Nitrogen inversion process in some camphor-based isoxazolidines

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Abstract
A series of isoxazolidines has been prepared via asymmetric nitroene cycloaddition reactions of a camphor-based methylenenitrone with several alkenes. The $^1$H NMR spectra of the N(2) and C(5)-disubstituted isoxazolidines in CDCl$_3$ at low temperatures revealed the predominant or exclusive presence of the diasteromer having trans disposition of the substituents. The presence of hydroxyl substituent on the camphor moiety permits H-bonding with the N or O of the isoxazolidine ring. The effect of H-bonding - intramolecular in CDCl$_3$ and intermolecular in CD$_3$OD - on the population ratio of the invertomers and nitrogen inversion process has been investigated. The nitrogen inversion barriers are determined using complete line-shape analysis, and their dependence on solvent is discussed.

Keywords: Isoxazolidines, nitrogen inversion, invertomers, inversion barriers

Introduction
The compounds containing nitroene functionality (-C=NH-O-) undergoes cycloaddition reaction with an alkene to produce isoxazolidines having an $\text{N-O}$ moiety embedded in the ring skeleton.$^1$ The presence of an $\text{N-O}$ moiety in an organic molecule has a distinctive place in conformational analysis,$^{2-4}$ oxygen being next to nitrogen raises the barrier to nitrogen inversion ($\text{Ni}$) to such an extent that at temperatures lower than the ambient, individual invertomers can be identified by NMR spectroscopy.$^5$ The asymmetric nitroene cycloaddition reactions involving camphor-derived intramolecularly H-bonded nitroene (Scheme 1) has been found to be very effective in transferring chirality to the newly created stereocenter at C(5) of the cycloadducts isoxazolidines.$^6$

However, it is often difficult to assign the stereochemistry of the substituted isoxazolidines by spectroscopic analysis owing to complications arising out of the relatively slow nitrogen inversion process as well as pseudorotation in a five-membered ring. We have prepared a number of 5-mono-, and 5,5-disubstituted isoxazolidines 4 and 5 of known configurations$^6$ using
nitrone (2)-alkene (3) cycloaddition reactions to examine the conformational aspects as well as nitrogen inversion process by NMR spectroscopy (Scheme 1). The study would provide us with the opportunity to examine the effect of H-bonding - intramolecular in CDCl₃ and intermolecular in CD₃OD- on the population ratio of the invertomers.

![Scheme 1](image)

\[ \text{Scheme 1} \]

**Results and Discussion**

Since nitrone 2 is optically pure, the isoxazolidines 4 and 5 differ only in the configuration of the C(5) substituents. During the course of a structural investigation of the isomeric isoxazolidines 4c and 5c (R¹ =H, R² = CO₂Me) it was interesting to observe the presence of a single invertomer for 4c, while 5c remained as an equilibrating mixture of two invertomers (cis and trans) at -40°C both in CDCl₃ and CD₃OD (Scheme 2). This is interesting since a look at their structures seems to convey that 2,5-trans-4c and 2,5-trans-5c (or 2,5-cis-4c and 2,5-cis-5c) should have a comparable steric environments, and as such a large discrepancy in the population ratio of the invertomers in 4c and 5c is quite unexpected. The current study helped us to provide a rationale for this observation (vide infra). The nitrogen inversions barriers are determined using NMR band shape analysis. Slow nitrogen inversion in most of the isoxazolidines has been observed to give broadened peaks in ^1^H and ^13^C spectra recorded at ambient temperature. On lowering the temperature, the spectral lines become sharper and show two distinct forms of the compound. The ^13^C chemical shifts in CDCl₃ and CD₃OD were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in Tables 1 and 2, respectively.
Scheme 2

Table 1. $^{13}$C NMR Chemical Shifts of compounds Studied in CDCl$_3$ at -30°C

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>N-C</th>
<th>O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>53.39</td>
<td>35.87</td>
<td>76.80</td>
<td>73.58</td>
<td>80.18</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major (trans)</td>
<td>54.19</td>
<td>37.91</td>
<td>78.17</td>
<td>74.34</td>
</tr>
<tr>
<td></td>
<td>Minor (cis)</td>
<td>56.97</td>
<td>36.88</td>
<td>79.20</td>
<td>74.55</td>
</tr>
<tr>
<td>4c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(trans)</td>
<td>52.32</td>
<td>32.75</td>
<td>73.73</td>
<td>73.67</td>
</tr>
<tr>
<td>5c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major (trans)</td>
<td>52.51</td>
<td>32.60</td>
<td>74.83</td>
<td>74.16</td>
</tr>
<tr>
<td></td>
<td>Minor (cis)</td>
<td>55.35</td>
<td>32.11</td>
<td>72.62</td>
<td>74.16</td>
</tr>
<tr>
<td>4d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major (H-bonded)</td>
<td>53.49</td>
<td>39.89</td>
<td>81.71</td>
<td>73.77</td>
</tr>
<tr>
<td></td>
<td>Minor (Non H-bonded)</td>
<td>56.99</td>
<td>38.46</td>
<td>81.06</td>
<td>74.51</td>
</tr>
<tr>
<td>5d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major (H-bonded)</td>
<td>53.35</td>
<td>38.84</td>
<td>81.39</td>
<td>74.27</td>
</tr>
<tr>
<td>4e</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major (H-bonded)</td>
<td>53.17</td>
<td>36.65</td>
<td>83.98</td>
<td>73.73</td>
</tr>
</tbody>
</table>
Around -10°C, the $^1$H NMR spectra of these compounds show well separated signals for the two invertomers. Integration of the relevant peaks gives the population trends in these systems. The proton spectra were used in the calculation of barriers in all compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>N-C</th>
<th>O-C</th>
</tr>
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<tr>
<td>4a</td>
<td>Major (trans)</td>
<td>54.63</td>
<td>37.00</td>
<td>78.16</td>
<td>75.24</td>
</tr>
<tr>
<td></td>
<td>Minor (cis)</td>
<td>56.70</td>
<td>37.00</td>
<td>77.76</td>
<td>75.10</td>
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<tr>
<td>4b</td>
<td>Major (trans)</td>
<td>55.37</td>
<td>39.10</td>
<td>79.56</td>
<td>75.88</td>
</tr>
<tr>
<td></td>
<td>Minor (cis)</td>
<td>57.60</td>
<td>38.64</td>
<td>80.16</td>
<td>77.88</td>
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<tr>
<td>4c</td>
<td>(trans)</td>
<td>52.84</td>
<td>33.75</td>
<td>74.70</td>
<td>74.77</td>
</tr>
<tr>
<td>5c</td>
<td>Major (trans)</td>
<td>53.92</td>
<td>34.32</td>
<td>76.04</td>
<td>75.99</td>
</tr>
<tr>
<td></td>
<td>Minor (cis)</td>
<td>56.07</td>
<td>34.28</td>
<td>75.68</td>
<td>75.60</td>
</tr>
<tr>
<td>4d</td>
<td>Major (Non H-bonded)</td>
<td>57.36</td>
<td>39.67</td>
<td>81.82</td>
<td>77.65</td>
</tr>
<tr>
<td></td>
<td>Minor (H-bonded)</td>
<td>54.64</td>
<td>40.68</td>
<td>83.14</td>
<td>75.51</td>
</tr>
<tr>
<td>5d</td>
<td>Major (H-bonded)</td>
<td>54.35</td>
<td>39.88</td>
<td>82.41</td>
<td>75.31</td>
</tr>
<tr>
<td>4e</td>
<td>Major (H-bonded)</td>
<td>54.35</td>
<td>37.37</td>
<td>85.29</td>
<td>74.94</td>
</tr>
<tr>
<td></td>
<td>Minor (Non H-bonded)</td>
<td>56.30</td>
<td>37.37</td>
<td>85.74</td>
<td>75.33</td>
</tr>
</tbody>
</table>

The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. The activation parameters $\Delta H^\neq$ and $\Delta S^\neq$ were calculated from plots of $\ln(k/T)$ vs. $1/T$. It is well known$^7$ that NMR band shape fitting frequently gives rather large but mutually compensating errors in $\Delta H^\neq$ and $\Delta S^\neq$ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of $\Delta G^\neq$ (within ±0.3 kJ/mol) in the vicinity of the coalescence temperature.$^7$ The $\Delta G^\neq$ values calculated at 0°C are reported in Table 3, along with the invertomer ratios and $\Delta G^o$ values.

The conformation of 5-membered ring system is indeed very complex to elucidate with some certainty. The complexity arises from the fact that changing the size of the substituent may lead to change in conformation (half chair/envelope/near planar) and the flap of the envelope. Earlier works$^{8,9}$ on 2,5-disubstituted isoxazolidines revealed the trans-invertomer as the major isomer. The 2-methyl-, 2-isopropyl-, and 2-tbutyl-5-tbutyldimethylsiloxymethylisoxazolidines were found to have the trans- and cis-invertomers in a ratio of 53:47, 55:45 and 63:37, respectively. The compounds studied in this work are sterically similar to the 2-isopropylisoxazolidines since
they also contain a secondary alkyl (i.e. camphor moiety) substituent at the N(2)-position (Scheme 2). Note that the isoxazolidines 4a-c in CDCl₃ exist almost as a single invertomer in each case (Table 3), and display sharp NMR signals at ambient as well as lower temperatures, while compound 5c revealed the presence of two invertomers at the lower temperatures. The analysis below will help us to provide a rationale for identifying the major invertomers as having the trans configuration.

**Table 3.** Free Energy of Activation (ΔGᵢ) for nitrogen inversion, Ratio of the Invertomers, and standard Free Energy Change (ΔGo) for major = minor isomerization in CDCl₃ and CD₃OD

<table>
<thead>
<tr>
<th>Compound</th>
<th>CDCl₃</th>
<th>CD₃OD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔGᵢ</td>
<td>Invertomer Ratio</td>
<td>ΔGo</td>
<td>ΔGᵢ</td>
<td>Invertomer Ratio</td>
<td>ΔGo</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>(kJ/mol)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>–</td>
<td>100*</td>
<td>–</td>
<td>65.7</td>
<td>80:20</td>
<td>+2.7</td>
<td></td>
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<tr>
<td>4b</td>
<td>67.8</td>
<td>97: 3</td>
<td>+6.7</td>
<td>64.8</td>
<td>81:19</td>
<td>+2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>4c</td>
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<td>100*</td>
<td>–</td>
<td>–</td>
<td>100*</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
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<td>5c</td>
<td>66.3</td>
<td>90: 10</td>
<td>+4.3</td>
<td>62.5</td>
<td>64:36</td>
<td>+1.1</td>
<td></td>
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<td></td>
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<tr>
<td>4d</td>
<td>64.4</td>
<td>87: 13</td>
<td>+3.7</td>
<td>61.0</td>
<td>57:43</td>
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<tr>
<td>5d</td>
<td>–</td>
<td>100*</td>
<td>–</td>
<td>–</td>
<td>100*</td>
<td>–</td>
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<tr>
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<td>100*</td>
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<td>68.7</td>
<td>94:6</td>
<td>+5.3</td>
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</table>

*aAt 0 °C. bAt -40 °C. *The other isomer was not detected.

The likely configuration of the invertomers of the disubstituted isoxazolidines is shown in Scheme 2. The camphor 'H' (attached to the carbon adjacent to N) is placed anti to the nitrogen lone pair in all the configurations since it will have the lower number of gauche interactions (two in these cases) around the C-N bond. The H-bonding with the nitrogen lone pair is possible in all the configurations having camphor 'H' placed gauche to the nitrogen lone pair, but it will be in a less favourable 5-membered ring structure and will develop considerable eclipsing between the camphor moiety and N-C(3) bond of the isoxazolidine ring. This would leave the possibility of H-bonding with the ring oxygen in 2,5-trans-4 and 2,5-cis-5 invertomers as shown in the Scheme 2. The 2,5-cis-4 and 2,5-trans-5 can not form H-bonded structure with the ring oxygen. The 2,5-trans-4 enjoys two advantages - sterically favored trans disposition of the substituents as well as H-bonding - rendering it overwhelmingly favored over the 2,5-cis-4 and as such it exists as the
sole invertomer. For the disubstituted isoxazolidines 5, each invertomer enjoys one advantage; while the *cis*-5 is H-bonded with the ring oxygen, the *trans*-5 enjoys the *trans* disposition of the substituents. As a result, both the invertomers exist for the isoxazolidines 5c in a 90:10 ratio for the *trans* and *cis* invertomers, respectively. Note that the overall steric environment provided by the camphor moiety is presumably much bulkier than a t-butyl group and as such the steric crowding in 2,5-*cis*-5 outweighs whatever advantage the H-bonding has to offer.

The situation becomes complicated in the trisubstituted isoxazolidines 4d and 4e. We believe the H-bonded forms remain to be the exclusive or overwhelmingly predominant invertomers (Scheme 3). While the isoxazolidine 4d exists in H-bonded and non H-bonded forms in a 87:13 ratio, the corresponding stereoisomer 5d remains exclusively in the H-bonded form. The H-bonded form in 5d presumably enjoys an extra stabilization as a result of an additional H-bonding with the *cis*-disposed C(5) CO2Me group (*vide infra*).

Scheme 3

The stereochemistry of adduct 4c has been earlier confirmed by crystallographic analysis (Scheme 4).
The isoxazolidine 4c exists in the solid state in the 2,5-trans form. It can be seen that the OH hydrogen is within the distance to demonstrate H-bonding with N, ring O as well as the O of the C(5)CO₂Me group. [The sum of Van der Waal radii of H,O and H,N are 2.72 Å and 2.75 Å, respectively]. Note the spread out angle of 114° for C-O-H is a clear indication of this moiety’s attempt to form H-bond with the ester functionality. The camphor 'H' is anti to the nitrogen lone pair as anticipated in Schemes 2 and 3.

In methanol, the intramolecular H-bonding is disrupted; the steric bulk of the solvation shell of the nitrogen lone pair increases in hydrogen-bonding solvents. This should diminish the preference for the trans-invertomers in CD₃OD as observed for most of the isoxazolidines (Table 3). However, the isoxazolidines, under study, have so many lone pairs on N and O involved in H-bonding that it may sometimes have unpredictable influence on the invertomeric ratios.

The chemical shift difference between the isomers for a particular ring carbon is generally less than 1 ppm for most carbons and as such the C-13 shifts are not very sensitive to the difference in the isomeric conformations (Tables 2 and 3). However the C-3 signals appeared upfield in the trans (Scheme 2) and H-bonded forms (Scheme 3) by over 2 ppm thus providing evidence that the major invertomers have the similar configuration. The corroborative findings of X-ray crystallography, study of invertomeric compositions in different solvents, the consideration of steric crowding in the cis invertomers, as well as upfield C-3 chemical shifts in the trans invertomers provided the evidence in identifying and distinguishing the configuration of the invertomers (vide supra).

The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines. The inversion barrier decreases to some extent in
hydrogen bonding solvent CD₃OD (Table 3). Usually it is known that the inversion barriers in CD₃OD increase in cyclic system as a result of an extra energy required for breaking of H-bonding prior to inversion. However, the inversion in CDCl₃ may also require extra energy to break the intramolecular OH···N hydrogen bond prior to inversion.

The NMR study at lower temperatures has thus successfully led to the determination of the stereochemistry of the nitrogen invertomers in camphor-derived isoxazolidines. The identification of nitrogen lone pair stereochemistry will indeed be a valuable information in per acid induced ring opening of the isoxazolidines.

Experimental Section

Compounds studied
A total of 7 compounds have been studied in the current work. The structures of these compounds are given in Scheme 1.

Physical methods
All mp are uncorrected. The variable temperature ¹H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm³ solutions in CDCl₃ and CD₃OD with TMS as internal standard. ¹³C NMR spectra were measured in CDCl₃ or CD₃OD using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Multiplicities of the carbons were determined using DEPT experiments. Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. I.r. spectra were recorded on a Perkin Elmer 16F PC FTIR spectrometer. X-ray crystallographic analysis was carried out on a Bruker-AXS Smart Apex system equipped with graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde from Fluka were used as received. Dimethyl methylenemalonate were prepared as described in the literature. The chiral 3-(hydroxyamino)borneol (1) was prepared as described.

Isoxazolidines
All the isoxazolidines except 4e were prepared using procedure as described. The compound 4e was prepared by cycloaddition reaction of nitrone 2 with dimethyl methylenemalonate (3e) (vide infra). The low temperature ¹H and ¹³C NMR data of these compounds are given below.

Isoxazolidine 4a
Both the ¹H and ¹³C NMR spectra in CDCl₃ revealed the presence of a single invertomer. A single invertomer. δH (CDCl₃, -40 °C) 0.78(3H, s), 0.88 (3H, t, J 7.0 Hz), 0.98 (3H, s), 1.15 (3H, s), 1.00-1.78 (11H, m), 1.93 (1H, m), 2.42 (1H, m), 2.70 (1H, apparent q, J 8.8 Hz), 2.78 (1H, d, J 6.7 Hz), 3.32 (1H, m), 3.67 (1H, d, J 6.7 Hz), 3.81 (1H, br, OH), 4.13 (1H, quint, J 6.7
In CD$_2$OD (-40°C) the $^1$H NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of 4a in a ratio of 80:20. While the methyl singlets of the major invertomer appeared at $\delta$ 0.79, 0.92 and 1.13 ppm, the two of three nonoverlapping methyl singlets of the minor invertomer appeared at $\delta$ 0.87 and 1.19 ppm. The C(5)H of the major and minor invertomer appeared at $\delta$ 4.12 (quint, $J$ 6.5 Hz) and 3.90 (quint, $J$ 6.5 Hz) ppm, respectively.

**Major invertomer.** $\delta_C$ (CD$_3$OD, -40 °C) 11.90, 14.64, 21.82, 22.07, 23.89, 27.90, 29.90, 32.65, 35.57, 37.00, 47.77, 50.02, 50.83, 54.63, 75.24, 78.16, 81.74.

**Minor invertomer.** $\delta_C$ (CD$_3$OD, -40 °C) 12.15, 14.64, 21.30, 22.77, 24.00, 27.54, 29.90, 33.96, 35.07, 37.00, 47.24, 50.53, 50.83, 56.70, 75.10, 77.76, 80.97.

**Isoxazolidine 4b**

The $^1$H NMR spectrum in CDCl$_3$ at -40 °C revealed the presence of two invertomers in a 97:3 ratio as determined by integration of several proton signals. The C(5)-H signal of 4b appeared at $\delta$ 5.18 (major) and $\delta$ 4.97 (minor).

**Major invertomer.** $\delta_H$ (CDCl$_3$, -40 °C) 0.80 (3H, s), 0.98 (3H, s), 1.08 (2H, m), 1.19 (3H, s), 1.48 (1H, m), 1.77 (2H, m), 2.39 (1H, m), 2.84 (2H, m), 2.93 (1H, d, $J$ 6.8 Hz), 3.51 (1H, dt, $J$ 1.6, 8.5 Hz), 3.65 (1H, d, $J$ 2.5 Hz, OH), 3.69 (1H, dd, $J$ 2.5, 6.7 Hz), 5.18 (1H, t, $J$ 7.5 Hz), 7.38 (5H, m); $\delta_C$ (CDCl$_3$, -40 °C) 11.45, 21.13, 21.58, 27.23, 32.65, 37.91, 46.70, 49.03, 49.76, 54.19, 74.34, 78.17, 80.34, 125.75 (2C), 127.43, 128.54 (2C), 143.09.

**Minor Invertomer.** $\delta_H$ (CDCl$_3$, -40 °C) The minor non overlapping signals were displayed at $\delta$ 4.97 (1H, t, $J$ 7.9 Hz); $\delta_C$ (CDCl$_3$, -40 °C) 20.57, 22.00, 26.45, 36.88, 46.15, 47.73, 49.48, 56.97, 74.55, 79.20, 79.91.

In CD$_3$OD (-40 °C) the $^1$H NMR spectrum revealed the presence of several nonoverlapping minor signals indicating the major/minor invertomers of 4b in a ratio of 81:19. While the methyl singlets of the major invertomer appeared at $\delta$ 0.81, 0.92 and 1.21 ppm, the corresponding methyl singlets of the minor invertomer appeared at $\delta$ 0.79, 0.89, and 1.25 ppm. The C(5)H of the major and minor invertomer appeared at $\delta$ 5.11 (1H, t, $J$ 7.5 Hz) and $\delta$ 4.86(1H, t, $J$ 7.8 Hz), respectively.

**Major invertomer.** $\delta_C$ (CD$_3$OD, -40 °C) 11.96, 21.91, 22.05, 27.94, 33.82, 39.10, 47.79, 50.03, 50.92, 55.37, 75.88, 79.56, 81.82, 127.18 (2C), 128.62, 129.54 (2C), 144.72.

**Minor invertomer.** $\delta_C$ (CD$_3$OD, -40 °C) 12.15, 21.38, 22.39, 27.56, 34.14, 38.64, 47.20, 49.75, 50.46, 57.60, 77.88, 80.16, 81.28, 127.78 (2C), 128.62, 129.35 (2C), 142.74.

**Isoxazolidine 4c**

Both the $^1$H and $^{13}$C NMR spectra in CDCl$_3$ revealed the presence of a single invertomer. The spectra at +20 °C and -40 °C were almost identical.
A single invertomer. \( \delta_H (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) 0.77 (3H, s), 1.00 (3H, s), 1.04 (2H, m), 1.10 (3H, s), 1.47 (1H, m), 1.74 (2H, m), 2.53 (2H, m), 2.68 (1H, m), 2.86 (1H, d, \( J \) 6.7 Hz), 3.33 (1H, m), 3.74 (1H, d, \( J \) 6.7 Hz), 3.79 (3H, s), 4.22 (1H, s, OH), 4.62 (1H, dd, \( J \) 3.4, 9.5 Hz); \( \delta_C (\text{CDCl}_3, -30 \, ^\circ\text{C}) \) 11.44, 21.01, 21.52, 27.30, 32.51, 32.75, 46.71, 49.16, 49.89, 52.32, 52.66, 73.67, 73.73, 80.41, 173.70.

In CD\(_3\)OD (-40 °C) the \( ^1\text{H} \) and \( ^13\text{C} \) NMR spectra also revealed the presence of a single invertomer. The spectra at +20 °C and -40 °C were almost identical.

A single invertomer. \( \delta_H (\text{CD}_3\text{OD}, -40 \, ^\circ\text{C}) \) 0.79 (3H, s), 0.94 (3H, s), 1.09 (5H, m including a 3H singlet), 1.50 (1H, m), 1.76 (2H, m), 2.44 (2H, m), 2.67 (1H, m), 2.84 (1H, d, \( J \) 6.7 Hz), 3.34 (1H, m), 3.65 (1H, d, \( J \) 6.7 Hz), 3.72 (3H, s), 4.66 (1H, dd, \( J \) 3.5, 9.6 Hz); \( \delta_C (\text{CD}_3\text{OD}, -40 \, ^\circ\text{C}) \) 12.02, 21.62, 22.04, 28.14, 33.67, 33.75, 47.88, 50.25, 51.13, 52.84, 53.38, 74.70, 74.77, 81.97, 175.43.

Isoxazolidine 5c

The \(^1\text{H} \) NMR spectrum in CDCl\(_3\) at -40 °C revealed the presence of two invertomers in a 90:10 ratio as determined by integration of several proton signals.

**Major invertomer.** \( \delta_H (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) 0.78 (3H, s), 0.97 (3H, s), 1.05 (2H, m), 1.12 (3H, s), 1.47 (1H, m), 1.73 (2H, m), 2.39 (1H, m), 2.71 (2H, m), 3.07 (1H, d, \( J \) 7.0 Hz), 3.36 (2H, m, including a 1H, s, OH), 3.73 (1H, d, \( J \) 7.0 Hz), 3.79 (3H, s), 4.58 (1H, dd, \( J \) 5.2, 9.5 Hz); \( \delta_C (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) 11.43, 21.16, 21.52, 27.10, 32.60, 33.49, 46.71, 49.03, 50.01, 52.51, 52.64, 74.16, 74.83, 80.13, 172.04.

**Minor Invertomer.** \( \delta_H (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) The minor non overlapping signals were displayed at \( \delta \) 0.81 (3H, s), 0.95 (3H, s); \( \delta_C (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) 11.43, 20.64, 21.99, 26.41, 32.11, 33.49, 46.32, 47.59, 49.42, 52.64, 55.35, 72.62, 74.16, 80.71, 172.56.

In CD\(_3\)OD (-40 °C) the \(^1\text{H} \) NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of 5c in a ratio of 64:36. While the methyl singlets of the major invertomer appeared at \( \delta \) 0.79, 0.92 and 1.12 and 3.73 ppm, the corresponding methyl singlets of the minor invertomer appeared at \( \delta \) 0.80, 0.86, 1.19 and 3.69 ppm. The C(5)H of the major and minor invertomer appeared at \( \delta \) 4.56 (1H, dd, \( J \) 4.9, 9.5 Hz) and an overlapping peak at \( \delta \) 4.53 (1H, dd, \( J \) 5.0, 9.7 Hz), respectively.

**Major invertomer: \( \delta_C (\text{CD}_3\text{OD}, -40 \, ^\circ\text{C}) \) 12.07, 21.76, 21.98, 28.13, 33.90, 34.32, 47.69, 50.17, 51.40, 52.80, 53.92, 75.99, 76.04, 81.69, 174.13.

**Minor invertomer: \( \delta_C (\text{CD}_3\text{OD}, -40 \, ^\circ\text{C}) \) 12.11, 21.31, 22.37, 27.31, 33.29, 34.28, 47.33, 49.52, 50.52, 52.59, 56.07, 74.60, 75.68, 81.33, 174.90.

Isoxazolidine 4d

The \(^1\text{H} \) NMR spectrum in CDCl\(_3\) at -40 °C revealed the presence of two invertomers in a 87:13 ratio as determined by integration of several proton signals.

**Major invertomer.** \( \delta_H (\text{CDCl}_3, -40 \, ^\circ\text{C}) \) 0.78 (3H, s), 0.97 (3H, s), 1.07 (2H, m), 1.16 (3H, s), 1.46 (1H, m), 1.57 (3H, s), 1.72 (2H, m), 2.30 (1H, m), 2.68 (1H, ddd, \( J \) 2.3, 7.5, 12.5 Hz), 2.85 (1H,
dt, J 7.6, 9.5 Hz), 2.96 (1H, d, J 6.7 Hz), 3.37 (1H, ddd, J 2.2, 7.5, 9.5 Hz), 3.45 (1H, d, J 2.4 Hz, OH), 3.71 (1H, dd, J 2.4, 6.7 Hz), 3.79 (3H, s); δ_C (CDCl₃, -40 °C) 11.38, 21.21, 21.53, 24.95, 27.01, 32.66, 46.16, 48.98, 49.71, 52.86, 53.49, 73.77, 80.27, 81.71, 173.84.

Minor Invertomer. δ_H (CDCl₃, -40 °C) The minor non overlapping signals were displayed at δ 0.81 (3H, s), 0.94 (3H, s), 1.19 (3H, s), 2.13 (1H, m), 2.46 (1H, q, J 8.3 Hz), 2.76 (1H, d, J 7.3 Hz), 2.90 (1H, m), 3.75 (3H, s); δ_C (CDCl₃, -40 °C) 11.46, 20.33, 21.96, 23.19, 26.35, 32.75, 38.46, 46.16, 47.88, 49.42, 52.48, 56.99, 74.51, 80.66, 81.06, 175.69.

In CD₃OD (-40 °C) the ¹H and ¹³C NMR spectra also revealed the presence of two invertomer in a 43: 57 ratio (stereo-preference reversed).

Major invertomer. δ_H (CD₃OD, -40 °C) 0.78 (3H, s), 0.84 (3H, s), 1.02 (2H, m), 1.13 (3H, s), 1.41 (3H, s), 1.47 (1H, m), 1.73 (2H, m), 2.03 (1H, ddd, J 2.5, 9.5, 12.5 Hz), 2.25 (1H, m), 2.62 (1H, d, J 7.6 Hz), 2.84 (2H, m), 3.54 (1H, d, J 6.7 Hz), 2.90 (1H, m), 3.75 (3H, s); δ_C (CD₃OD, -40 °C) 12.12, 21.22, 22.38, 23.51, 27.21, 34.36, 38.46, 46.67, 49.11, 52.80, 53.35, 74.27, 80.41, 81.39, 177.53.

Minor invertomer. The non overlapping signals at δ_H (CD₃OD, -40 °C) 0.91 (3H, s), 1.14 (3H, s), 1.47 (3H, s), 2.67 (1H, ddd, J 2.6, 7.1, 12.5 Hz), 2.94 (1H, d, J 6.7 Hz), 3.36 (1H, s), 3.61 (1H, d, J 6.7 Hz), 3.72 (3H, s); δ_C (CD₃OD, -40 °C) 12.01, 21.86, 22.04, 24.90, 27.97, 33.88, 40.68, 47.76, 50.06, 50.99, 53.13, 54.64, 75.51, 81.41, 83.14, 175.33.

Isoxazolidine 5d
Both the ¹H and ¹³C NMR spectra in CDCl₃ revealed the presence of a single invertomer. The spectra at +20 °C and -40 °C were almost identical.

A single invertomer. δ_H (CDCl₃, +20 °C) 0.76 (3H, s), 0.98 (3H, s), 1.05 (2H, m), 1.10 (3H, s), 1.43 (1H, m), 1.49 (3H, s), 1.68 (2H, m), 2.08 (1H, ddd, J 1.9, 9.0, 12.5 Hz), 2.58 (1H, app q, J 8.9 Hz), 2.81 (2H, m, including a 1H, d, J 6.7 Hz), 3.28 (1H, t, J 8.1), 3.72 (1H, d, J 6.7 Hz), 3.75 (3H, s), 4.01 (1H, s, OH); δ_C (CDCl₃, -40 °C) 11.44, 20.92, 21.52, 22.88, 27.26, 32.56, 38.84, 46.67, 49.11, 49.45, 52.80, 53.35, 74.27, 80.41, 81.39, 175.92.

Both the ¹H and ¹³C NMR spectra in CD₃OD revealed the presence of a single invertomer. The spectra at +20 °C and -40 °C were almost identical.

A single invertomer. δ_H (CD₃OD, -40 °C) 0.79 (3H, s), 0.94 (3H, s), 1.00 (2H, m), 1.09 (3H, s), 1.45 (3H, s), 1.49 (1H, m), 1.72 (2H, m), 2.18 (1H, m), 2.53 (1H, m), 2.70 (1H, m), 2.83 (1H, d, J 6.7), 3.35 (1H, m), 3.65 (1H, d, J 6.7 Hz), 3.72 (3H, s); δ_C (CD₃OD, -40 °C) 11.96, 21.53, 22.00, 23.04, 28.04, 33.63, 39.88, 47.77, 50.15, 50.60, 53.03, 54.35, 75.31, 81.96, 82.41, 177.23.

Isoxazolidine 4e
To a solution of the hydroxylamine 1 (556 mg, 3.00 mmol) in CHCl₃ (15 cm³), was added paraformaldehyde (150 mg, 5.0 mmol) and the mixture was stirred using a magnetic stir bar at 45 °C for 4 h. Thereafter, MgSO₄ (~ 2 g) was added followed by dimethyl methylenemalonate (3) (0.506 g, 3.51 mmol). After stirring in a closed vessel at 50 °C for 6 h, the reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether/hexane
as eluent to give isoxazolidine 4e (805 mg, 79 %). Mp 131-132 °C (ether); (Found: C, 59.7; H, 7.9; N, 4.0. C_{17}H_{27}NO_{6} requires C, 59.81; H, 7.97; N, 4.10 %); ν\text{max.} (KBr) 3515, 2958, 2881, 1753, 1440, 1290, 1270, 1216, 1095, 1003, 926, 828, and 771 cm\(^{-1}\).

Both the \(^1\)H and \(^13\)C NMR spectra in CDCl\(_3\) revealed the presence of a single invertonomer. The spectra at +20 °C and -40 °C were almost identical. A single invertonomer. δ\(_H\) (CDCl\(_3\), -40 °C) 0.77 (3H, s), 0.99 (3H, s), 1.06(2H, m), 1.09 (3H, s), 1.47 (1H, m), 1.71 (2H, m), 2.75 (1H, m), 2.90 (2H, m), 2.97(1H, d, J 6.4 Hz), 3.41 (1H, m), 3.78 (1H, d, J 6.4 Hz), 3.83 (1H, s, OH), 3.85 (3H, s), 3.86 (3H, s); δ\(_C\) (CDCl\(_3\), -40 °C) 11.37, 20.96, 21.35, 27.14, 32.42, 36.65, 46.77, 49.03, 49.79, 53.17, 53.63, 53.86, 73.73, 80.12, 83.98, 166.84, 170.27.

In CD\(_3\)OD (-40 °C) the \(^1\)H NMR spectrum revealed the presence of several nonoverlapping minor signals indicating the major/minor invertonomers of 4e in a ratio of 94:6. While the methyl singlets of the major invertonomer appeared at δ 0.79, 0.94 and 1.08 ppm, the non overlapping methyl singlets of the minor invertonomer appeared at δ 0.85, and 1.25 ppm. The major invertonomer displayed a proton at δ 2.90 (1H, d, J 6.7 Hz) and another proton at 3.67 (1H, d, J 6.7 Hz) ppm. The corresponding protons for the minor invertonomer appeared at δ 2.74 (1H, d, J 6.7 Hz) and 3.53 (1H, d, J 6.7 Hz).

Major invertonomer. δ\(_C\) (CD\(_3\)OD, -40 °C) 11.94, 21.61, 21.94, 28.07, 33.60, 37.37, 47.89, 50.23, 51.13, 53.74, 54.08, 54.35, 74.94, 81.87, 85.29, 167.48, 171.87.

Minor invertonomer. δ\(_C\) (CD\(_3\)OD, -40 °C) 12.17, 21.39, 22.29, 27.11, 34.27, 37.37, 47.26, 49.81, 50.65, 53.60, 54.44, 56.30, 75.33, 81.25, 85.74, 167.48, 171.87.

Inversion barrier calculations

The variable temperature \(^1\)H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm\(^3\) solutions in CDCl\(_3\) and CD\(_3\)OD with TMS as internal standard. Simulations of exchange-affected proton spectra for all compounds were carried out using a computer program AXEX,\(^{15}\) corresponding to a two non coupled sites exchange with unequal populations. The following signals were utilized: 4a, (CD\(_3\)OD), methyl singlets at δ 1.13 (major) and 1.19 ppm (minor); 4b, (CDCl\(_3\)), C(5)H at δ 4.97 (minor) and 5.18 ppm (major); 4b, (CD\(_3\)OD), methyl singlets at δ 0.79 (minor) and 0.81 ppm (major); 5c, (CDCl\(_3\)), methyl singlets at δ 0.78 ppm (major) and 0.81 (minor); 5c, (CD\(_3\)OD), methyl singlets at δ 3.69 (minor), 3.73 ppm (major); 4d, (CDCl\(_3\)), methyl singlets at δ 3.75 (minor) and 3.79 ppm (major); 4d: (CD\(_3\)OD) methyl singlets at δ 3.66 (major) and 3.72 ppm (minor); 4e, (CD\(_3\)OD), methyl singlets at δ 0.85 (minor) and 0.94 ppm (major). Simulations of exchange affected triplets were carried out by modifying the two-site exchange program.\(^{15}\) The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange. Simulations of exchange affected doublet of doublets were carried out by modifying the two-site exchange program.\(^{5a}\) The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange.
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References

15. The NMR Program Library, Science and Engineering Research Council, Daresbury Laboratory, Cheshire, U. K.