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Ring Expansion of 2-(α-Hydroxyalkyl)azetidines: A Synthetic Route to Functionalized Pyrrolidines

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A series of 2-(α-hydroxyalkyl)azetidines synthesized from enantiomerically pure β-amino alcohols and presenting various patterns both on the four-membered ring and on the adjacent hydroxy group were treated with either thionyl chloride or methanesulfonyl chloride in the presence of triethylamine. The thus-prepared 2-(α-chloro- or α-methanesulfonyloxyalkyl)azetidines were shown to rearrange stereospecifically into 3-(chloro- or methanesulfonyloxy)pyrrolidines. When this rearrangement is conducted in the presence of an added nucleophile (NaN_3, KCN, KOH, or NaOAc), the produced pyrrolidine incorporates the added nucleophile at C-3 stereospecifically. The relative configuration of the substituents in the formed pyrrolidines is consistent with a mechanism involving the formation of an intermediate bicyclic aziridinium ion, which is opened regioselectively at the bridgehead carbon atom.

Introduction

Nitrogen heterocycles, particularly pyrrolidines and piperidines, are ubiquitous in nature, and the search for new synthetic methodologies towards such heterocycles with the aim to control the relative and absolute stereochemistry of the stereocenters on the ring represents much efforts from the synthetic community.[1] Among the numerous approaches described so far, the ring expansion of functionalized pyrrolidines of general structure **1** and presenting a leaving group on the α-carbon atom of the C-2 side chain has been known for decades[2] to produce 3-substituted piperidines **2** (Figure 1), and this reaction has been used as a key step in a number of syntheses.[3] In contrast, the similar rearrangement involving azetidine **3** as starting material, leading to a pyrrolidine **4**, has been reported only recently by Outurquin,[4] us,[5] and later on by De Kimpe.[6] We report herein a full study of this rearrangement and its extension to the synthesis of pyrrolidines bearing various functional groups at C-3.

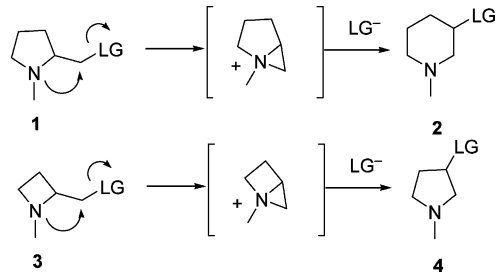

Figure 1. Ring expansion of functionalized pyrrolidines and azetidines.

Results

Synthesis of 2-(α-Hydroxyalkyl)azetidines

The 2-(α-hydroxyalkyl)azetidines required to conduct this study were prepared from 2-cyanoazetidines[7] as described previously.[8] Thus, primary alcohols **5**–**10** were prepared by $LiAlH_4$ reduction of the ethyl ester (prepared by treatment of the nitrile with H_2SO_4/EtOH), whereas secondary alcohols **11**–**13** were prepared by diastereoselective reduction of the corresponding ketone ($NaBH_4/ZnBr_2$). Finally, tertiary alcohols **14** and **15** were prepared by reaction of the corresponding ester with either methylmagnesium bromide or phenylmagnesium bromide. The structures of these hydroxylated azetidines are shown in Figure 2.

Having in hand a reasonable scope of hydroxylated azetidines with various substituent patterns, we next turned our attention towards the activation of the hydroxy moiety as a leaving group.

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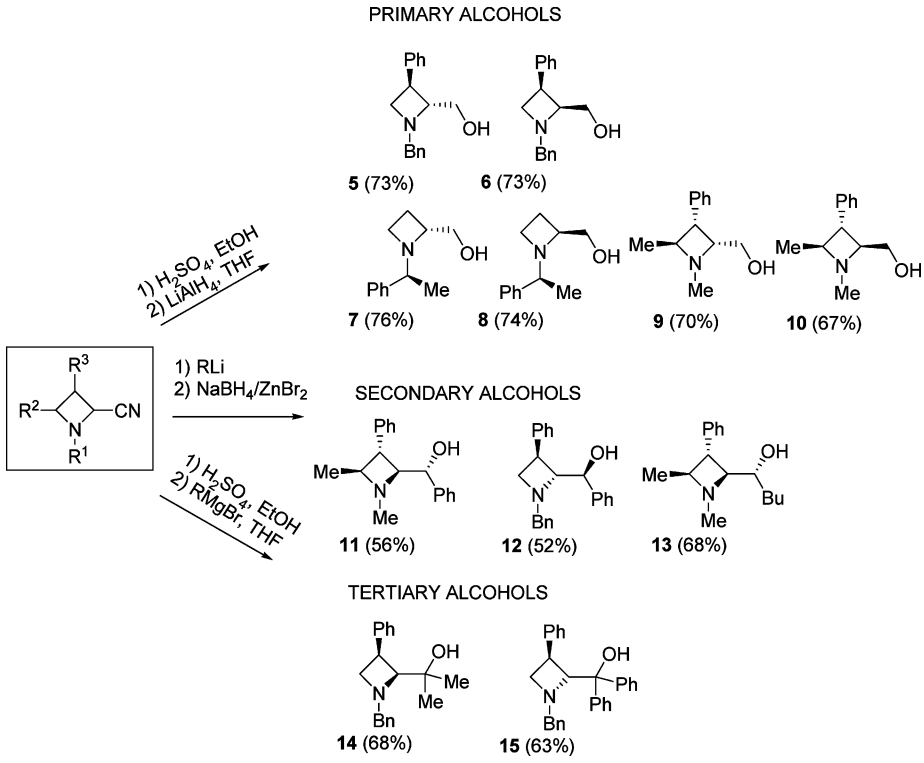


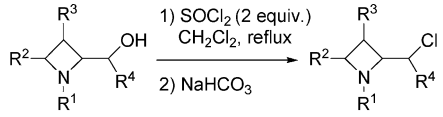
Figure 2. Structures of 2-(α-hydroxyalkyl)azetidines used in this study.

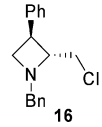
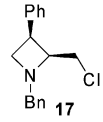
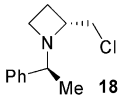
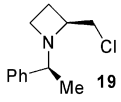
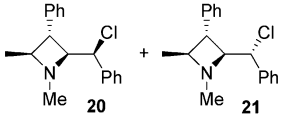
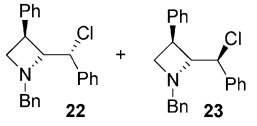
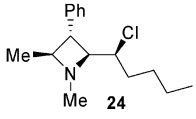
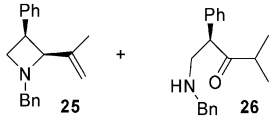
Activation of the Hydroxy Moiety

Two activation modes of the hydroxy moiety were envisioned in order to promote the ring enlargement mentioned in the introduction. First, treatment with thionyl chloride of these alcohols occurred with different outcomes, depending on the class of the hydroxy center. Thus, chlorination of primary alcohols **5**–**8** gave excellent yields of primary chlorides **16**–**19**, without any trace of rearranged product. In the case of secondary alcohols, compound **13** gave single diastereoisomer **24**, in which the absolute configuration of the chlorinated center was not unambiguously determined (Table 1, Entry 7). However, the stereochemistry of this stereocenter is not expected to result from anchimeric assistance of the α-amino moiety as a result of the absence of pyrrolidine formation. We therefore think that this compound results from clean inversion of the chlorosulfite intermediate by the chloride anion, and we have therefore attributed a *syn* relative stereochemistry to this compound. In the case of benzylic alcohols **11** and **12**, chlorination is not stereospecific, and epimeric chlorides **20**–**23** were obtained, probably through the intervention of an S_N1 pathway (Table 1, Entries 5 and 6). The relative configurations in the produced chlorides were determined on the basis of careful analysis of the rearranged pyrrolidines obtained from these chlorides (vide supra). Major *syn* isomers **20** and **22** produced in each case result from inversion of configuration, without anchimeric assistance of the α-amino moiety and, therefore, supports also the *syn* structure of **24**. Finally, tertiary alcohols behaved differently. Upon treatment of **15** with thionyl chloride, an intense purple color of the reaction medium was observed, which can be attributed to the formation of a stable diphenylcarbenium ion. Upon hydrolysis, this carbenium ion traps water and gives back the starting compound. In case of substrate **14**, the intermediate carbenium ion gives compounds **25** and **26** resulting from elimination and 1,2-hydride shift, respectively. In the last case, the resulting iminium ion then hydrolyzes into amino ketone **26**. Alternatively, **26** could be produced by the hydrolysis of an intermediate 2-methyleneazetidine resulting from proton removal at the C-2 carbon of the azetidine.[9] Structures of the obtained products are collected in Table 1.

The second mode of activation of the amino alcohols was mesylation. In this case, different outcomes were also observed, depending on the class of the alcohol. Primary alcohols **5**–**7**, **9**, and **10** were cleanly transformed into the corresponding primary mesylate upon treatment with methanesulfonyl chloride and triethylamine in THF at 0 °C. Workup gave crude mesylates that were contaminated with small amounts (5–10%) of the corresponding rearranged pyrrolidines. The rearrangement could be then completed by heating the crude mixture overnight at reflux in chloroform: 3-methanesulfonyloxypyrrolidines **27**–**31** were thus obtained in good yield and in a stereospecific manner (Table 2, Entries 1–5). Mesylation of secondary benzylic alcohols **11** and **12** directly furnished rearranged chlorides **34** and **35** in good yield if the reaction medium was heated at reflux for 1 h because of the presence of the chloride anion as an external nucleophile (Table 2, Entries 7, 8). However, when the mesylation was rapidly conducted at

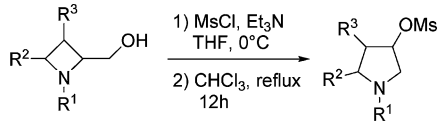
Table 1. $SOCl_2$ chlorination of hydroxylated azetidines.

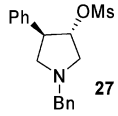
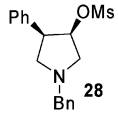
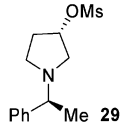
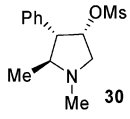
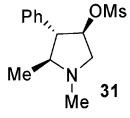
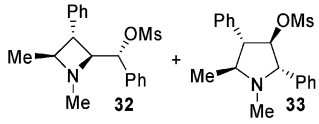
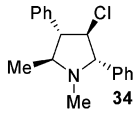
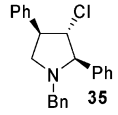
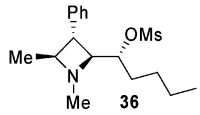


Entry	Substrate	Product(s)	Yield[a] [%]
1	**5**	 **16**	98
2	**6**	 **17**	79
3	**7**	 **18**	97
4	**8**	 **19**	88
5	**11**	 **20** + **21**	57 (**20**) 14 (**21**)
6	**12**	 **22** + **23**	66 (**22**) 17 (**23**)
7	**13**	 **24**	Quant.
8	**14**	 **25** + **26**	30 (**25**) 30 (**26**)
9	**13**	**13**	75

[a] Yield of isolated product.

Table 2. Mesylation of hydroxylated azetidines.



Entry	Substrate	Product(s)	Yield[a] [%]
1	**5**	 **27**	80
2	**6**	 **28**	79
3	**7**	 **29**	84
4	**9**	 **30**	76
5	**10**	 **31**	76
6	**11**	 **32** + **33**	96[b]
7	**11**	 **34**	77[c]
8	**12**	 **35**	65[c]
9	**13**	 **36**	96[b]

[a] Yield of isolated product. [b] Only the first step was conducted. Crude ratio of **32**/**33**, 85:15. [c] Only the first step was conducted, but the reaction mixture was heated at reflux for 1 h.

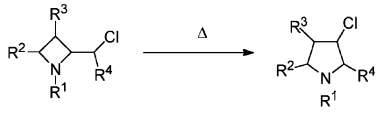
0 °C (0.5 h), a crude mixture of mesylate **32** and **33** (85:15 ratio) was obtained in good yield (Table 2, Entry 6). Finally, in the case of secondary alcohol **13**, corresponding mesylate **36** proved to be stable enough and was isolated in very good yield without a trace of rearranged product. Table 2 gathers the structures of the obtained compounds.

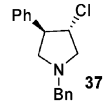
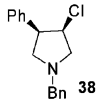
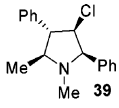
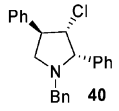
Ring Expansion of 2-(α-Chloroalkyl)azetidines

Although the 2-(α-methanesulfonyloxyalkyl)azetidines (except compound **36**) were not stable and were very prone to rearrange into 3-methanesulfonyloxypyrrolidines, the corresponding chlorides proved much more stable and required heating to promote the ring expansion. Furthermore, the ease of this rearrangement was shown to depend on the relative configuration (*syn* or *anti*) of the starting chloride and also on the class (primary or secondary) of

the chloride. Thus, primary chlorides required heating in refluxing DMF to promote the rearrangement to give **37** and **38** in fair-to-modest yields. It should be noted that an overnight reflux in chloroform left these products unchanged. The same behavior was observed with *syn* chlorides **20** and **22**: the first one, under protracted heating in refluxing DMF gave only a trace amount of the rearranged pyrrolidine together with extensive decomposition, whereas **22** gave **40** in fair yield. In contrast, *anti* secondary chlorides **21** and **23** rearranged smoothly in refluxing chloroform to afford **34** and **35** in excellent yields. These latter compounds proved to be identical to those obtained during the mesylation of *anti*-alcohols **11** and **12** (see Table 2, Entries 6 and 7). All these experiments are gathered in Table 3.

Table 3. Thermal ring expansion of 2-(α-chloroalkyl)azetidines.



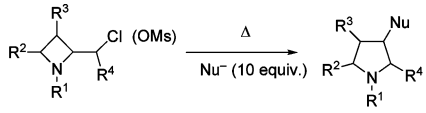
Entry	Substrate	Conditions	Product(s)	Yield[a] [%]
1	**16**	DMF reflux 12 h	 **37**	75
2	**17**	DMF reflux 12 h	 **38**	39
3	**20**	DMF reflux 24 h	 **39**	–[b]
4	**22**	DMF reflux 12 h	 **40**	65
5	**21**	$CHCl_3$ reflux 12 h	**34**	94
6	**23**	$CHCl_3$ reflux 12 h	**35**	95

[a] Yield of isolated product. [b] Only a trace amount of impure product was produced.

Ring Expansion of 2-(α-Chloro- and α-Methanesulfonyloxyalkyl)azetidines in the Presence of an Added Nucleophile

Having established that this ring expansion proceeds well and in a stereospecific manner, we turned our attention to broaden its scope by adding an external nucleophile that would be able to compete with the leaving group as the nucleophile. Four types of nucleophiles were selected (NaOH, KCN, NaOAc, and NaN_3). After some experimentation and guided by the work of De Kimpe,[6] we selected DMSO as the reaction solvent in order to solubilize a sufficient amount of added salt (10 equiv. in each case), and the rearrangements were conducted at strictly controlled temperature in order to limit the amount of formed byproducts. As a matter of fact, preliminary experiments conducted with chloride **18** in the presence of KOH demonstrated that the rearrangement occurred optimally at 50 °C to produce 3-hydroxypyrrolidine **42**. At lower temperature, only rearranged chloride **41** could be isolated, whereas higher temperatures promoted the elimination to give dehydropyrrole **43** almost exclusively (Table 4, Entries 1–4).

Table 4. Ring expansion in the presence of an added nucleophile.



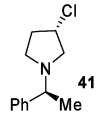
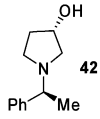
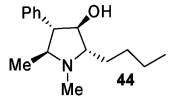
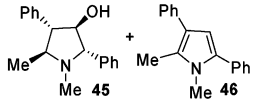
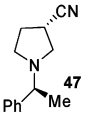
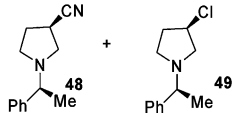
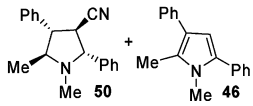
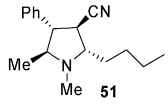
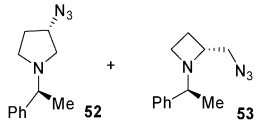
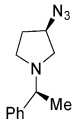
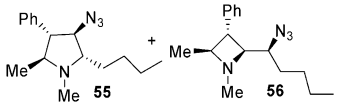
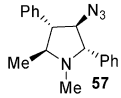
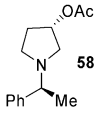
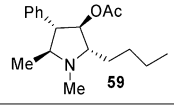
Entry	Substrate	Conditions	Product(s)	Yield[a] [%]
1	**18**	DMSO KOH r.t., 72 h	–	no reaction
2	**18**	DMSO KOH 40°C, 48 h	 **41**	39[b]
3	**18**	DMSO KOH 50°C, 48 h	 **42**	70
4	**18**	DMSO KOH 60°C, 24 h	 **43**	97
5	**24**	DMSO KOH 50°C, 48 h	Complex mixture	–
6	**36**	DMSO KOH 50°C, 48 h	 **44**	47
7	**32 + 33**	DMSO KOH 50°C, 72 h	 **45** + **46**	56 (**45**) 30 (**46**)
8	**18**	DMSO KCN 50°C, 72 h	 **47** + **41**	77 (**47**) 8 (**41**)
9	**19**	DMSO KCN 50°C, 12 h	 **48** + **49**	44 (**48**) 21 (**49**)
10	**32 + 33**	DMSO KCN 50°C, 72 h	 **50** + **46**	23 (**50**) 8 (**46**)

Table 4. *(Continued)*.

Entry	Substrate	Conditions	Product(s)	Yield[a] [%]
11	**36**	DMSO KCN 50°C, 72 h	 **51**	82
12	**18**	DMSO NaN_3 50°C, 72 h	 **52** + **53**	85 (**52**) 8(**53**)
13	**19**	DMSO NaN_3 50°C, 72 h	 **54**	87
14	**36**	DMSO NaN_3 50°C, 72 h	 **55** + **56**	26 (**55**) 16(**56**)
15	**32 + 33**	DMSO NaN_3 50°C, 72 h	 **57**	19
16	**18**	DMSO NaOAc 50°C, 72 h	 **58**	68
17	**36**	DMSO NaOAc 50°C, 72 h	 **59**	64

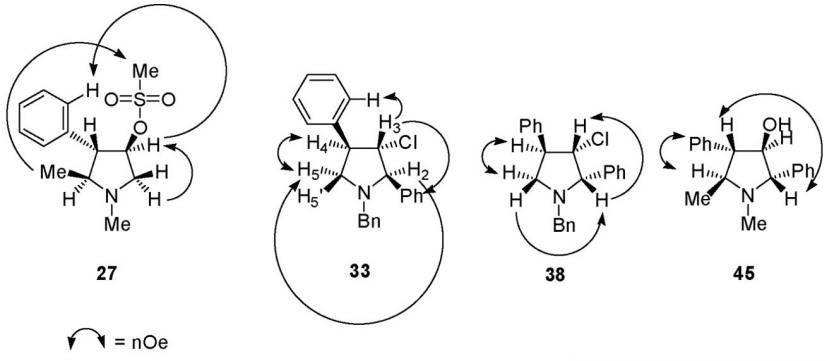
[a] Yield of isolated product. [b] Compound **43** was also isolated in 9% yield.

It can be concluded from these experiments that it is indeed possible to introduce all kinds of nucleophiles at C-3 with various yields, in a stereospecific manner. However, the yields are sometime modest and byproducts could be isolated and characterized in some cases. As a matter of fact, the success of the rearrangement in the presence of an external nucleophile is to a large extent substrate dependent, but some general trends become apparent. First, the reaction conditions (particularly the temperature), have to be strictly controlled for each substrate, as some of them are very prone to elimination and even aromatization to the corresponding pyrrole (Table 4, Entries 4, 7, 10). Secondly, *syn* chloride **24** again proved its reluctance to rearrange, as it gave a complex mixture (Table 4, Entry 5). Finally, reactions involving the azide anion as a nucleophile did not produce any azetidine product (aside from Table 4, Entries 12 and 14). This last point will be commented in the last part of this article.

Discussion

Determination of the Relative Configurations in the Produced Pyrrolidines

The relative configuration of the substituents in the produced pyrrolidines was determined on the basis of nOe experiments conducted with pyrrolidines **27**, **33**, **40** (resulting from rearrangement of α-chloro- or α-methanesulfonyloxyazetidines), and **45** (resulting from a rearrangement in the presence of KOH). Key nOe interactions for these compounds are shown in Figure 3. Furthermore, we were able to grow suitable crystals for X-ray analysis of compound **50**, whose ORTEP structure is shown in Figure 3.[10]



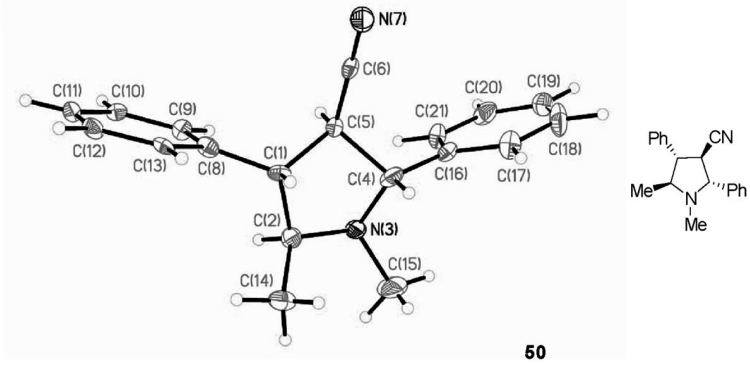
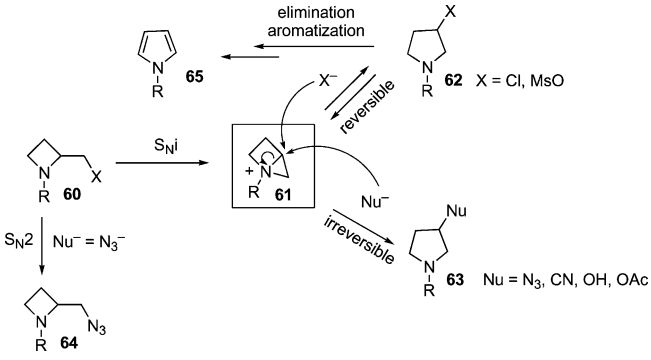


Figure 3. nOe measurements in pyrrolidines **27**, **33**, **38**, and **45**; ORTEP diagram of **50**.

Mechanistic Considerations

Considering the relative configuration of the substituents in the produced pyrrolidines, we can deduce that the stereospecificity of the rearrangement results from the production of intermediate bicyclic aziridinium ion **61**, which opens with high regioselectivity at the bridgehead carbon atom.[11] Taking into account the structure of the byproducts produced in some cases during the rearrangement performed in the presence of external nucleophiles, the detailed mechanism depicted in Scheme 1 can be proposed. The produced bicyclic intermediate **61** is opened by the leaving group X^- (chloride anion or methanesulfonate anion) at the bridgehead carbon atom to give 3-chloro- or 3-methanesulfonyloxypyrrolidine **62**. This is a *reversible process*, as this compound, produced as a byproduct in case of reactions conducted in the presence of an external nucleophile when the reaction time is too short or when the temperature is not high enough (Table 4 Entries 2, 8, 9; compounds **41** and **49**) is totally converted into the expected 3-hydroxy- or 3-cyanopyrrolidine in case of protracted reaction times or harsher conditions. In contrast, opening of **61** by the added nucleophile (HO^-, NC^-, AcO^-, or N_3^-) is expected to be an *irreversible process* and drives the equilibrium to **63**. The high regioselectivity observed in this reaction (i.e., opening of the intermediate at the bridgehead carbon atom under kinetic control) is reflected by the exclusive obtention of ring-expanded pyrrolidines by nucleophilic opening with HO^-, NC^-, or AcO^-. It should be noted that the opening of the homologous bicyclic intermediate shown in Figure 1 and leading to a piperidine has been reported to be much less regioselective in some cases under kinetic control.[12] In the case of N_3^-, minor amounts of α-azidoalkylazetidines **53** and **56** were, however, produced (Table 4, Entries 12 and 14). We think that these products arise from direct nucleophilic opening in starting azetidines **18** and **36**, rather than a nonregioselective opening of **61**. This assumption is guided by two points. First, the high nucleophilicity of the azide anion accounts for a possible competition between the formation of **64** (S_N2 reaction) and **61** (S_Ni reaction). Second, the absence of any azetidines in the case of other nucleophiles supports the high regioselectivity of the opening of **61** as a general rule. For these reasons, we have attributed a *syn* relative configuration to **56**, resulting from an S_N2 reaction.



Scheme 1. Proposed mechanism for the rearrangement.

Finally, the fact that *syn* chlorides or mesylates are more difficult to rearrange relative to their *anti* isomers can be explained by the examination of the corresponding azetidinium intermediates. These two intermediates, resulting from the S_Ni reaction involving *syn*-**22** and *anti*-**23** are depicted in Figure 4. In the bicyclic ammonium ion produced from *syn*-**22**, the phenyl group is placed in an *endo* position, which results in severe steric interaction. Therefore, formation of this intermediate can be expected to require more energy than the *exo* diastereoisomer. As a result, if the production of this strained intermediate is the rate-limiting step, then the reduced reactivity of *syn*-**22** relative to that of *anti*-**23** is easy to understand.

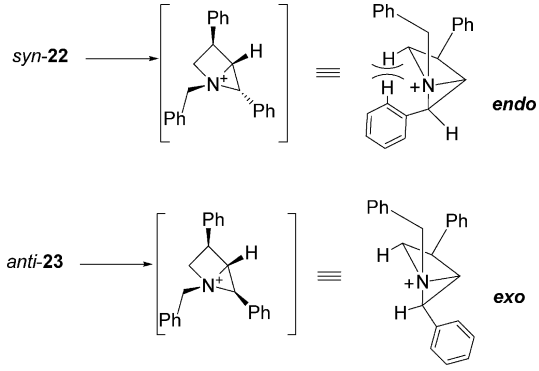


Figure 4. *syn*-Chlorides or mesylates produced highly strained *endo* bicyclic ammonium ions.

Conclusions

We showed that the recently disclosed rearrangement of 2-(α-chloro- or α-methanesulfonyloxyalkyl)azetidines into the corresponding 3-chloro- or 3-methanesulfonyloxypyrrolidines could be extended to the incorporation of an additional nucleophile to the synthesis of an array of pyrrolidines bearing various moieties at C-3. The stereospecificity of the mechanism was confirmed in all cases, and this rearrangement in the presence of an external nucleophile was studied for the first time with substrates involving primary and secondary chlorides (or mesylates). A very high regioselectivity of the nucleophilic opening of the azetidinium intermediate was observed in each case under kinetic control, which contrasts with the low regioselectivity observed in some cases for the homologous system leading to piperidines. Application of this new synthetic methodology to the synthesis of natural pyrrolidinic compounds is under study in our group.

Experimental Section

General Comments: ^1H and ^{13}C spectra were recorded with a Bruker Avance 300 spectrometer; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All the reactions were carried out under an atmosphere of argon. Column chromatography was performed on

silica gel 230–400 mesh by using various mixtures of diethyl ether (Et_2O), ethyl acetate (AcOEt) petroleum ether (PE), and cyclohexane (CyH). TLCs 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. The mention of a "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic layers over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Isomeric ratios were determined by NMR spectroscopic analysis of crude reaction mixtures before purification. Mass spectra were recorded with a Hewlett–Packard MS Engin HP5989B equipped with an ESI source Analytica Branford. Elementary analyses were performed by the Service de Microanalyses de Gif sur Yvette (France). HRMS analyses were performed by the Service d'analyses du CNRS (Vernaison, France).

General Procedure for the Preparation of 2-(α-Chloroalkyl)azetidines 16–24: To a solution of 2-hydroxyalkylazetidine (1 mmol) in DCM (5 mL) was added thionyl chloride (0.145 mL, 2 mmol) dropwise at room temperature. The reaction mixture was heated at reflux for 1.5 h and then hydrolyzed at 0 °C by dropwise addition of an aqueous saturated solution of $NaHCO_3$ until neutrality of the aqueous layer. After addition of water, usual workup gave crude chlorinated azetidines that were further purified by flash chromatography (see Table 1).

(2*S*,3*R*)-1-Benzyl-2-chloromethyl-3-phenylazetidine (16): Purified by flash chromatography (Et_2O/CyH, 10:90 then 15:85). R_f = 0.57 (Et_2O/PE, 7:3). Yield: 265 mg (98%); oil. $[\alpha]_D^{25}$ = +96 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 10 H, Ph), 3.96 (d, *J* = 12.5 Hz, 1 H, C*H*HCl), 3.79 (t, *J* = 6.9 Hz, 1 H, 3-H), 3.74 (d, *J* = 12.5 Hz, 1 H, CH*H*Cl), 3.63–3.48 (m, 4 H, 2-H, 4-H, NCH_2Ph), 3.08 (dd, *J* = 6.9 and 8.5 Hz, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 137.8 (C*ipso* Ph), 129.1–126.9 (CH Ph), 72.9 (C-2), 62.8 (C-5), 58.0 (C-4), 47.5 (*C*H_2Cl), 41.4 (C-3) ppm. MS (ESI+): *m*/*z* = 294.1 $[M + Na]^+$, 272.3 $[M + H]^+$.

(2*R*,3*R*)-1-Benzyl-2-chloromethyl-3-phenylazetidine (17): Purified by flash chromatography (Et_2O/CyH, 15:85). R_f = 0.81 (Et_2O/PE, 7:3). Yield: 214 mg (79%); oil. $[\alpha]_D^{25}$ = +16 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.31 (m, 10 H, Ph), 4.04 (A part of AB syst., *J* = 13.1 Hz, 1 H, C*H*HPh), 3.81 (td, *J* = 5.9 and 7.9 Hz, 1 H, 3-H), 3.70 (td, *J* = 2.3 and 7.5 Hz, 1 H, 2-H), 3.69 (B part of AB syst., *J* = 13.1 Hz, 1 H, CH*H*Ph), 3.58 (dd, *J* = 2.3 and 7.6 Hz, 1 H, C*H*HCl), 3.36 (t, *J* = 7.6 Hz, 1 H, CH*H*Cl), 3.18–3.06 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 138.3 (C*ipso* Ph), 129.1–127.0 (CH Ph), 69.3 (C-2), 62.5 (C-5), 57.0 (C-4), 43.7 (*C*H_2Cl), 39.1 (C-3) ppm. MS (ESI+): *m*/*z* = 294.1 $[M + Na]^+$, 272.1 $[M + H]^+$. $C_{17}H_{18}ClN$ (282.79): calcd. C 75.13, H 6.68, N 5.15; found C 74.97, H 6.77, N 5.07.

(2*R*)-2-(Chloromethyl)-1-[(1*S*)-1-phenylethyl]azetidine (18): Purified by flash chromatography (Et_2O/PE, 20:80). R_f = 0.30 (Et_2O/PE, 2:8). Yield: 203 mg (97%); white solid. M.p. 42 °C. $[\alpha]_D^{25}$ = +91.3 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.25 (m, 5 H, Ph), 3.75 (dd, *J* = 3.9 and 10.4 Hz, 1 H, C*H*HCl), 3.65–3.45 (m, 3 H, CH*H*Cl, C*H*Me, 2-H), 3.12 (td, *J* = 2.5 and 8.2 Hz, 1 H, 4-H), 2.75 (q, *J* = 8.6 Hz, 1 H, 4′-H), 2.26–2.16 (m, 1 H, 3-H), 2.01–1.89 (m, 1 H, 3′-H), 1.29 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4 (C*ipso* Ph), 128.4, 127.3, 127.2 (CH-Ph), 67.1 (C_2), 64.8 (CH), 49.2 (CH_2), 48.8 (C-4), 22.1 (CH_3), 21.9 (CH_2) ppm. MS (ESI+): *m*/*z* = 232.2, 210.2 $[M + H]^+$, 174.2, 105.0. HRMS: calcd. for $C_{12}H_{17}NCl$ $[M + H]^+$ 210.1050; found 210.1045.

(2*S*)-2-(Chloromethyl)-1-[(1*S*)-1-phenylethyl]azetidine (19): Purified by flash chromatography (Et_2O/PE, 40:60). R_f = 0.60 (Et_2O/PE, 4:6). Yield: 184 mg (88%); oil. $[\alpha]_D^{20}$ = 46.2 (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.15 (m, 5 H, Ph), 3.46–3.40 (m, 1 H, C*H*HCl), 3.26–3.13 (m, 2 H, C*H*Me, 2-H), 2.87–2.79 (m, 2 H, CH*H*Cl, 4-H), 2.49 (dd, *J* = 3.6 and 10.6 Hz, 1 H, 4′-H), 2.09–1.83 (m, 2 H, 3-H), 1.16 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5 (C*ipso* Ph), 128.5, 127.8, 127.7 (CH-Ph), 68.2 (C_2), 65.5 (CH), 50.2 (CH_2), 47.5 (C-4), 21.8 (CH_3), 20.3 (CH_2) ppm. MS (ESI+): *m*/*z* = 210.2 $[M + H]^+$, 192.3, 105.0. HRMS: calcd. for $C_{12}H_{17}NCl$ $[M + H]^+$ 210.1050; found 210.1055.

(2*S*,3*S*,4*S*,7*S*)-2-(Chlorophenylmethyl)-1,4-dimethyl-3-phenylazetidine (20): Purified by flash chromatography (Et_2O/PE, 10:90 then 20:80). R_f = 0.46 (Et_2O/PE, 1:1). Yield: 162 mg (57%); oil. $[\alpha]_D^{25}$ = +66 (*c* = 1.1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.22 (m, 2 H, Ph), 7.17–7.14 (m, 3 H, Ph), 7.13–7.05 (m, 3 H, Ph), 6.77–6.75 (m, 2 H, Ph), 4.97 (d, *J* = 8.9 Hz, 1 H, C*H*Cl), 3.40 (t, *J* = 8.5 Hz, 1 H, 3-H), 2.96 (m, 1 H, 4-H), 2.73 (t, *J* = 8.2 Hz, 1 H, 2-H), 2.65 (s, 3 H, 5-H), 1.27 (d, *J* = 5.7 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1, 137.7 (C*ipso* Ph), 128.6, 128.4, 128.1, 127.9, 127.5, 126.4 (CH Ph), 77.1 (*C*HCl), 68.4 (C-2), 66.7 (C-4), 50.6 (C-3), 44.1 (NMe), 20.5 (C-6) ppm. MS (ESI+): *m*/*z* = 308.4 $[M + Na]^+$, 286.3 $[M + H]^+$. $C_{18}H_{20}ClN$ (285.81): calcd. C 75.64, H 7.05, N 4.90; found C 75.58, H 6.98, N 4.95.

(2*S*,3*S*,4*S*,7*R*)-2-(Chlorophenylmethyl)-1,4-dimethyl-3-phenylazetidine (21): Purified by flash chromatography (Et_2O/PE, 10:90 then 20:80). R_f = 0.60 (Et_2O/PE, 1:1). Yield: 40 mg (14%); oil. $[\alpha]_D^{25}$ = –69 (*c* = 0.6, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.42 (m, 3 H, Ph), 7.40–7.33 (m, 4 H, Ph), 7.30–7.23 (m, 3 H, Ph), 4.87 (d, *J* = 8.5 Hz, 1 H, C*H*Cl), 3.42 (t, *J* = 7.9 Hz, 1 H, 3-H), 3.02 (t, *J* = 7.9 Hz, 1 H, 2-H), 2.90–2.81 (m, 1 H, 4-H), 1.94 (s, 3 H, NMe), 1.22 (d, *J* = 6.2 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 139.1 (C*ipso* Ph), 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.2, 126.8 (CH Ph), 76.2 (*C*HCl), 67.5 (C-2), 66.7 (C-4), 51.8 (C-3), 42.9 (NCH_3), 20.5 (Me) ppm. MS (ESI+): *m*/*z* = 308.5 $[M + Na]^+$, 286.4 $[M + H]^+$.

(2*R*,3*R*,6*R*)-1-Benzyl-2-(chlorophenylmethyl)-3-phenylazetidine (22): Purified by flash chromatography (Et_2O/PE, 10:90 then 20:80). R_f = 0.62 (Et_2O/PE, 1:1). Yield: 229 mg (66%); oil. $[\alpha]_D^{25}$ = +60 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 7 H, Ph), 7.23–7.19 (m, 3 H, Ph), 7.09–7.06 (m, 3 H, Ph), 6.74–6.71 (m, 2 H, Ph), 5.11 (d, *J* = 8.4 Hz, 1 H, C*H*Cl), 4.43 (A part of AB syst., *J* = 12.9 Hz, 1 H, NC*H*HPh), 3.83 (t, *J* = 8.5 Hz, 1 H, 2-H), 3.70–3.62 (m, 2 H, 4-H, NCH*H*Ph), 3.30 (q, *J* = 8.1 Hz, 1 H, 3-H), 3.01 (dd, *J* = 7.0 and 8.8 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1, 138.0, 137.7 (C*ipso* Ph), 129.0, 128.5, 128.4, 128.3, 128.0, 127.9, 127.3, 127.1, 126.3 (CH Ph), 77.6 (CHCl), 68.0 (C-2), 62.7 (N*C*H_2Ph), 57.0 (C-4), 41.5 (C-3) ppm. MS (ESI+): *m*/*z* = 370.1 $[M + Na]^+$, 312.2 $[M – HCl]^+$. $C_{23}H_{22}ClN$ (347.88): calcd. C 79.41, H 6.37, N 4.03; found C 79.21, H 6.30, N 4.00.

(2*R*,3*R*,6*S*)-1-Benzyl-2-(chlorophenylmethyl)-3-phenylazetidine (23): Purified by flash chromatography (Et_2O/PE, 10:90 then 20:80). R_f = 0.59 (Et_2O/PE, 1:1). Yield: 59 mg (17%); oil. $[\alpha]_D^{25}$ = +26 (*c* = 0.9, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.61 (m, 2 H, Ph), 7.51–7.20 (m, 12 H, Ph), 7.12–7.07 (m, 1 H, Ph), 5.99 (d, *J* = 7.9 Hz, 1 H, CHCl), 3.92 (A part of AB syst., *J* = 10.5 Hz, 1 H, NC*H*HPh), 3.80–3.57 (m, 3 H, 2-H, 4-H, NCH*H*Ph), 3.50–3.40 (m, 1 H, 3-H), 2.97 (t, *J* = 9.9 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 138.9, 138.5 (C*ipso* Ph), 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.4, 127.2, 127.0, 126.9 (CH Ph), 72.0 (CHCl), 58.9 (C-2), 57.9 (N*C*H_2Ph), 52.2 (C-4), 42.7 (C-3) ppm. MS (ESI+): *m*/*z* = 348.1 $[M + H]^+$, 312.1 $[M – HCl]^+$.

(1*R*,2*S*,3*S*,4*S*)-2-(1-Chloropentyl)-1,4-dimethyl-3-phenylazetidine (24): Purified by flash chromatography (Et_2O/PE, 40:60). R_f =0.50 (Et_2O/PE, 4:6). Yield: 265 mg (quant.); oil. $[\alpha]_D^{20}$ = –41.1 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.13 (m, 5 H, Ph), 3.90 (td, *J* = 2.5 and 8.5 Hz, 1 H, C*H*Cl), 3.05 (t, *J* = 7.0 Hz, 1 H 2-H), 2.80–2.72 (m, 2 H, 3-H, 4-H), 2.50 (s, 3 H, NMe), 1.51–1.01 [m, 6 H, (CH_2)$_3$], 1.16 (d, *J* = 5.4 Hz, 3 H, Me), 0.70 (t, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8 (C*ipso* Ph), 128.6, 127.9, 126.3 (CH-Ph), 75.6 (C_2), 68.7, 67.4, 50.6 (CH), 44.2 (CH_3), 33.2, 27.9, 21.9 (CH_2), 20.2, 13.1 (CH_3) ppm. MS (ESI+): *m*/*z* = 266.3 [M + H$^+$], 230.3. HRMS: calcd. for $C_{16}H_{25}NCl$ [M + H]$^+$ 266.1676; found 266.1675.

(2*S*,3*R*)-1-Benzyl-2-isopropenyl-3-phenylazetidine (25) and (2*R*)-1-Benzylamino-4-methyl-2-phenylpentan-3-one (26): Starting with tertiary alcohol **14** and following the general procedure used for chlorination with thionyl chloride, a crude residue was obtained that was purified by flash chromatography (Et_2O/PE, gradient from 2:98 to 100:0). Title compounds were obtained by order of elution. Compound **25**: R_f = 0.81 (Et_2O/PE, 5:95). Yield: 79 mg (30%); oil. $[\alpha]_D^{25}$ = +13 (*c* = 0.9, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.27 (m, 10 H, Ph), 5.22 (s, 1 H, C=C*H*H), 4.77 (s, 1 H, C=CH*H*), 4.07 (A part of AB syst., *J* = 13.6 Hz, 1 H, NC*H*HPh), 3.99 (d, *J* = 8.1 Hz, 1 H, 2-H), 3.68 (td, *J* = 2.2 and 8.1 Hz, 1 H, 3-H), 3.39 (B part of AB syst., *J* = 13.6 Hz, 1 H, NC*H*HPh), 3.29–3.40 (m, 1 H, 4-H), 3.27 (t, *J* = 6.2 Hz, 1 H, 4′-H), 1.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 140.7, 139.0 (C*ipso* Ph, *C*=CH_2), 129.1, 128.5, 128.4, 127.7, 126.9, 126.3 (CH Ph), 111.3 (C=*C*H$_2$), 73.0 (C-2), 61.8 (C-5), 57.4 (C-4), 41.2 (C-3), 19.2 (Me) ppm. MS (ESI+): *m*/*z* = 264.5 [M + H]$^+$. Compound **26**: R_f = 0.35 (Et_2O). Yield: 84 mg (30%); oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.21 (m, 10 H, Ph), 4.10 (dd, *J* = 6.2 and 7.7 Hz, 1 H, 2-H), 3.78 (s, 2 H, NCH_2Ph), 3.26 (dd, *J* = 8.1 and 11.9 Hz, 1 H, NC*H*H), 2.82 (dd, *J* = 6.6 and 12.1 Hz, 1 H, NCH*H*), 2.69–2.60 [m, 1 H, C*H*(Me)$_2$], 1.11 (d, *J* = 7.0 Hz, 3 H, Me), 0.92 (d, *J* = 7.0 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.0 (C=O), 140.2, 137.4 (C*ipso* Ph), 129.0, 128.6, 128.5, 128.1, 127.6, 127.0 (CH Ph), 57.6 (CH_2), 54.1 (CH), 52.0 (CH_2), 40.1 (CH), 19.1, 18.2 (CH_3) ppm.

General Procedure for the Preparation of 2-(α-Methanesulfonyloxyalkyl)azetidines and Their Rearrangement Into Pyrrolidines: To a solution of 2-(α-hydroxyalkyl)azetidine (1 mmol) in THF (5 mL) was added dropwise at room temperature methanesulfonyl chloride (84 μL, 1.5 mmol) and triethylamine (0.41 mL, 4 mmol). The reaction mixture was stirred at 0 °C for 1 h and then hydrolyzed by addition of an aqueous solution of NaOH (1 M). Usual workup gave crude mesylate (contaminated with 5–10% of the rearranged pyrrolidine) that was used as such for the ensuing rearrangement.

(3*S*,4*R*)-1-Benzyl-3-methanesulfonyloxy-4-phenylpyrrolidine (27): A solution of 2-mesyloxyazetidine (332 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/CyH, 3:7 then 1:1). R_f = 0.44 (CH_2Cl_2/MeOH, 99:1). Yield: 265 mg (80%); colorless oil. $[\alpha]_D^{25}$ = –14 (*c* = 2.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 10 H, Ph), 5.09–5.15 (m, 1 H, 3-H), 3.72 (m, 2 H, NCH_2Ph), 3.59–3.47 (m, 1 H, 4-H), 3.25 (dd, *J* = 8.2 and 9.5 Hz, 1 H, 2-H), 3.14–3.03 (m, 2 H, 5-H, 5′-H), 2.84 (s, 3 H, Me), 2.61 (dd, *J* = 7.5 and 9.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7, 138.1 (C*ipso* Ph), 128.9–127.5 (CHPh), 86.8 (C-3), 60.1–59.9 (C-2, C-5, C-6), 51.1 (C-4), 38.2 (Me) ppm. MS (ESI+): *m*/*z* = 354.1 [M + Na]$^+$, 332.1 [M + H]$^+$, 236.1 [M – MsOH]$^+$.

(3*R*,4*R*)-1-Benzyl-3-methanesulfonyloxy-4-phenylpyrrolidine (28): A solution of 2-mesyloxyazetidine (332 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/CyH, 7:3). Compound **28** was obtained as a colorless solid. R_f = 0.19 (Et_2O/CyH, 7:3). Yield: 262 mg (79%). M.p. 131 °C. $[\alpha]_D^{25}$ = +378 (*c* = 0.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 10 H, Ph), 5.28 (m, 1 H, 3-H), 3.81 (m, 2 H, NCH_2Ph), 3.62 (m, 1 H, 4-H), 3.44 (dd, *J* = 5.6 and 11.8 Hz, 1 H, 2-H), 3.13 (dd, *J* = 7 and 9.5 Hz, 1 H, 5-H), 3.03 (d, *J* = 9.5 Hz, 1 H, 5′-H), 2.96 (dd, *J* = 2.3 and 11.8 Hz, 1 H, 2′-H), 2.28 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 136.8 (C*ipso* Ph), 129.5–127.3 (CHPh), 82.7 (C-3), 61.1–60.4 (C-2, C-5), 57.2 (C-6), 48.7 (C-4), 37.6 (CH_3) ppm. MS (ESI+): *m*/*z* = 354.1 [M + Na]$^+$, 332.1 [M + H]$^+$, 236.2 [M – MsOH]$^+$. $C_{18}H_{21}NO_3S$ (331.43): calcd. C 65.23, H 6.39, N 4.23; found C 66.16, H 6.33, N 3.95.

(3*S*)-3-Methanesulfonyloxy-1-[(1*S*)-1-phenylethyl]pyrrolidine (29): A solution of 2-mesyloxyazetidine (269 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/PE, 9:1). R_f = 0.32 (Et_2O/PE, 9:1). Yield: 226 mg (84%); colorless oil. $[\alpha]_D^{20}$ = +20 (*c* = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.25 (m, 5 H, Ph), 5.22–5.16 (m, 1 H, 3-H), 3.21 (q, *J* = 6.3 Hz, 1 H, C*H*Me), 2.91 (s, 3 H, Me), 2.79–2.68 (m, 2 H, 2-H), 2.59–2.44 (m, 2 H, 5-H), 2.27–2.15 (m, 1 H, 4-H), 2.02–1.92 (m, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6 (C*ipso* Ph), 128.5, 127.2, 127.1 (CH Ph), 80.4 (C-3), 58.8 (C-2), 50.5 (C-5), 38.5 (Me), 32.4 (C-4), 22.9 (Me) ppm. MS (ESI+): *m*/*z* = 270.3 [M + H]$^+$, 192.3, 174.3, 105.0.

(3*S*,4*S*,5*S*)-3-Methanesulfonyloxy-1,5-dimethyl-4-phenylpyrrolidine (30): A solution of 2-mesyloxyazetidine (269 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/CyH, 8:2; then Et_2O/MeOH, 9:1). R_f = 0.30 (CH_2Cl_2/MeOH, 95:5). Yield: 204 mg (76%); clear oil. $[\alpha]_D^{25}$ = +67 (*c* = 0.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H, Ph), 5.15 (td, *J* = 3.7 and 6.6 Hz, 1 H, 3-H), 3.82 (dd, *J* = 6.6 and 11.8 Hz, 1 H, 2-H), 3.01 (dd, *J* = 6.6 and 11 Hz, 1 H, 4-H), 2.82 (qd, *J* = 3.3 and 5.9 Hz, 1 H, 6-H), 2.72 (dd, *J* = 3.7 and 11.8 Hz, 1 H, 2′-H), 2.44 (s, 3 H, Me), 2.20 (s, 3 H, Me), 1.07 (d, *J* = 5.9 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7 (C*ipso* Ph), 130.1, 128.4, 127.5 (CH Ph), 81.4 (C-3), 63.6 (C-5), 63.2 (C-2), 57.0 (C-4), 39.9, 37.3, 16.7 (Me) ppm. MS (ESI+): *m*/*z* = 270.1 [M + H]$^+$, 174.1 [M – MsOH]$^+$.

(3*R*,4*S*,5*S*)-3-Methanesulfonyloxy-1,5-dimethyl-4-phenylpyrrolidine (31): A solution of 2-mesyloxyazetidine (269 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2). R_f = 0.59 (CH_2Cl_2/MeOH, 9:1). Yield: 204 mg (76%); clear oil. $[\alpha]_D^{25}$ = +14 (*c* = 1.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5 H, Ph), 5.11 (m, 1 H, 3-H), 3.48 (d, *J* = 11.8 Hz, 1 H, 2-H), 3.00 (dd, *J* = 4.4 and 9.9 Hz, 1 H, 4-H), 2.86 (s, 3 H, 6-H), 2.74 (dd, *J* = 6.3 and 11.8 Hz, 1 H, 2′-H), 2.35 (s, 3 H, Me), 2.20 (m, 1 H, 5-H), 1.12 (d, *J* = 6.2 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.4 (C*ipso* Ph), 129.0, 128.1, 127.5 (CH Ph), 85.5 (C-3), 69.0 (C-5), 63.1 (C-2), 60.7 (C-4), 39.7 (C-6), 38.5 (C-8), 16.5 (C-7) ppm. MS (ESI+): *m*/*z* = 292.1 [M + Na]$^+$, 270.1 [M + H]$^+$, 174.1 [M – MsOH]$^+$. $C_{13}H_{19}NO_3S$ (269.36): calcd. C 57.97, H 7.11, N 5.20; found C 57.93, H 7.23, N 5.02.

(2*S*,3*R*,4*S*,5*S*)-3-Chloro-1,5-dimethyl-2,4-diphenylpyrrolidine (34): A solution of 2-chloromethylazetidine (286 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evap-

orated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/PE, 5:95 then 2:8). R_f = 0.80 (Et_2O/PE, 4:6). Yield: 268 mg (94%); orange oil. $[\alpha]_D^{25}$ = +91 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 10 H, Ph), 3.96–3.82 (m, 2 H, 2-H, 3-H), 3.56–3.48 (m, 1 H, 5-H), 3.00–2.94 (m, 1 H, 4-H), 2.11 (s, 3 H, Me), 1.16 (d, *J* = 7.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 139.5 (C*ipso* Ph), 128.9, 128.7, 128.2, 127.8, 127.2 (CH Ph), 75.4 (C-2), 71.2 (C-3), 65.1 (C-5), 62.2 (C-4), 34.7, 15.8 (Me) ppm. MS (ESI+): 286.1 $[M + H]^+$. The same compound was obtained by the following procedure: To a solution of hydroxymethylazetidine **11** (1 mmol) in THF (5 mL) was added methanesulfonyl chloride (0.084 mL, 1.5 mmol) and triethylamine (0.41 mL, 4 mmol). The reaction mixture was heated at reflux for 2 h and then hydrolyzed by addition of NaOH (1 M, 10 mL). Addition of ether was followed by usual workup and purification as above to give the title compound (77%).

(2*R*,3*S*,4*R*)-1-Benzyl-3-chloro-2,4-diphenylpyrrolidine (35): A solution of 2-chloromethylazetidine (348 mg, 1 mmol) in chloroform (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/PE, 5:95 then 2:8). R_f = 0.82 (Et_2O/PE, 4:6). Yield: 328 mg (95%); orange oil. $[\alpha]_D^{25}$ = –42 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 6.9 Hz, 2 H, Ph), 7.48–7.27 (m, 13 H, Ph), 4.01 (dd, *J* = 6.9 and 8.5 Hz, 1 H, 3-H), 3.94 (A part of AB syst., *J* = 13.1 Hz, 1 H, NC*H*HPh), 3.71 (d, *J* = 8.2 Hz, 1 H, 2-H), 3.51–3.44 (m, 1 H, 4-H), 3.24 (dd, *J* = 3.6 and 9.8 Hz, 1 H, 5-H), 3.17 (B part of AB syst., *J* = 13.1 Hz, 1 H, NCH*H*Ph), 3.00 (t, *J* = 9.8 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 138.9, 138.5 (C*ipso* Ph), 128.9, 128.8, 128.7, 128.4, 128.2, 127.4, 127.2, 127.0 (CH Ph), 78.0 (C-2), 72.0 (C-5), 58.8 (CH_2), 57.9 (C-4), 52.1 (C-3) ppm. MS (ESI+): *m*/*z* = 348.1 $[M + H]^+$. $C_{23}H_{22}ClN$ (331.43): calcd. C 79.41, H 6.37, N 4.03; found C 79.11, H 6.51, N 4.02. The same compound was obtained by the following procedure: To a solution of hydroxymethylazetidine **12** (1 mmol) in THF (5 mL) was added methanesulfonyl chloride (0.084 mL, 1.5 mmol) and triethylamine (0.41 mL, 4 mmol). The reaction mixture was heated at reflux for 2 h and then hydrolyzed by addition of NaOH (1 M, 10 mL). Addition of ether was followed by usual workup and purification as above to give title compound (65%).

(1*S*,2*S*,3*S*,4*S*)-2-(1-Methanesulfonyloxypentyl)-1,4-dimethyl-3-phenylazetidine (36): Following the general procedure used for the synthesis of the mesylates, crude compound **36** was obtained and used as such for the ensuing rearrangement. R_f = 0.50 (Et_2O/PE, 4:6). Yield: 96%; clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.17 (m, 5 H, Ph), 4.72–4.78 (m, 1 H, C*H*OMs), 3.14 (s, 3 H, Me), 3.15–3.05 (m, 2 H, 2-H, 3-H), 2.92 (quint., *J* = 6.5 Hz, 1 H, 4-H), 2.39 (s, 3 H, NMe), 1.51–1.01 [m, 6 H, $(CH_2)_3$], 1.14 (d, *J* = 6.4 Hz, 3 H, Me), 0.79 (br. t, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1 (C*ipso* Ph), 128.6, 127.8, 126.9 (CH-Ph), 83.6 (CHO), 72.8 (C_2), 68.2 (CH), 50.6 (CH), 46.7, 42.2, 39.3, 31.0, 27.4, 23.0 (CH_2), 19.8, 13.8 (CH_3) ppm.

Thermal Ring Expansion of 2-(α-Chloroalkyl)azetidines (Table 3)

(3*S*,4*R*)-1-Benzyl-3-chloro-4-phenylpyrrolidine (37): A solution of **16** in DMF (10 mL for 1 mmol) was heated at reflux for 12 h. Evaporation of the solvent and purification by flash chromatography (Et_2O/CyH, 1:9 then 3:7) afforded the title compound. R_f = 0.75 (Et_2O/CyH, 3:7). Yield: 203 mg (75%); oil. $[\alpha]_D^{25}$ = –41 (*c* = 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.23 (m, 10 H, Ph), 4.33–4.21 (m, 1 H, 3-H), 3.73 (m, 2 H, NCH_2Ph), 3.51 (ddd, *J* = 1.8, 6.6, and 13.0 Hz, 1 H, 4-H), 3.25 (dd, *J* = 6.8 and 10.3 Hz, 1 H, 2-H), 3.17 (t, *J* = 8.6 Hz, 1 H, 5-H), 2.95 (dd, *J* = 5.7 and 10.1 Hz, 1 H, 5′-H), 2.78 (dd, *J* = 6.8 and 9.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 138.5 (C*ipso* Ph), 128.8–127.5 (CH Ph), 63.4 (*C*H_2Ph), 63.3 (C-3), 60.6 and 60.1 (C-5, C-2), 54.8 (C-4) ppm. MS (ESI+): *m*/*z* = 272.1 $[M + H]^+$. $C_{17}H_{18}ClN$ (271.78): calcd. C 75.13, H 6.68, N 5.15; found C 74.96, H 6.51, N 5.12.

(3*R*,4*R*)-1-Benzyl-3-chloro-4-phenylpyrrolidine (38): A solution of **17** in DMF (10 mL for 1 mmol) was heated at reflux for 12 h. Evaporation of the solvent under reduced pressure, followed by purification by flash chromatography (Et_2O/CyH, 1:9 then 2:8) gave the title compound. R_f = 0.46 (Et_2O/CyH, 3:7). Yield: 106 mg (39%); oil. $[\alpha]_D^{25}$ = –340 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.42 (m, 10 H, Ph), 4.70–4.65 (td, *J* = 3.0 and 5.9 Hz, 1 H, 3-H), 3.89 (m, 2 H, NCH_2Ph), 3.76 (td, *J* = 6.6 and 10.2 Hz, 1 H, 4-H), 3.63 (dd, *J* = 5.6 and 11.5 Hz, 1 H, 2-H), 3.26 (dd, *J* = 6.9 and 9.2 Hz, 1 H, 5-H), 3.16 (t, *J* = 9.2 Hz, 1 H, 5′-H), 3.06 (dd, *J* = 3.0 and 11.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 138.2 (C*ipso* Ph), 128.9–127.1 (CH Ph), 63.6 (*C*H_2Ph), 62.1 (C-3), 61.0 (C-2), 56.3 (C-5), 49.5 (C-4) ppm. MS (ESI+): *m*/*z* = 272.1 $[M + H]^+$, 236.1 $[M – HCl]^+$. $C_{17}H_{18}ClN$ (271.78): calcd. C 75.13, H 6.68, N 5.15; found C 75.43, H 6.89, N 5.12.

(2*S*,3*S*,4*R*)-1-Benzyl-3-chloro-2,4-diphenylpyrrolidine (40): A solution of **22** (348 mg, 1 mmol) in DMF (10 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (Et_2O/PE, 2:98 then 1:9). R_f = 0.88 (Et_2O/PE:4:6). Yield: 215 mg (65%); pink oil. $[\alpha]_D^{25}$ = +60 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 6.9 Hz, 2 H, Ph), 7.48–7.27 (m, 13 H, Ph), 4.01 (dd, *J* = 6.9 and 8.5 Hz, 1 H, 3-H), 3.94 (A part of AB syst., *J* = 13.1 Hz, 1 H, NC*H*HPh), 3.71 (d, *J* = 8.2 Hz, 1 H, 2-H), 3.51–3.44 (m, 1 H, 4-H), 3.24 (dd, *J* = 3.6 and 9.8 Hz, 1 H, 5-H), 3.17 (B part of AB syst., *J* = 13.1 Hz, 1 H, NCH*H*Ph), 3.00 (t, *J* = 9.8 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 138.9, 138.5 (C*ipso* Ph), 128.9, 128.8, 128.7, 128.4, 128.2, 127.4, 127.2, 127.0 (CH Ph), 78.0 (C-2), 72.0 (C-5), 58.8 (C-6), 57.9 (C-4), 52.1 (C-3) ppm. MS (ESI+): *m*/*z* = 348.1 $[M + H]^+$. $C_{23}H_{22}ClN$ (331.43): calcd. C 79.41, H 6.37, N 4.03; found C 79.23, H 6.47, N 4.07.

General Procedure for the Rearrangement of Activated 2-(α-Hydroxyalkyl)azetidines in the Presence of an External Nucleophile: To a solution of 2-(α-chloro- or α-methanesulfonyloxyalkyl)azetidine (1 mmol) in DMSO (8 mL) was added the required nucleophile (KOH, NaN_3, KCN, or AcONa, 10 equiv.). When the added nucleophile was KOH, water (60 μL) was added as a cosolvent. The mixture was heated whilst stirring at 50 °C until complete consumption of the starting material (see Table 4). Usual workup (AcOEt) followed by flash chromatography gave the following compounds.

(3*S*)-3-Chloro-1-[(1*S*)-1-Phenylethyl]pyrrolidine (41): Following the above procedure, but with heating at 40 °C for 48 h and starting from **18**, compound **41** was obtained as a clear oil after purification by flash chromatography (Et_2O/PE, 7:3). R_f = 0.5 (Et_2O/PE:7:3). Yield: 81 mg (39%). $[\alpha]_D^{25}$ = –81 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H, Ph), 4.28–4.20 (m, 1 H, 3-H), 3.27 (q, *J* = 6.4 Hz, 1 H, CHMe), 2.90 (dd, *J* = 6.4 and 10.7 Hz, 1 H, 2-H), 2.70 (td, *J* = 4.1 and 8.4 Hz, 1 H, 5-H), 2.60–2.50 (m, 2 H, 5-H and 2-H), 2.38–2.26 (m, 1 H, 4-H), 2.01–1.91 (m, 1 H, 4′-H), 1.29 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0 (C*ipso* Ph), 128.4, 127.2, 127.1 (CH Ph), 65.3 (CH), 62.3 (C-2), 56.4 (C-3), 51.1 (C-5), 35.9 (C-4), 22.9 (Me) ppm. MS (ESI+): *m*/*z* = 210.2 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{17}NCl$ $[M + H]^+$ 210.1046; found 210.1050.

(3*S*)-3-Hydroxy-1-[(1*S*)-1-Phenylethyl]pyrrolidine (42): Following the above procedure, but with heating at 50 °C for 48 h and starting from **18**, compound **42** was obtained as a clear oil after purification by flash chromatography (DCM/EtOH, 9:1). R_f = 0.12 (DCM/EtOH, 9:1). Yield: 134 mg (70%). $[\alpha]_D^{25}$ = +14 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.26 (m, 5 H, Ph), 4.40–4.35 (m, 1 H, 3-H), 3.38–3.31 (q, *J* = 6.6 Hz, 1 H, CHMe), 2.93–2.89 (m, 1 H, 2-H), 2.77–2.71 (m, 1 H, 5-H), 2.56 (q, *J* = 5.2 Hz, 1 H, 2′-H), 2.40–2.32 (m, 1 H, 5′-H), 2.23–2.16 (m, 1 H, 4-H), 1.78–1.74 (m, 1 H, 4′-H), 1.45 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4 (C*ipso* Ph), 128.5, 127.3, 127.2 (CH Ph), 71.3 (CHOH), 65.4 (CH), 61.5 (C-2), 51.2 (C-5), 34.7 (C-4), 22.7 (Me) ppm. MS (ESI+): *m*/*z* = 192.3 $[M + H]^+$, 105.1. HRMS: calcd. for $C_{12}H_{18}NO$ $[M + H]^+$ 192.1388; found 192.1396.

(1*S*)-1-Phenylethyl-2,5-dihydro-1*H*-pyrrole (43): Following the above procedure, but with heating at 60 °C for 24 h and starting from **18**, compound **43** was obtained as a clear oil after purification by flash chromatography (Et_2O/PE, 7:3). R_f = 0.2 (Et_2O/PE, 7:3). Yield: 168 mg (97%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.14 (m, 5 H, Ph), 5.71 (s, 2 H, 3,4-H), 3.50–3.24 (m, 5 H, 2,5-H and CHMe), 1.32 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6 (C*ipso* Ph), 128.4, 127.8, 127.3 (CH Ph), 126.9 (C-3,4), 65.2 (CH), 58.6 (C-2,5), 23.6 (Me) ppm. MS (ESI+): *m*/*z* = 174.3 $[M + H]^+$.

(2*S*,3*S*,4*S*,5*S*)-2-Butyl-3-hydroxy-1,5-dimethyl-4-phenylpyrrolidine (44): Following the above procedure, and starting from **36**, compound **44** was obtained as a clear oil after purification by flash chromatography on basic alumina (DCM/MeOH, 95:5). R_f = 0.3 (DCM/MeOH, 95:5). Yield: 116 mg (47%). $[\alpha]_D^{20}$ = +34 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.06 (m, 5 H, Ph), 3.91 (dd, *J* = 4.0 and 6.3 Hz, 1 H, 3-H), 3.11–3.00 (m, 2 H, 5-H and 2-H), 2.86–2.76 (m, 1 H, 4-H), 2.37 (s, 3 H, Me), 1.77–1.66 (m, 1 H, Bu), 1.45–1.14 (m, 5 H, Bu), 1.08 (d, *J* = 6.2 Hz, 3 H, Me), 0.85 (t, *J* = 6.9 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4 (C*ipso* Ph), 128.8, 127.8, 127.1 (CH Ph), 82.6 (C-3), 70.7 (C-2), 64.5 (C-5), 61.7 (C-4), 34.5 (Me) 27.9, 27.4, 23.0 (CH_2), 14.0 (Me) ppm. MS (ESI+): *m*/*z* = 248.3 $[M + H]^+$, 230.3. HRMS: calcd. for $C_{16}H_{26}NO$ $[M + H]^+$ 248.2014; found 248.2019.

(2*S*,3*S*,4*S*,5*S*)-3-Hydroxy-1,5-Dimethyl-2,4-diphenylpyrrolidine (45): Following the above procedure, and starting from **32** + **33**, compound **45** was obtained as a white solid after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.25 (PE/Et_2O, 6:4). Yield: 150 mg (56%). $[\alpha]_D^{20}$ = +41 (*c* = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.16 (m, 10 H, Ph), 4.02 (t, *J* = 7.2 Hz, 1 H, 3-H), 3.66 (d, *J* = 7.2 Hz, 1 H, 2-H), 3.46 (q, *J* = 6.3 Hz, 1 H, 5-H), 2.75–2.71 (m, 1 H, 4-H), 2.09 (s, 3 H, Me), 1.92 (br. s, 1 H, OH), 1.14 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 140.8 (C*ipso* Ph), 128.7, 128.6, 128.1, 127.8, 127.7, 126.7 (CH Ph), 86.5 (C-3), 74.3 (C-2), 64.5 (C-5), 60.9 (C-4), 34.5, 16.7 (Me) ppm. MS (ESI+): *m*/*z* = 268.2 $[M + H]^+$, 250.3, 148.1. HRMS: calcd. for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701; found 268.1708.

1,5-Dimethyl-2,4-diphenylpyrrole (46): Following the above procedure, and starting from **32** + **33**, compound **46** was obtained as a white solid after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.7 (PE/Et_2O, 6:4). Yield: 72 mg (29%). M.p. 155 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 10 H, Ph), 6.26 (s, 1 H, 3-H), 3.50 (s, 3 H, Me), 2.35 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3 (C-2), 133.9, 133.6 (C*ipso* Ph), 128.9, 128.5, 128.4, 128.2, 128.1, 126.9 (CHPh), 126.7 (C-4), 125.3 (C-5), 108.1 (C-3), 32.1, 11.5 (Me) ppm. MS (ESI+): *m*/*z* = 248.3 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{17}N$ $[M + H]^+$ 248.1439; found 248.1438.

(3*S*)-3-Cyano-1-[(1*S*)-1-phenylethyl]pyrrolidine (47): Following the above procedure, and starting from **18**, compound **47** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.4 (PE/Et_2O, 6:4). Yield: 152 mg (76%). $[\alpha]_D^{20}$ = –57 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.03 (m, 5 H, Ph), 3.35–3.32 (m, 1 H, CHMe), 3.02–2.93 (m, 2 H, 3-H and 5-H), 2.85–2.65 (m, 2 H, 2-H), 2.57–2.51 (m, 1 H, 5′-H), 2.27–2.09 (m, 2 H, 4-H), 1.45 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6 (C*ipso* Ph), 128.5, 127.3, 127.1 (CH Ph), 122.5 (CN), 64.6 (CH), 56.1, 51.4 (CH_2), 29.1 (C-4), 26.3 (C-3), 23.0 (Me) ppm. MS (ESI+): *m*/*z* = 201.1 $[M + H]^+$, 185.0. HRMS: calcd. for $C_{13}H_{17}N_2$ $[M + H]^+$ 201.1392; found 201.1387.

(3*R*)-3-Cyano-1-[(1*S*)-1-phenylethyl]pyrrolidine (48): Following the above procedure, and starting from **19**, compound **48** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 1:1). R_f = 0.4 (PE/Et_2O, 1:1). Yield: 88 mg (44%). $[\alpha]_D^{20}$ = –3 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.09 (m, 5 H, Ph), 3.33 (q, *J* = 6.5 Hz, 1 H, CHMe), 3.05–2.95 (m, 2 H, 3-H and 2-H), 2.85–2.65 (m, 2 H, 2′-H and 5-H), 2.56–2.50 (m, 1 H, 5′-H), 2.25–2.07 (m, 2 H, 4-H), 1.43 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.5 (Cipso Ph), 128.6, 127.3, 127.0 (CH Ph), 122.1 (CN), 64.6 (CH), 55.9, 51.4 (CH_2), 29.1 (C-4), 26.4 (C-3), 22.3 (Me) ppm. MS (ESI+): *m*/*z* = 201.1 $[M + H]^+$, 185.0, 123.0, 105, 0. HRMS: calcd. for $C_{13}H_{17}N_2$ $[M + H]^+$ 201.1392; found 201.1386.

(3*R*)-3-Chloro-1-[(1*S*)-1-phenylethyl]pyrrolidine (49): Following the above procedure, but with heating at 50 °C for 24 h and starting from **19**, compound **49** was obtained as a clear oil after purification by flash chromatography (Et_2O/PE, 7:3). R_f =0.5 (Et_2O/PE, 7:3). Yield: 44 mg (21%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H, Ph), 4.25–4.18 (m, 1 H, 3-H), 3.19 (q, *J* = 6.4 Hz, 1 H, CHMe), 2.85–2.68 (m, 3 H, 2-H, 3-H, 5-H), 2.62–2.52 (m, 2 H, 5-H and 2-H), 2.35–2.24 (m, 1 H, 4-H), 1.98–1.91 (m, 1 H, 4′-H), 1.28 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9 (C*ipso* Ph), 128.4, 127.2, 126.9 (CH Ph), 65.2 (CH), 61.9 (C-2), 56.2 (C-3), 49.8 (C-5), 35.7 (C-4), 22.8 (Me) ppm. MS (ESI+): *m*/*z* = 210.2 $[M + H]^+$.

(2*S*,3*S*,4*S*,5*S*)-3-Cyano-1,5-dimethyl-2,4-diphenylpyrrolidine (50): Following the above procedure, and starting from **32** + **33**, compound **50** was obtained as a white solid after purification by flash chromatography (PE/Et_2O, 8:2). R_f = 0.5 (PE/Et_2O, 8:2). Yield: 63 mg (23%). $[\alpha]_D^{20}$ = +55 (*c* = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.30 (m, 10 H, Ph), 4.02 (d, *J* = 8.9 Hz, 1 H, 2-H), 3.60 (br. s, 1 H, 5-H), 3.10 (dd, *J* = 4.6 and 8.6 Hz, 1 H, 4-H), 2.88 (br. s, 1 H, 3-H), 2.14 (s, 3 H, Me), 1.16 (d, *J* = 6.7 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 140.3 (C*ipso* Ph), 129.1, 129.0, 128.7, 127.7, 127.4 (CH Ph), 120.2 (CN), 71.0 (C-2), 65.5 (C-5), 56.6 (C-4), 47.3 (C-3), 34.3, 15.1 (Me) ppm. MS (ESI+): *m*/*z* = 299.3, 277.3 $[M + H]^+$. HRMS: calcd. for $C_{19}H_{21}N_2$ $[M + H]^+$ 277.1705; found 277.1699.

(2*S*,3*S*,4*S*,5*S*)-2-Butyl-3-cyano-1,5-dimethyl-4-phenylpyrrolidine (51): Following the above procedure, and starting from **36**, compound **51** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.3 (PE/Et_2O, 6:4). Yield: 210 mg (82%). $[\alpha]_D^{20}$ = +66 (*c* = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.16 (m, 5 H, Ph), 3.20–3.06 (m, 2 H, 5-H and 2-H), 2.96 (dd, *J* = 3.3 and 6.4 Hz, 1 H, 3-H), 2.58 (t, *J* = 7.6 Hz, 1 H, 4-H), 2.29 (s, 3 H, Me), 1.77–1.66 (m, 1 H, Bu), 1.43–1.23 (m, 5 H, Bu), 1.01 (d, *J* = 6.3 Hz, 3 H, Me), 0.85 (t, *J* = 6.9 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0 (C*ipso* Ph), 129.0, 127.5, 127.4 (CH Ph), 121.8 (CN), 66.7 (C-2), 64.9 (C-5), 56.8 (C-3), 42.0 (C-4), 34.7 (Me) 31.2, 27.6, 23.0 (CH_2), 15.2, 14.1

(Me) ppm. MS (ESI+): *m*/*z* = 279.3, 257.3 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{24}N_2$ [M + H]$^+$ 257.2018; found 257.2013.

(3*S*)-3-Azido-[(1*S*)-1-phenylethyl]pyrrolidine (52): Following the above procedure, and starting from **18**, compound **52** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 2:1). R_f = 0.2 (PE/Et_2O, 2:1). Yield: 184 mg (85%). $[\alpha]_D^{20}$ = –43 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.25 (m, 5 H, Ph), 3.96 (m, 1 H, 3-H), 3.31 (q, *J* = 6.5 Hz, 1 H, CHMe), 2.73–2.58 (m, 4 H, 2-H and 5-H), 2.93–2.17 (m, 1 H, 4-H), 1.94–1.84 (m, 1 H, 4′-H), 1.43 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (C*ipso* Ph), 128.6, 128.4, 127.1 (CH Ph), 65.2 (CH), 59.8 (C-3), 58.4, 51.4, 31.4 (CH_2), 22.3 (Me) ppm. MS (ESI+): *m*/*z* = 217 [M + H]$^+$, 160, 105. HRMS: calcd. for $C_{12}H_{17}N_4$ [M + H]$^+$ 217.1453; found 217.1442.

(2*R*)-2-(Azidomethyl)-1-[(1*S*)-1-phenylethyl]azetidine (53): Following the above procedure, and starting from **18**, compound **53** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 2:1). R_f = 0.3 (PE/Et_2O, 2:1). Yield: 17 mg (8%). $[\alpha]_D^{20}$ = –10 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.09 (m, 5 H, Ph), 3.96–3.48 (m, 3 H, CHMe, $CHHN_3$ and 2-H), 3.30–3.27 (d, *J* = 9.3 Hz, 1 H, $CHHN_3$), 3.16–3.11 (m, 1 H, 4-H), 2.74 (q, *J* = 9.0 Hz, 1 H, 4′-H), 2.11–2.04 (m, 2 H, 3-H), 1.18 (d, *J* = 6.0 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5 (C*ipso* Ph), 128.4, 127.3, 127.1 (CH Ph), 67.5 (C-2), 63.9 (CH), 56.1 (C-2), 49.8 (CH_2), 22.2 (Me), 20.1 (C-3) ppm. MS (ESI+): *m*/*z* = 217 [M + H]$^+$, 160, 105.

(3*R*)-3-Azido-1-[(1*S*)-1-phenylethyl]pyrrolidine: Following the above procedure, and starting from **19**, compound **54** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.3 (PE/Et_2O, 6:4). Yield: 189 mg (87%). $[\alpha]_D^{20}$ = +15 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.14 (m, 5 H, Ph), 3.85–3.74 (m, 1 H, 3-H), 3.15 (q, *J* = 6.5 Hz, 1 H, CHMe), 2.80 (td, *J* = 5.4 and 8.7 Hz, 1 H, 5-H), 2.63–2.57 (m, 1 H, 2-H), 2.45 (dd, *J* = 3.3 and 10.3 Hz, 1 H, 2′-H), 2.25 (td, *J* = 6.3 and 8.6 Hz, 1 H, 5′-H), 2.16–2.04 (m, 1 H, 4-H), 1.86–1.76 (m, 1 H, 4′-H), 1.31 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0 (C*ipso* Ph), 128.5, 128.4, 127.1 (CH Ph), 65.2 (CH), 59.8 (C-3), 58.6, 51.5, 31.1 (CH_2), 23.1 (Me) ppm. MS (ESI+): *m*/*z* = 217 [M + H]$^+$. HRMS: calcd. for $C_{12}H_{17}N_4$ [M + H]$^+$ 217.1453; found 217.1446.

(2*S*,3*S*,4*S*,5*S*)-3-Azido-2-butyl-1,5-dimethyl-4-phenylpyrrolidine (55): Following the above procedure, and starting from **36**, compound **55** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.3 (PE/Et_2O, 6:4). Yield: 71 mg (26%). $[\alpha]_D^{20}$ = +7 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H, Ph), 3.65 (dd, *J* = 6.5 and 5.2 Hz, 1 H, 3-H), 3.10 (quint., *J* = 6.2 Hz, 1 H, 5-H), 3.02–2.96 (m, 1 H, 2-H) 2.81 (t, *J* = 7.6 Hz, 1 H, 4-H), 2.40 (s, 3 H, Me), 1.80–1.78 (m, 1 H, Bu), 1.49–1.27 (m, 5 H, Bu), 1.11 (d, *J* = 6.3 Hz, 3 H, Me), 0.98 (t, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4 (C*ipso* Ph), 128.8, 127.8, 127.1 (CH Ph), 72.3 (C-3), 68.0 (C-2), 64.3 (C-5), 59.1 (C-4), 34.7 (Me) 28.6, 27.7, 23.1 (CH_2), 15.8, 14.1 (Me) ppm. MS (ESI+): *m*/*z* = 273.3 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{25}N_4$ [M + H]$^+$ 273.2079; found 273.2078.

(2*S*,3*S*,4*S*,7*R*)-2-(Azidopentyl)-1,4-dimethyl-3-phenylazetidine (56): Following the above procedure, and starting from **36**, compound **56** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.4 (PE/Et_2O, 6:4). Yield: 43 mg (16%). $[\alpha]_D^{20}$ = –6 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.13 (m, 5 H, Ph), 3.37–3.25 (m, 1 H, CHN_3), 3.01–2.93 (m, 1 H, 2-H), 2.91–2.77 (m, 2 H, 3-H and 4-H), 2.43 (s, 3 H, Me), 1.37–1.09 (m, 9 H, Me and Bu), 0.73 (t, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9 (C*ipso* Ph), 128.6, 127.8, 127.0 (CH Ph), 73.7 (C-3), 68.2 (C-2), 67.6 (C-5), 49.0 (C-4), 43.8 (Me) 30.1, 28.1, 22.4 (CH_2), 20.1 (CH), 13.9 (Me) ppm. MS (ESI+): *m*/*z* = 295.3, 273.3 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{24}N_4$ [M + H]$^+$ 273.2079; found 273.2083.

(2*S*,3*S*,4*S*,5*S*)-3-Azido-1,5-dimethyl-2,4-diphenylpyrrolidine (57): Following the above procedure, and starting from **32** + **33**, compound **57** was obtained as an oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.6 (PE/Et_2O, 6:4). Yield: 55 mg (19%). $[\alpha]_D^{20}$ = +44 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 10 H, Ph), 3.98–3.78 (m, 2 H, 2-H and 3-H), 3.67–3.59 (m, 1 H, 5-H), 2.90 (dd, *J* = 4.2 and 6.5 Hz, 1 H, 4-H), 2.22 (s, 3 H, Me), 1.25 (d, *J* = 6.7 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.7, 140.2 (C*ipso* Ph), 129.9, 128.8, 128.1, 127.9, 127.6, 127.1 (CH Ph), 76.1 (C-3), 72.4 (C-2), 64.8 (C-5), 58.6 (C-4), 34.4, 15.4 (Me) ppm. MS (ESI+): *m*/*z* = 293.3 [M + H]$^+$.

(3*S*)-3-Acetoxy-1-[(1*S*)-1-phenylethyl]pyrrolidine (58): Following the above procedure, and starting from **18**, compound **58** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 3:7). R_f = 0.2 (PE/Et_2O, 3:7). Yield: 158 mg (68%). $[\alpha]_D^{20}$ = –8 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.24 (m, 5 H, Ph), 5.21–5.14 (m, 1 H, 3-H), 3.28 (q, *J* = 6.0 Hz, 1 H, CHMe), 2.82–2.70 (m, 2 H, 2-H), 2.67–2.59 (m, 1 H, 5-H), 2.54–2.45 (m, 1 H, 5′-H), 2.32–2.20 (m, 1 H, 4-H), 2.08 (s, 3 H, Me), 1.89–1.79 (m, 1 H, 4′-H), 1.42 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C=O), 144.8 (C*ipso* Ph), 128.4, 127.2, 127.1 (CH Ph), 74.1 (C-3), 65.6 (CH), 59.2, 51.5, 31.8 (CH_2), 22.9, 21.3 (Me) ppm. MS (ESI+): *m*/*z* = 256.3 [M + Na]$^+$. HRMS: calcd. for $C_{14}H_{20}NO_2$ [M + H]$^+$ 234.1494; found 234.1480.

(2*S*,3*S*,4*S*,5*S*)-3-Acetoxy-2-butyl-1,5-dimethyl-4-phenylpyrrolidine (59): Following the above procedure, and starting from **36**, compound **59** was obtained as a clear oil after purification by flash chromatography (PE/Et_2O, 6:4). R_f = 0.2 (PE/Et_2O, 6:4). Yield: 185 mg (64%). $[\alpha]_D^{20}$ = +26 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.16 (m, 5 H, Ph), 4.98 (dd, *J* = 4.8 and 2.2 Hz, 1 H, 3-H), 3.02–2.98 (m, 1 H, 2-H), 2.85–2.72 (m, 2 H, 4-H and 5-H), 2.31 (s, 3 H, Me), 1.96 (s, 3 H, Me), 1.74–1.61 (m, 1 H, Bu), 1.50–1.13 (m, 5 H, Bu), 1.03 (d, *J* = 5.7 Hz, 3 H, Me), 0.85 (t, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (C=O), 141.2 (C*ipso* Ph), 128.6, 127.9, 126.7 (CH Ph), 84.1 (C-3), 69.3 (C-2), 64.7 (C-5), 59.9 (C-4), 34.8 (Me) 28.4, 26.0, 23.1 (CH_2), 16.4, 14.1 (Me) ppm. MS (ESI+): *m*/*z* = 312.3, 290.3 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{28}NO_2$ [M + H]$^+$ 290.2120; found 290.2131.

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