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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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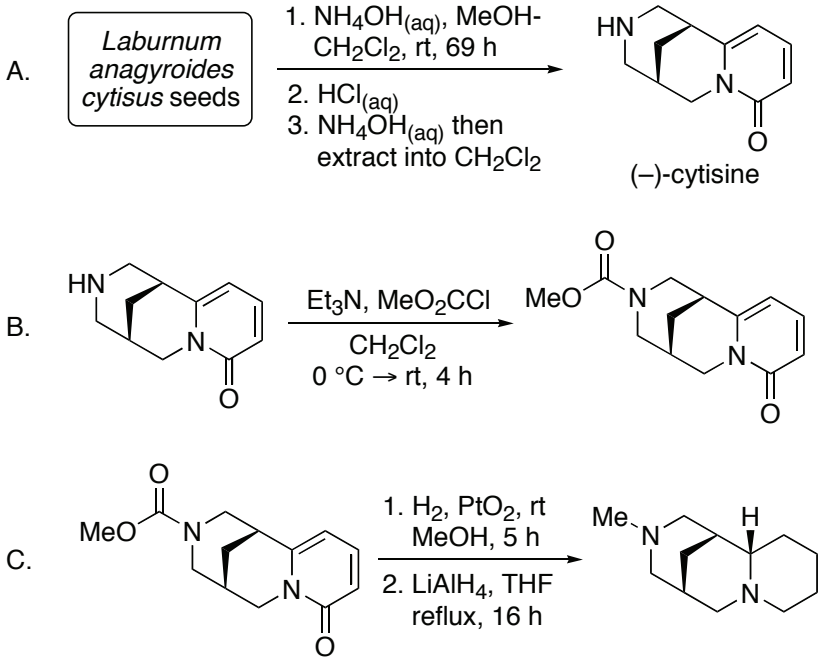
# SYNTHESIS OF (+)-(1*R*,2*S*,9*S*)-11-METHYL-7,11-DIAZATRICYCLO[7.3.1.$0^{2,7}$]TRIDECANE, A (+)-SPARTEINE SURROGATE

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Checked by Sigrid Holle and Alois Fürstner.

## 1. Procedure

*A. (–)-Cytisine.* A 2-L, three-necked round-bottomed flask equipped with an overhead mechanical stirrer with large Teflon-coated blades (Note 1) and two glass stoppers is charged with finely ground *Laburnum anagyroides* seeds (598 g) (Notes 2 and 3), dichloromethane (837 mL), methanol (239 mL) and aqueous 25% w/v ammonium hydroxide (90 mL) (Note 4). The resulting mixture is stirred vigorously (Note 1) at room temperature. After a short induction period, a slight exotherm is observed lasting for the first ~24 h, accompanied with the formation of a thick gel (Note 1), which slowly disappears on prolonged stirring. After stirring the suspension for a total of 69 h, the mixture is filtered in three separate batches and the filter cake is washed with $CH_2Cl_2$ until the filtrate is colorless (Note 5). The filtrate is transferred to a 5-L separatory funnel and shaken with 3.3 M HCl (500 mL). After 2 h (Note 6), the two layers are separated and the aqueous layer is transferred to a 2-L conical flask equipped with a magnetic

stirring bar. The stirred aqueous solution is basified to pH 9-10 by the careful, portionwise addition of aqueous 25% w/v ammonium hydroxide (~150 mL) over 1 h (Note 7), followed by stirring for an additional 2 h (Note 8). The resulting solution is extracted with $CH_2Cl_2$ (10 × 100 mL) (Note 9). The $CH_2Cl_2$ extracts are combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give crude (–)-cytisine (8.31 g) (Note 10) as a yellow-brown solid. The crude (–)-cytisine is purified by recrystallization (Note 11) from toluene (25-30 mL) to afford 5.25 g (0.9 % mass yield) of pure (–)-cytisine (Note 12) as a yellow-brown solid, having greater than 99.5% ee (Note 13).

*B. (–)-Methyl (1R,9R)-6-Oxo-7,11-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4-diene-11-carboxylate.* A flame-dried 250-mL, two-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a glass stopper and a vacuum take-off adapter attached to the argon line is charged with (–)-cytisine (5.25 g, 27.5 mmol), $CH_2Cl_2$ (80 mL) (Note 4) and triethylamine (4.21 mL, 30.2 mmol) (Note 14). The resulting magnetically stirred solution is immersed in an ice bath and methyl chloroformate (2.34 mL, 30.2 mmol) (Note 14) is added dropwise via syringe over 10 min at 0 °C. The resulting mixture is stirred for 1 h at 0 °C and then for 3 h at room temperature before the solvent is evaporated under reduced pressure. Ethyl acetate (EtOAc) (40 mL) is added to the residue and the solids are removed by filtration through Celite (Note 15). The filter cake is washed with EtOAc (3 × 15 mL) and the filtrate is evaporated under reduced pressure. The residue is purified by column chromatography over a short plug of silica (Note 16) with $CH_2Cl_2$:MeOH (9:1) as eluent. The fractions containing the product ($R_f$ = 0.51; 9:1, $CH_2Cl_2$:MeOH) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying ($10^{-3}$ mbar) for 2 h to afford 6.45 g (94%) of pure cytisine methyl carbamate (Note 17) as a thick colorless oil.

*C. (+)-(1R,2S,9S)-11-Methyl-7,11-diazatricyclo[7.3.1.0$^{2,7}$]tridecane.* A flame-dried, 250-mL, three-necked round-bottomed flask equipped with a magnetic stir bar, a glass stopper, and a vacuum take-off adapter that can be attached either to the argon line or to the $H_2$ supply is charged with cytisine methyl carbamate (6.50 g, 26.2 mmol), MeOH (100 mL) and platinum(IV) oxide (600 mg, 2.7 mmol) (Note 18). The resulting magnetically-stirred suspension is carefully evacuated and backfilled with argon (three times) before evacuating and backfilling with hydrogen (*via* hydrogen balloons attached to the two-tap adaptor). The cloudy black mixture is stirred

vigorously under a hydrogen atmosphere for 5-12 h (Note 19). The solids are removed by filtration through Celite (Note 20) and the filter cake is washed with $CH_2Cl_2$:MeOH (9:1) (50 mL). The filtrate is evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying ($10^{-3}$ mbar) to afford 5.93 g (90 %) of crude hydrogenation product (Note 21) as an off-white solid.

A flame-dried, 500-mL, two-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser attached to the argon line, and a glass stopper is charged with lithium aluminium hydride (5.12 g, 134.6 mmol) and tetrahydrofuran (THF) (150 mL) (Note 22). The resulting magnetically-stirred suspension is immersed in an ice bath and a solution of the crude hydrogenation product (5.93 g, 23.5 mmol) in THF (150 mL) is added dropwise over 10 min *via* a cannula at 0 °C. The mixture is allowed to warm to room temperature and then refluxed under argon for 16 h (Note 23). After cooling to 0 °C, diethyl ether (150 mL) is added, followed by the careful, portionwise addition of solid hydrated sodium sulfate ($Na_2SO_4$•$10H_2O$) (17 g) (Note 22), which causes a vigorous evolution of hydrogen gas. The resulting viscous mixture is stirred for 30 min until gas evolution has ceased and the solids are removed by filtration through Celite (Note 24). The filter cake is washed with $CH_2Cl_2$:MeOH (9:1) (150 mL) and the washings are combined, dried ($Na_2SO_4$), filtered and evaporated under reduced pressure to give crude diamine (3.95 g). The crude diamine is purified by Kugelrohr distillation (oven temperature 150–160 °C at 0.07 mbar) to afford 2.65 g (52% over two steps) of pure diamine (Note 25) as a colorless oil, having greater than 95% ee (Note 26).

## 2. Notes

1. Effective stirring is essential for the success of the isolation process. Because the reaction mixture temporarily forms a thick gel for several hours that slowly disappears, the use of a strong mechanical stirrer is required. The checkers used a mechanical stirrer with approximately 9 x 2 cm Teflon-coated blades. An effective extraction was ensured at 300 turns/min of this stirrer.

2. *Laburnum Anagyroides* seeds were purchased from Vilmorin, Division Semences d'Arbres, Route du Manoir, 49250 La Ménitré, France.

3. The seeds are ground to a fine (< 2 mm), non-uniform powder by using a standard coffee grinder. Typically, 30-50 g batches of the seeds are

ground for ~30 sec. The use of coarse particles results in an inefficient extraction and/or extended extraction times.

4. Dichloromethane, methanol, toluene and 12 M hydrochloric acid (diluted with water to 3.3 M) were purchased from Aldrich and used as received. Ammonium hydroxide (25% w/v) purchased from Reininghaus was used as received.

5. The following procedure is used for the filtration process: (i) approximately one third of the stirred reaction mixture slurry is rapidly poured into a 14 cm-diameter Büchner funnel (fitted with a 12.5 cm-diameter Whatman No. 1 filter paper) attached to a 2-L Büchner flask. The filter cake is sucked dry and then washed with $CH_2Cl_2$ (~100-150 mL) until the filtrate runs through colorless. The filter cake is discarded. (ii) $CH_2Cl_2$ (150 mL) is added to the extraction mixture in the round-bottomed flask and approximately half of the remaining stirred mixture slurry is rapidly poured into the Büchner funnel/flask set-up. The filter cake is sucked dry and then washed with $CH_2Cl_2$ (150 mL) until the filtrate runs through colorless. The filter cake is discarded. (iii) The final portion of the reaction mixture slurry is filtered by repeating step (ii). The total volume of the filtrate at this stage is typically 1.8 L.

6. The mixture is left for 2 h to complete acidification and is periodically shaken with frequent venting to ensure good mixing. The pH is 1–2 as tested by pH paper (E. Merck, Darmstadt).

7. The basification is exothermic and a slow addition of the aqueous 25% w/v ammonium hydroxide is necessary.

8. The solution is left for at least 2 h so that a stable pH of 9-10 (pH paper, E. Merck, Darmstadt) is obtained. The solution can be left overnight at this stage without any detrimental effect on the isolated yield of (–)-cytisine.

9. If the mixture is not extracted with 10 × 100 mL portions of $CH_2Cl_2$, lower yields of (–)-cytisine are obtained.

10. The yield of crude (–)-cytisine can vary widely (8-15 g) depending on the particular crop of the seeds that is used, but ≥ 5 g of pure (–)-cytisine is typically obtained after recrystallization from 25-30 mL of toluene.

11. For recrystallization, the crude product is dissolved in 25-30 mL of boiling toluene in a 50-mL conical flask and then allowed to cool slowly by standing overnight at room temperature. The flask is cooled at 0 °C for 1 h before collecting the crystals by filtration. The submitters report that on

some occasions it is necessary to collect a second crop of crystals to ensure that >5 g of pure (–)-cytisine is obtained.

12. The properties are as follows: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 1.94 (br s, 2 H), 2.24 (br s, 1 H), 2.32 (br s, 1 H), 2.89 (br s, 1 H), 2.97–3.13 (m, 4 H), 3.90 (dd, 1 H, *J* = 15.5, 6.5 Hz), 4.10 (d, 1 H, *J* = 15.5 Hz), 5.98 (dd, 1 H, *J* = 6.8, 1.4 Hz), 6.42 (dd, 1 H, *J* = 9.1, 1.4 Hz), 7.27 (dd, 1 H, *J* = 9.1, 6.9 Hz); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ: 26.1, 27.6, 35.3, 49.6, 52.6, 53.6, 105.1, 116.8, 138.8, 150.7, 163.6; IR (film): 1649, 1546 $cm^{-1}$; $[\alpha]_D^{20}$ –59.3 ($CHCl_3$, *c* 0.84); mp 153–154 °C; $R_f$ = 0.16 (9:1, $CH_2Cl_2$:MeOH).

13. The submitters determined the enantiomeric excess by conversion into *N*-benzyl cytisine and analysis by chiral HPLC: A 10-mL, one-necked round-bottomed flask equipped with a magnetic stirrer bar and reflux condenser (fitted with a rubber septum, attached to a nitrogen line) is charged with (–)-cytisine (100 mg, 0.52 mmol), benzyl bromide (0.14 mL, 1.04 mmol), potassium carbonate (380 mg, 2.6 mmol) and acetonitrile (3 mL). The resulting magnetically-stirred suspension is heated at reflux under nitrogen for 5 h. After cooling to room temperature, the solvent is evaporated under reduced pressure. Dichloromethane (10 mL) is added to the residue and the solids are removed by filtration through Celite. The filtrate is evaporated under reduced pressure and the residue is purified by column chromatography over silica with $CH_2Cl_2$ and then $CH_2Cl_2$:MeOH (97:3) as eluent. The fractions containing the product ($R_f$ = 0.6; 9:1, $CH_2Cl_2$:MeOH) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying to afford 137 mg (94%) of pure *N*-benzyl cytisine as a white solid. The properties are as follows: $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.77–1.94 (m, 2 H), 2.32 (dd, 1 H, *J* = 11.0, 2.0), 2.37 (br d, 1 H, *J* = 11.0), 2.40–2.48 (m, 1 H), 2.83–2.96 (m, 3 H), 3.39 (d, 1 H, *J* = 14.0), 3.46 (d, 1 H, *J* = 14.0), 3.89 (dd, 1H, *J* = 15.0, 7.0), 4.12 (d, 1 H, *J* = 15.0), 5.84 (dd, 1 H, *J* = 7.0, 1.0), 6.50 (dd, 1 H, *J* = 9.0, 1.0), 6.98–7.01 (m, 2 H), 7.17–7.23 (m, 3 H), 7.29 (dd, 1 H, *J* = 9.0, 7.0); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ: 25.9, 28.1, 35.4, 49.9, 59.9, 60.0, 61.9, 104.6, 116.5, 126.8, 128.1, 138.0, 138.5, 151.4, 163.6 (one aromatic resonance not resolved); IR ($CH_2Cl_2$) $cm^{-1}$ 1650, 1560, 1545; $[\alpha]_D^{20}$ –302 ($CHCl_3$, *c* 0.5); mp 139-141 °C; $R_f$ = 0.6 (9:1 $CH_2Cl_2$-MeOH). HPLC analysis using a Chiralcel-OD column with 20% 2-propanol in heptane containing 0.1% diethylamine as eluent, and a flow rate of 0.5 mL/min indicates a single peak with retention time of 18 min. HPLC

analysis of the corresponding racemic *N*-benzyl cytisine affords two peaks at 18 min and 23 min corresponding to (–)- and (+)-cytisine, respectively.

14. Triethylamine was purchased from Aldrich and distilled over potassium hydroxide before use. Methyl chloroformate was purchased from Aldrich Chemical Company, Inc. and used as received. Ethyl acetate (EtOAc) was purchased from Fisher Scientific and used as received.

15. Filtration is through a 1 cm-depth of Celite in a 5 cm-diameter Büchner funnel (fitted with a 42.5 mm-diameter Whatman No. 1 filter paper) attached to a 250-mL Büchner flask.

16. Flash silica gel 60 (220-440 mesh) purchased from E. Merck, Darmstadt, is placed in a 4 cm-diameter column (8 cm-depth of silica) and eluted with ~300-400 mL of solvent.

17. The submitters reported a yield of 99%. The properties are as follows: $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.85–2.00 (m, 2 H), 2.42 (br s, 1 H), 3.02 (br s, 3 H), 3.41–3.60 (m, 3 H), 3.83 (dd, 1 H, $J$ = 15.6, 6.6 Hz), 4.09 (d, 1 H, $J$ = 15.6 Hz), 4.01–4.32 (m, 2 H), 6.02 (d, 1 H, $J$ = 5.6 Hz), 6.40 (dd, 1 H, $J$ = 9.1, 1.5 Hz), 7.25 (dd, 1 H, $J$ = 9.1, 6.5 Hz); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) rotamers observed, δ for major rotamer: 25.7, 27.1, 34.3, 48.9, 50.1, 51.0, 52.7, 105.6, 117.3, 138.9, 148.8, 156.1, 163.4; IR (film): 1700, 1656, 1546 cm$^{-1}$; $[\alpha]_D^{20}$ –207.9 ($CHCl_3$, $c$ 0.47); $R_f$ = 0.51 (9:1, $CH_2Cl_2$:MeOH).

18. Platinum(IV) oxide (surface area ≥60 m$^2$/g, 81-83% Pt) was purchased from Heraeus and used as received.

19. The time required for the hydrogenation reaction to reach completion varies from 5-12 h (even when the same batch of platinum(IV) oxide was employed). The disappearance of starting methyl carbamate can be identified qualitatively by TLC: $R_f$ = 0.5 (9:1, $CH_2Cl_2$:MeOH) for methyl carbamate.

20. Filtration is through a 2-cm depth of Celite in a 5-cm diameter Büchner funnel (fitted with a 42.5 mm-diameter Whatman No. 1 filter paper) attached to a 250-mL Büchner flask.

21. The crude hydrogenation product is of sufficient purity for direct use in the next step. It can be purified by column chromatography over silica with $CH_2Cl_2$:MeOH:aqueous 25% w/v ammonium hydroxide (97:2:1) as eluent. The fractions containing the product ($R_f$ = 0.3; 97:2:1 $CH_2Cl_2$:MeOH:aqueous 25% w/v ammonium hydroxide) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying ($10^{-3}$ mbar) to afford pure hydrogenation

product as a white solid. The physical properties are as follows: $^1$H NMR ($CDCl_3$, 400 MHz) approx. 4:1 mixture of rotamers, δ: 1.52–1.67 (m, 2 H), 1.73–1.98 (m, 5 H), 2.06–2.21 (m, 1 H), 2.27–2.49 (m, 2 H), 2.77 (br d, 1 H, $J$ = 13.5 Hz), 2.84 (dd, 0.85 H, $J$ = 13.9, 2.0 Hz), 2.92 (br d, 0.15 H, $J$ = 13.9 Hz), 2.98 (br d, 0.15H, $J$ = 13.0 Hz), 3.04 (br dt, 0.85H, $J$ = 13.5, 2.1 Hz), 3.40–3.47 (m, 1 H), 3.57 (s, 2.5 H), 3.64 (s, 0.5 H), 4.17 (d, 0.85 H, $J$ = 13.5 Hz), 4.26 (br d, 0.15 H, $J$ = 13.0 Hz), 4.34 (br d, 0.15 H, $J$ = 13.5 Hz), 4.58 (d, 0.85 H, $J$ = 13.9 Hz), 4.71 (br, 0.15 H), 4.74 (d, 0.85 H, $J$ = 13.5 Hz); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ: 20.1, 27.7, 27.8. 32.7, 33.1, 33.3, 44.3, 45.8, 49.0, 52.6, 59.5, 156.1, 169.6; IR (film): 1695, 1635 cm$^{-1}$; $[\alpha]_D^{20}$ –169.9 ($CHCl_3$, *c* 1.05); mp 118–120 °C; $R_f$ = 0.2 (97:2:1, $CH_2Cl_2$:MeOH:aq. 25% w/v ammonium hydroxide).

22. Lithium aluminum hydride and hydrated sodium sulfate were purchased from Aldrich Chemical Company, Inc. and used as received. Tetrahydrofuran was purchased from Fisher Scientific and distilled from sodium/benzophenone ketyl under nitrogen. Diethyl ether was purchased from Fisher Scientific and used as received.

23. The reaction mixture should not be heated at reflux for more than 16 h as a lower yield of diamine is obtained.

24. Filtration is through a 2-cm depth of Celite in a 5-cm diameter Büchner funnel (fitted with a 42.5-mm diameter Whatman No. 1 filter paper) attached to a 1-L Büchner flask.

25. The submitters report a yield of 62% over two steps. A similar yield (61%) was obtained by the checkers when the reaction was performed on half-scale. The physical properties of the product are as follows: $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.18–1.31 (m, 2 H), 1.41–1.80 (m, 9 H), 1.85 (br d, 1 H, $J$ = 11.0 Hz), 1.92 (dd, 1 H, $J$ = 11.5, 3.1 Hz), 2.10 (s, 3 H), 2.08–2.13 (m, 1 H), 2.19 (ddd, 1 H, $J$ = 11.2, 3.5, 1.6 Hz), 2.79–2.87 (m, 2 H), 2.92–2.98 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ: 25.1, 25.7, 30.6, 30.8, 33.9, 35.2, 47.4, 56.3, 57.6, 60.4, 60.5, 66.4; IR (film): 2930 cm$^{-1}$; $[\alpha]_D^{20}$ + 29.7 (c = 1.10, EtOH).

26. The enantiomeric excess was determined by high resolution $^1$H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 3.0 equivalents of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol: A 0.12 M solution of the diamine in $CDCl_3$ is prepared by dissolving the diamine (46 mg, 0.24 mmol) in $CDCl_3$ (2.0 mL) and a 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ is prepared by dissolving (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (33 mg, 0.12 mmol) in $CDCl_3$ (2.0 mL). The sample for $^1$H

NMR spectroscopy analysis is then prepared by using 0.06 mL of the 0.12 M solution of the diamine in $CDCl_3$ (0.006 mmol), 0.36 mL of the 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ (0.018 mmol, 3.0 equiv.) and 0.18 mL of $CDCl_3$ (total volume of NMR sample ~ 0.6 mL). Key signals: $^1$H NMR ($CDCl_3$, 400 MHz) δ: 2.11 (s, 3 H), 2.53 (br s, 1 H), 2.66 (br s, 1 H), 2.87 (br d, 1 H, $J$ = 11.0 Hz), 2.95 (br d, 1 H, $J$ = 11.0 Hz). In a similar fashion, a sample for $^1$H NMR spectroscopy analysis is prepared using 0.05 mL of the 0.12 M solution of the diamine in $CDCl_3$ (0.006 mmol), 0.30 mL of a 0.06 M solution of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ (0.018 mmol, 3.0 equiv) and 0.15 mL of $CDCl_3$ (total volume of NMR sample ~ 0.5 mL). Key signals: $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.97 (s, 3 H), 2.65–2.85 (m, 2 H), 2.93 (br d, 1 H, $J$ = 11.0). The absence of any signals due to the other diastereomeric complex in each of these $^1$H NMR spectra indicates that the diamine is present in greater than 95% ee. (*R*)- and (*S*)-2,2,2-Trifluoro-1-(9-anthryl)ethanol were purchased from Aldrich Chemical Company, Inc. and used as received.

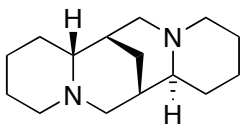
## Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

(–)-Sparteine is a widely used ligand in asymmetric synthesis[2] but suffers from the drawback that it is only commercially available in one enantiomeric form. Diamine (+)-**1** was designed as a (+)-sparteine surrogate because it possesses most of the three-dimensional architecture of (+)-sparteine. The procedure described here is a simple, three-step synthesis of diamine (+)-**1** from *Laburnum anagyroides cytisus* seeds.[3,4] The route has been successfully used by other research groups.[5-7] The extraction process is a modified version of a protocol reported by Rouden, Lasne and coworkers[8] and is a simple and high yielding alkaloid isolation. Subsequent *N*-protection (as a methyl carbamate), pyridone hydrogenation (completely diastereoselective in the sense depicted, as established by X-ray crystallography)[4] and lithium aluminum hydride reduction furnishes diamine (+)-**1** in good overall yield. Distillation (Kugelrohr) of the diamine

immediately before use is recommended (as is usual when using (–)-sparteine with organolithium reagents).[9] Two multi-step, asymmetric syntheses of (–)-**1**[10] and (+)-**1**[11] have also been described. Other analogues of which **2**-**4**[5,12] are representative, have been prepared by using the appropriate acid chloride in the first step of the synthesis and analogue **5** was prepared by using a modified route.[5,13] In terms of applications, we[12,13] and others[5,6] have found that diamine (+)-**1** is the most effective and versatile (+)-sparteine surrogate of those diamines prepared from (–)-cytisine.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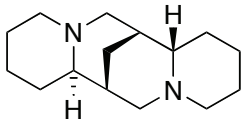
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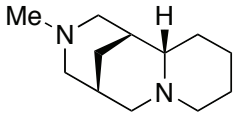
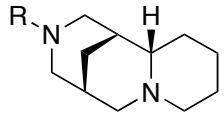

**1**


**2**, R = Et; **3**, R = $^{n}$Bu
**4**, R = $CH_2{}^{t}$Bu; **5**, R = $^{i}$Pr

A diverse range of examples that utilizes diamine (+)-**1** in asymmetric synthesis with organolithium reagents is presented in Table 1. All of the products show opposite enantioselectivity to those obtained with (–)-sparteine and a similarly high degree of enantioselection, thus demonstrating that (+)-**1** is an excellent (+)-sparteine surrogate. Lithiations and subsequent rearrangement (Entry 3) or electrophilic trapping (Entries 1-2 and 4-8), including three examples reported by other groups (Entries 6-8),[5,6] are particularly successful. Recently, (+)-**1** was used to control the *regioselectivity* of deprotonation of an enantiomerically enriched functionalized *N*-Boc pyrrolidine used in a route to (–)-kainic acid.[7] In a similar fashion, inter- and intramolecular carbolithiations work well (Entries 9-10).

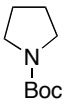
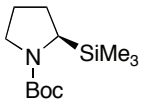
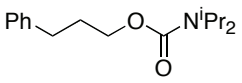
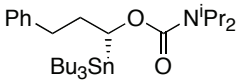
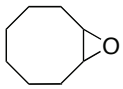
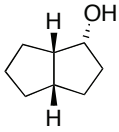
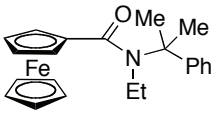
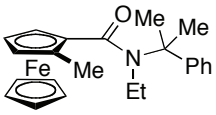
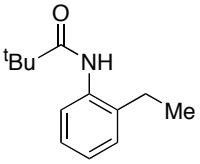
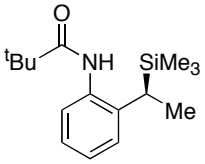
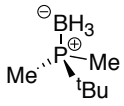
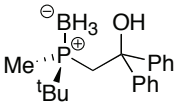
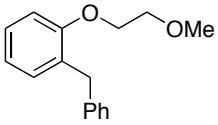
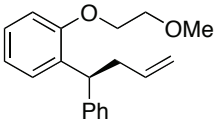
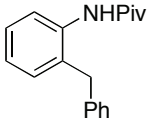
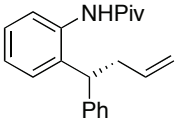
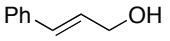
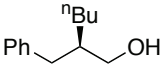
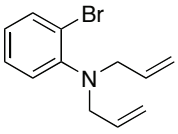
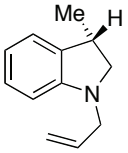
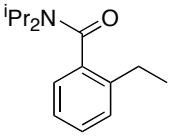
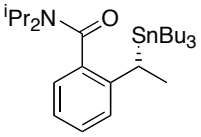
The use of diamine (+)-**1** is not limited to organolithium-mediated processes; reactions including magnesium (Entry 1), copper (Entry 2) and palladium (Entry 3) are also successful (Table 2). The results in Tables 1 and 2 cover a wide range of mechanistic pathways and processes (namely asymmetric deprotonation and substitution, carbometallation, anhydride ring opening, dynamic thermodynamic resolution and kinetic resolution).

Examples where diamine (+)-**1** actually outperforms (–)-sparteine include phosphine borane lithiation (Table 1, entry 6), benzylic organolithium functionalization (Table 1, entries 7-8) and copper(II)-mediated dynamic thermodynamic resolution of racemic BINOL (Table 2, Entry 2). In recent work, we have introduced a new ligand exchange

catalytic approach for asymmetric deprotonation using sub-stoichiometric amounts of (–)-sparteine and (+)-**1**. In all cases, (+)-**1** gives higher enantioselectivity than (–)-sparteine.[14]

In contrast, we are aware of three processes where diamine (+)-**1** is significantly inferior to (–)-sparteine. First, dynamic kinetic resolution of *N*,*N*-diisopropyl-*o*-ethylbenzamide gave an enantiomeric ratio of 68:32 with (+)-**1** (Table 1, entry 11) but an enantiomeric ratio of 94:6 with (–)-sparteine. Second, attempted kinetic resolution of racemic indanol using palladium(II) and molecular oxygen in the presence of (+)-**1** gave a selectivity factor (s) of 6.8 whereas s = 8.3 was obtained using (–)-sparteine (Table 2, entry 3).

**Table 1.** Asymmetric Synthesis Using (+)-Sparteine Surrogate **1** and Organolithium Reagents

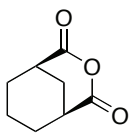
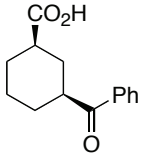
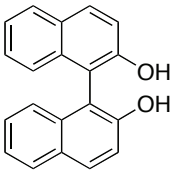
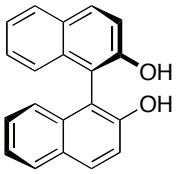
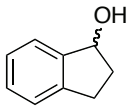
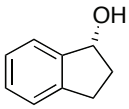
| Entry | Substrate | Product | Yield (%) | er | Ref |
|---|---|---|---|---|---|
| 1 |  |  | 84[a] | 95:5 | 3, 4, 16 |
| 2 |  |  | 84[b] | 96:4 | 3, 17 |
| 3 |  |  | 70[c] | 81:19 | 3, 12, 18 |
| 4 |  |  | 78[d] | 96:4 | 19, 20 |
| 5 |  |  | 58[e] | 93:7 | 12, 21 |
| 6 |  |  | 78[f] | 96:4 | 5, 22 |
| 7 |  |  | 90[g] | 96:4 | 6 |
| 8 |  |  | 89[h] | 90:10 | 6 |
| 9 |  |  | 71[i] | 87:13 | 12, 23 |
| 10 |  |  | 84[j] | 85:15 | 24, 25 |
| 11 |  |  | 41[k] | 68:32 | 21, 26 |

[a] (i) $^{s}$BuLi, (+)-**1**, –78 °C, $Et_2O$, 5 h; (ii) $Me_3SiCl$. [b] (i) $^{s}$BuLi, (+)-**1**, –78 °C, $Et_2O$, 5 h; (ii) $Bu_3SnCl$.
[c] $^{s}$BuLi, (+)-**1**, –78 °C, $Et_2O$, 5 h. [d] (i) $^{n}$BuLi, (+)-**1**, –78 °C, 6:1 $Et_2O$-toluene, 2 h; (ii) MeI.
[e] $^{s}$BuLi, $Et_2O$, –25 °C, 2 h; (ii) (+)-**1**, –25 °C, 45 min; (iii) –78 °C then $Me_3SiCl$.[f] (i) $^{s}$BuLi, (+)-**1**, –78 °C, 3 h; (ii) $Ph_2CO$; (iii) $HCl_{(aq)}$. [g] (i) $^{s}$BuLi, (+)-**1**, –78 °C, $Et_2O$; (ii) –20 °C, 1 h; (iii) –78 °C then 0.5 eq allyl tosylate; (iv) –20 °C, 1 h; (v) –78 °C then 0.5 eq allyl tosylate, warm to rt.
[h] $^{s}$BuLi, $Et_2O$, 0 °C, 3 h; (ii) (+)-**1**, –78 °C, 2 h; (iii) allyl bromide, warm to rt . [i] $^{n}$BuLi, (+)-**1**, 0 °C, cumene, 1 h. [j] (i) $^{t}$BuLi, –78 °C, $Et_2O$-pentane, 10 min; (ii) (+)-**1**, –40 °C, 1.5 h; (iii) MeOH.
[k] (i) $^{s}$BuLi, (+)-**1**, –78 °C, pentane, 90 min; (ii) $Bu_3SnCl$, –78 °C, 1 h.

Finally, the attempted dynamic thermodynamic resolution of lithiated *tert*-butylphenylphosphine borane using (+)-**1** generated a racemic adduct (95% ee with (–)-sparteine).[12] Crucial to the success of this protocol is the formation of a "voluminous precipitate" during the equilibration, and this was not observed with (+)-**1**.[15]

To summarize, the procedure presented here is a simple synthesis of diamine (+)-**1**. Evaluation of diamine (+)-**1** by us and others has demonstrated that it is a very good mimic of (+)-sparteine and can be employed in reactions where (–)-sparteine is a successful ligand. It thus allows access to a range of products of opposite absolute configuration to those obtained by using (–)-sparteine.

**Table 2.** Asymmetric Synthesis Using (+)-Sparteine Surrogate **1** and Magnesium, Copper and Palladium.

| Entry | Substrate | Product | Yield (%) | er | Ref |
|---|---|---|---|---|---|
| 1 |  |  | 78[a] | 89:11 | 12, 27 |
| 2 |  *racemic* |  | 86[b] | 99:1 | 12, 28 |
| 3 |  *racemic* |  | –[c,d] | – | 12, 29 |

[a] PhMgCl, (+)-**1**, –78 °C, toluene, 20 h. [b] (i) CuCl, air, MeOH, (+)-**1**, rt, sonicate, 30 min; (ii) Ar, rt, sonicate, 1 h; (iii) *rac*-BINOL, $CH_2Cl_2$-MeOH, rt, 8 h; (iv) –25 °C, 16 h; (v) –25 °C, conc. HCl. [c] (+)-**1**, $Pd(nbd)Cl_2$, $O_2$, 3Å MS, 60 °C, toluene, 54 h. [d] Selectivity factor for kinetic resolution, s =6.8.


**1.** Department of Chemistry, University of York, Heslington, York YO10 5DD UK.

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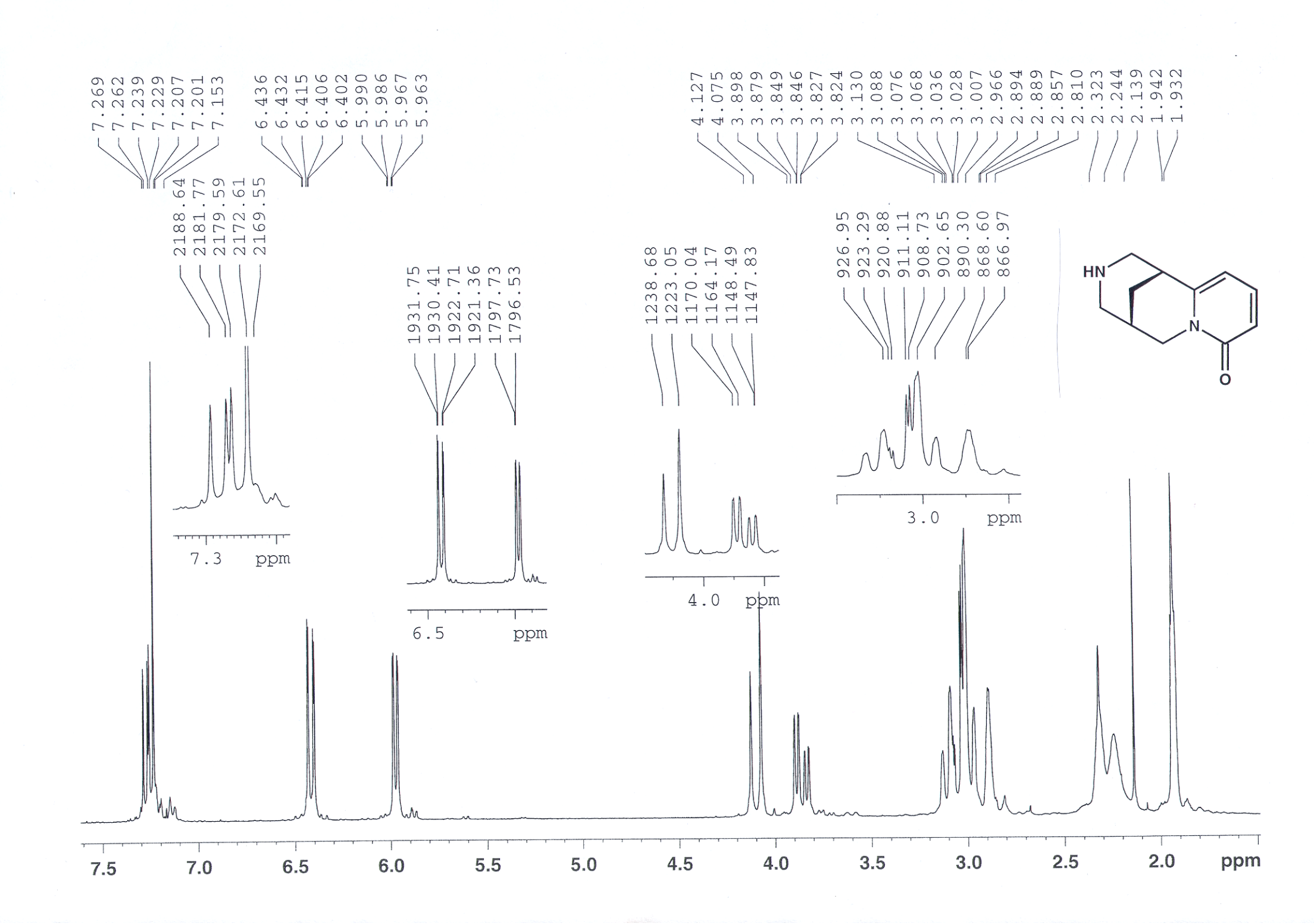
## Appendix
## Chemical Abstracts Nomenclature; (Registry Number)

(–)-Cytisine: 1,5-Methano-8*H*-pyrido[1,2-a][1,5]diazocin-8-one, 1,2,3,4,5,6-hexahydro-, (1*R*,5*S*)-; (485-35-8)

(–)-Methyl (1*R*,9*R*)-6-Oxo-7,11-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4-diene-11-carboxylate: 1,5-Methano-2*H*-pyrido[1,2-a][1,5]diazocine-3(4*H*)-carboxylic acid, 1,5,6,8-tetrahydro-8-oxo-, methyl ester, (1*R*,5*R*)-; (125109-97-9)

(+)-(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane: 1,5-Methano-2*H*-pyrido[1,2-a][1,5]diazocine, decahydro-3-methyl-, (1*R*,5*S*,11a*S*)-; (475301-86-1)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5.967
5.963
4.127
4.075
3.898
3.879
3.849
3.846
3.827
3.824
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2.894
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2.857
2.810
2.323
2.244
2.139
1.942
1.932
2188.64
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2179.59
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1921.36
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911.11
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902.65
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O
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6.5 ppm
4.0 ppm
3.0 ppm
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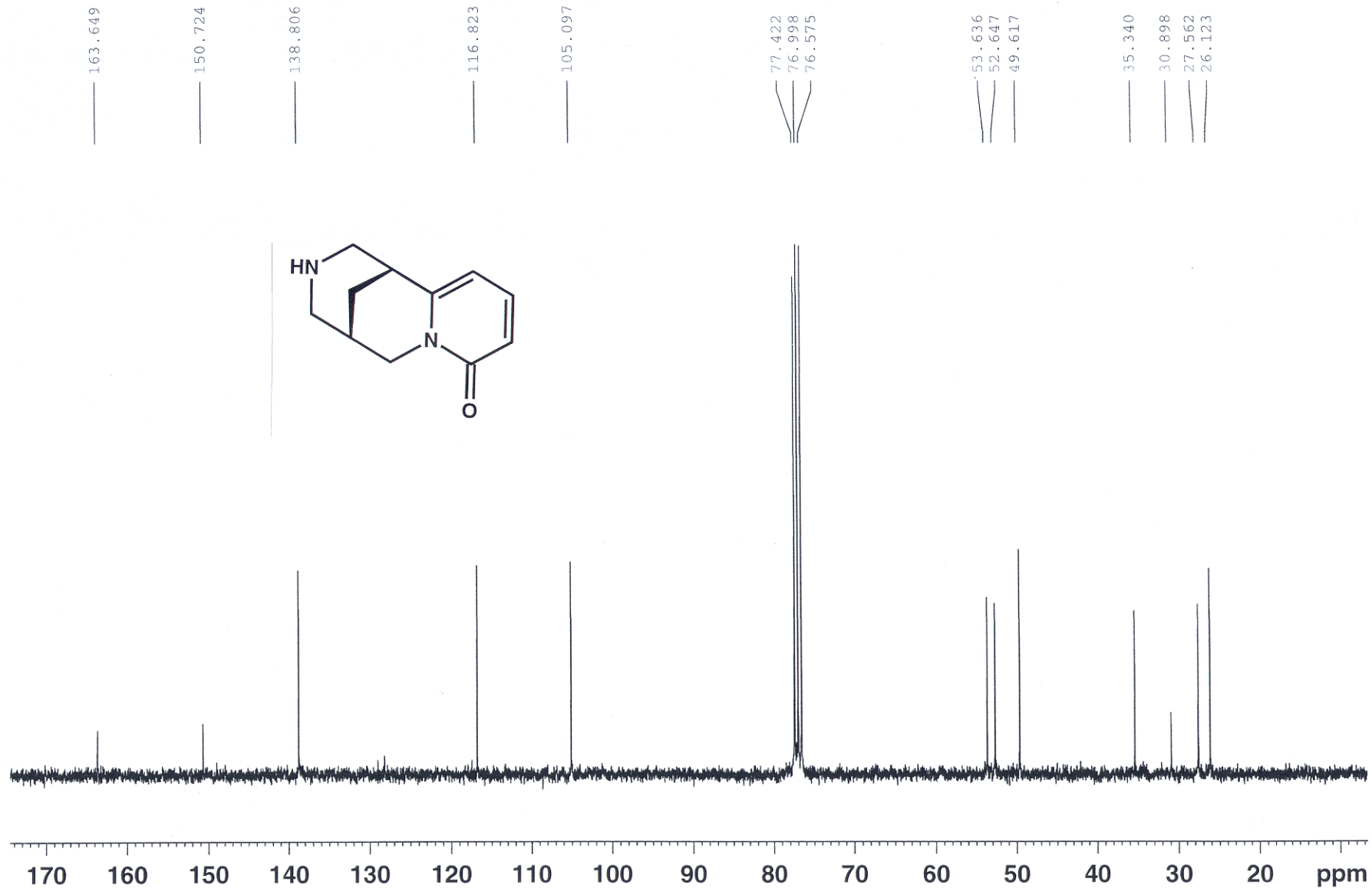
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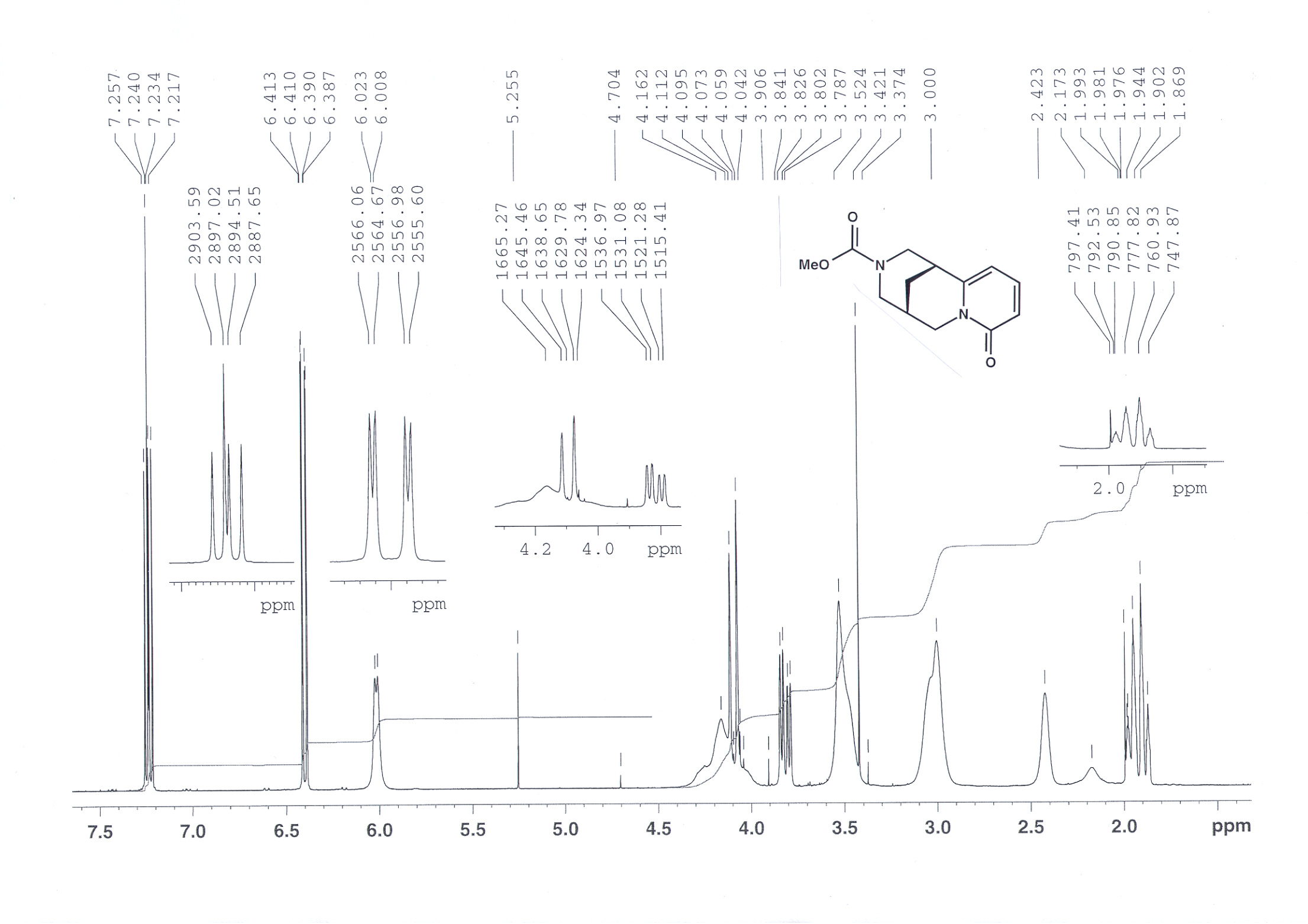
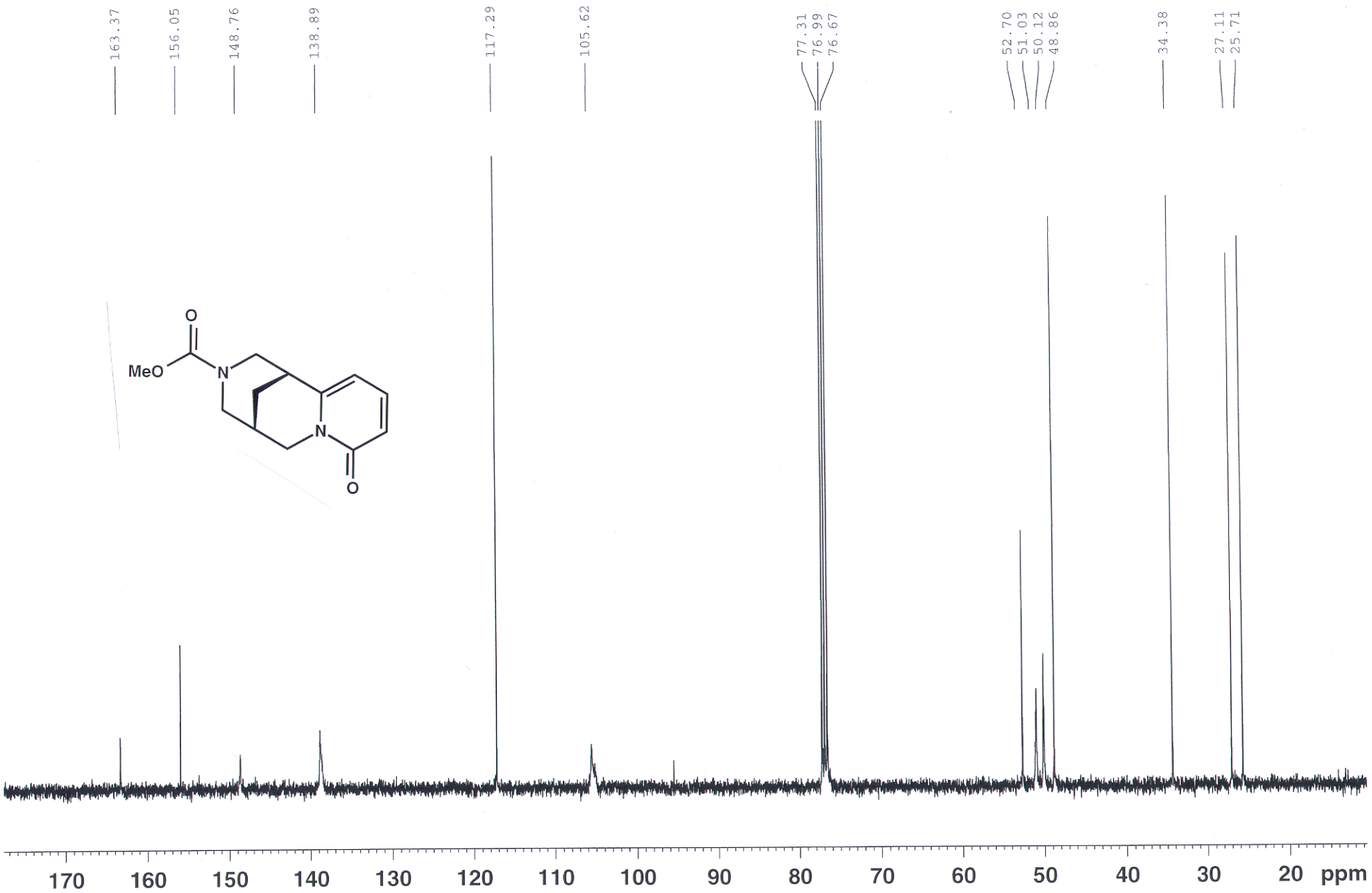
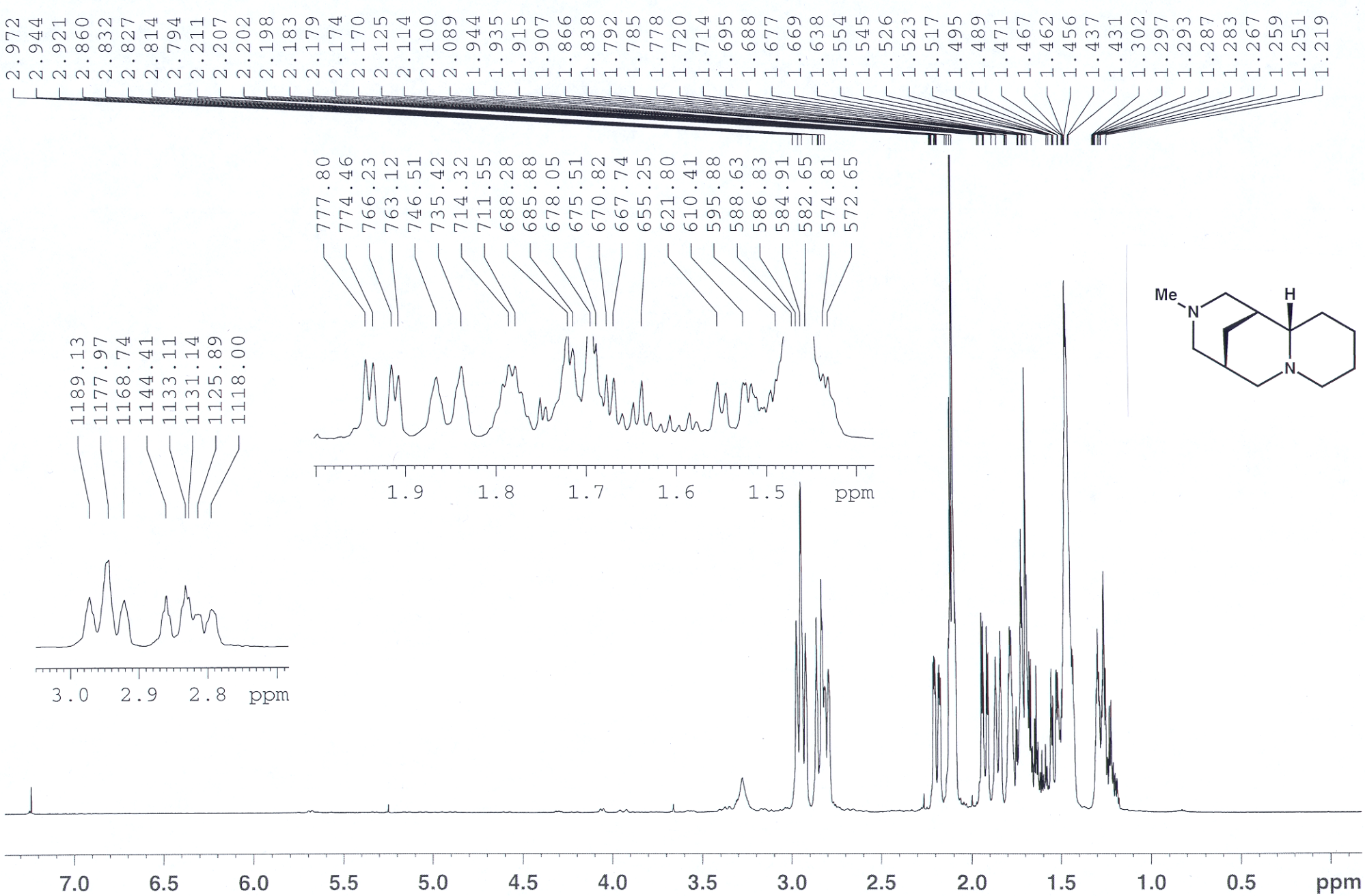
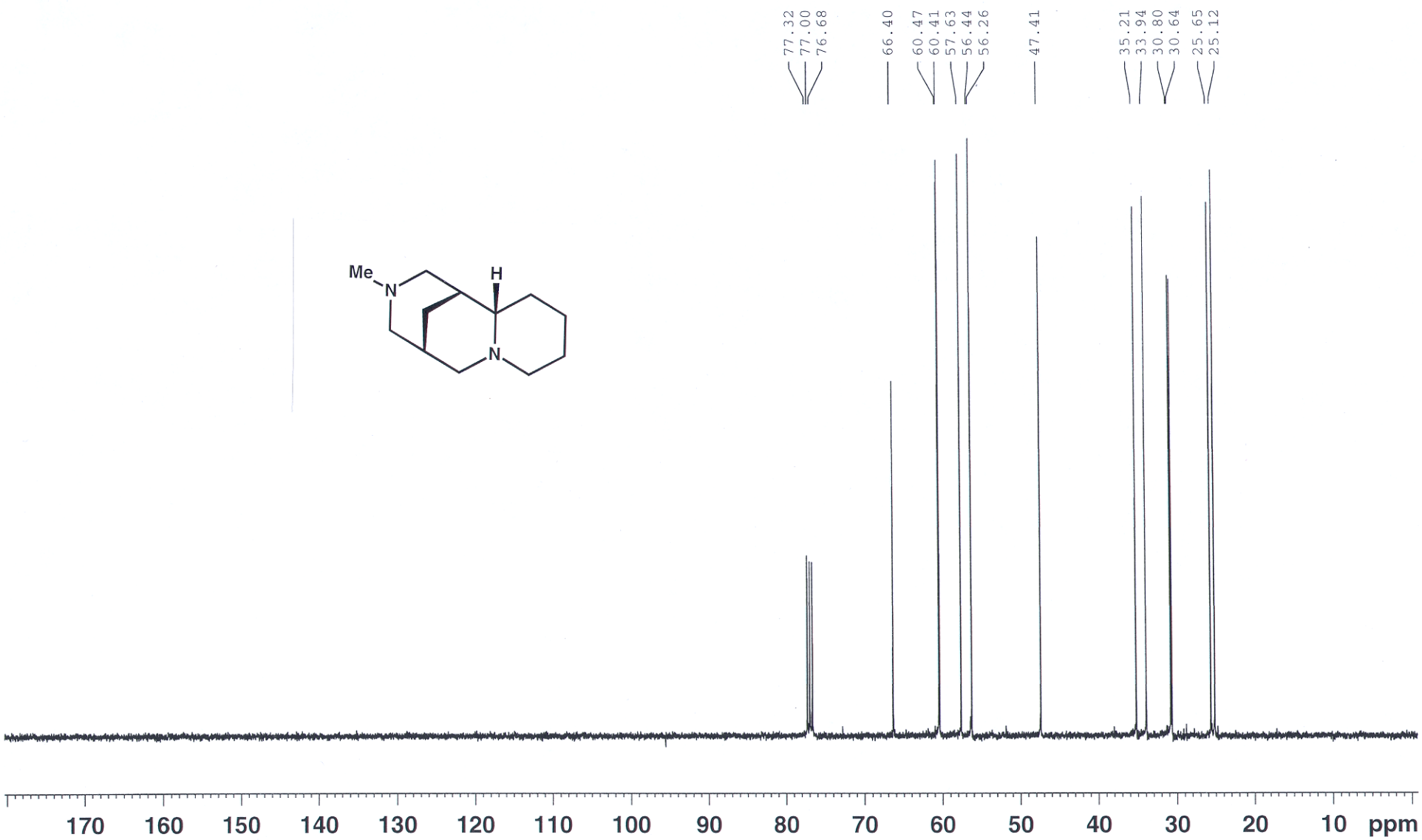
20
ppm


7.257
7.240
7.234
7.217
6.413
6.410
6.390
6.387
6.023
6.008
5.255
4.704
4.162
4.112
4.095
4.073
4.059
4.042
3.906
3.841
3.826
3.802
3.787
3.524
3.421
3.374
3.000
2.423
2.173
1.993
1.981
1.976
1.944
1.902
1.869
2903.59
2897.02
2894.51
2887.65
2566.06
2564.67
2556.98
2555.60
1665.27
1645.46
1638.65
1629.78
1624.34
1536.97
1531.08
1521.28
1515.41
797.41
792.53
790.85
777.82
760.93
747.87
MeO
N
N
O
O
ppm
ppm
4.2
4.0
ppm
2.0
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm


163.37
156.05
148.76
138.89
117.29
105.62
77.31
76.99
76.67
52.70
51.03
50.12
48.86
34.38
27.11
25.71
MeO
O
N
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


2.972 2.944 2.921 2.860 2.832 2.827 2.814 2.794 2.211 2.207 2.202 2.198 2.183 2.179 2.174 2.170 2.125 2.114 2.100 2.089 1.944 1.935 1.915 1.907 1.866 1.838 1.792 1.785 1.778 1.720 1.714 1.695 1.688 1.677 1.669 1.638 1.554 1.545 1.526 1.523 1.517 1.495 1.489 1.471 1.467 1.462 1.456 1.437 1.431 1.302 1.297 1.293 1.287 1.283 1.267 1.259 1.251 1.219
777.80 774.46 766.23 763.12 746.51 735.42 714.32 711.55 688.28 685.88 678.05 675.51 670.82 667.74 655.25 621.80 610.41 595.88 588.63 586.83 584.91 582.65 574.81 572.65
1.9 1.8 1.7 1.6 1.5 ppm
1189.13 1177.97 1168.74 1144.41 1133.11 1131.14 1125.89 1118.00
3.0 2.9 2.8 ppm
Me
N
H
N
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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77.00
76.68
66.40
60.47
60.41
57.63
56.44
56.26
47.41
35.21
33.94
30.80
30.64
25.65
25.12
Me
N
H
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm