Preparation and structure of homochiral tetrahydro-2*H*-1,3-oxazines

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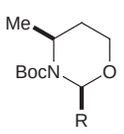
The synthesis, and structural elucidation using NMR and X-ray crystallography, of homochiral *N*-*tert*-butoxycarbonyl-tetrahydro-2*H*-1,3-oxazines are described.

Introduction

Homochiral propargyl (prop-2-ynyl) amines are of great importance as therapeutic agents,[1] in particular as inhibitors of pyridoxyl-5′-pyrophosphate-dependent enzymes,[2] and possibly also as antifungal agents.[3] They are also important as building blocks in synthesis, as precursors to allylic amines and other targets.[4] Although an impressive range of methods for the synthesis of homochiral amines and amino acids is available to the synthetic chemist,[5,6] most approaches are inappropriate for the synthesis of propargyl and other α-unsaturated amines. The synthesis of homochiral propargyl amines has been largely restricted to two methods; elaboration of amino aldehydes, commonly derived from available amino acids, *via* the Gilbert[7] and Corey–Fuchs[8] methodologies; or synthesis of homochiral propargyl alcohols, followed by stereospecific insertion of nitrogen.[1] Both of these methods can be problematic in the case of sensitive substrates, leading to both racemisation and decomposition of the chiral amine. There is therefore a need for more direct and general methods for enantioselective synthesis of these compounds.

Addition of organometallic reagents to the C=N double bond has proved to be a good general method for the asymmetric synthesis of amines[9] and a recent report by Enders[10] has demonstrated that homochiral propargyl amines can be synthesised by hydride addition to homochiral imines. We have chosen to approach the enantioselective synthesis of propargyl amines *via* a complementary strategy, using the stereoselective ring-opening of cyclic homochiral aminals (*N*,*O*-acetals) by acetylenic anions. In a previous communication[11] we reported the first successful synthesis of homochiral propargyl amines *via* the ring-opening of *N*-*tert*-butoxycarbonyl-tetrahydro-2*H*-1,3-oxazines **1**. In this paper, we describe the preparation and full structural analysis of the tetrahydro-2*H*-1,3-oxazines; in the accompanying paper[12] we report full details of the synthesis of the propargyl amines from these oxazines, and the determination of the absolute configuration of the newly formed chiral centre.



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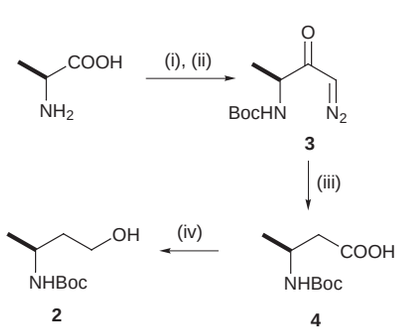
1a R = cyclohexyl
1b R = *n*-hexyl
1c R = *n*-propyl
1d R = isopropyl
1e R = $((CH_3)_2CH)_3SiOCH_2CH_2CH_2CH_2CH_2$
1f R = $((CH_3)_2CH)_3SiOCH_2CH_2CH_2$
1g R = CH_2Ph

Results and discussion

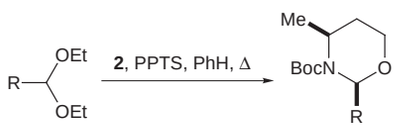
Synthesis of the tetrahydro-2*H*-1,3-oxazines 1a–g

It was envisaged that the tetrahydro-2*H*-1,3-oxazines **1a**–**g** would be synthesised from (*S*)-3-[(*tert*-butoxycarbonyl)amino]-butan-1-ol **2** and an appropriate aldehyde. As chiral 1,3-amino alcohols are important building blocks in asymmetric synthesis, many strategies for their synthesis have been described.[13] We required a short synthesis of **2** based on cheap starting materials, and therefore used an Arndt–Eistert homologation[14,15] of alanine, as follows (Scheme 1). L-Alanine was N-protected with *tert*-butyl pyrocarbonate, converted to the mixed anhydride and treated with diazomethane to give **3**. Wolff rearrangement with Ag_2O or AgOAc gave **4** in high yield; this was followed by conversion to the mixed anhydride and reduction with sodium borohydride to give the desired compound **2** in 55% overall yield from alanine. The integrity of the chiral centre in **2** was checked by conversion to the Mosher's ester[16] with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl), followed by HPLC analysis: as expected,[17] no racemisation had taken place during the Wolff rearrangement.



Scheme 1 *Reagents and conditions*: (i) $(^tBuOCO)_2O$, NaOH, rt, 18 h; (ii) Et_3N, ^{i}BuOCOCl, THF, 0 °C, then CH_2N_2, 3 h, rt; (iii) Ag_2O, Na_2CO_3, $Na_2S_2O_3$, H_2O, 20 min; (iv) Et_3N, ^{i}BuOCOCl, THF, 0 °C, then $NaBH_4$, 1 h.

Table 1

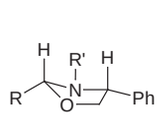


Oxazine	Yield (%)
1a	76
1b	83
1c	69
1d	50
1e	60
1f	50
1g	51

Attempts to produce the tetrahydro-2*H*-1,3-oxazines **1** by heating **2** with the required aldehyde,[18,19] by heating in the presence of PPTS,[20] or removing water using $MgSO_4$[21] or Dean–Stark conditions,[20] gave no reaction. Increasing either temperature or acidity led only to significant deprotection of the amine. However, a PPTS-catalysed reaction of **2** with the corresponding diethyl acetals in refluxing benzene led to tetrahydro-2*H*-1,3-oxazines **1a**–**g** in good to excellent yields (Table 1). The reasons for this remain unclear, but may be due to the fact that the σ bond of the acetal is more readily cleaved than the π bond of the aldehyde.

Structure of the tetrahydro-2*H*-1,3-oxazines 1

In order to understand the mechanism of the subsequent ring-opening of these tetrahydro-2*H*-1,3-oxazines, it is crucial that their structures are known. It is particularly important to determine the relative configuration of the C-2 and C-4 substituents, and whether they are axial or equatorial. In addition, NMR spectra of the tetrahydrooxazines showed, in the majority of cases, two distinct signals for H-2, in ratios ranging from 86:14 to 100:0. Although previous work had indicated that 1,3-oxazolidines **6** are formed as a mixture of *cis* and *trans*



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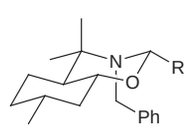

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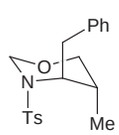

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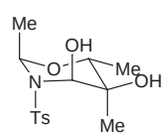

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isomers,[22] it was initially not clear whether the two tetrahydrooxazine isomers were diastereoisomers, or whether the two signals in the NMR spectra arose from the presence of two different Boc rotamers. Furthermore, in all cases the two isomers were inseparable by chromatography. In order to resolve these issues, we undertook a detailed structural analysis of two of the tetrahydrooxazines.

The structure of the tetrahydro-2*H*-1,3-oxazines was first determined by X-ray diffraction analysis of **1g** (Fig. 1) and the previously reported[11] structure of **1a** (Fig. 2). With both of these compounds, a distorted chair conformation is seen, with the 4-methyl group and the 2-substituents pseudoaxial, and the Boc group equatorial. It was assumed that these structures correspond to the major isomers of **1a** and **1g**.

We then undertook a full analysis of both isomers of **1a** by NMR spectroscopy. The reaction product (mixture of crystalline solid and viscous oil) was analysed using high-resolution

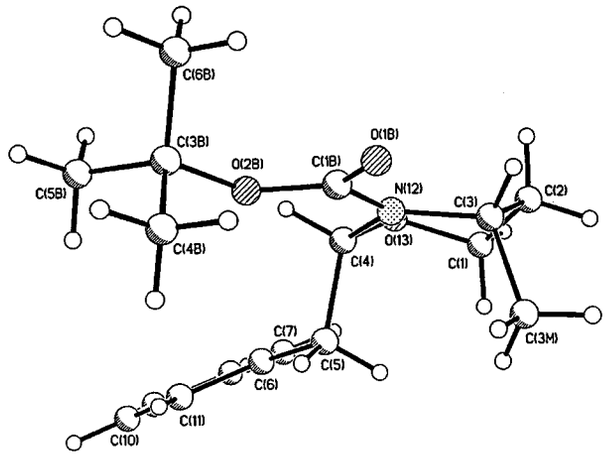


Fig. 1 X-Ray crystal structure of **1g**.

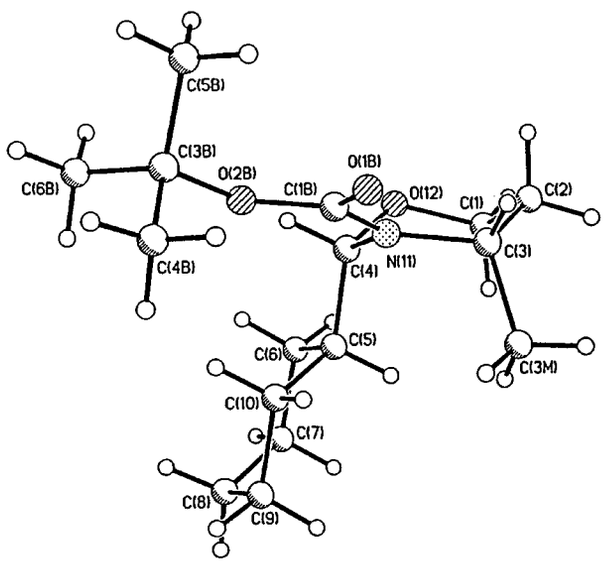
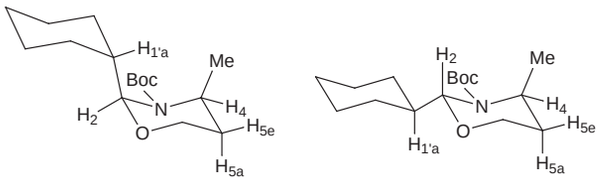


Fig. 2 X-Ray crystal structure of **1a**.

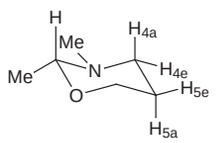
solid-state ^{13}C NMR and solution ^{1}H and ^{13}C NMR techniques. 2-D Homo- and heteronuclear correlation experiments, together with 1-D homonuclear decoupling experiments were used to determine the chemical shifts and coupling constants for both isomers; selected values are given in Tables 2 and 3. A series of 1-D NOE experiments was then performed on the major isomer, in order to determine the solution conformation. Although most NOEs observed could be satisfied by a chair conformation with both cyclohexyl and methyl groups axial (Boc equatorial), a small NOE between H2 and H4 gave evidence of distortion. NOE data were processed using SYBYL and TRIAD to generate 26 unique distance constraints. The result of molecular modelling with energy minimisation under these constraints was that **1a** existed as a distorted chair in solution, with the cyclohexyl and methyl groups in pseudoaxial positions and the Boc group in a pseudoequatorial position (Fig. 3), much as in the crystal structure. These results were further confirmed by inspection of the $^{3}J_{HH}$ coupling constants at the 4-position of the major and minor isomers (Table 3). The coupling constants for both major and minor isomers are consistent with H4 being equatorial; however, the distortion of the chair conformation is evident from the differences between the major and minor isomers, and the coupling constants previously reported for *N*-methyltetrahydro-2*H*-1,3-oxazines such as **5**.[23] Similar 1-D NOE experiments showed that the major isomer of 2-benzyltetrahydro-2*H*-1,3-oxazine **1g** also adopts a distorted chair conformation, with both benzyl and methyl groups axial and the Boc group equatorial (Fig. 4).

Table 2 Selected ^{1}H NMR chemical shifts for **1a** (major) and **1a** (minor)



1a (major)

1a (minor)



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	1a Major isomer/ppm	**1a** Minor isomer/ppm
H2	5.10	4.76
H4	4.37	4.00
H5a	2.02	2.00
H5e	1.38	1.58
H6a	3.86	3.54
H6e	3.77	3.84
Cyc H1′a	1.93	1.92
4-Me	1.25	1.32

Table 3 Selected coupling constants for **1a** (major), **1a** (minor) and **5**

	1a Major isomer/Hz	**1a** Minor isomer/Hz	**5**/Hz [23]
$^3J_{H4eH5a}$	7.3	4.8	4.5
$^3J_{H4eH5e}$	2.9	4.8	2.0
$^3J_{H5aH6a}$	10.8	9.8	*
$^3J_{H5aH6e}$	5.1	7.1	*
$^3J_{H5eH6a}$	3.3	6.2	*
$^3J_{H5eH6e}$	4.2	3.4	*
$^3J_{H1'aH2}$	10.1	9.5	*

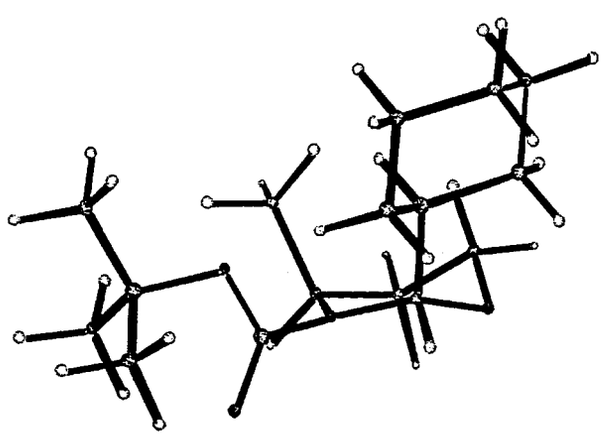

Fig. 3 Solution structure of **1a**.

Identification of the minor isomer of **1a** initially proved problematic. Although it was clear from the $^3J_{H4eH5a}$ and $^3J_{H4eH5e}$ coupling constants that H4 was equatorial, the orientation of the H2 proton was more difficult to determine, as there are no heterocyclic protons vicinal to H2. However, a NOESY experiment on the mixture of isomers in CD_2Cl_2 (ratio of major : minor 11 : 1) showed a clear cross-peak between H2-(minor) at 4.76 ppm and the axial Me group at 1.38 ppm, indicating that H2(minor) is in fact axial (Fig. 5). A NOESY cross-peak between H6a(minor) and 4-Me(minor) further confirmed

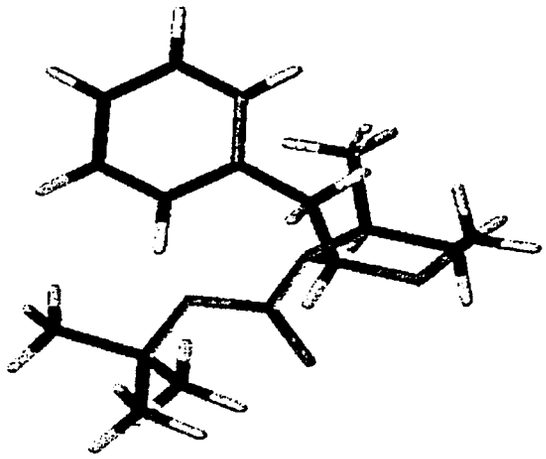

Fig. 4 Solution structure of **1g**.

the axial orientation of the 4-Me group. For the major isomer, an equivalent cross-peak between H2(major) at 5.10 ppm and the axial Me group at 1.31 ppm was not observed. Instead, an intensive cross-peak between H1′(major) at 2.02 ppm and the 4-Me group at 1.31 ppm was found. No cross-peak for the H1′,4-Me pair is observed for the minor isomer. These results were further confirmed using the double pulse field gradient spin echo technique (DPFGSE, also known as "excitation sculpting"), the main advantage of which is the capability to detect small transient NOEs.[24] Fig. 6 shows the results of applying this technique to both major and minor isomers. In both cases proton H2 was chosen as a target. For the minor isomer notable NOE enhancements were observed with H6a and 4-Me, whereas corresponding NOE enhancements for the major isomer are much smaller (>5 times). These results confirm that the major and minor isomers of the tetrahydro-2*H*-1,3-oxazines are in fact diastereomeric; the major diastereoisomer is the *cis*-isomer, with both substituents diaxial, and the minor diastereoisomer is the *trans*-isomer, in which the C-2 substituent occupies the equatorial position.

To further confirm that the minor isomer of **1a** did not correspond to a second rotameric form, caused by restricted rotation about the C–N bond of the bulky Boc group, variable temperature NMR studies were performed on the mixture of isomers. At 373 K (in d_8-toluene) no significant change of the spectrum was found. At 193 K (Fig. 7: in CD_2Cl_2), the H2 and H4 signals for both isomers had each resolved into two peaks, with the other signals less clearly resolved. For the major isomer these peaks were in a 4 : 1 ratio, and for the minor isomer these peaks were in a 1 : 1 ratio. For the major isomer, $^3J_{H4H5a}$ values measured from the {4-Me} homodecoupling experiment at 193 K were 6.6 Hz for both peaks. The doublet splitting of the H2 proton at 193 K is 10.8 Hz for both species (this corresponds to a dihedral angle of *ca.* 180° between H2 and H1′a) and is in close agreement with that measured at room temperature. These observations, together with the fact that significant chemical shift differences at low temperatures are observed only for protons spatially close to the Boc group, suggests that the observed lineshape changes are (mainly) due to π-flip jump motion of the Boc group about the N–C bond, and not to conformational change of the heterocycle (which presumably remains in a chair conformation). At temperatures below −80 °C this motion is slow relative to the timescale of the ^{1}H NMR, which in this case is of the order of the ^{1}H chemical shift difference. Chemical shift changes for H2 and H4 in two different rotamers A and B (with population ratio $p_A : p_B = 4 : 1$) are most likely to be caused by the magnetic anisotropy of the C=O bond, which is particularly strong when neighbouring protons are in the vicinity of the >C=O plane. Consideration of the anisotropy of the C=O group suggests that in rotamers A and B protons H2e and H4e, respectively, are in the proximity of the

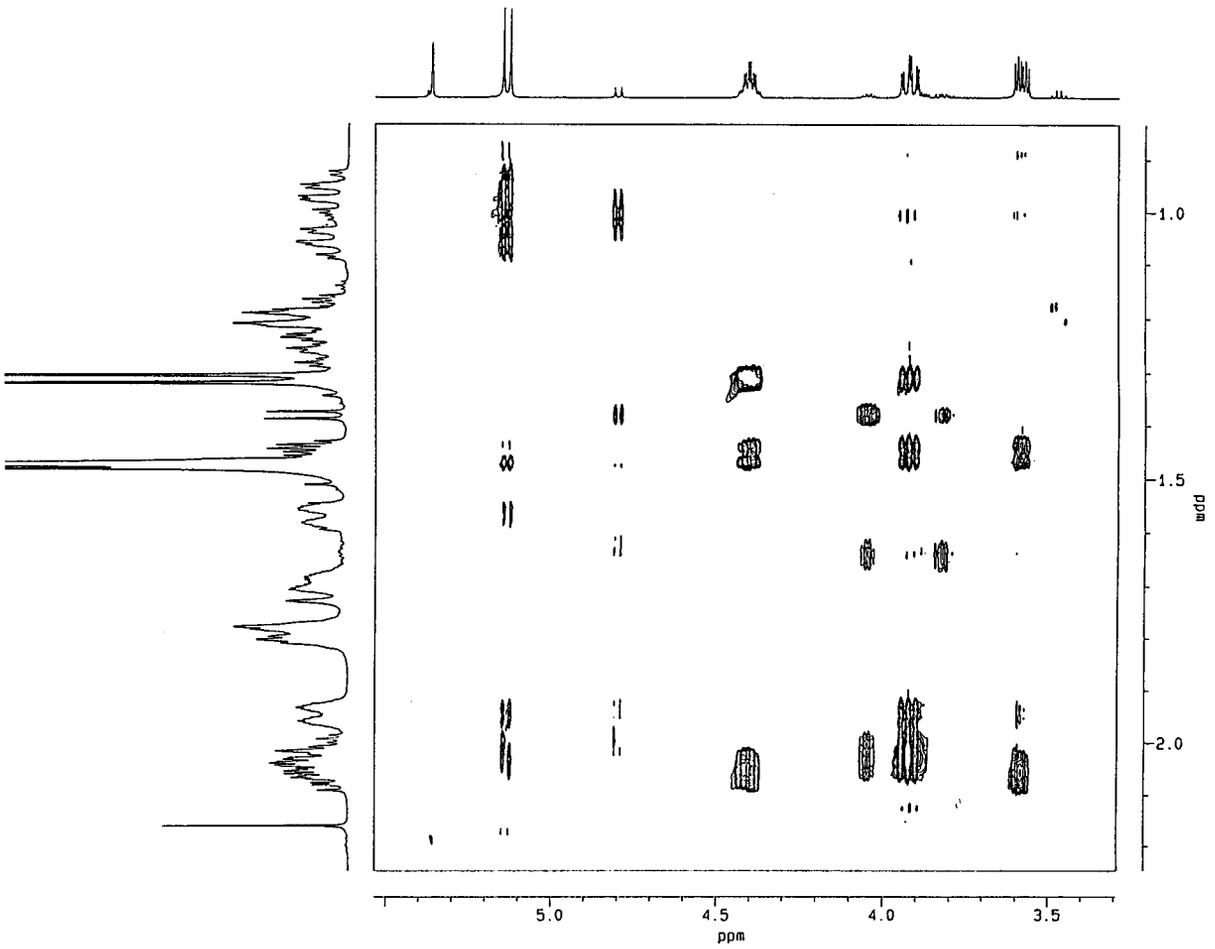

Fig. 5 Section of the NOESY spectrum of **1a** (500 MHz, solvent CD_2Cl_2, mixing time 1.5 s).

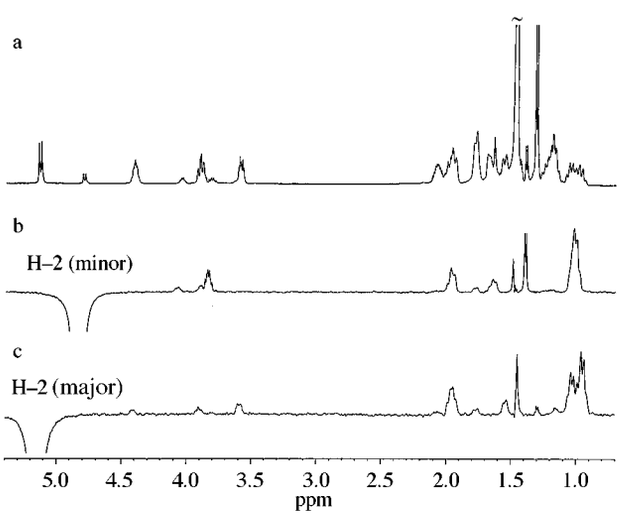

Fig. 6 (a) The ^{1}H NMR spectrum of **1a** (500 MHz, solvent $CDCl_3$). The transient DPFGSE NOE spectra (mixing time 0.6 s) for the (b) minor and (c) major isomers. In both cases proton H-2 was selectively refocused using two 50 ms Gaussian shaped pulses.

C=O group. Therefore, preferred rotamer A has a *Z*-configuration of the –O–t-Bu and the cyclohexyl fragments. It is interesting to note that this configuration was also found in the solid state by the X-ray diffraction analysis (Fig. 2). The following free energies of activation ($\Delta G^{\ddagger}$) have been evaluated at the coalescence temperatures using methods previously reported:[25] 48 kJ mol^{-1} [223 K; major isomer, $Z \rightarrow E$], 45.5 kJ mol^{-1} [223 K; major isomer, $E \rightarrow Z$], 44 kJ mol^{-1} [223 K; minor isomer, $Z \leftrightarrow E$]. With simple *tert*-butyl carbamates,[26] the energy barrier to rotation about the C–N bond is sufficiently low that separate signals for rotational isomers are not seen at room temperature; clearly, even in this sterically congested cyclic system, the same holds true.

We have also undertaken solid-state ^{13}C MAS NMR studies of **1a**. Fig. 8 shows the spectra obtained at room temperature for the mixture of the reaction product (mainly polycrystalline solid with a small amount of liquid phase) using the single-pulse experiment (SPE) and the cross-polarisation technique. Chemical shifts are compared with those determined from the solution NMR (Table 4). Comparison of the SPE and CP spectra reveals that peaks due to the minor isomer are not detectable by the CP technique, which makes use of the heteronuclear dipole–dipole interactions. These interactions are averaged to zero in liquids due to translational and reorientational motions, and, therefore, the liquid phase at room temperature can be assigned to the minor isomer. Table 4 also shows that there are no significant differences in the solution and the solid-state (liquid for the minor isomer) chemical shifts. This confirms our assumption that no significant change of the (ring) conformation has occurred on dissolving the sample.

The room temperature ^{13}C CPMAS NMR spectrum shows relatively broad lines for the carbon nuclei directly bonded to nitrogen. Low-temperature measurements were undertaken in order to reveal reasons for these broadening effects. Fig. 9 shows the ^{13}C CPMAS NMR spectra of **1a** in the temperature range 183–297 K. On lowering the temperature below 213 K a multiplicity increase occurs for carbons C2, C6 and COO. The observed lineshape changes cannot be explained by dynamic effects, as no significant exchange broadening of peaks is observed on cooling. A plausible explanation for the observed line shapes at 203 and 183 K is the second order quadrupolar effect transferred from ^{14}N to ^{13}C *via* dipolar interactions

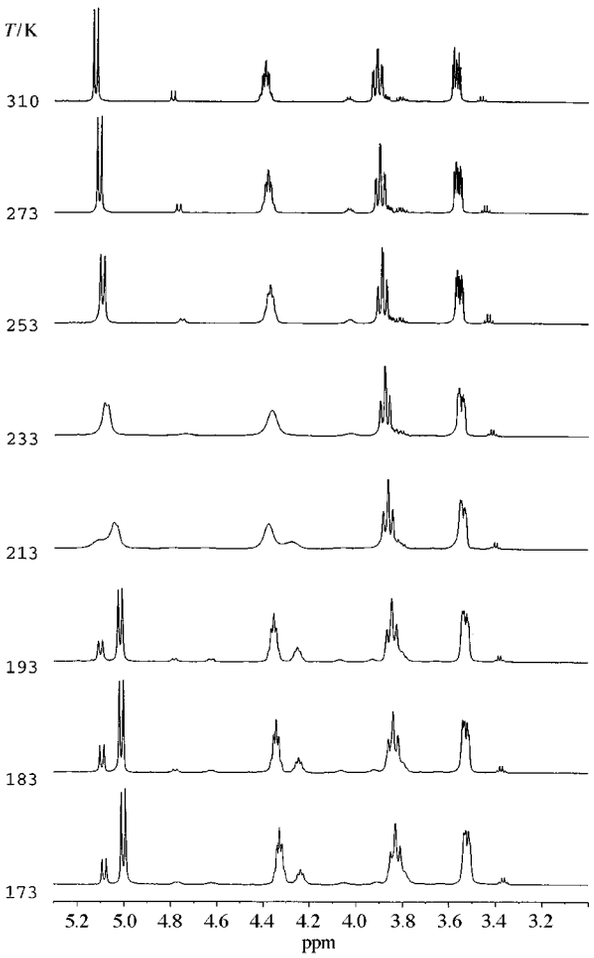

Fig. 7 VT NMR studies on the mixture of isomers of **1a** (600 MHz, CD_2Cl_2).

(known as residual dipolar coupling). This effect, together with the contribution of indirect $^1J(^{13}C,^{14}N)$ coupling, usually manifests itself in high-resolution solid-state ^{13}C NMR spectra as scaled by MAS powder pattern consisting of 1:2 (or to 2:1, depending on the sign of the ^{14}N quadrupole coupling constant) doublets for ^{13}C nuclei directly bonded to ^{14}N. Spectral simulations using values of quadrupole parameters and *J*-couplings for structurally related compounds (Table 5 and Fig. 10) show that the observed line shapes for ^{13}C nuclei directly bonded to ^{14}N can be adequately described by the combined effect of residual and indirect dipolar couplings. Temperature dependence of this effect ("self-decoupling" at temperatures above 223 K) is likely to be caused by the acceleration of the ^{14}N spin-lattice relaxation time on heating or as a result of phase transition. Previously, similar behaviour was reported for the $^{31}P,^{35/37}Cl$ spin pairs.[30]

It is interesting to note that both the solution and solid-state structures of the tetrahydro-2*H*-1,3-oxazines **1a**–**g** are different from the conformation predicted from the structure of bicyclic *N*-benzyl-tetrahydro-2*H*-1,3-oxazines **7**,[19,31] where the substituents are in equatorial positions. Instead, in the predominant diastereoisomer of tetrahydro-2*H*-1,3-oxazines **1a**–**g**, the substituents at C2 and C4 adopt axial positions, to minimise the number of *gauche* interactions with the Boc group. The difference must arise from the fact that the geometry of the nitrogen atom in the *N*-benzyl-tetrahydro-2*H*-1,3-oxazines **7** is tetrahedral, whereas in the tetrahydrooxazines **1a**–**g**, delocalisation of the nitrogen lone pair into the Boc group results in a planar geometry at nitrogen. Indeed, similar structures have been reported for *N*-sulfonyl-tetrahydro-2*H*-1,3-oxazines **8**[32] and **9**,[33] in which delocalisation of the nitrogen lone pair also results in a planar geometry. It is

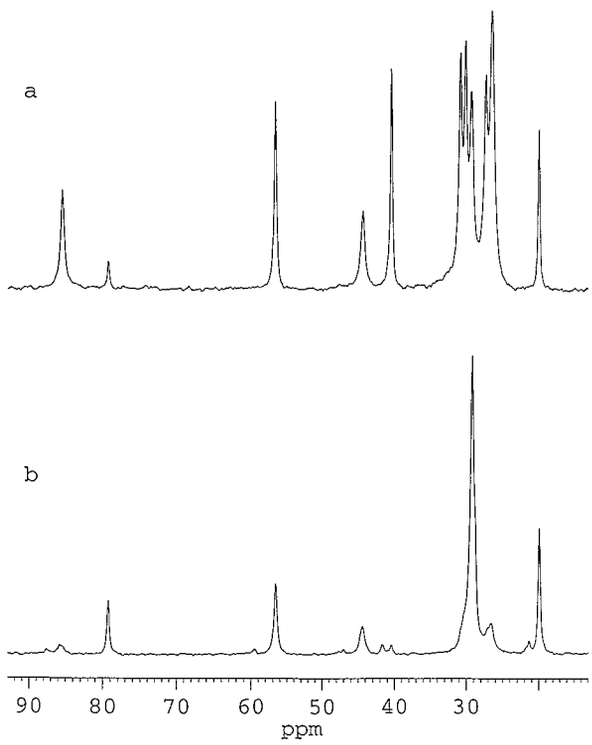

Fig. 8 Aliphatic region of the high-resolution solid-state ^{13}C NMR spectra for **1a** recorded using (a) the CPMAS technique and (b) single pulse experiment.

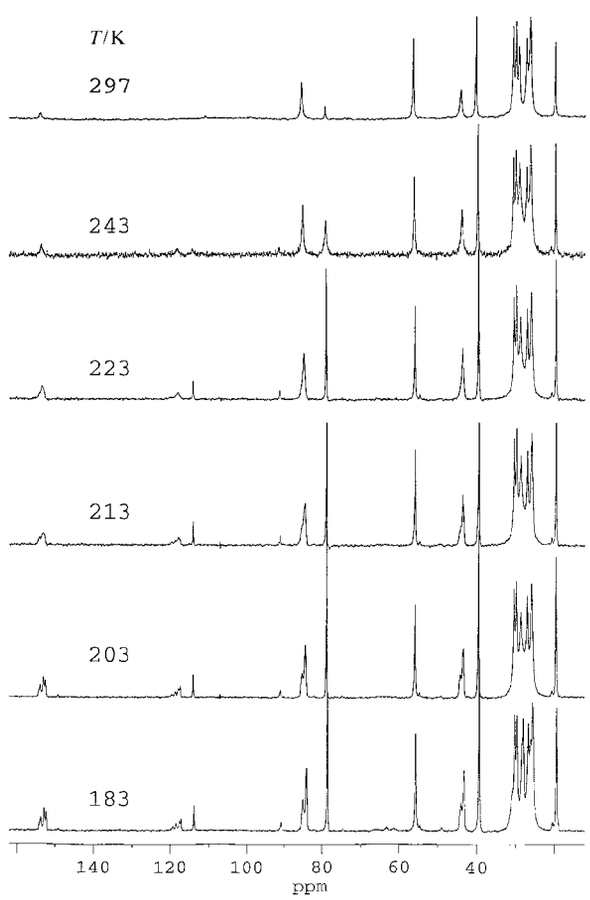

Fig. 9 ^{13}C CPMAS NMR spectra of **1a** recorded as a function of temperature (MAS frequency 2.65 kHz).

also notable that, whereas the major diastereoisomer of **1a** adopts a flattened chair conformation, the coupling constants and 1-D NOEs measured for the minor, *trans*-

Table 4 ^{13}C NMR chemical shifts for **1a** (major) and **1a** (minor)

	Liquid, 50 °C		Solid state, 30 °C		Solution ($CDCl_3$), 30 °C	
	1a Major isomer/ppm	**1a** Minor isomer/ppm	**1a** Major isomer/ppm	**1a** Minor isomer/ppm	**1a** Major isomer/ppm	**1a** Minor isomer/ppm
C2	86.3	88.1	85.5	87.5	85.7	87.4
C4	45.0	47.2	44.4	47.1	44.2	46.9
C5	30.8	29.4	31.0	*	30.0	29.6
C6	57.5	60.0	56.7	59.5	56.5	59.6
Cyc C1	42.4	41.5	40.6	*	41.2	41.3
Cyc C2	29.5	*	29.4	*	29.1	28.8
Cyc C3	26.6	*	26.7	*	26.2	26.2
Cyc C4	27.2	*	27.5	*	26.6	26.7
Cyc C5	26.8	*	26.7	*	26.4	26.4
Cyc C6	30.3	*	30.3	*	30.0	30.5
4-CH_3	21.8	19.8	20.0	21.4	21.1	19.6
NOCO	154.5	155.2	153.8	*	154.6	155.4
$C(CH_3)_3$	79.4	79.4	79.4	*	80.0	79.9
$C(CH_3)_3$	28.9	28.9	29.4	*	28.7	28.7

Table 5 Calculated ^{14}N–^{13}C residual dipolar splittings for the high-resolution solid-state ^{13}C NMR spectrum of the major isomer of **1a**. Values of the quadrupole coupling constant, $\chi = 4.7$ MHz, and asymmetry parameter, $\eta = 0$, are those determined for the methyl ester of *N*,*N*-dimethylcarbamic acid.[27] Values of $|^1J(^{14}N,^{13}C)|$ determined for Me-N(NO_2)-COOMe *via* solution state ^{13}C NMR measurements[28] are 15.0 Hz for $|^1J(^{14}N,^{13}COO)|$ and 5.7 Hz for $|^1J(^{14}N,^{13}CH_3)|$ and were used as starting values in our simulations. As in amides,[29] the *z*-axis of the ^{14}N electric field gradient tensor is assumed to be perpendicular to the C2-N(COO)-C4 plane

Carbon	$\lvert J(^{14}N,^{13}C)\rvert$/Hz	r_{CN}/Å	Experimental splittings/Hz	Calculated splittings/Hz
C-2	6	1.469	65	64
C-4	6	1.476	61	63
N-COO	16	1.352	68 and 35	65 and 31

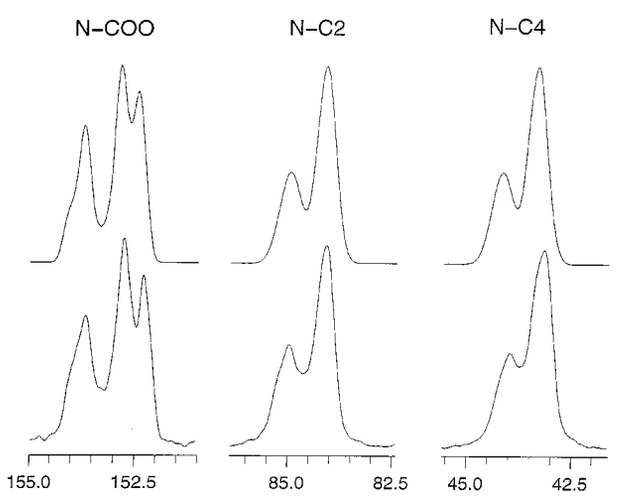

Fig. 10 Bottom trace: experimental ^{13}C CPMAS NMR spectra (recorded at 183 K) for the major isomer of **1a** showing the isotropic peaks for the NCOO (left), C-2 (middle) and C-4 (right) carbons. Top trace: simulated ^{13}C NMR lineshape for the ^{14}N–^{13}C spin pair of the NCOO (left), C-2 (middle) and C-4 (right) carbons at 7.05 T, calculated using parameters listed in Table 5.

diastereoisomer of **1a** indicate significant distortion from a chair conformation.

Experimental

Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium–benzophenone. Benzene was distilled from sodium. DMSO and Et_3N were distilled from CaH_2 and stored over 4 Å molecular sieves. Ethanol was distilled from magnesium and iodine. Hexane is described as the fraction boiling between 67–70 °C unless otherwise stated. Flash column chromatography[34] was carried out using silica gel (particle size 40–63 mm) purchased from BDH, or aluminium oxide (neutral, Brockman grade 1, 100–125 mesh) purchased from Fluka.

NMR spectra were recorded on Bruker AC250, AC300, AM360, AMX500, Avance 500, AMX600 and Varian VXR400 spectrometers. Chemical shift (δ) values are measured relative to the residual (undeuterated) solvent peak as an internal standard for ^1H and ^{13}C. Solid-state ^{13}C NMR spectra were recorded at 75.5 MHz on a Bruker MSL300 spectrometer using standard Bruker magic angle spinning (MAS) probes with double-bearing rotation mechanism. The standard single-pulse and ^1H–^{13}C cross-polarization (CP) techniques were employed (^{13}C 90° pulse duration = 3.0 μs; ^1H 90° pulse duration = 3.5 μs; CP contact time = 5 ms; MAS frequency ≈ 2–6 kHz), with high-power ^1H decoupling applied during acquisition. ^{13}C chemical shifts are given relative to tetramethylsilane, established *via* the use of adamantane as an external standard.

Nominal and high resolution mass spectra were taken on a VG ZAB-SE spectrometer with sources for FAB and EI^+; some nominal mass spectra were also measured on a VG Quattro mass spectrometer with sources for EI^+ and APCI. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Optical rotations of chiral compounds were measured on a JASCO 600 spectrophotometer and an Optical Activity POLAAR 2000 polarimeter using sucrose as a standard and are given in units of 10^{-1} deg cm^2 g^{-1}. All rotations were taken as solutions in $CHCl_3$ unless otherwise stated. CHN analyses were carried out on a Perkin Elmer 2400 CHN elemental analyser. Melting points were taken on an electrothermal 9100 instrument and are uncorrected.

(3*S*)-3-[(*tert*-Butoxycarbonyl)amino]butyric acid 4

Compound **4** was prepared from (*S*)-alanine *via* a similar procedure to that described by Seebach.[15] Mp 70–71 °C; $[a]_D$ −12.7 (*c* 20.0 mg cm^{-3}) [lit[35a] $[a]_D$ −14.0 (*c* 14.0 mg cm^{-3}), lit[35b] $[a]_D$ −14.1 (*c* 10.0 mg cm^{-3})] (Found: C, 53.2; H, 8.4; N, 6.85. $C_9H_{17}NO_4N$ requires C, 53.2; H, 8.4; N, 6.9%); $\nu_{max}(CHCl_3)$/cm^{-1} 3610 (OH), 3435 (NH), 3015, 1812 (C=O acid), 1707 (C=O urethane); δ_H (360 MHz; $CDCl_3$) 1.24 (3H, d, *J* 6.8, CH_3), 1.43 (9H, s, C(CH_3)$_3$), 2.55 (2H, t, *J* 5.1, CH_2COOH), 4.05 (1H, m, CH_3CH), 4.93 (1H, br s, N*H*); δ_C (90 MHz; $CDCl_3$) 20.30, 28.24, 40.52, 79.49, 155.15, 176.53; *m*/*z* (FAB) 226.2050 (M + Na^+. $C_9H_{17}NO_4Na$ requires 226.1055), 226 (M + Na, 100%), 204 (M + 1, 7%), 104 (M − Boc, 28%).

(3*S*)-3-[(*tert*-Butoxycarbonyl)amino]butan-1-ol 2

To a solution of (3*S*)-[(*tert*-butoxycarbonyl)amino]butyric acid **4** (2.01 g, 10 mmol) in THF (30 cm^3) at 0 °C under N_2 was added Et_3N (139 cm^3, 10 mmol) and isobutyl chloroformate (1.42 cm^3, 11 mmol) dropwise. The mixture was stirred for 1 h and the cold solution was filtered into an ice cooled flask with the solid being washed with dry THF (20 cm^3). The filtered solution was then added slowly, by cannula, to an ice cooled solution of $NaBH_4$ (1.1 g, 30 mmol) in water (5 cm^3). The mixture was stirred for 1 h and was then concentrated *in vacuo*. EtOAc (15 cm^3) was added and the organics were washed with saturated $NaHCO_3$ solution (10 cm^3), brine (10 cm^3) and then dried over Na_2SO_4. The solvent was removed *in vacuo* to give **2** as a white crystalline solid (1.77 g, 93%). Mp 59–60 °C (lit[36] 56 °C); $[\alpha]_D$ +9.0 (*c* 17 mg cm^{-3}) [lit[36] +10.7 (*c* 5 mg cm^{-3})] (Found: C, 57.2; H, 10.35; N, 7.2. $C_9H_{19}O_3N$ requires C, 57.15; H, 10.1; N, 7.0%); ν_{max}(Nujol mull)/cm^{-1} 3400 (NH), 3175 (OH), 1700 (C=O); δ_H (360 MHz; $CDCl_3$) 1.18 (3H, d, *J* 7.2, CH_3), 1.41 (9H, s, $C(CH_3)_3$), 1.72–1.79 (2H, m, CH_2CH_2OH), 3.59 (2H, dd, *J* 7.2, 3.6, CH_2CH_2OH), 3.73–3.80 (1H, m, CH_3CH), 4.52 (1H, br s, NH); δ_C (90 MHz; $CDCl_3$) 21.47, 28.32, 40.75, 43.03, 58.92, 79.72, *C*=O missing; *m*/*z* (FAB) 212.1260 (M + Na^+. $C_9H_{19}O_3NNa$ requires 212.1263) (81%), 190 (9%), 134 (100%).

The optical purity of **2** was found to be greater than 99% by HPLC of its *O*-(*S*)-Mosher's ester. HPLC analysis was carried out using an AlphaS15 silica column (HPLC Technologies, 250 × 4.5 mm), using isocratic elution with 10% ethyl acetate in hexane, flow rate 2 cm^3 min^{-1}. The retention time for the MTPA ester of **2** was 7.14 min; no evidence for the other diastereoisomer was seen. Racemic **2** was also prepared from β-aminobutyric acid, and converted to the MTPA amides: the retention times for these diastereomers were 6.64 and 7.16 min respectively.

Cyclohexanecarbaldehyde diethyl acetal,[37] heptaldehyde diethyl acetal,[38] butyraldehyde diethyl acetal,[39] isobutyraldehyde diethyl acetal[40] and phenylacetaldehyde diethyl acetal[41] were prepared by standard methods from their respective aldehydes; the analytical data were identical with the literature.

4-Triisopropylsilyloxybutanal diethyl acetal

To a solution of 4-triisopropylsilyloxybutanal[42] (15 mmol, 3.66 g) in dry ethanol (100 cm^3) was added a trace amount of PPTS. The mixture was heated under Dean–Stark conditions for 1 hour. The solution was then cooled and solid $NaHCO_3$ (0.25 g) added. After 15 minutes the solution was filtered and then concentrated *in vacuo*. Distillation gave the title compound as a clear oil (3.62 g, 72%). Bp 69 °C, 7 mmHg; δ_H (300 MHz; $CDCl_3$) 1.05 (21H, s, $((CH_3)_2CH)_3Si$), 1.20 (6H, t, *J* 7.1, OCH_2CH_3), 1.57–1.62 (2H, m, aliphatic), 1.66–1.80 (2H, m, aliphatic), 3.44–3.52 (2H, m, OCH_2CH_3), 3.60–3.66 (2H, m, OCH_2CH_3), 3.69 (2H, t, *J* 6.2, CH_2OSi), 4.51 (1H, t, *J* 5.8, CH_2CH); *m*/*z* ($APCI^+$) 318 (M), 317 (M − 1), 316 (M − 2); δ_C 11.92, 15.25, 17.93, 28.15, 29.92, 60.75, 63.03, 102.81; *m*/*z* ($APCI^+$) 318 (M), 317 (M − 1), 316 (M − 2).

6-Triisopropylsilyloxyhexanal diethyl acetal

To a solution of hexane-1,6-diol (2.16 g, 18.3 mmol) in THF (33 cm^3) was added NaH (0.73 g, 18.3 mmol). After 1 h triisopropylchlorosilane (3.9 cm^3, 18.3 mmol) was added and the mixture was stirred for a further hour. The mixture was poured into Et_2O (30 cm^3) and washed with saturated aqueous $NaHCO_3$ (30 cm^3) and brine (30 cm^3). The organics were then dried over Na_2SO_4 and the solvent was removed *in vacuo* to give a clear oil. Flash column chromatography (silica gel; 20% EtOAc in hexane; R_F 0.24) gave 6-triisopropylsilyloxyhexan-1-ol as a clear viscous oil (1.98 g, 42%). δ_H (300 MHz; $CDCl_3$) 1.04 (21H, s, $((CH_3)_2CH)_3Si$), 1.34–1.42 (4H, m, aliphatic), 1.51–1.62 (4H, m, aliphatic), 3.64 (4H, m, CH_2OSi and CH_2OH); *m*/*z* ($APCI^+$) 275 (M + 1).

To a solution of 6-triisopropylsilyloxyhexan-1-ol (0.50 g, 1.94 mmol) in THF (1.5 cm^3) were added DMSO (13 cm^3) and Et_3N (1.94 cm^3). The SO_3·pyridine complex (0.77 g, 5.82 mmol) was then added over 10 min. The reaction was stirred for 45 min after which it was cooled to 0 °C, acidified to pH 4 with HCl (1 M) and extracted with EtOAc–hexane (1 : 1; 3 × 20 cm^3). The organics were washed with water (40 cm^3) and dried over Na_2SO_4. The solvents were removed *in vacuo* to give a clear oil. Column chromatography (alumina; 15% EtOAc in hexane; R_F 0.6) gave 6-triisopropylsilyloxyhexanal as a clear viscous oil (0.454 g, 91%). δ_H (300 MHz; $CDCl_3$) 1.04 (21H, s, $((CH_3)_2CH)_3Si$), 1.31–1.62 (6H, m, aliphatic), 2.44 (2H, td, *J* 7.3, 1.8, CH_2CHO), 3.68 (2H, t, *J* 6.3, CH_2OSi), 9.76 (1H, t, *J* 1.8, CHO); *m*/*z* ($APCI^+$) 273 (M + 1).

To a solution of 6-triisopropylsilyloxyhexanal (0.39 g, 1.5 mmol) in dry ethanol (30 cm^3) was added a trace amount of PPTS. The mixture was heated under Dean–Stark conditions for 1 h. The solution was then cooled and poured into saturated aqueous $NaHCO_3$ (20 cm^3) and then concentrated *in vacuo*. The residue was taken up in water and extracted with CH_2Cl_2 (2 × 30 cm^3). The organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give the title compound as a clear oil (0.26 g, 53%). Bp 42 °C, 10 mmHg; δ_H (300 MHz; $CDCl_3$) 1.07 (21H, s, $((CH_3)_2CH)_3Si$), 1.22 (6H, t, *J* 7.1, OCH_2CH_3), 1.36–1.42 (4H, m, aliphatic), 1.55–1.65 (4H, m, aliphatic), 3.45–3.56 (2H, m, OCH_2CH_3), 3.60–3.79 (4H, m, OCH_2CH_3 and CH_2OSi), 4.45 (1H, t, *J* 5.8, CH_2CH); δ_C (90 MHz; $CDCl_3$) 11.94, 15.25, 17.93, 24.53, 25.66, 32.88, 33.58, 60.77, 63.26, 102.86; mass spectrum (ES^+); *m*/*z* 301 (M − OEt, 80%), 273 (100%).

General procedure for the synthesis of tetrahydro-2*H*-1,3-oxazines 1a–g

(3*S*)-3-[(*tert*-Butoxycarbonyl)amino]butan-1-ol **2** (1.25 g, 6.6 mmol), the appropriate diethyl acetal (6.6 mmol) and a trace of PPTS were heated in dry benzene (50 cm^3) under reflux for 2 h. The mixture was cooled to room temperature, washed with $NaHCO_3$ (50 cm^3), water (2 × 20 cm^3) and brine (20 cm^3). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a pale yellow oil. Flash column chromatography over neutral alumina or silica, as indicated, using the eluants indicated, gave the required compound.

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-cyclohexyl-4-methyltetrahydro-2*H*-1,3-oxazine 1a. 76% (white crystalline solid); mp 47.1–48.5 °C; $[\alpha]_D$ +2.7 (*c* 45 mg cm^{-3}) (Found: C, 67.8; H, 10.2; N, 5.0. $C_{16}H_{30}NO_3$ requires C, 68.05; H, 10.0; N, 5.0%); R_F 0.50 (silica gel, 20% EtOAc in hexane); ν_{max}($CHCl_3$)/cm^{-1} 2985, 1720 (C=O), 1695 (C=O), 1177 (C–O–C); δ_H (360 MHz; $CDCl_3$) 1.31 (3H, d, *J* 7.2, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.50–1.82 (11H, m, cyclohexyl), 1.92–2.13 (2H, m, CH_2CH_2O), 3.61 (1H, dt, *J* 11.9, 4.3, $CH_2CH_{ax}H_{eq}O$), 3.91 (1H, td, *J* 11.2, 3.2, $CH_2CH_{ax}H_{eq}O$), 4.42 (1H, quintet of d, *J* 7.2, 3.0, CH_3CHCH_2), 5.18 (1H, d, *J* 10.8, NCHO); δ_C (90 MHz; $CDCl_3$) 20.78, 25.82, 26.25, 28.29, 28.69, 29.63, 40.90, 43.83, 56.20, 79.67, 85.43, 154.29; *m*/*z* (FAB) 284.2220 (M + 1^+. $C_{16}H_{30}NO_3$ requires 284.2226), 284 (M + 1, 22%), 200 (M − C_6H_{11}, 21), 184 (M − Boc, 100). Ratio of major : minor isomers (by ^1H NMR) 98 : 2 (96% de).

Solution conformation of **1a**: ^1H 1D spectrum was assigned by DQF-COSY on a Bruker AMX500. A NOESY experiment was then performed, and processed using SYBYL/TRIAD to generate distance constraints for a unique solution conformation.

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-hexyl-4-methyltetrahydro-2*H*-1,3-oxazine 1b. 83% (viscous oil); $[\alpha]_D$ +7.5 (*c* 15.4

mg cm^{-3}); R_F 0.48 (alumina, 10% EtOAc in hexane); ν_{max}(CHCl$_3$)/cm^{-1} 2929, 2865, 1695 (C=O), 1177 (C–O–C); δ_H (360 MHz; CDCl$_3$) 0.87 (3H, t, *J* 6.9, CH_3CH$_2$), 1.28 (3H, d, *J* 7.0, CH_3CH), 1.30–1.38 (8H, m, aliphatic), 1.44 (9H, s, C(CH_3)$_3$), 1.62–1.70 (2H, m, aliphatic), 1.82–1.92 (1H, m, CH_2CH$_2$O), 2.00–2.13 (1H, m, CH_2CH$_2$O), 3.58 (1H, dt, *J* 11.9, 5.0 CH$_2$CH$_{ax}H_{eq}$O), 3.92 (1H, m, CH$_2$CH_{ax}H$_{eq}$O), 4.35 (1H, quintet of d, *J* 6.8, 2.9, CH$_3$C*H*CH$_2$), 5.34 (1H, dd, *J* 9.0, 4.7, NC*H*O); δ_C (90 MHz; CDCl$_3$) 13.9, 21.5, 22.5, 25.7, 28.4, 29.5, 31.8, 33.8, 43.6, 56.4, 79.6, 82.8, 110.0, 153.6; *m*/*z* (FAB) 286.2370 (M + 1$^+$. $C_{16}H_{32}NO_3$ requires 286.2382), 286 (M + 1, 21%), 200 (20%), 186 (M − Boc, 100%). Ratio of major : minor isomers (by ^{1}H NMR) 86 : 14 (72% de).

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-propyl-4-methyl-tetrahydro-2*H*-1,3-oxazine 1c. 69% (viscous oil); [*a*]$_D$ +7.77 (*c* 100 mg cm^{-3}); R_F 0.48 (alumina, 10% EtOAc in hexane); ν_{max}(CHCl$_3$)/cm^{-1} 2966, 2873, 1695 (C=O), 1177 (C–O–C); δ_H (360 MHz; CDCl$_3$) 0.95 (3H, t, *J* 7.2, CH_3CH$_2$), 1.28 (3H, d, *J* 6.8, CH_3CH), 1.32–1.41 (2H, m, aliphatic), 1.46 (9H, s, C(CH_3)$_3$), 1.58–1.68 (2H, m, aliphatic), 1.85–1.92 (1H, m, CH_2CH$_2$O), 2.00–2.08 (1H, m, CH_2CH$_2$O), 3.58 (1H, dt, *J* 11.5, 5.0, CH$_2$CH$_{ax}H_{eq}$O), 3.92 (1H, dt, *J* 11.9, 4.0, CH$_2$CH_{ax}H$_{eq}$O), 4.35 (1H, quintet of d, *J* 7.2, 2.5, CH$_3$C*H*CH$_2$), 5.36 (1H, dd, *J* 9.0, 4.3, NC*H*O); δ_C (90 MHz; CDCl$_3$) 13.8, 19.0, 21.5, 28.5, 29.5, 37.0, 43.6, 56.4, 79.7, 82.5, 153.6; *m*/*z* (FAB) 244.1920 (M + 1$^+$. $C_{13}H_{26}NO_3$ requires 244.1913), 244 (M + 1, 15%), 144 (M − Boc, 100%). Ratio of major : minor isomers (by ^{1}H NMR) 86 : 14 (72% de).

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-isopropyl-4-methyl-tetrahydro-2*H*-1,3-oxazine 1d. 55% (viscous oil); [*a*]$_D$ +31.8 (*c* 6.85 mg cm^{-3}); R_F 0.35 (alumina, 10% EtOAc in hexane); ν_{max}(CHCl$_3$)/cm^{-1} 2972, 2874, 1694 (C=O), 1176 (C–O–C); δ_H (300 MHz; CDCl$_3$) 0.90 (3H, d, *J* 6.7, (CH_3)$_2$CH), 1.00 (3H, d, *J* 6.5, (CH_3)$_2$CH), 1.32 (3H, d, *J* 7.1, CH_3), 1.48 (9H, s, C(CH_3)$_3$), 1.60–1.62 (1H, m, (CH$_3$)$_2$C*H*), 2.03–2.12 (1H, m, CH_2CH$_2$O), 2.29–2.39 (1H, m, CH_2CH$_2$O), 3.62 (1H, dt, *J* 11.7, 4.2, CH$_2$CH$_{ax}H_{eq}$O), 3.93 (1H, td, *J* 11.0, 3.5, CH$_2$CH_{ax}H$_{eq}$O), 4.45 (1H, quintet of d, *J* 6.9, 2.8, CH$_3$C*H*CH$_2$), 5.11 (1H, d, *J* 10.2, NC*H*O); δ_C (75 MHz; CDCl$_3$) 18.5, 19.2, 20.8, 28.3, 29.5, 31.3, 43.8, 56.1, 79.7, 86.1; *m*/*z* (FAB) 244.1900 (M + 1$^+$. $C_{13}H_{26}NO_3$ requires 244.1913), 244 (M + 1, 9%), 144 (M − Boc, 15%), 116 (100%). Ratio of major : minor isomers (by ^{1}H NMR) 89 : 11 (78% d.e).

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(5-triisopropylsilyloxy)-pentyl-4-methyl-tetrahydro-2*H*-1,3-oxazine 1e. 63% (viscous oil); [*a*]$_D$ +1.4 (*c* 76 mg cm^{-3}); R_F 0.52 (alumina, 10% EtOAc in hexane); ν_{max}(CHCl$_3$)/cm^{-1} 2939, 2866, 1695 (C=O), 1176 (C–O–C), 1105 (RO–Si); δ_H (300 MHz; CDCl$_3$) 1.04 (21H, s, ((CH_3)$_2$C*H*)$_3$Si), 1.24 (3H, d, *J* 7.2, CH_3CH), 1.35–1.43 (4H, m, aliphatic), 1.42 (9H, s, C(CH_3)$_3$), 1.52–1.57 (2H, m, aliphatic), 1.62–1.70 (2H, m, aliphatic), 1.86–1.95 (1H, m, CH_2CH$_2$O), 2.01–2.16 (1H, m, CH_2CH$_2$O), 3.60 (1H, dt, *J* 11.5, 5.0, CH$_2$CH$_{ax}H_{eq}$O), 3.64 (2H, t, *J* 6.5, CH_2OSi), 3.91 (1H, dt, *J* 11.9, 4.0, CH$_2$CH_{ax}H$_{eq}$O), 4.31 (1H, quintet of d, *J* 7.2, 2.5, CH$_3$C*H*CH$_2$), 5.34 (1H, dd, *J* 9.0, 4.3, NC*H*O); δ_C (75 MHz; CDCl$_3$) 11.96, 17.99, 21.49, 25.50, 25.62, 28.42, 29.43, 32.97, 33.90, 43.57, 56.36, 63.26, 82.74, 153.59, ^{t}Bu*C* missing; *m*/*z* (FAB) 444.3500 (M + 1$^+$. $C_{24}H_{50}NO_4Si$ requires 444.3509), 444 (M + 1, 4%), 344 (M − Boc, 100%). Ratio of major : minor isomers (by ^{1}H NMR) 90 : 10 (80% de).

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(3-triisopropylsilyloxy-propyl-4-methyl-tetrahydro-2*H*-1,3-oxazine 1f. 74% (viscous oil); [*a*]$_D$ −0.8 (*c* 5 mg cm^{-3}); R_F 0.65 (alumina, 10% EtOAc in hexane); ν_{max}(CHCl$_3$)/cm^{-1} 2942, 2866, 1695 (C=O), 1175 (C–O–C), 1105 (RO–Si); δ_H (300 MHz; CDCl$_3$) 1.08 (21H, s, ((CH_3)$_2$C*H*)$_3$Si), 1.30 (3H, d, *J* 7.0, CH_3CH), 1.48 (9H, s, C(CH_3)$_3$), 1.59–1.84 (5H, m, aliphatic and CH_2CH$_2$O), 2.00–2.15 (1H, m, CH_2CH$_2$O), 3.61 (1H, dt, *J* 9.3, 4.0, CH$_2$CH$_{ax}$-H_{eq}O), 3.74 (2H, t, *J* 6.1, CH_2OSi), 3.96 (1H, td, *J* 10.3, 3.7, CH$_2$CH_{ax}H$_{eq}$O), 4.38 (1H, quintet of d, *J* 7.2, 2.2, CH$_3$C*H*CH$_2$), 5.40 (1H, dd, *J* 9.0, 4.8, NC*H*O); δ_C (75 MHz; CDCl$_3$) 1.86, 17.90, 21.26, 28.30, 29.30, 30.22, 43.50, 53.30, 56.06, 62.89, 79.62, 82.58, 153.48; *m*/*z* (FAB) 416.3180 (M + H$^+$. $C_{22}H_{46}NO_4Si$ requires 416.3196), 416 (M + 1, 7%), 316 (M − Boc, 100%). No minor diastereoisomer was observed.

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-2-benzyl-4-methyl-tetrahydro-2*H*-1,3-oxazine 1g. 51% (white crystalline solid); mp 62.8–64.0 °C; [*a*]$_D$ +35.7 (*c* 2.1 mg cm^{-3}) (Found: C, 70.0; H, 8.4; N, 4.8. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.7; N, 4.8%); R_F 0.33 (alumina, 4% EtOAc in toluene); ν_{max}(CHCl$_3$)/cm^{-1} 2995, 1725 (C=O), 1694 (C=O), 1176 (C–O–C); δ_H (250 MHz; CDCl$_3$) 1.37 (3H, d, CH_3CH), 1.44 (9H, s, C(CH_3)$_3$), 1.48–1.56 (1H, m, CH_2CH$_2$O), 2.07–2.17 (1H, m, CH_2CH$_2$O), 2.96 (1H, dd, *J* 13.7, 3.8, PhCH_2), 3.17 (1H, dd, *J* 13.7, 9.0, PhCH_2), 3.62 (1H, dt, *J* 11.7, 5.1, CH$_2$CH$_{ax}H_{eq}$O), 4.07 (1H, m, CH$_2$CH_{ax}-H_{eq}O), 4.43 (1H, quintet of d, *J* 7.1, 5.1, CH$_3$C*H*CH$_2$), 5.51 (1H, dd, *J* 9.0, 3.8, NC*H*O), 7.20–7.35 (5H, m, *Ph*CH$_2$); δ_C (75 MHz; CDCl$_3$) 21.8, 28.3, 29.3, 40.3, 43.5, 56.9, 57.5, 79.9, 84.2, 126.3, 128.3, 129.2, 137.8; *m*/*z* (FAB) 292 (M + 1, 6%), 200 (10%), 192 (M − Boc, 100%). No minor diastereoisomer was observed.

Solution conformation of **1g**: ^{1}H 1-D spectrum was assigned by DQF-COSY on a Bruker AMX500. A NOESY experiment was then performed, and processed using SYBYL/TRIAD to generate distance constraints for a unique solution conformation.

X-Ray crystallographic data for 1g

Empirical formula $C_{17}H_{25}NO_3$, formula weight 291.38, wavelength 1.54184 Å, crystal system orthorhombic, space group $P2_12_12_1$, unit cell dimensions $a = 6.0668(10)$, $b = 11.952(3)$, $c = 23.096(9)$ Å, volume 1674.7(8) Å^3, $Z = 4$, $D_c = 1.156$ mg m^{-3}, $\mu = 0.628$ mm^{-1}, $F(000)$ 632, crystal description colourless column, crystal size 0.43 × 0.12 × 0.08 mm, θ range for data collection 3.83 to 60.09° (diffraction was quite weak, and so data were not collected to higher resolution), reflections collected 1488, independent reflections 1447 [R(int) = 0.0358], scan type ω–θ. $T = 220$ K. Data were collected on a Stoe Stadi-4 diffractometer equipped with an Oxford cryosystems l.t. device.[43] Following data reduction, the structure was solved by direct methods (SHELXTL)[44] and refined by full-matrix least-squares against F^2. H-atoms were placed in calculated positions and subsequently allowed to ride on their parent atoms. All non-H atoms were refined with anisotropic displacement parameters, but because the data were generally quite weak, global rigid bond and rigid body restraints were applied (109 restrictions total). The refinement converged to a conventional R of 9.97% [based on F and 552 data with $F > 4\sigma(F)$] and $wR2 = 28.11\%$ [based on F^2 and all 1411 unique data] for 185 parameters. The final ΔF-map extremes were +0.26 and −0.34 e Å^{-3}, respectively. The absolute structure is not defined by these X-ray data, although C3 was known to have the *S*-configuration. CCDC reference number 207/331. See http://www.rsc.org/suppdata/p1/1999/1933 for crystallographic files in .cif format.

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Paper 9/02667C