

Highly Stereoselective *trans* Addition of π -Type Nucleophiles to a Bicyclic *N*-Acyliminium Ion – Application to the Synthesis of Indolizidine and Pyrrolizidine Alkaloids

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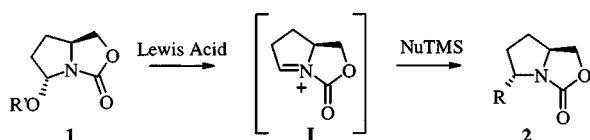
Enantiopure bicyclic 5-ethoxytetrahydropyrrolo[1,2-*c*]oxazol-3-one **1b** was prepared in two steps from the known tosylate **4**, which is readily available from (*S*)-pyroglutamic acid. Trapping of the *N*-acyliminium ion (**I**), generated in situ from **1b** in the presence of Lewis acid, with various silylated π -type nucleophiles gave rise selectively to *trans* adducts **2**. The usefulness of this stereoselective access to *trans*-2,5-

disubstituted pyrrolidines was illustrated by formal syntheses of 3,5-disubstituted indolizidine toxins, starting from 5-allyltetrahydropyrrolo[1,2-*c*]oxazol-3-one **2a**. Moreover, an enantiodivergent synthesis of the pyrrolizidine alkaloids (+) and (–)-xenovenine was achieved starting from the same chiral building block **2a**.

Introduction

Access to enantiopure *trans*-2,5-disubstituted pyrrolidines has attracted particular attention on account of their occurrence in natural products such as pyrrolizidine^[1] and indolizidine^[2] alkaloids, and of their utilisation as chiral auxiliaries^[3] in enantioselective synthesis. Consequently, many efforts have been devoted to devise methods for their preparation, with modest to high *trans* selectivities.^[4] Among these methods the nucleophilic addition of organo-copper reagents to *N*-acyliminium ions derived from proline constitutes a highly stereoselective route to *trans*-2,5-disubstituted pyrrolidines,^[5] which has been exploited in the synthesis of indolizidine alkaloids.^[6] However, potentially more versatile π -type nucleophiles are known to add to these latter *N*-acyliminium ions with a high degree of *cis* selectivity.^[7] In sharp contrast to these results, we recently found that bicyclic *N*-acyliminium ion **I**, when treated with silylated π -type nucleophiles, selectively led to *trans* adducts **2**^[8] (Scheme 1).

Scheme 1



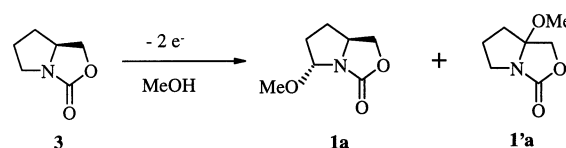
We report herein our study toward the synthesis of carbamolamine **1**, precursor of iminium ion **I**, and its reactivity with various silylated π -type nucleophiles in the presence of Lewis acid. Then, we describe the use of this methodology in the synthesis of pyrrolizidine and indolizidine alkaloids, constituents of ant venom and frog poison.

Results and Discussion

Preparation and Reactivity of Chiral Oxazolidinone **1**

We initially envisioned straight access to the required amino ether **1** by oxidation of the known readily available bicyclic oxazolidinone **3**.^[9] Since ruthenium-catalysed α -oxidation following Murahashi's procedure^[10] was ineffective, we considered α -electromethoxylation, which is known to take place selectively at the less substituted α position of the nitrogen atom.^[11] Unfortunately, anodic electromethoxylation (C–C, Et₄NOTs, –10 °C, MeOH) of bicyclic carbamate **3** mainly afforded the undesired regioisomer **1'a** along with the expected compound **1a** as an inseparable mixture (ratio **1a**/**1'a** = 1:3) (Scheme 2).

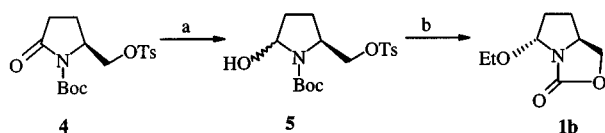
Scheme 2



Screening of various conditions (temperature, electrolyte, current density, etc.) did not significantly modify this result. A similar reverse regioselectivity has been observed for electromethoxylation of bicyclic oxazinones.^[12] These disappointing results prompted us to consider the preparation of compound **1** by a reductive method, starting from the known tosylate **4**,^[13] easily available in multigram quantities from (*S*)-pyroglutamic acid (Scheme 3).

Treatment of compound **4** with lithium triethylborohydride (Super-H) at –78 °C and subsequent oxidative workup resulted in the chemoselective partial reduction of

Scheme 3



Reagents: (a) LiEt_3BH , CH_2Cl_2 , -78°C , then NaOH , H_2O_2 ; – (b) EtOH-CHCl_3 , reflux.

the lactam moiety,^[14] cleanly providing hemiaminal **5** as a (1:1) diastereomeric mixture in a quantitative yield. When refluxed without further purification in the binary system $\text{CHCl}_3\text{--EtOH}$, the latter compound gave rise to *trans*- α -ethoxyoxazolidinone **1b** in 43% overall yield starting from **4**.^[15] This chemical transformation is the result of a one-pot two-step procedure, i.e. intramolecular nucleophilic displacement of the tosylate by an *N*-Boc group,^[16] then etherification of the hemiaminal moiety, or vice versa.^[17] Attempts to perform the intramolecular nucleophilic displacement prior to semireduction of the lactam group failed, probably because of a low nucleophilicity of the *N*-Boc moiety due to the delocalisation of the nitrogen lone pair on the lactam carbonyl group. The *N*-Boc cleavage is the only observed reaction when **4** is refluxed in toluene, whereas no reaction was observed in other solvents (EtOH , CHCl_3 , THF, etc.).

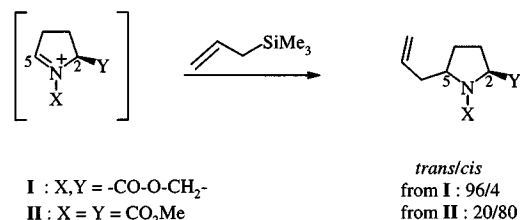
Once the access to the required ion precursor **1b** was settled, we investigated its reactivity towards various silylated π -type nucleophiles (Table 1). Reaction of **1b** was first examined with allyltrimethylsilane as nucleophile catalysed by a variety of Lewis acids ($\text{BF}_3\cdot\text{OEt}_2$, TiCl_4 , TMSOTf), giving rise to compound **2a**. Except for some differences in the chemical yields, the observed diastereoselectivity (96:4) remained unchanged whatever the nature of the Lewis acid used (entries 1–3). Extension of this study to silylated enol ethers showed that only TMSOTf gave satisfactory results in term of chemical yields, while the diastereomeric excesses, ranging from 88 to 100%, were in all cases satisfactory (entries 4–7). However, attempted reaction of **1b** with *tert*-butyl isocyanide, 1-trimethylsiloxy-1,3-butadiene, azido-trimethylsilane or [(1-ethoxycyclopropyl)oxy]trimethylsilane failed, resulting in unidentifiable dark mixtures. Lastly, the small nucleophile cyanotrimethylsilane reacted efficiently with substrate **1b**, to afford cyanooxazolidinone

adducts **2f**, with a significant drop in facial selectivity (*de* = 40%) (entry 8).

The stereochemistry of the major isomers was found to be *trans* in all cases **2a–2f**. On the one hand, the *trans* stereochemistry of the major allylated adduct **2a** was assigned based on chemical correlation after comparison of its analytical data with those of a *cis*-enriched sample.^[18] On the other hand, X-ray analyses performed on two crystalline compounds secured the *trans* stereochemistry of the major isomer of aromatic ketone **2c**, and the *cis* stereochemistry of the minor isomer of cyano adduct **2f**. Finally, examination of ^{13}C -NMR data allowed the extension of this stereochemical assignment to all the obtained major oxazolidinones **2**.^[8]

The observed diastereoselectivity of the nucleophilic attack of allyltrimethylsilane on iminium ion **I** was indeed opposite to that obtained for the monocyclic iminium ion **II**, which led preferentially to the *cis* stereoisomer^[7] (Scheme 4). The latter result was explained by Barrett et al. as the result of a balance between steric and stereoelectronic effects.^[19] In the case of bicyclic iminium ion **I**, the observed facial selectivity can be explained on the basis of steric effects due to its concave shape. However, in order to have some more insight regarding these effects, we performed AM_1 calculations^{[20][21]} on the initial states of the *N*-acyliminium moieties **I** and **II**, and on the transition states of the nucleophilic reaction of allyltrimethylsilane on these species (Table 2).

Scheme 4



The main difference between these substrates lies in the geometry around the nitrogen atom. It appears that the five-membered ring monocyclic iminium ion **II** exhibits only very little distortion from planarity, whereas the nitrogen atom of bicyclic iminium **I**, due to the presence of two five-membered fused rings, shows an important distortion

Table 1: Reactions of aminoether **1b** with various π -type nucleophiles

Entry	NuTMS	Lewis acid	R –	Yield ^[a] of 2 (%)	Ratio ^[b] <i>trans/cis</i>
1	$\text{CH}_2=\text{CHCH}_2\text{TMS}$	$\text{BF}_3\cdot\text{Et}_2\text{O}$	$\text{CH}_2=\text{CHCH}_2-$	2a (60)	96:4
2	$\text{CH}_2=\text{CHCH}_2\text{TMS}$	TiCl_4	$\text{CH}_2=\text{CHCH}_2-$	2a (90)	95:5
3	$\text{CH}_2=\text{CHCH}_2\text{TMS}$	TMSOTf	$\text{CH}_2=\text{CHCH}_2-$	2a (65)	96:4
4	$\text{Me}_2\text{C}=\text{CHOtMS}$	TMSOTf	HOCCMe_2-	2b (43) ^[c]	100:0
5	$\text{CH}_2=\text{C(Ph)OTMS}$	TMSOTf	PhCOCH_2-	2c (86)	94:6
6	$\text{CH}_2=\text{C}(t\text{Bu})\text{OTMS}$	TMSOTf	$t\text{BuCOCH}_2-$	2d (83)	100:0
7	$\text{Me}_2\text{C}=\text{C(OMe)OTMS}$	TMSOTf	$\text{MeO}_2\text{CCMe}_2-$	2e (73)	97:3
8	$\text{N}\equiv\text{CTMS}$	TMSOTf	$\text{NC}-$	2f (95)	70:30

^[a] Isolated yields. – ^[b] The diastereomeric ratios were determined by capillary GC. – ^[c] This yield does not take into account an other batch of aldehyde **2b** which remained contaminated by an unidentified compound after chromatography.

Table 2. Variation in dihedral angles for *trans* and *cis* approaches of the allyltrimethylsilane nucleophile

Substrate		$\Phi_{\text{X-N-C5/C2-N-C5}}$	$\Phi_{\text{Nu-C5-N-X}}^{[a]}$	$\Phi_{\text{X-N-C2-Y}}$
 I	initial state	150.3	-	-19.5
	<i>trans</i> approach ^[b]	148.5	-110.5	-16.9
	<i>cis</i> approach ^[b]	144.6	39.3	-14.6
 II	initial state	179.7	-	-65.3
	<i>trans</i> approach ^[b]	179.9	-76.3	-63.7
	<i>cis</i> approach ^[b]	-176.1	71.6	-66.1

[a] Nu = allyl. – [b] Dihedral angles for transition states.

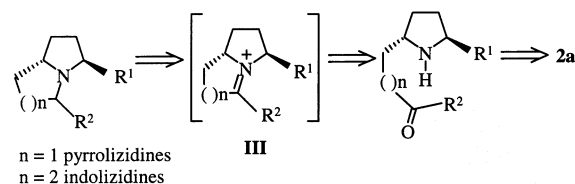
from planarity, the dihedral angle between Acyl–N–C5 and C2–N–C5 being 150.3° (instead of 180° for a planar nitrogen atom). As expected in the monocyclic compound **II**, the ester group is in a pseudoaxial position due to the steric repulsion with the *N*-acyl substituent. The facial selectivity in the approach of the allylsilane depends essentially upon steric hindrance between the incoming allyl group and the substituents (X,Y) of the iminium moiety, but also upon the changes in hindrance between the latter. For the bicyclic iminium ion **I**, an insight in the dihedral angles in the transition states reveals that the steric hindrance between the incoming allyl moiety and the carbamate group is more important for the *cis* approach ($\phi \approx 40^\circ$) than for the *trans* one ($\phi \approx 110^\circ$). Such a discrimination does not appear for the monocyclic iminium ion **II**. For this latter ion however, the important term seems to be the changes in the dihedral angle between the two methoxycarbonyl groups. The allyl attack on the double bond pushes the acyl substituent on the nitrogen atom towards the opposite side to minimise the steric hindrance between these groups (allyl and carbamate). During the approach *trans* to the ester substituent, the dihedral angle between the two methoxycarbonyl groups diminishes, thus increasing the steric hindrance. Conversely, *cis* approach pushes the *N*-acyl group apart from the ester one, widening this dihedral angle. As a conclusion, *trans* attack on the bicyclic iminium ion **I** is favoured due to lower steric hindrance between the incoming nucleophile and the *N*-acyl group, whereas for the monocyclic ion **II**, the *cis* approach is preferred due to a relief in the steric hindrance existing between the two methoxycarbonyl groups. Moreover, the calculated values of the differences in the energy of the transition states between the *trans* and *cis* approaches of iminium ions **I** and **II** are indicative of the observed diastereoselectivities, even if they do not fit exactly with the experimental data [for **I**: $\Delta E(\text{trans} - \text{cis}) = -1.34 \text{ kcal mol}^{-1}$; for **II**: $\Delta E(\text{trans} - \text{cis}) = 3.24 \text{ kcal mol}^{-1}$].

Synthesis of Naturally Occurring Alkaloids

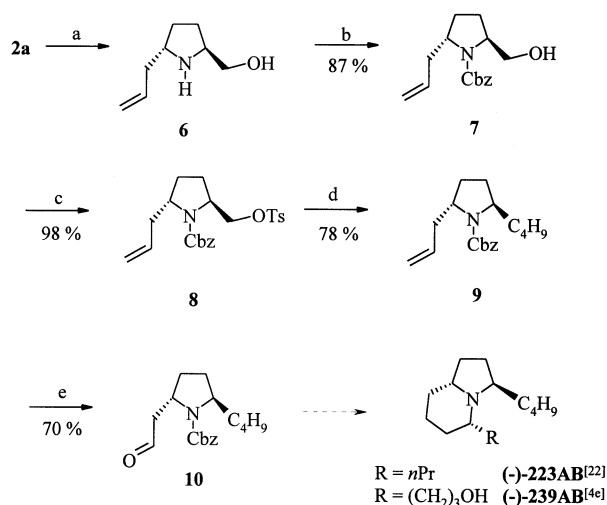
As an application of this highly stereoselective methodology for the obtention of chiral *trans* 2,5-disubstituted pyrrolidines, we now describe the (formal or total) syntheses of

some indolizidine (gephyrotoxines) and pyrrolizidine (xeno-venines) alkaloids in order to illustrate the usefulness of the chiral synthon *trans* 5-allyloxazolidinopyrrolidine **2a**, readily available on multigram scale. The stereoselective construction of the bicyclic skeletons relies on catalytic hydrogenation of the transient iminium ion **III**, generated in situ by debenzoyloxycarbonylation and subsequent annulative amination from appropriate ketopyrrolidines. The latter compound can be elaborated from chiral synthon **2a**, depending on the required substituents (Scheme 5).

Scheme 5



Previous investigations in our laboratory have revealed that the enantiopure *trans*-5-butyl-2-(2-oxoethyl)pyrrolidine compound **10** serves as a common chiral building block in the preparation of (–)-indolizidines **223AB**^[22] and **239AB**,^[4c] which are extracted from the skin of the Colombian poison-frog *Dendrobates histrionicus*^[23] (Scheme 6).

Scheme 6: Formal synthesis of (–)-indolizidines **223AB** and **239AB**

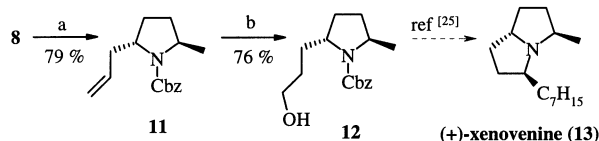
Reagents: (a) 30% KOH-1,4-dioxane, reflux. – (b) $\text{C}_6\text{H}_5\text{CH}_2\text{O-COCl}$, Na_2CO_3 , CH_2Cl_2 . – (c) *p*-TsCl, NEt_3 , CH_2Cl_2 . – (d) $n\text{Pr}_2\text{CuLi}$, Et_2O , -20°C . – (e) Cat.OsO₄, NaIO₄, THF/H₂O.

In our case, this intermediate was obtained in five steps from key compound **2a** (Scheme 6). Opening of oxazolidinone ring was achieved by the action of aqueous 30% KOH in refluxing 1,4-dioxane to give quantitatively amino alcohol **6**, which was converted without further purification to the *N*-(benzyloxycarbonyl)prolinol derivative **7** in 87% overall yield. Treatment of the latter with tosyl chloride and NEt_3 in CH_2Cl_2 smoothly gave *p*-toluenesulfonate **8** in 98% yield. Subsequent 3-carbon homologation, necessary to install the *n*-butyl group, was accomplished by the action of $(n\text{-C}_3\text{H}_7)_2\text{CuLi}$ in Et_2O at -20°C to afford compound **9** in 78% yield. Finally, ozonolysis at -78°C of the allyl group

of **9** resulted in formation of the target aldehyde **10** in moderate yield (50%). The latter, however, was raised to 70% by treating **9** with a catalytic amount of OsO₄ in the presence of NaIO₄ in THF·H₂O.

On the other hand, *trans*-2,5-disubstituted pyrrolidine substructures are equally found in some naturally occurring pyrrolizidines.^[1] We thus envisioned enantiodivergent synthesis of both enantiomers of xenovenine **13**, which is found in ant venom^[24] (*Solenopsis xenovenum*), starting from the common key intermediate **8**, previously involved in the formal synthesis of (–)-indolizidines **223AB** and **239AB**. Adequate functional transformations of both 2- and 5-substituents of enantiopure pyrrolidine **8** must indeed selectively lead to either (+)- or (–)-xenovenines. As depicted in Scheme 7, the synthesis of (+)-xenovenine began with treatment of tosylate **8** with Super-H in THF at room temperature giving rise to pyrrolidine **11** in 79% yield. Subsequent oxidative hydroboration of the allyl substituent afforded alcohol **12** in 76% yield. This compound exhibited analytical spectroscopic data identical with those of the synthetic material previously obtained in our laboratory^[25] by kinetically controlled carbamate formation of a (1:1) diastereomeric mixture of the corresponding amino alcohols. The effective transformation of **12** into (+)-xenovenine has indeed already been established.^[25]

Scheme 7: Formal synthesis of (+)-xenovenine

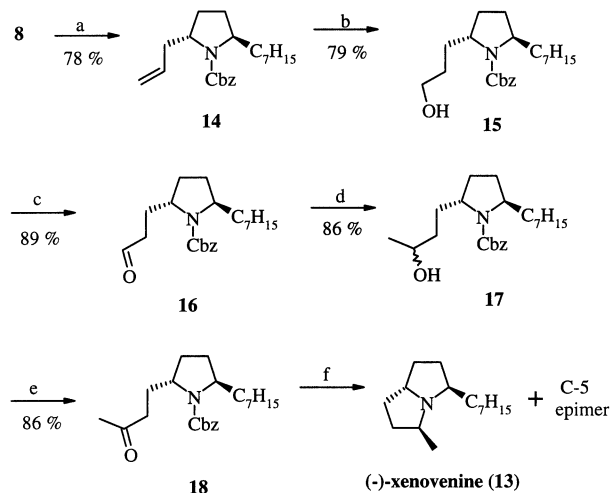


Reagents: (a) LiEt₃BH, THF, room temp. – (b) BH₃·(CH₃)₂S, Et₂O, then NaOH, H₂O₂.

After this formal synthesis, we undertook the total synthesis of levorotatory enantiomer (–)-xenovenine (Scheme 8). Our synthesis was initiated with the nucleophilic displacement of the tosylate group of intermediate **8** with *n*-Hex₂CuLi in Et₂O at –20°C in 78% yield. Resulting *trans*-pyrrolidine **14** was next subjected to oxidative hydroboration to afford alcohol **15** in 79% yield. Further oxidation of this primary alcohol **15** using pyridinium dichromate as reagent gave aldehyde **16** only in modest yield (47%) after two days reaction. Compound **16** was, however, smoothly obtained in better yield (87%) following Swern's conditions. The transformation of aldehyde **16** into the required methyl ketone **18** was performed according to a two-step procedure, i.e. nucleophilic addition of methylmagnesium chloride and subsequent Swern oxidation of the resulting diastereomeric mixture of alcohols **17**. Finally, exposure of **18** to hydrogen in the presence of Pd/BaSO₄ as a catalyst in methanol provided the desired pyrrolizidine alkaloid (–)-xenovenine **13**, along with its C-5 epimer^[24] (10% as estimated by GC). The obtained diastereoselectivity is comparable with that reported previously by Oppolzer and coworkers^[26] in similar conditions starting from **18**. Removal of the minor C-5 epimer by column chromatography gave the pure (–)-xenovenine (**13**) in 60% yield. The sample thus

obtained exhibited ¹H- and ¹³C-NMR analytical data in full accordance with those reported for dextrorotatory enantiomer.^{[25][27]} Moreover, the optical rotation of (–)-**13** was –11.4 (*c* = 1.37, CHCl₃), which is very close to the values of –11.6 (*c* = 0.6, CHCl₃) and –11.5 (*c* = 0.5, CHCl₃) cited for samples obtained by Oppolzer et al.^[26] and Momose et al.^[27], respectively.

Scheme 8: Total synthesis of (–)-xenovenine



Reagents: (a) *n*Hex₂CuLi, Et₂O, –20°C. – (b) BH₃·(CH₃)₂S, then NaOH, H₂O₂. – (c) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, –60°C. – (d) MeMgCl, THF. – (e) (COCl)₂, DMSO, NEt₃, CH₂Cl₂. – (f) H₂, Pd/BaSO₄, MeOH.

Conclusion

The first part of this study was devoted to the reactivity of the bicyclic *N*-acyliminium ion **1** towards various π -type nucleophiles. In most cases, the nucleophilic additions took place with good to excellent facial selectivity giving rise to *trans*-2,5-disubstituted pyrrolidine derivatives. The effectiveness of this method was then illustrated by using the allylic adduct **2a** as a common precursor in the formal or total syntheses of some naturally occurring indolizidine and pyrrolizidine alkaloids.

Experimental Section

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. – THF and Et₂O were distilled from Na benzophenone ketyl immediately prior to use. – CH₂Cl₂ was distilled from calcium hydride. – All reactions involving organometallic reagents were carried out under argon. – Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F₂₅₄) plates and column chromatography on silica gel Gerudan SI 60 (40–60 μ m) (Merck). – Melting points are uncorrected. – IR: Philips PU 9700. – Optical rotations: Perkin-Elmer 241 polarimeter. – Elemental analyses: Service Régional de Microanalyse de l'Université P. et M. Curie. – NMR: Bruker ARX 250 spectrometer (250 MHz and 62.9 MHz for ¹H and ¹³C, respectively). Spectra were recorded in CDCl₃ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual CHCl₃ at δ = 7.27 for ¹H and to CDCl₃ at δ = 77.1 for ¹³C. When an acyclic carbamate moiety is present in a molecule, peak doubling due to the presence of two rotamers is observed in ¹H and ¹³C NMR.

Electromethoxylation of Oxazolidinone 3: A 25-ml undivided jacketed cell was charged with a magnetic stir-bar, oxazolidinone **3**^[9] (1 g, 7.87 mmol), dry MeOH (15 ml) and tetraethylammonium *p*-toluenesulfonate (0.31 g, 2 mmol). Two graphite plates (2.5 × 3 cm) spaced 4–5 mm apart were immersed into the methanolic solution. While the electrolysis cell temperature was maintained at –5°C, under inert atmosphere, a constant current of 0.12 A (voltage 8–12 V) was passed through the solution. Progress of the anodic oxidation was monitored by GC. After 4 F/mol had passed through the solution, the electrolysis was stopped and the reaction mixture was concentrated in vacuo. The resulting residue was dissolved in CH₂Cl₂ (15 ml) and washed with water (20 ml). The aqueous phase was extracted with CH₂Cl₂ (2 × 10 ml) and the combined organic extract dried with Na₂SO₄ and concentrated in vacuo. Examination of the NMR data of the crude residue essentially revealed the presence of a mixture of isomers **1a** and **1'a** (ratio 1:3 according to GC). The oily residue was chromatographed (AcOEt/cyclohexane, 1:2) to give 707 mg (57%) of an inseparable mixture of **1a** and **1'a**, which were characterised as follow.^[28]

(5*R*,7*aS*)-5-Methoxytetrahydropyrrolo[1,2-*c*]oxazol-3-one (1a): IR (neat): $\tilde{\nu}_{\max}$ = 1755 cm⁻¹. – ¹H NMR: δ = 1.4–1.55 (m, 1 H), 1.75–1.9 (m, 1 H), 2.05–2.15 (m, 1 H), 2.3–2.45 (m, 1 H), 3.36 (s, 3 H), 3.95–4.10 (m, 2 H), 4.45 (td, *J* = 1 and 8.6 Hz, 1 H), 5.01 (dd, *J* = 4.7 and 6.4 Hz, 1 H). – ¹³C NMR: δ = 30.10, 33.28, 55.73, 57.45, 67.75, 91.38, 160.20.

7*a*-Methoxytetrahydropyrrolo[1,2-*c*]oxazol-3-one (1'a): ¹H NMR: δ = 1.85–2 (m, 1 H), 2.1–2.3 (m, 3 H), 3.25 (s, 3 H), 3.3–3.4 (m, 1 H), 3.55–3.7 (m, 1 H), 4.17 (d, *J* = 10.3 Hz, 1 H), 4.43 (d, *J* = 10.3 Hz, 1 H). – ¹³C NMR: δ = 25.6, 37.1, 44.6, 49.5, 69.7, 98.9, 158.7.

(5*S*)-1-[*(tert*-Butyloxy)carbonyl]-2-hydroxy-5-(*toluene-4-sulfonyloxymethyl*)pyrrolidine (5): To a stirred cooled solution of **4**^[13] (10 g, 27 mmol) in CH₂Cl₂ (100 ml) at –78°C under argon, was added dropwise a 1 M solution of LiEt₃BH in THF (40 ml, 40 mmol). The mixture was stirred for 4 h at this temperature, then quenched with saturated aqueous NaHCO₃ solution (75 ml). The reaction mixture was slowly allowed to reach 0°C, then 35% H₂O₂ solution (10 ml) was carefully added. After stirring for an additional 2 h at room temp., the reaction mixture was concentrated in vacuo, then extracted with CH₂Cl₂ (3 × 150 ml). The organic layer was dried with Na₂SO₄ and concentrated to yield crude, syrupy (1:1) diastereomeric mixture of compound **5** (10.1 g) virtually pure as seen by NMR and TLC, and which was used in the next step without further purification. – IR (neat): $\tilde{\nu}_{\max}$ = 3360, 1750 cm⁻¹. – ¹H NMR: δ = 1–2.2 (series of m including s, 13 H), 2.3 (s, 3 H), 3.39–3.42 and 3.86–4.17 (m, 4 H), 5.1–5.4 (m, 1 H), 7.20 (br. d, *J* = 6.3 Hz, 2 H), 7.7 (dd, *J* = 6.5 and 8.4 Hz, 2 H). – ¹³C NMR: δ = 21.62, 24.90, 25.75, 28.22, 30.42, 30.86, 31.57, 55.84, 62.72, 81.14, 82.17, 82.76, 127.81, 127.92, 129.92, 132.74, 145.03, 154.35.

(5*R*,7*aS*)-5-Ethoxytetrahydropyrrolo[1,2-*c*]oxazol-3-one (1b): A stirred solution of crude **5** (10.1 g, 27 mmol) in a mixture of EtOH (250 ml)/CHCl₃ (30 ml) was refluxed for 24 h. The solvents were evaporated and the oily residue was dissolved in CH₂Cl₂. The organic layer was washed with 1 M NaOH solution (50 ml), dried with Na₂SO₄, then concentrated in vacuo. The residue was chromatographed (AcOEt/cyclohexane, 1:1) to give 2 g (43% overall from **5**) of expected **1b**, as white solid, m.p. 76°C (AcOEt/cyclohexane). – $[\alpha]_{\text{D}}^{21}$ = –7.3 (*c* = 1.05, MeOH). – IR (CHBr₃): $\tilde{\nu}_{\max}$ = 1750 cm⁻¹. – ¹H NMR: δ = 1.21 (t, *J* = 7 Hz, 3 H), 1.4–1.5 (m, 1 H), 1.8–2 (m, 1 H), 2.1–2.2 (m, 1 H), 2.3–2.4 (m, 1 H), 3.58 (qd, *J* = 7 and 9 Hz, 1 H), 3.75 (qd, *J* = 7 and 9 Hz, 1 H), 4.0–4.1 (m, 2

H), 4.50 (dd, *J* = 1 and 8.5 Hz, 1 H), 5.17 (dd, *J* = 4.8 and 6.4 Hz, 1 H). – ¹³C NMR: δ = 14.86, 31.17, 33.77, 57.81, 64.30, 67.93, 90.13, 160.72. – C₈H₁₃NO₃ (171.19): calcd. C 56.12, H 7.65, N 8.18; found C 56.29, H 7.60, N 8.11.

(5*S*,7*aS*)-5-Allyltetrahydropyrrolo[1,2-*c*]oxazol-3-one (2a): To a cooled stirred solution of **1b** (3.35 g, 19.6 mmol) and allyltrimethylsilane (15.6 ml, 98.1 mmol) in CH₂Cl₂ (150 ml) at –78°C under argon, was added dropwise TiCl₄ (2.36 ml, 21.5 mmol). The reaction mixture was allowed to warm slowly to room temp. under stirring overnight. Hydrolysis with saturated aqueous NaHCO₃ solution (150 ml) was followed by extraction with CH₂Cl₂ (3 × 100 ml). The combined organic layers were washed with water (100 ml), then dried with Na₂SO₄ prior to concentration. Column chromatography (AcOEt/cyclohexane, 1:1) of the residue afforded 2.95 g (90%) of oily **2a**. – $[\alpha]_{\text{D}}^{22}$ = –75 (*c* = 1.02, MeOH). – IR (neat): $\tilde{\nu}_{\max}$ = 1740 cm⁻¹. – ¹H NMR: δ = 1.4–1.7 (m, 2 H), 2.0–2.1 (m, 1 H), 2.1–2.4 (m, 3 H), 3.9–4 (m, 2 H), 4.19 (dd, *J* = 3.2 and 8.9 Hz, 1 H), 4.5 (dd, *J* = 7.9 and 8.9 Hz, 1 H), 5.1–5.2 (m, 2 H), 5.75–5.9 (m, 1 H). – ¹³C NMR: δ = 31.46, 31.96, 40.27, 58.20, 58.90, 67.46, 117.52, 134.22, 161.53. – C₉H₁₃NO₂ (167.21): calcd. C 64.65, H 7.83, N 8.37; found C 64.50, H 7.91, N 8.35.

Typical Procedure for Reaction of π -Type Nucleophiles with 1b in the Presence of TMSOTf as Lewis Acid: To a cooled stirred solution of **1b** (100 mg, 0.584 mmol) and nucleophile (5 equiv.) in CH₂Cl₂ (5 ml) at –78°C under argon, was added dropwise TMSOTf (3 equiv.). The reaction mixture was allowed to warm slowly to room temp. under stirring overnight. Hydrolysis with saturated aqueous NaHCO₃ solution (10 ml) was followed by extraction with CH₂Cl₂ (3 × 20 ml). The combined organic layers were washed with water (20 ml), then dried with Na₂SO₄ prior to concentration and purification by column chromatography.

(5*S*,7*aS*)-5-(1,1-Dimethyl-2-oxoethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3-one (2b): The crude product obtained from **1b** and 2-methyl-1-(trimethylsiloxy)-1-propene as outlined in the typical procedure was purified by column chromatography (AcOEt/cyclohexane, 1:1) to give 50 mg (43%) of pure **2b** as an oil. – $[\alpha]_{\text{D}}^{22}$ = –64 (*c* = 0.75, MeOH). – IR (neat): $\tilde{\nu}_{\max}$ = 1755 cm⁻¹. – ¹H NMR: δ = 1.07 (s, 3 H), 1.13 (s, 3 H), 1.4–1.5 (m, 1 H), 1.7–1.8 (m, 1 H), 1.8–2.2 (m, 2 H), 3.8–3.85 (m, 1 H), 3.92 (t, *J* = 8.1 Hz, 1 H), 4.17 (dd, *J* = 2.5 and 9 Hz, 1 H), 4.46 (dd, *J* = 7.9 and 9 Hz, 1 H), 9.6 (s, 1 H). – ¹³C NMR: δ = 18.39, 19.36, 28.14, 31.53, 50.07, 60.30, 64.09, 66.99, 162.18, 205.11. – C₁₀H₁₅NO₃ (197.23): calcd. C 60.89, H 7.66, N 7.10; found C 61.01, H 7.62, N 7.02.

(5*S*,7*aS*)-5-(2-Oxo-2-phenylethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3-one (2c): The crude product obtained from **1b** and 1-phenyl-1-(trimethylsiloxy)ethylene as outlined in the typical procedure was purified by column chromatography (AcOEt/cyclohexane, 1:1) to give 126 mg (88%) of **2c** as a white solid. Recrystallisation from AcOEt/cyclohexane afforded white crystals which structure was confirmed by X-ray analysis^[31], m.p. 93–94°C. – IR (neat): $\tilde{\nu}_{\max}$ = 1750, 1680, 1600 cm⁻¹. – ¹H NMR: δ = 1.45–1.6 (m, 1 H), 1.65–1.8 (m, 1 H), 2–2.1 (m, 1 H), 2.45–2.55 (m, 1 H), 3.15 (dd, *J* = 9 and 16.9 Hz, 1 H), 3.48 (dd, *J* = 4 and 16.9 Hz, 1 H), 3.95–4.1 (m, 1 H), 4.14 (dd, *J* = 3.7 and 8.9 Hz, 1 H), 4.25–4.4 (m, 1 H), 4.46 (t, *J* = 8.3 Hz, 1 H), 7.4–7.6 (m, 3 H), 7.95 (m, 2 H). – ¹³C NMR: δ = 31.76, 33.51, 44.61, 55.53, 59.00, 67.82, 128.02, 128.65, 133.32, 136.63, 161.29, 197.79. – C₁₄H₁₅NO₃ (245.28): calcd. C 68.55, H 6.16, N 5.71; found C 68.32, H 6.21, N 5.73.

(5*S*,7*aS*)-5-(3,3-Dimethyl-2-oxobutyl)tetrahydropyrrolo[1,2-*c*]oxazol-3-one (2d): The crude product obtained from **1b** and (2,2-dimethyl-1-methylenepoxy)trimethylsilane as outlined in the

typical procedure was purified by column chromatography (AcOEt/cyclohexane, 1:1) to give 109 mg (83%) of **2d** as a white solid, m.p. 95.5°C. – $[\alpha]_D^{21} = -66$ ($c = 0.77$, MeOH). – IR (neat): $\tilde{\nu}_{\max} = 1740, 1700 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 1.14$ (s, 9 H), 1.45–1.65 (m, 2 H), 2.05–2.1 (m, 1 H), 2.45–2.5 (m, 1 H), 2.74 (dd, $J = 9$ and 17.7 Hz, 1 H), 3.03 (dd, $J = 3.8$ and 17.7 Hz, 1 H), 4–4.1 (m, 1 H), 4.1–4.2 (m, 1 H), 4.16 (dd, $J = 3.7$ and 8.8 Hz, 1 H), 4.49 (dd, $J = 8$ and 8.8 Hz, 1 H). – ^{13}C NMR: $\delta = 26.30, 31.84, 33.62, 42.60, 44.16, 55.32, 59.11, 67.80, 161.33, 213.83$. – $\text{C}_{12}\text{H}_{19}\text{NO}_3$ (225.29): calcd. C 63.97, H 8.50, N 6.21; found C 64.00, H 8.60, N 6.14.

(5*S*,7*aS*)-5-(1-Methoxycarbonyl-1-methylethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3-one (**2e**): The crude product obtained from **1b** and [(1-methoxy-2-methyl-1-propenyl)oxy]trimethylsilane as outlined in the typical procedure was purified by column chromatography (AcOEt/cyclohexane, 1:1) to give 99 mg (73%) of **2e**. – $[\alpha]_D^{22} = -53$ ($c = 1.045$, MeOH). – IR (neat): $\tilde{\nu}_{\max} = 1745 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 1.20$ (s, 3 H), 1.28 (s, 3 H), 1.4–1.55 (m, 1 H), 1.75–1.9 (m, 1 H), 2–2.25 (m, 2 H), 3.67 (s, 3 H), 3.85–3.95 (m, 1 H), 4.0 (t, $J = 8$ Hz, 1 H), 4.15 (dd, $J = 2.5$ and 8.9 Hz, 1 H), 4.48 (dd, $J = 7.8$ and 8.9 Hz, 1 H). – ^{13}C NMR: $\delta = 20.69, 23.54, 28.30, 31.39, 46.49, 51.79, 60.15, 65.49, 66.85, 161.98, 176.35$. – $\text{C}_{11}\text{H}_{17}\text{NO}_4$ (227.25): calcd. C 58.13, H 7.54, N 6.16; found C 58.07, H 7.54, N 5.97.

5-Cyanotetrahydropyrrolo[1,2-*c*]oxazol-3-one (**2f**): The crude product obtained from **1b** and cyanotrimethylsilane as outlined in the typical procedure was purified by column chromatography (AcOEt) to give 31 mg of pure *trans*-**2f** as an oil, and 53 mg of a mixture of *trans*- and *cis*-**2f** (95% overall yield).

(5*S*,7*aS*)-5-Cyanotetrahydropyrrolo[1,2-*c*]oxazol-3-one (*trans*-**2f**): Oil. – IR (neat): $\tilde{\nu}_{\max} = 2240, 1750 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 1.35$ –1.7 (m, 1 H), 2.2–2.4 (m, 2 H), 2.55–2.65 (m, 1 H), 4.0–4.18 (m, 1 H), 4.27 (dd, $J = 2.7$ and 9.2 Hz, 1 H), 4.60 (dd, $J = 7.5$ and 9.2 Hz, 1 H), 4.71 (dd, $J = 6.1$ and 8.3 Hz, 1 H). – ^{13}C NMR: $\delta = 30.10, 32.34, 47.43, 58.96, 67.66, 118.72, 160.09$.

(5*R*,7*aS*)-5-Cyanotetrahydropyrrolo[1,2-*c*]oxazol-3-one (*cis*-**2f**): Recrystallization from Et_2O of a *cis*-enriched sample afforded colourless needles whose structure was confirmed by X-ray analysis^[31], m.p. 114–115°C. – ^1H NMR: $\delta = 1.85$ –1.95 (m, 1 H), 2.2–2.3 (m, 1 H), 2.5–2.7 (m, 2 H), 4.15–4.25 (m, 2 H), 4.35 (dd, $J = 1.7$ and 8 Hz, 1 H), 4.55–4.65 (m, 1 H). – ^{13}C NMR: $\delta = 30.55, 35.17, 45.40, 59.78, 69.38, 116.36, 156.79$.

(2*S*,5*S*)-5-Allyl-2-hydroxymethylpyrrolidine (**6**): A stirred solution of oxazolidinone **2a** (0.38 g, 2.27 mmol) in a mixture of 30% aqueous KOH solution (5 ml) and 1,4-dioxane (10 ml) was refluxed for 64 h. The reaction mixture was concentrated and the resulting residue was partitioned between CH_2Cl_2 (20 ml) and brine (15 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml) and the combined organic phases were dried with Na_2SO_4 . Concentration in vacuo gave 0.32 g (100%) of amino alcohol **6** as a yellow oil, which was used in the next step without further purification. – ^1H NMR: $\delta = 1.30$ –1.45 (m, 2 H), 1.8–1.95 (m, 2 H), 2.18 (t, $J = 6.7$ Hz, 2 H), 2.4 (br. s, 2 H), 3.1–3.15 (m, 1 H), 3.25 (dd, $J = 7$ and 9.6 Hz, 1 H), 3.3–3.5 (m, 2 H), 5.0–5.1 (m, 2 H), 5.7–5.84 (m, 1 H). – ^{13}C NMR: $\delta = 27.07, 31.15, 39.97, 56.67, 58.69, 64.52, 116.28, 135.35$.

(2*S*,5*S*)-5-Allyl-1-[(benzyloxy)carbonyl]-2-hydroxymethylpyrrolidine (**7**): A mixture of **6** (0.32 g, 2.27 mmol), benzyl chloroformate (0.36 ml, 2.52 mmol) and Na_2CO_3 (0.46 g, 4.34 mmol) in CH_2Cl_2 (15 ml) was stirred overnight at room temp. The reaction mixture was then filtered and the solid residue was thoroughly

washed with CH_2Cl_2 . Concentration and purification of the residue by column chromatography (AcOEt/cyclohexane, 1:1) yielded 0.54 g (87% overall from **6**) of **7** as an oil. – $[\alpha]_D^{22} = -54$ ($c = 0.99$, CHCl_3). – IR (neat): $\tilde{\nu}_{\max} = 3400, 1670 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 1.67$ –1.75 (m, 2 H), 1.91–2.16 (m, 3 H), 2.4–2.55 (m, 0.7 H), 2.6–2.75 (m, 0.3 H), 3.4–3.75 (m, 2 H), 3.85–4.10 (m, 3 H), 4.95–5.05 (m, 2 H), 5.15 (m, 2 H), 5.55–5.8 (m, 1 H), 7.35 (m, 5 H). – ^{13}C NMR: $\delta = 25.89, 26.20, 27.40, 36.66, 37.94, 57.90, 58.88, 60.15, 63.07, 65.13, 66.49, 66.94, 117.12, 117.37, 127.74, 127.89, 128.34, 134.56, 135.03, 136.25, 136.58, 154.13, 155.78$. – $\text{C}_{16}\text{H}_{21}\text{NO}_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.67, H 7.76, N 5.03.

(2*S*,5*S*)-5-Allyl-1-[(benzyloxy)carbonyl]-2-(toluene-4-sulfonyloxymethyl)pyrrolidine (**8**): To an ice-cooled solution of alcohol **7** (9.36 g, 34 mmol) in CH_2Cl_2 (100 ml) was added NEt_3 (9.4 ml, 67.4 mmol), then *p*-TsCl (9.4 g, 49.3 mmol) portionwise. The reaction mixture was stirred at room temp. for 4 h, then concentrated in vacuo. The resulting residue was dissolved in NEt_3 (15 ml) and water was added (40 ml). The mixture was stirred for an additional 4 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml) and the combined organic layers were washed successively with 1 M HCl solution (2 × 100 ml), saturated aqueous NaHCO_3 solution (100 ml) and brine (100 ml). After drying with Na_2SO_4 and concentration, purification of the residue by column chromatography (AcOEt/cyclohexane, 1:2) afforded 14.3 g (98%) of **8** as an oil. – $[\alpha]_D^{22} = -45$ ($c = 0.98$, CHCl_3). – IR (neat): $\tilde{\nu}_{\max} = 1680 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 1.63$ –1.77 (m, 1 H), 1.80–2.03 (m, 4 H), 2.25–2.40 (m including 2 s at $\delta = 2.34$ and 2.36, 3.4 H), 2.5–2.6 (m, 0.6 H), 3.75–4.18 (m, 4 H), 4.85–5.05 (m, 4 H), 5.55–5.70 (m, 1 H), 7.1–7.28 (m, 7 H), 7.65 (dd, $J = 8.3$ and 19.6 Hz, 2 H). – ^{13}C NMR: $\delta = 21.52, 25.25, 26.10, 27.49, 36.63, 38.14, 55.70, 56.33, 57.50, 57.92, 66.67, 68.99, 69.29, 117.49, 127.62, 127.73, 127.89, 128.42, 129.79, 132.59, 132.73, 134.51, 134.69, 136.25, 136.34, 144.69, 144.79, 153.42, 154.05$. – $\text{C}_{23}\text{H}_{27}\text{NO}_5$ (429.53): calcd. C 64.31, H 6.33, N 3.26; found C 64.16, H 6.43, N 3.22.

(2*S*,5*R*)-2-Allyl-1-[(benzyloxy)carbonyl]-5-butylpyrrolidine (**9**): To a cold stirred suspension of CuI (3.43 g, 18 mmol) in Et_2O (40 ml) at -40°C was added dropwise a solution of 1-propyllithium, freshly prepared from lithium (570 mg, 82.1 mmol) and 1-bromopropane (3.3 ml, 36.8 mmol) in Et_2O (30 ml). Stirring was continued at -30 to -35°C for 30 min, then a solution of **8** (1.32 g, 3.09 mmol) in Et_2O (10 ml) was added dropwise by syringe. The reaction mixture was allowed to stir overnight at -20°C , then quenched with saturated aqueous NH_4Cl solution (30 ml). After stirring for an additional 20 min, the reaction mixture was filtered through a Celite pad, and the solid residue washed with Et_2O (200 ml). The organic layer was washed with brine (20 ml), dried with Na_2SO_4 and concentrated. Purification by column chromatography (AcOEt/cyclohexane, 5:95) gave 718 mg (78%) of **9** as an oil. – $[\alpha]_D^{22} = -64$ ($c = 1.115$, CHCl_3). – IR (neat): $\tilde{\nu}_{\max} = 1680 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 0.72$ and 0.82 (2 t, $J = 6.1$ Hz, 3 H), 1.0–1.3 (m, 5 H), 1.5–1.65 (m, 2.5 H), 1.8–2.0 (m, 3.5 H), 2.3–2.4 (m, 0.5 H), 2.55–2.7 (m, 0.5 H), 3.65–3.9 (m, 2 H), 4.8–5.2 (m, 4 H), 5.5–5.8 (m, 1 H), 7.20–7.30 (m, 5 H). – ^{13}C NMR: $\delta = 13.89, 14.02, 22.43, 22.57, 26.10, 26.35, 27.08, 27.35, 28.66, 32.22, 33.58, 36.90, 38.34, 56.87, 57.24, 57.90, 58.38, 66.29, 116.97, 127.71, 127.77, 128.28, 135.08, 135.28, 136.93, 154.06, 154.15$. – $\text{C}_{19}\text{H}_{27}\text{NO}_2$ (301.42): calcd. C 75.71, H 9.03, N 4.64; found C 75.74, H 8.98, N 4.60.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-5-butyl-2-(2-oxoethyl)pyrrolidine (**10**): To a stirred solution of **9** (312 mg, 1.03 mmol) in a 1:1 mixture of THF/ H_2O (14 ml) was added a 4% (w/w) solution

of OsO₄ in H₂O (0.45 ml, 0.07 mmol). The reaction mixture was stirred for 15 min until becoming dark brown, then NaIO₄ (650 mg, 3.1 mmol) was added portionwise. Stirring was continued for 20 min, and the obtained white precipitate was collected on a Celite pad. After washing the latter with Et₂O (150 ml), the organic layer was washed with 15% aqueous Na₂S₂O₄ solution (10 ml), saturated Na₂S₂O₃ solution (25 ml), then brine. After drying with Na₂SO₄ and concentration, the dark residue was purified by column chromatography (AcOEt/cyclohexane, 2:8) to yield 221 mg (70%) of aldehyde **10**^{[22][4e]} as a colourless oil. – $[\alpha]_{\text{D}}^{22} = -46.3$ ($c = 1.505$, CHCl₃). – IR (neat): $\tilde{\nu}_{\text{max}} = 1730, 1700 \text{ cm}^{-1}$. – ¹H NMR: $\delta = 0.81$ and 0.88 (2t, $J = 6.8 \text{ Hz}$, 3 H), 1.1–1.4 (m, 6 H), 1.55–1.75 (m, 2 H), 1.8–2.0 (m, 1 H), 2.05–2.20 (m, 1 H), 2.3–2.45 (m, 1 H), 2.75–2.85 (m, 0.4 H), 3.1–3.2 (m, 0.6 H), 3.75–3.85 (m, 1 H), 4.20–4.40 (m, 1 H), 5.02–5.19 (m, 2 H), 7.25–7.35 (m, 5 H), 9.61 (s, 0.4 H), 9.75 (t, $J = 1.75 \text{ Hz}$, 0.6 H). – ¹³C NMR: $\delta = 14.02, 14.14, 22.53, 22.68, 26.45, 27.49, 28.45, 28.73, 29.34, 32.27, 33.56, 47.93, 48.95, 52.04, 52.72, 57.96, 58.47, 66.76, 127.98, 128.14, 128.49, 136.72, 154.40, 200.53, 200.77$.

(2*S*,5*R*)-2-Allyl-1-[(benzyloxy)carbonyl]-5-methylpyrrolidine (**11**): To a stirred cooled solution of tosylate **8** (372 mg, 0.866 mmol) in THF (6 ml) at 0°C was added dropwise a 1 M solution of LiEt₃BH in THF (2.5 ml, 2.5 mmol). The reaction mixture was stirred at room temp. for 4 h. Then, water (0.5 ml), 3 M NaOH solution (1 ml, 3 mmol) and 35% H₂O₂ solution (1 ml, 1 mmol) were successively added, before stirring for an additional 30 min. The reaction mixture was concentrated in vacuo, then extracted with CH₂Cl₂ (3 × 10 ml). The organic layer was washed with water, dried with Na₂SO₄ and concentrated. Purification by column chromatography (AcOEt/cyclohexane, 1:9) yielded 177 mg (79%) of pyrrolidine **11**. – $[\alpha]_{\text{D}}^{22} = -56.5$ ($c = 1.01$, CHCl₃). – IR (neat): $\tilde{\nu}_{\text{max}} = 1680 \text{ cm}^{-1}$. – ¹H NMR: $\delta = 1.12$ and 1.19 (2d, $J = 6.3 \text{ Hz}$, 3 H), 1.47–1.55 (m, 1 H), 1.70–1.75 (m, 1 H), 1.95–2.10 (m, 3 H), 2.35–2.45 (m, 0.5 H), 2.5–2.7 (m, 0.5 H), 3.85–4.0 (m, 2 H), 5.0–5.2 (m, 4 H), 5.6–5.8 (m, 1 H), 7.26–7.37 (m, 5 H). – ¹³C NMR: $\delta = 19.41, 20.61, 25.95, 26.94, 29.51, 30.41, 37.13, 38.50, 53.34, 53.77, 57.11, 57.51, 66.46, 117.13, 127.86, 128.46, 135.21, 135.40, 137.05, 154.39$. – C₁₆H₂₁NO₂ (259.34): calcd. C 74.10, H 8.16, N 5.40; found C 73.98, H 8.26, N 5.31.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-2-(3-hydroxypropyl)-5-methylpyrrolidine (**12**): To an ice-cooled stirred solution of **11** (250 mg, 0.965 mmol) in Et₂O (5 ml), was added dropwise by syringe a 2 M solution of BH₃·(CH₃)₂S in THF (0.19 ml, 0.366 mmol). The reaction mixture was stirred at room temp. under inert atmosphere for 4 h. EtOH (1 ml) was then added, followed by 3 M aqueous NaOH solution (0.12 ml, 0.36 mmol). After cooling the reaction mixture to 0°C, 35% H₂O₂ solution (0.1 ml, 1 mmol) was carefully added. The cooling bath was then removed and the reaction mixture was heated at reflux for 1 h. The reaction mixture was then poured into ice water (10 ml) and extracted with Et₂O (3 × 20 ml). The organic layer was washed with water, dried with Na₂SO₄ and concentrated in vacuo. Column chromatography of the residue (AcOEt/cyclohexane, 1:1) afforded 203 mg (76%) of alcohol **12** as a colourless oil. – $[\alpha]_{\text{D}}^{22} = -56$ ($c = 1.01$, CHCl₃) {ref.^[25] $[\alpha]_{\text{D}}^{22} = -55$ ($c = 1.36$, CHCl₃)}. – IR (neat): $\tilde{\nu}_{\text{max}} = 3420, 1680 \text{ cm}^{-1}$. – ¹H NMR: $\delta = 1.10$ and 1.17 (2 d, $J = 6.3 \text{ Hz}$, 3 H), 1.20–1.65 (m, 6 H), 1.7–2.3 (series of m, 3 H), 3.4–4.0 (series of m, 4 H), 5.0–5.2 (m, 2 H), 7.28–7.36 (m, 5 H). – ¹³C NMR: $\delta = 19.05, 20.21, 26.45, 27.17, 28.97, 29.12, 29.39, 29.46, 30.22, 52.83, 53.25, 57.39, 57.48, 61.73, 61.98, 66.20, 66.30, 127.62, 128.19, 136.66, 154.03, 154.35$.

(2*S*,5*R*)-2-Allyl-1-[(benzyloxy)carbonyl]-5-heptylpyrrolidine (**14**): To a stirred cold suspension of CuI (4.5 g, 23.6 mmol) in Et₂O

(60 ml) at –50°C, was added dropwise a 2.5 M commercial solution of *n*-hexyllithium in hexane (19 ml, 47.5 mmol). After stirring at –40 to –30°C for 40 min, the dark reaction mixture was cooled to –50°C and a solution of tosylate **8** (2 g, 4.75 mmol) in Et₂O (20 ml) was added dropwise by syringe. The reaction mixture was stirred overnight at –20°C. After warming to 0°C, the reaction was quenched by addition of a (1:1) mixture of saturated aqueous NH₄Cl solution (30 ml) and concentrated aqueous NH₄OH solution (30 ml). The mixture was vigorously stirred for 30 min, then filtered through a Celite pad. The solid residue was thoroughly washed with CH₂Cl₂, and the organic layer was washed successively with a (1:1) mixture of saturated solution of NH₄Cl/NH₄OH (30 ml) and water (30 ml), then dried with Na₂SO₄. Concentration gave an oily yellow residue which was purified by column chromatography (AcOEt/cyclohexane, 5:95) yielding 1.28 g (79%) of **14** as a colourless oil. – $[\alpha]_{\text{D}}^{22} = -56.7$ ($c = 1.015$, CHCl₃). – IR (neat): $\tilde{\nu}_{\text{max}} = 1710 \text{ cm}^{-1}$. – ¹H NMR: $\delta = 0.88$ (t, $J = 6.4 \text{ Hz}$, 3 H), 1.12–1.4 (m, 11 H), 1.6–1.8 (m, 2.5 H), 1.85–2.15 (m, 3.5 H), 2.40–2.45 (m, 0.5 H), 2.60–2.70 (m, 0.5 H), 3.75–4 (m, 2 H), 4.95–5.25 (m, 4 H), 5.60–5.80 (m, 1 H), 7.30–7.40 (m, 5 H). – ¹³C NMR: $\delta = 14.17, 22.69, 26.24, 26.49, 26.68, 27.22, 27.49, 29.28, 29.42, 29.49, 29.62, 31.88, 32.69, 34.05, 37.06, 38.49, 57.02, 57.38, 58.08, 58.59, 66.46, 117.14, 127.92, 128.45, 135.29, 135.47, 137.09, 154.34$. – C₂₂H₃₃NO₂ (343.50): calcd. C 76.92, H 9.68, N 4.07; found C 76.99, H 9.75, N 4.03.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-5-heptyl-2-(3-hydroxypropyl)pyrrolidine (**15**): To an ice-cooled stirred solution of **14** (555 mg, 1.61 mmol) in Et₂O (10 ml), was added dropwise by syringe a 2 M solution of BH₃·(CH₃)₂S in THF (0.5 ml, 1 mmol). The reaction mixture was stirred at room temp. under inert atmosphere for 4 h. EtOH (2 ml) was then added, followed by 3 M aqueous NaOH solution (0.25 ml, 0.75 mmol). After cooling the reaction mixture to 0°C, 35% H₂O₂ solution (0.2 ml, 2 mmol) was carefully added. The cooling bath was then removed and the reaction mixture was heated at reflux for 1 h. The reaction mixture was then poured into ice-cold water (15 ml) and extracted with Et₂O (3 × 40 ml). The organic layer was washed with water, dried with Na₂SO₄ and concentrated in vacuo. Column chromatography of the residue (AcOEt/cyclohexane, 1:1) afforded 463 mg (79%) of alcohol **14** as a colourless oil. – $[\alpha]_{\text{D}}^{22} = -50.4$ ($c = 1.31$, CHCl₃). – IR (neat): $\tilde{\nu}_{\text{max}} = 3440, 1710 \text{ cm}^{-1}$. – ¹H NMR: $\delta = 0.86$ (t, $J = 6.3 \text{ Hz}$, 3 H), 1.20–2.4 (series of m, 21 H), 3.4–3.9 (m, 4 H), 5.03 and 5.04 (1/2 AB q, $J = 12.4 \text{ Hz}$, 1 H), 5.17 and 5.19 (1/2 AB q, $J = 12.4 \text{ Hz}$, 1 H), 7.30–7.35 (m, 5 H). – ¹³C NMR: $\delta = 14.05, 22.56, 26.57, 26.99, 27.46, 27.61, 29.13, 29.33, 29.51, 29.64, 30.25, 31.74, 32.49, 33.79, 57.31, 57.71, 58.22, 61.95, 62.28, 66.37, 66.48, 127.80, 128.33, 136.64, 136.78, 154.14, 154.47$. – C₂₂H₃₅NO₃ (361.51): calcd. C 73.09, H 9.76, N 3.87; found C 73.09, H 9.82, N 3.79.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-5-heptyl-2-(3-oxopropyl)pyrrolidine (**16**): To a stirred cooled solution of oxalyl chloride (0.28 ml, 3.22 mmol) in CH₂Cl₂ (8 ml) at –60°C, was added dropwise by syringe a solution of DMSO (0.46 ml, 6.45 mmol) in CH₂Cl₂ (1.5 ml). After 5 min stirring, a solution of alcohol **15** (1.06 g, 2.93 mmol) in CH₂Cl₂ (4 ml) was slowly added. Stirring was continued for an additional 45 min at –60°C, then NEt₃ (2 ml, 14.66 mmol) was added and the reaction mixture was allowed to warm slowly to room temp. Water (25 ml) was then added and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 ml). The combined organic layers were washed successively with 1% HCl solution (20 ml), 2% aqueous NaHCO₃ solution (20 ml) and brine (20 ml). After drying with Na₂SO₄ and concentration, column chromatography of the residue (AcOEt/cyclohexane, 1:2) yielded 935 mg (89%) of alde-

hyde **16** as an oil. – $[\alpha]_D^{24} = -67$ ($c = 1.00$, CHCl_3). – IR (neat): $\tilde{\nu}_{\text{max}} = 1720, 1680 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 0.85$ (t, $J = 6.4 \text{ Hz}$, 3 H), 1.20–1.25 (m, 11 H), 1.55–2.45 (series of m, 9 H), 3.75–3.85 (m, 2 H), 5.05 and 5.17 (AB q, $J = 12.4 \text{ Hz}$, 2 H), 7.28–7.35 (m, 5 H), 9.56 and 9.73 (2 s, 1 H). – ^{13}C NMR: $\delta = 14.06, 22.57, 25.48, 26.56, 26.93, 27.59, 29.15, 29.33, 31.75, 32.42, 33.80, 40.95, 41.05, 55.69, 57.22, 57.87, 58.39, 66.52, 127.87, 128.09, 128.40, 136.80, 154.00, 154.45, 201.47, 201.89$.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-5-heptyl-2-(3-hydroxybutyl)pyrrolidine (**17**): To an ice-cooled solution of aldehyde **16** (385 mg, 1.07 mmol) in THF (10 ml) was added dropwise a commercial 3 M solution of MeMgCl in THF (1.8 ml, 5.4 mmol). After stirring for 1.5 h at 0°C , the reaction mixture was quenched with ice-cold water (10 ml). The aqueous phase was extracted with Et_2O ($3 \times 20 \text{ ml}$) and the combined organic layers were washed with brine (20 ml) and dried with Na_2SO_4 . Concentration in vacuo and purification by column chromatography ($\text{AcOEt}/\text{cyclohexane}$, 1:1) gave 349 mg (86%) of a diastereomeric mixture of alcohol **17**. – IR (neat): $\tilde{\nu}_{\text{max}} = 3440, 1700, 1680 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 0.85$ (t, $J = 6.3 \text{ Hz}$, 3 H), 1–1.5 (m, 17 H), 1.5–2.1 (m, 7 H), 3.6–3.9 (m, 3 H), 5–5.25 (m, 2 H), 7.25–7.35 (m, 5 H). – ^{13}C NMR: $\delta = 14.15, 22.67, 23.27, 23.47, 26.68, 27.26, 27.57, 29.26, 29.46, 29.62, 30.22, 31.85, 32.61, 33.89, 35.79, 36.03, 56.99, 57.47, 57.77, 57.88, 58.05, 58.34, 66.53, 67.63, 68.00, 68.51, 127.95, 128.18, 128.45, 136.98, 154.23, 154.59$. – $\text{C}_{23}\text{H}_{37}\text{NO}_3$ (375.55): calcd. C 73.56, H 9.93, N 3.73; found C 73.45, H 10.15, N 3.73.

(2*S*,5*R*)-1-[(Benzyloxy)carbonyl]-5-heptyl-2-(3-oxobutyl)pyrrolidine (**18**): To a stirred cooled solution of oxalyl chloride (0.1 ml, 1.14 mmol) in CH_2Cl_2 (4 ml) at -60°C , was added dropwise by syringe a solution of DMSO (0.16 ml, 2.25 mmol) in CH_2Cl_2 (1 ml). After 5 min stirring, a solution of alcohol **17** (349 mg, 0.93 mmol) in CH_2Cl_2 (2 ml) was slowly added. Stirring was continued for an additional 45 min at -60°C , then NEt_3 (0.65 ml, 4.72 mmol) was added and the reaction mixture was allowed to warm slowly to room temp. Water (10 ml) was then added and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 15 \text{ ml}$). The combined organic layers were washed successively with 1% HCl solution (10 ml), 2% aqueous NaHCO_3 solution (10 ml) and brine (10 ml). After drying with Na_2SO_4 and concentration, column chromatography of the residue ($\text{AcOEt}/\text{cyclohexane}$, 1:2) yielded 300 mg (86%) of ketone **18** as an oil. – $[\alpha]_D^{23} = -61.4$ ($c = 1.1$, CHCl_3). – IR (neat): $\tilde{\nu}_{\text{max}} = 1700 \text{ cm}^{-1}$. – ^1H NMR: $\delta = 0.86$ (t, $J = 6.5 \text{ Hz}$, 3 H), 1.1–1.35 (m, 11 H), 1.45–1.70 (m, 4 H), 1.8–2.5 (series of m including 2 s at 1.99 and 2.13, 8 H), 3.65–3.85 (m, 2 H), 5.05 and 5.16 (ABq, $J = 12.4 \text{ Hz}$, 2 H), 7.27–7.4 (m, 5 H). – ^{13}C NMR: $\delta = 14.06, 22.57, 26.58, 26.86, 26.97, 27.32, 27.60, 27.75, 28.25, 29.15, 29.36, 29.49, 29.64, 31.75, 32.44, 33.85, 40.87, 41.05, 56.83, 57.31, 57.76, 58.34, 66.45, 127.84, 128.10, 128.36, 136.88, 154.06, 154.42, 208.04, 208.45$. – $\text{C}_{23}\text{H}_{35}\text{NO}_3$ (373.53): calcd. C 73.95, H 9.44, N 3.75; found C 73.90, H 9.44, N 3.71.

(3*R*,5*S*,8*R*)-3-Heptyl-5-methylpyrrolizidine [(–)-Xenovenine] (**13**): A suspension of ketone **18** (300 mg, 0.8 mmol) and 10% Pd/ BaSO_4 (90 mg) in MeOH (10 ml) was vigorously stirred under hydrogen for 6 h. The insoluble material was removed by filtration and the filtrate was concentrated to give a residue. The latter was treated with 1 M aqueous NaOH solution (10 ml) and the aqueous layer was extracted with Et_2O ($3 \times 15 \text{ ml}$). Drying of the organic layer with Na_2SO_4 and concentration gave a residue which was column-chromatographed ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 4:1) yielding 110 mg (60%) of (–)-(**13**) – $[\alpha]_D^{23} = -11.4$ ($c = 1.37$, CHCl_3) {ref.^[26] $[\alpha]_D^{20} = -11.6$ ($c = 0.6$, CHCl_3); ref.^[27] $[\alpha]_D^{24} = -11.5$ ($c = 0.5$,

CHCl_3)}. – ^1H NMR: $\delta = 0.86$ (t, $J = 6.1 \text{ Hz}$, 3 H), 1.08 (d, $J = 6.3 \text{ Hz}$, 3 H), 1.10–1.6 (m, 16 H), 1.85–2.05 (m, 4 H), 2.55–2.65 (m, 1 H), 2.70–2.80 (m, 1 H), 3.55–3.65 (m, 1 H). – ^{13}C NMR: $\delta = 14.07, 21.74, 22.65, 27.24, 29.33, 29.86, 31.66, 31.86, 32.04, 32.40, 34.42, 36.90, 61.78, 65.04, 66.72$.

X-ray Crystal Structure of trans-2c: All data were obtained with an Enraf Nonius CAD4 diffractometer with graphite-monochromated Mo-K_α radiation. Accurate unit-cell dimensions and crystal-orientation matrix together with their estimated standard deviations were obtained from least-squares refinements of the setting angles of 25 reflections. Crystal data: $\text{C}_{14}\text{H}_{15}\text{NO}_3$ (245.27); monoclinic, space group $P2_1$; $a = 5.791(1)$, $b = 23.826(4)$, $c = 9.412(1)$ Å, $\beta = 104.82(1)^\circ$, $V = 1255.4(4) \text{ Å}^3$; $Z = 4$; $D = 1.30 \text{ g cm}^{-3}$; $F(000) = 520.15$; $\mu(\text{Mo-K}_\alpha) = 0.9 \text{ cm}^{-1}$. The intensities were measured using $\omega/2\theta$ scans up to 56° . Two standard reflections were monitored periodically and remained constant during data collection. Lorentz and polarization factors were applied while absorption corrections were not considered as necessary. Of the 3093 independent reflections collected, 892 reflections with $I > 3 \sigma(I)$ were used for the structure determination and refinement. The structure was solved by direct methods using SHELXS86.^[29] Computations were performed using a PC version of CRYSTALS.^[30] Scattering factors for all atoms were as incorporated in CRYSTALS. All remaining non-hydrogen atoms were found by electron-density map calculations. Their atomic coordinates were refined together with the isotropic displacement parameter. All hydrogen atoms were calculated at geometrical position with an overall isotropic temperature factor. The refinement of atomic parameters was carried out by full-matrix least-squares refinement. The final refinement converged with $R = 0.077$ and $R_w = 0.072$ for 147 parameters. The minimum and maximum peaks in the final difference Fourier map were -0.38 and 0.44 e Å^{-3} . The supplementary material includes the list of atomic coordinates, the bond lengths and angles.^[31]

X-ray Crystal Structure of cis-2f: All data were obtained with an Enraf Nonius CAD4 diffractometer with graphite-monochromated Mo-K_α radiation. Accurate unit-cell dimensions and crystal-orientation matrix together with their estimated standard deviations were obtained from least-squares refinements of the setting angles of 25 reflections. Crystal data: $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$ (152.15); monoclinic, space group $P2_1$, $a = 6.5015(9)$, $b = 8.253(7)$, $c = 7.343(1)$ Å, $\beta = 114.10(1)^\circ$, $V = 359.7(3) \text{ Å}^3$; $Z = 2$; $D = 1.40 \text{ g cm}^{-3}$; $F(000) = 160.04$; $\mu(\text{Mo-K}_\alpha) = 1.0 \text{ cm}^{-1}$. The intensities were measured using $\omega/2\theta$ scans up to 60° . Two standard reflections were monitored periodically and remained constant during data collection. Lorentz and polarization factors were applied while absorption corrections were not considered as necessary. Of the 1115 independent reflections collected, 897 reflections with $I > 3 \sigma(I)$ were used for the structure determination and refinement. The structure was solved by direct methods using SHELXS86.^[29] Computations were performed using a PC version of CRYSTALS.^[30] Scattering factors for all atoms were as incorporated in CRYSTALS. All remaining non-hydrogen atoms were found by electron-density map calculations. Their atomic coordinates were refined together with the anisotropic displacement parameter. All hydrogen atoms were located from difference electron-density maps; their coordinates were refined with an overall isotropic temperature factor. The refinement of atomic parameters was carried out by full-matrix least-squares refinement. The final refinement converged with $R = 0.037$ and $R_w = 0.035$ for 125 parameters. The minimum and maximum peaks in the final difference Fourier map were -0.19 and 0.18 e Å^{-3} . The supplementary material includes the list of atomic coordinates, the bond lengths and angles.^[31]

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