.88 (3H, t, J=6.6 Hz, CH_3). ^{13}C NMR: δ 156.6, 85.1, 70.5, 56.2, 31.6, 30.0, 28.3, 27.4, 22.5, 18.0, 13.9. $C_{12}H_{25}NO_3$ (231.34): C 62.30, H 10.89, N 6.05; found C 62.6, H 11.3, N 6.3.

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