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TETRAHEDRON: *ASYMMETRY*

A straightforward synthesis of enantiopure 2-cyano azetidines from β-amino alcohols

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Abstract—Enantiopure 2-cyano azetidines were prepared in high yields from β-amino alcohols. This synthesis was shown to be general and is based on two important steps: (i) chlorination of a *N*-cyanomethylated β-amino alcohol and (ii) a 4-*exo*-*trig* ring closure through the alkylation of a lithiated α-amino nitrile. The former step is stereoselective when ephedrine-derived β-amino alcohols are used. In the case of a phenylglycinol-derived β-amino alcohol, this step also involves a rearrangement.

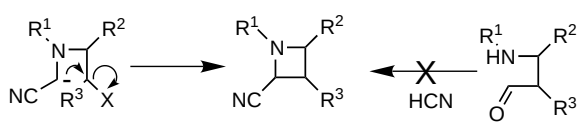
1. Introduction

α-Amino nitriles are popular intermediates in organic synthesis and they continue to find numerous applications[1] in the preparation of nitrogen-containing molecules. This is due to their dual reactivity as *Umpolung* acyl anion or iminium ion precursors, as well as their well-known transformation into α-amino acids. The synthesis of an α-amino nitrile most often involves a Strecker reaction which has been studied extensively and catalytic versions have recently appeared in the literature.[2] When the iminium ion involved in this reaction results from an intramolecular condensation between amine and carbonyl moieties, then 2-cyano piperidines[3] and 2-cyano pyrrolidines[4] can be prepared, and these compounds are useful intermediates in alkaloid syntheses. However, the Strecker reaction has not been reported, to our knowledge, for the preparation of 2-cyano azetidines, despite the growing interest in these four-membered nitrogen heterocycles;[5] this might be attributed to the difficulty of generating highly strained azetidinium ions. Herein, we report a straightforward entry to 2-cyano azetidines in enantiomerically pure form starting from available β-amino alcohols. This preparation relies on a 4-*exo*-*trig* ring closure through the alkylation[6] of a lithiated amino nitrile (Scheme 1). This strategy has been reported only once, to our knowledge, for the preparation of 2-cyano pyrrolidines.[7]

2. Results

Four enantiopure commercially available β-amino alcohols **1**–**4** were selected in order to investigate the scope of this anionic cyclization. Transformation of these amino alcohols into *N*-alkyl,*N*-cyanomethyl derivatives was effected as shown in Scheme 2: while (1*R*,2*S*)-ephedrine **1** and (1*S*,2*S*)-pseudoephedrine **2** were alkylated in excellent yields with bromoacetonitrile to give **5** and **6**, (*R*)-*N*-benzyl phenylglycinol **7** and (*S*)-*N*-benzyl phenylalaninol **8**, prepared through reductive alkylation, were conveniently cyanomethylated in a two-step procedure involving ring opening of intermediate oxazolidines **9** and **10**. Actually, in these cases, direct alkylation of the secondary amine with bromoacetonitrile occurred in low yield, which might be attributed to the high steric hindrance of these amines.

The chlorination of these cyanomethylated amino alcohols was studied next. The most simple case refers to (*S*)-phenylalaninol-derived substrate **12**: treatment of this compound with two equivalents of thionyl chloride in dichloromethane at 0°C, followed by heating under reflux for 4 h gave, after aqueous alkaline workup, the stable chloride **13** in high yield.



Scheme 1. Synthesis of 2-cyano azetidines through intramolecular alkylation.

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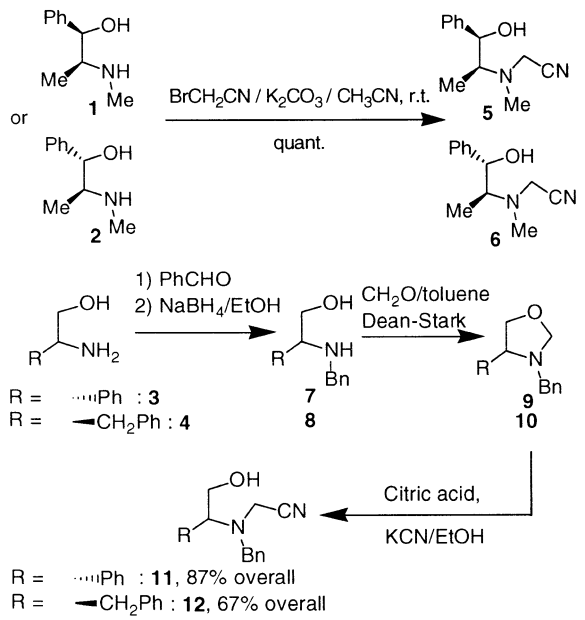


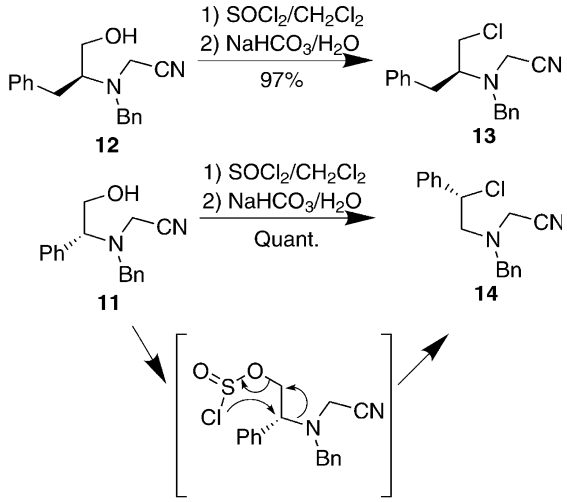
Scheme 2. Synthesis of *N*-alkyl,*N*-cyanomethyl-β-amino alcohols.

When the same reaction was performed using (*R*)-phenylglycinol as substrate, the rearranged chloride **14** was produced (Scheme 3). This rearrangement, previously reported[7] for a related substrate, probably involves concerted nucleophilic attack of the chloride anion at the benzylic carbon of the intermediate sulfinate ester, the intermediacy of an aziridinium ion being improbable since both compound **14** and the trifluoromethanesulfonate derivative of **11** were shown to be stable upon reflux in dichloromethane.

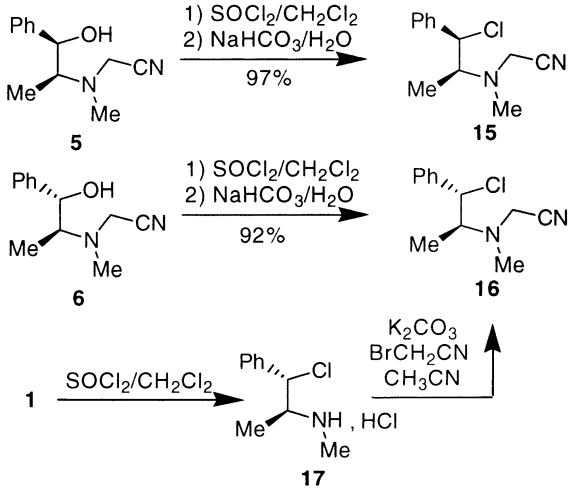
On the other hand, chlorination of compounds **5** and **6** were highly stereoselective and occurred in both cases with retention of configuration (Scheme 4). This was indirectly proven through examination of the azetidines obtained from these chlorides (vide infra). Furthermore, chlorination of (−)-ephedrine is known[8a] to occur with total inversion of configuration under the same conditions to give **17**. Alkylation of this chlorinated ephedrine **17** with bromoacetonitrile gave a complex mixture in which only **16** could be detected by NMR (ca. 15% of the mixture) besides other uncharacterized products. No traces of isomer **15** were present. This is, to our knowledge, the first case of stereospecific chlorination of ephedrin family-derived amino alcohols, and there is no doubt that the *N*-cyanomethyl group plays an important part in the stereochemical outcome of this reaction.

Cyclization of the chlorinated *N*-cyanomethylated compounds **13**–**16** was next effected by treatment with LiHMDS in THF at −78°C. This reaction proceeded in all cases rapidly at this temperature and afforded in good to excellent yields 2-cyano azetidines **18**–**25** as mixtures of stereoisomers at C(2) (Scheme 5). Starting from phenyl-substituted compounds **14**–**16**, the corresponding *trans* 2-cyano-3-phenyl azetidines **21**, **23** and **25** were predominant in the mixture. On the other hand, compound **13**, unsubstituted at the electrophilic center, produced in this case a 1:1 mixture of azetidines **18** and **19** that could not be separated by chromatography. Nonetheless, azetidines **20**–**25** were conveniently separated, and, assuming that an S*N*2 process is operating in these cyclizations, the relative configurations in these heterocycles were determined by ^{1}H NMR and radiocrystallography. First, X-ray crystallography performed on crystalline azetidines **20** and **24** allowed the determination of relative configurations in these compounds and therefore in **21** and **25**. Furthermore, NOE experiments performed on azetidines **22** and **23** permitted the determination of the relative configurations in these heterocycles.

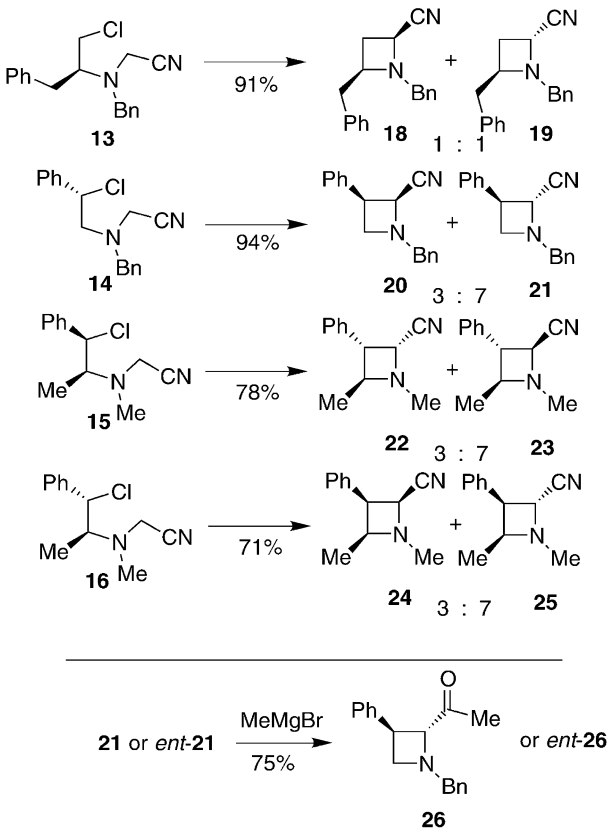
The enantiomeric purity of the azetidines **20** or **21** resulting from alkylation of the rearranged chloride **14** had to be checked since the above-mentioned rearrangement might proceed with some degree of racemization. To this end, compounds **21** and *ent*-**21**



Scheme 3. Chlorination of **11** and **12**: radically different reactivity.



Scheme 4. Stereospecificity in the chlorination of the ephedrine-derived family of β-amino alcohols.



Scheme 5. Synthesis of 2-cyano azetidines through a 4-*exo-trig* alkylation of a metallated α-amino nitrile. Functionalization of **21** and *ent*-**21**.

(prepared starting from (*S*)-phenylglycinol *ent*-**3**) were reacted with methylmagnesium bromide and gave 2-acetyl azetidines **26** and *ent*-**26** (Scheme 5). The enantiomeric excesses of these compounds were determined by ^{1}H NMR through complexation with Eu(hfc)$_3$. In these spectra, the isolated acetyl signal allowed accurate determination of the e.e. and it appeared that these compounds are enantiomerically pure within the precision of NMR (250 MHz).

In conclusion, we have shown that enantiopure 2-cyano azetidines can be prepared in a few steps and with high overall yields (59–82%) from β-amino alcohols. This reaction is of broad scope and further functionalization of these heterocycles are currently studied in our group and will be reported in due course.

3. Experimental

3.1. General comments

^{1}H and ^{13}C spectra ($CDCl_3$ solution) were, respectively, recorded on a Bruker ARX 250 spectrometer at 250 and 62.9 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin Elmer 141 instrument. All reactions were carried out under argon. Column chromatography was performed on silica gel 230–400 mesh by using various mixtures of diethyl ether (Et_2O), ethyl acetate (AcOEt) and petroleum ether (PE). TLC were run on Merck Kieselgel 60F$_{254}$ plates. Melting points are uncorrected. THF and ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Mention of 'usual workup' means: (i) decantation of the organic layer; (ii) extraction of the aqueous layer with ether; (iii) drying of the combined organic phases over $MgSO_4$, and (iv) solvent evaporation under reduced pressure. The composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

3.2. (1*R*,2*S*)-*N*-Cyanomethyl-ephedrine 5

A suspension of (1*R*,2*S*)-ephedrine **1** (4.0 g, 24.2 mmol), bromoacetonitrile (2.0 mL, 28.7 mmol) and potassium carbonate (4.7 g, 34.0 mmol) in acetonitrile (150 mL) was stirred at rt for 4 h. Evaporation of the solvent under reduced pressure was followed by addition of water and ether to the residue. Usual workup gave quantitatively (4.9 g) the title compound as white crystals that were washed with a small portion of PE. Mp 59°C; R_f 0.55 (E/PE: 8/2); $[\alpha]_D^{20}$ +19 (*c* 1.7, $CHCl_3$); IR 3165, 2233, 1265, 1201, 1122, 1004 cm^{-1}; ^{1}H NMR 0.84 (d, $J=6.7$ Hz, 3H), 2.45 (s, 3H), 2.69–2.77 (m, 2H), 3.56 (s, 2H), 4.87 (d, $J=3.2$ Hz, 1H), 7.16–7.28 (m, 5H); ^{13}C NMR 10.2, 40.3 (CH_3), 43.2 (CH_2), 63.4, 72.6 (CH), 116.0 (Cq), 126.2, 127.8, 128.7 (CH), 141.8 (Cq); anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.44; H, 7.86; N, 13.91%.

3.3. (1*S*,2*S*)-*N*-Cyanomethyl-pseudoephedrine 6

Following the procedure described for the preparation of **5**, and starting with (1*S*,2*S*)-*pseudo*ephedrine **2** (4.0 g, 24.2 mmol), the title compound **6** was quantitatively obtained as a white solid (4.90 g). Mp 69°C; R_f 0.55 (E/PE: 8/2); $[\alpha]_D^{20}$ +33 (*c* 2.1, $CHCl_3$); IR 3339, 2228, 1598, 1157, 778, 748, 702 cm^{-1}; ^{1}H NMR 0.79 (d, $J=6.7$ Hz, 3H), 2.40 (s, 3H), 2.70 (dq, $J=9.5$ and 6.7 Hz, 1H), 3.52 (s, 2H), 3.90 (bs, 1H), 4.16 (d, $J=9.5$ Hz, 1H), 7.18–7.27 (m, 5H); ^{13}C NMR 8.8, 35.8 (CH_3), 43.1 (CH_2), 65.9, 75.1 (CH), 116.6 (Cq), 127.3, 128.2, 128.5 (CH), 140.8 (Cq).

3.4. (*S*)-3,4-Dibenzyloxazolidine 10

A suspension of (*S*)-*N*-benzyl-phenylalaninol **8** (3.0 g, 12.4 mmol) and paraformaldehyde (1.90 g, 62.2 mmol) in toluene (100 mL) was heated under aezotropic reflux for 3 h. Evaporation of the solvent followed by flash chromatography gave oxazolidine **10** as colorless crystals (4.85 g, 90%). Mp 50°C; R_f 0.6 (E/PE: 8/2); $[\alpha]_D^{20}$ −67 (*c* 0.7, $CHCl_3$); IR 1306, 1280, 1260, 1147 cm^{-1}; ^{1}H NMR 2.53 (dd, $J=13.7$ and 7.7 Hz, 1H), 2.80 (dd, $J=13.7$ and 6.9 Hz, 1H), 3.13–3.24 (m, 1H), 3.41 (dd, $J=8$ and 5.2 Hz, 1H), 3.63 (AB syst, $J=13.2$, 2H), 3.87 (dd, $J=8.0$ and 6.7 Hz, 1H), 4.23 (d, $J=5.7$ Hz, 1H), 4.34 (d, $J=5.7$ Hz, 1H), 7.04–7.21 (m, 10H); ^{13}C NMR 40.0, 59.0 (CH_2), 64.9 (CH), 69.5, 86.1 (CH_2), 126.3, 127.2, 128.4, 128.5, 128.8, 129.3 (CH), 139.0, 139.1 (Cq); anal. calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.70; N, 5.50%.

3.5. (*R*)-*N*-Benzyl-*N*-cyanomethyl-phenylglycinol 11

A suspension of oxazolidine **9** (1.37 g, 5.7 mmol), citric acid (1.1 g, 5.7 mmol) and potassium cyanide (1.37 g, 21 mmol) in ethanol (50 mL) was heated under reflux for 1 h. To this mixture was then added a saturated aqueous solution of $NaHCO_3$ (30 mL), and the ethanol was distilled off. Usual workup followed by flash chromatography (E/PE: 1/1) gave **11** as a white solid (1.46 g, 96%). Mp 76°C; R_f 0.58 (E/PE: 6/4); $[\alpha]_D^{20}$ −54 (*c* 1.5, $CHCl_3$); IR 3513, 2228, 1060, 927 cm^{-1}; ^1H NMR 1.96 (bs, 1H), 3.61 (AB system, $J=17.6$ Hz, 2H), 3.84 (AB system, $J=13.4$ Hz, 2H), 3.97 (dd, $J=10.4$ and 5.1 Hz, 1H), 4.10 (bt, $J=5.1$ Hz, 2H), 7.37–7.60 (m, 10H); ^{13}C NMR 39.1, 55.7, 64.2 (CH_2), 68.1 (CH), 115.4 (Cq), 128.0, 128.4, 128.6, 128.9, 129.0, 129.2 (CH), 137.1, 138.4 (Cq); anal. calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.82; H, 6.74; N, 10.30%.

3.6. (*S*)-*N*-Benzyl-*N*-cyanomethyl-phenylalaninol 12

Following the procedure described for the preparation of **11**, compound **12** was obtained as a clear oil after flash chromatography (E/PE: 6/4). Yield 78%; R_f 0.66 (E/PE: 7/3); $[\alpha]_D^{20}$ −14 (*c* 2.8, $CHCl_3$); IR 3454, 3027, 2930, 2230, 1600 cm^{-1}; ^1H NMR 2.35 (s, 1H), 2.55 (dd, $J=14.5$ and 10.7 Hz, 1H), 3.05–3.14 (m, 2H), 3.43 (s, 2H), 3.47–3.50 (m, 2H), 3.74 (AB system, $J=13.4$ Hz, 2H), 7.10–7.26 (m, 10H); ^{13}C NMR 33.5, 38.5, 54.0, 60.9 (CH_2), 65.9 (CH), 117.0 (Cq), 126.6, 126.9, 128.0, 128.7, 128.9, 129.0, 129.1 (CH), 136.9, 138.4 (Cq); anal. calcd for $C_{18}H_{20}N_2O$: C, 72.35; H, 6.41; N, 9.38. Found: C, 72.41; H, 6.45; N, 9.30%.

3.7. (*S*)-*N*-Benzyl-*N*-cyanomethyl-1-benzyl-2-chloro-ethylamine 13

To a solution of **12** (5.2 g, 0.018 mol) in dichloromethane (130 mL) was added dropwise thionyl chloride (2.7 mL, 0.037 mol) at 0°C. The mixture was then heated under reflux for 4 h and hydrolyzed by addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). Usual workup (dichloromethane) followed by flash chromatography (AcOEt/PE: 8/92) gave **13** as white crystals (5.4 g, 97%). Mp 44°C; R_f 0.77 (E/PE: 3/7); $[\alpha]_D^{20}$ −14 (*c* 1.8, $CHCl_3$); IR 2855, 1456 cm^{-1}; ^1H NMR 2.87 (dd, $J=13.7$ and 8.7 Hz, 1H), 3.05 (dd, $J=13.7$ and 5.8 Hz, 1H), 3.25 (ddt, $J=8.7$, 5.8 and 5.5 Hz, 1H), 3.50 (d, $J=3.2$ Hz, 2H), 3.59 (d, $J=5.5$ Hz, 2H), 3.88 (s, 2H), 7.12–7.28 (m, 10H); ^{13}C NMR 35.3, 38.6, 44.5, 54.5 (CH_2), 65.3 (CH), 117.0 (Cq), 126.9, 128.0, 128.9, 129.3 (CH), 137.1, 138.2 (Cq); anal. calcd for $C_{18}H_{19}ClN_2$: C, 72.35; H, 6.41; N, 9.38. Found: C, 72.41; H, 6.45; N, 9.36%.

3.8. (*R*)-*N*-Benzyl-*N*-cyanomethyl-2-chloro-2-phenyl-ethylamine 14

A solution of **11** (2.29 g, 8.63 mmol) and thionyl chloride (1.25 mL, 17.2 mmol) in dichloromethane (60 mL) was heated under reflux for 2.5 h and hydrolyzed by addition of a saturated aqueous solution of $NaHCO_3$ (30 mL). Usual workup (dichloromethane) followed by flash chromatography (E/PE: 1/1) gave **14** as white crystals (2.55 g, quant.). Mp 90°C; R_f 0.66 (E/PE: 1/1); IR 3047, 2230 cm^{-1}; $[\alpha]_D^{20}$ +83 (*c* 0.7, $CHCl_3$); ^1H NMR 3.29 (dd, $J=14.0$ and 6.7 Hz, 1H); 3.38 (dd, $J=14.0$ and 7.5 Hz, 1H), 3.50 (d, $J=17.6$ Hz, 1H), 3.61 (d, $J=17.6$, 1H), 3.89 (AB system, $J=13.7$ Hz, 2H), 5.04 (dd, $J=7.5$ and 6.7 Hz, 1H) 7.39–7.53 (m, 10H); ^{13}C NMR 42.2, 58.9 (CH_2), 60.7 (CH), 61.9 (CH_2), 115.1 (Cq), 127.4, 128.1, 128.8, 128.9, 129.1 (CH), 136.7, 139.5 (Cq); anal. calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.64; H, 6.09; N, 9.74%.

3.9. (1*R*,2*S*)-*N*-Cyanomethyl-*N*-methyl-1-phenyl-2-chloro-ethylamine 15

To a solution of **5** (4.8 g, 24.0 mmol) in dichloromethane (200 mL) was added thionyl chloride (3.5 mL, 48.2 mmol). The mixture was heated under reflux for 2 h and treated with saturated aqueous $NaHCO_3$ until neutral. Usual workup (dichloromethane) then gave **15** as white crystals (5.2 g, 97%) that were washed with a small portion of pentane. Mp 64°C; R_f 0.56 (E/PE: 1/1); $[\alpha]_D^{20}$ −85 (*c* 1.5, $CHCl_3$); IR 2226, 1331, 1209, 1162, 1122, 717 cm^{-1}; ^1H NMR 1.16 (d, $J=6.4$ Hz, 3H), 2.33 (s, 3H), 3.05 (quint., $J=6.4$ Hz, 1H), 3.41 (s, 2H), 4.88 (d, $J=6.4$ Hz, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR 11.7, 38.3 (CH_3), 43.5 (CH_2), 64.0, 65.4 (CH), 116.2 (Cq), 127.5, 128.3, 128.5 (CH), 139.6 (Cq); anal. calcd for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.77; H, 7.07; N, 12.35%.

3.10. (1*S*,2*S*)-*N*-Cyanomethyl-*N*-methyl-1-phenyl-2-chloro-ethylamine 16

To a solution of **6** (1.0 g, 4.9 mmol) in dichloromethane (40 mL) was added thionyl chloride (0.575 mL, 7.9 mmol). The mixture was stirred for 1 h at rt and treated with saturated aqueous $NaHCO_3$ until neutral. Usual workup (dichloromethane) followed by flash chromatography gave **16** as white crystals (1.0 g, 92%). Mp 41°C; R_f 0.84 (E/PE: 7/3); $[\alpha]_D^{20}$ +130 (*c* 1.7, $CHCl_3$); IR 2228, 1332, 1209, 1163, 1122, 717 cm^{-1}; ^1H NMR 0.99 (d, $J=7.0$ Hz, 3H), 2.48 (s, 3H), 3.15–3.35 (m, 1H), 3.62 (s, 2H), 4.74 (d, $J=8.2$ Hz, 1H), 7.33–7.76 (m, 5H); ^{13}C NMR 12.2, 36.7 (CH_3), 43.8 (CH_2), 64.5, 66.0 (CH), 117.0 (Cq), 127.9, 128.7, 128.8 (CH), 139.3 (Cq); anal. calcd for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.617; H, 6.91; N, 12.56%.

3.11. (2*RS*,4*S*)-1,4-Dibenzyl-azetidin-2-carbonitrile 18 and 19

To a solution of **13** (500 mg, 1.67 mmol) in THF (30 mL) was added dropwise at −90°C a THF solution of lithium bis-trimethylsilylamide (1 M, 2 mL, 2 mmol). The mixture was then gradually (3 h) allowed to reach 0°C and hydrolyzed by addition of a saturated aqueous solution of NH_4Cl. Usual workup followed by flash chromatography (AcOEt/PE: 8/92) gave azetidines **18** and **19** as a 1/1 mixture of isomers (400 mg, 91%). Faster eluting isomer: R_f 0.75 (AcOEt/PE: 8/92); ^1H NMR 2.17–2.24 (m, 2H), 2.70 (d, $J=6.5$ Hz, 2H), 3.57

(s, 2H), 3.70–3.80 (m, 1H), 3.99 (ddd, $J=6.5$, 3.2 and 0.7 Hz, 1H), 7.06–7.28 (m, 10H); ^{13}C NMR 29.1, 42.2 (CH_2), 49.6 (CH), 57.0 (CH_2), 65.9 (CH), 118.1 (Cq), 126.7, 127.6, 128.2, 128.7, 128.9, 129.2 (CH), 136.9, 137.4 (Cq). Slower eluting isomer: R_f: 0.67 (AcOEt/PE: 8/92); ^{1}H NMR 2.25–2.35 (m, 2H), 2.66 (d, $J=6.5$ Hz, 2H), 3.23–3.35 (m, 1H), 3.38–3.55 (m, 3H), 7.06–7.28 (m, 10H); ^{13}C NMR 29.2, 42.8 (CH_2), 47.9 (CH), 61.1 (CH_2), 64.8 (CH), 119.6 (Cq), 126.7, 127.9, 128.6, 128.2, 129.2, 129.4 (CH), 136.7, 137.5 (Cq); IR (mixture of isomers): 3085, 3062, 3028, 2960, 2239, 1495, 1453 cm^{-1}; anal. calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68. Found: C, 82.14; H, 7.01; N, 10.79%.

3.12. (2*S*,3*R*)-1-Benzyl-3-phenyl-azetidine-2-carbonitrile 20 and (2*R*,3*R*)-1-benzyl-3-phenyl-azetidine-2-carbonitrile 21

To a solution of **14** (2.55 g, 8.96 mmol) in dry THF (170 mL) was added dropwise at −90°C a solution of lithium bis-trimethylsilylamide in THF (1 M solution, 10.7 mL, 10.7 mmol). The mixture was gradually (1.5 h) warmed at −10°C and hydrolyzed by addition of an aqueous saturated solution of NH_4Cl (30 mL). Usual workup followed by flash chromatography (E/PE: 15/85) first gave **21** as a clear oil (1.40 g, 63%), followed by **20** as colorless crystals (700 mg, 31%). Compound **20**: Mp 101–102°C; R_f 0.57 (E/PE: 4/6); IR 2854, 2240, 1455 cm^{-1}; $[\alpha]_D^{20}$ −37 (*c* 0.5, $CHCl_3$); GC (OV 17, 200°C): t_R 7.31 min; ^{1}H NMR 3.53–3.61 (m, 2H), 3.71–3.99 (m, 3H), 4.43 (d, $J=7.7$ Hz, 1H), 7.17–7.36 (m, 10H); ^{13}C NMR 39.0 (CH), 58.0 (CH_2), 58.6 (CH), 60.1 (CH_2), 116.7 (Cq), 127.7, 128.0, 128.6, 128.8, 128.9 (CH), 136.3, 137.4 (Cq); anal. calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.01; H, 6.42; N, 11.18. Compound **21**: R_f 0.71 (E/PE: 4/6); IR 3030, 2842, 2238, 1454 cm^{-1}; $[\alpha]_D^{20}$ −42 (*c* 0.6, $CHCl_3$); GC (OV 17, 200°C): t_R 6.62 min; ^{1}H NMR 3.24 (dd, $J=7.7$ and 6.7 Hz, 1H), 3.72 (d, $J=12.6$ Hz, 1H), 3.74–3.87 (m, 2H), 3.84 (d, $J=12.6$ Hz, 1H), 3.96 (quint., $J=7.4$ Hz, 1H), 7.23–7.38 (m, 10H); ^{13}C NMR 41.3, 58.3 (CH), 58.4, 61.4 (CH_2), 118.7 (Cq), 126.9, 127.8, 127.9, 128.7, 128.9, 129.0 (CH), 135.9, 138.5 (Cq); anal. calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.26; H, 6.45; N, 11.18%.

3.13. (2*R*,3*S*,4*S*)-1,4-Dimethyl-3-phenyl-azetidine-2-carbonitrile 22 and (2*S*,3*S*,4*S*)-1,4-dimethyl-3-phenyl-azetidine-2-carbonitrile 23

To a solution of **15** (5.4 g, 24.2 mmol) in dry THF (400 mL) at −90°C was added dropwise a solution (1 M in THF, 30 mL, 30 mmol) of LiHMDS. The reaction mixture was gradually (1 h) warmed to −30°C and quenched by addition of a saturated aqueous solution of NH_4Cl. Usual workup, followed by flash chromatography (AcOEt/EP: 15/85 then 30/70) gave **22** (faster eluting isomer: 1 g, 22%), followed by **23** (slower eluting isomer, 2.51 g, 56%). Overall yield 78%. Compound **22**: Mp 24°C; R_f 0.63 (E/PE: 7/3); $[\alpha]_D^{20}$ +42 (*c* 1.0, $CHCl_3$); IR 3027, 2218, 1270, 1178, 1127, 733, 702 cm^{-1}; ^{1}H NMR 1.25 (d, $J=6.0$ Hz, 3H), 2.39 (s, 3H), 3.09 (dq, $J=7.5$ and 6.0 Hz, 1H), 3.42 (t, $J=7.8$ Hz, 1H), 3.48 (d, $J=8.0$, 1H), 7.12–7.32 (m, 5H); ^{13}C NMR 20.3, 42.6 (CH_3), 49.8, 57.5, 68.6 (CH), 119.1 (Cq), 127.0, 127.8, 128.9 (CH), 137.4 (Cq); anal. calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.13; H, 7.35; N, 15.19. Compound **23**: Mp 42°C; R_f 0.31 (E/PE: 7/3); $[\alpha]_D^{20}$ −95 (*c* 1.4, $CHCl_3$); IR 3020, 2215, 1265, 1127, 730, 700 cm^{-1}; ^{1}H NMR 1.22 (d, $J=5.5$ Hz, 3H), 2.38 (s, 3H), 3.49–3.62 (m, 2H), 4.55 (d, $J=6.7$ Hz, 1H), 7.17–7.33 (m, 5H); ^{13}C NMR 19.7, 38.3 (CH_3), 47.1, 59.2, 66.8 (CH), 115.9 (Cq), 127.9, 128.0, 128.7 (CH), 135.6 (Cq); anal. calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.33; H, 7.60; N, 15.09%.

3.14. (2*S*,3*R*,4*S*)-1,4-Dimethyl-3-phenyl-azetidine-2-carbonitrile 24 and (2*R*,3*R*,4*S*)-1,4-dimethyl-3-phenyl-azetidine-2-carbonitrile 25

Following the procedure reported above for the preparation of **22** and **23** and starting with **16** (1.0 g, 4.5 mmol), a crude mixture was obtained. Flash chromatography (AcOEt/EP: 8/92 then 15/85) gave **25** (faster eluting stereoisomer, 470 mg, 56%), followed by **24** (slower eluting stereoisomer, 125 mg, 15%). Overall yield: 71%. Compound **24**: Mp 93–95°C; R_f 0.63 (E/PE: 1/1); $[\alpha]_D^{20}$ −148 (*c* 1.0, $CHCl_3$); IR 2238, 1236, 1291, 1249, 1219, 1183 cm^{-1}; ^{1}H NMR 0.86 (d, $J=6.2$ Hz, 3H), 2.43 (s, 3H), 3.45 (quint., $J=6.6$ Hz, 1H), 3.71 (t, $J=7.7$ Hz, 1H), 4.04 (d, $J=7.5$ Hz, 1H), 7.26–7.43 (m, 3H), 7.53–7.56 (m, 2H); ^{13}C NMR 15.3, 42.5 (CH_3), 45.1, 56.9, 65.5 (CH), 117.6 (Cq), 127.9, 128.40, 130.0 (CH), 134.7 (Cq). Compound **25**: Oil, R_f 0.79 (E/PE: 1/1); $[\alpha]_D^{20}$ −74 (*c* 2.7, $CHCl_3$); IR 2223, 1260, 1229, 1203, 743, 697 cm^{-1}; ^{1}H NMR 0.79 (d, $J=6.2$ Hz, 3H), 2.44 (s, 3H), 3.73 (dd, $J=7.9$ and 2.6 Hz, 1H), 3.77–3.89 (m, 1H), 4.33 (dd, $J=2.6$ and 0.9 Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR 15.2, 38.3 (CH_3), 45.8, 56.9, 65.1 (CH), 117.5 (Cq), 127.6, 128.5, 128.6 (CH), 136.4 (Cq); anal. calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.49; H, 7.79; N, 15.13%.

3.15. (2*R*,3*R*)-2-Acetyl-1-benzyl-3-phenyl-azetidine 26

To a solution of **21** (300 mg, 1.21 mmol) in THF (15 mL) was added dropwise a solution of methylmagnesium bromide (3 M in ether, 1.6 mL, 4.8 mmol). After stirring at rt for 24 h, the mixture was hydrolyzed by addition of saturated aqueous NH_4Cl. Usual workup, followed by flash chromatography (AcOEt/EP: 2/8) gave **26** as a clear oil (241 mg, 75%). R_f 0.52 (E/PE: 1/1); $[\alpha]_D^{20}$ −10 (*c* 1.5, $CHCl_3$); IR 3027, 2832, 1701, 1490, 1357, 1234, 697 cm^{-1}; ^{1}H NMR 1.94 (s, 3H), 3.01 (dd, $J=8.0$ and 6.0 Hz, 1H), 3.53–3.73 (m, 5H), 7.12–7.24 (m, 10H); ^{13}C NMR 26.1 (CH_3), 40.2 (CH), 57.6, 62.8 (CH_2), 78.3 (CH), 127.0, 127.2, 127.5, 128.5, 128.6, 129.1 (CH), 137.0, 140.1, 209.1 (Cq); anal. calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.33; H, 7.32; N, 5.40%.

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