Supplementary Information

Assignment of $^1$H and $^{13}$C NMR spectra

Due to the nature of the project it was essential that we were certain of the structure of the compounds that were prepared. It was our aim was to unambiguously assign the proton and carbon signals in every molecule prepared. This involved numerous NMR experiments and a representative example of the analysis performed on amine 27 (Figure 1) is outlined below.

![Figure 1 NMR assignment for amine 27](image)

A HSQC (heteronuclear single quantum coherence) experiment was performed (Figure 2). This allows the construction of a large portion of Table 1 which displays the direct connectivity of proton and carbon signals. The chemical shift for the quaternary carbons was taken from the standard $^{13}$C 1-D spectrum. (Figure 3) The DEPT 135 (distortionless enhancement by polarization transfer) experiment displayed on the y-axis in Figure 2 facilitated identification of the CH$_2$ carbon signals which were phase shifted by 180°. It was possible to distinguish between CH and CH$_3$ carbon signals from a DEPT 90 experiment (not shown). The area highlighted in Figure 2 is shown in greater detail in Figure 4 which allowed one to distinguish between the $^1$H signals for carbon 5 and 6 which were separated by 0.1 ppm in the $^{13}$C spectrum.

The information required to complete the ‘position’ column in Table 1 will be outlined in due course.
Figure 2: HSQC experiment: $^1$H NMR on x axis and DEPT 135 on y-axis
Table 1 Complete NMR assignment of amine 27

<table>
<thead>
<tr>
<th>Carbon (ppm)</th>
<th>Type</th>
<th>Proton (ppm)</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9</td>
<td>CH₃ (t)</td>
<td>0.88</td>
<td>11</td>
</tr>
<tr>
<td>22.4</td>
<td>CH₃ (s)</td>
<td>0.91</td>
<td>9</td>
</tr>
<tr>
<td>23.0</td>
<td>CH₂ (m)</td>
<td>1.29-1.40</td>
<td>6</td>
</tr>
<tr>
<td>23.1</td>
<td>CH₂ (m)</td>
<td>1.19-1.27 and 1.54-1.62</td>
<td>5</td>
</tr>
<tr>
<td>26.2</td>
<td>CH₃ (s)</td>
<td>0.99</td>
<td>8</td>
</tr>
<tr>
<td>27.0</td>
<td>CH₂ (m)</td>
<td>1.20-1.27 and 1.62-1.70</td>
<td>10</td>
</tr>
<tr>
<td>33.8</td>
<td>CH₂ (m)</td>
<td>1.04-1.11 and 1.89-1.96</td>
<td>7</td>
</tr>
<tr>
<td>43.0</td>
<td>q</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>48.5</td>
<td>CH (m)</td>
<td>1.86-1.90</td>
<td>1</td>
</tr>
<tr>
<td>50.1</td>
<td>CH (m)</td>
<td>1.68-1.72</td>
<td>4</td>
</tr>
<tr>
<td>61.5</td>
<td>q</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 3: 13C and DEPT 135 experiments for amine 27
A TOCSY (total correlation spectroscopy) experiment was performed to analyse the interactions between protons on adjacent carbons (or on the same carbon if the protons were diastereotopic).
Figure 5: TOCSY experiment: $^1$H NMR on both x and y axes

The methyl triplet signal at 0.88 ppm showed a response at 1.20-1.27 ppm and 1.62-1.70 ppm which corresponds to the CH$_2$ at 27.0 ppm. Hence, carbons 10 and 11 were assigned. Also evident, is an interaction between the CH at 1.86-1.90 ppm and the CH$_2$ at 1.29-1.40 although unambiguous assignment of these signals was not yet possible. As a result, a HMBC (heteronuclear multiple bond coherence) experiment was performed to analyse long range carbon-hydrogen interactions in an attempt to characterise the relevant CH position.
An interaction was observed between the quaternary carbon 3 and the CH at 1.86-1.90 ppm. HMBC responses are generally strongest between atoms separated by three bonds, implying the CH in question is at position 1. The HH-COSY interaction (Figure 5) observed for this signal implies that the CH$_2$ at 1.29-1.40 ppm is at position 6. A number of the remaining signals could also be identified at this point. The second CH (51.1 ppm) was assigned to position 4. It was thought to be highly likely that carbons 5 and 6 would have very similar chemical shifts allowing the CH$_2$ at 23.1 ppm to be assigned to position 5. Further evidence to support this claim was available from the HMBC experiment (Figure 6) which shows an interaction between both methyl singlets and the CH$_2$ at 23.1 ppm (C5). The remaining CH$_2$ was attributed to position 7.

In order to confirm the proposed characterization and also to define the stereochemistry in this system, a series of nOe (nuclear Overhauser effect) experiments were performed in order to analyse the ‘through space’ interactions for a selected number of protons.
In the spectrum for the experiment irradiating at 0.99 ppm, the response visible for the CH at 1.68 - 1.72 ppm confirms the earlier assignment of position 4. The response at 1.89-1.96 ppm corresponds to the interaction shown in Figure 8.

**Figure 7: nOe experiments irradiating the methy substituents in amine 27 and original 1H NMR**

**Figure 8: nOe response between H8 and H7b in amine 27**
This confirms the assignment of position 7 and allows unambiguous assignment of the exo methyl substituent. The NOE experiments irradiating the two remaining methyl groups proved to be less informative, as their chemical shifts were too close to allow selective irradiation of each signal individually. Vitally however, there was clearly no response observed with the NOE experiments irradiating at 0.91 or 0.88 ppm for the signal at 1.89-1.96 ppm, thereby confirming these substituents reside in an endo orientation.

This methodical approach was applied to every compound synthesised. Analysis of the stereochemistry of the alkyl substituents at positions 2 and 3 was generally carried out only for one of the azide, amine or methylated amine of each analogue as it was known that the stereochemistry was immutable throughout these transformations.

In certain cases, unambiguous stereochemical assignment was not possible. This generally arose in the case of 3,3-diethyl compounds, in which NOE analysis of the type described above was prevented by the fact that the 1H NMR signals for CH₂ protons on ethyl substituents tended to give rise to overlapping multiplets that could not be selectively irradiated. In these cases, the ethyl substituents were assigned arbitrarily. An example is shown in Figure 9.

Figure 9: Inability to unambiguously assign NMR spectra in amine 27

Overlapping signals preclude the possibility of selectively irradiating the required ethyl CH₂ groups

Unable to distinguish between these carbons
NMR spectra
The nature of the formation of azides is such that there is a concern of cross contamination with mixtures of isomeric compounds being tested. To highlight that this is not the case (at least to the limit of 13C detection) stack plots of the appropriate final compounds from the dimethylethyl series (19, 33, 34) and the diethylmethyl series (35, 36, 37) are shown below. Compound 19\textsuperscript{25} (unfortunately in a different solvent) is included for the sake of completeness.