08/02/03

Lithium Diisopropylamide (LDA)-Mediated Lithiation of Imines: Insights into Highly Structure-Dependent Rates and Selectivities

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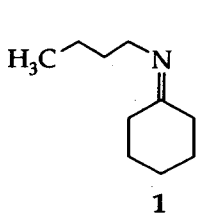
Supporting Information

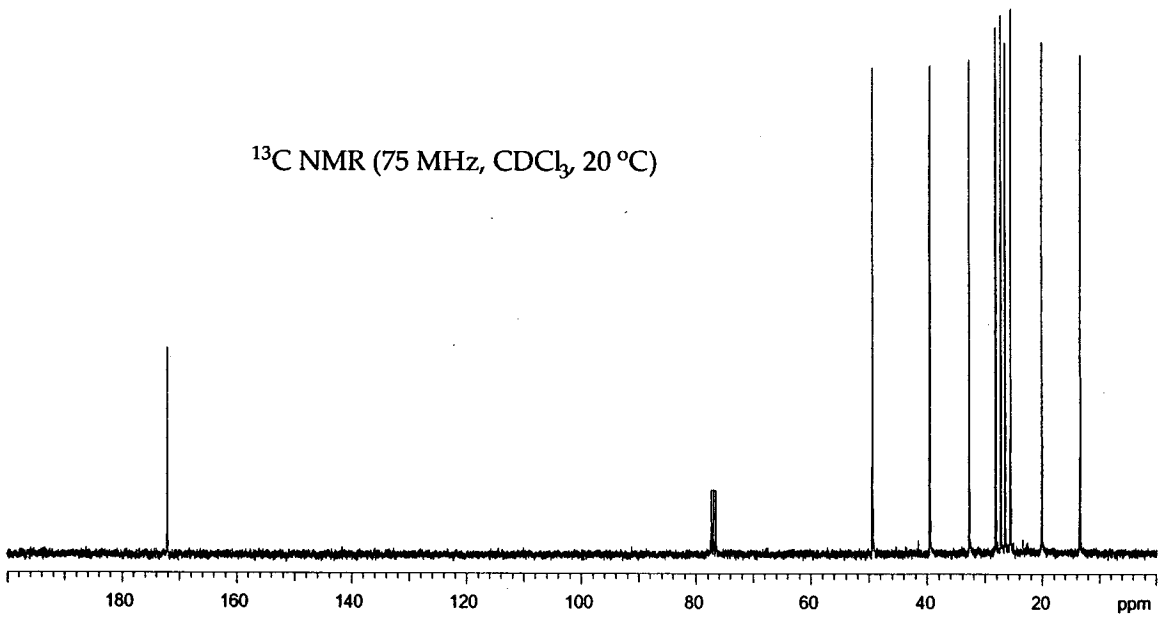
I. ^{1}H and ^{13}C NMR spectra of imine **1** in $CDCl_3$.



1

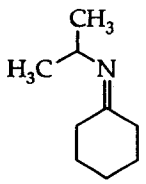
^{1}H NMR (300 MHz, $CDCl_3$, 20 °C)

^{13}C NMR (75 MHz, $CDCl_3$, 20 °C)



^{1}H NMR: δ 0.75 (t, J = 7.2 Hz, 3H), 1.18 (sext, J = 10.0 Hz, 2H), 1.33-1.61 (m, 8H), 2.10 (m, 4H), 3.11 (t, J = 10.0 Hz, 2H). ^{13}C NMR: δ 13.6, 20.3, 25.7, 26.6, 27.4, 28.3, 32.9, 39.6, 49.5, 172.0.

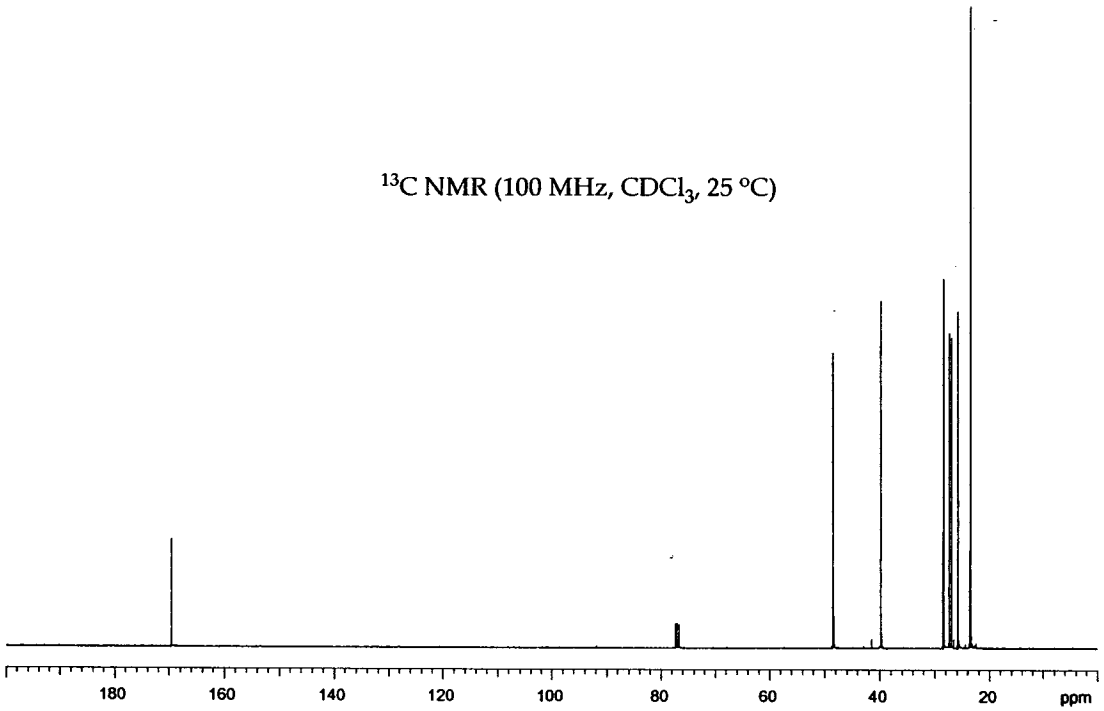
II. ^{1}H and ^{13}C NMR spectra of imine **2** in $CDCl_3$.



2

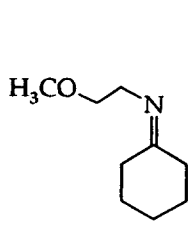
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C)

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C)



^{1}H NMR: δ 0.86 (d, J = 6.4 Hz, 6H), 1.34 (m, 4H), 1.47 (m, 2H), 2.00 (t, J = 6.6 Hz, 2H), 2.05 (t, J = 6.0 Hz, 2H), 3.45 (sept, J = 6.4 Hz, 1H). ^{13}C NMR: δ 23.4, 25.7, 26.9, 27.3, 28.3, 39.7, 48.4, 169.6.

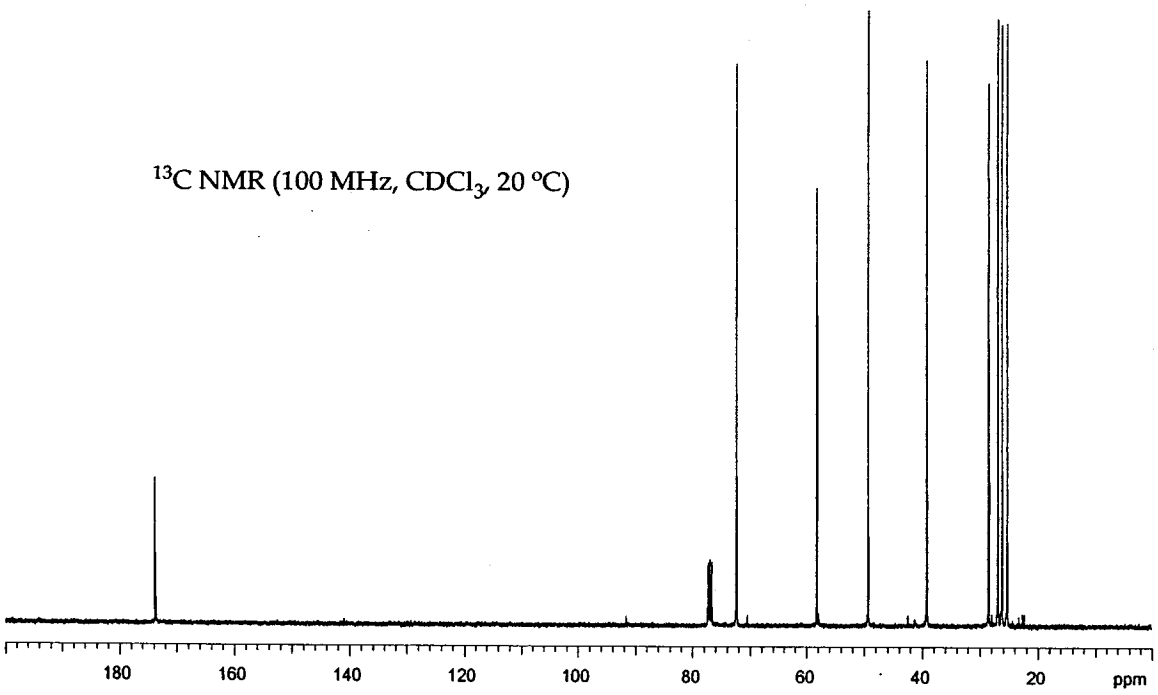
III. ^{1}H and ^{13}C NMR spectra of imine **3** in $CDCl_3$.



3

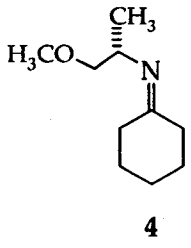
^{1}H NMR (400 MHz, $CDCl_3$, 20 °C)

^{13}C NMR (100 MHz, $CDCl_3$, 20 °C)

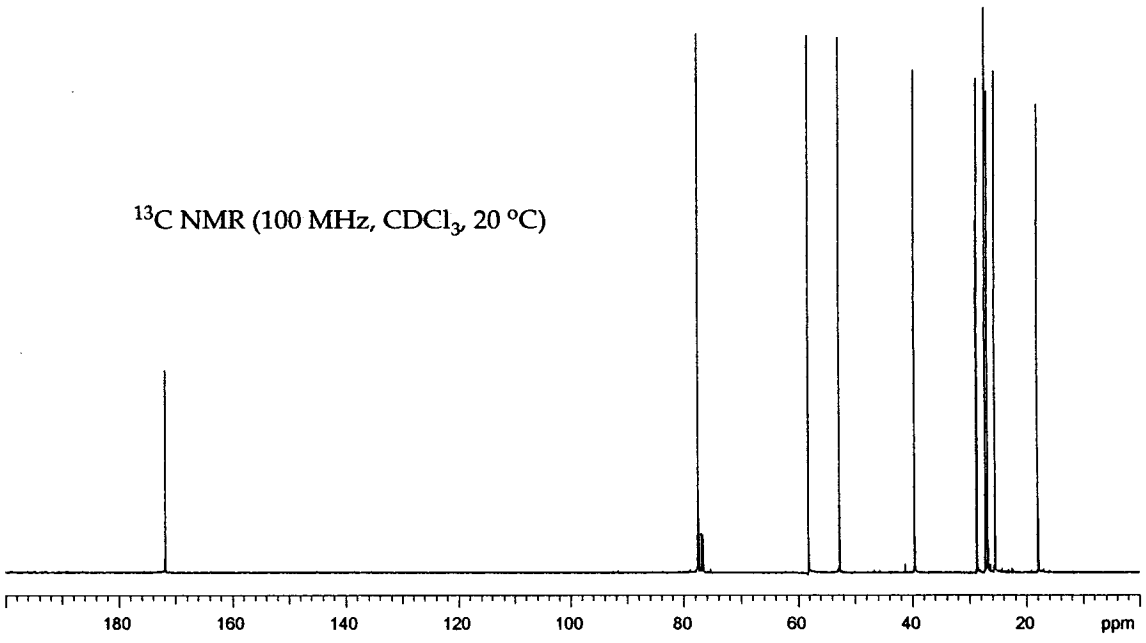


^{1}H NMR: δ 1.50 (m, 4H), 1.59 (m, 2H), 2.16 (t, J = 6.2 Hz, 4H), 3.25 (s, 3H), 3.32 (t, J = 6.0 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H). ^{13}C NMR: δ 25.3, 26.2, 27.0, 28.5, 39.2, 49.4, 58.3, 72.4, 173.8.

IV. ^{1}H and ^{13}C NMR spectra of imine **4** in $CDCl_3$.

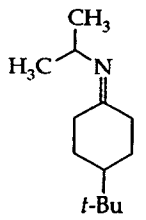


4

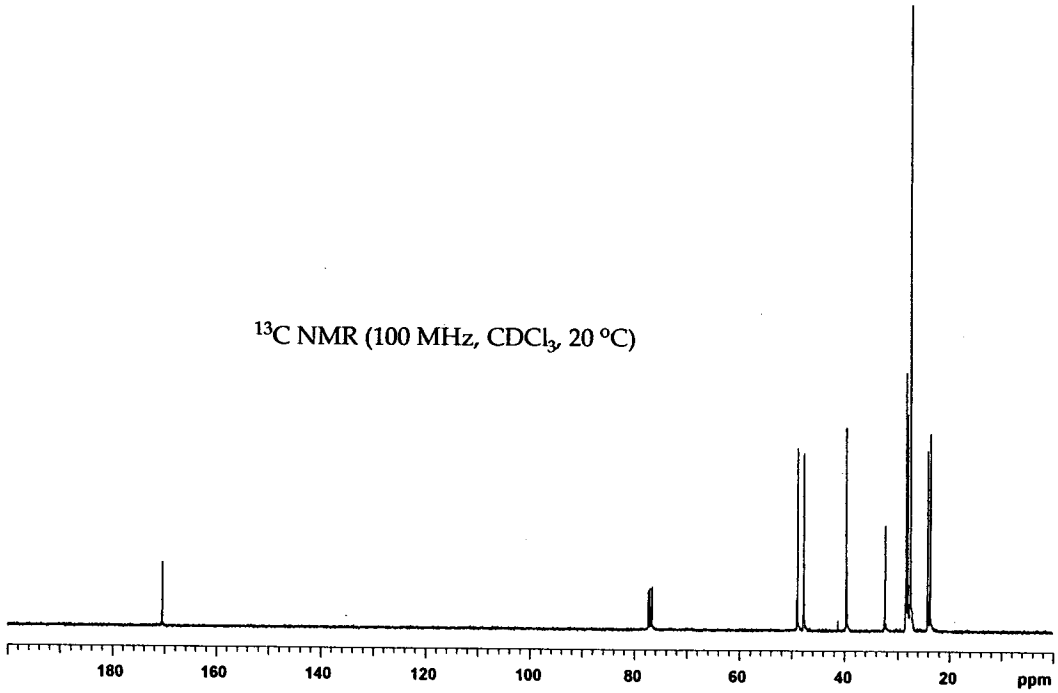


^{1}H NMR: δ 0.76 (d, J = 6.4 Hz, 3H), 1.30-1.50 (m, 6H), 1.99 (t, J = 6.4 Hz, 2H), 2.02 (t, J = 6.4 Hz, 2H), 3.04 (s, 3H), 3.06 (t, J = 6.4 Hz, 2H), 3.48 (sext, J = 6.4 Hz, 1H). ^{13}C NMR: δ 17.9, 25.5, 26.8, 27.2, 28.7, 39.6, 52.7, 58.2, 77.6, 171.8.

V. ^{1}H and ^{13}C NMR spectra of imine **5** in $CDCl_3$.

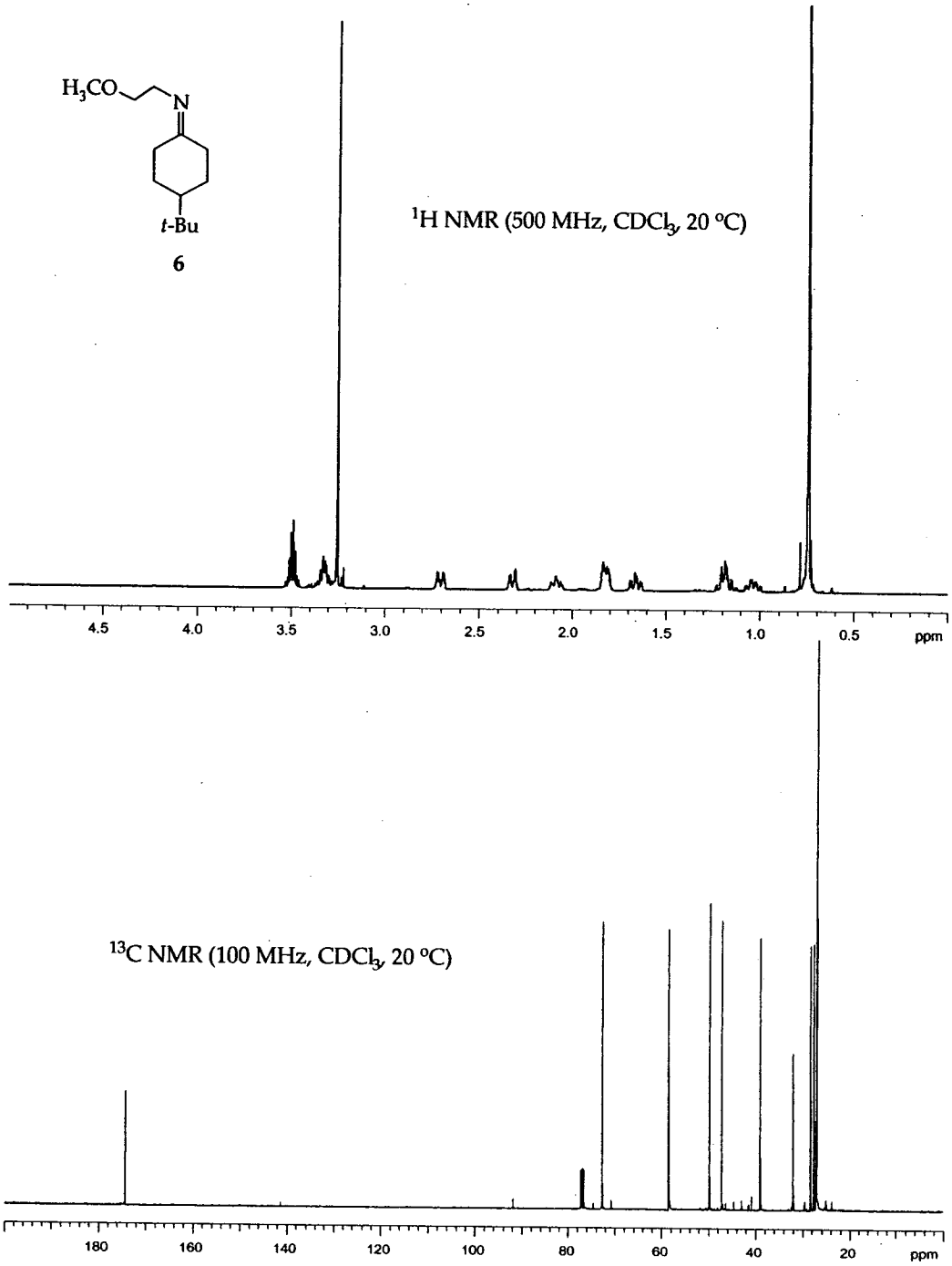


5



^{1}H NMR: δ 0.88 (s, 9H), 1.09 (d, J = 6.5 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.14 (m, 1H), 1.29-1.38 (m, 2H), 1.77 (td, J = 14.0, 5.0 Hz, 1H), 1.96-2.01 (m, 2H), 2.18 (td, J = 14.0, 5.0 Hz, 1H), 2.37 (dq, J = 13.5, 3.0 Hz, 1H), 2.86 (dq, J = 13.5, 3.0 Hz, 1H), 3.69 (sept, J = 6.5 Hz, 1H). ^{13}C NMR: δ 23.7, 24.1, 27.5, 27.9, 28.2, 28.3, 32.3, 39.6, 47.7, 48.9, 170.5.

VI. ^{1}H and ^{13}C NMR spectra of imine **6** in $CDCl_3$.[a]

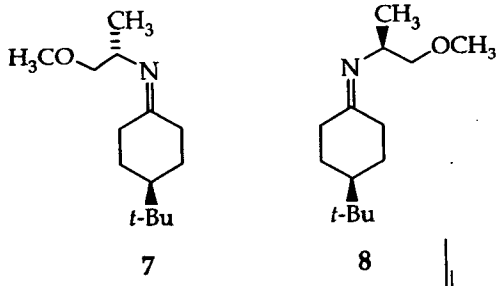


^{1}H NMR: δ 0.74 (s, 9H), 1.03 (m, 1H), 1.11-1.24 (m, 2H), 1.66 (td, J = 14.5, 4.9 Hz, 1H), 1.78-1.86 (m, 2H), 2.09 (tm, J = 13.2 Hz, 1H), 2.32 (dq, J = 14.0, 3.0 Hz, 1H), 2.70 (dq, J = 14.0, 3.0 Hz, 1H), 3.25 (s, 3H), 3.27-3.38 (m, 2H), 3.50 (m, 2H). ^{13}C NMR: δ 27.0, 27.2, 27.7, 28.3, 32.1, 39.0, 47.2, 49.8, 58.6, 72.7, 174.3.

[a]The sample contains $\approx$ 5% enamine isomer as evidenced by ^{13}C peaks at 92.0 and 140.8 ppm (Barillier, D.; Strobel, M. P.; Morin, L.; Paquer, D. *Tetrahedron* **1983**, *39*, 767).

VII. Conformational assignments of a 1:1 mixture of imines **7** and **8** in THF-d_8.

VII-A. ^{1}H and ^{13}C NMR spectra of a 1:1 mixture of imines **7** and **8** in THF-d_8.[a]

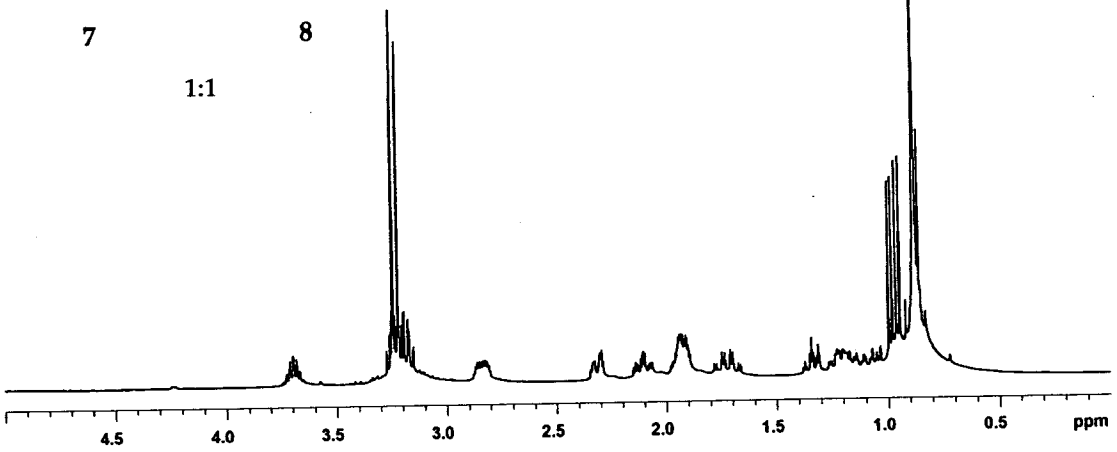


7

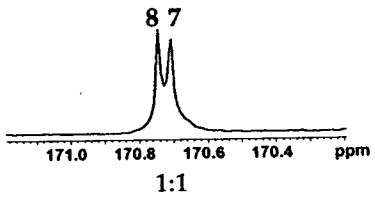
8

1:1

^{1}H NMR (400 MHz, THF-d_8, 25 °C)



^{13}C NMR (100 MHz, THF-d_8, 25 °C)

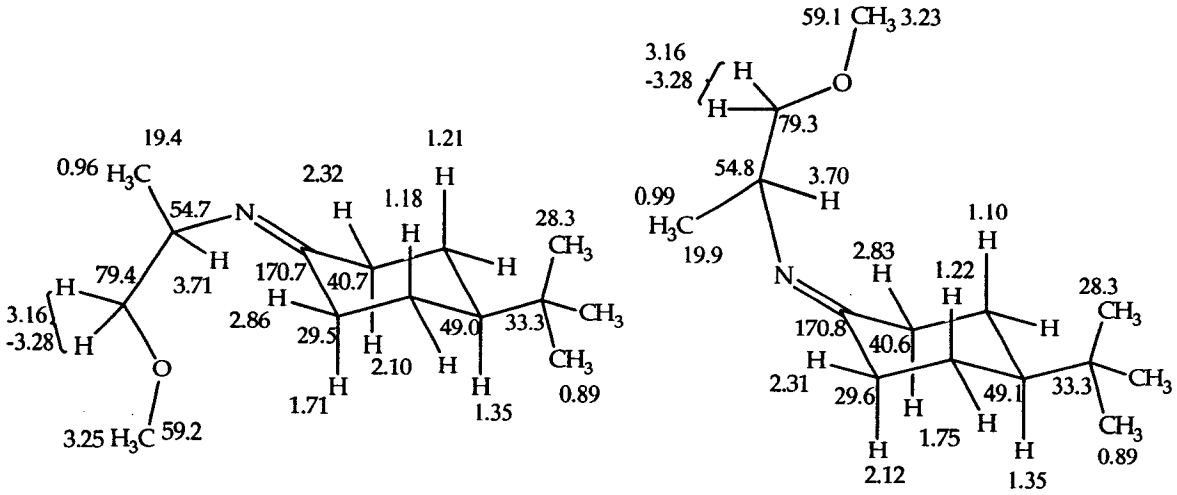


1:1

[a]The sample contains ≈ 5% enamine isomer as evidenced by ^{13}C peaks at 91.1 and 141.1 ppm. (See reference in section **VI.**)

VII-B. ^{1}H NMR (**7**): δ 0.89 (s, 9H, **7** and **8**), 0.96 (d, J = 6.5 Hz, 3H), 1.18 (qt, J = 13.5, 3.3 Hz, 1H), 1.21 (qt, J = 13.5, 3.3 Hz, 1H), 1.35 (tt, J = 12.5, 7.3 Hz, 1H, **7** and **8**), 1.71 (td, J = 14.0, 4.9 Hz, 1H), 1.90 - 2.00 (dm, J = 14.0 Hz, 2H, **7** and **8**), 2.10 (td, J = 14.0, 4.5 Hz, 1H), 2.32 (dq, J = 13.0, 3.3 Hz, 1H, **7** and **8**), 2.86 (dq, J = 13.5, 3.1 Hz, 1H), 3.16-3.28 (m, 2H, **7** and **8**), 3.25 (s, 3H), 3.71 (sext, J = 6.4 Hz, 1H); (**8**): δ 0.99 (d, J = 6.5 Hz, 3H), 1.10 (qt, J = 13.5, 3.3 Hz, 1H), 1.22 (qt, J = 13.5, 3.3 Hz, 1H), 1.75 (td, J = 14.0, 4.9 Hz, 1H), 2.12 (td, J = 14.0, 4.5 Hz, 1H), 2.83 (dq, J = 13.5, 3.1 Hz, 1H), 3.23 (s, 3H), 3.71 (sext, J = 6.4 Hz, 1H). ^{13}C NMR (**7**): δ 19.4, 28.3, 29.0, 29.2, 29.5, 33.3, 40.7, 49.0, 54.7, 59.2, 79.4, 170.7; (**8**): δ 19.9, 28.3, 29.2, 29.3, 29.6, 33.3, 40.6, 49.1, 54.8, 59.1, 79.3, 170.8.

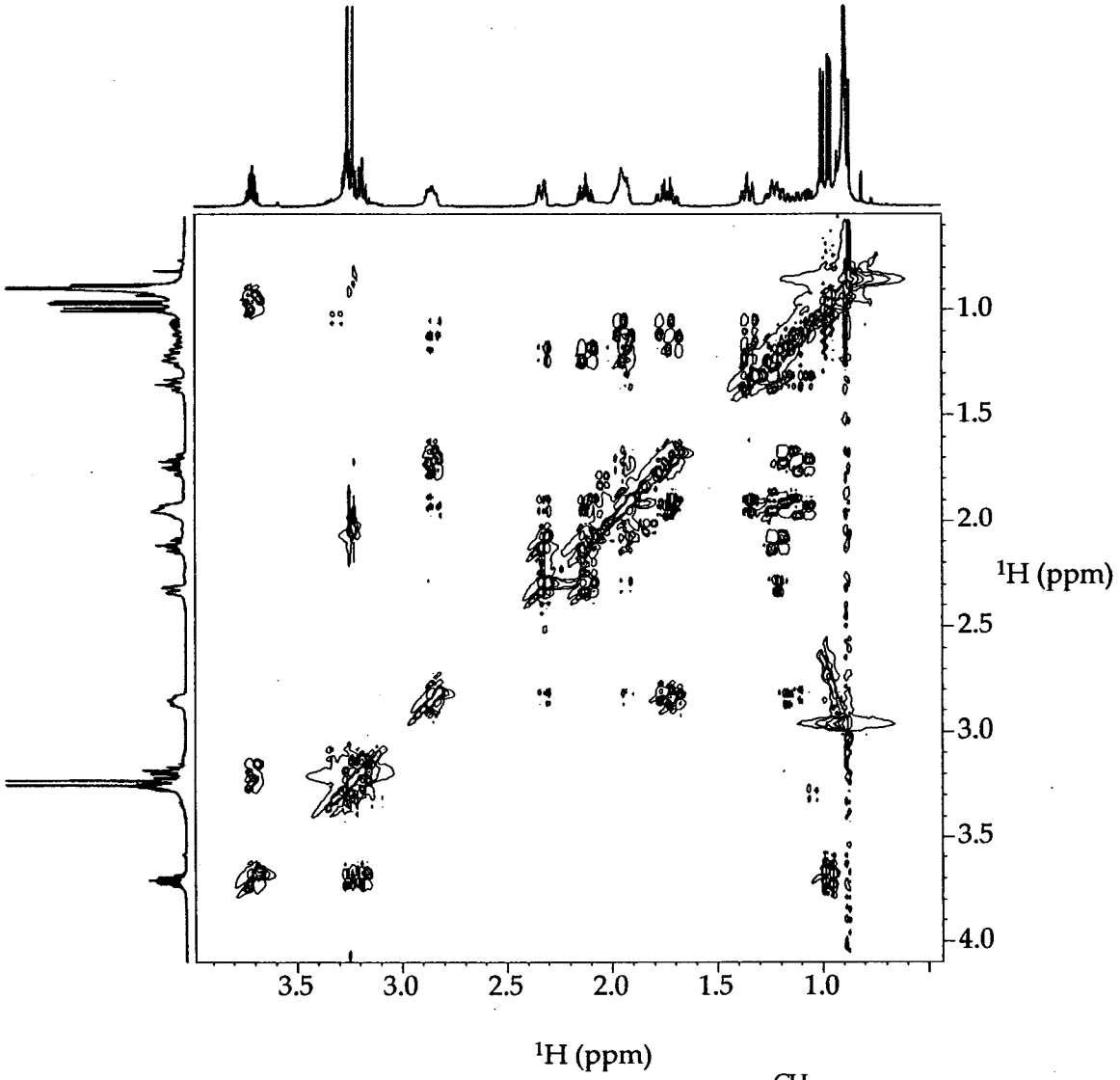
The structures of **7** and **8** are shown below. See 2D NMR spectra (section **VII**: **C-G**) for detailed assignments.[a]

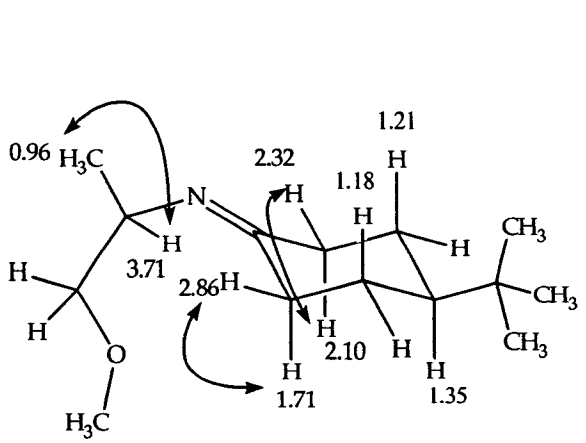


7 **8**

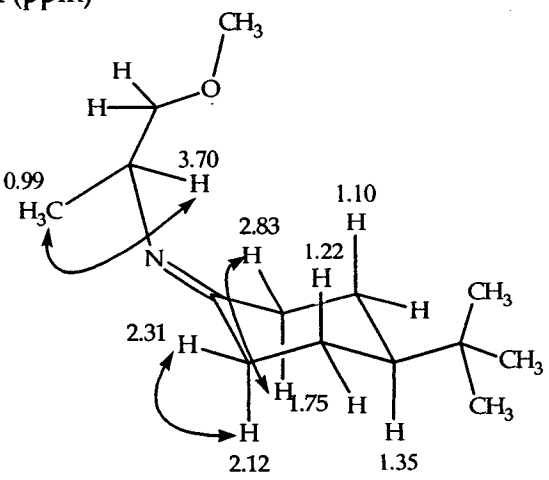
[a]The assignments were not directly available from NMR data, but related to the fact that one of the isomers reacts faster in the LDA mediated lithiation (both rate data and NMR data; Figure 1 of text and **XXI**). The fast reacting isomer was assigned as the one that accommodates axial deprotonation, which is **7**.

VII-C. ^{1}H,^{1}H-COSY spectrum of a 1:1 mixture of imines **7** and **8** (500 MHz, THF-d_8, 25 °C).





7



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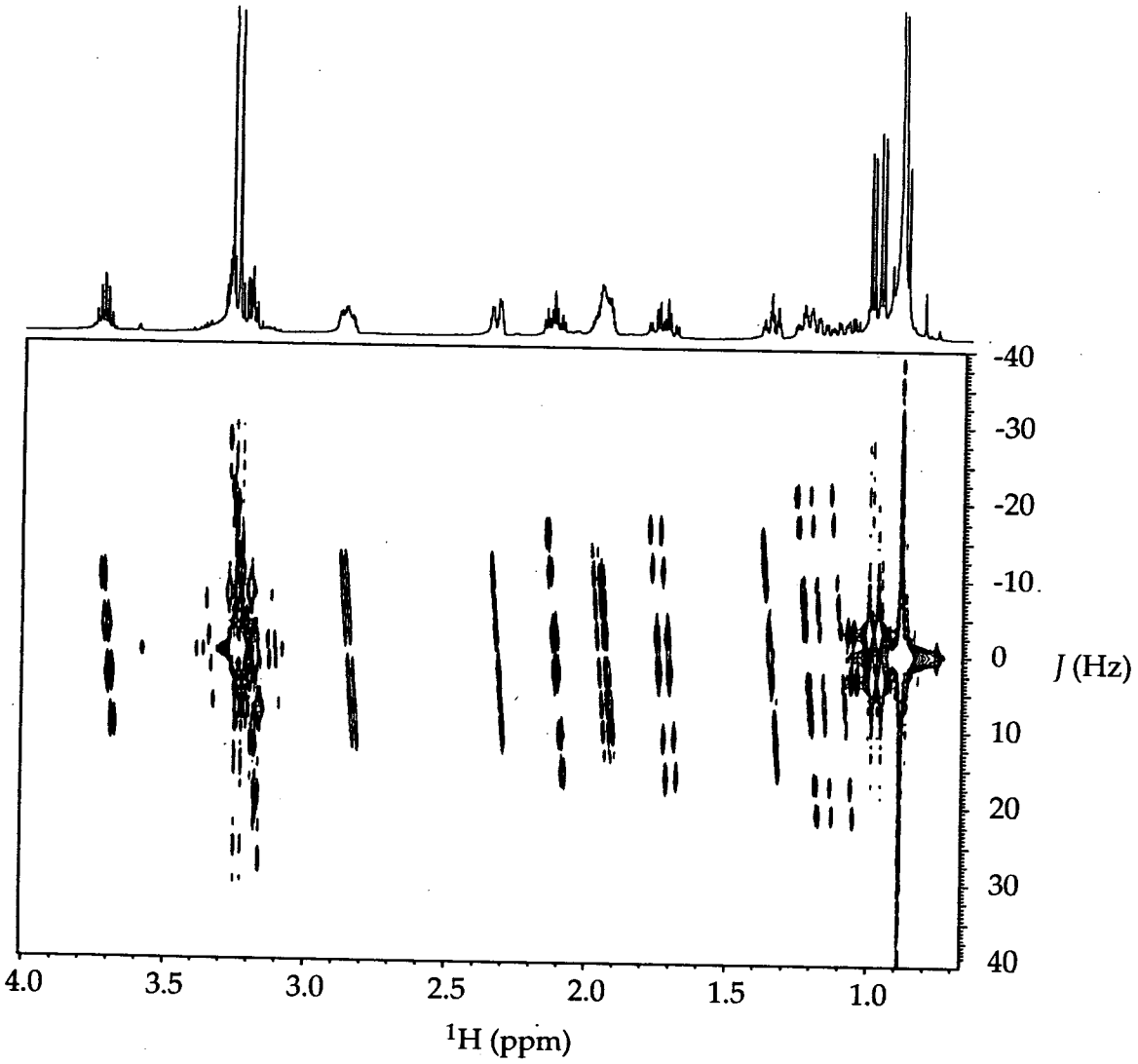
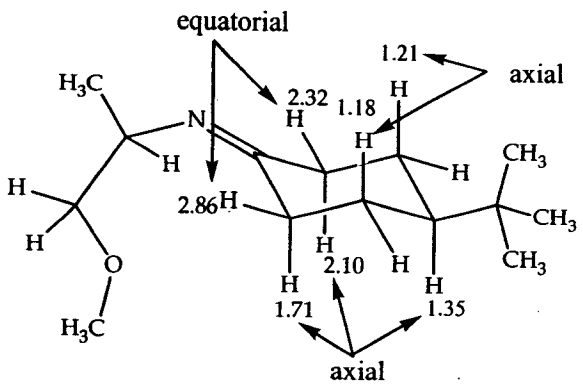
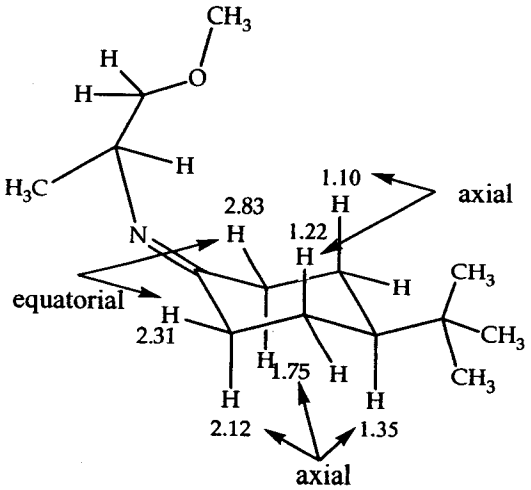
VII-D. $J(^1H,^1H)$-resolved spectrum of a 1:1 mixture of imines **7** and **8** (500 MHz, THF-d_8, 25 °C).





7



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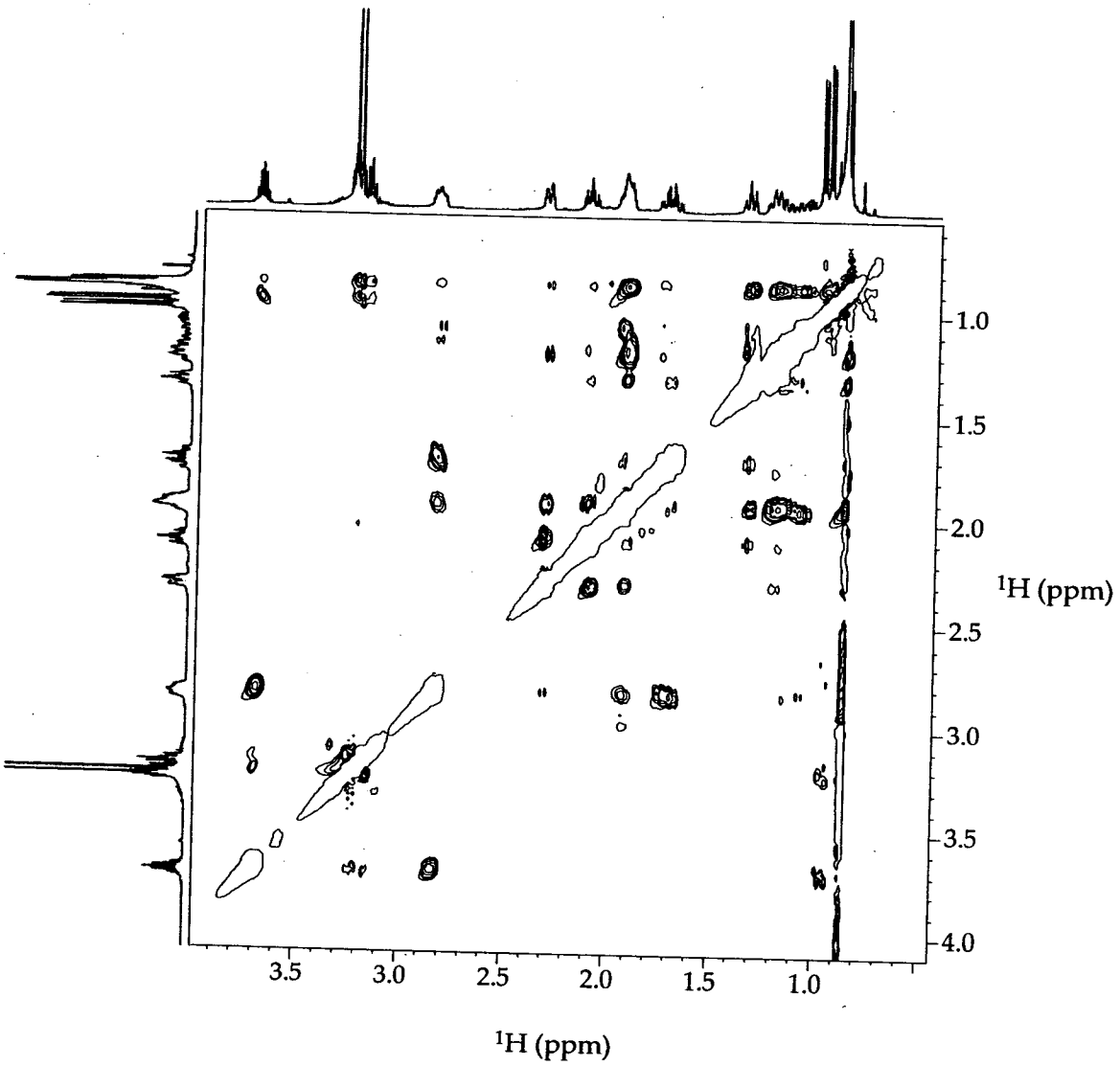
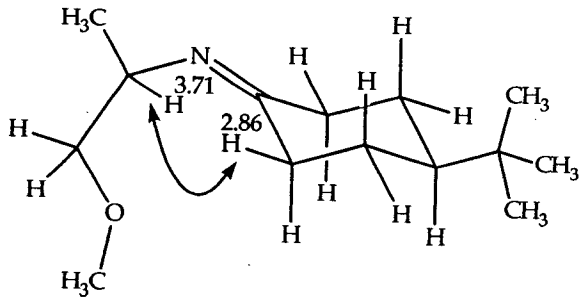
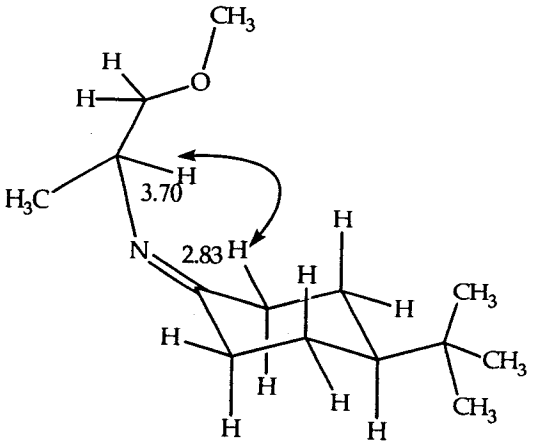
VII-E. ^{1}H,^{1}H-NOESY spectrum of a 1:1 mixture of imines **7** and **8**. (500 MHz, THF-d_8, 25 °C).



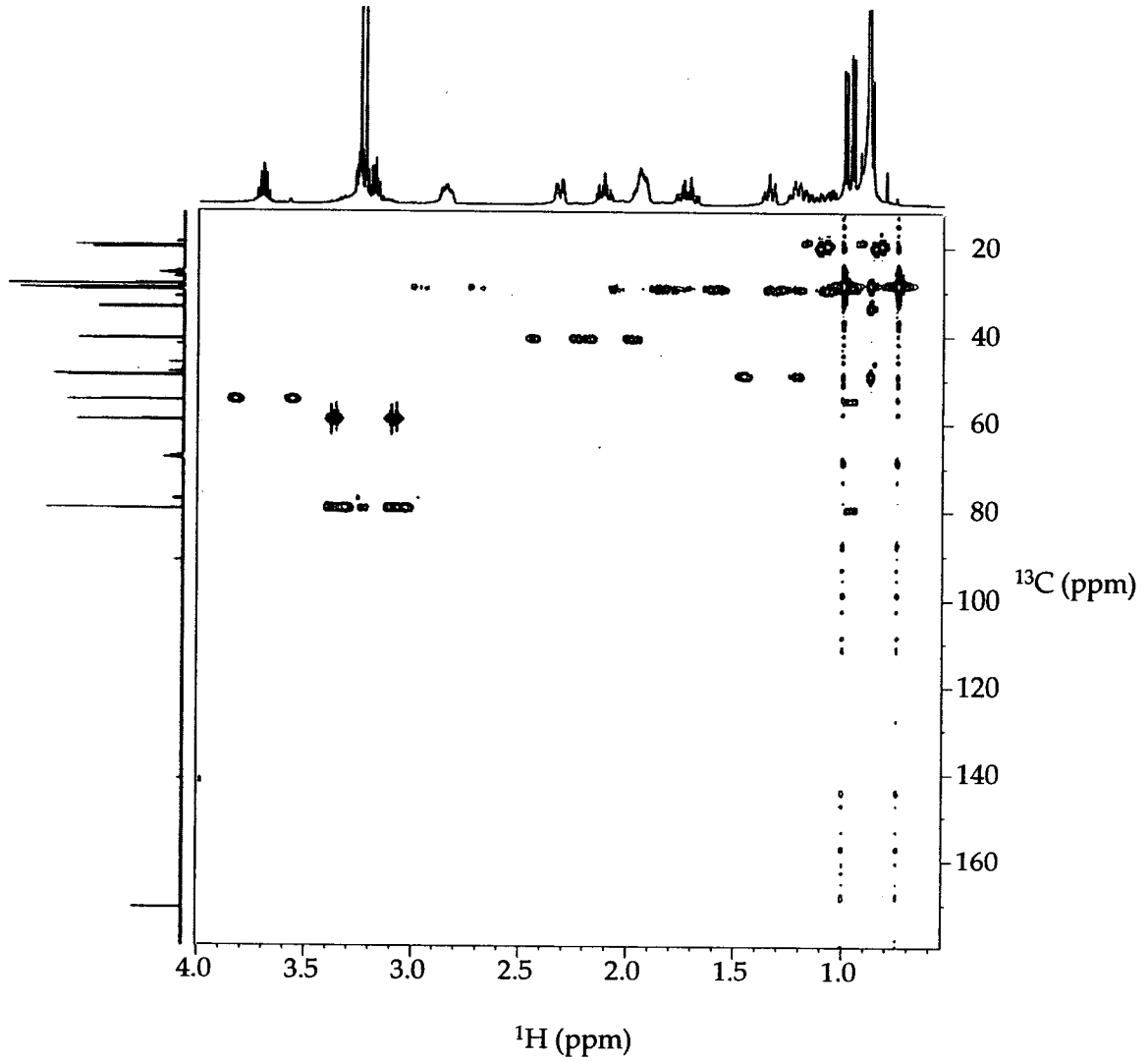


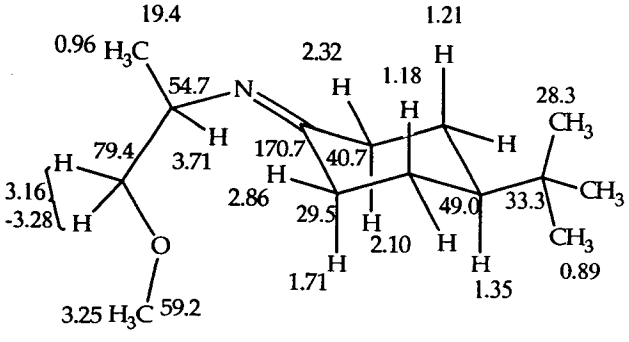
7



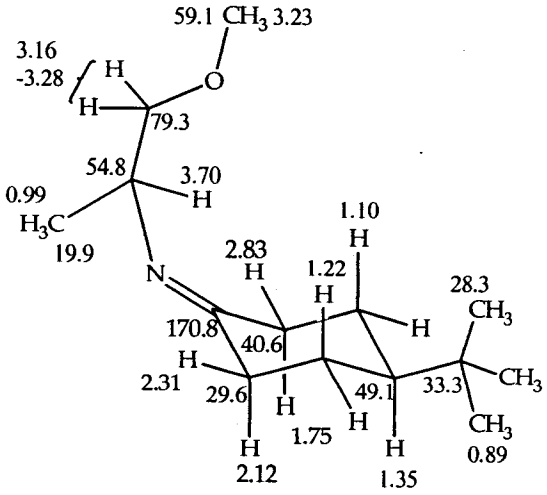
8

VII-F. $^{1}H,^{13}C$-HMQC spectrum of a 1:1 mixture of imines **7** and **8** (500 MHz, THF-d_8, 25 °C).



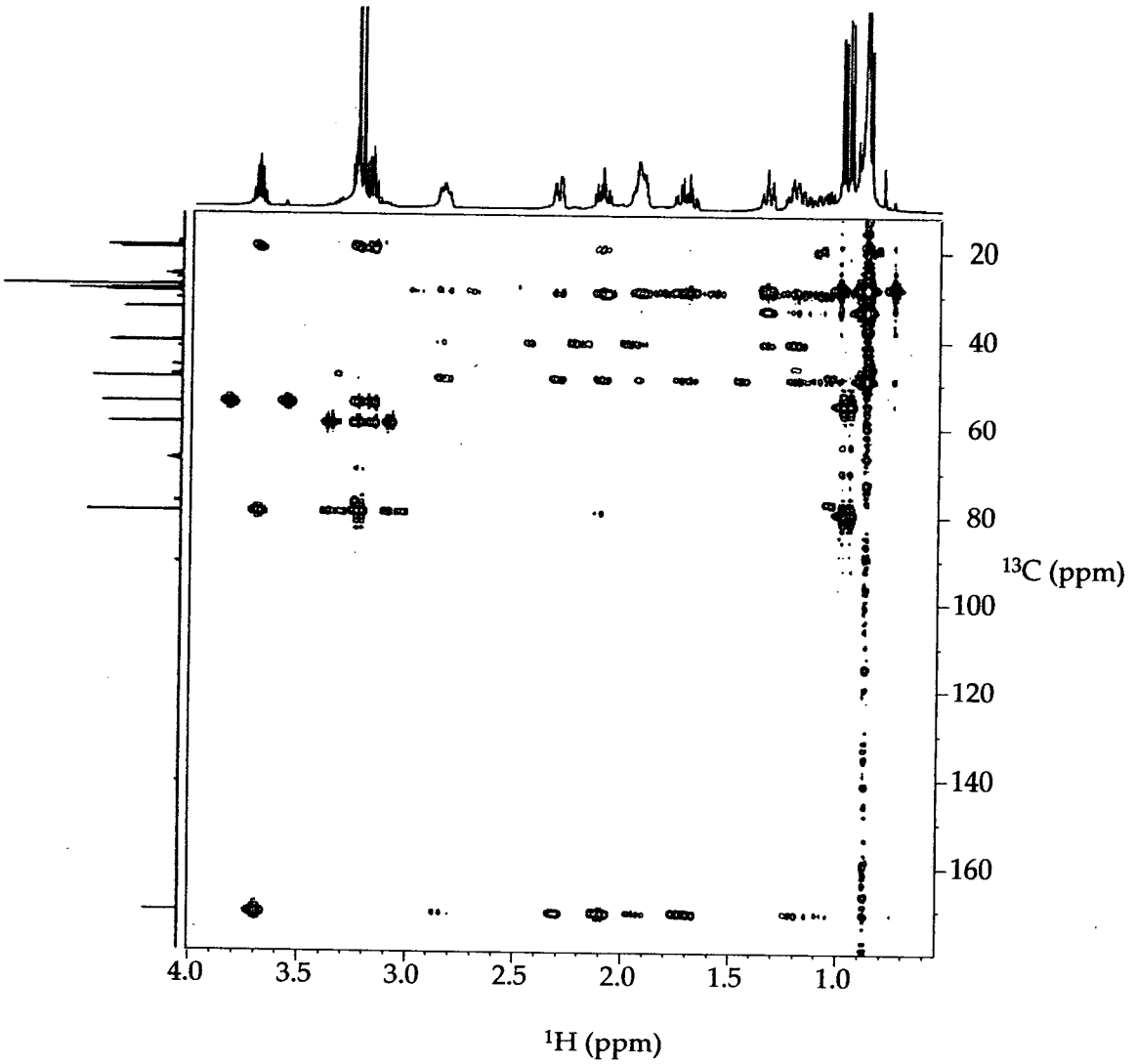


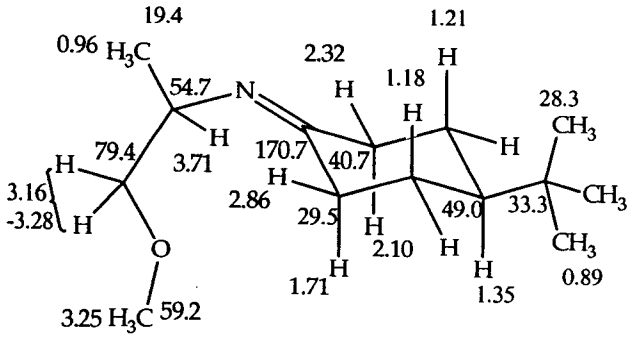
7



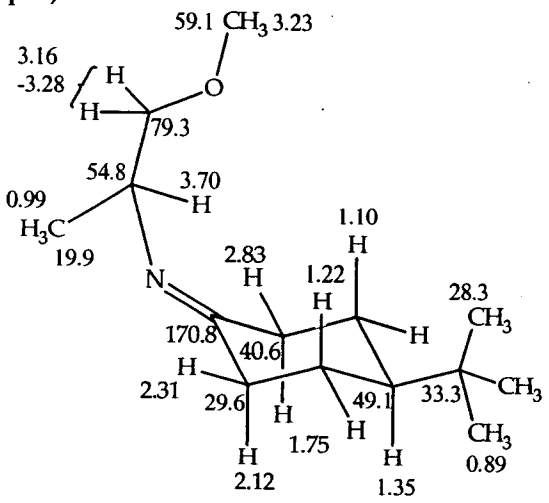
8

VII-G. $^{1}H,^{13}C$-HMBC spectrum of a 1:1 mixture of imines **7** and **8** (500 MHz, THF-d_8, 25 °C).



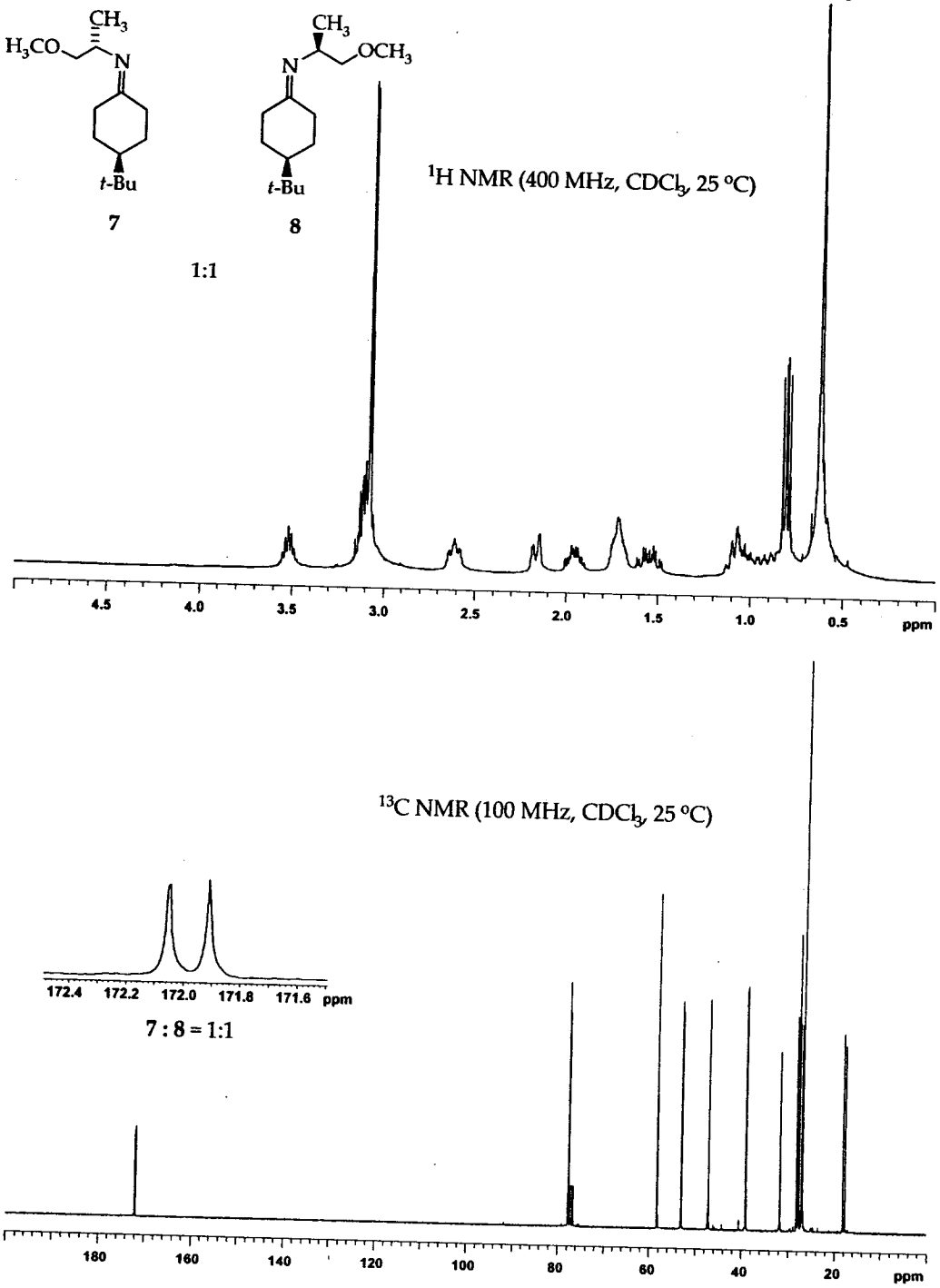


7



8

VII-H. ^{1}H and ^{13}C NMR spectra of a 1:1 mixture of imines **7** and **8** in $CDCl_3$.

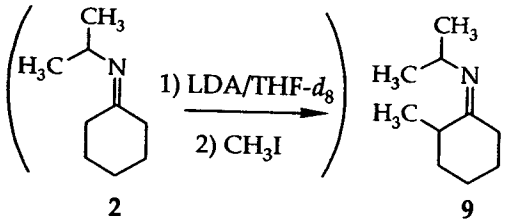


^{1}H NMR (**7** and **8**): δ 0.63 (s, 9H), 0.80 (d, J = 6.4 Hz, 3H, one isomer), 0.82 (d, J = 6.4 Hz, 3H, one isomer), 0.84-1.15 (m, 3H), 1.55 (m, 1H), 1.72 (m, 2H), 1.95 (m, 1H), 2.17 (dq, J = 14.0, 3.0 Hz, 1H), 2.61 (tm, J = 12.0 Hz, 1H), 3.05-3.16 (m, 2H), 3.08 (s, 3H, one isomer), 3.09 (s, 3H, one isomer), 3.51 (sept, J = 6.4 Hz, 1H). ^{13}C NMR (**7** and **8**)[a]: δ 17.8/18.3, 27.0 (both), 27.3/27.6, 27.8 (both), 28.2/28.3, 31.8 (both), 39.1/39.2, 47.1/47.2, 52.9/53.0, 58.3 (both), 77.6/77.8, 171.9/172.0.

[a]Chemical shifts are listed in pairs as the two isomers are not distinguishable.

VIII. Conformational assignments of imine **9** in THF-d_8.

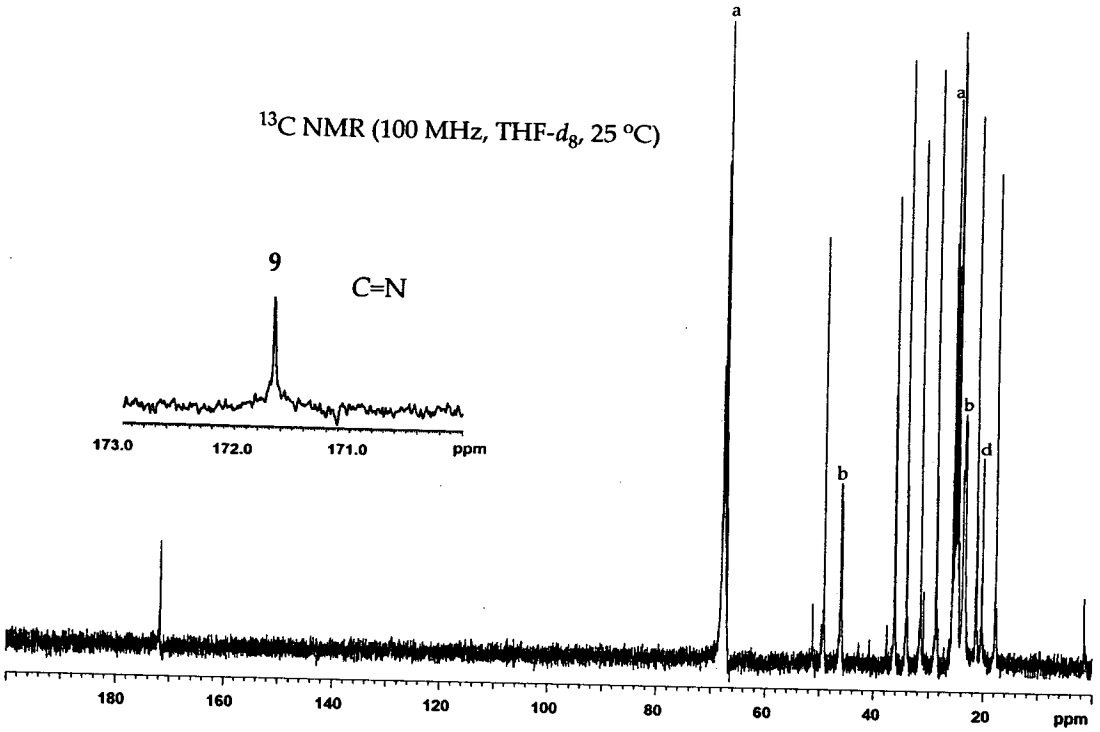
VIII-A. ^{1}H and ^{13}C NMR spectra of imine **9**[a] made from imine **2** in THF-d_8.



2 **9**

^{1}H NMR (500 MHz, THF-d_8, -90 °C)

^{13}C NMR (100 MHz, THF-d_8, 25 °C)

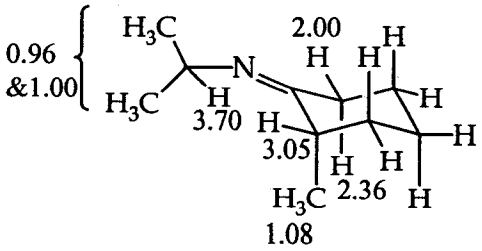


a = THF, b = HN(*i*-Pr)$_2$, c = CH_3I, d = $CH_3N(i\text{-Pr})_2$ (?)

[a]Imine **9** was prepared in situ by lithiation (LDA, 1.1 equiv, 0 °C) and alkylation (CH_3I, 1.1 equiv, -78 °C) of imine **2** (0.26 M).

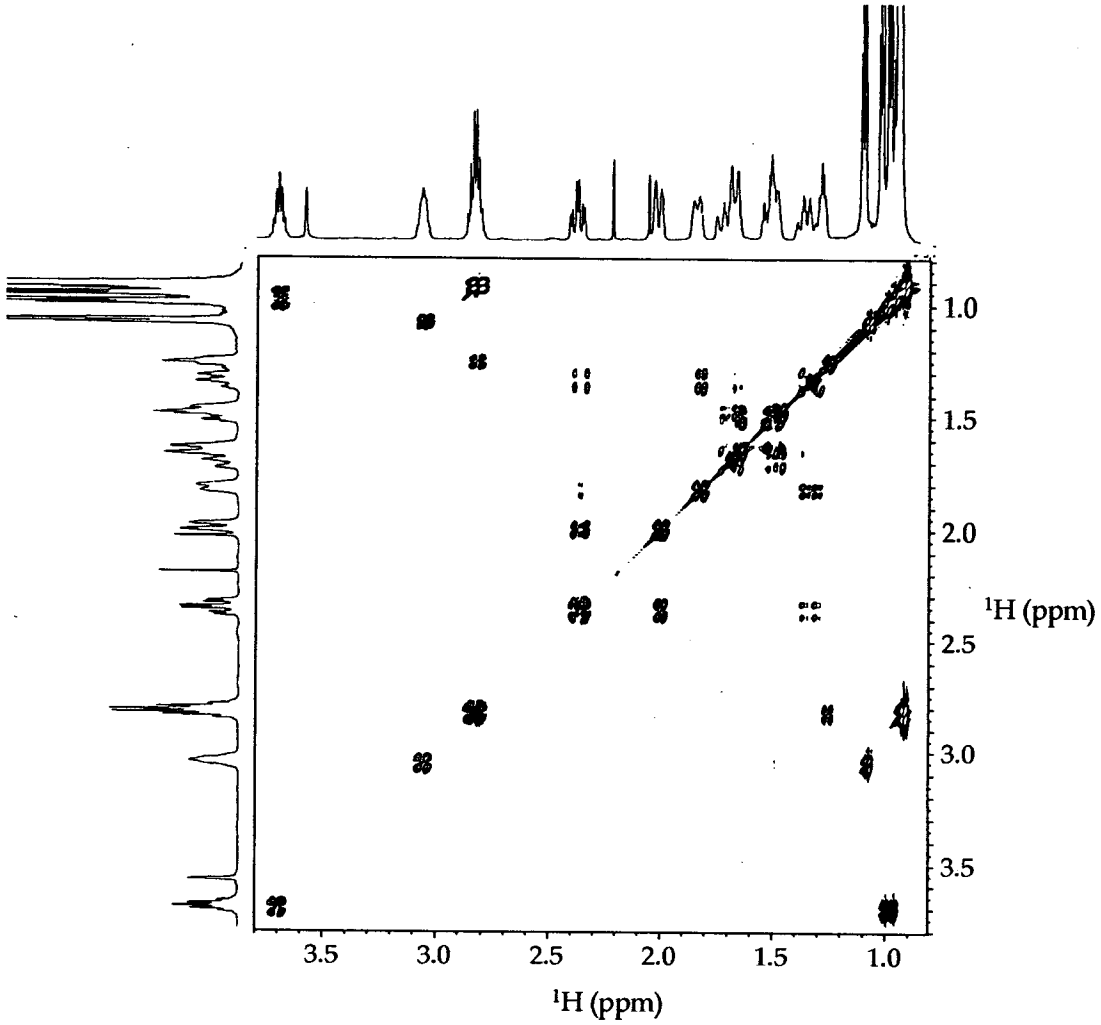
VIII-B. ^{1}H NMR: δ 0.96 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.33 (qt, J = 13.7, 4.1 Hz, 1H), 1.47 (m, 1H), 1.50 (tt, J = 14.5, 4.1 Hz, 1H), 1.65 (dm, J = 14.0 Hz, 1H), 1.69 (qt, J = 14.2, 3.9 Hz, 1H) 1.82 (dm, J = 12.5 Hz, 1H), 2.00 (dm, J = 13.5 Hz, 1H), 2.36 (td, J = 14.2, 4.9 Hz, 1H), 3.05 (quint, J = 6.5 Hz, 1H), 3.70 (sept, J = 6.0 Hz, 1H). ^{13}C NMR: δ 17.9, 21.4, 24.8, 24.9, 28.7, 31.6, 34.1, 36.3, 49.2, 171.7.

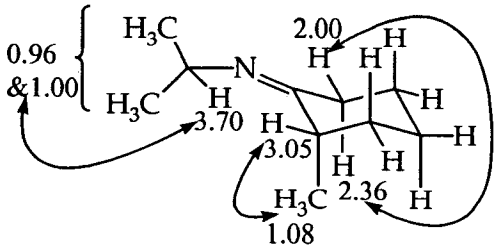
The structure of **9** is shown below. See 2D NMR spectra (section **VIII**: **C-E**) for detailed assignments.



9

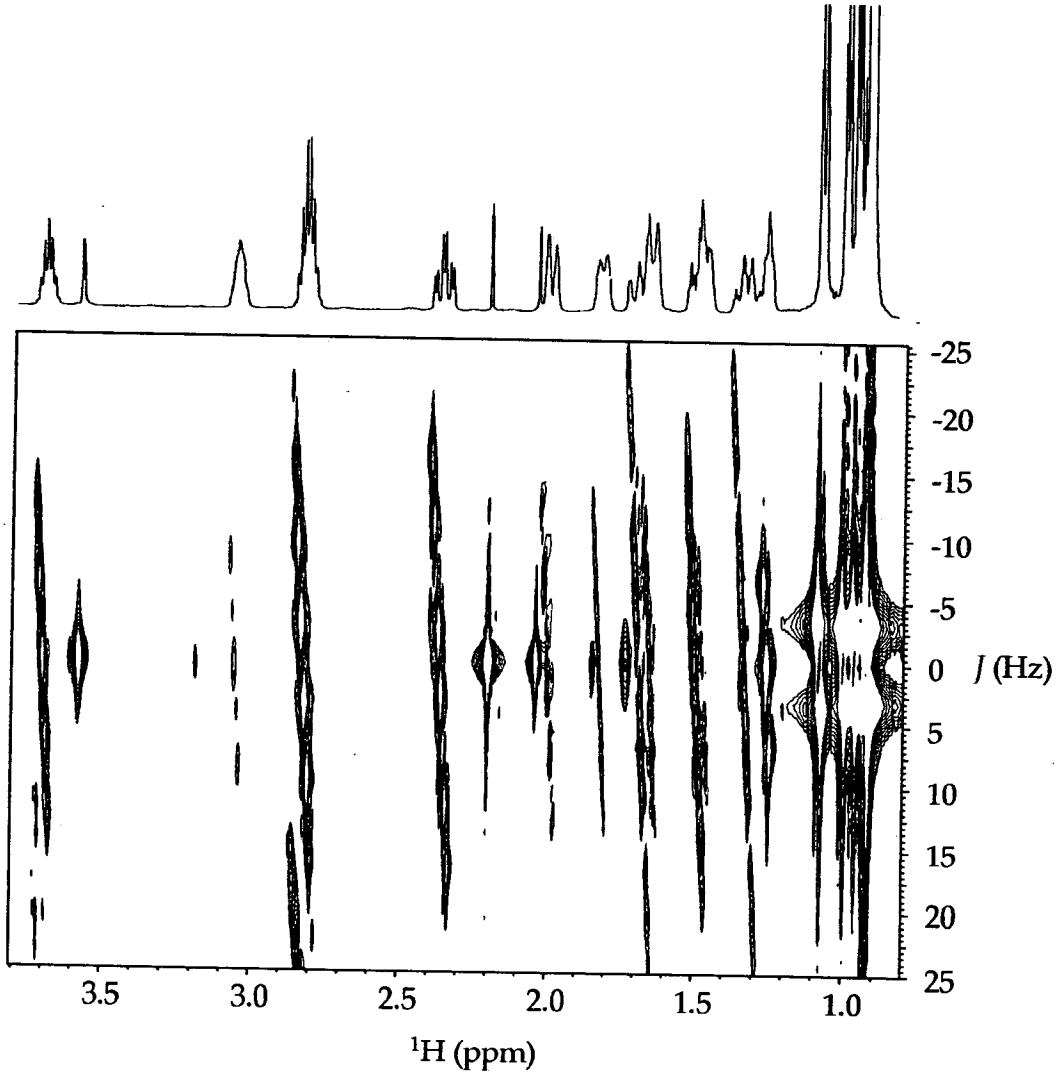
VIII-C. ^{1}H,^{1}H-COSY spectrum of imine **9** made from imine **2** (500 MHz, THF-d_8, -90 °C).

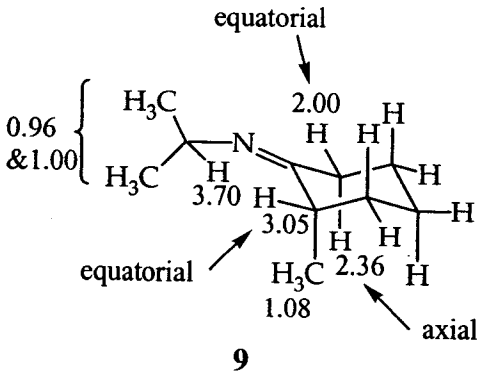




9

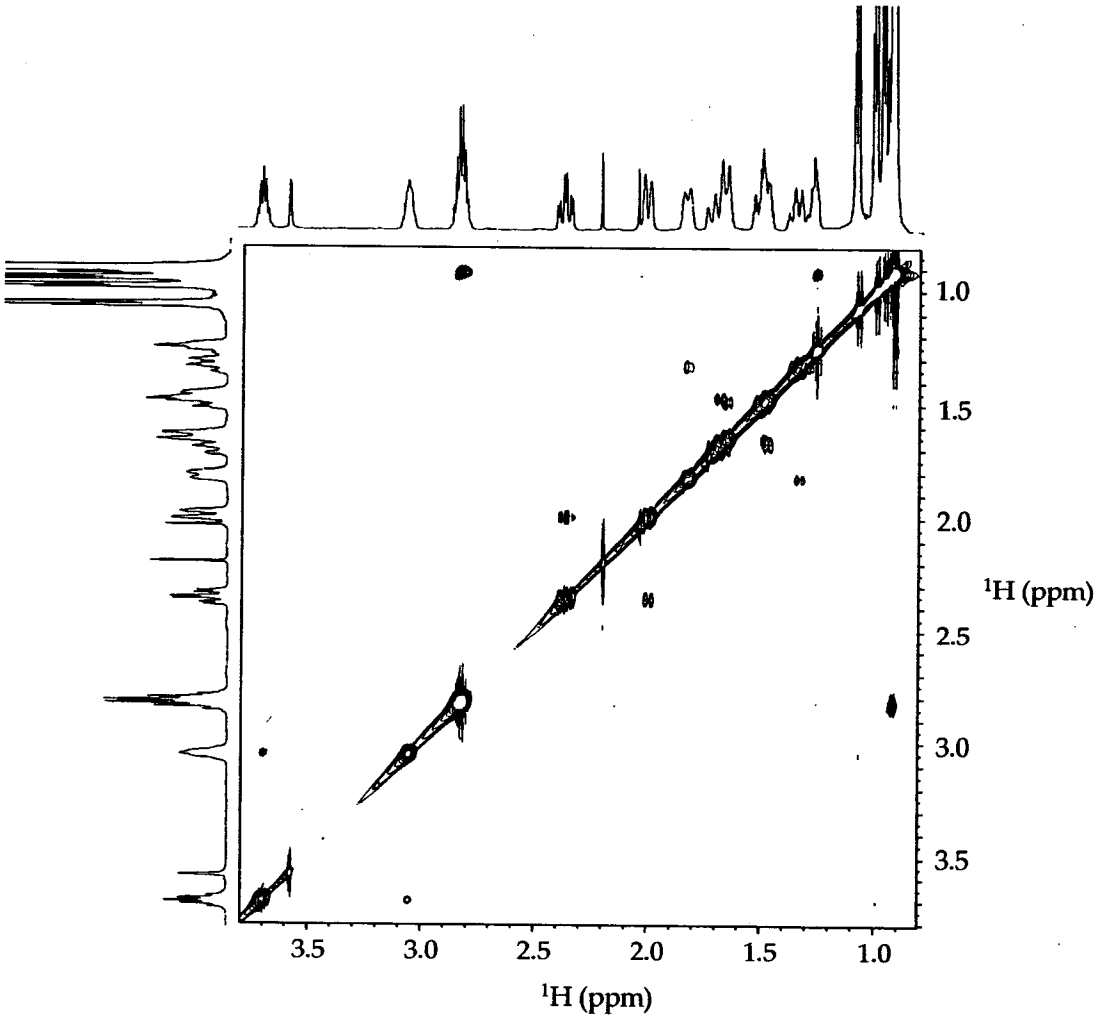
VIII-D. $J(^1H,^1H)$-resolved spectrum of imine **9** made from imine **2** (500 MHz, THF-d_8, -90 °C).

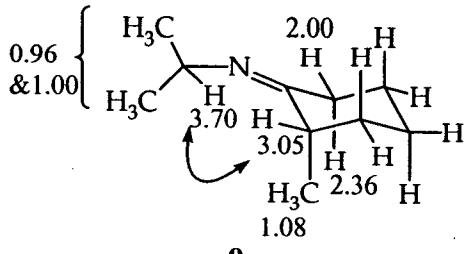




9

VIII-E. ^{1}H,^{1}H-NOESY of imine **9** made from imine **2** (500 MHz, THF-d_8, -90 °C).

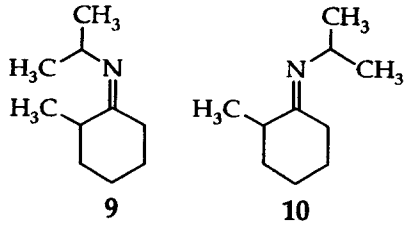




9

IX. Conformational assignments of imine **10** in THF-d_8.

IX-A. ^{1}H and ^{13}C NMR spectra of a 1:10 mixture of imines **9** and **10** in THF-d_8.



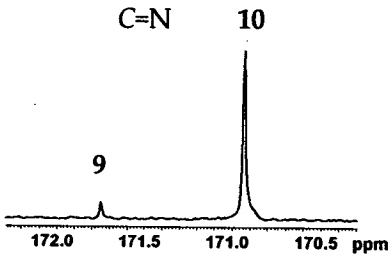
9

10

1:10 mixture

^{1}H NMR (500 MHz, THF-d_8, 25 °C)

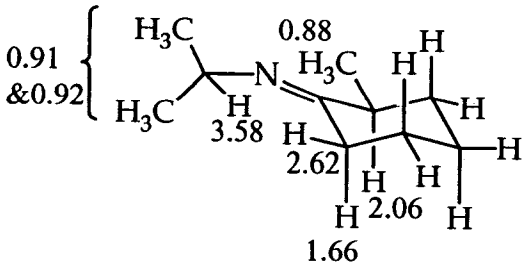
^{13}C NMR (100 MHz, THF-d_8, 25 °C)



1 : 10

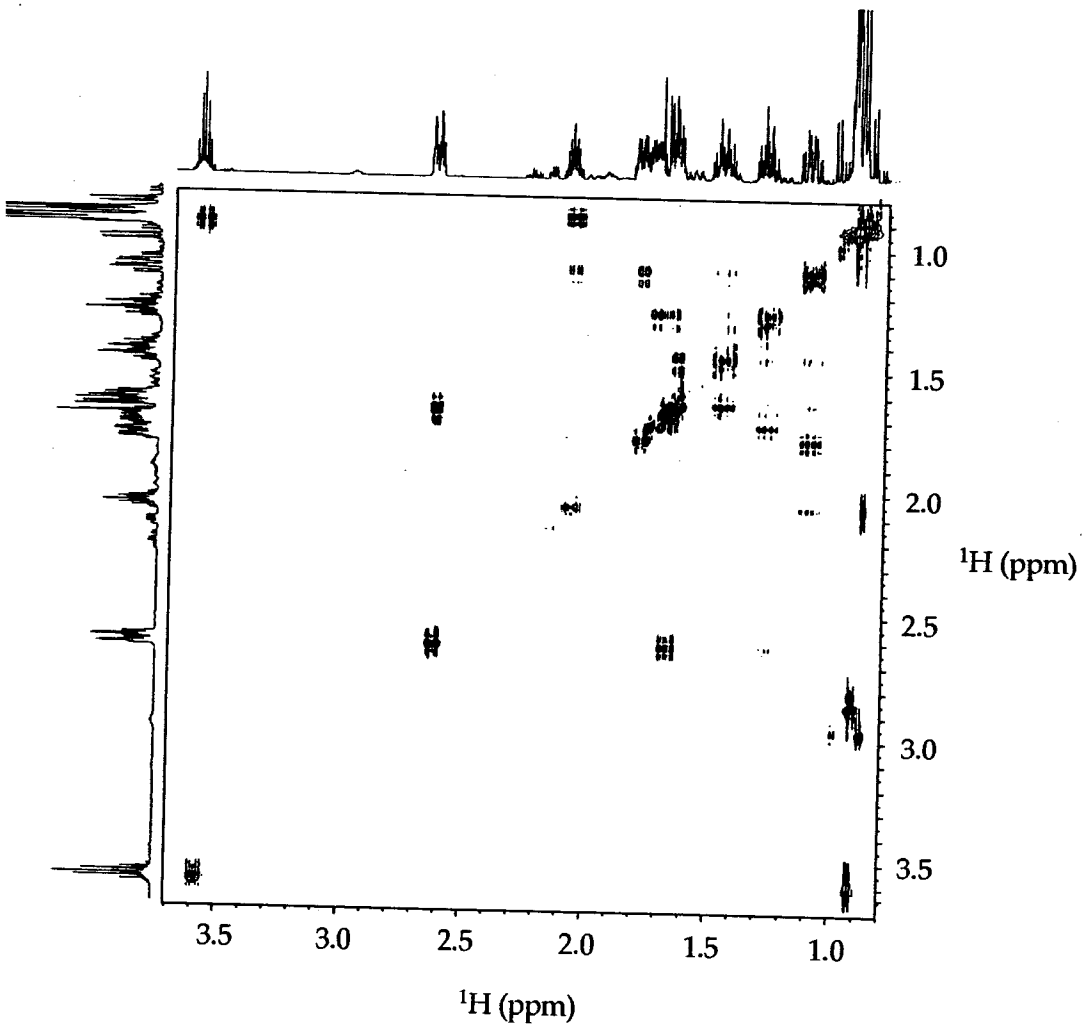
IX-B. ^{1}H NMR (**10** only): δ 0.88 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.10 (qd, J = 12.5, 4.1 Hz, 1H), 1.27 (qt, J = 12.5, 4.1 Hz, 1H), 1.45 (qt, J = 12.5, 4.1 Hz, 1H), 1.63 (m, 1H), 1.66 (ddd, J = 13.0, 12.5, 4.3 Hz, 1H), 1.72 (m, 1H), 1.78 (m, 1H), 2.06 (dqd, J = 12.5, 6.9, 4.3 Hz, 1H), 2.62 (dt, J = 13.0, 4.3 Hz, 1H), 3.58 (sept, J = 6.5 Hz, 1H). ^{13}C NMR (**9**): δ 18.0, 21.5, 24.9, 31.7, 34.3, 36.4, 49.4, 171.8; (**10**): δ 17.8, 24.8, 25.0, 26.6, 29.0, 29.1, 37.8, 43.0, 49.8, 170.9.

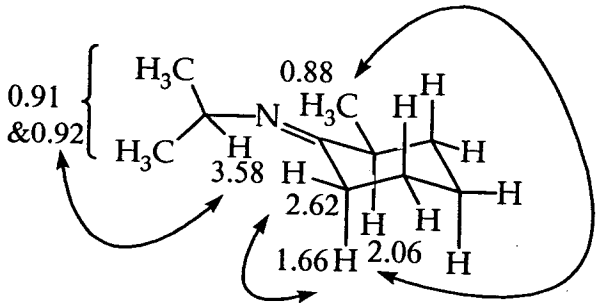
The structure of **10** is shown below. See 2D NMR spectra (section **IX**: **C-E**) for detailed assignments.



10

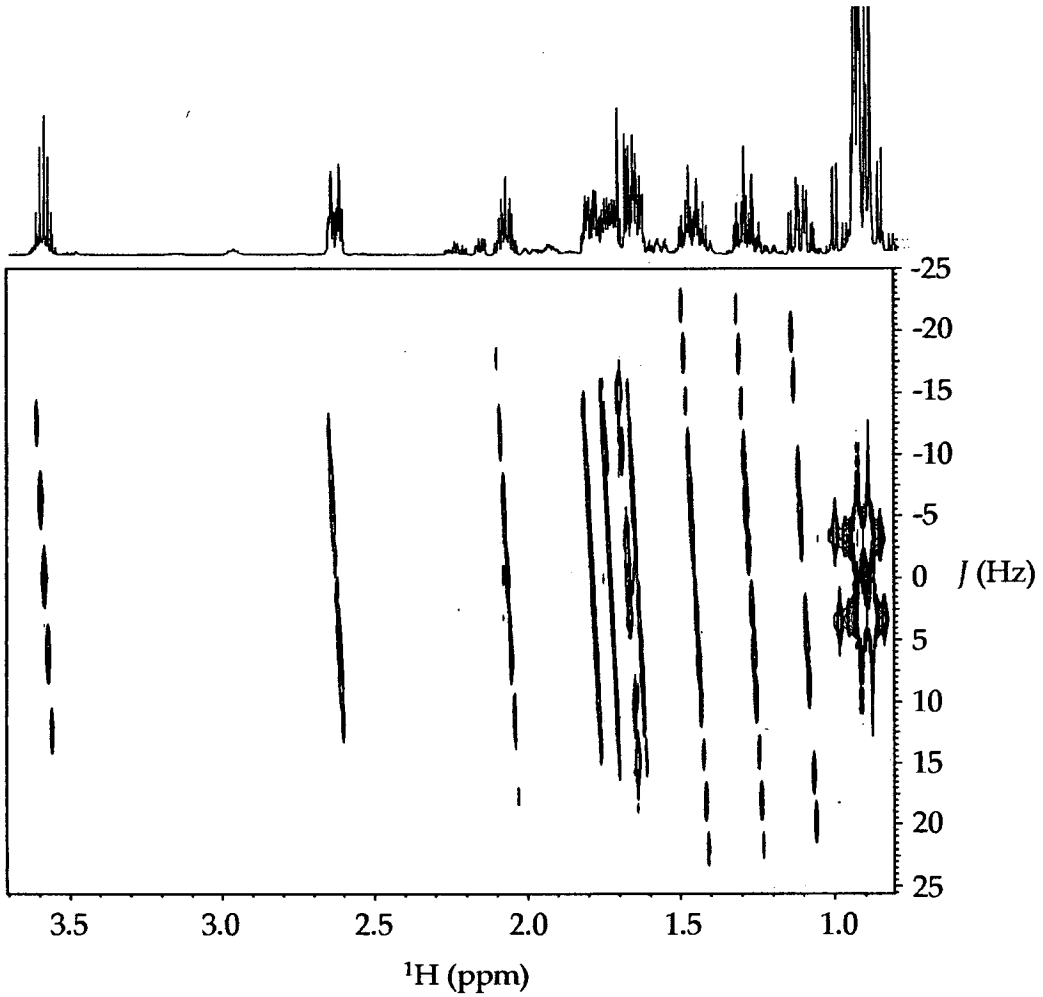
IX-C. ^{1}H,^{1}H-COSY spectrum of a 1:10 mixture of imines **9** (minor) and **10** (major) (500 MHz, THF-d_8, 25 °C).

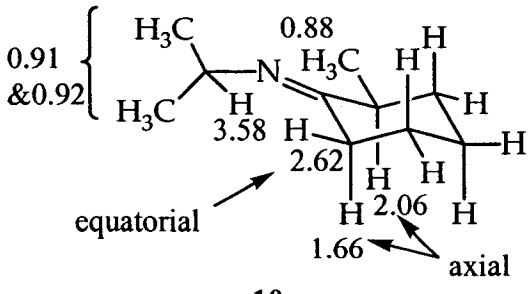




10

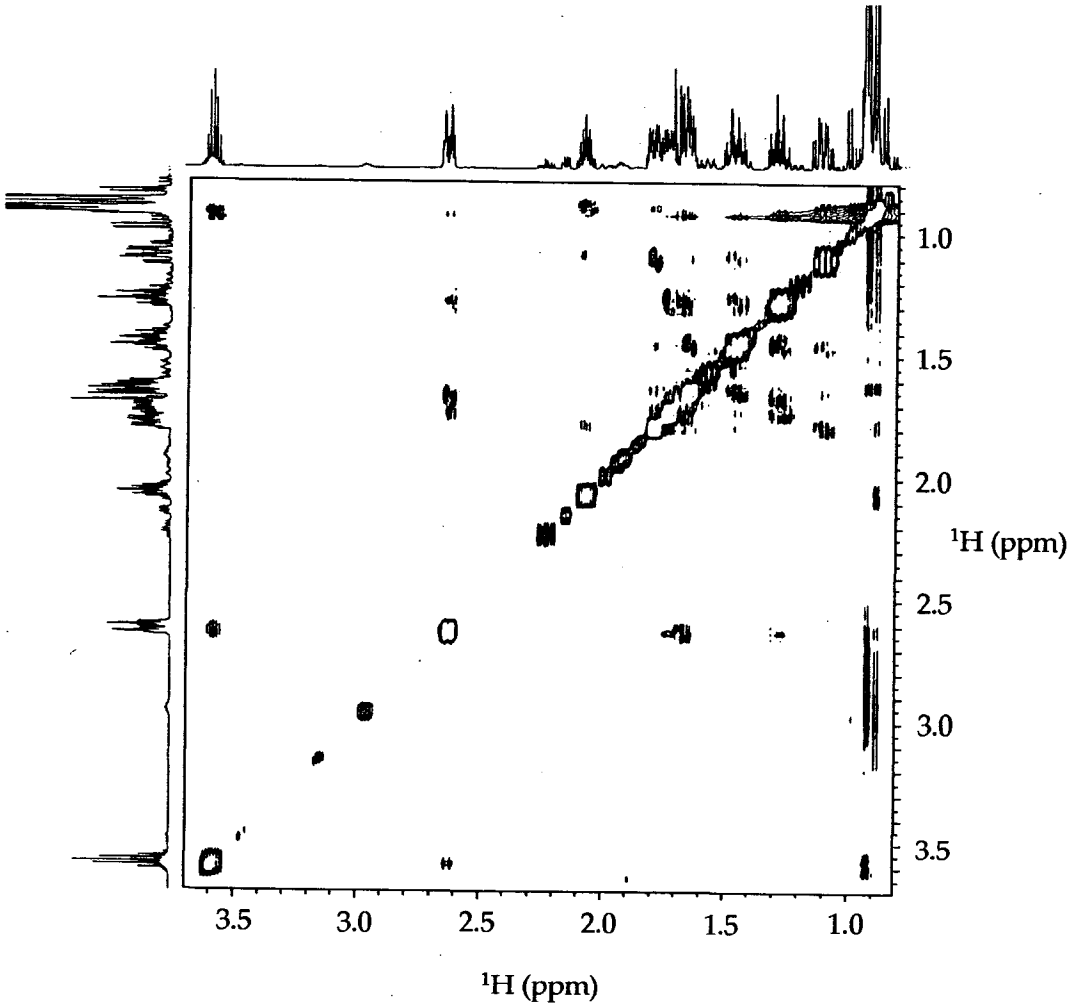
IX-D. $J(^1H,^1H)$-resolved spectrum of a 1:10 mixture of imines **9** (minor) and **10** (major) (500 MHz, THF-d_8, 25 °C).

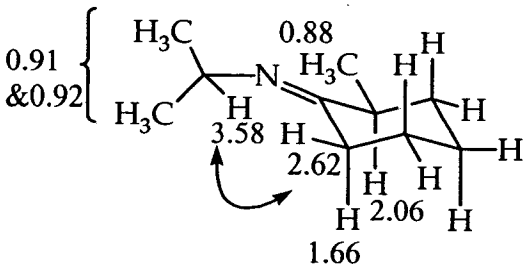




10

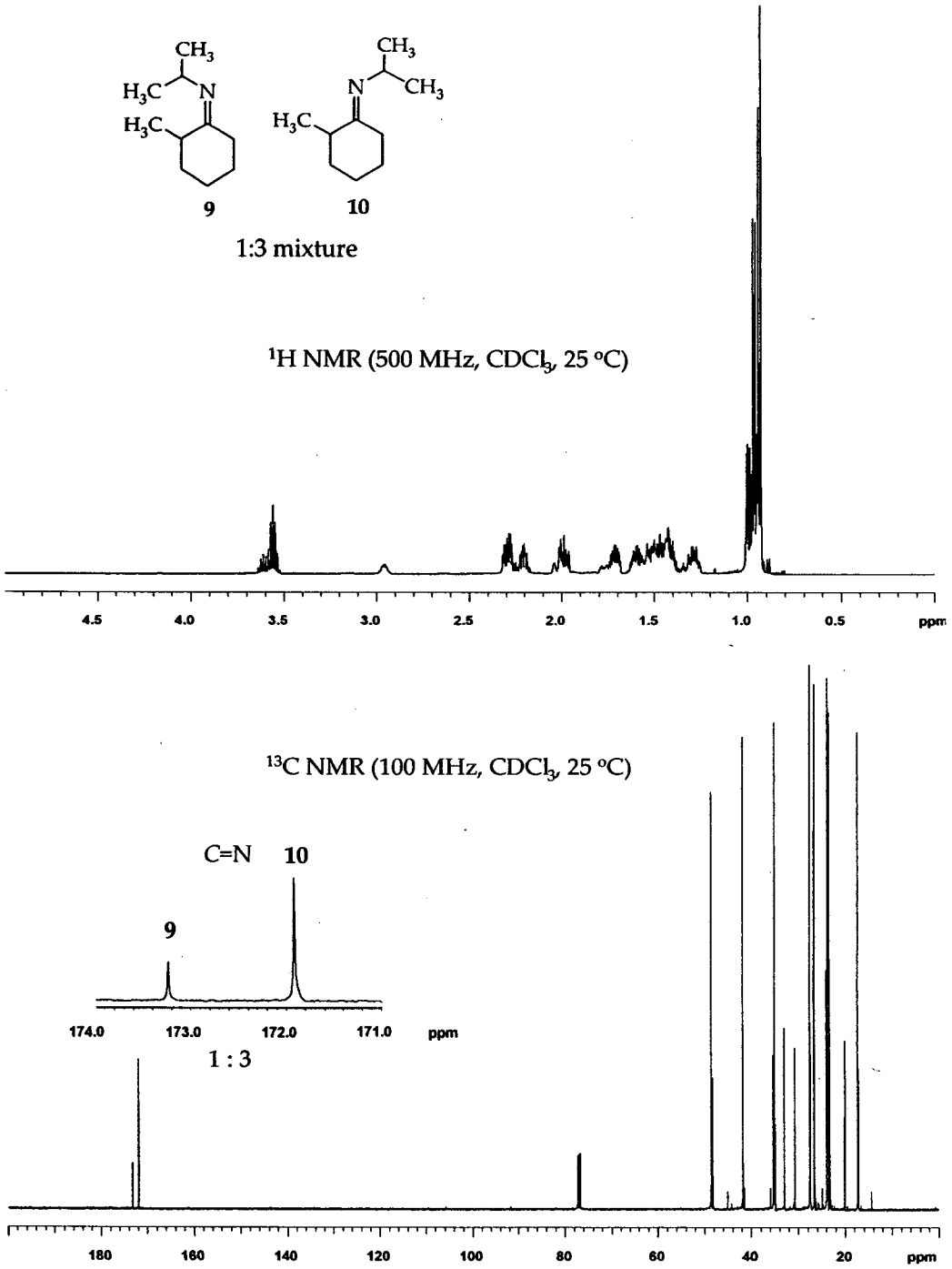
IX-E. ^{1}H,^{1}H-NOESY spectrum of a 1:10 mixture of imines **9** (minor) and **10** (major) (500 MHz, THF-d_8, 25 °C).





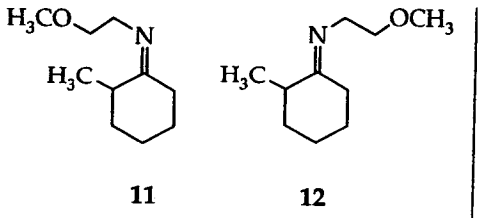
10

IX-F. ^{1}H and ^{13}C NMR spectra of a 1:3 mixture of imines **9** and **10** in $CDCl_3$.



^{1}H NMR: δ 0.94 (d, J = 6.5 Hz, 6H, **10**), 0.96 (d, J = 6.5 Hz, 3H, **9**), 0.97 (d, J = 6.0 Hz, 3H, **10**), 0.99 (d, J = 7.5 Hz, 3H, **9**), 1.00 (d, J = 6.5 Hz, 3H, **9**), 1.25-1.36 (m, 1H, **9** and **10**), 1.37-1.65 (m, 4H, **9** and **10**), 1.67-1.80 (m, 1H, **9** and **10**), 1.95-2.05 (m, 1H, **9** and **10**), 2.17-2.23 (m, 2H, **9** and **10**), 2.96 (m, 1H, **9**), 3.56 (sept, J = 6.5 Hz, 1H, **10**), 3.61 (sept, J = 6.5 Hz, 1H, **9**). ^{13}C NMR (**9**): δ 17.1, 20.1, 23.9, 23.9, 27.4, 30.7, 32.9, 35.3, 48.1, 173.2; (**10**): δ 17.2, 23.3, 23.7, 23.8, 26.6, 27.5, 35.0, 41.7, 48.5, 171.9.

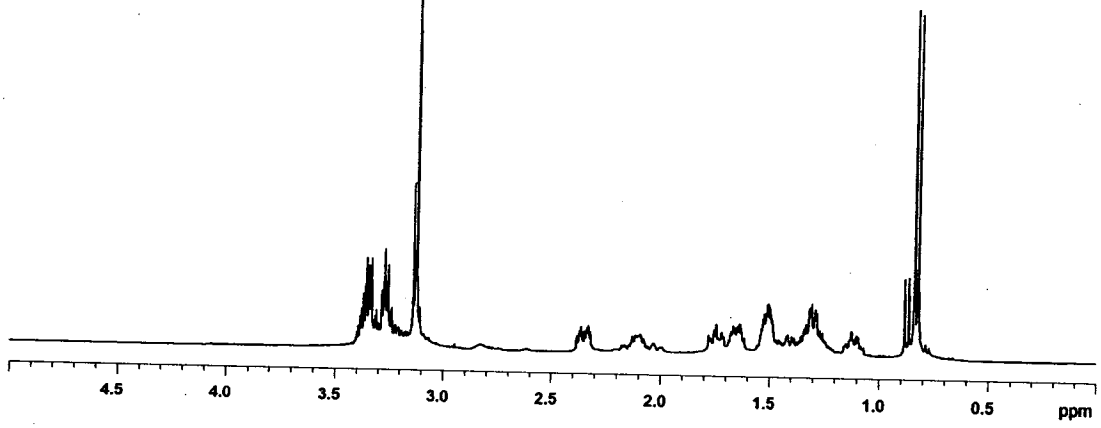
X. Conformational assignments of a 1:4 mixture of imines **11** and **12** in $CDCl_3$.
X-A. ^1H and ^{13}C NMR spectra of a 1:4 mixture of imines **11** and **12** in $CDCl_3$.



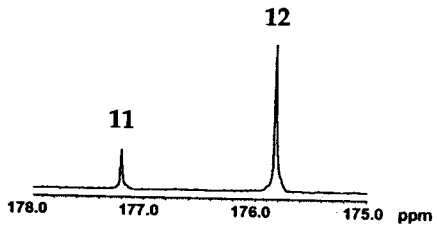
11 **12**

1:4

^1H NMR (400 MHz, $CDCl_3$, 25 °C)



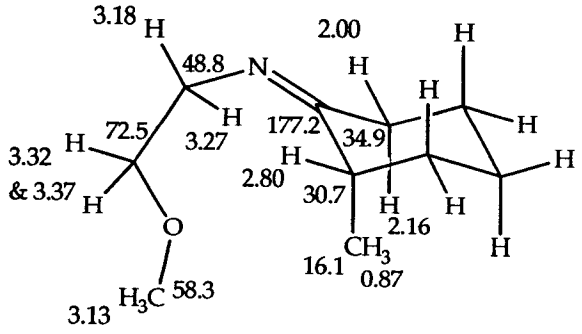
^{13}C NMR (100 MHz, $CDCl_3$, 25 °C)



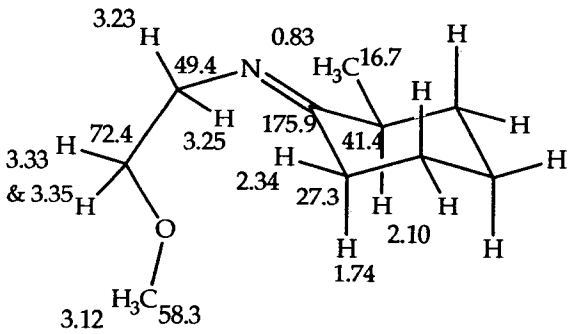
1 : 4

X-B. ^{1}H NMR (**11**): δ 0.87 (d, J = 7.2 Hz, 3H), 1.23 (qm, J = 11.2 Hz, 1H), 1.29 (qm, J = 10.4 Hz, 1H), 1.33 (tm, J = 12.8 Hz, 1H), 1.42 (dm, J = 12.8 Hz, 1H), 1.49 (m, 1H), 2.00 (dt, J = 14.0, 3.8 Hz, 1H), 2.16 (td, J = 14.0, 5.4 Hz, 1H), 2.80 (t, J = 5.4 Hz, 1H), 3.13 (s, 3H), 3.18 (dt, J = 14.0, 7.0 Hz, 1H), 3.27 (m, 1H), 3.32 (m, 1H), 3.37 (m, 1H); (**12**): δ 0.83 (d, J = 6.8 Hz, 3H), 1.11 (qm, J = 11.2 Hz, 1H), 1.27 (qd, J = 10.4, 3.4 Hz, 1H), 1.31 (qd, J = 11.2, 3.4 Hz, 1H), 1.50 (m, 2H), 1.65 (dm, J = 12.8 Hz, 1H), 1.74 (td, J = 12.8, 4.0 Hz, 1H), 2.10 (dqm, J = 14.0, 6.8 Hz, 1H), 2.34 (ddd, J = 14.0, 6.4, 4.0 Hz, 1H), 3.12 (s, 3H), 3.23 (dt, J = 14.0, 7.0 Hz, 1H), 3.25 (m, 1H), 3.33 (m, 1H), 3.35 (m, 1H). ^{13}C NMR (**11**): δ 16.1, 19.7, 30.7, 32.1, 34.9, 48.8, 58.3, 72.5, 177.2; (**12**): δ 16.7, 23.8, 26.8, 27.3, 35.2, 41.4, 49.4, 58.3, 72.4, 175.9.

The structures of **11** and **12** are shown below.[a] See 2D NMR spectra (section **X: C-G**) for detailed assignments.



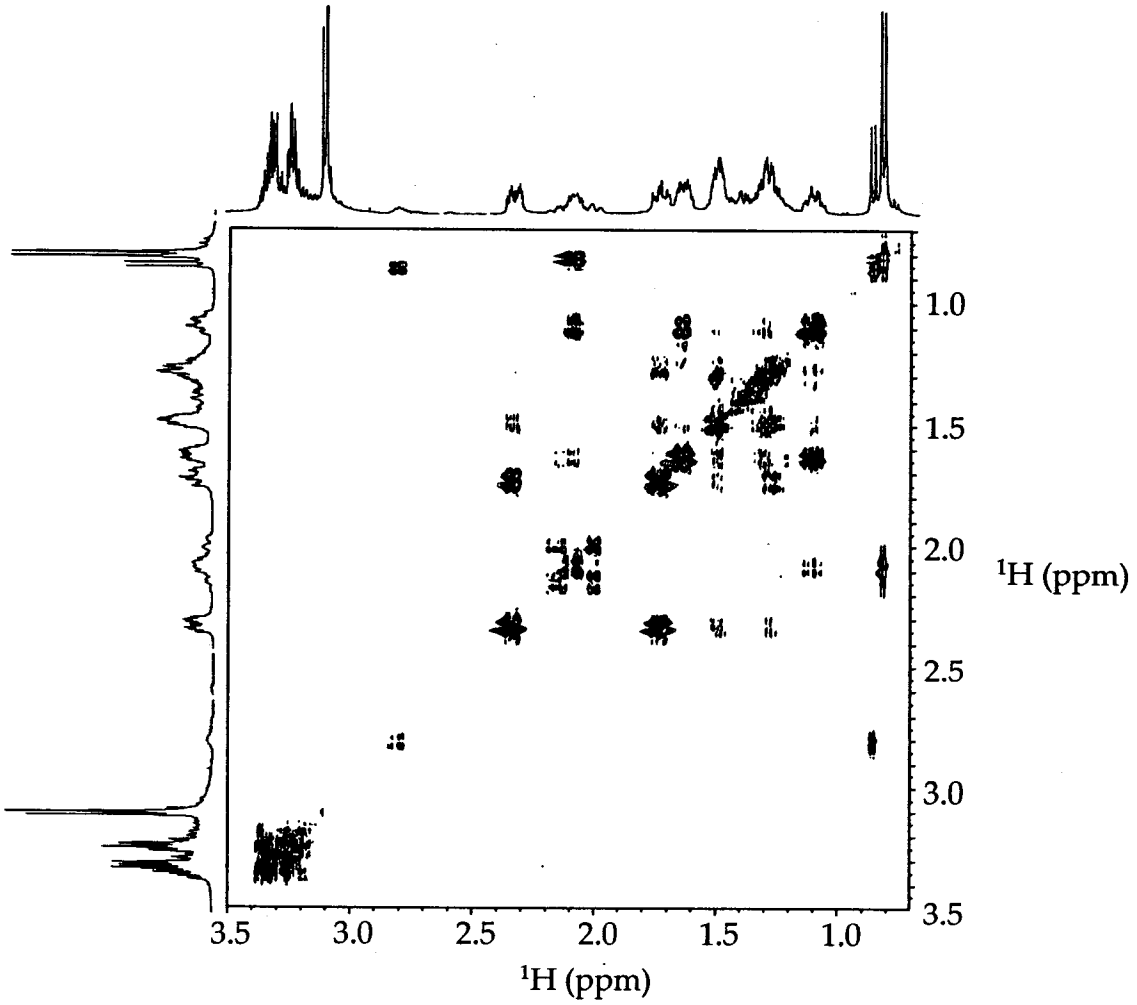
11

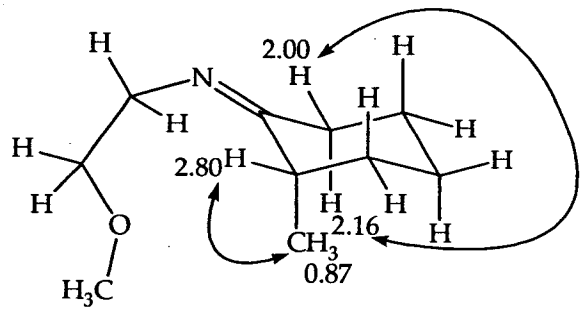


12

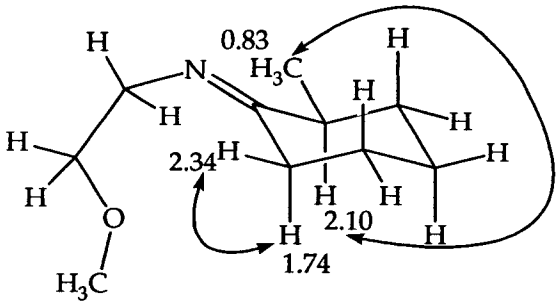
[a]The attempt to make **11** in situ from **3** and carry out 2-D NMR experiments at low temperature failed due to precipitate formed in the sealed NMR tube. The conformational assignments also apply to the 1:10 mixture of **11** (minor) and **12** (major) in THF. (See solvent effect on *syn/anti* ratio in section **XVIII**.)

X-C. ^{1}H,^{1}H-COSY spectrum of a 1:4 mixture of imines **11** (minor) and **12** (major) (500 MHz, $CDCl_3$, 25 °C).



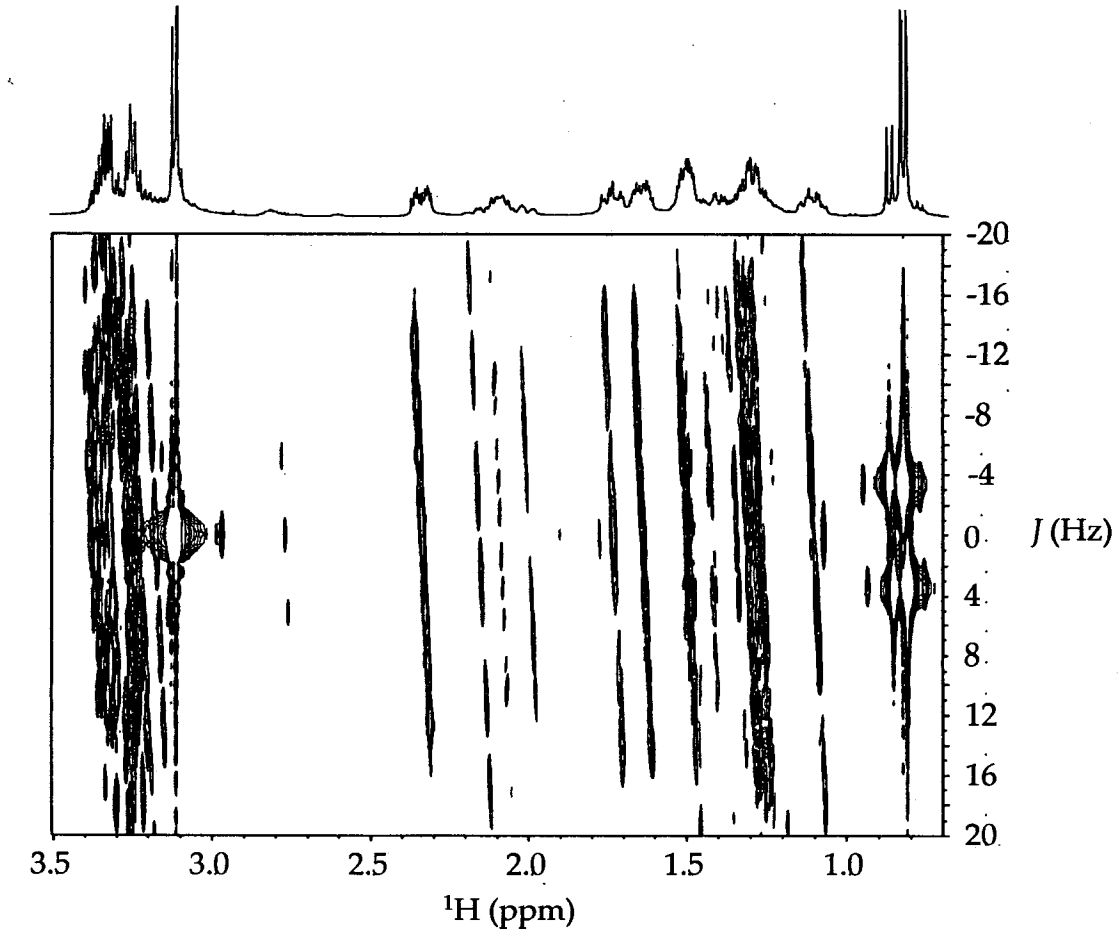


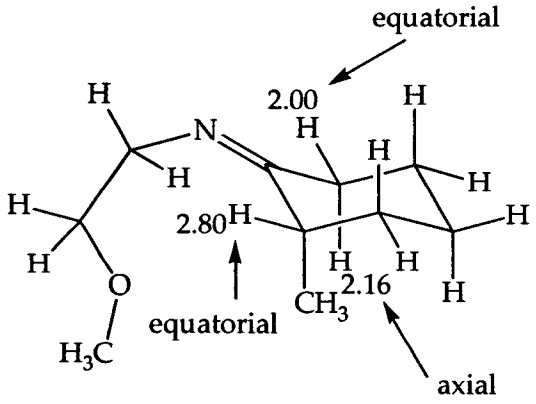
11



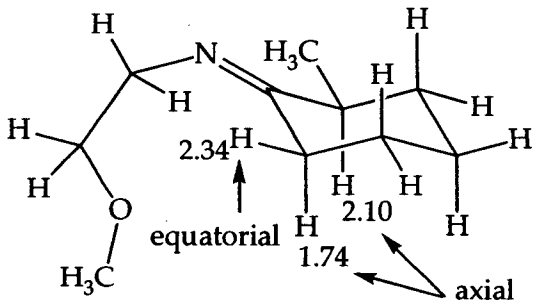
12

X-D. $J(^1H,^1H)$-resolved spectrum of a 1:4 mixture of imines **11** (minor) and **12** (major) (500 MHz, $CDCl_3$, 25 °C).



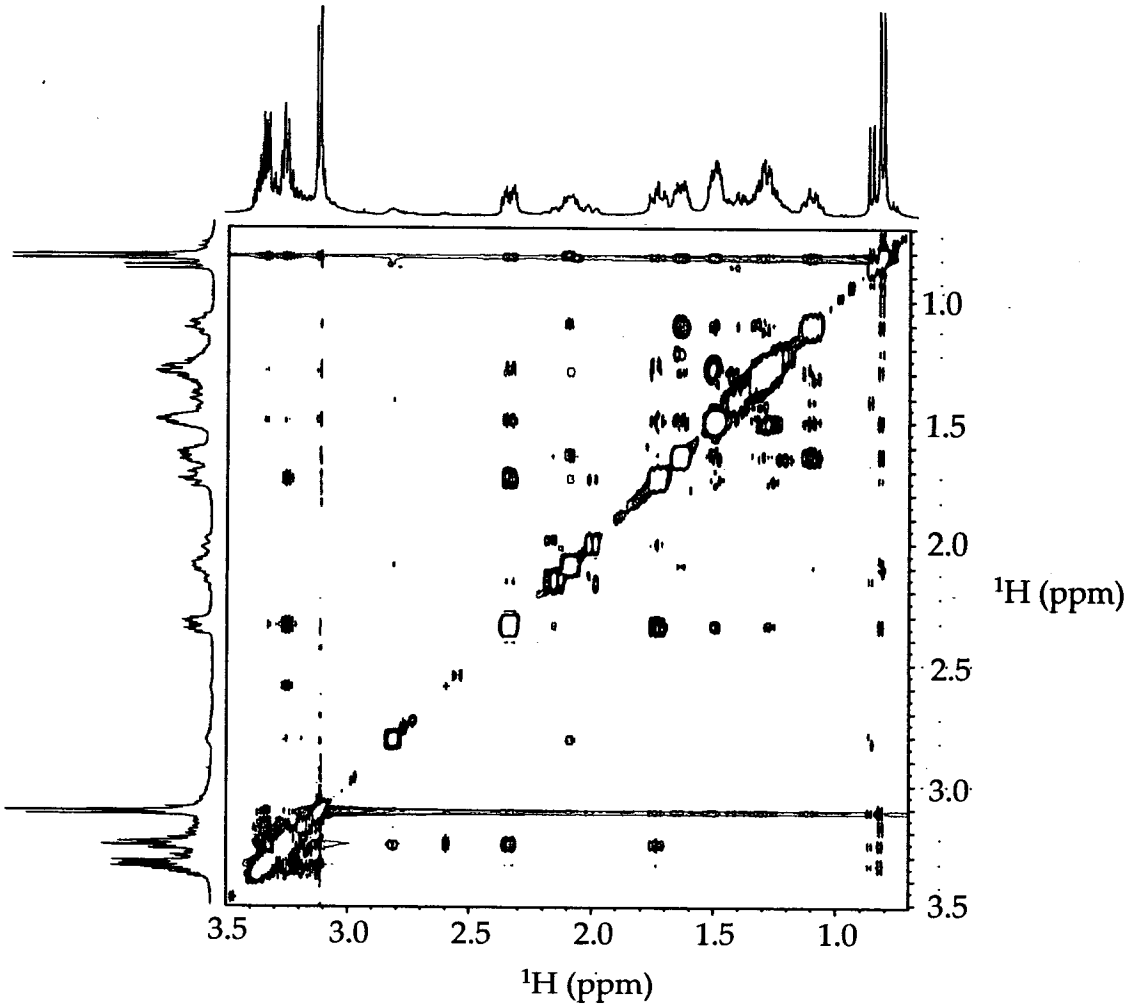


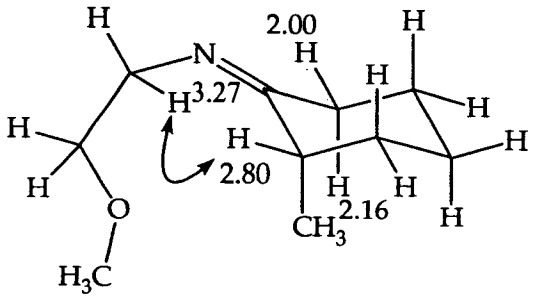
11



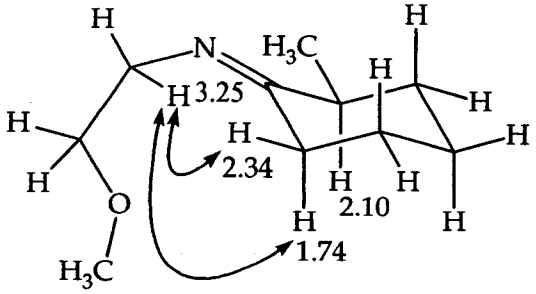
12

X-E. ^{1}H,^{1}H-NOESY spectrum of a 1:4 mixture of imines **11** (minor) and **12** (major) (500 MHz, $CDCl_3$, 25 °C).



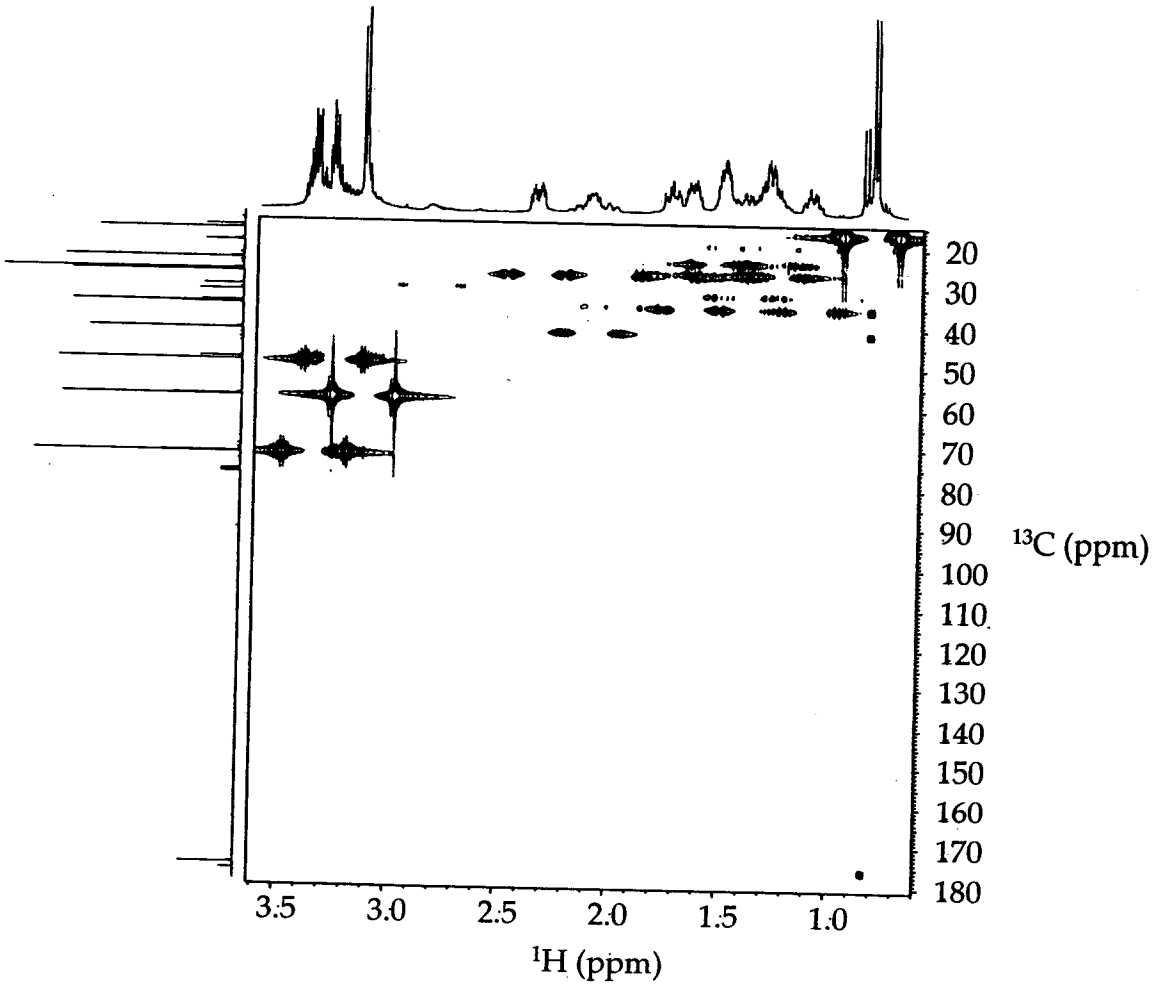


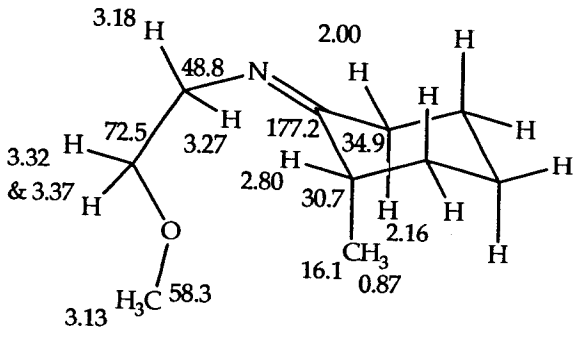
11



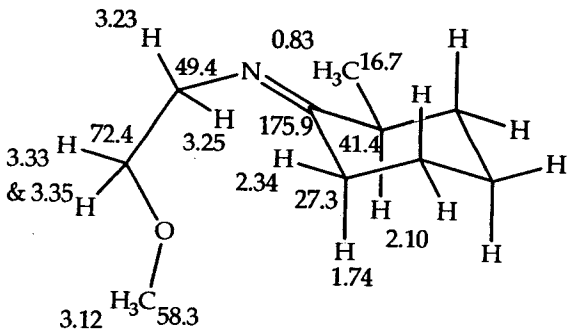
12

X-F. $^{1}H,^{13}C$-HMQC spectrum of a 1:4 mixture of imines **11** (minor) and **12** (major) (500 MHz, $CDCl_3$, 25 °C).



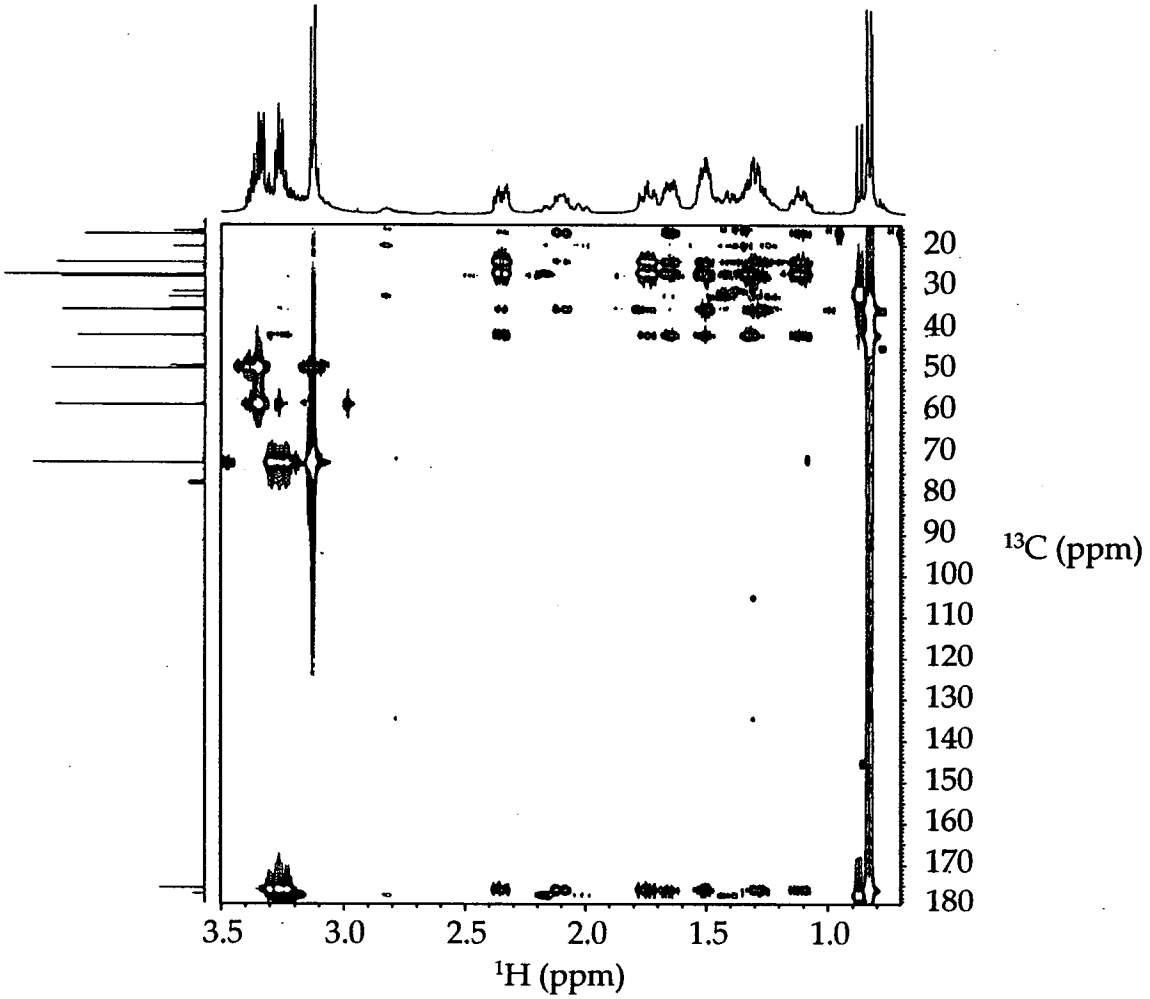


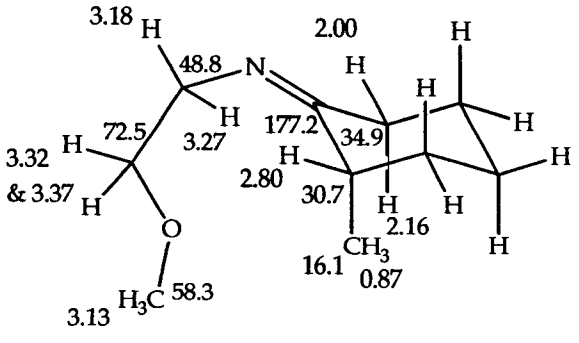
11



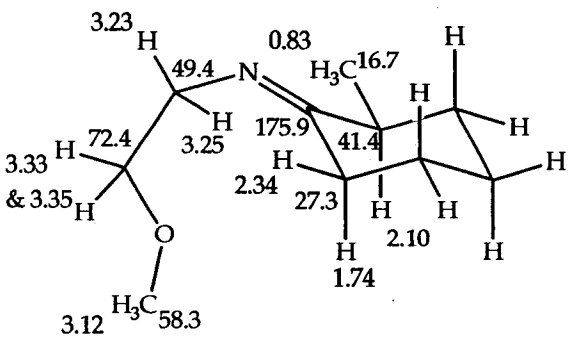
12

X-G. $^{1}H,^{13}C$-HMBC spectrum of a 1:4 mixture of imines **11** (minor) and **12** (major) (500 MHz, $CDCl_3$, 25 °C).



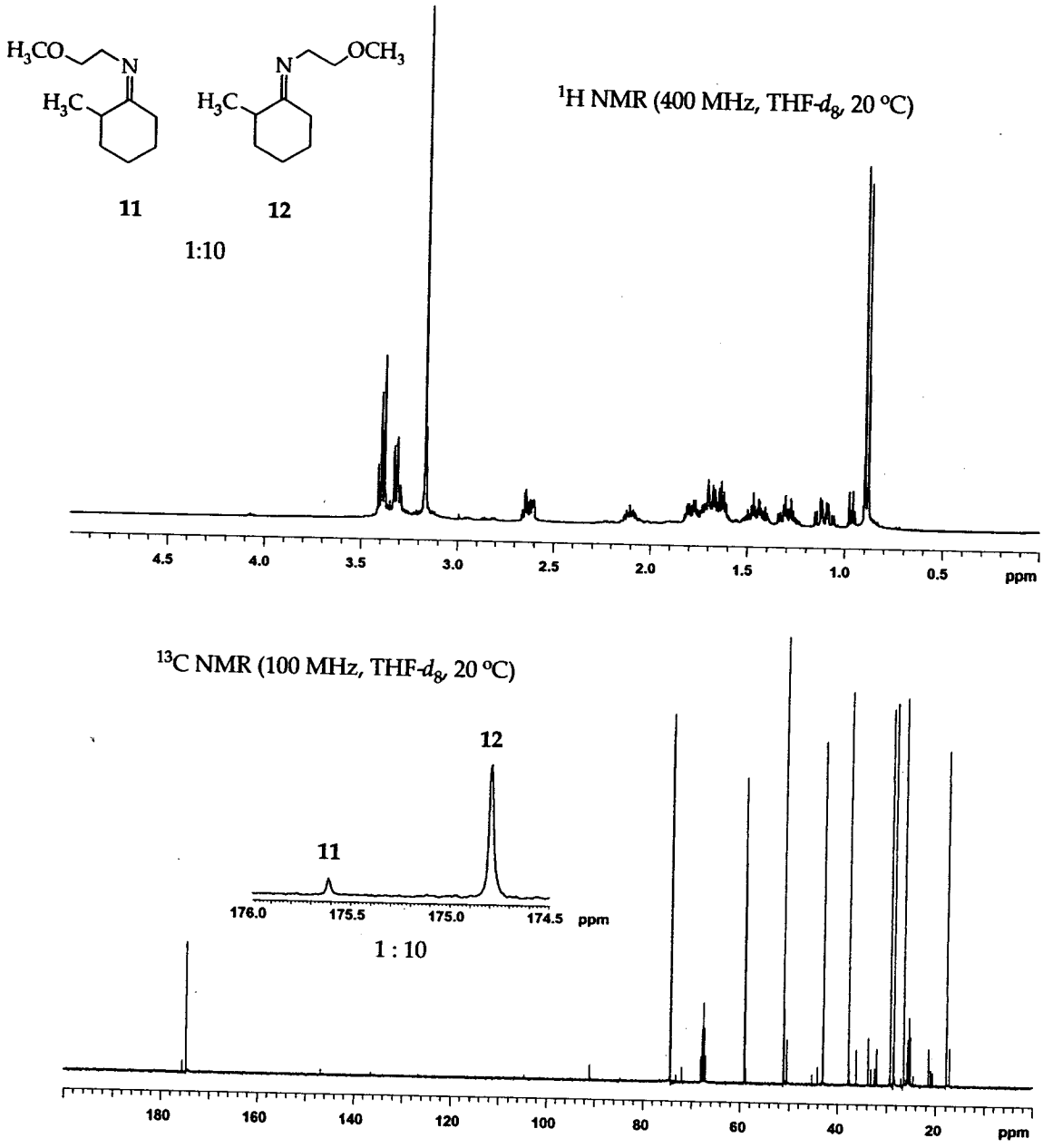


11



12

X-H. ^{1}H and ^{13}C NMR spectra of a 1:10 mixture of imines **11** and **12** in THF-d_8.[a]



^{1}H NMR (**12**): δ 0.89 (d, J = 6.4 Hz, 3H), 1.10 (qd, J = 12.4, 4.4 Hz, 1H), 1.29 (qt, J = 12.4, 4.4 Hz, 1H), 1.45 (qt, J = 12.4, 4.4 Hz, 1H), 1.58-1.74 (m, 3H), 1.79 (dm, J = 12.8 Hz, 1H), 2.10 (m, 1H), 2.63 (dm, J = 13.6 Hz, 1H), 3.17 (s, 3H), 3.31 (t, J = 6.4 Hz, 2H), 3.39 (t, J = 6.4 Hz, 2H). ^{13}C NMR (**12**): δ 17.8, 26.6, 28.6, 29.3, 37.7, 43.0, 51.1, 59.1, 74.3, 174.8. (**11**): δ 17.1, 175.6.

[a]The sample contains ≈ 5% enamine isomer as evidenced by ^{13}C peaks at 91.0 and 146.7 ppm. (See reference in section **VI.**)