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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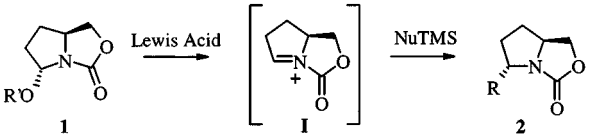
Enantiopure bicyclic 5-ethoxytetrahydropyrrolo[1,2-c]oxazol-3-one **1b** was prepared in two steps from the known tosylate **4**, which is readily available from (*S*)-pyroglutamic acid. Trapping of the *N*-acyliminium ion (**I**), generated in situ from **1b** in the presence of Lewis acid, with various 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 organocopper 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



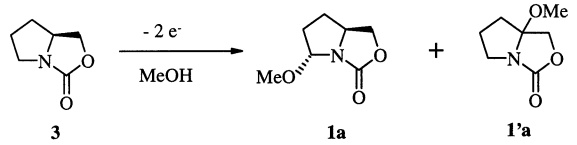
We report herein our study toward the synthesis of carbinolamine **1**, precursor of iminium ion **I**, and its reactivity with various silylated π-type nucleophiles in the presence of Lewis acid. Then, we describe the use of this methodology in the synthesis of pyrrolizidine and indolizidine alkaloids, 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, Et_4NOTs, −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

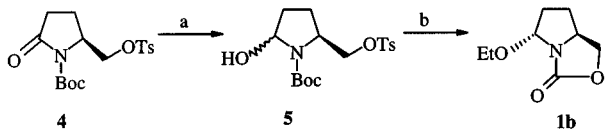


Screening of various conditions (temperature, electrolyte, current density, etc.) did not significantly modify this result. A similar reverse regioselectivity has been observed for electromethoxylation of bicyclic oxazinones.[12] These disappointing results prompted us to consider the preparation of 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

  1434−193X/98/0909−1955 $ 17.50+.50/0

Scheme 3



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

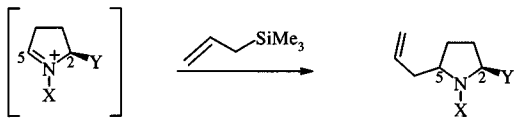
the lactam moiety,[14] cleanly providing hemiaminal **5** as a (1:1) diastereomeric mixture in a quantitative yield. When refluxed without further purification in the binary system $CHCl_3$−EtOH, the latter compound gave rise to *trans*-α-ethoxyoxazolidinone **1b** in 43% overall yield starting from **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 ($BF_3{\cdot}OEt_2$, $TiCl_4$, 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, azidotrimethylsilane 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



I : X,Y = -CO-O-CH_2-
II : X = Y = CO,Me

trans/cis
from **I** : 96/4
from **II** : 20/80

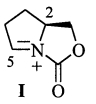
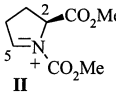
The main difference between these substrates lies in the geometry around the nitrogen atom. It appears that the five-membered ring monocyclic iminium ion **II** exhibits only very little distortion from planarity, whereas the nitrogen atom of bicyclic iminium **I**, due to the presence of two five-membered 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] *trans*/*cis*
1	CH_2=$CHCH_2$TMS	$BF_3{\cdot}Et_2O$	CH_2=$CHCH_2$−	**2a** (60)	96:4
2	CH_2=$CHCH_2$TMS	$TiCl_4$	CH_2=$CHCH_2$−	**2a** (90)	95:5
3	CH_2=$CHCH_2$TMS	TMSOTf	CH_2=$CHCH_2$−	**2a** (65)	96:4
4	Me_2C=CHOTMS	TMSOTf	HOCCMe_2−	**2b** (43)[c]	100:0
5	CH_2=C(Ph)OTMS	TMSOTf	$PhCOCH_2$−	**2c** (86)	94:6
6	CH_2=C(*t*Bu)OTMS	TMSOTf	*t*$BuCOCH_2$−	**2d** (83)	100:0
7	Me_2C=C(OMe)OTMS	TMSOTf	MeO_2CCMe_2−	**2e** (73)	97:3
8	N≡CTMS	TMSOTf	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 allytrimethylsilane nucleophile

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

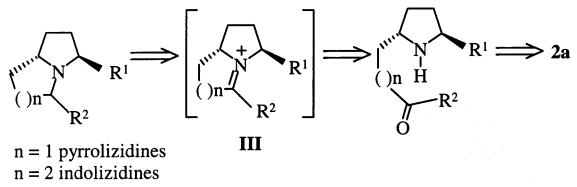
[a] Nu = allyl. − [b] Dihedral angles for transition states.

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 ($\phi \approx 40°$) than for the *trans* one ($\phi \approx 110°$). 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**: $\Delta E(trans - cis) = -1.34$ kcal mol^{-1}; for **II**: $\Delta E(trans - cis) = 3.24$ kcal mol^{-1}].

Synthesis of Naturally Occuring Alkaloids

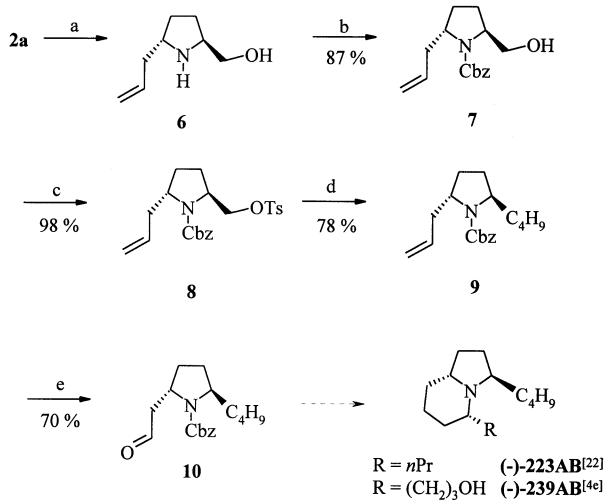
As an application of this highly stereoselective methodology for the obtention of chiral *trans* 2,5-disubstituted pyrrolidines, we now describe the (formal or total) syntheses of some indolizidine (gephyrotoxines) and pyrrolizidine (xenovenines) alkaloids in order to illustrate the usefulness of the 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 debenzyloxycarbonylation 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**,[4e] 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**



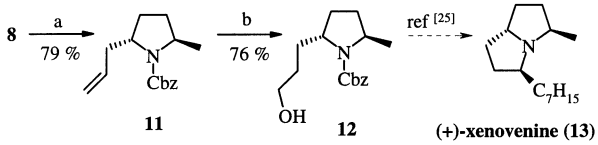
Reagents: (a) 30% KOH-1,4-dioxane, reflux. − (b) $C_6H_5CH_2OCOCl$, Na_2CO_3, CH_2Cl_2. − (c) *p*-TsCl, NEt_3, CH_2Cl_2. − (d) nPr_2CuLi, Et_2O, −20°C. − (e) Cat.OsO_4, $NaIO_4$, THF/H_2O.

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 $(n\text{-}C_3H_7)_2CuLi$ 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 OsO_4 in the presence of $NaIO_4$ in $THF{\cdot}H_2O$.

On the other hand, *trans*-2,5-disubstituted pyrrolidine substructures are equally found in some naturally occuring 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]

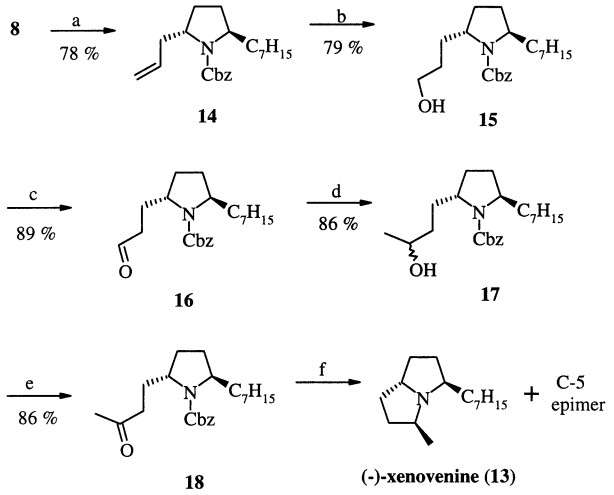
Scheme 7: Formal synthesis of (+)-xenovenine



Reagents: (a) $LiEt_3BH$, THF, room temp. − (b) $BH_3{\cdot}(CH_3)_2S$, Et_2O, then NaOH, H_2O_2.

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*-Hex_2CuLi in Et_2O 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 $Pd/BaSO_4$ 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 ^{13}C-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, $CHCl_3$), which is very close to the values of −11.6 (c = 0.6, $CHCl_3$) and −11.5 (c = 0.5, $CHCl_3$) cited for samples obtained by Oppolzer et al.[26] and Momose et al.[27], respectively.

Scheme 8: Total synthesis of (−)-xenovenine



Reagents: (a) $nHex_2CuLi$, Et_2O, −20°C. − (b) $BH_3{\cdot}(CH_3)_2S$, then NaOH, H_2O_2. − (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2. −60°C. − (d) MeMgCl, THF. − (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2. − (f) H_2, $Pd/BaSO_4$, MeOH.

Conclusion

The first part of this study was devoted to the reactivity of the bicyclic *N*-acyliminium ion **I** 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 occuring indolizidine and pyrrolizidine alkaloids.

Experimental Section

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. − THF and Et_2O were distilled from Na benzophenone ketyl immediately prior to use. − CH_2Cl_2 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 F_{254}) plates and column chromatography on silica gel Gerudan SI 60 (40−60 μm) (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 ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at δ = 7.27 for ^1H and to $CDCl_3$ at δ = 77.1 for ^{13}C. When an acyclic carbamate moiety is present in a molecule, peak doubling due to the presence of two rotamers is observed in ^1H and ^{13}C 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 CH_2Cl_2 (15 ml) and washed with water (20 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 ml) and the combined organic extract dried with Na_2SO_4 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]

(5R,7aS)-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). − ^{13}C NMR: δ = 30.10, 33.28, 55.73, 57.45, 67.75, 91.38, 160.20.

7a-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). − ^{13}C NMR: δ = 25.6, 37.1, 44.6, 49.5, 69.7, 98.9, 158.7.

(5S)-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 CH_2Cl_2 (100 ml) at −78°C under argon, was added dropwise a 1 M solution of $LiEt_3BH$ in THF (40 ml, 40 mmol). The mixture was stirred for 4 h at this temperature, then quenched with saturated aqueous $NaHCO_3$ solution (75 ml). The reaction mixture was slowly allowed to reach 0°C, then 35% H_2O_2 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 CH_2Cl_2 (3 × 150 ml). The organic layer was dried with Na_2SO_4 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). − ^{13}C 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.

(5R,7aS)-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)/$CHCl_3$ (30 ml) was refluxed for 24 h. The solvents were evaporated and the oily residue was dissolved in CH_2Cl_2. The organic layer was washed with 1 M NaOH solution (50 ml), dried with Na_2SO_4, 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). − $[\alpha]_D^{21}$ = −7.3 (*c* = 1.05, MeOH). − IR ($CHBr_3$): $\tilde{\nu}_{max}$ = 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). − ^{13}C NMR: δ = 14.86, 31.17, 33.77, 57.81, 64.30, 67.93, 90.13, 160.72. − $C_8H_{13}NO_3$ (171.19): calcd. C 56.12, H 7.65, N 8.18; found C 56.29, H 7.60, N 8.11.

(5S,7aS)-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 CH_2Cl_2 (150 ml) at −78°C under argon, was added dropwise $TiCl_4$ (2.36 ml, 21.5 mmol). The reaction mixture was allowed to warm slowly to room temp. under stirring overnight. Hydrolysis with saturated aqueous $NaHCO_3$ solution (150 ml) was followed by extraction with CH_2Cl_2 (3 × 100 ml). The combined organic layers were washed with water (100 ml), then dried with Na_2SO_4 prior to concentration. Column chromatography (AcOEt/cyclohexane, 1:1) of the residue afforded 2.95 g (90%) of oily **2a**. − $[\alpha]_D^{22}$ = −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). − ^{13}C NMR: δ = 31.46, 31.96, 40.27, 58.20, 58.90, 67.46, 117.52, 134.22, 161.53. − $C_9H_{13}NO_2$ (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 CH_2Cl_2 (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 $NaHCO_3$ solution (10 ml) was followed by extraction with CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed with water (20 ml), then dried with Na_2SO_4 prior to concentration and purification by column chromatography.

(5S,7aS)-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. − $[\alpha]_D^{22}$ = −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). − ^{13}C NMR: δ = 18.39, 19.36, 28.14, 31.53, 50.07, 60.30, 64.09, 66.99, 162.18, 205.11. − $C_{10}H_{15}NO_3$ (197.23): calcd. C 60.89, H 7.66, N 7.10; found C 61.01, H 7.62, N 7.02.

(5S,7aS)-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). − ^{13}C 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. − $C_{14}H_{15}NO_3$ (245.28): calcd. C 68.55, H 6.16, N 5.71; found C 68.32, H 6.21, N 5.73.

(5S,7aS)-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-methylenepropoxy)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 cm^{-1}. – ^1H NMR: δ = 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: δ = 26.30, 31.84, 33.62, 42.60, 44.16, 55.32, 59.11, 67.80, 161.33, 213.83. – $C_{12}H_{19}NO_3$ (225.29): calcd. C 63.97, H 8.50, N 6.21; found C 64.00, H 8.60, N 6.14.

(5S,7aS)-5-(1-Methoxycarbonyl-1-methylethyl)tetrahydropyrrolo[1,-2c]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 cm^{-1}. – ^1H NMR: δ = 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: δ = 20.69, 23.54, 28.30, 31.39, 46.49, 51.79, 60.15, 65.49, 66.85, 161.98, 176.35. – $C_{11}H_{17}NO_4$ (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).

(5S,7aS)-5-Cyanotetrahydropyrrolo[1,2-c]oxazol-3-one (*trans*-**2f**): Oil. – IR (neat): $\tilde{\nu}_{max}$ = 2240, 1750 cm^{-1}. – ^1H NMR: δ = 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: δ = 30.10, 32.34, 47.43, 58.96, 67.66, 118.72, 160.09.

(5R,7aS)-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: δ = 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: δ = 30.55, 35.17, 45.40, 59.78, 69.38, 116.36, 156.79.

(2S,5S)-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 (10ml) 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: δ = 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: δ = 27.07, 31.15, 39.97, 56.67, 58.69, 64.52, 116.28, 135.35.

(2S,5S)-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 cm^{-1}. – ^1H NMR: δ = 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: δ = 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. – $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.67, H 7.76, N 5.03.

(2S,5S)-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 cm^{-1}. – ^1H NMR: δ = 1.63–1.77 (m, 1 H), 1.80–2.03 (m, 4 H), 2.25–2.40 (m including 2 s at δ = 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: δ = 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. – $C_{23}H_{27}NO_5S$ (429.53): calcd. C 64.31, H 6.33, N 3.26; found C 64.16, H 6.43, N 3.22.

(2S,5R)-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 cm^{-1}. – ^1H NMR: δ = 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: δ = 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. – $C_{19}H_{27}NO_2$ (301.42): calcd. C 75.71, H 9.03, N 4.64; found C 75.74, H 8.98, N 4.60.

(2S,5R)-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 OsO_4 in H_2O (0.45 ml, 0.07 mmol). The reaction mixture was stirred for 15 min until becoming dark brown, then $NaIO_4$ (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 Et_2O (150 ml), the organic layer was washed with 15% aqueous $Na_2S_2O_4$ solution (10 ml), saturated $Na_2S_2O_3$ solution (25 ml), then brine. After drying with Na_2SO_4 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. − $[\alpha]_D^{22} = -46.3$ (c = 1.505, $CHCl_3$). − IR (neat): $\tilde{\nu}_{max}$ = 1730, 1700 cm^{-1}. − ^1H NMR: δ = 0.81 and 0.88 (2t, J = 6.8 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 Hz, 0.6 H). − ^{13}C NMR: δ = 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.

(2S,5R)-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 $LiEt_3BH$ 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% H_2O_2 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 CH_2Cl_2 (3 × 10 ml). The organic layer was washed with water, dried with Na_2SO_4 and concentrated. Purification by column chromatography (AcOEt/cyclohexane, 1:9) yielded 177 mg (79%) of pyrrolidine **11**. − $[\alpha]_D^{22} = -56.5$ (c = 1.01, $CHCl_3$). − IR (neat): $\tilde{\nu}_{max}$ = 1680 cm^{-1}. − ^1H NMR: δ = 1.12 and 1.19 (2d, J = 6.3 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). − ^{13}C NMR: δ = 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. − $C_{16}H_{21}NO_2$ (259.34): calcd. C 74.10, H 8.16, N 5.40; found C 73.98, H 8.26, N 5.31.

(2S,5R)-1-[(Benzyloxy)carbonyl]-2-(3-hydroxypropyl)-5-methylpyrrolidine (**12**): To an ice-cooled stirred solution of **11** (250 mg, 0.965 mmol) in Et_2O (5 ml), was added dropwise by syringe a 2 M solution of $BH_3{\cdot}(CH_3)_2S$ 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% H_2O_2 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 Et_2O (3 × 20 ml). The organic layer was washed with water, dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue (AcOEt/cyclohexane, 1:1) afforded 203 mg (76%) of alcohol **12** as a colourless oil. − $[\alpha]_D^{22} = -56$ (c = 1.01, $CHCl_3$) {ref.[25] $[\alpha]_D^{22} = -55$ (c = 1.36, $CHCl_3$)}. − IR (neat): $\tilde{\nu}_{max}$ = 3420, 1680 cm^{-1}. − ^1H NMR: δ = 1.10 and 1.17 (2 d, J = 6.3 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). − ^{13}C NMR: δ = 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.

(2S,5R)-2-Allyl-1-[(benzyloxy)carbonyl]-5-heptylpyrrolidine (**14**): To a stirred cold suspension of CuI (4.5 g, 23.6 mmol) in Et_2O (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 Et_2O (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 NH_4Cl solution (30 ml) and concentrated aqueous NH_4OH solution (30 ml). The mixture was vigorously stirred for 30 min, then filtered through a Celite pad. The solid residue was thoroughly washed with CH_2Cl_2, and the organic layer was washed successively with a (1:1) mixture of saturated solution of NH_4Cl/NH_4OH (30 ml) and water (30 ml), then dried with Na_2SO_4. 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. − $[\alpha]_D^{22} = -56.7$ (c = 1.015, $CHCl_3$). − IR (neat): $\tilde{\nu}_{max}$ = 1710 cm^{-1}. − ^1H NMR: δ = 0.88 (t, J = 6.4 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). − ^{13}C NMR: δ = 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. − $C_{22}H_{33}NO_2$ (343.50): calcd. C 76.92, H 9.68, N 4.07; found C 76.99, H 9.75, N 4.03.

(2S,5R)-1-[(Benzyloxy)carbonyl]-5-heptyl-2-(3-hydroxypropyl)pyrrolidine (**15**): To an ice-cooled stirred solution of **14** (555 mg, 1.61 mmol) in Et_2O (10 ml), was added dropwise by syringe a 2 M solution of $BH_3{\cdot}(CH_3)_2S$ 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% H_2O_2 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 Et_2O (3 × 40 ml). The organic layer was washed with water, dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue (AcOEt/cyclohexane, 1:1) afforded 463 mg (79%) of alcohol **15** as a colourless oil. − $[\alpha]_D^{22} = -50.4$ (c = 1.31, $CHCl_3$). − IR (neat): $\tilde{\nu}_{max}$ = 3440, 1710 cm^{-1}. − ^1H NMR: δ = 0.86 (t, J = 6.3 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 Hz, 1 H), 5.17 and 5.19 ($^1/_2$ AB q, J = 12.4 Hz, 1 H), 7.30−7.35 (m, 5 H). − ^{13}C NMR: δ = 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. − $C_{22}H_{35}NO_3$ (361.51): calcd. C 73.09, H 9.76, N 3.87; found C 73.09, H 9.82, N 3.79.

(2S,5R)-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 CH_2Cl_2 (8 ml) at −60°C, was added dropwise by syringe a solution of DMSO (0.46 ml, 6.45 mmol) in CH_2Cl_2 (1.5 ml). After 5 min stirring, a solution of alcohol **15** (1.06 g, 2.93 mmol) in CH_2Cl_2 (4 ml) was slowly added. Stirring was continued for an additional 45 min at −60°C, then NEt_3 (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 CH_2Cl_2 (3 × 30 ml). The combined organic layers were washed successively with 1% HCl solution (20 ml), 2% aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml). After drying with Na_2SO_4 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): $\tilde{\nu}_{max}$ = 1720, 1680 cm^{-1}. − ^1H NMR: δ = 0.85 (t, J = 6.4 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 Hz, 2 H), 7.28−7.35 (m, 5 H), 9.56 and 9.73 (2 s, 1 H). − ^{13}C NMR: δ = 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.

(2S,5R)-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 × 20 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 (AcOEt/cyclohexane, 1:1) gave 349 mg (86%) of a diastereomeric mixture of alcohol **17**. − IR (neat): $\tilde{\nu}_{max}$ = 3440, 1700, 1680 cm^{-1}. − ^1H NMR: δ = 0.85 (t, J = 6.3 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: δ = 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. − $C_{23}H_{37}NO_3$ (375.55): calcd. C 73.56, H 9.93, N 3.73; found C 73.45, H 10.15, N 3.73.

(2S,5R)-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 × 15 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 (AcOEt/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): $\tilde{\nu}_{max}$ = 1700 cm^{-1}. − ^1H NMR: δ = 0.86 (t, J = 6.5 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 Hz, 2 H), 7.27−7.4 (m, 5 H). − ^{13}C NMR: δ = 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. − $C_{23}H_{35}NO_3$ (373.53): calcd. C 73.95, H 9.44, N 3.75; found C 73.90, H 9.44, N 3.71.

(3R,5S,8R)-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 × 15 ml). Drying of the organic layer with Na_2SO_4 and concentration gave a residue which was column-chromatographed (CH_2Cl_2/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: δ = 0.86 (t, J = 6.1 Hz, 3 H), 1.08 (d, J = 6.3 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: δ = 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: $C_{14}H_{15}NO_3$ (245.27); monoclinic, space group $P2_1$; a = 5.791(1), b = 23.826(4), c = 9.412(1) Å, β = 104.82 (1)°, V = 1255,4(4) $Å^3$; Z = 4; D = 1.30 g cm^{-3}; $F(000)$ = 520.15; μ(Mo-K_α) = 0.9 cm^{-1}. The intensities were measured using ω/2θ 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 no 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: $C_7H_8N_2O_2$ (152.15); monoclinic, space group $P2_1$, a = 6.5015(9), b = 8.253(7), c = 7.343(1) Å, β = 114.10 (1)°, V = 359,7(3) $Å^3$; Z = 2; D = 1.40 g cm^{-3}; $F(000)$ = 160.04 ; μ(Mo-K_α) = 1.0 cm^{-1}. The intensities were measured using ω/2θ 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]

[1] A. R. Mattock, in *Chemistry and Toxycology of Pyrrolidine Alkaloids,* Academic Press, London, **1986**.
[2] T. Tokuyama, N. Nishimori, I. L. Karle, M. W. Edwards, J. W. Daly, *Tetrahedron* **1986**, *42*, 3453−3460.
[3] [3a] T. Katsuki, M. Yamaguchi, *J. Syn. Org. Chem. Jpn*. **1986**, *44*, 532−544. − [3b] L.-Y. Chen, L. Ghosez, *Tetrahedron Lett*. **1990**, *31*, 4467−4470. − [3c] K. Fugi, M. Node, Y. Naniwa, T. Kawabata, *Tetrahedron Lett*. **1990**, *31*, 3175−3178. − [3d] J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581−1590 and references cited herein. − [3e] S. Ikegami, H. Uchiyama, T. Hayama, T. Katsuki, M. Yamagushi, *Tetrahedron* **1988**, *44*, 5333−5342.
[4] [4a] P. Q. Huang, S. Arseniyadis, H. P. Husson, *Tetrahedron Lett*. **1987**, *28*, 547−550. − [4b] H. Takahata, H. Takehara, N. Ohkubo, T. Momose, *Tetrahedron: Asymmetry* **1990**, *1*, 561−566. − [4c] M. Skrinjar, L. G. Wistrand, *Tetrahedron Lett*. **1990**, *31*, 1775−1778. − [4d] S. Rosset, J.-P. Célérier, G. Lhommet, *Tetrahedon Lett*. **1991**, *32*, 7521−7526. − [4e] G. Vo Thanh, J.-P. Célérier, G. Lhommet, *Tetrahedron: Asymmetry* **1996**, *7*, 2211−2212. − [4f] G. Vo Thanh, J.-P. Célérier, A. Fleurant, C. Grandjean, S. Rosset, G. Lhommet, *Heterocycles* **1996**, *43*, 1381−1384.
[5] L. G. Wistrand, M. Skrinjar, *Tetrahedron* **1991**, *47*, 573−582.
[6] C. Célimène, H. Dhimane, G. Lhommet, *Tetrahedron*, in press.
[7] T. Shono, T. Fujita, Y. Matsumura, *Chem. Lett*. **1991**, *81*, 80−84.
[8] H. Dhimane, C. Vanucci, G. Lhommet, *Tetrahedron Lett*. **1997**, *38*, 1415−1418.
[9] [9a] Y. Imada, M. Yasushi, Y. Mitsue, K. Ike, K. Washizuta, *Bull. Chem. Soc. Jpn*. **1996**, *69*, 2079−2090. − [9b] W. Wiegrebe, E.-G. Herrmann, U. P. Schlunegger, H. Budzikiewicz, *Helv. Chem. Acta* **1974**, *57*, 301−314.
[10] S.-I. Murahashi, T. Naota, N. Miyaguchi, T. Nakato, *Tetrahedron Lett*. **1992**, *33*, 6991−6994.
[11] T. Shono, *Tetrahedron* **1984**, *40*, 811−850.
[12] F. Driessens, C. Hootele, *Can. J. Chem*. **1991**, *69*, 211−217.
[13] S.-B. Huang, J. S. Nelson, D. D. Weller, *J. Org. Chem*. **1991**, *56*, 6007−6018.
[14] C. Pedregal, J. Ezquerra, A. Escribano, M. C. Carreno, J. L. Garcia Ruano, *Tetrahedron Lett*. **1994**, *35*, 2053−2056.
[15] Various binary systems ROH/$CHCl_3$ (R = Me, *i*Pr, CF_3CH_2) were tested without notable improvement of the observed yield (36 to 42%).[8]
[16] C. Agami, F. Couty, L. Hamon, O. Venier, *Tetrahedron Lett*. **1994**, *34*, 4509−4512.
[17] A stepwise procedure, i.e. etherification of compound **5** [$HC(OMe)_3$, PPTS, MeOH] followed by cyclisation, resulted in a poor overall yield of **1a** (25%).
[18] A *cis*-enriched sample of **2a** was synthesised according to an opposite sequence,[8] i.e. allylation of a monocyclic *N*-Boc protected iminium of type **II** (X = CO_2tBu, Y = CO_2Me), followed by a three-step procedure leading to the required bicyclic oxazolidinone.
[19] A. G. M. Barrett, D. Pilipauska, *J. Org. Chem*. **1991**, *56*, 2787−2800.
[20] The geometries of the initial states were optimised by using the Davidson-Fletcher-Powell algorithm (FLEPO procedure), minimising the energy with respect to all internal coordinates. Approximate transition states were obtained from the energy profiles in a reaction path (the reaction coordinates being the distance between the carbon atom of C=N and the reactive terminal carbon atom of the allylsilane); then the transition states were optimised by minimising the energy gradient (NLLSQ procedure).
[21] M. J. Dewar, E. G. Zoebisch, E. F. Herly, J. J. P. Stewart, *J. Amer. Chem. Soc*. **1985**, *107*, 3902−3909; AMPAC version 2.14.
[22] A. Fleurant, J.-C. Célérier, G. Lhommet, *Tetrahedron: Asymmetry* **1993**, *4*, 1429−1430.
[23] J. W. Daly, *J. Nat. Prod*. **1998**, *61*, 162−172.
[24] [24a] T. H. Jones, M. S. Blum, *J. Org. Chem*. **1980**, *45*, 4778−4780. − [24b] T. H. Jones, S. M. Stahly, A. W. Don, M. S. Blum, *J. Chem. Ecol*. **1988**, *14*, 2197. − [24c] The optical rotation of naturally occuring sample of xenovenine has not been determined so far because of its scarcity.
[25] O. Provost, J.-P. Célérier, H. Petit, G. Lhommet, *J. Org. Chem*. **1992**, *57*, 2163−2166.
[26] W. Oppolzer, C. G. Bochet, E. Merifield, *Tetrahedron Lett*. **1994**, *35*, 7015−7018.
[27] H. Takahata, H. Bandoh, T. Momose, *J. Org. Chem*. **1992**, *57*, 4401−4404.
[28] Compound **1a** was equally prepared by refluxing **5** in MeOH in 39% yield. The spectral data of **1′a** were deduced by difference with those of **1a**.
[29] G. M. Sheldrick, *SHELXS86*, *Program for the solution of crystal structures*, University of Göttingen, Federal Republic of Germany, **1986.**
[30] D. J Watkin, C. K Prout, R. J Carruthers, P. W Betteridge, *CRYSTALS*, Issue 10, Chemical Crystallography Laboratory, Oxford, UK, **1996.**
[31] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101210. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code + 44-(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

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