A New Enantioselective Access to 1-Alkyl-1,2,3,4-tetrahydroisoquinolines. Application to a New Synthesis of (–)-Argemonine.

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SUPPORTING INFORMATION

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2-(1*S*)-(–)-2-(1-Phenylethyl)-isoquinolinone (7). To a solution of isoquinolinium salt **1** (2.1 g, 7.8 mmol), in MeOH (40 mL), was added, at 0° C, an excess of potassium ferricyanide (28 g, 86.3 mmol) and , after 0.6 h, solid KOH (6.2 g, 109.8 mmol). The resulting mixture was stirred during an additional 1 h and then toluene (40 mL) and H_2O (40 mL) were added . After 15 h at 45° C extraction with AcOEt and usual work-up gave a residue which was chromatographed over silica gel using a gradient of AcOEt / heptane (from 0 / 100 to 30 / 70). Isoquinolinone **7** was obtained as a pale yellow oil (1.5 g, 6 mmol, 77% yield): $[\alpha]_D$ –337 (c 2.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1656, 1625; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73 (d, *J*= 7 Hz, 3H), 6.42 (d, *J*= 7.5 Hz, 1H), 6.55 (q, *J*= 7 Hz, 1H), 6.89 (d, *J*= 7.5 Hz, 1H), 7.28 (m, 5H), 7.50 (m, 2H), 7.61 (ddd, *J*= 1.1, 7, 8.2 Hz, 1H), 8.47 (dd, *J*= 1.1, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 52.1, 106.5, 125.8, 126.0, 126.8, 127.3 (2C), 127.7, 128.0, 128.2, 128.7 (2C), 132.2, 136.5, 140.6, 162.0; MS (CI, isobutane) *m/z* 250 (MH^+), 146, 105; HRMS (CI, isobutane) calcd for $C_{17}H_{16}NO$ (MH^+) 250.1239, found 250.1230.

Preparation of isoquinolinium salts 5a-e from reaction of Grignard reagents with isoquinolinone 7. The preparation of salt 5d is presented as a typical procedure: To a solution of isoquinolinone **7** (200 mg, 0.75 mmol), in anhydrous toluene (4 mL), was added, under stirring, cerium chloride (91 mg, 2.4 mmol). To the resulting suspension was added, after 0.25 h, a THF solution of 4-methoxybenzyl magnesium chloride (0.11 M, 27 mL). After 1 h under vigourous stirring at ambient temperature the resulting mixture was quenched with H_2O (1 mL), followed by treatment with a 16% aqueous solution of HBr. After stirring during 0.5 h at ambient temperature the residue was diluted with H_2O and the resulting aqueous solution washed with EtOAc. The aqueous phase was collected and evaporated under reduced pressure to give crude salt **5d** with was purified by chromatography on silica gel (MeOH / CH_2Cl_2, gradient from 0 / 100 to 5 / 95) to give isoquinolinium salt **5d** as a yellow solid (292 mg, 0.67 mmol, 90% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (d, *J*= 6.9 Hz, 3H), 3.76 (s, 3H), 5.40 (d, *J*= 16.9 Hz, 1H), 5.51 (d, *J*= 17 Hz, 1H), 6.62 (q, *J*= 6.8 Hz, 1H), 6.85 (m, 2H), 7.11 (m, 4H), 7.32 (m, 3H), 8.04 (ddd, *J*= 1.3, 7.1, 8.6 Hz, 1H), 8.15 (ddd, *J*= 1, 7.1, 8.3 Hz, 1H), 8.34 (dd, *J*= 1, 8.2 Hz, 1H), 8.61 (d, *J*= 7.1 Hz, 1H), 8.65 (dd, *J*= 1.3, 8.7 Hz, 1H), 8.69 (d, *J*= 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 34.2, 55.2, 65.3, 114.8 (2C), 126.1, 126.5, 127.3 (2C), 128.2, 128.6, 128.7, 129.3 (2C), 129.3 (2C), 129.4, 132.1, 133.1, 136.1, 136.5, 137.5, 159.0, 159.1; MS (electrospray) *m/z* 354 (M^+), 250.

Isoquinolinium salts 5a-c and 5e were prepared using the same procedure:

Salt 5a: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (d, *J*= 6.7 Hz, 3H), 3.63 (s, 3H), 7.01 (q, *J*= 6.7 Hz, 1H), 7.37 (m, 5H), 7.98 (ddd, *J*= 1.2, 7, 8.3 Hz, 1H), 8.09 (ddd, *J*= 1.1, 7, 8.2 Hz, 1H), 8.19 (dd, *J*= 1.1, 8.3, 1H), 8.47 (d, *J*= 7.1 Hz, 1H), 8.62 (dd, *J*= 1.1, 8.3 Hz, 1H), 8.74 (d, *J*= 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4, 22.1, 66.1, 125.3, 127.0 (2C), 127.8, 128.2, 128.5, 129.2, 129.5 (2C), 131.5, 132.2, 136.4, 136.8, 137.2, 159.4; MS (electrospray) *m/z* 248 (M^+), 143, 105.

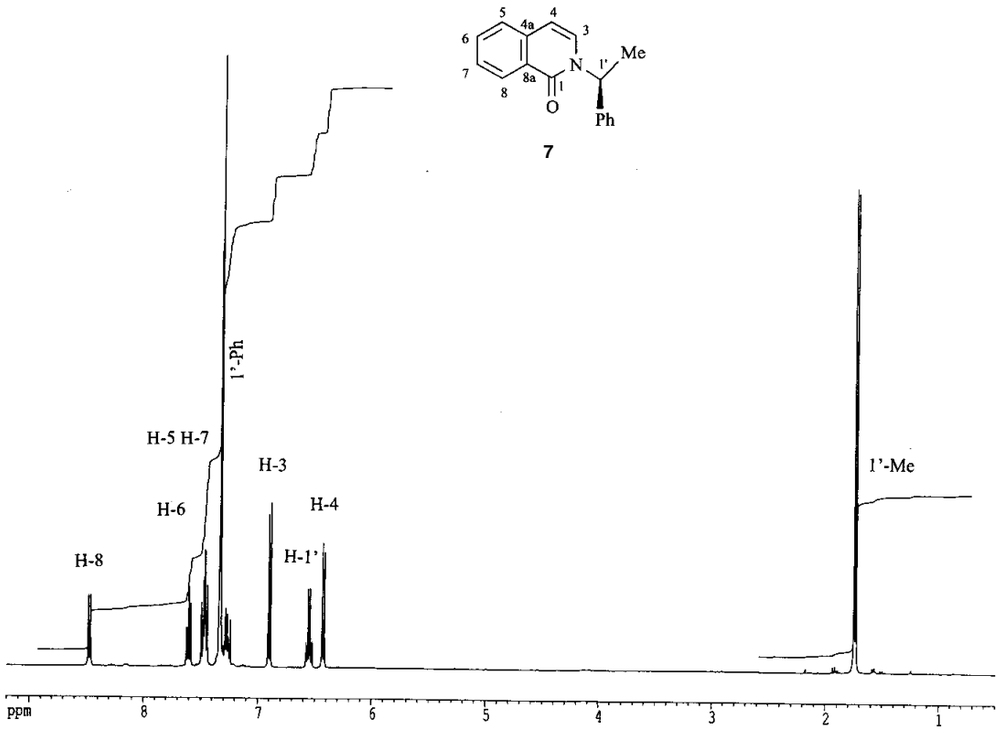
Salt 5b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (d, *J*= 7 Hz, 3H), 6.03 (q, *J*= 7 Hz, 1H), 7.35 (m, 5H), 7.46 (m, 1H), 7.62 (dd, *J*= 1.1, 8.3 Hz, 1H), 7.81 (m, 5H), 8.13 (ddd, *J*= 1.1, 7.1, 8.3 Hz, 1H), 8.4 (dd, *J*= 1.1, 8.3 Hz, 1H), 9.00 (d, *J*= 7.1 Hz, 1H), 9.16 (d, *J*= 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4, 22.1, 66.1, 125.3, 127.00 (2C), 127.8, 128.2, 128.5, 129.2, 129.5 (2C), 131.5, 132.2, 136.4, 136.8, 137.2, 159.4; MS (electrospray) *m/z* 310 (M^+), 206.

Salt 5c: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (d, *J*= 6.9 Hz, 3H), 3.63 (s, 3H), 5.35 (d, *J*= 17.1 Hz, 1H), 5.49 Hz (d, *J*= 17.1 Hz, 1H), 6.51 (m, 2H), 6.75 (m, 2H), 7.09 (m, 6H), 7.92 (ddd, *J*= 1.1, 7.3, 8.2 Hz, 1H), 8.04 (ddd, *J*= 1.2, 7.1, 8.3 Hz, 1H), 8.23 (dd, *J*= 1.1, 8.3 Hz, 1H), 8.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 35.0, 55.3, 65.4, 113.0, 114.4, 120.1, 126.5, 127.3 (2C), 128.2, 128.5, 128.6, 129.2 (2C), 129.2, 129.3, 130.3, 132.1, 133.0, 135.7, 136.0, 136.5, 137.3, 158.6, 160.1; MS (electrospray) *m/z* 354 (M^+), 206.

Salt 5e: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.11 (d, *J*= 6.9 Hz, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 5.48 (d, *J*= 1.7 Hz, 1H), 5.62 (d, *J*= 17 Hz, 1H), 6.33 (dd, *J*= 2.1, 8.2 Hz, 1H), 6.69 (m, 2H), 7.15 (m, 2H), 7.20 (d, *J*= 1.9 Hz, 1H), 7.31 (m, 3H), 8.02 (ddd, *J*= 1.3, 7.1, 8.6 Hz, 1H), 8.14 (ddd, *J*= 0.9, 7.1, 8.1 Hz, 1H), 8.59 (d, *J*= 7.1 Hz, 1H), 8.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 34.5, 56.0, 56.3, 65.6, 111.6, 112.3, 120.1, 126.6, 127.0, 127.5 (2C), 128.4, 128.8, 128.9, 129.5 (2C), 129.6, 132.2, 133.1, 136.4, 136.7, 137.6, 148.7, 149.9, 159.4; MS (electrospray) *m/z* 384 (M^+), 250.

Preparation of isoquinoline (+)-6d by borohydride reduction of salt 5d as a typical procedure for preparation of isoquinolines 6: To a solution of isoquinolinium salt **5d** (490 mg, 1.1 mmol), in MeOH (10 mL), was added portionwise, at ambient temperature during 1 h, an excess of sodium borohydride (200 mg). To the resulting mixture was added H_2O (100 mL) and the product was extracted with Et_2O (3x100 mL). Usual work-up gave a mixture of isomers **6d** and **8d** as a pale yellow oil (380 mg, 95% yield) and in a 91/9 ratio respectively as determined by GC analysis and integration of methyl signals in the ^{1}H NMR spectrum (*vide infra* for a copy of this spectrum). Chromatography over silica gel (AcOEt/pentane) furnished a pure sample of major isoquinoline **(+)-6d** for analysis: $[\alpha]_D$ +12 (c=0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (d, *J*= 6.5 Hz, 3H), 2.54 (m, 1H), 2.69 (dd, *J*= 6.3, 13.6 Hz, 1H), 2.93 (m, 1H), 3.03 (dd, *J*= 7.5, 13.6, 1H), 3.25 (m, 1H), 3.75 (m, 5H), 6.59 (d, *J*= 7.5 Hz, 1H), 6.76 (d, *J*= 8.7 Hz, 2H), 6.85 (d, *J*= 8.6 Hz, 2H), 7.00 (m, 3H), 7.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 24.0, 39.5, 41.7, 55.3, 59.1, 61.00, 113.2, 125.2, 125.9, 126.4, 127.4 (2C), 128.1, 128.6, 128.8, 130.7, 132.1, 134.9, 138.1, 146.0, 157.8; HRMS (CI, isobutane) calcd for $C_{25}H_{28}NO$ (MH^+) 358.2181, found 358.2192.

Isoquinolines (+)-**6a**, (+)-**6b**, (+)-**6c** and (+)-**6e** were authentified by comparison with the corresponding (–)-enantiomers previously prepared in our laboratory.[Error! Bookmark not defined.]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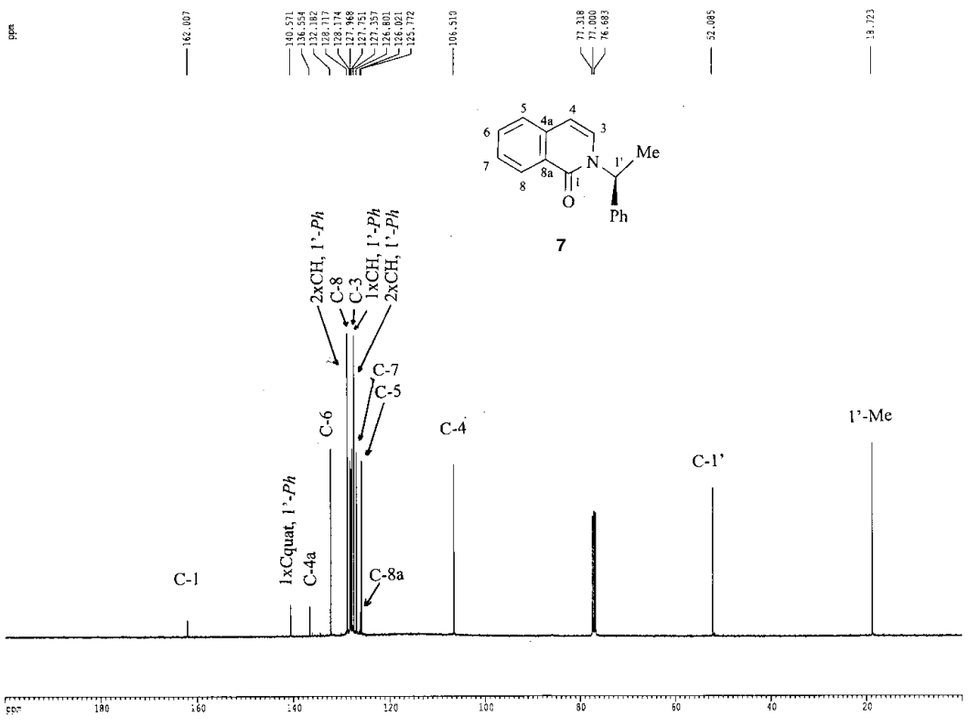
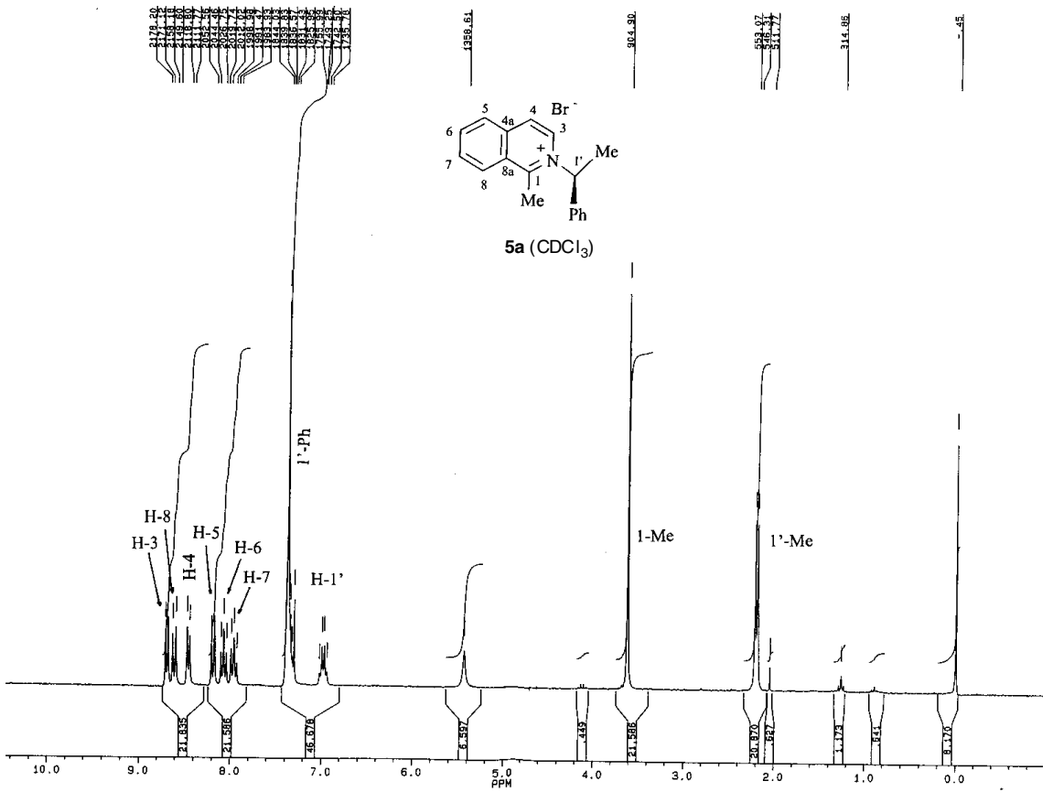
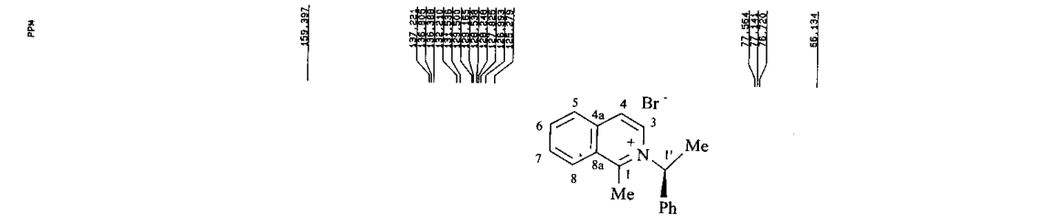
H-8
H-6
H-5 H-7
1'-Ph
H-3
H-4
H-1'
1'-Me
ppm

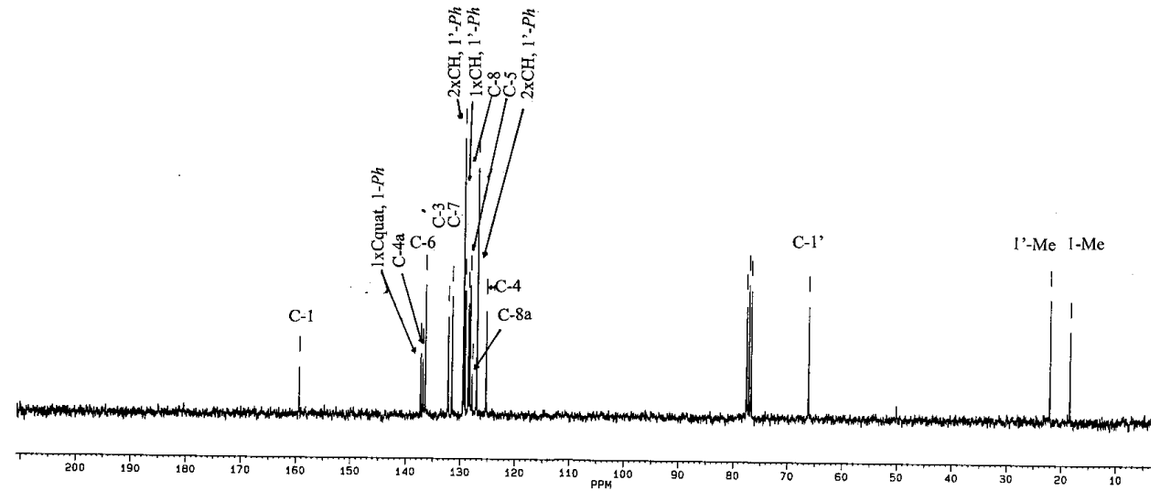

7
2xCH, 1'-Ph
C-8
C-3
1xCH, 1'-Ph
2xCH, 1'-Ph
C-7
C-5
C-6
C-4
C-1'
1'-Me
1xCquat, 1'-Ph
C-4a
C-1
C-8a

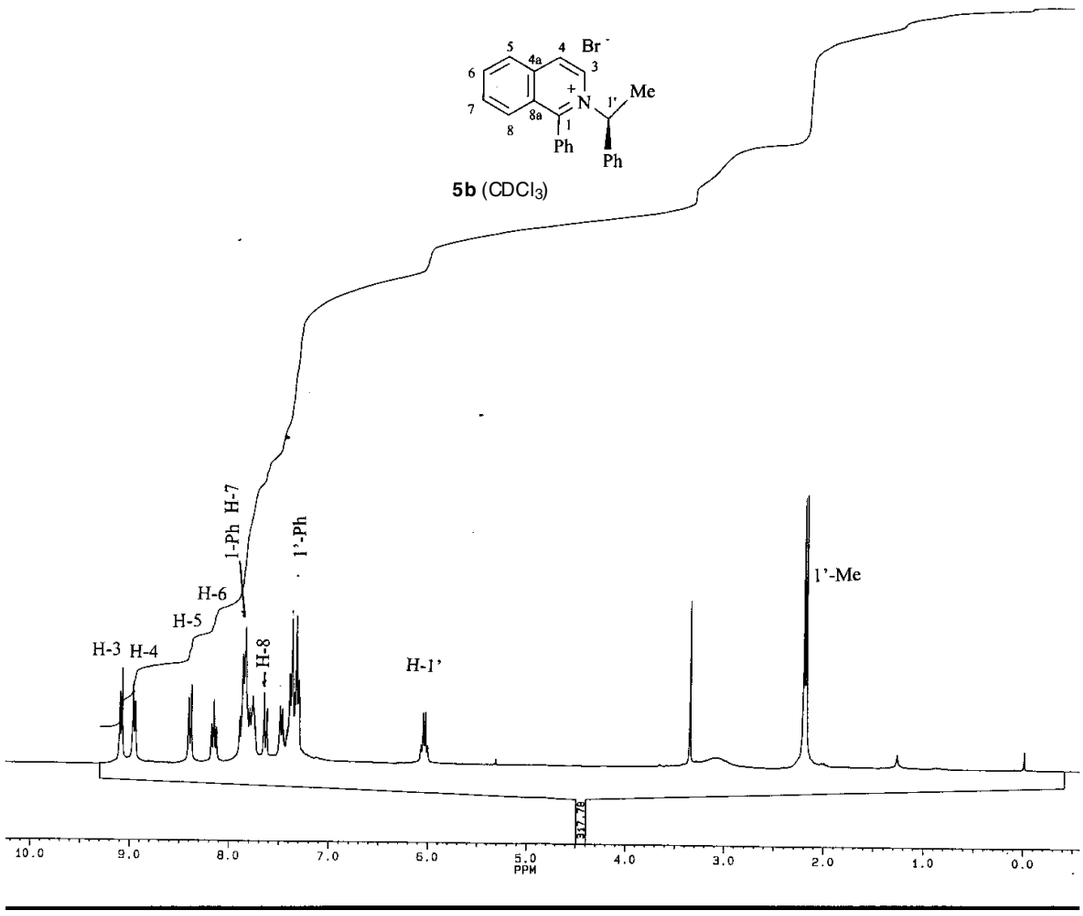


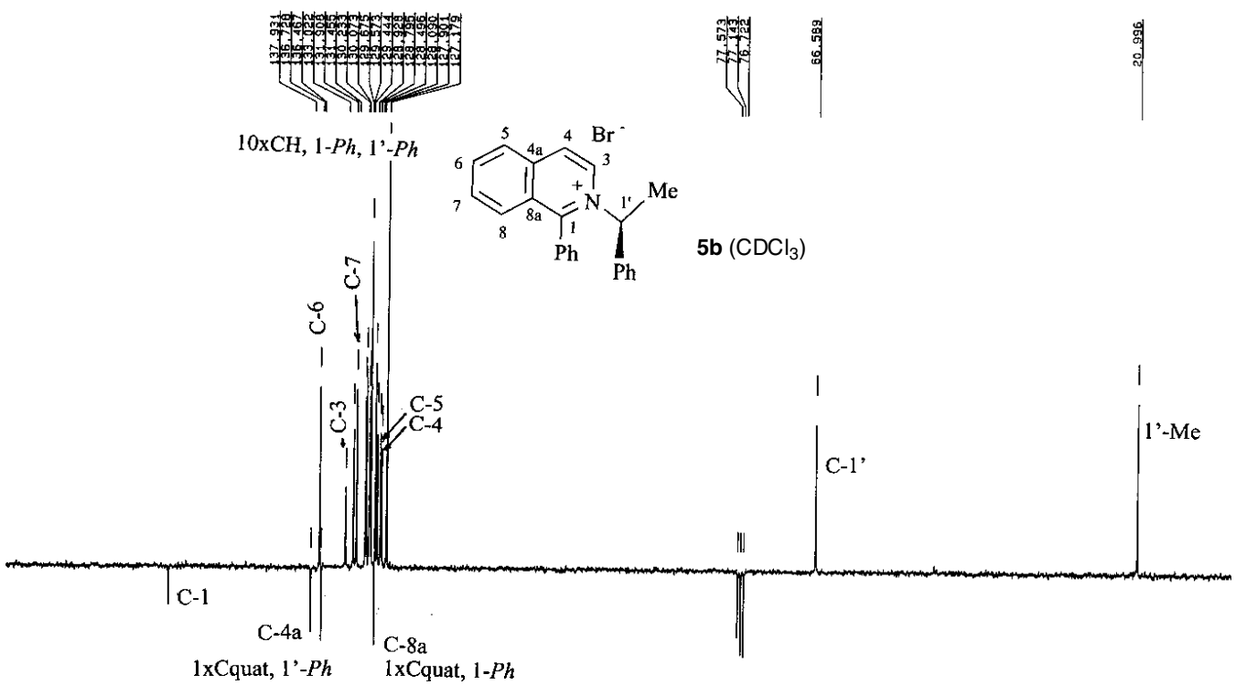
5a ($CDCl_3$)

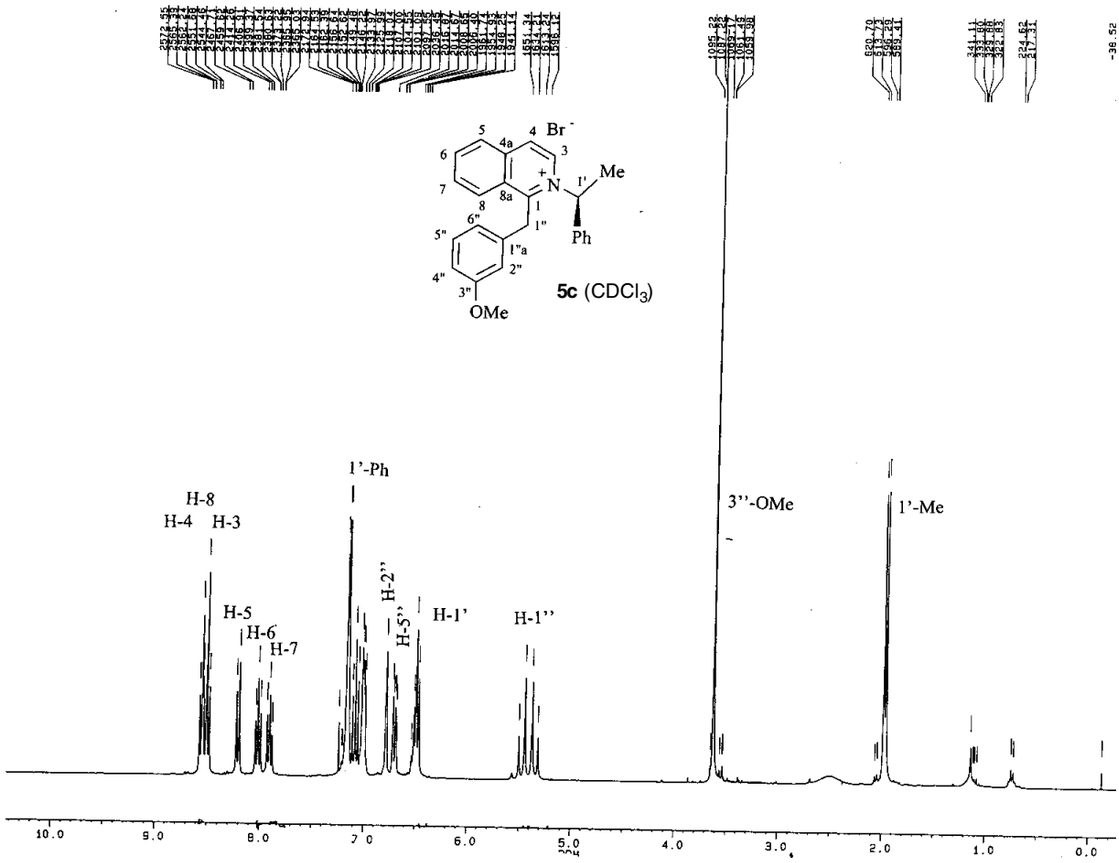


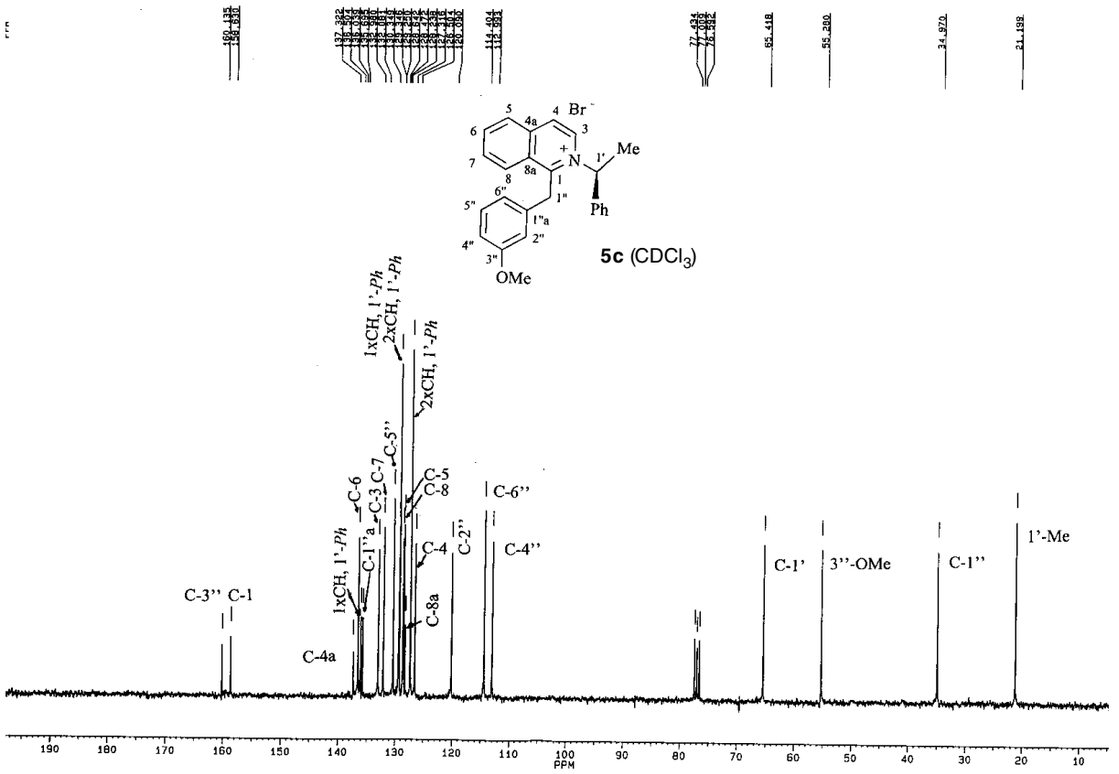
5a ($CDCl_3$)

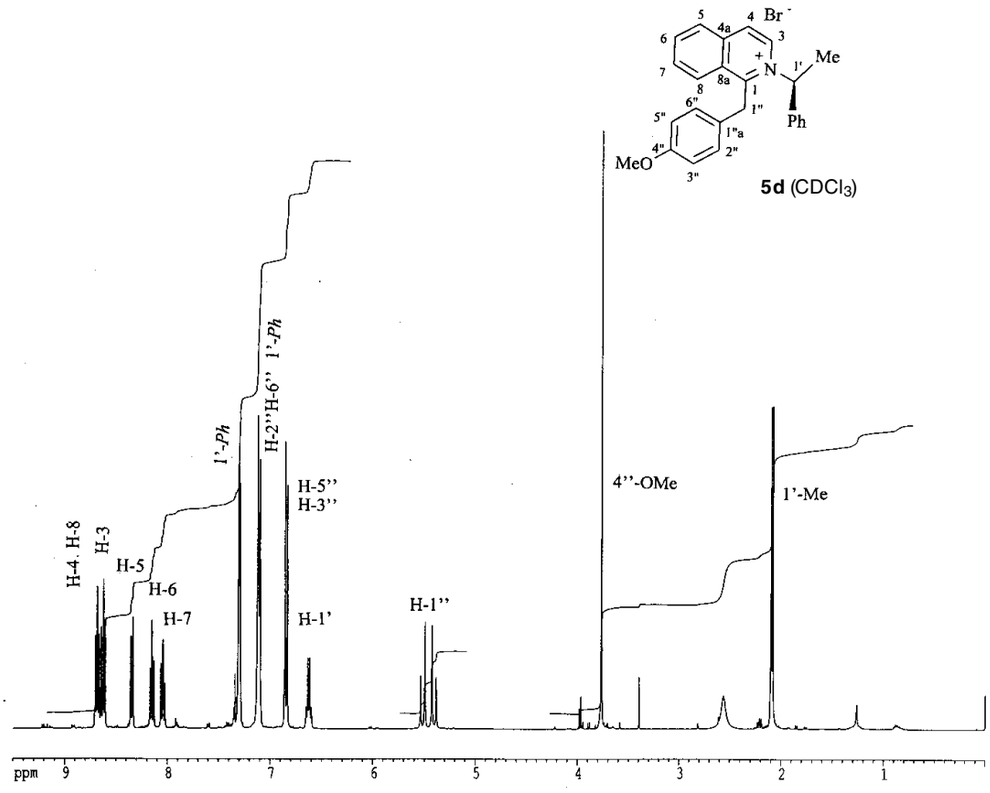


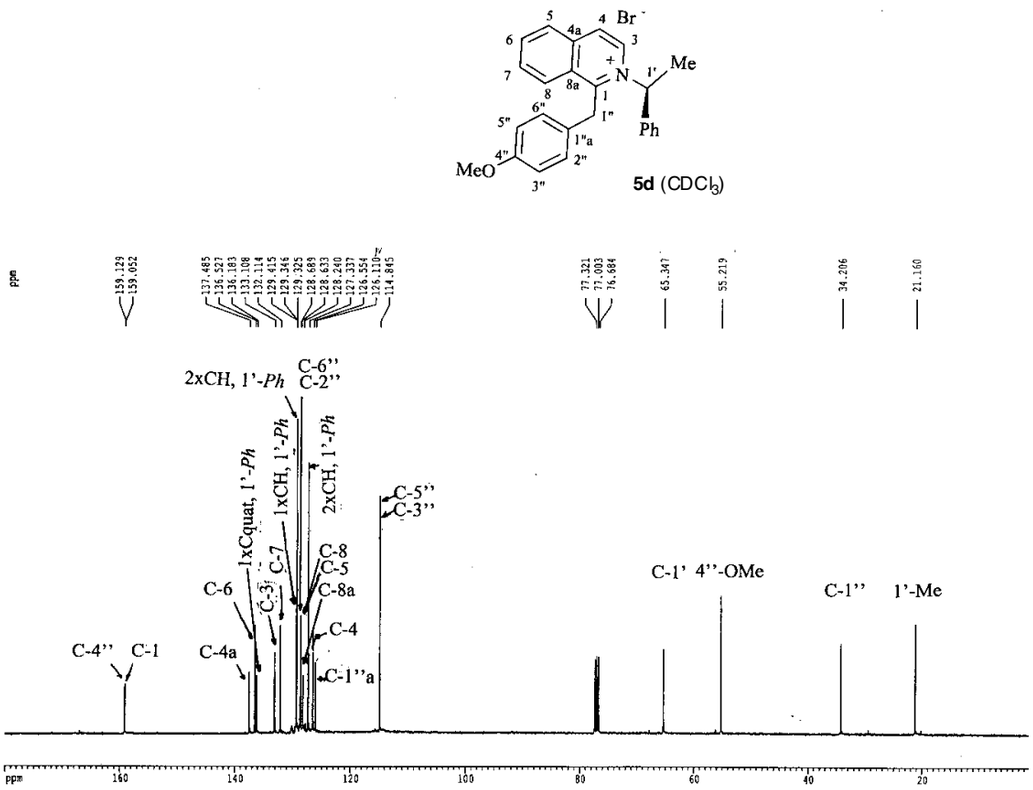

5b (CDCl3)
1-Ph H-7
1'-Ph
H-6
H-5
H-3 H-4
H-8
H-1'
1'-Me
317.78
10.0
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0

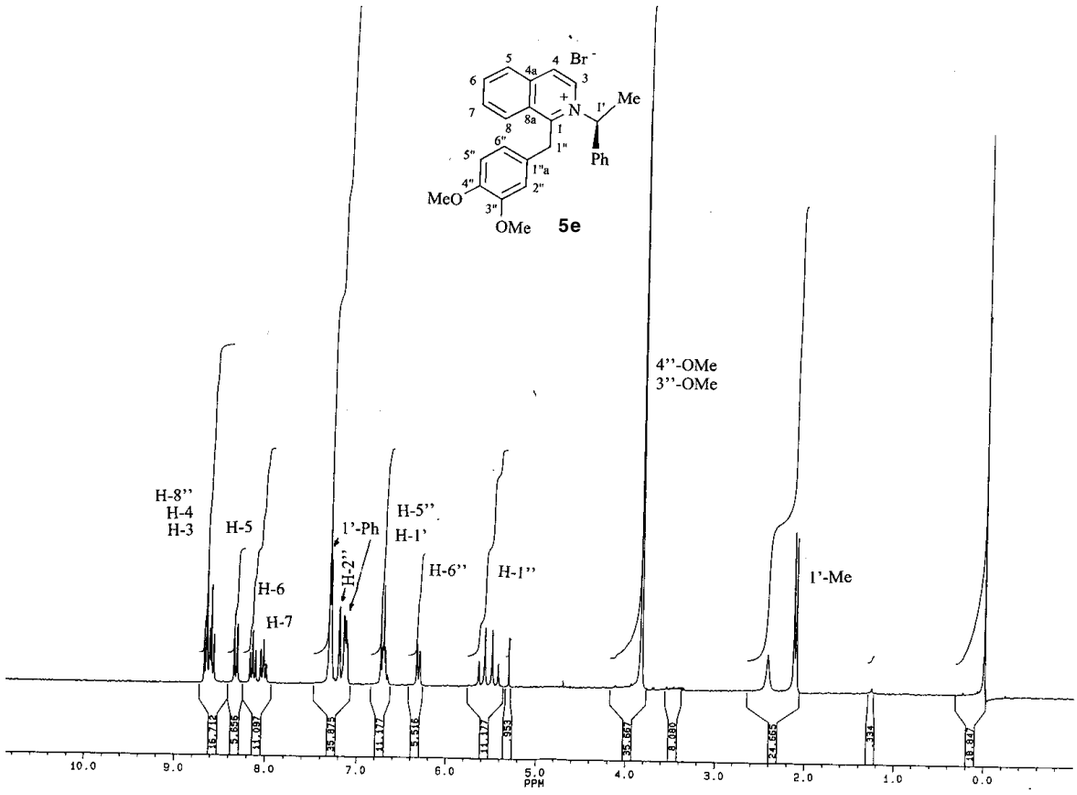

10xCH, 1-Ph, 1'-Ph
5b (CDCl3)
C-6
C-7
C-3
C-5
C-4
C-1'
1'-Me
C-1
C-4a
C-8a
1xCquat, 1'-Ph
1xCquat, 1-Ph

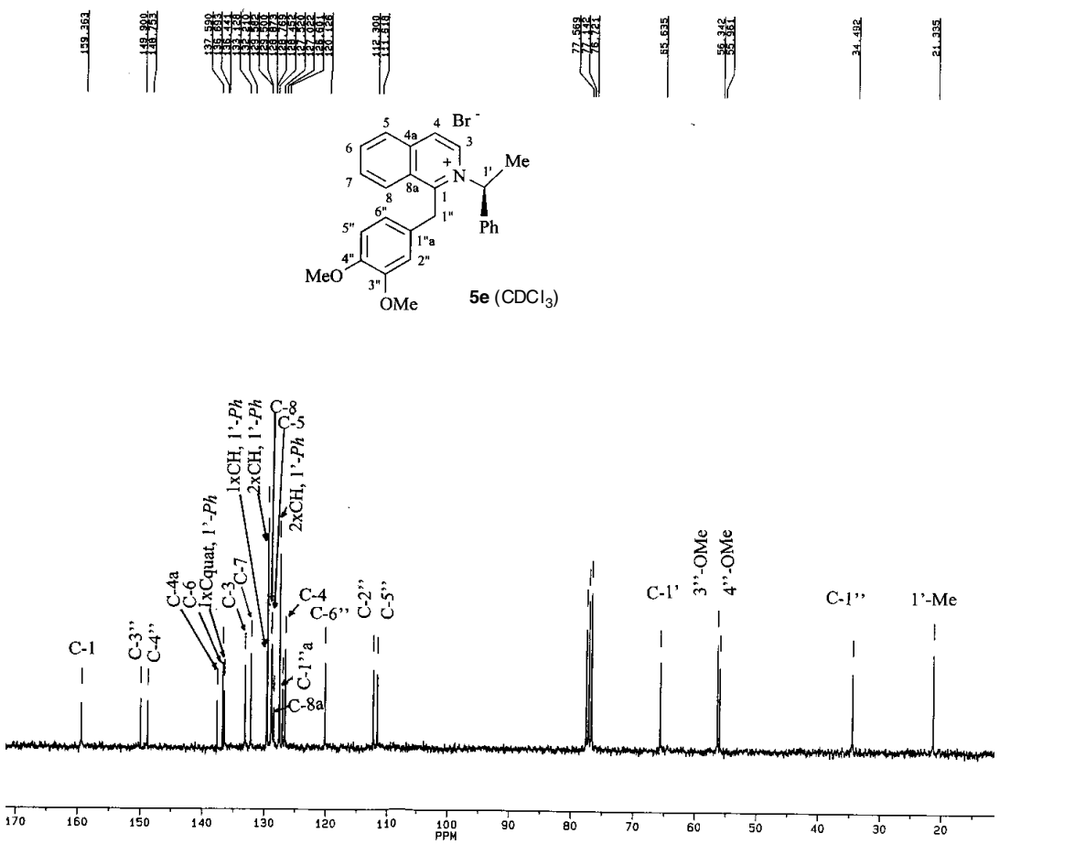

5 4a 4 Br⁻
6 3
7 8a N 1' Me
8 1
6" 1"
5" 1"a Ph
4" 2"
3" OMe
5c (CDCl3)
H-8
H-4 H-3
H-5
H-6
H-7
1'-Ph
H-2''
H-5''
H-1'
H-1''
3''-OMe
1'-Me
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

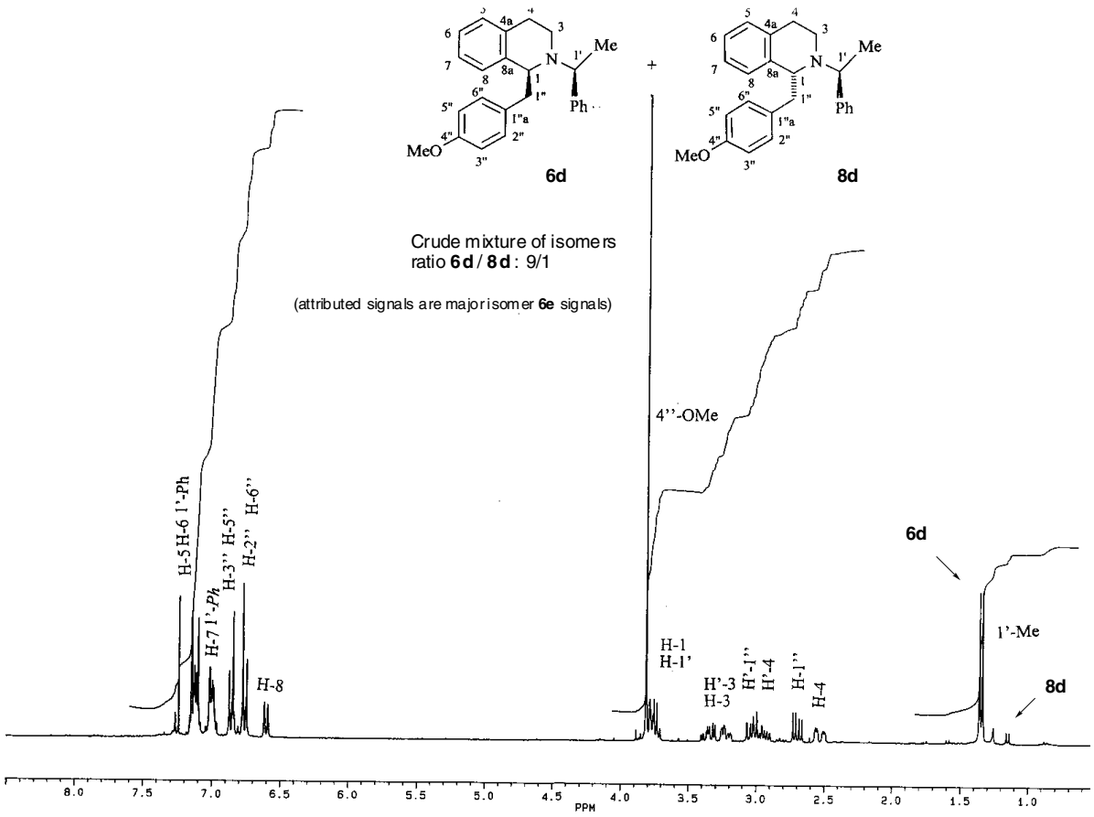

5 4a 4 Br⁻
6 3
7 8a N 1' Me
8 1
6" 1"
5" 1"a Ph
4" 2"
3" OMe
5c (CDCl3)
1xCH, 1'-Ph
2xCH, 1'-Ph
2xCH, 1'-Ph
C-6
C-3
C-7
C-5''
C-5
C-8
C-1''a
C-4
C-2''
C-6''
C-4''
C-8a
C-4a
C-3'' C-1
C-1'
3''-OMe
C-1''
1'-Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
PPM

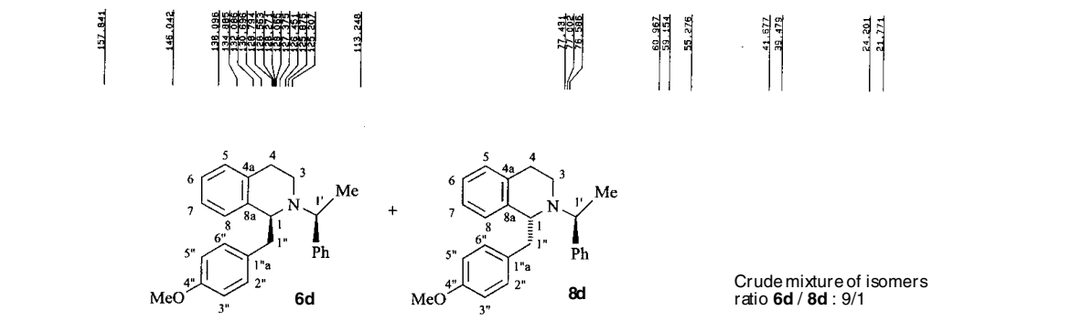

5d (CDCl3)
H-4. H-8
H-3
H-5
H-6
H-7
1'-Ph
H-2'' H-6'' 1'-Ph
H-5''
H-3''
H-1'
H-1''
4''-OMe
1'-Me
ppm

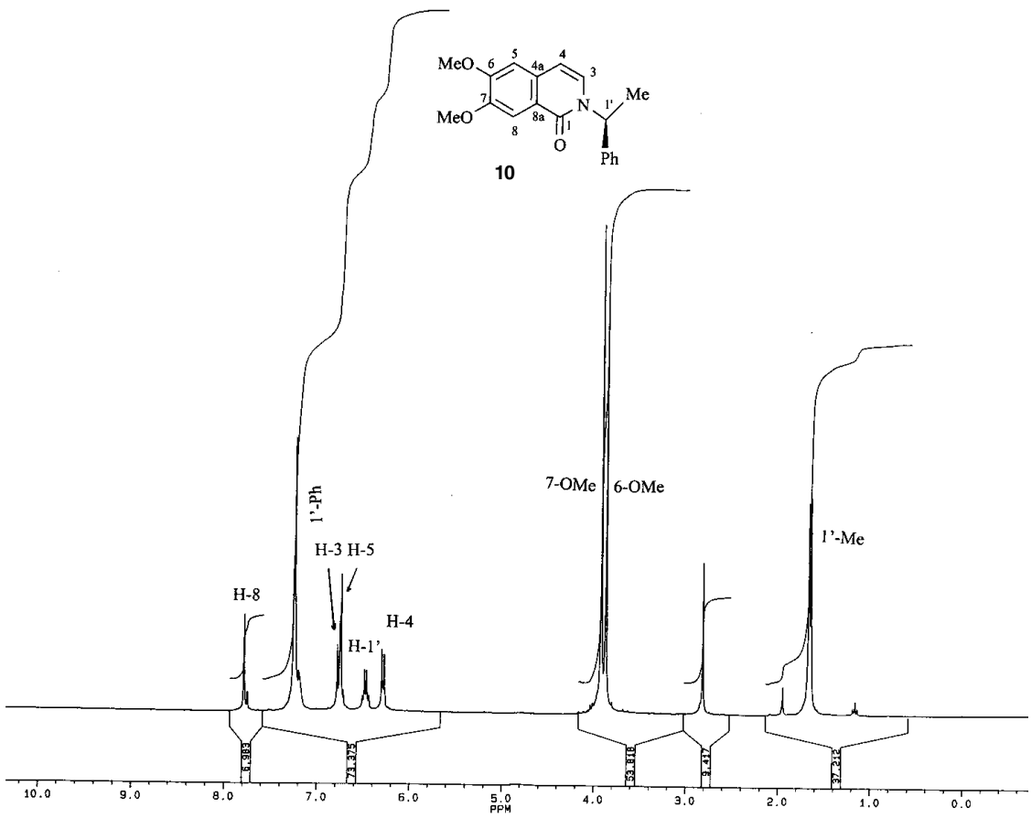

5d (CDCl3)
2xCH, 1'-Ph
C-6''
C-2''
1xCquat, 1'-Ph
1xCH, 1'-Ph
2xCH, 1'-Ph
C-5''
C-3''
C-7
C-8
C-5
C-6
C-3
C-8a
C-4
C-4''
C-1
C-4a
C-1''a
C-1' 4''-OMe
C-1''
1'-Me
ppm

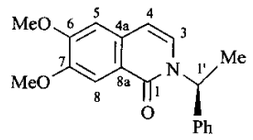

5e
H-8''
H-4
H-3
H-5
H-6
H-7
1'-Ph
H-2''
H-5''
H-1'
H-6''
H-1''
4''-OMe
3''-OMe
1'-Me
PPM


5e (CDCl3)
C-1
C-3''
C-4''
C-4a
C-6
1xCquat, 1'-Ph
C-3
C-7
1xCH, 1'-Ph
2xCH, 1'-Ph
C-8
C-5
2xCH, 1'-Ph
C-4
C-6''
C-2''
C-5''
C-1''a
C-8a
C-1'
3''-OMe
4''-OMe
C-1''
1'-Me
PPM


6d
8d
Crude mixture of isomers
ratio 6d / 8d : 9/1
(attributed signals are major isomer 6e signals)
H-5 H-6 1'-Ph
H-7 1'-Ph
H-3'' H-5''
H-2'' H-6''
H-8
4''-OMe
H-1
H-1'
H'-3
H-3
H'-1''
H'-4
H-1''
H-4
6d
1'-Me
8d
PPM


6d
8d
Crude mixture of isomers
ratio 6d / 8d : 9/1
(attributed signals are major isomer 6d signals
note that isomer 8d signals are not clearly visible)
C-2'', C-6''
2xCH, 1'-Ph
C-5''
C-3''
1xCH, 1'-Ph
C-8
C-7
C-5
C-6
C-4''
1xCquat, 1'-Ph
C-8a
C-4a
C-1''a
C-1
C-1'
4''-OMe
C-1''
C-3
C-4
1'-Me
PPM


MeO
MeO
Me
Ph
10
H-8
H-3 H-5
H-4
H-1'
1'-Ph
7-OMe
6-OMe
1'-Me
PPM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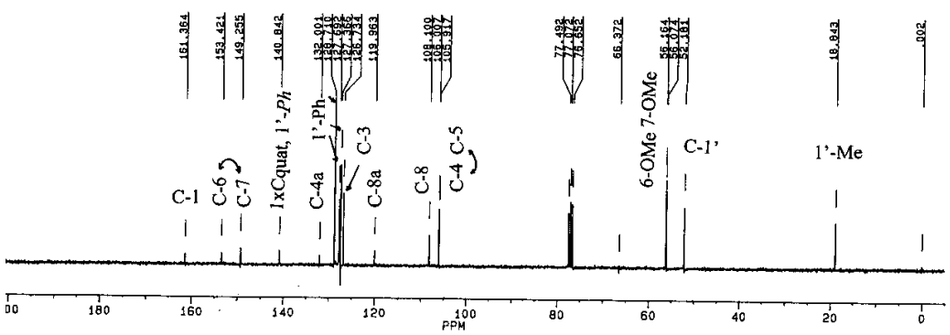
MeO
Me
Ph
10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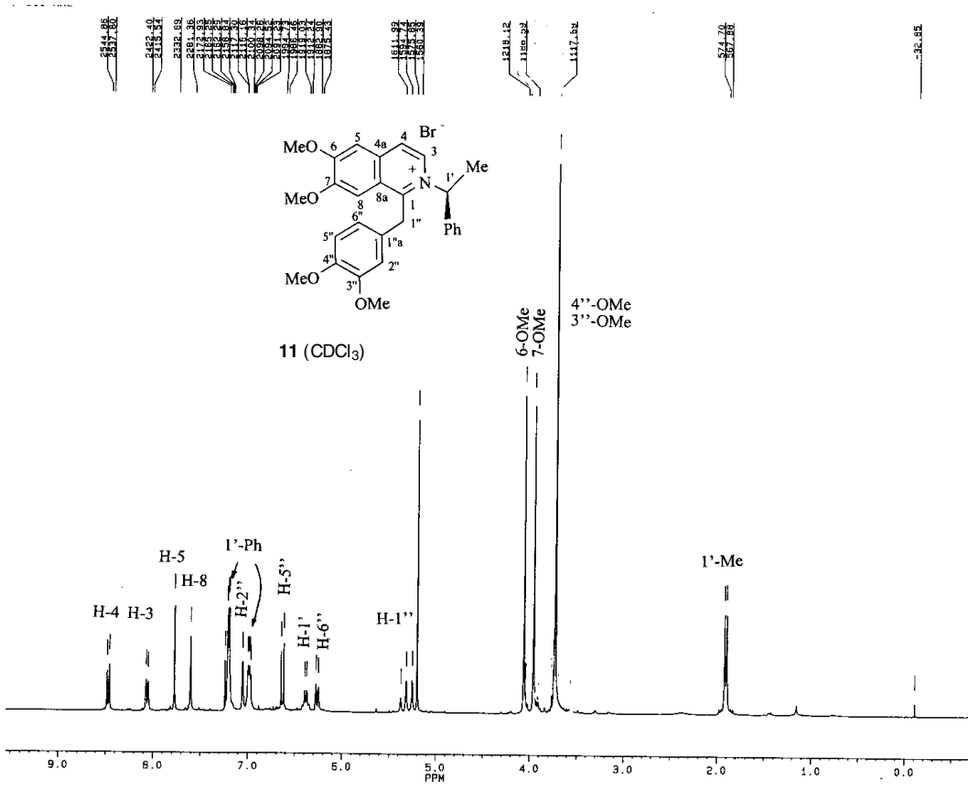
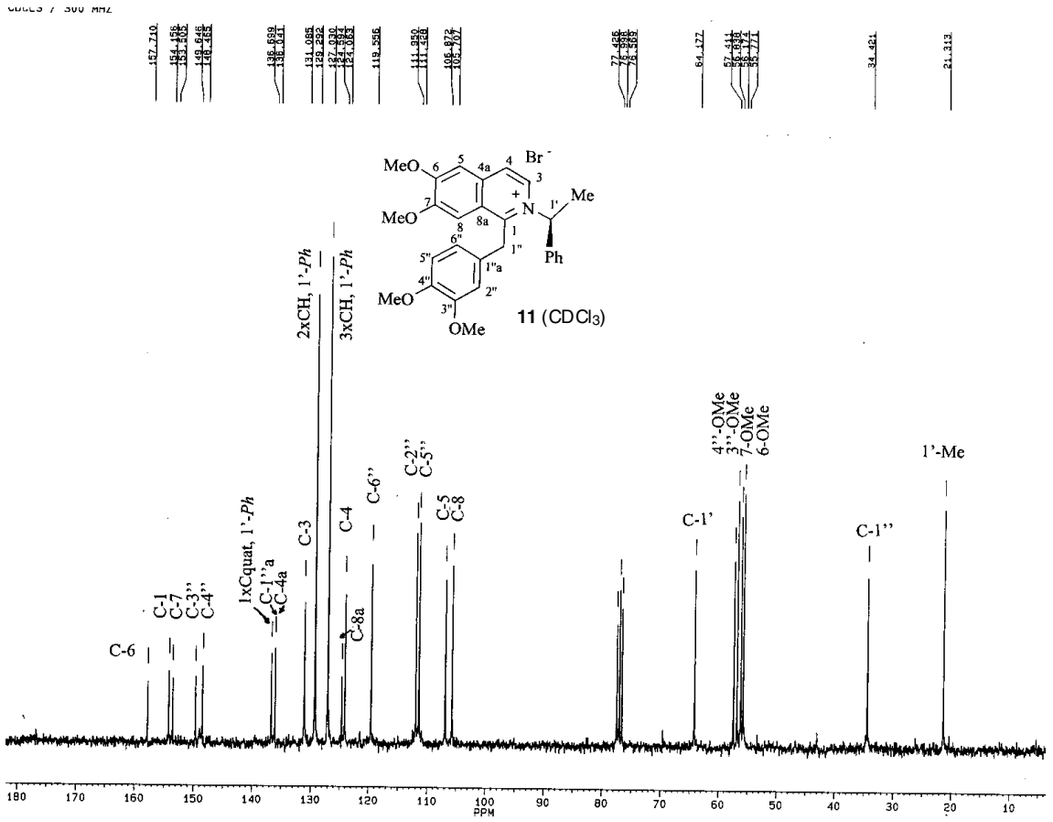
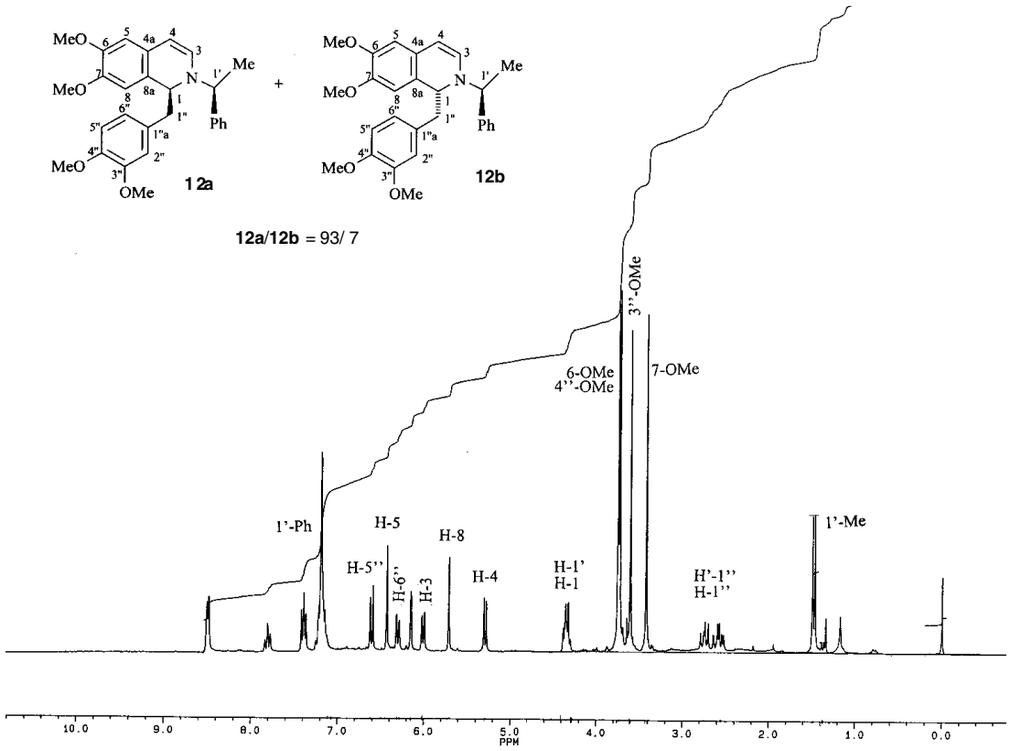
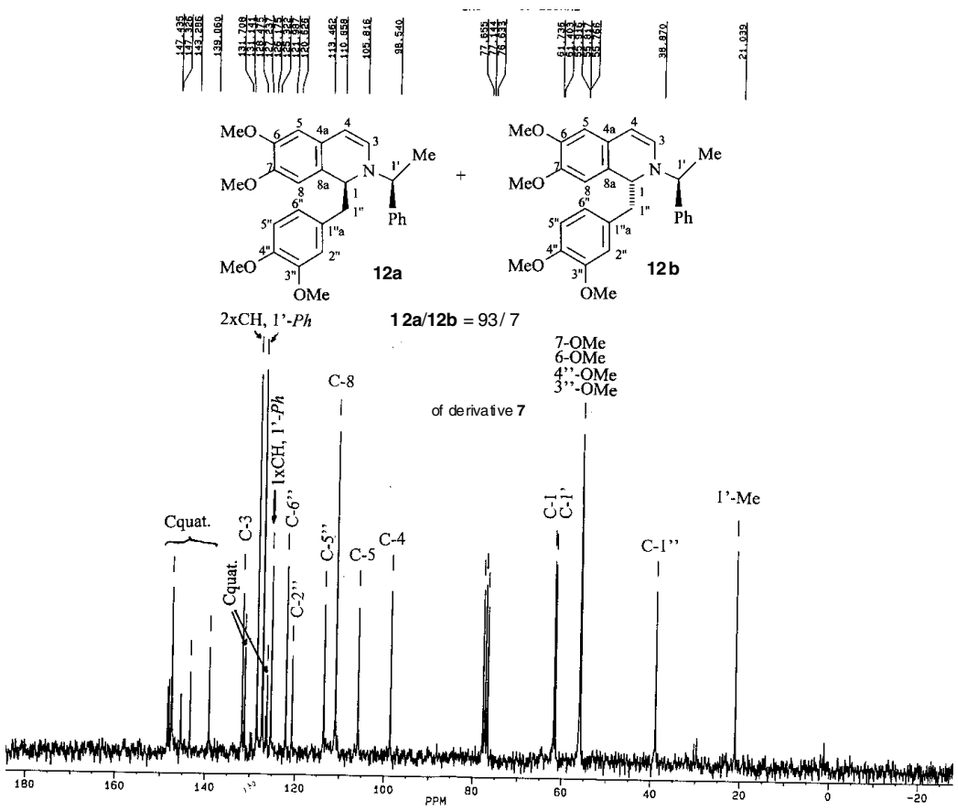
C-6
C-7
1xCquat, 1'-Ph
C-4a
1'-Ph
C-3
C-8a
C-8
C-4 C-5
6-OMe 7-OMe
C-1'
1'-Me
PPM

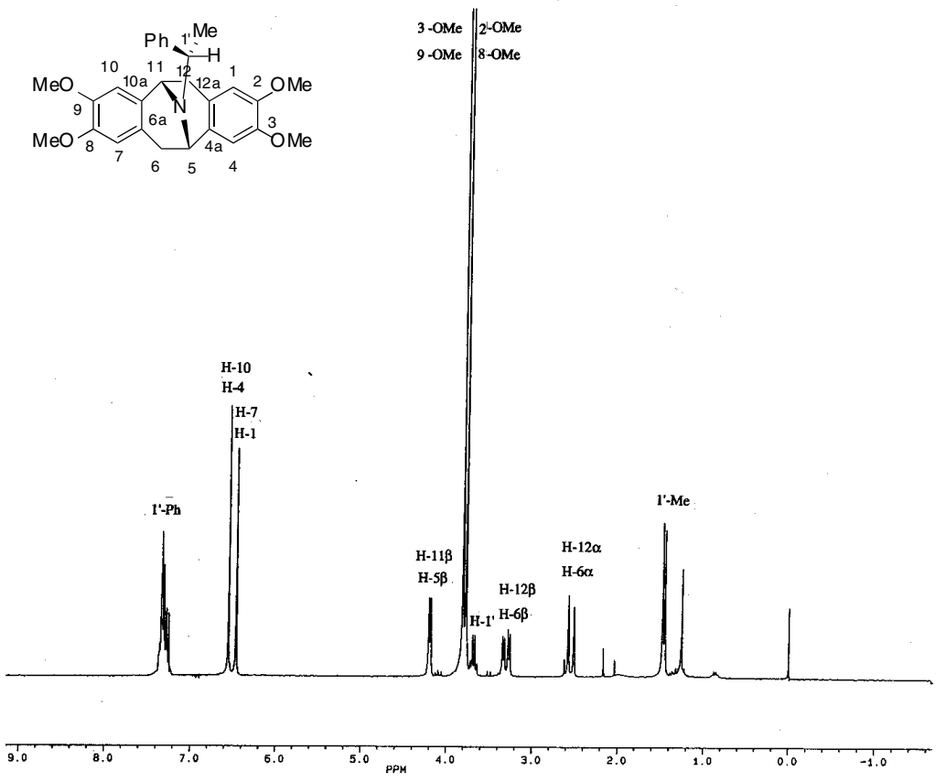

MeO
MeO
MeO
OMe
Br
Me
Ph
11 (CDCl3)
H-4
H-3
H-5
H-8
1'-Ph
H-2''
H-5''
H-1'
H-6''
H-1''
6-OMe
7-OMe
4''-OMe
3''-OMe
1'-Me
PPM

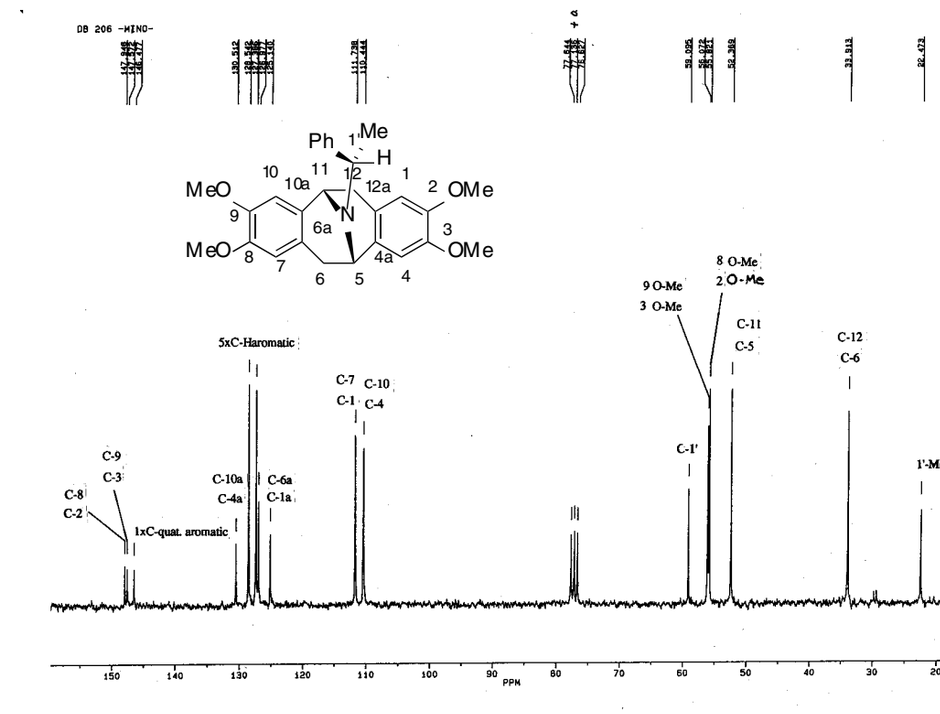

MeO
MeO
MeO
OMe
Br
Me
Ph
11 (CDCl3)
2xCH, 1'-Ph
3xCH, 1'-Ph
1xCquat, 1'-Ph
C-6
C-1
C-7
C-3''
C-4''
C-1''a
C-4a
C-3
C-4
C-8a
C-6''
C-2''
C-5''
C-5
C-8
C-1'
4''-OMe
3''-OMe
7-OMe
6-OMe
C-1''
1'-Me
PPM


12a
12b
12a/12b = 93/ 7
3''-OMe
6-OMe
4''-OMe
7-OMe
1'-Ph
H-5
H-8
H-5''
H-6''
H-3
H-4
H-1'
H-1
H'-1''
H-1''
1'-Me
PPM

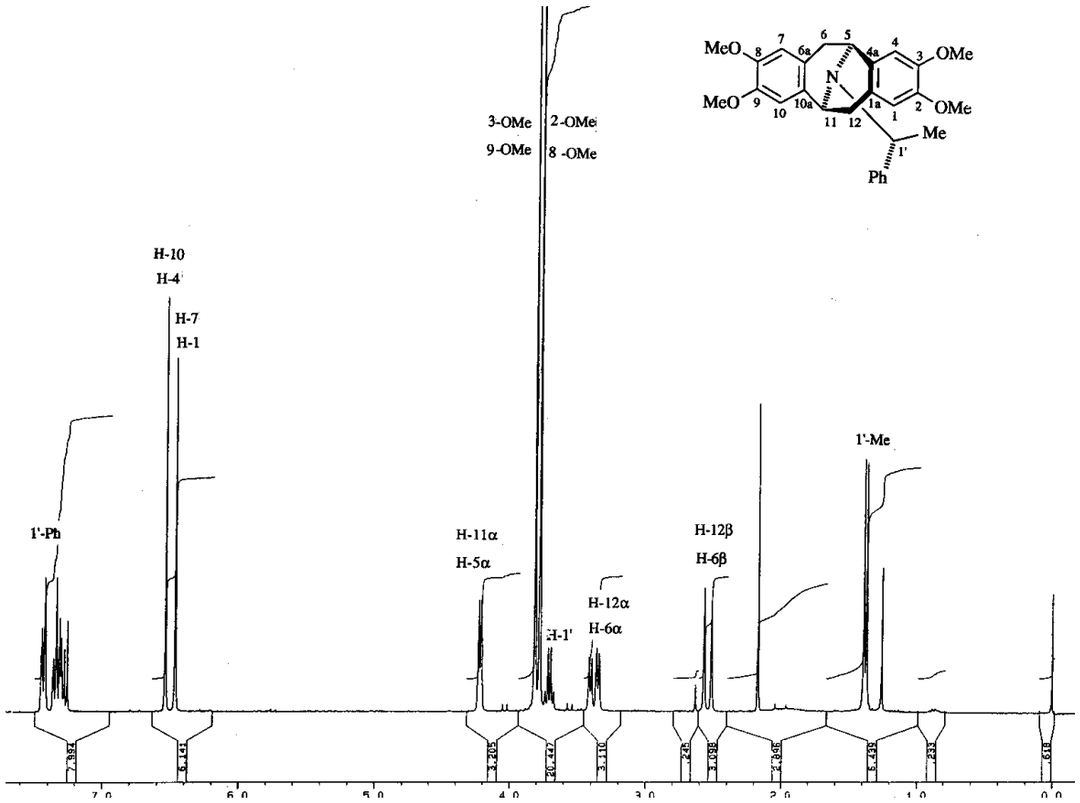

12a
12b
2xCH, 1'-Ph
12a/12b = 93/ 7
7-OMe
6-OMe
4''-OMe
3''-OMe
of derivative 7
C-8
1xCH, 1'-Ph
Cquat.
C-3
C-6''
C-5''
C-5
C-4
C-2''
C-1
C-1'
C-1''
1'-Me
PPM

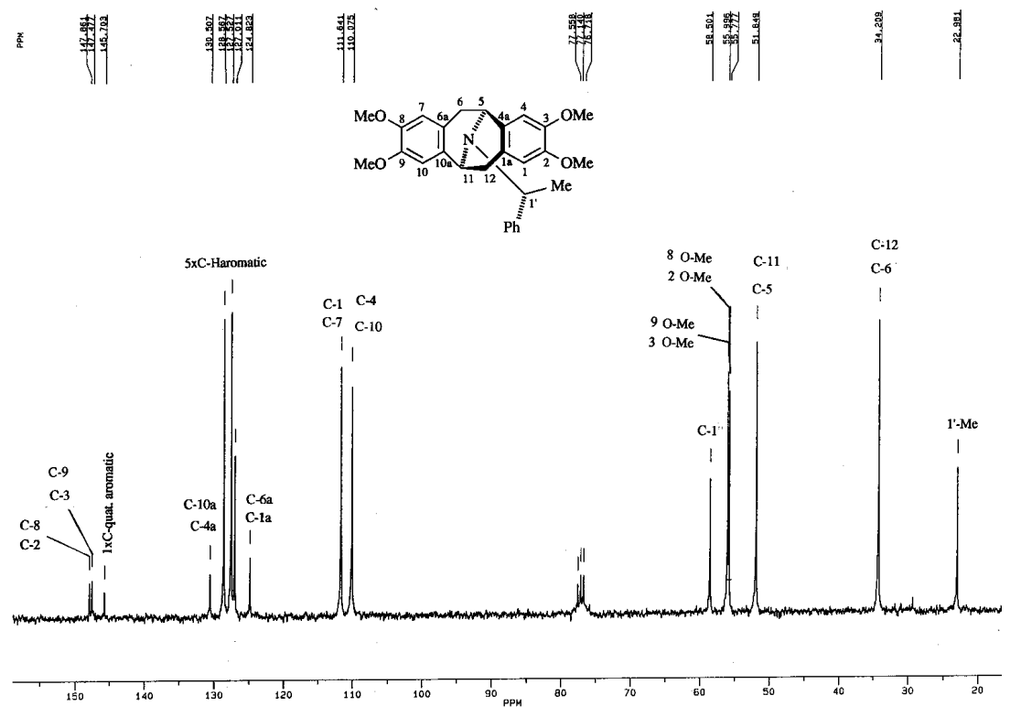
(–)-13a

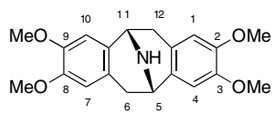

Ph
1'
Me
H
10
11
12
1
10a
12a
2
OMe
MeO
9
6a
N
3
OMe
MeO
8
7
4a
6
5
4
3-OMe
2-OMe
9-OMe
8-OMe
H-10
H-4
H-7
H-1
1'-Ph
H-11β
H-5β
H-12β
H-6β
H-1'
H-12α
H-6α
1'-Me
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
PPM


DB 206 -MINO-
Ph
1'
Me
H
10
11
12
1
10a
12a
2
OMe
MeO
9
6a
N
3
OMe
MeO
8
7
4a
6
5
4
8 O-Me
2 O-Me
9 O-Me
3 O-Me
C-11
C-5
C-12
C-6
5xC-Haromatic
C-7
C-1
C-10
C-4
C-1'
C-9
C-3
C-8
C-2
C-10a
C-4a
C-6a
C-1a
1'-Me
1xC-quat. aromatic
150
140
130
120
110
100
90
80
70
60
50
40
30
20
PPM

(–)-**13b**


MeO
MeO
OMe
OMe
Me
Ph
3-OMe
9-OMe
2-OMe
8 -OMe
H-10
H-4
H-7
H-1
1'-Ph
H-11α
H-5α
H-1'
H-12α
H-6α
H-12β
H-6β
1'-Me

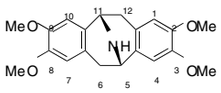

5xC-Haromatic
C-1
C-7
C-4
C-10
8 O-Me
2 O-Me
9 O-Me
3 O-Me
C-11
C-5
C-12
C-6
C-1''
1'-Me
C-9
C-3
C-8
C-2
1xC-quat. aromatic
C-10a
C-4a
C-6a
C-Ia
PPM


MeO
OMe
MeO
OMe
NH
1
2
3
4
5
6
7
8
9
10
11
12

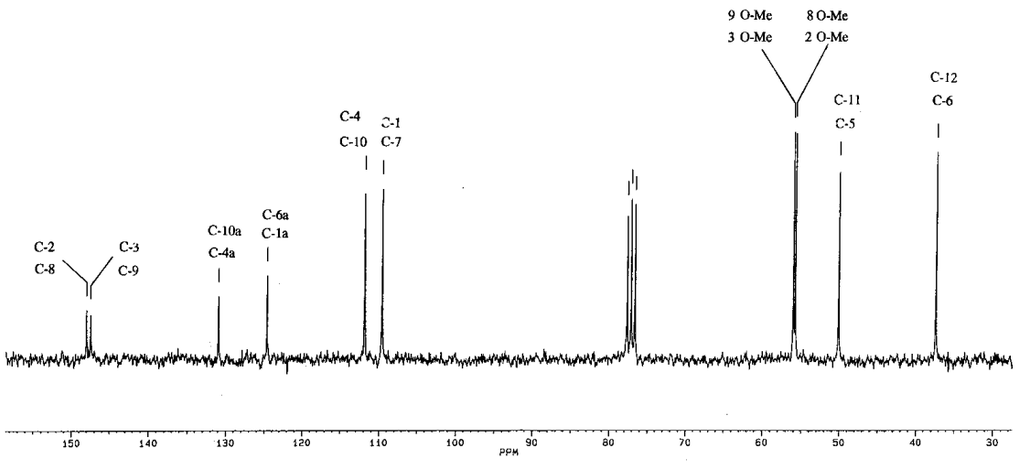
14

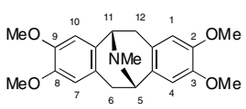
3-OMe
9-OMe
2-OMe
8-OMe
H-5α
H-11α
H-4
H-10
H-7
H-1
H-6α
H-12α
H-6β
H-12β
N-H
INTEGRAL
PPM


PPM

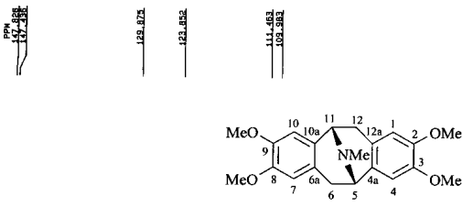

MeO
OMe
MeO
OMe
NH

14


9 O-Me
3 O-Me
8 O-Me
2 O-Me
C-12
C-6
C-11
C-5
C-4
C-10
C-1
C-7
C-6a
C-1a
C-10a
C-4a
C-2
C-8
C-3
C-9
PPM



(—)-argemonine



(—)-argemonine