Total Synthesis of Hyacinthacine A2: Stereocontrolled 5-aza-cyclooctene Photoisomerization and Transannular Hydroamination with Planar-to-Point Chirality Transfer

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Supporting Information

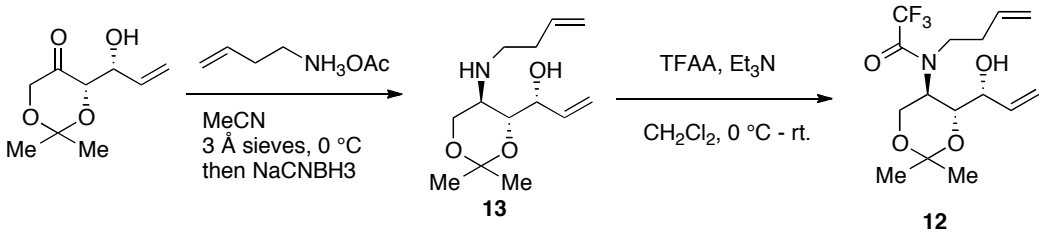
General Considerations

In addition to general cleaning procedures, quartz glassware for photoisomerizations were rinsed with concentrated nitric acid and then distilled water to remove any metal contamination from the glass surface. Photoisomerizations were performed using laboratory grade ethyl ether (Fisher Scientific cat # E134-4) and hexanes (Fisher Scientific cat # H292-4). Silica gel was purchased from Silicycle, 60 Å (cat # R12030B). The abbreviation 'app' stands for apparent (e.g. 'app t' = apparent triplet). For ^{13}C NMR, multiplicities were distinguished using a APT pulse sequence: typical methylene and quartenary carbons appear 'up' (u); methine and methyl carbons 'down' (dn). Reagents were used directly as purchased from commercial sources. Silver impregnated silica was prepared using the procudure described previously.[2]

Homoallylamine hydroacetate

To a stirring solution of 1-[*N,N*-Bis(trimethylsilyl)amino]-but-3-ene[1] (19.69 g, 91.3 mmol) in methanol (10mL) was added glacial acetic acid (5.8 mL, 100 mmol) at room temperature. The solution was allowed to stir for 1 hour at room temperature, and then the methanol solution was extracted with hexanes. The methanol solution was then concentrated under reduced pressure to yield 12.75 grams of an orange oil. ^{1}H NMR

analysis indicated that this oil was an 87:13 (weight ratio) of homoallylamine hydroacetate: methanol. The yield of homoallylamine hydroacetate was 93% (85 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): 6.98 (s, br, 3H), 5.83-7.83 (m, 1H), 5.20-5.13 (m, 2H), 2.91 (t, *J*= 7.4 Hz, 2H), 2.39 (app q, *J*= 7.1 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.2 (u), 133.5 (dn), 118.2 (u), 38.9 (u), 32.8 (u), 23.8 (dn).



To a dry 100 mL round-bottomed flask equipped with a magnetic stir bar was added[2] 0.93 g, 5.00 mmol), activated 3 Å molecular sieves (0.93 g, 100 wt%), 4-buten-1-amine hydroacetate (1.31 g, 10.0 mmol), and anhydrous acetonitrile (50 mL). The reaction mixture was cooled by an ice water bath (0 °C). The reaction mixture was allowed to stir at 0 °C for 5 minutes, and $NaBH_3CN$ (0.79 g, 12.5 mmol) of was added in one portion. The mixture was allowed to stir at 0 °C for an additional 5 minutes, and then the ice bath was removed and the reaction was allowed to warm to ambient temperature and stir for 4 h. It was then filtered through a plug of celite, diluted with CH_2Cl_2 (100 mL), and added to sat. $NaHCO_3$ (100 mL). The aqueous phase was extracted with three 100 mL portions of CH_2Cl_2. The combined organic extracts were washed with sat. aq. NaCl (100 mL), dried over anhydrous K_2CO_3, and concentrated in vacuo. The diastereomer ratio was measured to be 7:3 by integration of the resonances at 4.3 – 4.5 ppm in the ^{1}H NMR spectrum of the crude reaction product.

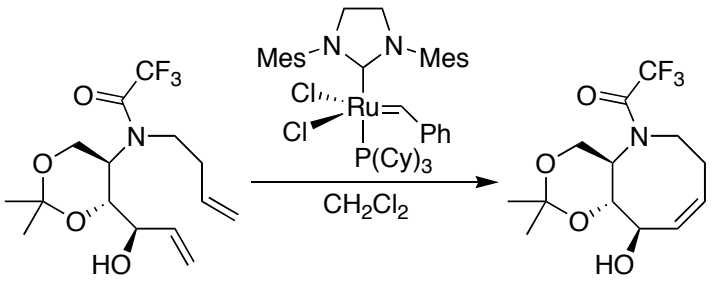
Spectral data[3] due to the major diastereomer of **13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (ddd, *J* = 17.3, 10.7, 3.9 Hz, 1H), 5.74 (m, 1H), 5.47 (app dt, *J* = 17.4, 2.0 Hz, 1H), 5.28 (app dt, *J* = 10.7, 2.0 Hz, 1H), 5.13–5.04 (m, 2H), 4.32–4.28 (m, 1H), 3.99 (dd, *J* =11.4, 5.3 Hz, 1H), 3.75 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.51 (dd, *J* = 11.3, 9.8 Hz, 1H), 3.05–2.71 (m, 4H), 2.57 (dt, *J* = 11.4, 6.7 Hz, 1H), 2.28–1.94 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9 (dn), 135.7 (dn), 117.2 (u), 115.2 (u), 98.7 (u), 73.4 (dn), 73.2 (dn), 63.6 (u), 52.4 (dn), 45.9 (u), 34.6 (u), 28.7 (dn), 19.3 (dn).

Without attempting to separate the diasteromers, the crude product **13** was then dissolved in 50 mL of anhydrous CH_2Cl_2 and the mixture was cooled by a bath of ice water (0 °C). Et_3N (7.0 mL, 50 mmol) was then added followed by syringe pump addition of a solution of trifluoroacetic anhydride (1.53 mL, 11.0 mmol) in anhydrous CH_2Cl_2 (10 mL) at a rate of 0.13 mL/min. The solution was then allowed to warm to ambient temperature and stir for an additional 4 h. The reaction mixture was then concentrated onto silica gel and chromatographed on silica gel with 0-20% ethyl acetate/hexanes as the eluent to give 0.51 g (1.51 mmol, 30% over 2 steps) of the title compound. The compound was an ~7:1 mixture of amide rotamers by NMR. Small peaks attributable to impurities were detected in the ^{1}H NMR at 5.10, 4.92, 4.59, 4.42–4.30, 3.80 and 1.62 ppm.

$[\alpha]_D$ +10 (c 2.0, $CHCl_3$). Spectral properties for the major conformer of **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.95–5.85 (m, 1H), 5.80–5.67 (m, 1H), 5.40–5.12 (m, 4H), 4.85 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.65 (app t, *J* = 11.0 Hz, 1H), 4.10–3.97 (m, 1H), 3.75 (dd, *J* = 10.9, 5.5 Hz, 1H), 3.62–3.52 (m, 2H), 3.45–3.35 (m, 1H), 2.50–2.42 (m, 2H), 2.20 (d, *J* = 9.9 Hz, 1H), 1.59 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3 (dn)(q, J_{CF}

= 36 Hz), 137.2 (u), 132.9 (u), 118.4 (dn), 116.1 (u)(q, J_{CF} = 289 Hz), 70.6 (u), 69.2 (u), 58.5 (dn), 56.7 (u), 50.1 (dn)(q, J_{CF} = 3.1 Hz), 33.3 (dn), 28.6 (u), 19.6 (u); IR (neat, cm^{-1}): 3366, 2922, 2368, 1682, 1429, 1202, 1145, 927. HRMS (CI) *m/z*: [M+H] calcd. for $C_{15}H_{23}NO_4F_3$ 338.1579; found 338.1563.

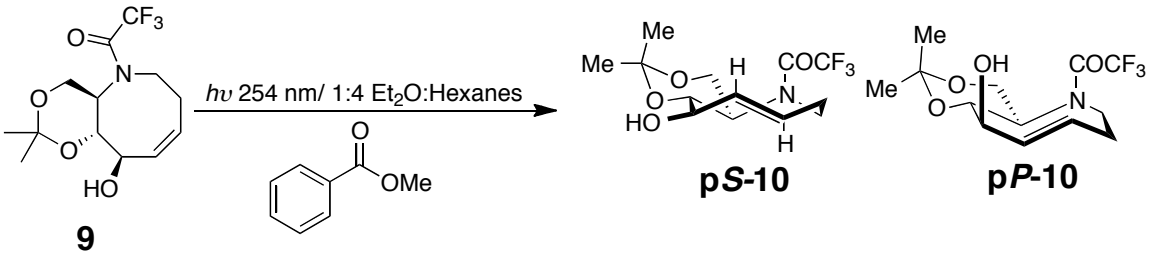
2,2,2-Trifluoro-1-((*Z*,4a*R*,10*R*,10a*R*)-4,4a,6,7,10,10a-hexahydro-10-hydroxy-2,2-dimethyl-[1,3]dioxino[5,4-*b*]azocin-5-yl)ethanone (9)



Diene **12** (0.61 g, 1.8 mmol) was dissolved in CH_2Cl_2 (100 mL). To this solution was added the Grubbs 2nd generation catalyst (CAS# 246047-72-3, 77 mg, 0.090 mmol) in one portion. The resulting solution was stirred for 18 h at room temperature. Silica gel (3 g) was added to the flask, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (1:4 EtOAc:hexanes) provided 0.50 g (1.6 mmol, 90%) of the title compound as a colorless oil. A similar experiment that started with 0.33 g of the diene provided the title compound in 91% isolated yield. TLC R_f (1:2 EtOAc:hexanes) = 0.26. $[\alpha]_D$ -24 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80-5.76 (m, 1H), 5.61-5.54 (m, 1H), 4.74 (app t, *J* = 11.0 Hz, 1H), 4.46 (app t, *J* = 10.0 Hz, 1H), 4.34-4.30 (m, 1H), 3.73-3.61 (m, 2H), 3.29-3.24 (m, 1H), 3.17-3.10 (m, 1H), 2.97 (bs, 1H), 2.58-2.47 (m, 1H), 2.38-2.32 (m, 1H), 1.65 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5 (u) (q, ^2J(CF)=36 Hz), 135.4 (dn), 125.4 (dn), 115.8 (u) (q,

^{1}J(CF)=288 Hz), 99.4 (u), 72.2 (dn), 67.7 (dn), 57.1 (u), 56.4 (dn), 46.9 (u), 28.8 (dn), 26.2 (u), 19.7 (dn). IR (neat, cm^{-1}): 3487, 2995, 2944, 1689, 1458, 1382, 1266, 1190, 1150, 1095, 1026. HRMS (CI) *m/z*: [M+Na] calcd. for $C_{13}H_{18}NO_4F_3Na$ 332.1086; found 332.1079.

2,2,2-trifluoro-1-((*E*,p*S*, 4a*R*,10*R*,10a*R*)-4,4a,6,7,10,10a-hexahydro-10-hydroxy-2,2-dimethyl-[1,3]dioxino[5,4-*b*]azocin-5-yl)ethanone (p*S*-10)



(*Z*)-Aza-cyclooctene **9** (0.40 g, 1.3 mmol) and methyl benzoate (0.27 g, 1.9 mmol) were dissolved in 500 mL of 1:4 solution of Et_2O and hexanes in a quartz flask that was equipped with a magnetic stir bar. The quartz flask was placed in a Rayonet® reactor and connected via PTFE tubing to a column (ISCO RediSep™, 40 g) and an FMI pump, as previously described.[4] The bottom of the column was packed with dry silica gel (8 cm), and the top of the column was packed with silver nitrate impregnated silica[4] (3.3 g). The column was flushed with a 1:4 solution of Et_2O and hexanes. The pump was turned on and the rate of circulation was adjusted to about 100 mL per minute. Eight lamps of the Rayonet reactor were turned on, and irradiation of the mixture was carried out for 24 h. The column was washed with additional solvent (200 mL) and then dried by a stream of compressed air. The column was emptied into an Erlenmeyer flask (500 mL), and the silica gel was stirred with acetonitrile (200 mL) for 30 min. The silica gel was filtered,

and the filtrate was concentrated under reduced pressure. Conc. aqueous ammonium hydroxide (100 mL) was added to the filtrate, and the product was extracted with methylene chloride (2x100 mL). The organic layers were combined, washed with 100 mL of water, dried ($MgSO_4$), filtered and concentrated to provide the title compound as 7.8:1 mixture of diastereomers. The diastereomers were separated by flash chromatography (1:4 EtOAc:hexanes) yielding 0.028 g (7%) of the minor diastereomer (**p*R*-10**) and 0.22 g (55%) of the major diastereomer (**p*S*-10**). The title compounds were obtained as white solids, m.p. = 75-78 °C (major); 82-84 °C (minor).

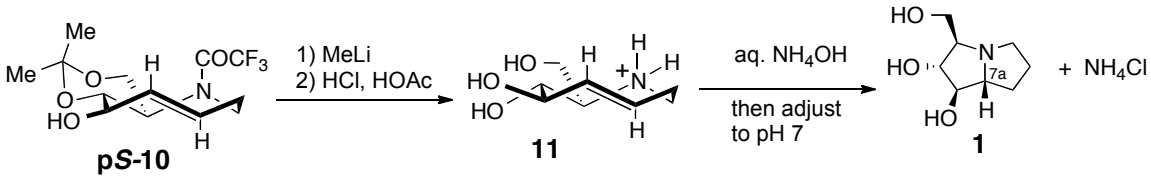
TLC R_f (1:2 EtOAc:hexanes) = 0.28 (major), 0.35 (minor).

Spectral properties of major diastereomer **p*S*-10:** $[\alpha]_D$ +117 (c 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.82-5.74 (m, 1H), 5.50-5.42 (m, 1H), 4.92-4.88 (m, 1H), 4.45 (app t, J = 11.2 Hz, 1H), 4.21-4.17 (m, 1H), 4.07 (m, 1H), 3.67-3.62 (m, 1H), 2.84 (m, 1H), 2.69-2.61 (m, 1H), 2.55-2.39 (m, 3H), 1.65 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8 (u) (q, ^2J(CF)=36 Hz), 134.3 (dn), 127.7 (dn), 115.9 (u) (q, ^1J(CF) = 288 Hz), 99.1 (u), 80.4 (dn), 75.7 (dn), 63.2 (dn), 57.2 (u), 53.6 (dn), 35.5 (u), 28.6 (dn), 19.8 (dn). IR (neat, cm^{-1}): 3449, 2927, 1686, 1446, 1380, 1260, 1201, 1146, 1099, 1036. HRMS (CI) *m/z*: [M+Na] calcd. for $C_{13}H_{18}NO_4F_3Na$ 332.1086; found 332.1080.

Spectral properties of minor diastereomer: **p*R*-10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (ddd, J = 16.0, 11.1, 4.2 Hz, 1H), 5.27 (d, J = 16.2 Hz, 1H), 4.99 (dd, J = 9.3, 3.9 Hz, 1H), 4.56 (br s, 1H), 4.38 (t, J = 11.2, 1H), 3.97 (dd, J = 15.0, 5.1 Hz, 1H), 3.60 (dd, J = 11.3, 7.1 Hz, 1H), 2.90–2.70 (m, 3H), 2.58–2.50 (m, 1H), 2.46–2.34 (m, 1H), 1.62 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) 157.9 (u)(q, ^1J(CF) = 36.2 Hz), 132.9

(dn), 125.9 (dn), 117.4 (u), (q, ^{1}J(CF) = 289 Hz), 98.8 (u), 71.2 (dn), 70.7 (dn), 58.4 (dn), 57.2 (u), 53.3 (u) (q, ^{1}J(CF) = 2.4 Hz), 36.1 (u), 28.6 (dn), 20.2 (dn)

(+) Hyacinthacine A_2



(+) Hyacinthacine A_2 was synthesized in three sequential steps. Intermediates were not chromatographically stable, and were directly carried forward without purification.

The (*E*)-cyclooctene (40 mg, 0.13 mmol) was dissolved in THF (5 mL), and the solution was cooled by a bath of dry ice/acetone (–78 °C). A 1.6 M solution of MeLi in Et_2O (0.2 mL, 0.32 mmol) was added dropwise. After 15 minutes at –78 °C, the reaction was quenched by the addition of water (0.2 mL). The reaction mixture was warmed up to room temperature, and saturated aqueous $NaHCO_3$ (10 mL) was added. The product was extracted with CH_2Cl_2 (2x20 mL). The organic layers were combined, dried with K_2CO_3 and concentrated under reduced pressure.

To the resulting amino alcohol was added a methanolic HCl solution, which was prepared by dissolving aqueous 4 M HCl (0.8 mL) in MeOH (10 mL). The mixture was stirred for 30 minutes. The solvent was evaporated and the product was re-dissolved in a 4:1 solution of 4:1 AcOH:H_2O (10 mL). The solution was stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure.

^{1}H NMR of **11** (D_2O, 400 MHz) δ 5.84–5.70 (m, 1H), 5.66–5.55 (m, 1H), 4.00 (dd, *J* = 9.6, 7.9 Hz, 1H), 3.77–3.64 (m, 2H), 3.49 (app t, *J* = 8.6 Hz, 1H), 3.41 (dd, *J* =13.2, 5.8 Hz, 1H), 2.92–2.72 (m, 2H), 2.61–2.51 (m, 1H), 2.45–2.27 (m, 1H).

The product was re-dissolved in aqueous ammonia (5 mL) and stirred at room temperature for 5 minutes. The aqueous layer was washed with CH_2Cl_2 (2x10 mL) and the aqueous layer concentrated under reduced pressure, yielding 0.25 g (85 %) of (+) hyacinthacine A_2 as a yellow oil. The NMR spectra of (+)-hyacinthacine are pH sensitive.[5] Copies of the ^{1}H and ^{13}C NMR spectra of hyacinthicine A2 have been published by Ribes *et al.,*[5,6g] and the presently described NMR spectra for hyacinthicine A2 at pH 9.0 correspond to the spectra of Ribes *et al*. A table comparing the ^{1}H and ^{13}C NMR data is provided to compare the spectra of our hyacinthacine A2 to that described for natural hyacinthacine A2,[6b] and the synthetic hyacinthacine A2 of Ribes *et al.*[5,6g]

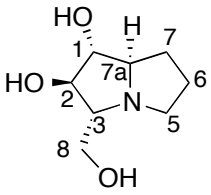
The following spectral data were observed at pH 9.0:

$[\alpha]_D$ +12 (c 0.40, H_2O); lit.[6a] $[\alpha]_D$ +12.5 (c 0.4, H_2O); lit.[6b] $[\alpha]_D$ +20.1 (c 0.44, H_2O); lit.[6c] $[\alpha]_D$ +10.6 (c 1.64, H_2O); lit.[6d] $[\alpha]_D$ +10.5 (c 0.6, H_2O); lit.[6e] $[\alpha]_D$ +12.7 (c 0.13, H_2O); lit.[6f] $[\alpha]_D$ +11.2 (c 0.6, H_2O); lit.[6g] $[\alpha]_D$ +12.1 (c 0.3, H_2O). ^{1}H NMR (D_2O, 400 MHz) δ 3.87–3.76 (m, 3H), 3.70 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.37–3.30 (m, 1H). 3.08–2.99 (m, 1H), 2.95-2.82 (m, 2H), 2.07–1.91 (m, 2H), 1.91–1.77 (m, 2H). ^{13}C NMR (D_2O, 100 MHz) δ 82.5 (dn), 79.3 (dn), 72.2 (dn), 69.7 (dn), 64.4 (u), 57.8 (u), 32.4 (u), 27.3 (u). HRMS (CI) *m/z*: [M+H] calcd. for $C_8H_{16}NO_3$ 174.1130; found 174.1123.

The following NMR spectral data were observed at pH 7.6: ^{1}H NMR (D_2O, 400 MHz) δ 4.08–3.97 (m, 3H), 3.95–3.87 (m, 2H), 3.54–3.45 (m, 1H), 3.42–3.32 (m, 2H), 2.30–2.07

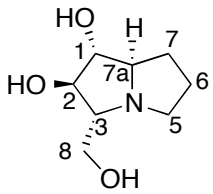
(m, 4H); ^{13}C NMR (D_2O, 100 MHz) δ 81.0 (dn), 77.2 (dn), 73.0 (dn), 72.3 (dn), 60.3 (u), 58.5 (u), 31.7 (u). 27.3 (u).

^{1}H NMR data comparison for hyacinthacine A2



	Asano *et al.*[6b] **Isolated natural product**	**Ribes *et al.*[6g]** **Synthetic material**	**This work (pH 9.0)**
H-2	3.81 (t, *J*=8.8 Hz, 1H)	3.87–3.78 (m, 3H)	3.87–3.76 (m, 3H),
H-8′	3.80 (dd, *J* =3.9, 11.8 Hz, 1H,)	overlapping with H-2	overlapping with H-2
H-1	3.76 (dd, *J*=8.8, 7.1 Hz, 1H)	overlapping with H-2	overlapping with H-2
H-8	3.67 (dd, *J*=11.8, 6.5 Hz, 1H)	3.70 (dd, *J* = 12, 6 Hz, 1H)	3.70 (dd, *J* = 12.0, 6.3 Hz, 1H)
H-7a	3.32 (m, 1H)	3.36 (m, 1H)	3.37–3.30 (m, 1H)
H-5β	2.96 (ddd, *J*=11.0, 7.3, 5.9 Hz, 1H)	3.06 (br dt, *J* = 11.4, 6.3 Hz, 1H)	3.08–2.99 (m, 1H)
H-5α	2.81 (dt, 11.0, 5.6 Hz, 1H)	2.95–2.85 (m, 1H)	2.95-2.82 (m, 2H)
H-3	2.77 (ddd, *J*=8.8, 6.5, 3.9 Hz, 1H)	Overlapping with H–5α	Overlapping with H–5α
H-7β	1.97 (m, 1H)	2.05–2.00 (m, 1H)	2.07–1.91 (m, 2H)
H-6α	1.90 (m, 1H)	2.00–1.90 (m, 1H)	overlapping with H-7β
H-6β	1.82 (m, 1H)	1.90–1.80 (m, 2H)	1.91–1.77 (m, 2H)
H-7α	1.77 (m, 1H, m)	overlapping with H-6β	overlapping with H-6β

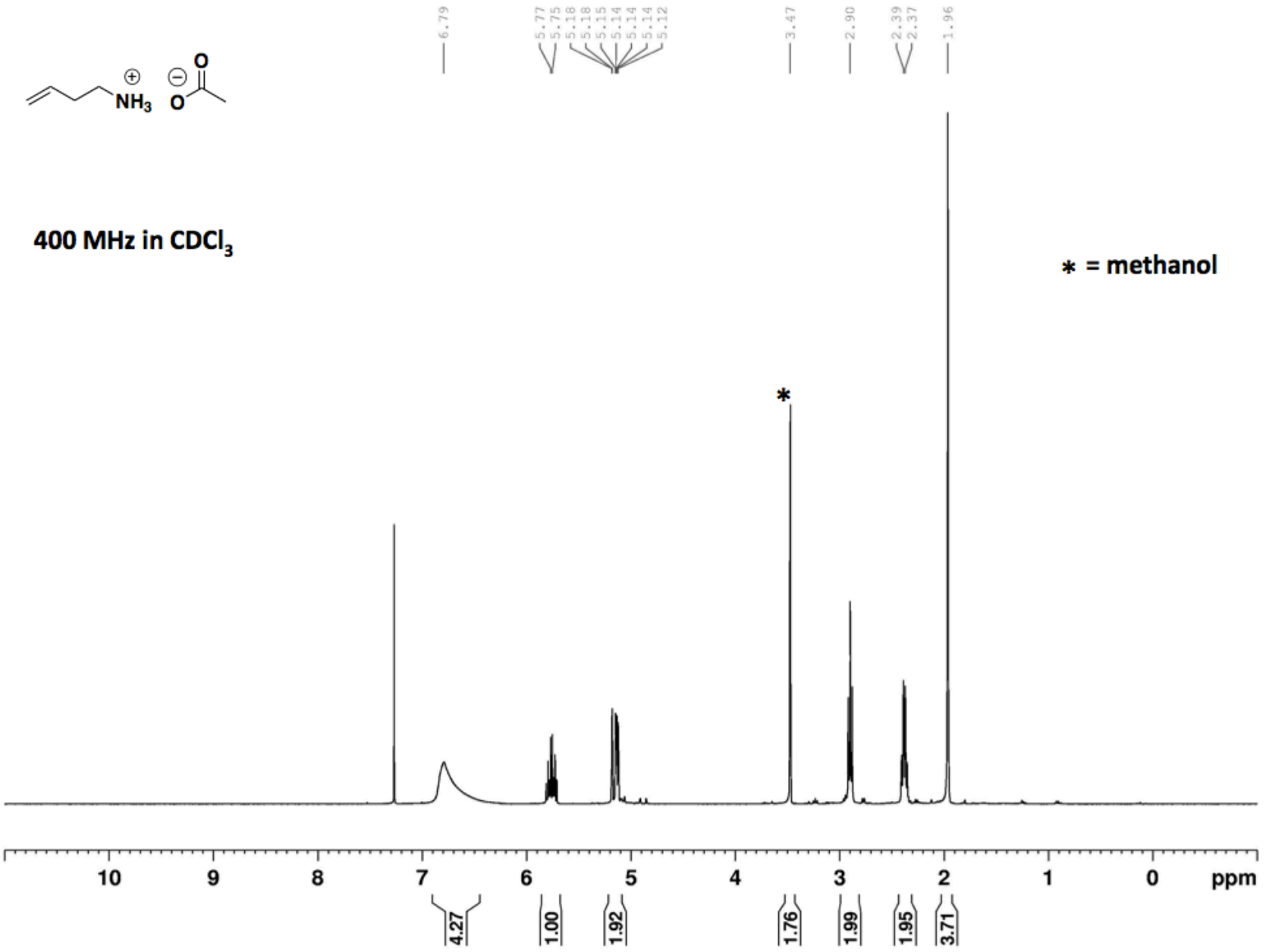
^{13}C NMR data comparison for hyacinthacine A2

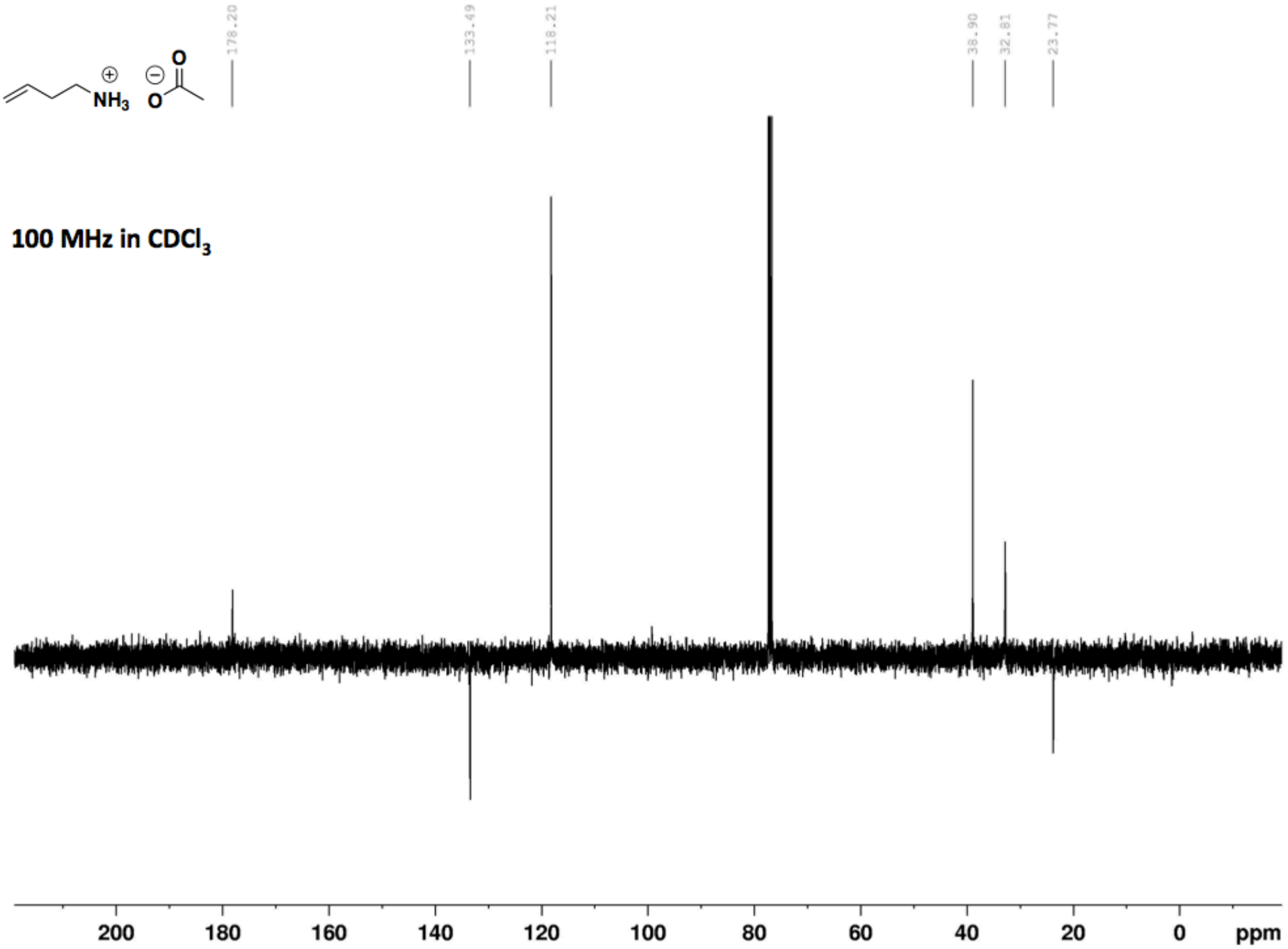


	Asano *et al.*[6b] **Isolated natural product**	**Ribes *et al.*[6g]** **Synthetic material**	**This work (pH 9.0)**
C-1	82.9 (CH)	82.2	82.5 (CH)
C-2	79.8 (CH)	79.0	79.3 (CH)
C-3	72.1 (CH)	72.1	72.2 (CH)
C-7a	69.2 (CH)	69.7	69.7 (CH)
C-8	65.3 (CH_2)	63.9	64.4 (CH_2)
C-5	57.7 (CH_2)	57.7	57.8 (CH_2)
C-7	32.5 (CH_2)	32.1	32.4 (CH_2)
C-6	27.3 (CH_2)	27.1	27.3 (CH_2)

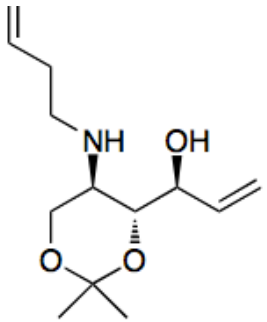
References

[1] (a) T. Morimoto; T. Takhashi; M. Sekiya *J. Chem. Soc., Chem. Commun*. **1984**, *12* , 794-795. (b) H. J. Bestmann, G. Wölfel, K. Mederer *Synthesis*, **1987**, *9*, 848-850.
[2] A. Lauritsen, R. Madsen *Org. Biomol. Chem.*, **2006**, *4*, 2898-2905.
[3] Diastereomers of **13** are not separable. Analytical samples of the separate diastereomers of **13** could be obtained by reacting the separated diastereomers of **12** with $NaBH_4$/EtOH.
[4] M. Royzen, G. P. A. Yap, J. M. Fox *J. Am. Chem. Soc.* **2008**, *130*, 3760-3761
[5] For a prior report on the pH sensitivity of the NMR spectra of hyacinthacine A2, and a tabulation of the ^{1}H NMR and ^{13}C NMR spectra reported in the literature for hyacinthacine A2, see the supporting information of C. Ribes, E. Falomir, M. Carda, and J. A. Marco, Tetrahedron, **2009**, *65*, 6965-6971.
[6] (a) L. Rambaud, P. Compain, O. R. Martin *Tetrahedron: Asymmetry*, **2001**, *12*, 1807-1809. (b) N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, **2000**, 11, 1-8. (c) X. Liu, S. Qiu, Y. Xiang, Y. Ruan, X. Zheng, and P. Huang, *J. Org. Chem.* **2011**, *76*, 4952-4963. (d) I. Izquierdo, M. T. Plaza, and F. Franco, *Tetrahedron: Asymmetry*, **2003**, *14*, 3933-3935. (e) S. Desvergnes, S. Py, and Y. Vallée, *J. Org. Chem.*, **2005**, *70*, 1459-1462. (f) P. Dewi-Wülfing and S. Blechert, *Eur. J. Org. Chem.*, **2006**, *2006*, 1852-1856. (g) C. Ribes, E. Falomir, M. Carda, and J. A. Marco, Tetrahedron, **2009**, *65*, 6965-6971.

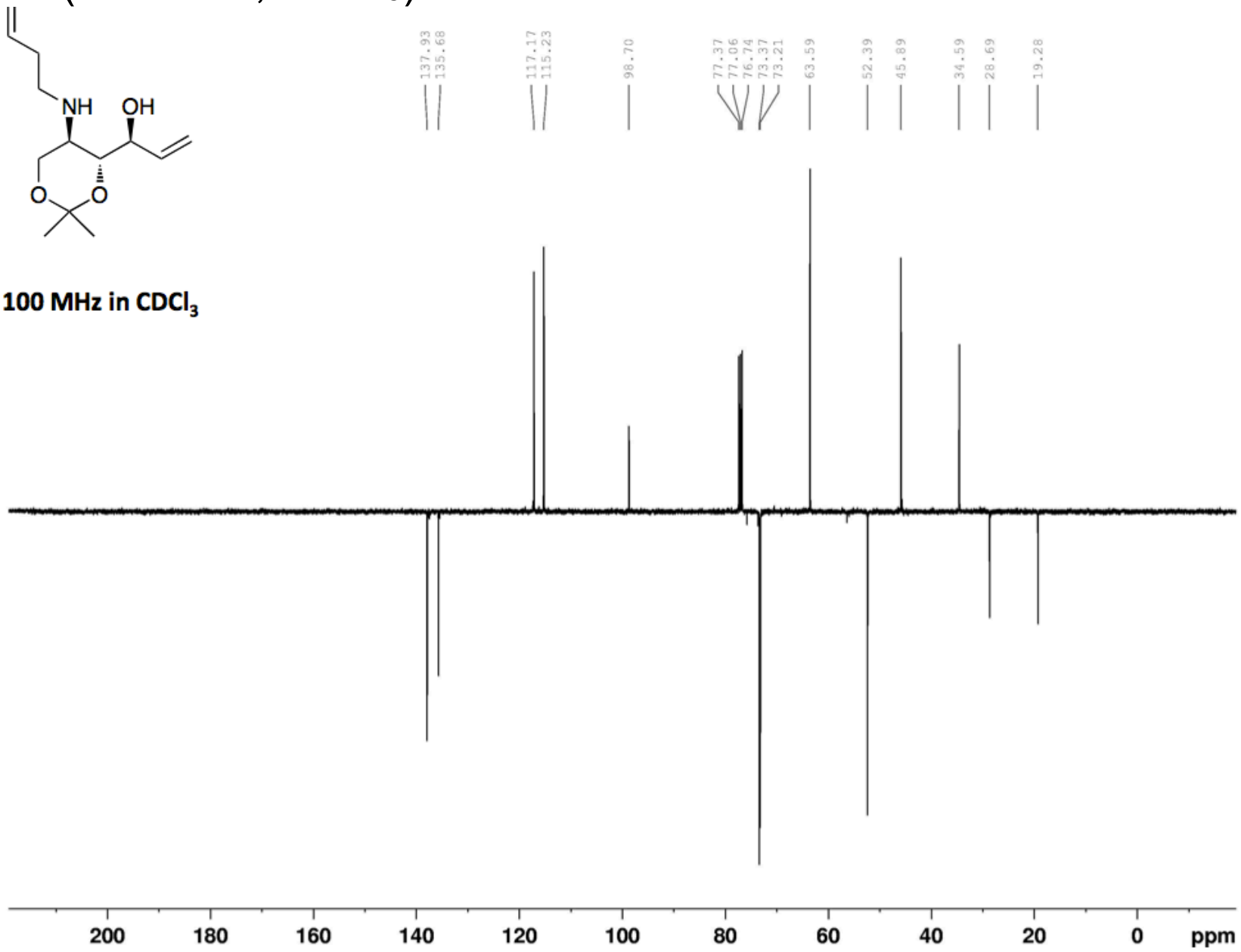




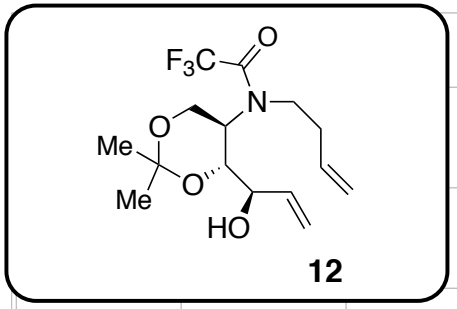
^{1}H NMR (400 MHz, $CDCl_3$) of **13**



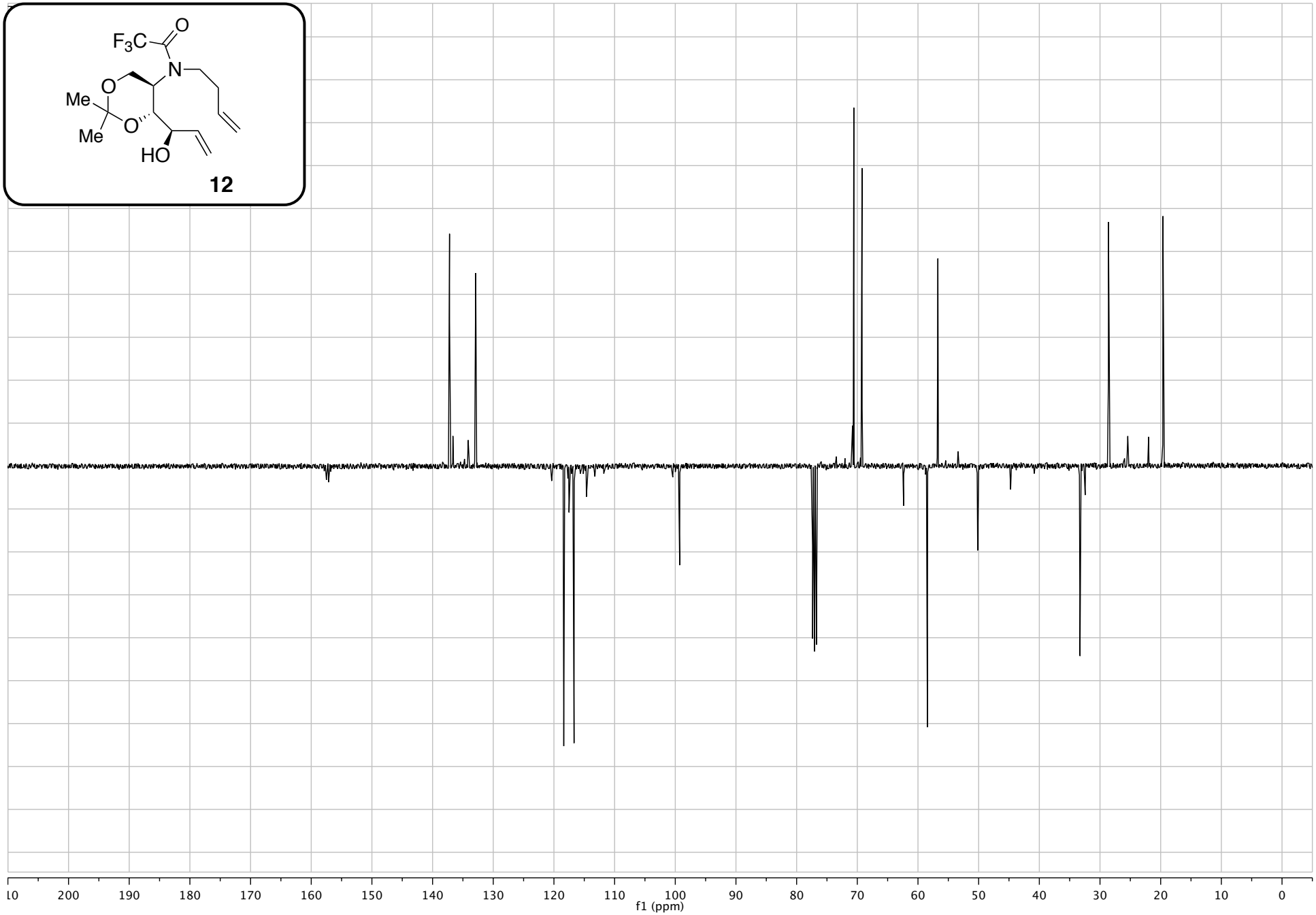
^{13}C NMR (100 MHz, $CDCl_3$) of **13**



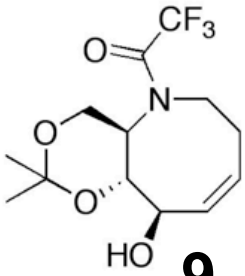
^{1}H NMR (400 MHz, $CDCl_3$) of **12**



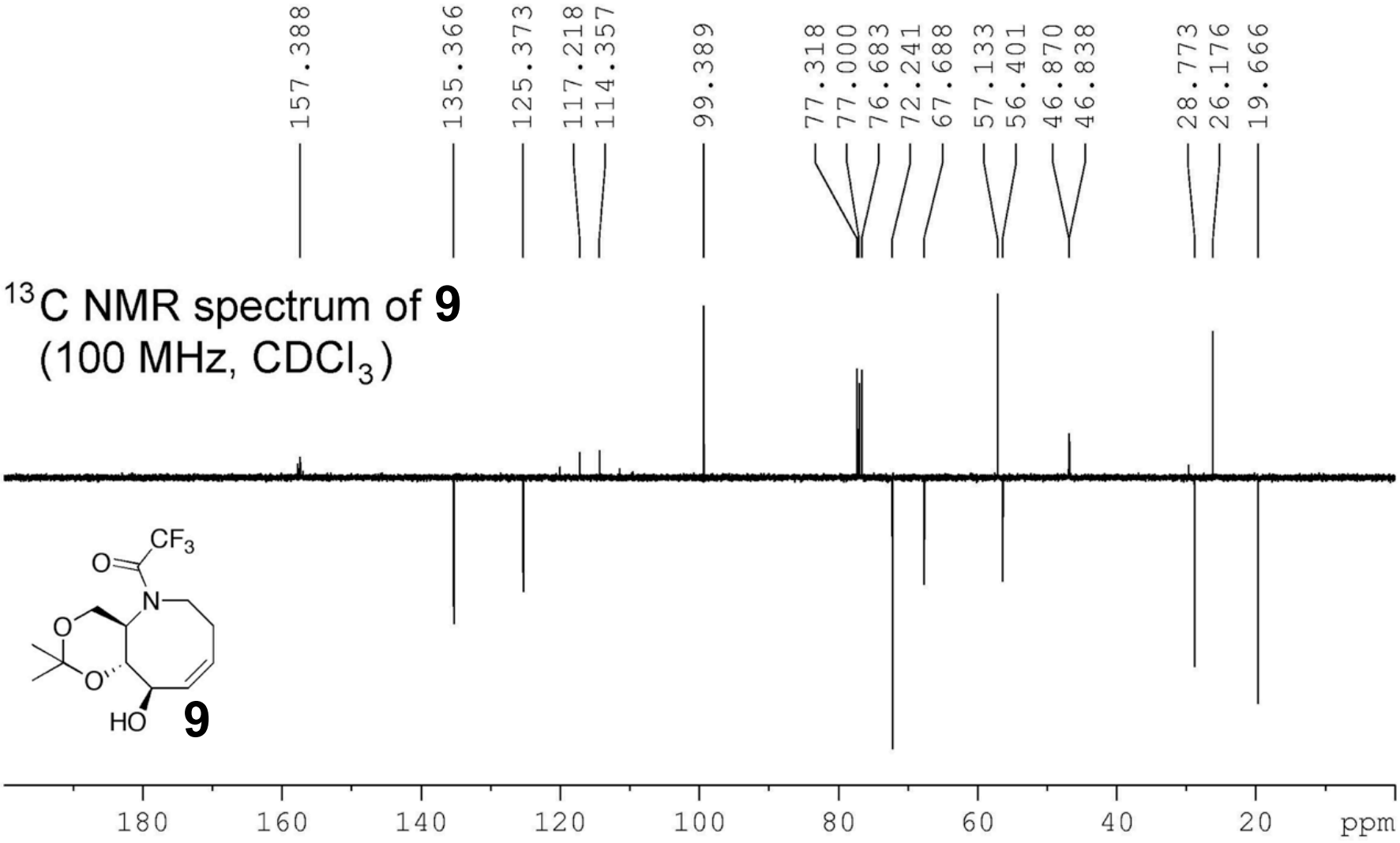
^{13}C NMR (100 MHz, $CDCl_3$) of **12**



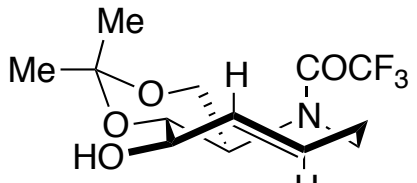
^{1}H NMR spectrum of **9** (400 MHz, $CDCl_3$)



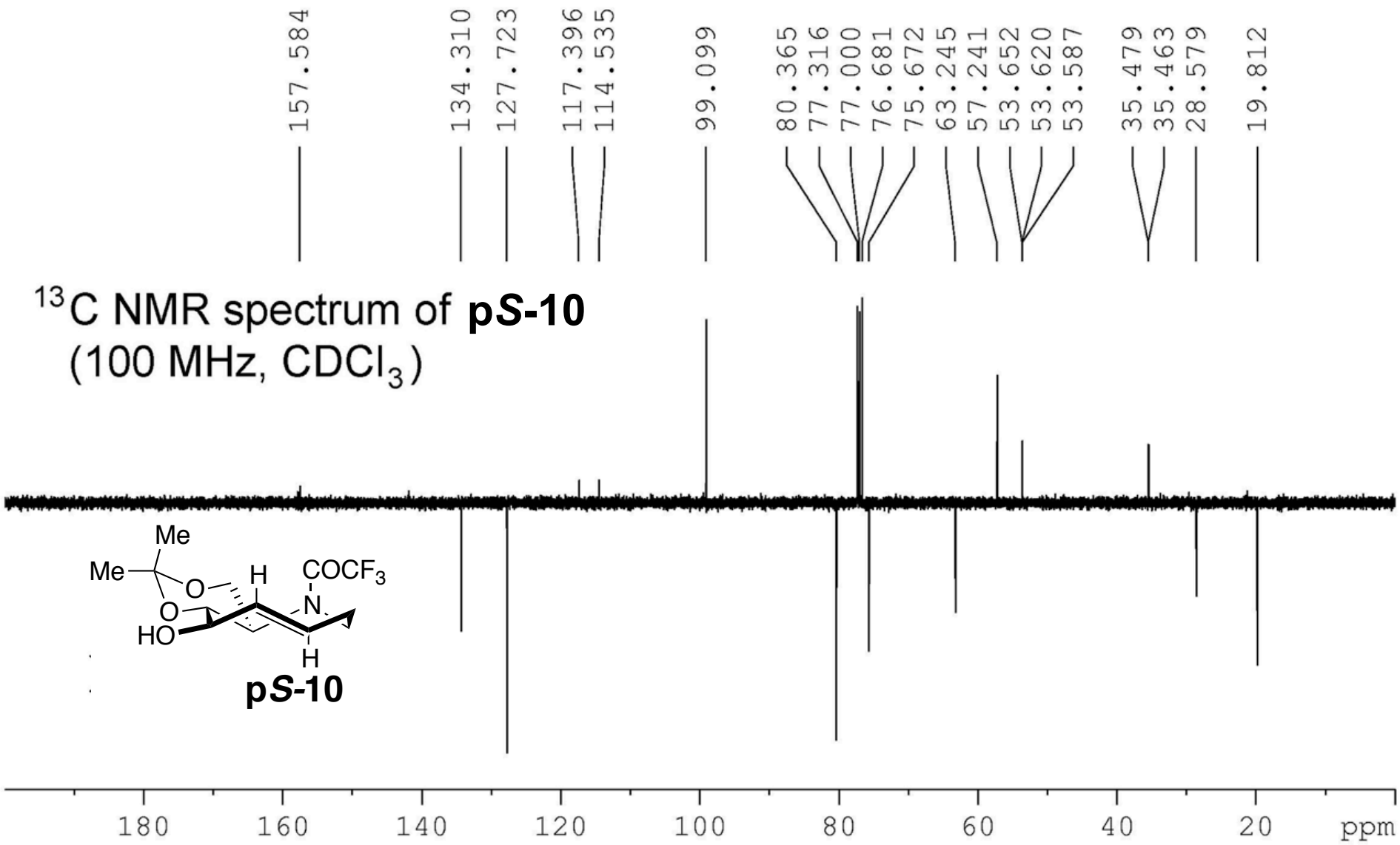
9



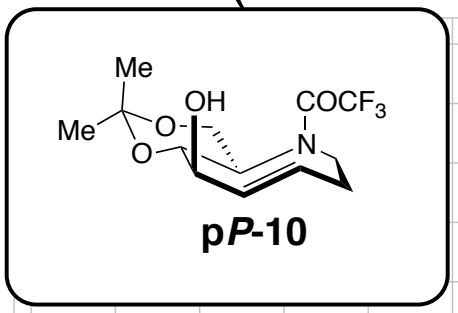
^{1}H NMR spectrum of **p*S*-10** (400 MHz, $CDCl_3$)



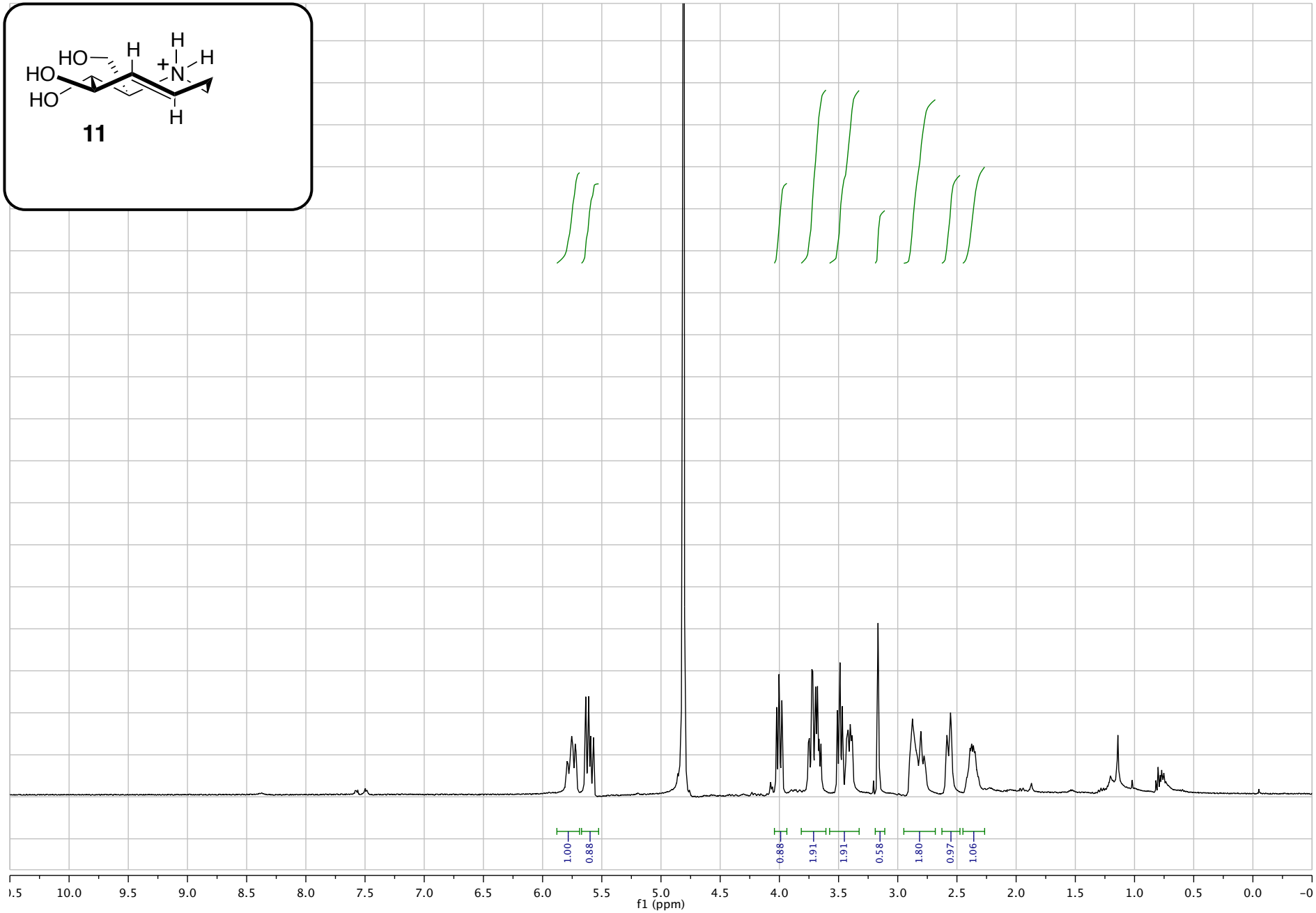
p*S*-10



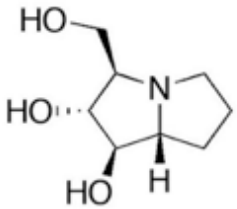
^{1}H NMR (400 MHz, $CDCl_3$) of **p*P*-10**



^{1}H NMR (400 MHz, D_2O) of **p*P*-11** (unpurified)



^{1}H NMR spectrum of (400 MHz, $CDCl_3$)



1

pH 7.6