Solvent-free double aza-Michael under ultrasound irradiations: diastereoselective sequential one-pot scalable synthesis of pyrrolidine Lobelia alkaloids analogues

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

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2. nOesy correlation spectra of 13α,β,γ for relative configuration determination

Relative stereochemistry has been assigned by nOesy correlations between Hα and Hβ, Hα and Hγ, Hβ and Hγ.
General characterization of the cis-stereochemistry is highlighted on spectra.

2.1 nOesy correlation spectra of 13a for relative configuration determination
2.2. nOesy correlation spectra of 13c for relative configuration determination
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3. X-Ray structures for compounds 13d and 18


A colourless plate-like single crystal (0.60 x 0.46 x 0.10 mm) grown from cyclohexane was mounted on an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å) at ambient temperature (293(2)K). A preliminary orientation matrix and unit cell parameters were determined from a 10° φ–scan of 1°-oscillation, followed by spot integration and least-squares refinement. A φ–scan of a 179° range with 1.3° oscillation, followed by two ω-scans of successive lengths: 38.1, 62.5°, with the detector at a distance of 41.9 mm from the crystal and at θ = 7.453° (respectively 7.166°) was designed for complete collection of data in mmm Laue system with significant measured intensities up to a resolution of 0.90 Å. «Dezingering» was accomplished by measuring each frame twice with exposure of 40s per degree. Data reduction and cell dimension post-refinement were performed, altogether with multi-scan absorption correction with SCALEPACK. The structure was solved using direct methods (SIR97) and all non-hydrogen atoms were refined with anisotropic displacement parameters using SHELX-L97 by full-matrix least squares on \( F^2 \) values. All hydrogen atoms were located on difference–Fourier syntheses but were refined with a riding model and with \( U_{iso} \) set to 1.2 times that of the attached C-atom. One low-resolution reflection shaded by the beamstop was omitted during the stage of the model refinement using the OMIT instruction in SHELX-L97.

The crystallographic data are summarized as follows: thin colourless plate of dimensions 0.60 x 0.46 x 0.10 mm, C\(_{33}\) H\(_{29}\) N O\(_2\), \( M_r = 471.57 \), orthorhombic system, space group \( P b c \) \( m \), \( Z = 4 \), \( a = 8.806 (4) \), \( b = 11.377 (5) \) Å, \( c = 26.118 (8) \) Å, \( V = 2616.7(2) \) Å\(^3\), \( D_{calc} = 1.197 \) g/cm\(^3\), \( F(000) = 1000 \), \( \mu = 0.074 \) mm\(^{-1}\), 11516 collected reflections (1.98° ≤ θ ≤ 46.58°), -9 ≤ h ≤ 9, -12 ≤ k ≤ 12, -28 ≤ l ≤ 28), 1920 independent reflections (\( R_{int} = 0.0245 \), goodness-of-fit on \( F^2 \): \( S = 1.050 \), \( R_1 = 0.0885 \) and \( wR_2 = 0.1925 \) for all 1919 reflections, \( R_1 = 0.0635 \) and \( wR_2 = 0.1708 \) for 1361 observed reflections \( I > 2\sigma(I) \), refining 167 parameters, semi-empirical absorption correction from multi-scans (\( T_{min} = 0.89 \), \( T_{max} = 0.99 \), final electron density between -0.180 and 0.385 e Å\(^{-3}\). The programs used in the crystallographic study were as follows: data collection, cell refinement and data reduction: COLLECT\(^4\) / HKL2000; structure solution: SIR97; structure refinement: SHELXL97\(^4\) within CRYSTALBUILDER; molecular graphics: ORTEP\(^6\) within PLATON.\(^7\) CCDC 854591 (compound 13d) contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).
Figure 1. ORTEP diagram (30% probability ellipsoids) showing crystallographic atom numbering and solid-state conformation for compound 13d.

3.2. Crystal data of N-methyl-2,5-cis-di-(2-phenethyl)-pyrrolidine hydrochloride 18.

The X-ray crystallographic data were measured on a Rigaku MM007 HF copper (\(\lambda = 1.54187 \, \text{Å}\)) rotating-anode generator equipped with Osnic confocal optics and a rapid II Curved Image Plate at 200(2)K. A total of 42 oscillation images were collected in two sweeps using \(\phi\) oscillations from 20.0 to 200.0° and from 70 to 100°, respectively, in 5.0° steps. The exposure rate was 120.0 sec./°. The crystal-to-detector distance was 127.40 mm and the configuration set-up allowed the measurement of data to a maximum 2θ value of 136.5°. Out of the 12865 reflections that were collected, 1894 were unique (Rint = 0.0359). The linear absorption coefficient, \(\mu\), for Cu-Kα radiation is 1.721 cm\(^{-1}\). An empirical absorption correction was applied which resulted in transmission factors ranging from 0.648 to 0.866. The data were corrected for Lorentz and polarization effects.

Compound (18) crystallized in the orthorhombic system (from diethylether). From the manner in which the data were integrated (with a < b < c), the systematic absences allowed the space group to be either C2cb or Cmca. Both possibilities were examined and the non-centrosymmetric spacegroup C2cb shown to be correct, allowing the structure to be solved by conventional direct methods and refined by full-matrix least-squares on \(F^2\). The C2cb system was then transformed to the equivalent standard Aba2 system before the final refinement. The meso-molecules were subjected to a 2-fold rotational crystallographically imposed symmetry, passing through the pyrrolidine group, and the chloride ion, thus in special position. This heterocycle ring adopts an envelope conformation, folded across the line C2 ... C2_a, with atom N1 at the apex out of the least-squares plane defined by the other non-H atoms of the ring, by 0.610 (6) Å, and oriented toward the chloride ion (N1–H1 ... Cl1 2.155 Å and 170.8°). Phenacyl substituents at the opposite sides of the ring are in bisectional positions and in syn conformation but in anti with respect to the methyl substituent also in bisectional position. All non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were located from difference Fourier maps but refined as a riding model with \(U_{iso}\) set to 1.5 (methyl) and 1.2 (other) times the equivalent isotropic displacement parameter of their parent atoms. Soft restraints were applied on distances (by the use of the DFIX and DANG instructions) to regularize the geometry of the pyrrolidine group and its alkyl substituents, which appear also disordered over two possible orientations with occupancy factors freely refined to 0.548(12)/0.452(12).

The crystallographic data are summarized as follows: elongated rectangular cuboid of dimensions
0.59 x 0.18 x 0.16 mm, C\textsubscript{21} H\textsubscript{28} N\textsuperscript{+}, Cl\textsuperscript{-}, Mr = 329.89, orthorhombic system, space group A\textit{b}a\textit{2}, Z = 4, \(a = 25.438(2)\) b = 10.6710 (5) \AA, c = 7.1250 (2) \AA, \(V = 1934.07(19)\) \AA\textsuperscript{3}, \(D_{\text{calc}} = 1.133\) g/cm\textsuperscript{3}, \(F(000) = 712, \mu = 1.721\) mm\textsuperscript{-1}, 12865 collected reflections (6.96° \(\leq \theta \leq 73.14°\), -31 \(\leq h \leq 31, -12 \leq k \leq 8, -8 \leq l \leq 8\)), 1894 independent reflections \((R_{\text{int}} = 0.0375)\), goodness-of-fit on \(F^2\): \(S = 1.136, R_1 = 0.0718\) and \(wR_2 = 0.1763\) for all 1891 reflections, \(R_1 = 0.0544\) and \(wR_2 = 0.1467\) for 1405 observed reflections \([I > 2\sigma(I)]\), refining 131 parameters and 4 restraints on bond lengths with respect the pyrrolidine group, semi-empirical absorption correction from multi \(\omega\)-scans \((T_{\text{min}} = 0.680, T_{\text{max}} = 1.000)\), final electron density between -0.312 and 0.205 e \AA\textsuperscript{-3}. 

The programs used in the crystallographic study were as follows: data collection, cell refinement and data reduction: CRYSTALCLEAR™ software package;\textsuperscript{8} structure solution: SHELXS97; structure refinement: SHELXL97\textsuperscript{4} within CRYSTALBUILDER; molecular graphics: ORTEP\textsuperscript{6} within PLATON.\textsuperscript{7}

CCDC 828848 (compound 18) contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

**Figure 2.** ORTEP diagram (30% probability ellipsoids) showing crystallographic atom numbering and solid-state conformation for compound 18. For clarity the disordered part of the molecule was not shown.

**References:**


4. $^1$H NMR monitoring of double conjugate addition of (+)-phenylethylamine to 12a

4.1. $^1$H NMR monitoring of double aza-Michael reaction in methanol-$d^4$
4.2. $^1$H NMR monitoring of double aza-Michael reaction in chloroform-$d^1$