

Total Synthesis of the Amaryllidaceae Alkaloid Clivonine

Helmut Haning,^{a,b} Carles Giró Mañas,^c Victoria L. Paddock,^c Christian G. Bochet,^{d,b}
Andrew J. P. White,^c Gerald Bernardinelli,^b Inderjit Mann,^e Wolfgang Oppolzer^{†b} and Alan
C. Spivey^{*c,b}

¹*Department of Chemistry, South Kensington Campus, Imperial College London, London SW7
2AZ, UK*

²*Department of Chemistry, University of Fribourg, 9 Ch. du Musée, CH-1700 Fribourg,
Switzerland*

³*Department of Organic Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211
Geneva 4, Switzerland*

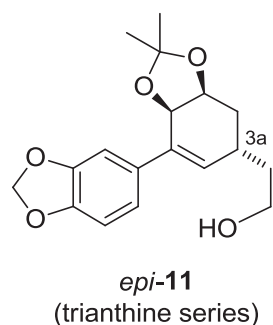
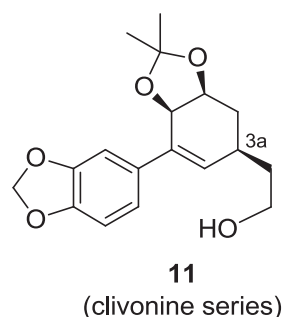
⁴*GSK Tonbridge, Old Powder Mills, Leigh, Tonbridge, Kent, TN11 9AN, UK.*

SUPPORTING INFORMATION

Details of DFT molecular modelling for alcohol 11 and its C3a epimer, including coordinates	2-3
NMR spectra (compounds 1, 8, 9, 11-13, 16 and 25-31)	4-22

[†] Deceased March 15th, 1996.

DFT Procedures for Compound 11 and its C3a Epimer



DFT calculations were performed at the B3LYP 6-31G(d,p) level using Gaussian 09[‡]

Coordinates for 11 (clivonine series): Total energy: -1075.2678728 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	1.669277	3.663338	1.525224
2	6	0	1.176000	3.158283	0.175270
3	6	0	0.367818	4.210494	-0.586844
4	8	0	0.406109	1.974953	0.396291
5	6	0	0.659265	1.105222	-0.723033
6	1	0	0.058813	1.440006	-1.582719
7	6	0	2.144848	1.377282	-0.987434
8	1	0	2.385904	1.266963	-2.052068
9	8	0	2.292923	2.756143	-0.640261
10	6	0	3.047841	0.481500	-0.143493
11	6	0	2.753652	-1.002430	-0.408050
12	1	0	3.066807	-1.236267	-1.441521
13	6	0	3.574341	-1.911653	0.531454
14	6	0	3.620929	-3.382873	0.110879
15	8	0	4.355112	-4.188648	1.023663
16	6	0	1.267988	-1.263439	-0.298435
17	6	0	0.301035	-0.334241	-0.414857
18	6	0	-1.143396	-0.684372	-0.341627
19	6	0	-2.068718	0.227778	0.226744
20	6	0	-3.390647	-0.157629	0.278869
21	8	0	-4.463242	0.556013	0.766000
22	6	0	-5.578115	-0.339604	0.717249
23	8	0	-5.193059	-1.488525	-0.048798
24	6	0	-3.831793	-1.385344	-0.207253
25	6	0	-2.958935	-2.287361	-0.781773
26	6	0	-1.607487	-1.911284	-0.844282
27	1	0	2.247816	2.884524	2.025985
28	1	0	0.823185	3.939059	2.160807
29	1	0	2.304337	4.542290	1.386443
30	1	0	-0.007538	3.800409	-1.527826
31	1	0	0.999696	5.072041	-0.819793
32	1	0	-0.482017	4.548321	0.013081
33	1	0	4.097820	0.717104	-0.348253
34	1	0	2.860715	0.697924	0.914225
35	1	0	3.181008	-1.845794	1.553048

[‡] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

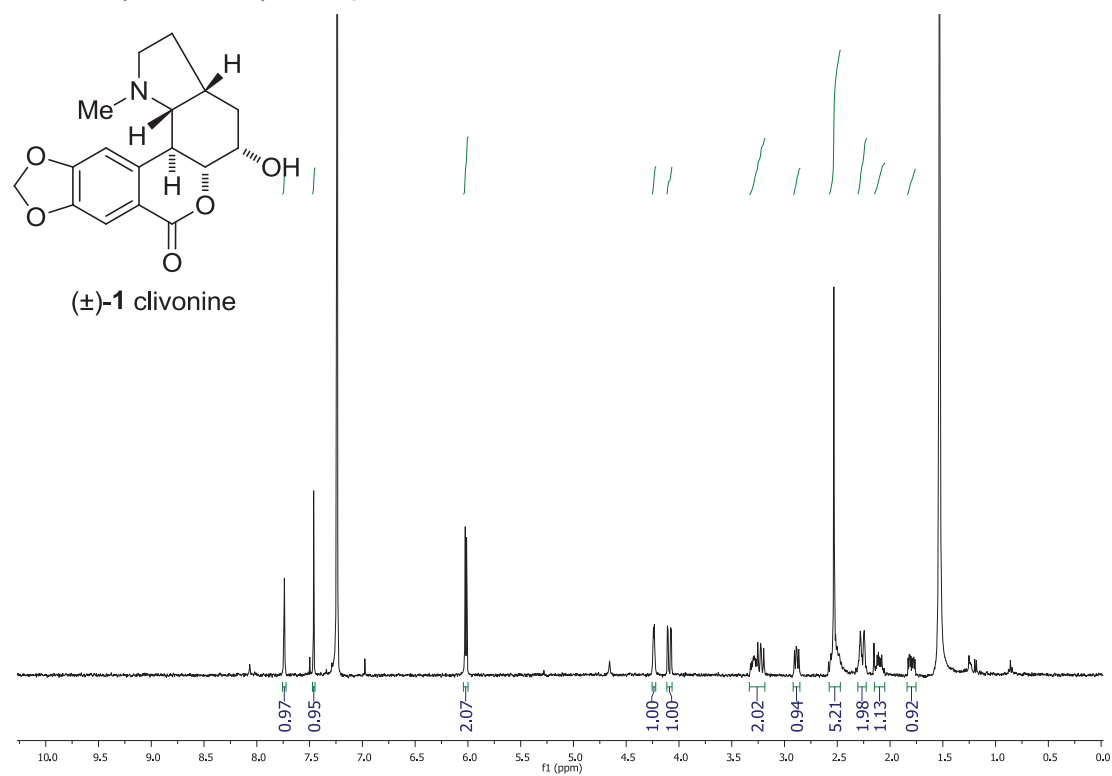
36	1	0	4.605967	-1.532004	0.565973
37	1	0	4.026671	-3.464029	-0.911763
38	1	0	2.616171	-3.816383	0.088971
39	1	0	5.260654	-3.851810	1.046828
40	1	0	0.966897	-2.289724	-0.100675
41	1	0	-1.740654	1.181652	0.619301
42	1	0	-6.423518	0.155294	0.229578
43	1	0	-5.844861	-0.652651	1.737090
44	1	0	-3.305644	-3.233313	-1.181859
45	1	0	-0.904404	-2.585102	-1.321658

Coordinates for *epi-11* (trianthine series): Total energy: -1075.2667877 Hartrees

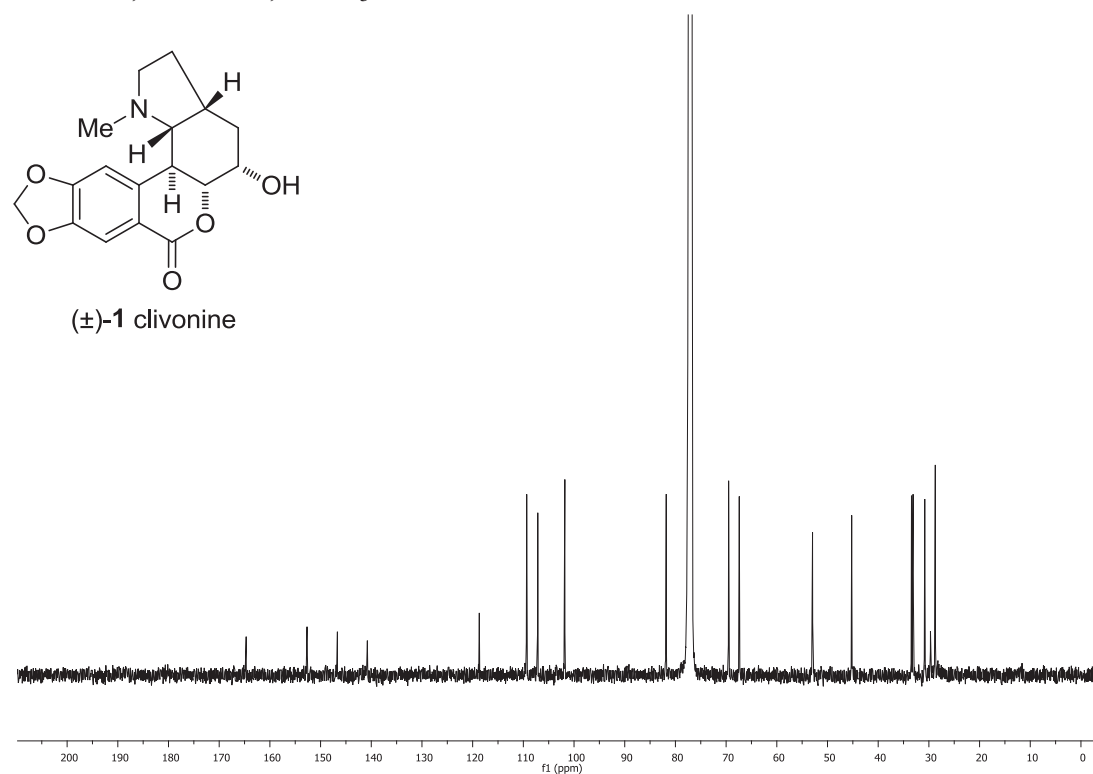
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-1.511717	4.019454	-1.091961
2	6	0	-1.254713	3.129709	0.117539
3	6	0	-0.648200	3.897636	1.294133
4	8	0	-0.405382	2.055914	-0.291472
5	6	0	-0.817529	0.897064	0.457130
6	1	0	-0.396616	0.954710	1.472632
7	6	0	-2.337687	1.094942	0.511916
8	1	0	-2.756340	0.690572	1.440402
9	8	0	-2.483338	2.517642	0.550489
10	6	0	-3.034651	0.495551	-0.709037
11	6	0	-2.709260	-0.999703	-0.872942
12	1	0	-3.020273	-1.299575	-1.884407
13	6	0	-3.509529	-1.891361	0.112362
14	6	0	-3.332746	-3.395124	-0.108304
15	8	0	-4.199877	-4.169722	0.711499
16	6	0	-1.217185	-1.222913	-0.775569
17	6	0	-0.338284	-0.386938	-0.191093
18	6	0	1.111090	-0.708629	-0.088794
19	6	0	2.076063	0.329295	-0.143366
20	6	0	3.403358	-0.030970	-0.059570
21	8	0	4.507704	0.791948	-0.074163
22	6	0	5.639543	-0.082499	-0.111887
23	8	0	5.182778	-1.412995	0.164948
24	6	0	3.812181	-1.354231	0.082221
25	6	0	2.897196	-2.385282	0.156998
26	6	0	1.539547	-2.036699	0.074148
27	1	0	-1.943260	3.429932	-1.903234
28	1	0	-0.577497	4.468914	-1.439989
29	1	0	-2.207939	4.819318	-0.826438
30	1	0	-0.439153	3.222806	2.128116
31	1	0	-1.348062	4.661783	1.643567
32	1	0	0.283879	4.384428	0.993325
33	1	0	-4.114986	0.659988	-0.637386
34	1	0	-2.678503	1.032172	-1.594022
35	1	0	-4.577478	-1.661611	0.013528
36	1	0	-3.224723	-1.646981	1.145458
37	1	0	-2.281693	-3.687199	0.041586
38	1	0	-3.594259	-3.654851	-1.140479
39	1	0	-3.952601	-4.008412	1.631601
40	1	0	-0.834583	-2.136285	-1.225354
41	1	0	1.776293	1.361902	-0.267425
42	1	0	6.361118	0.220199	0.652763
43	1	0	6.095131	-0.053352	-1.112388
44	1	0	3.213681	-3.413336	0.291421
45	1	0	0.797912	-2.823213	0.162770

NMR Spectra for compounds **1**, **8**, **9**, **11-13**, **16** and **25-31**[§]

¹H NMR, 400 MHz, CDCl₃

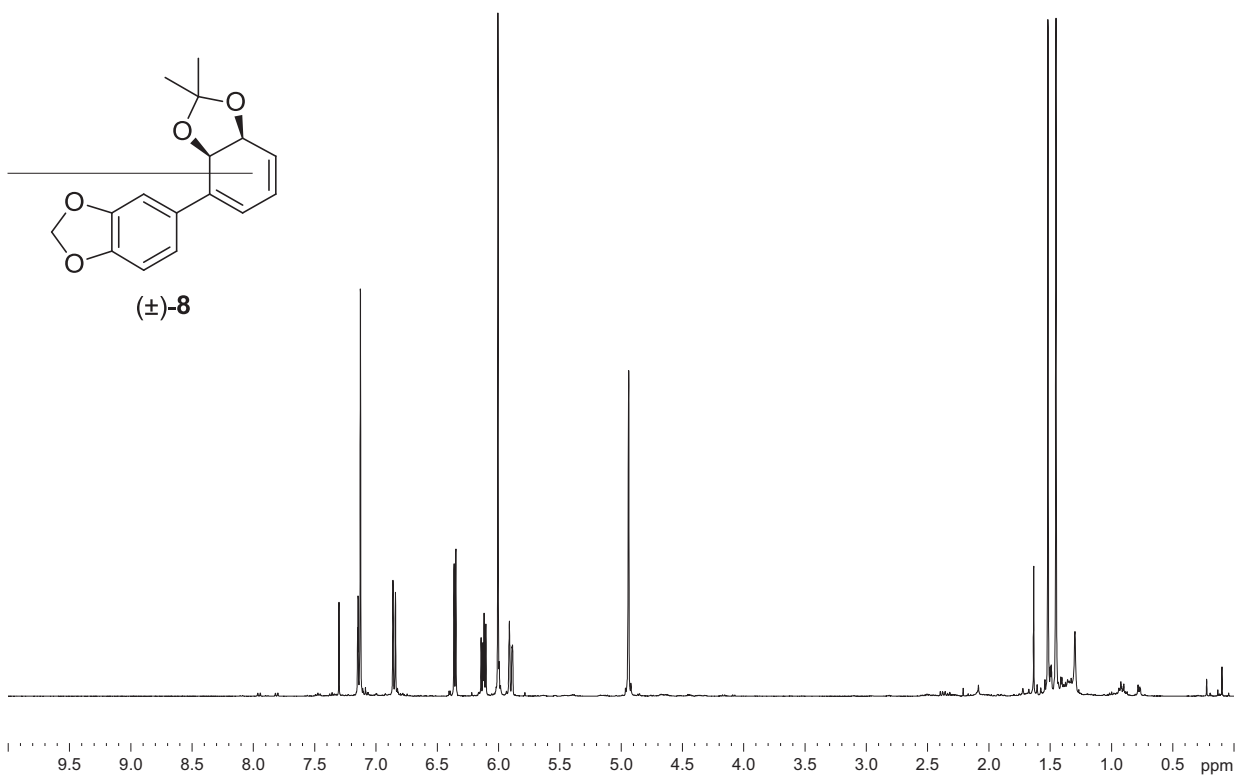


¹³C NMR, 125 MHz, CDCl₃

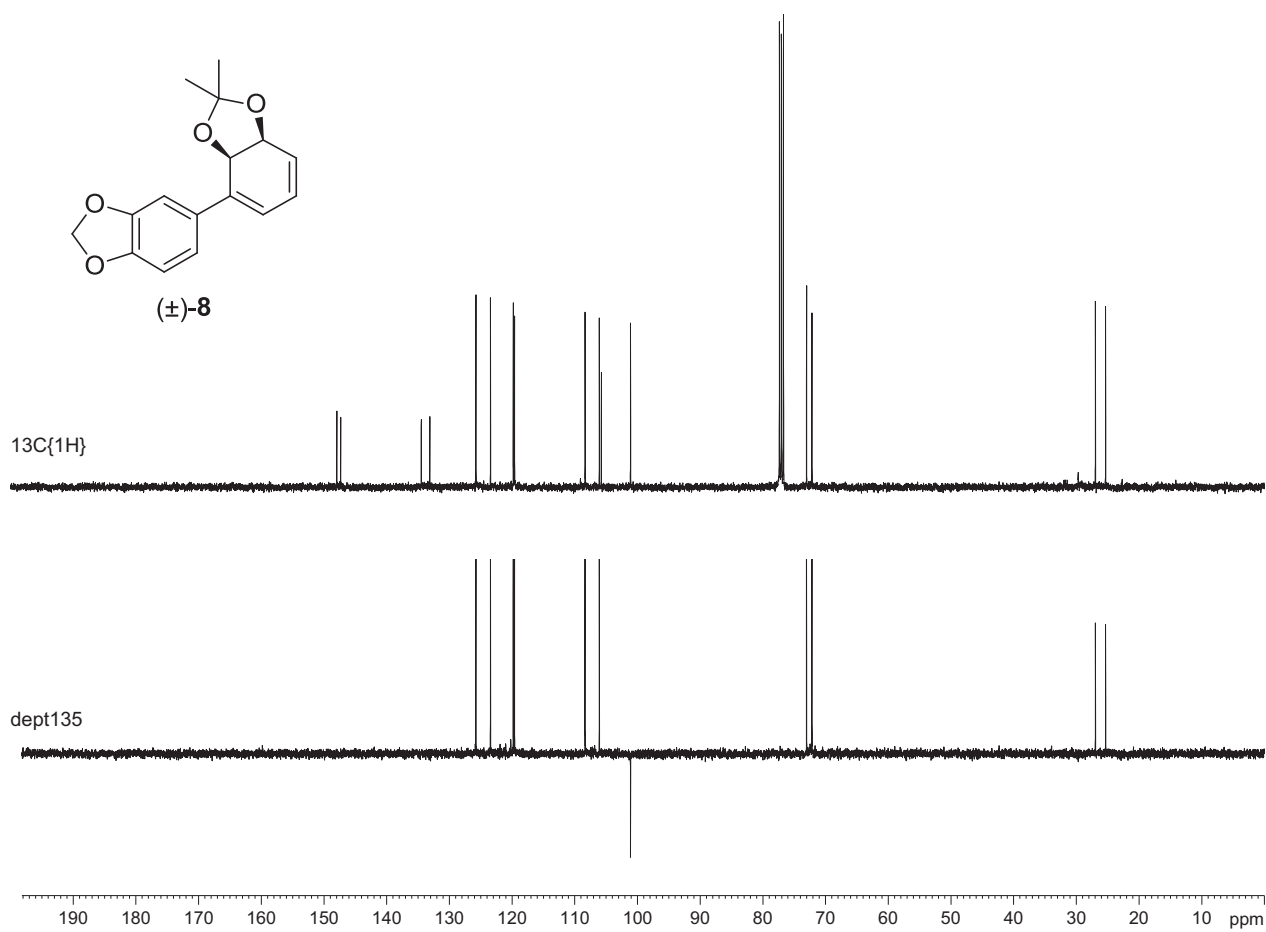


[§] Spectra for compounds **18-24** absent. These were recorded in the Department of Organic Chemistry, University of Geneva in 1995 and were unfortunately destroyed following the untimely death of Prof. Wolfgang Oppolzer in Mar 1996.

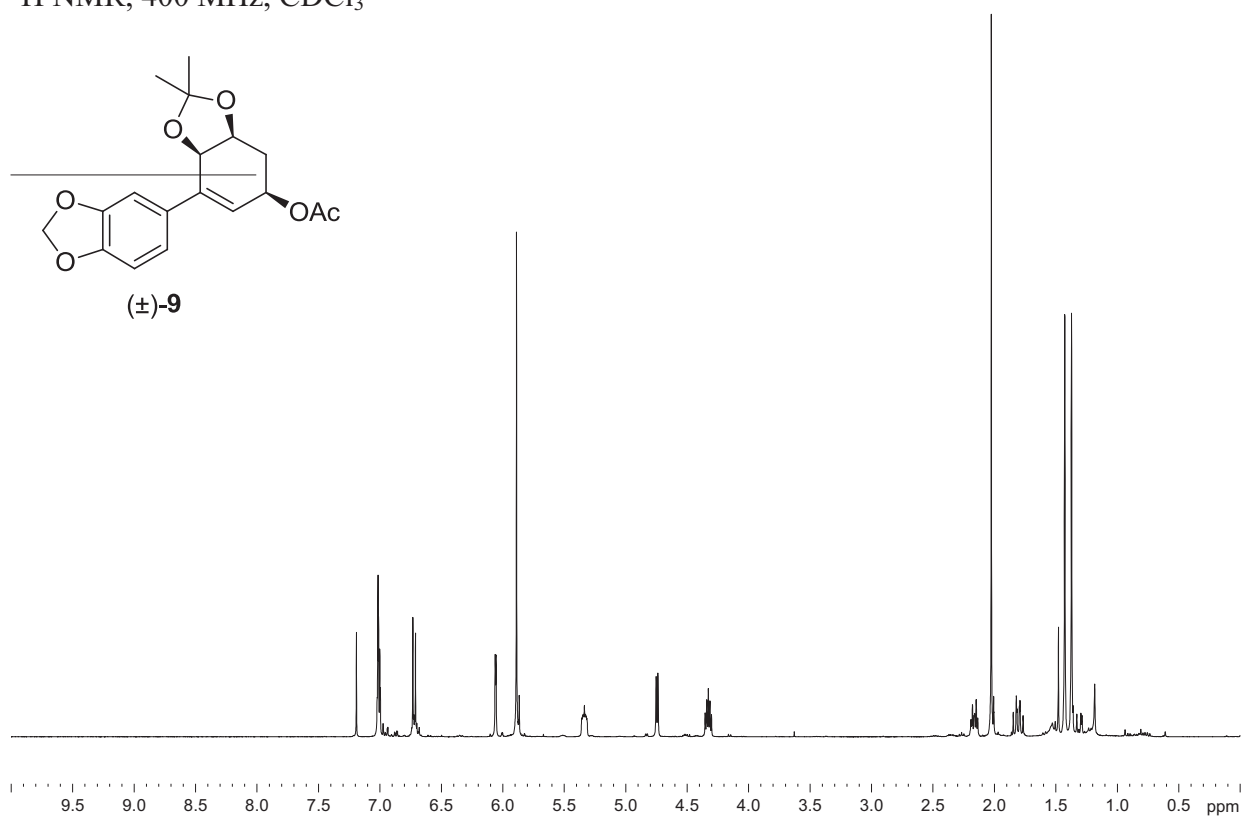
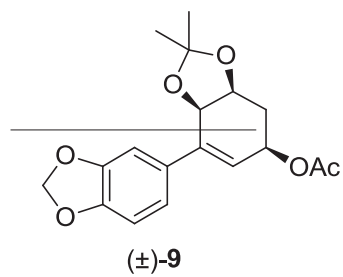
^1H NMR, 400 MHz, CDCl_3



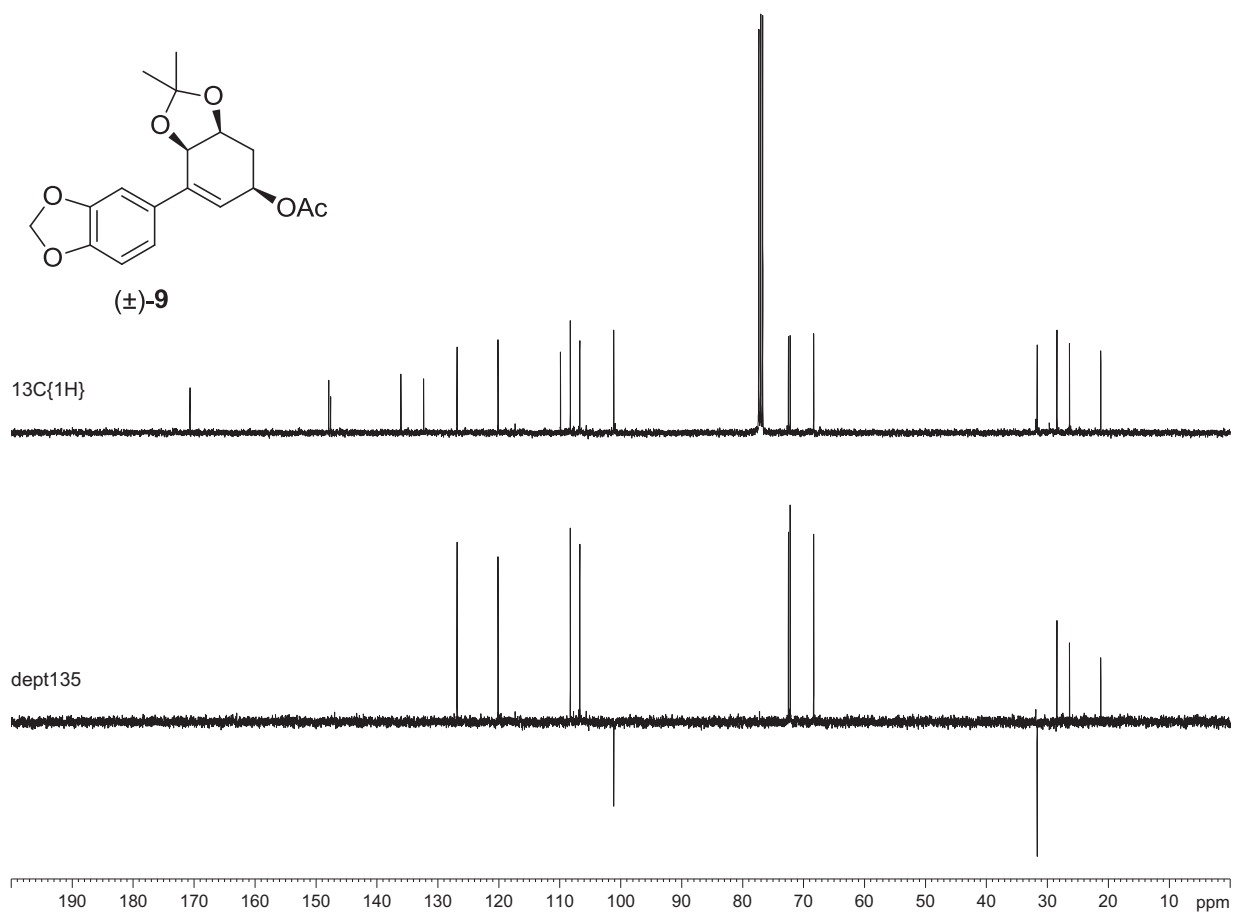
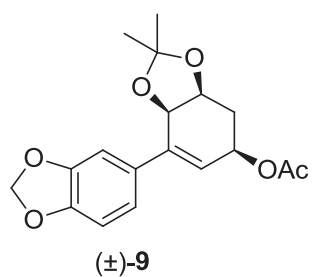
^{13}C NMR, 100 MHz, CDCl_3



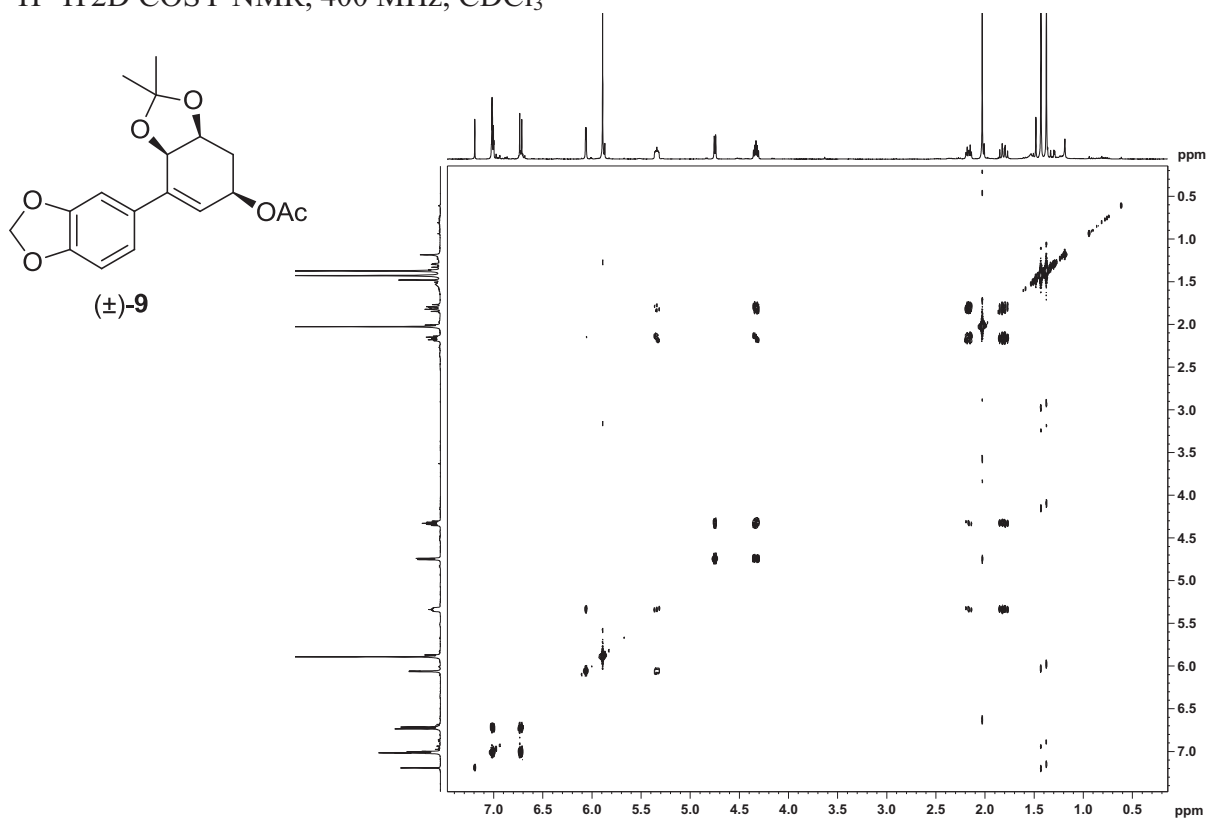
^1H NMR, 400 MHz, CDCl_3



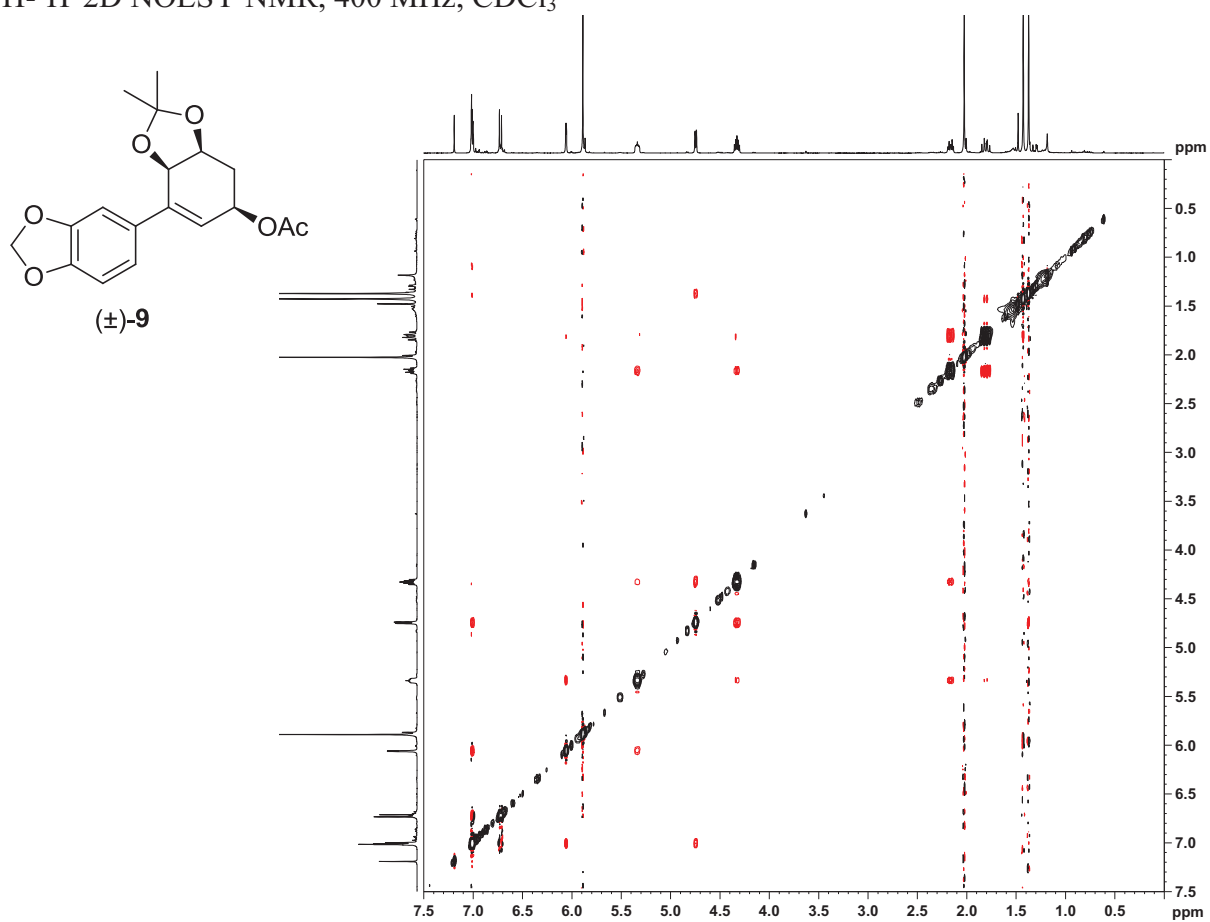
^{13}C NMR, 100 MHz, CDCl_3



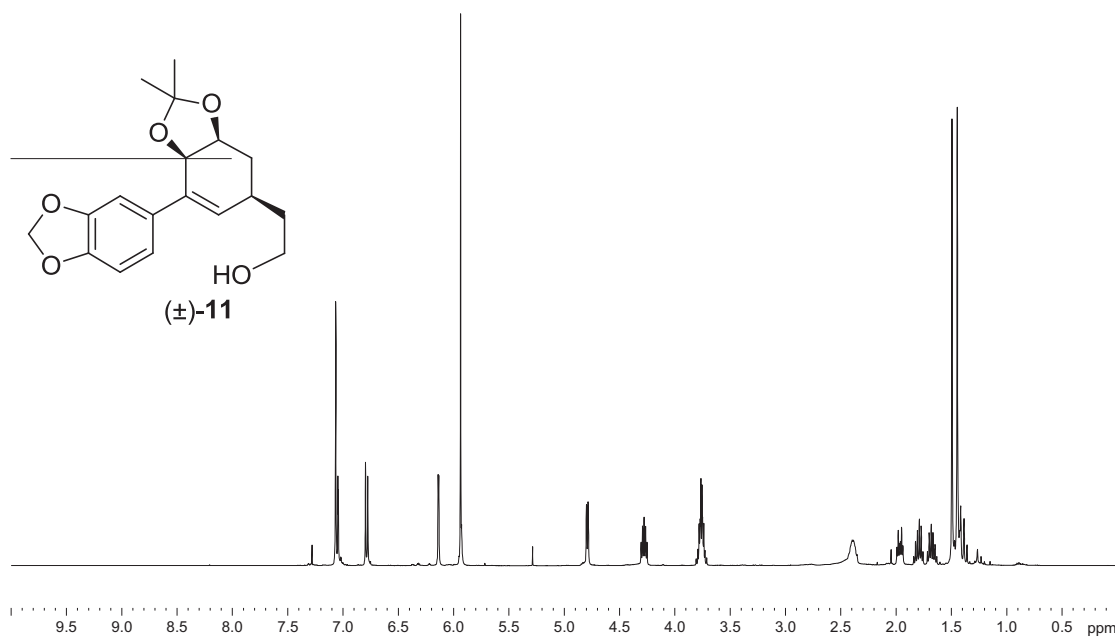
^1H - ^1H 2D COSY NMR, 400 MHz, CDCl_3



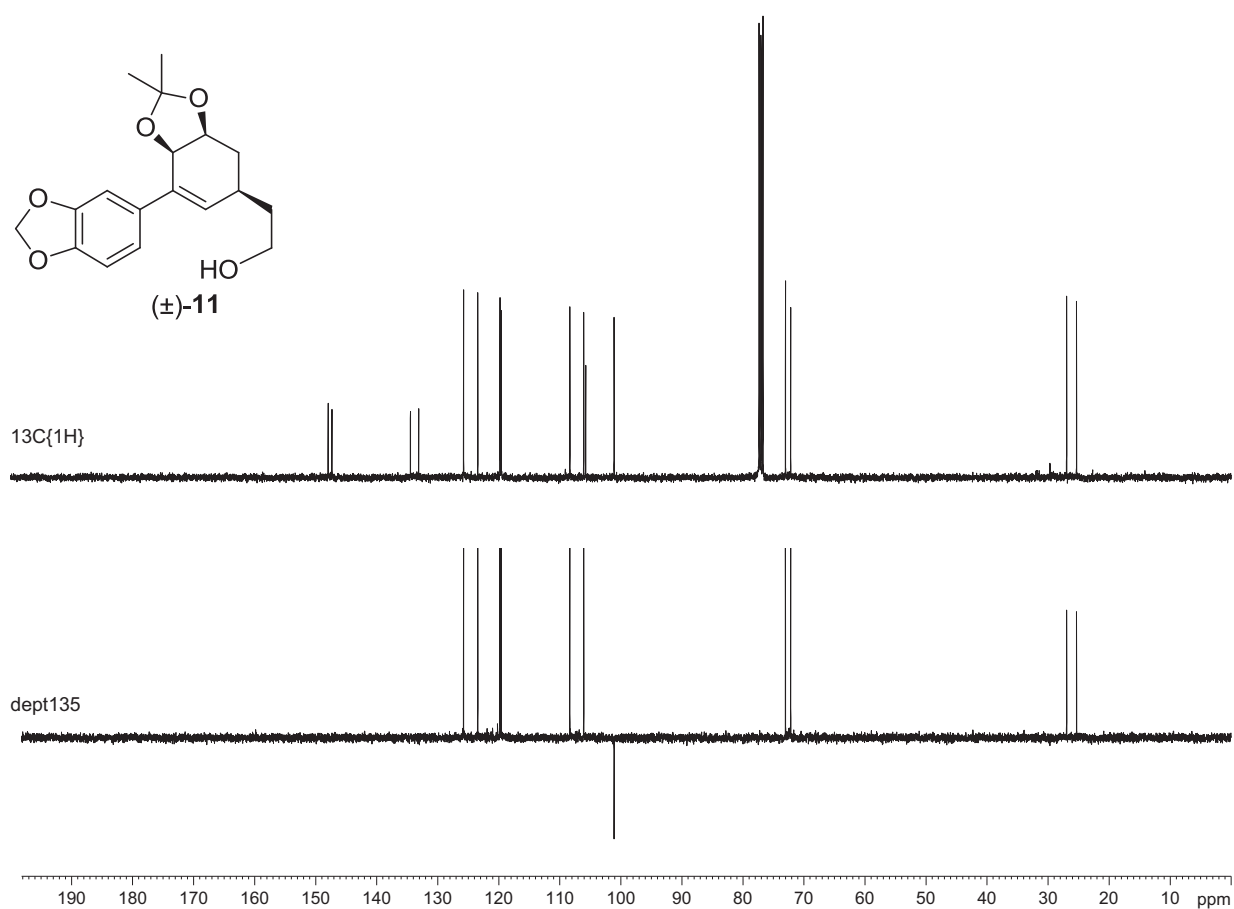
^1H - ^1H 2D NOESY NMR, 400 MHz, CDCl_3



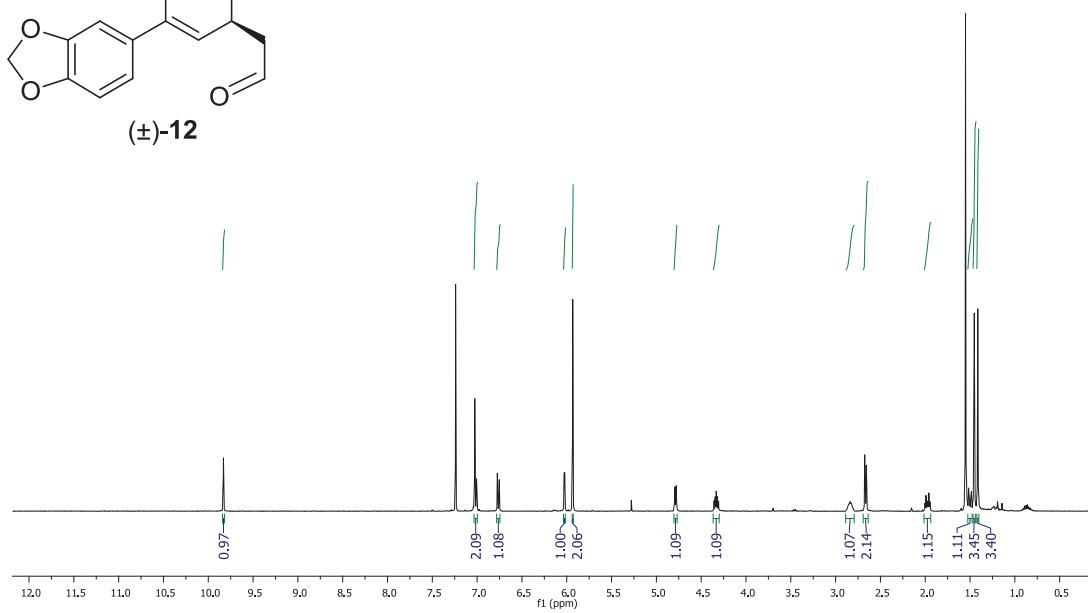
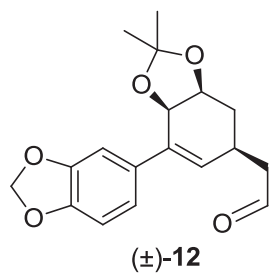
^1H NMR, 400 MHz, CDCl_3



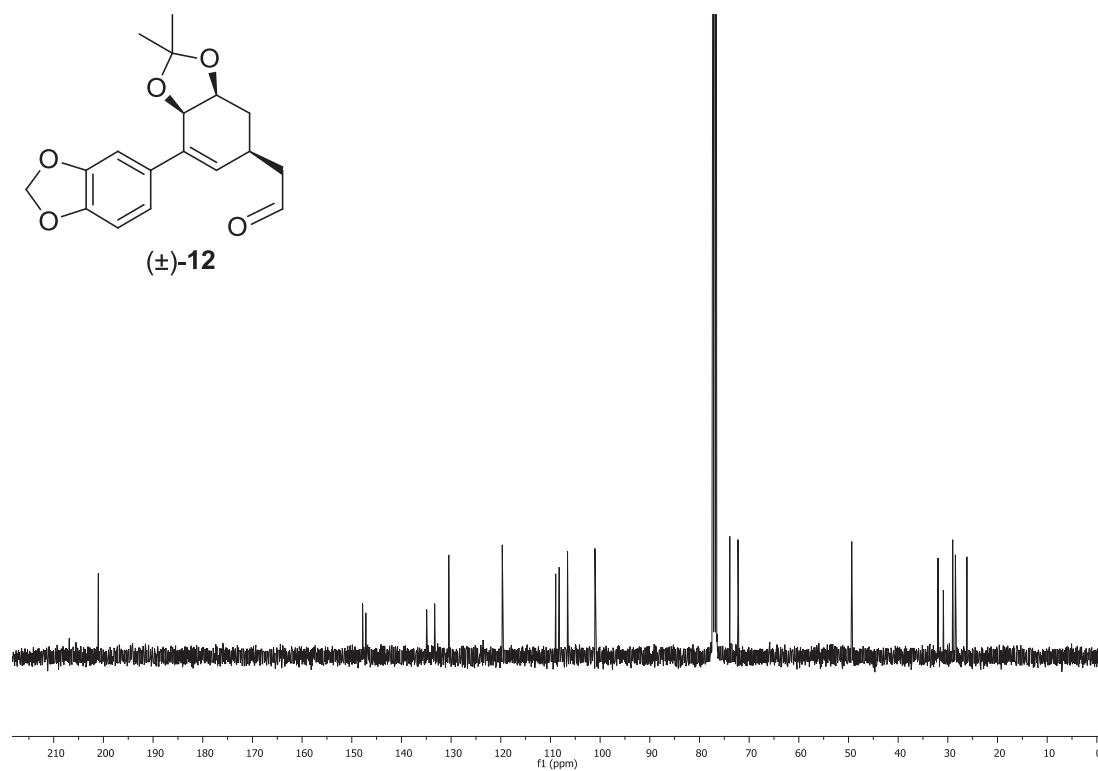
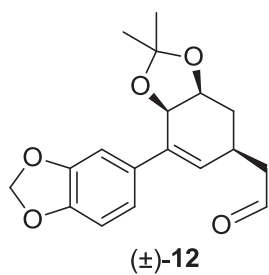
^{13}C NMR, 100 MHz, CDCl_3



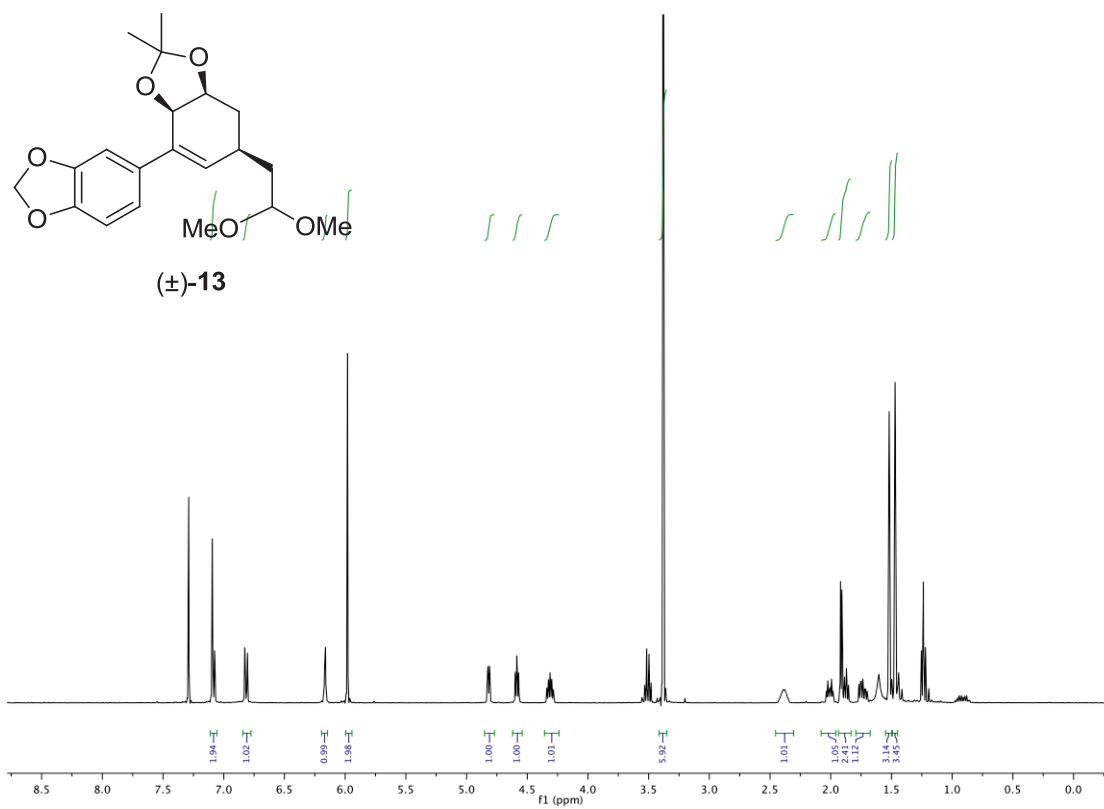
^1H NMR, 400 MHz, CDCl_3



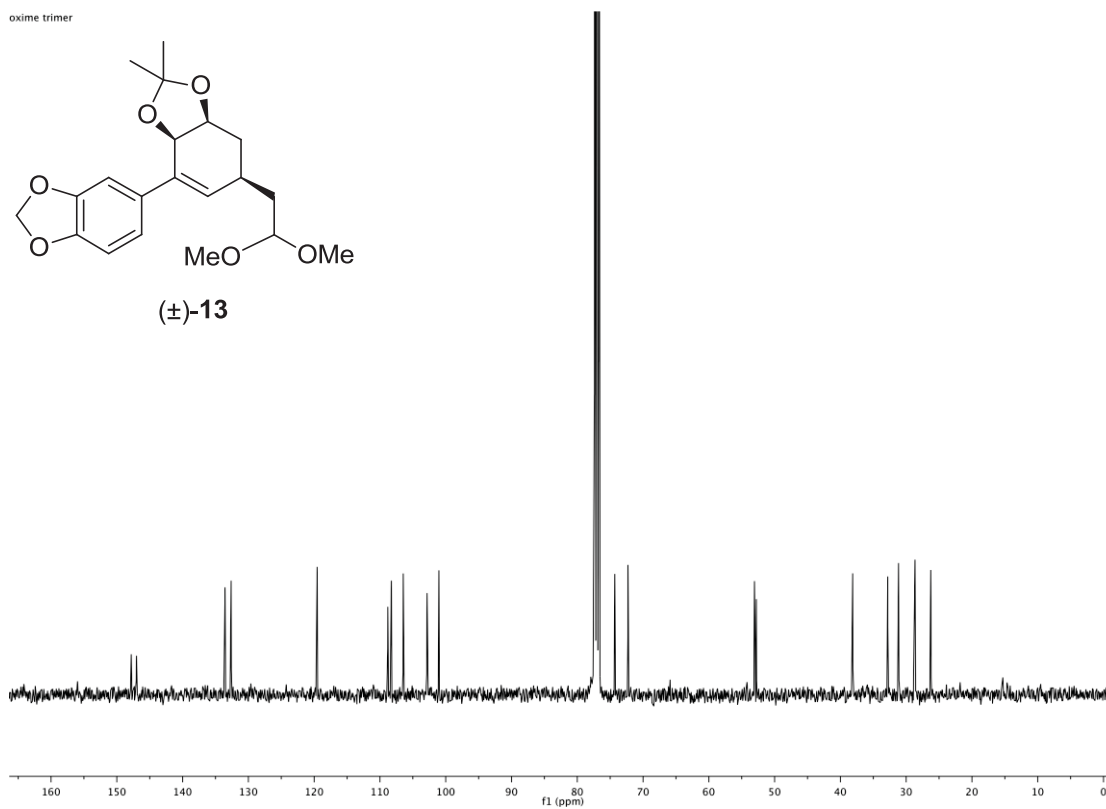
^{13}C NMR, 100 MHz, CDCl_3



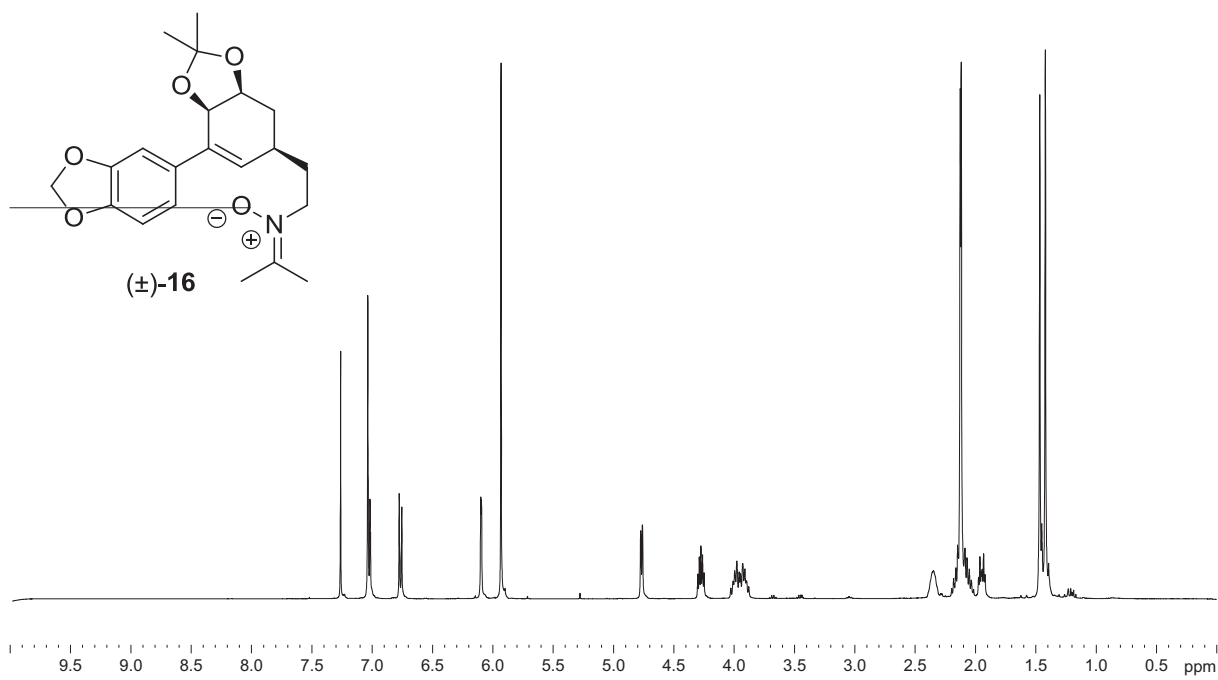
^1H NMR, 400 MHz, CDCl_3



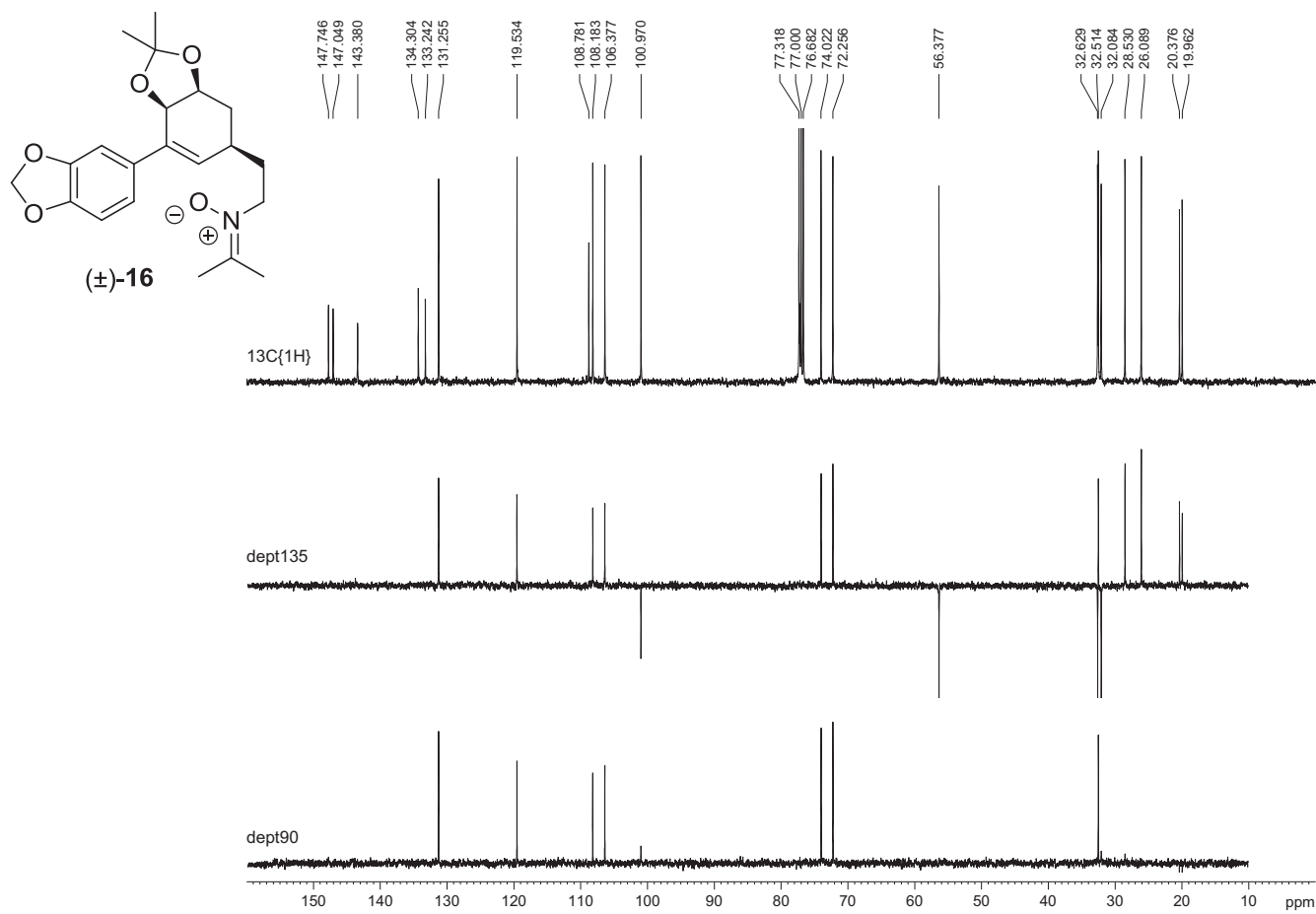
^{13}C NMR, 100 MHz, CDCl_3



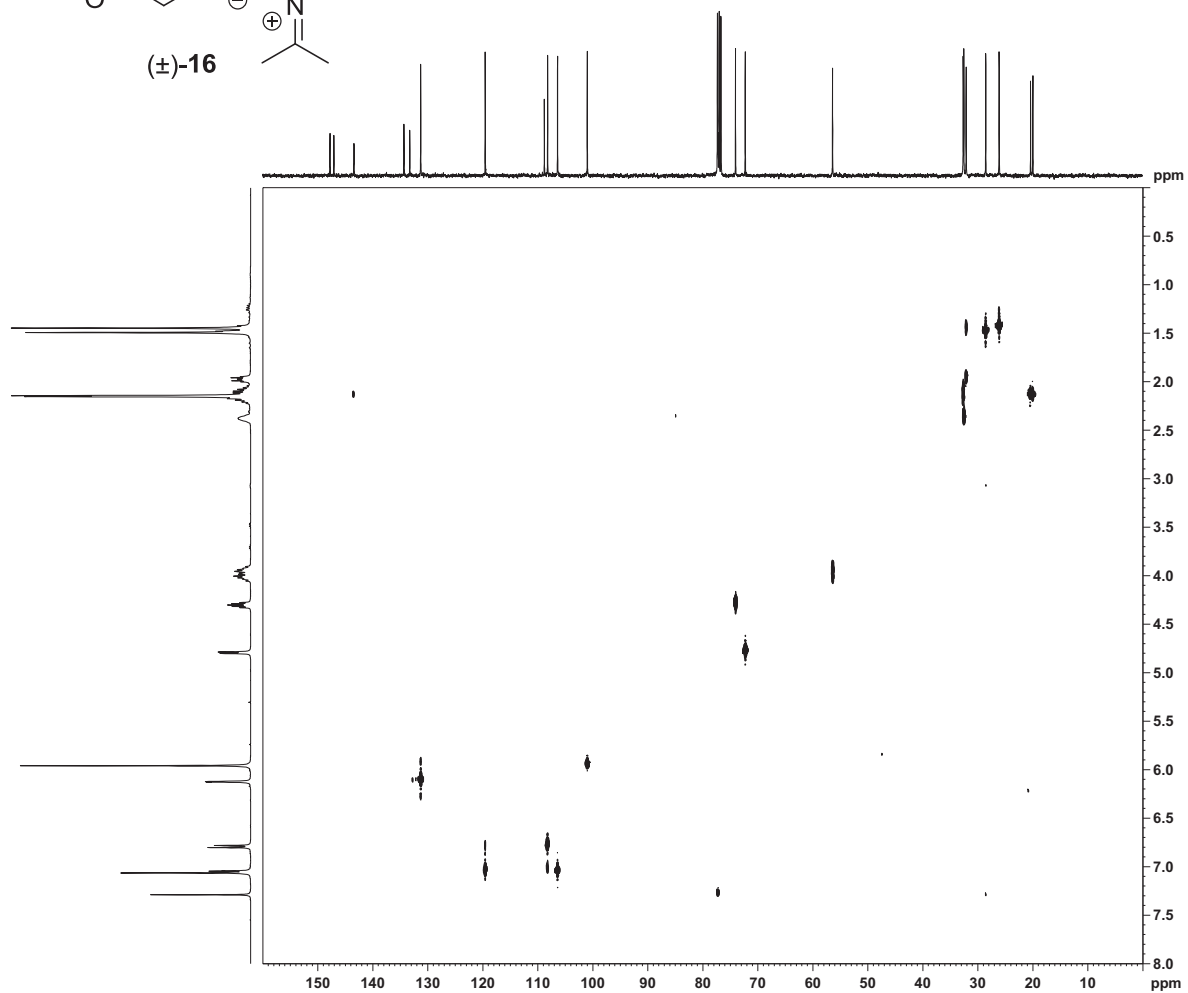
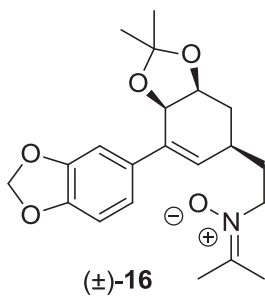
¹H NMR, 400 MHz, CDCl₃



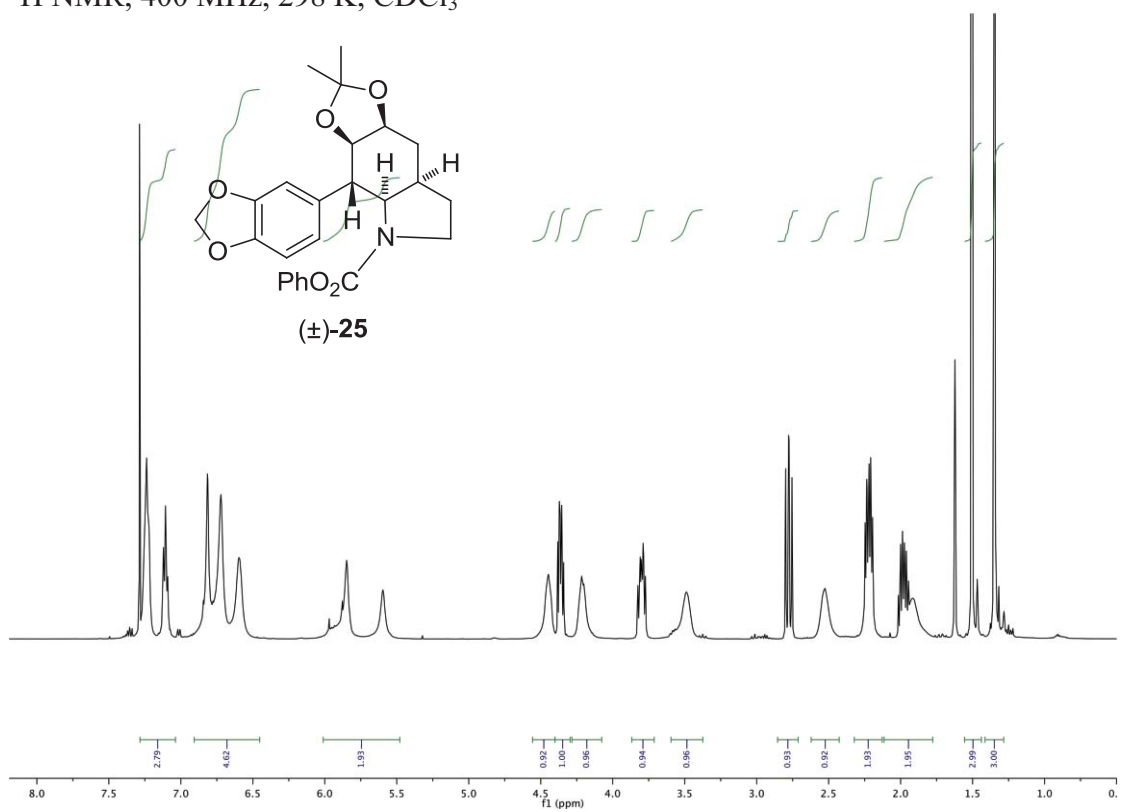
¹³C NMR, 100 MHz, CDCl₃



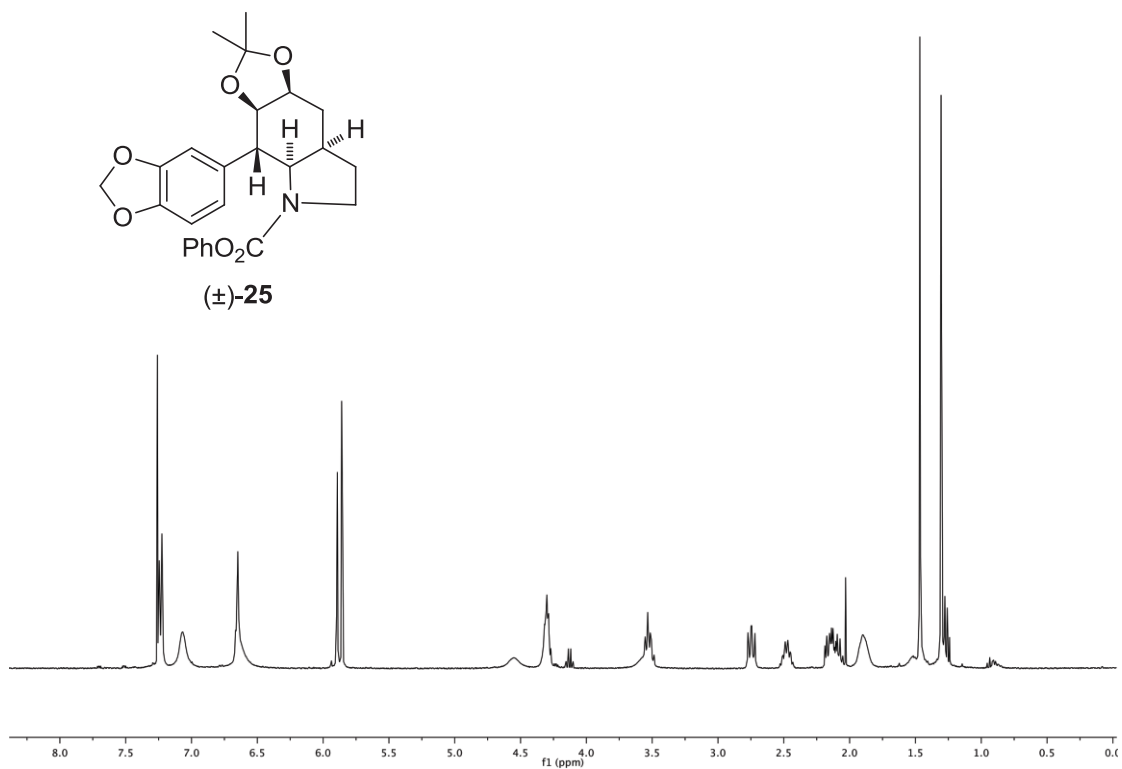
^1H - ^{13}C 2D HXCOQF NMR, 400 MHz, CDCl_3



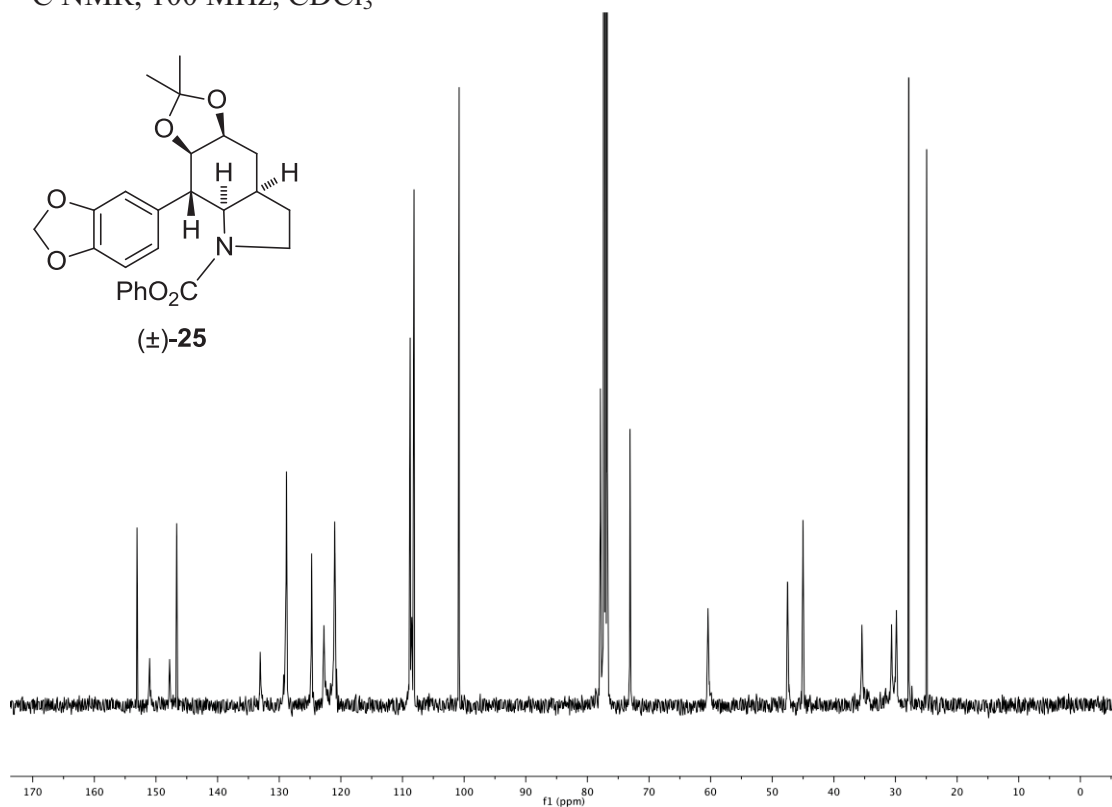
^1H NMR, 400 MHz, 298 K, CDCl_3



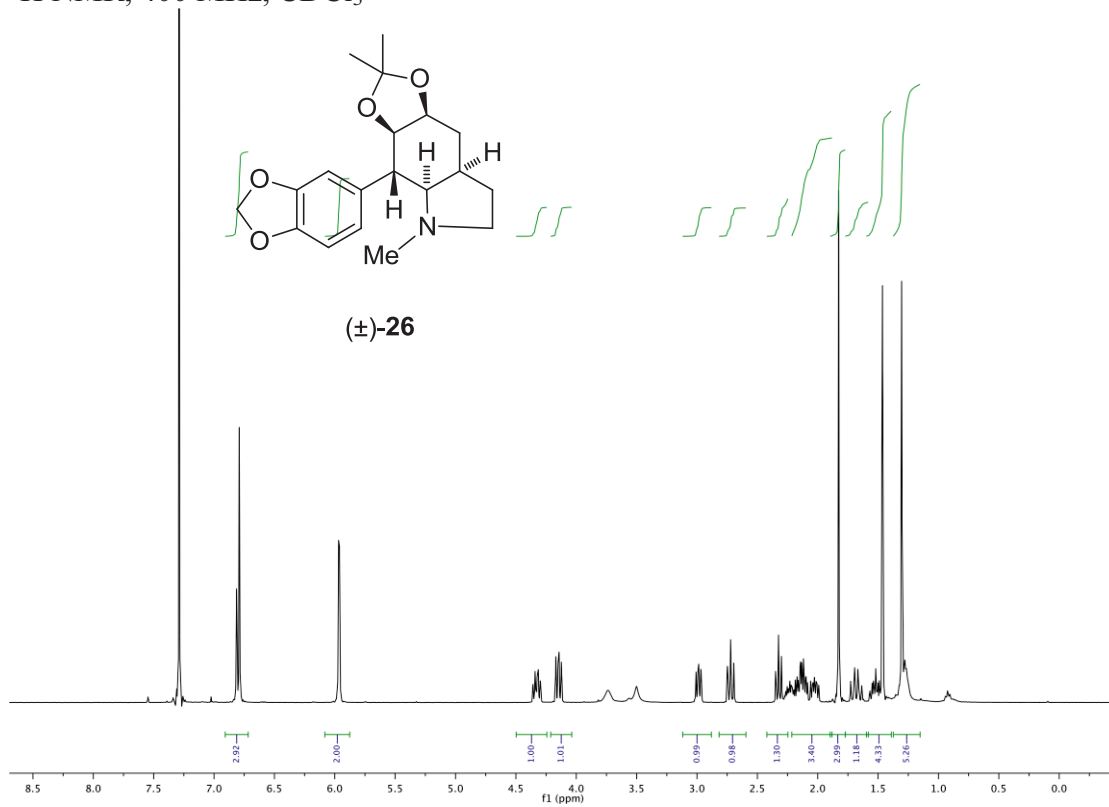
^1H NMR, 400 MHz, 328 K, CDCl_3



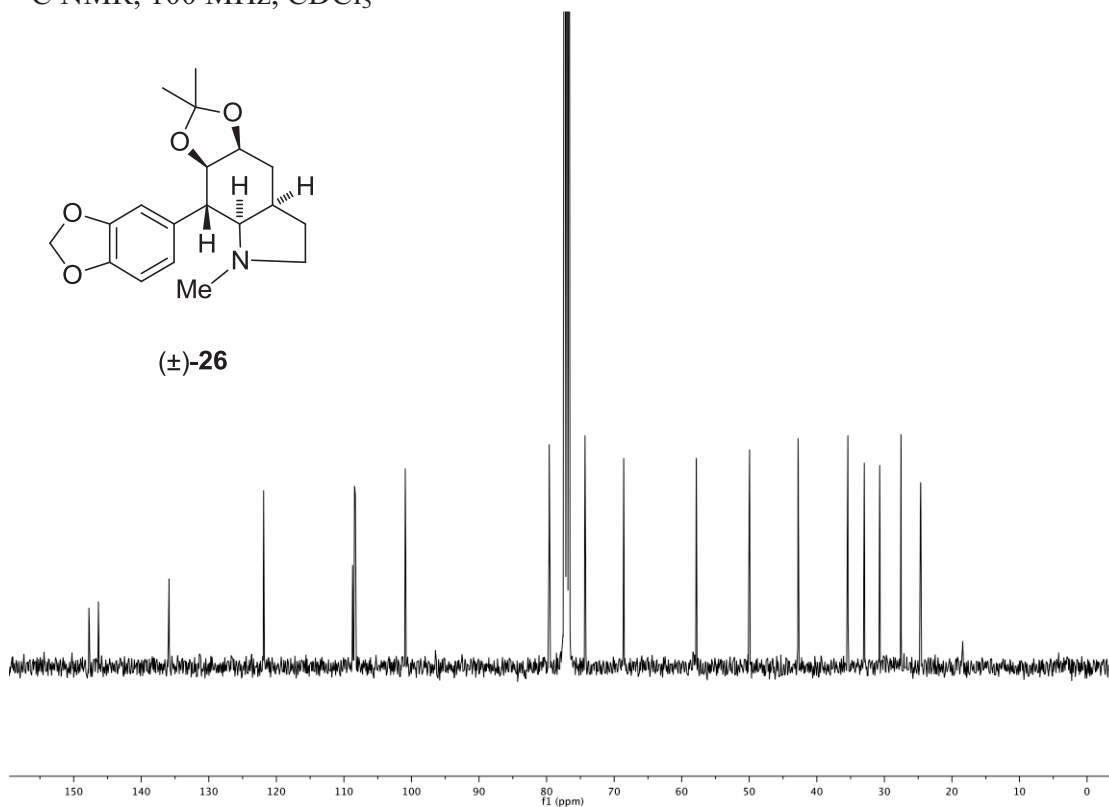
^{13}C NMR, 100 MHz, CDCl_3



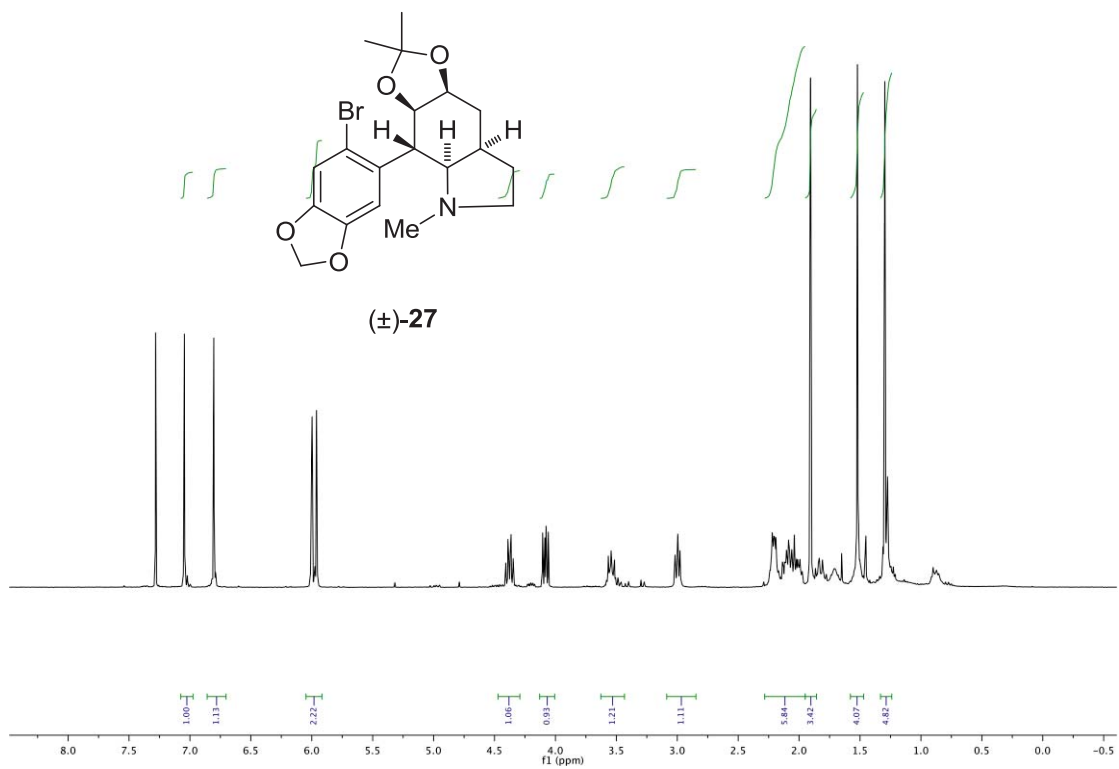
^1H NMR, 400 MHz, CDCl_3



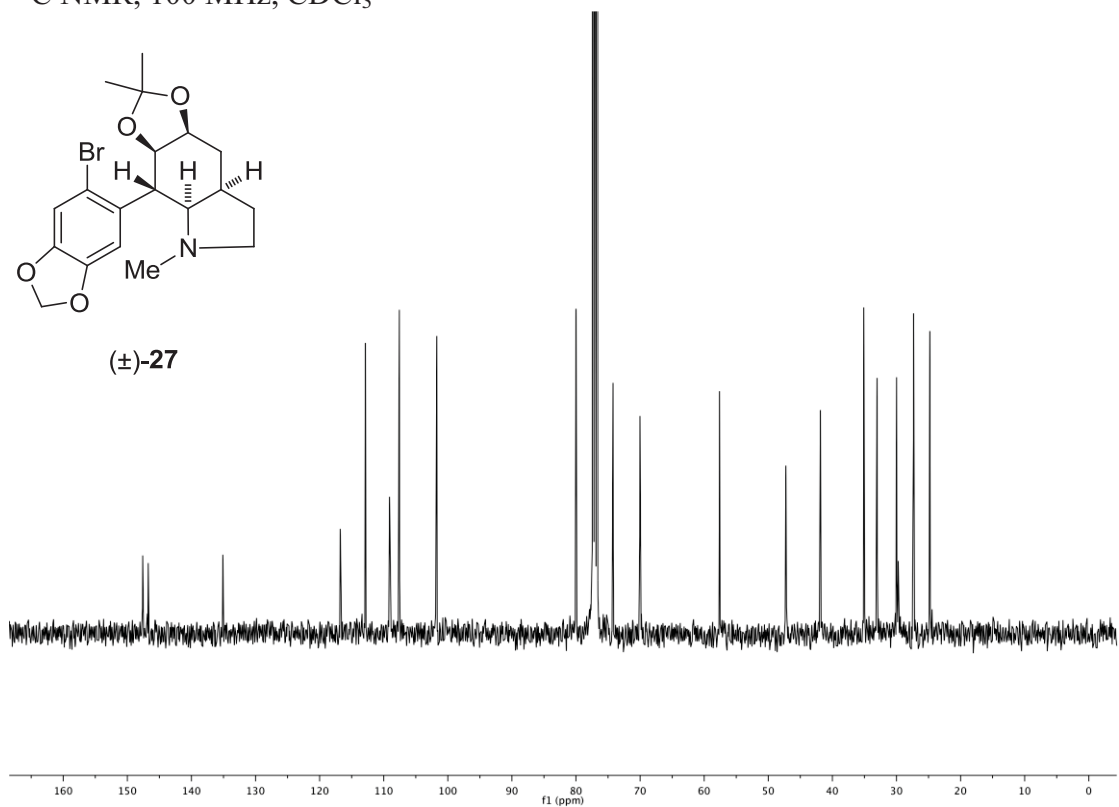
^{13}C NMR, 100 MHz, CDCl_3



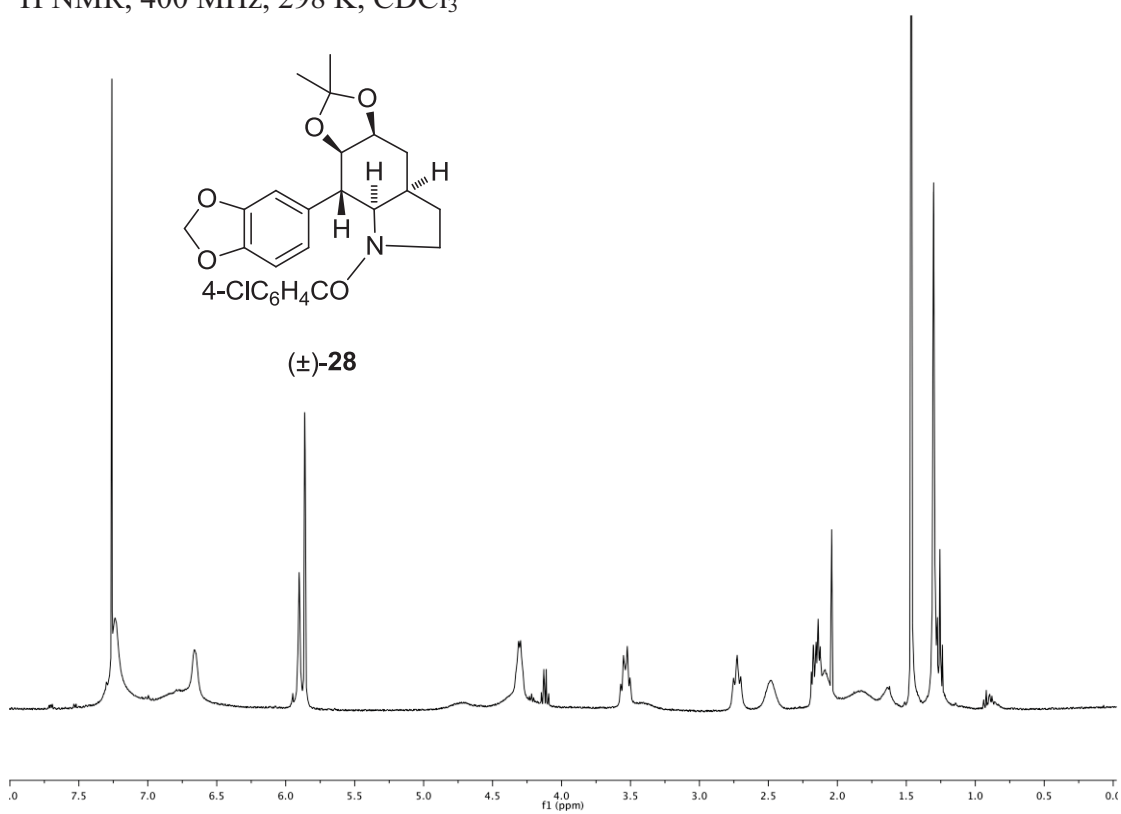
^1H NMR, 400 MHz, CDCl_3



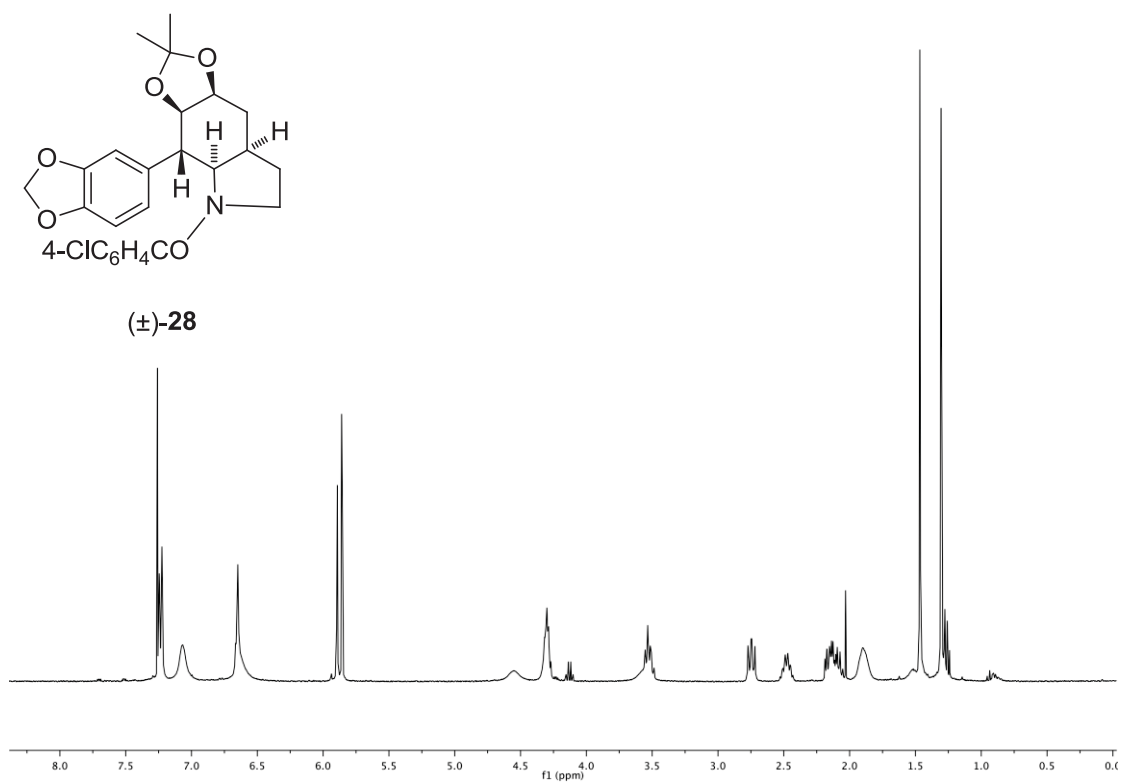
^{13}C NMR, 100 MHz, CDCl_3



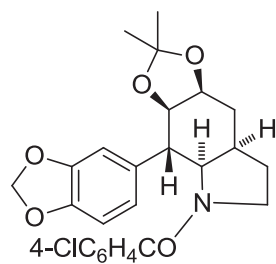
^1H NMR, 400 MHz, 298 K, CDCl_3



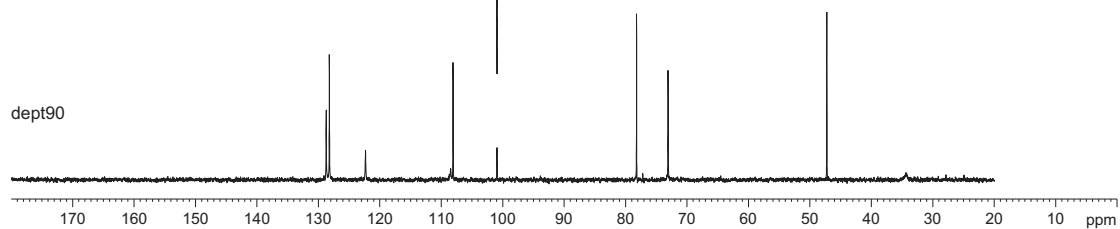
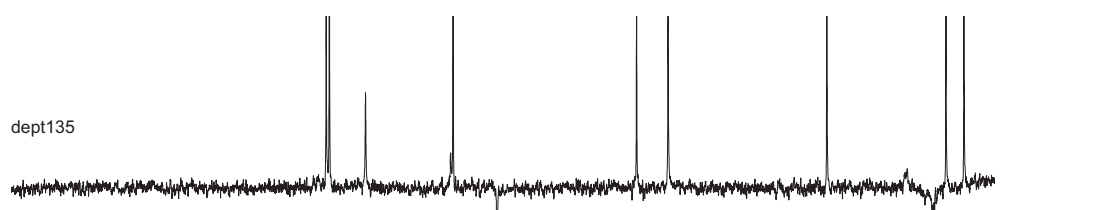
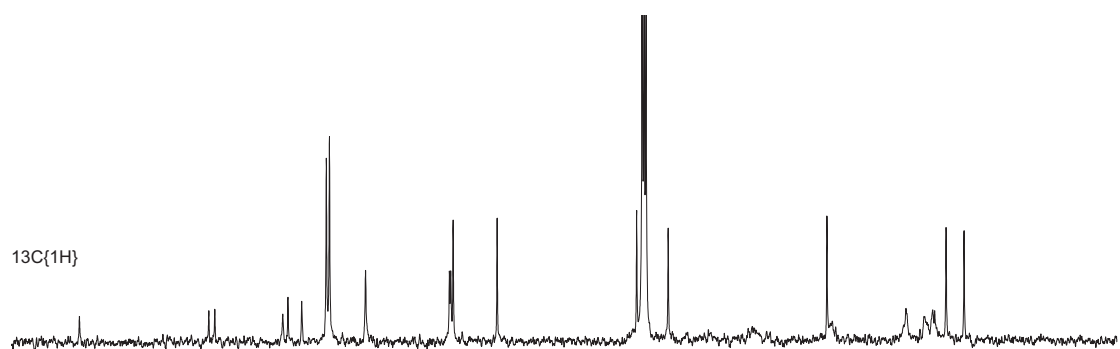
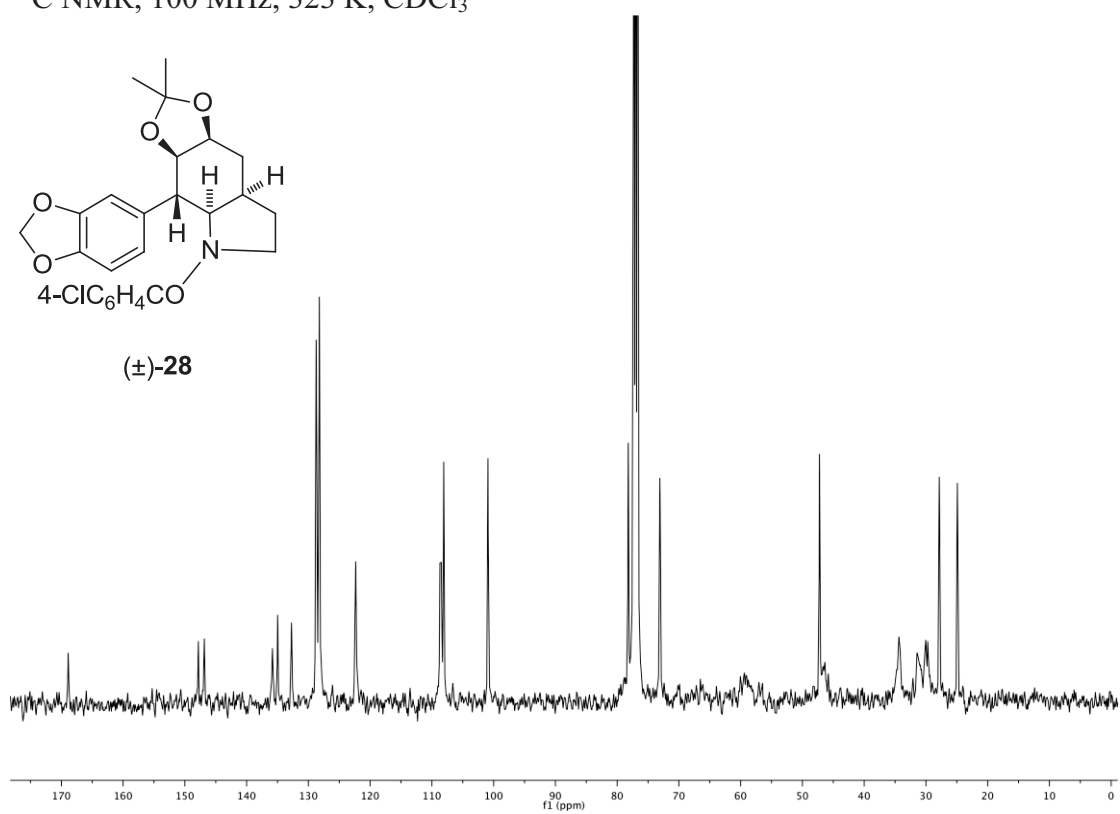
^1H NMR, 400 MHz, 328 K, CDCl_3



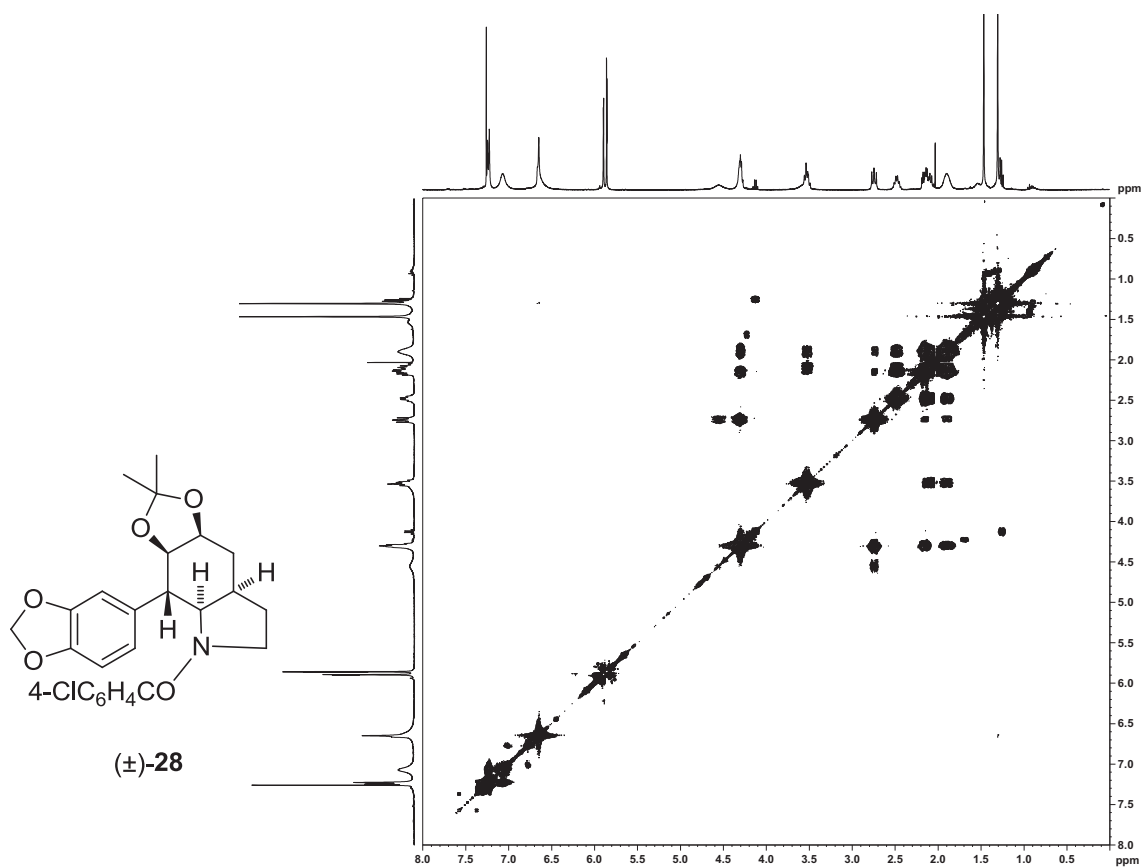
^{13}C NMR, 100 MHz, 323 K, CDCl_3



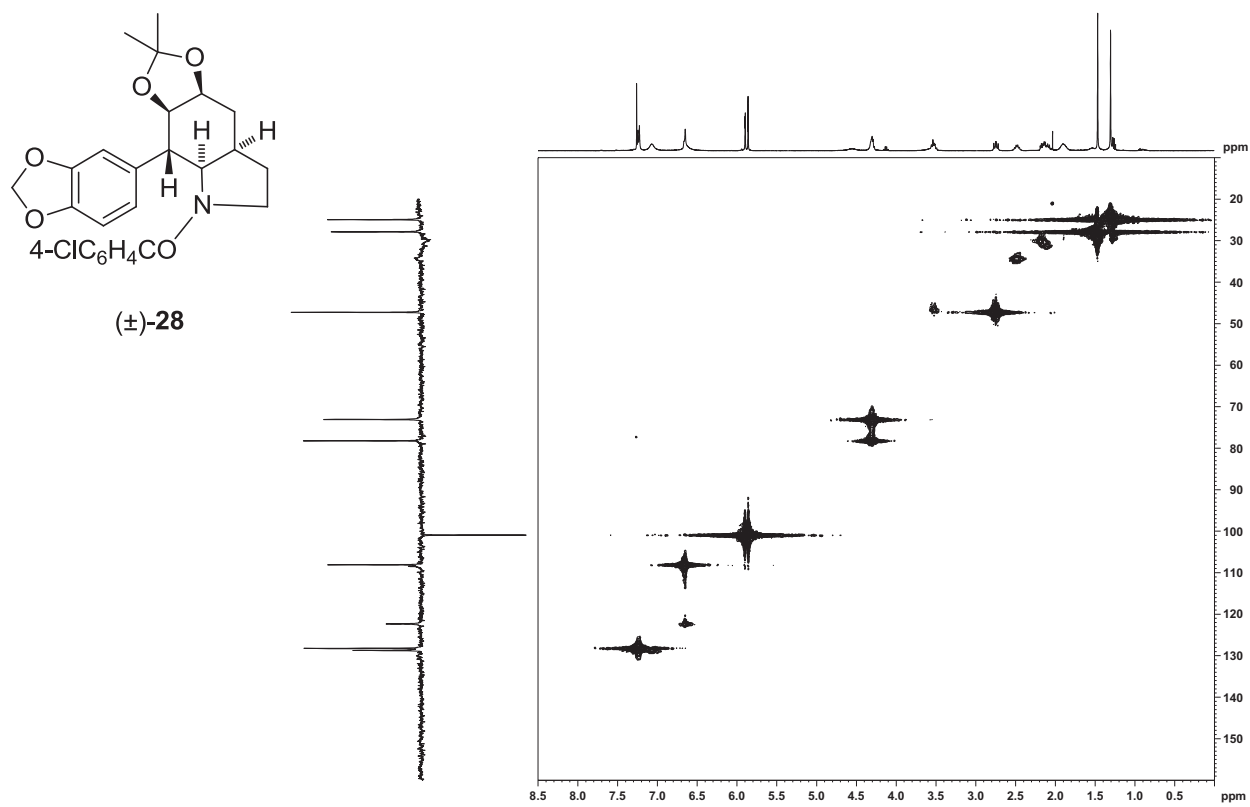
(±)-28



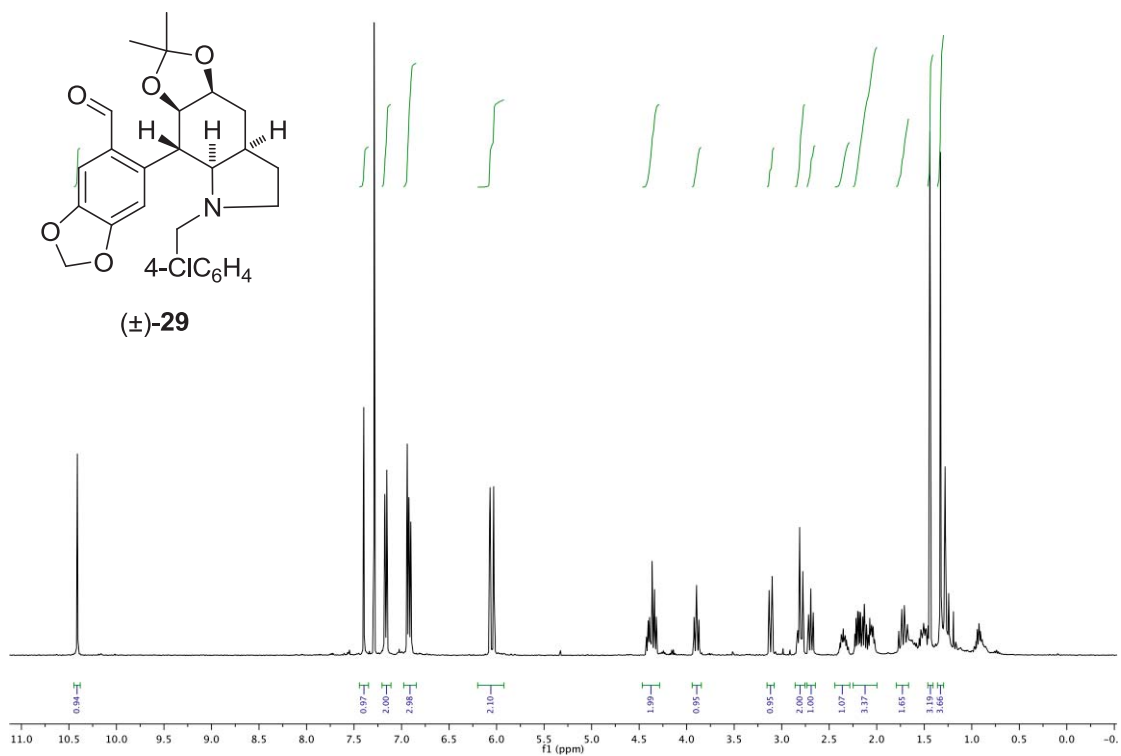
^1H - ^1H 2D COSY NMR, 400 MHz, 323 K, CDCl_3



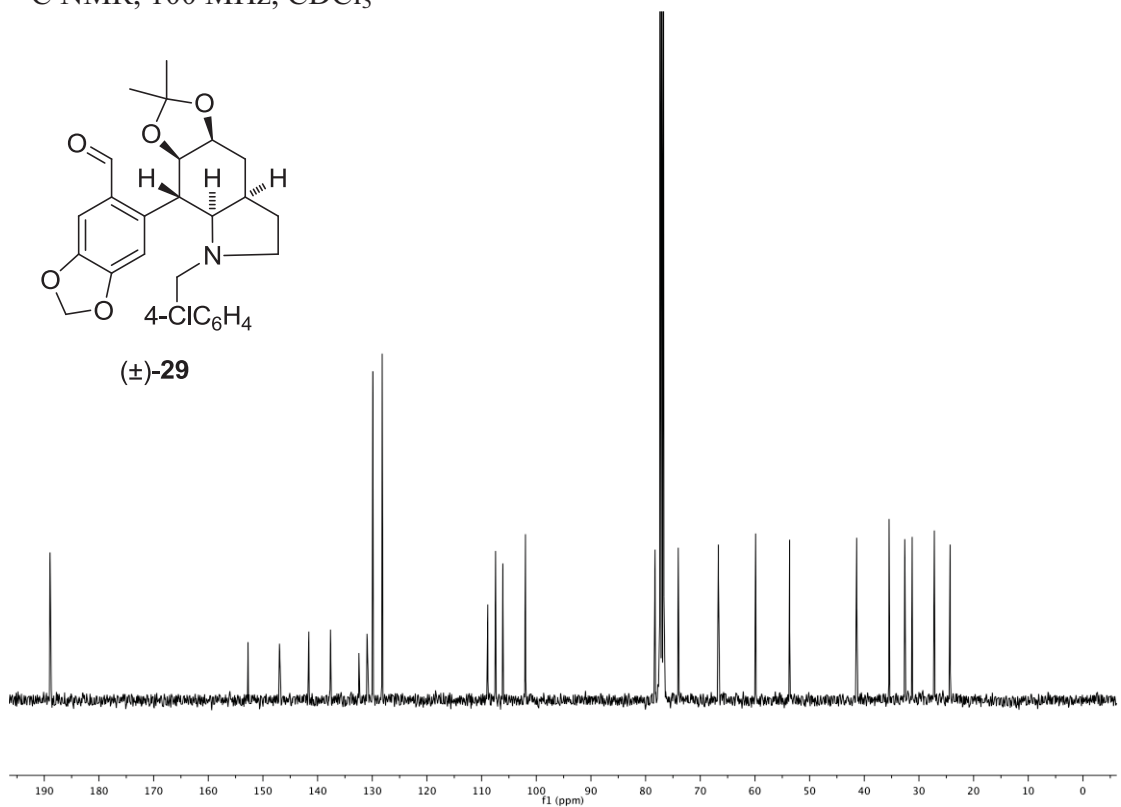
^1H - ^{13}C 2D HMC NMR, 500 MHz, 323 K, CDCl_3



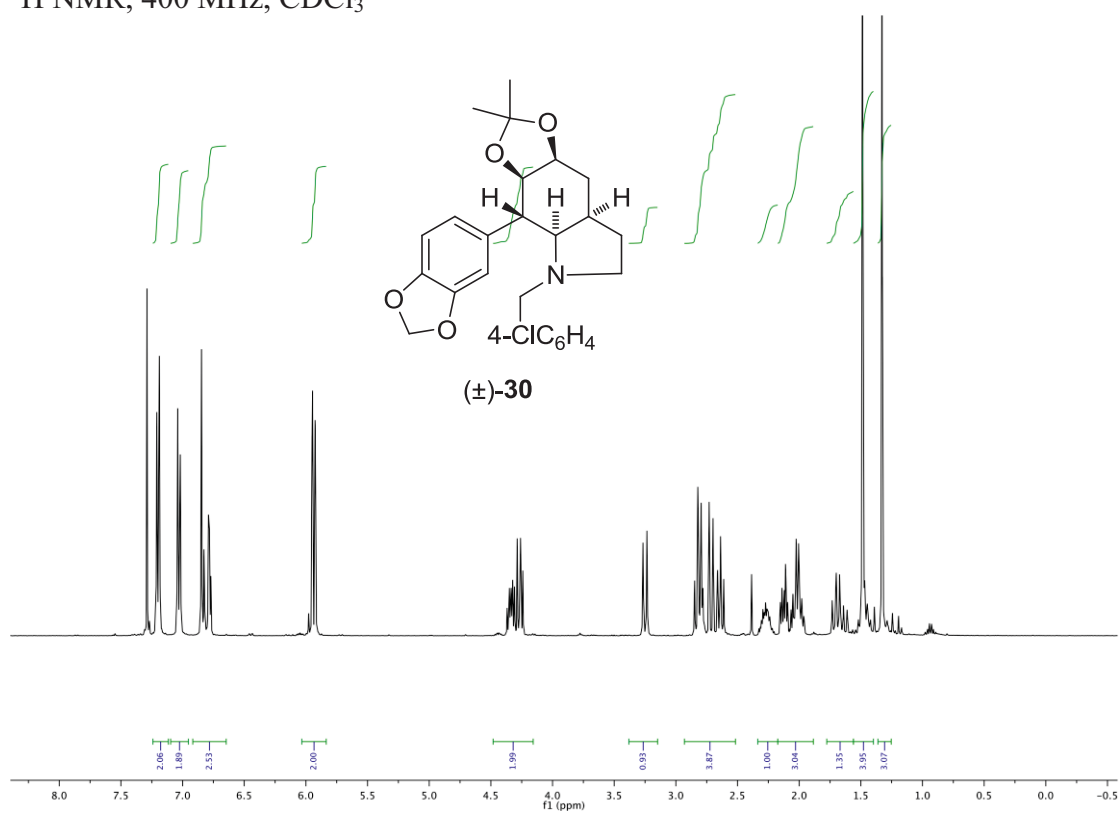
^1H NMR, 400 MHz, CDCl_3



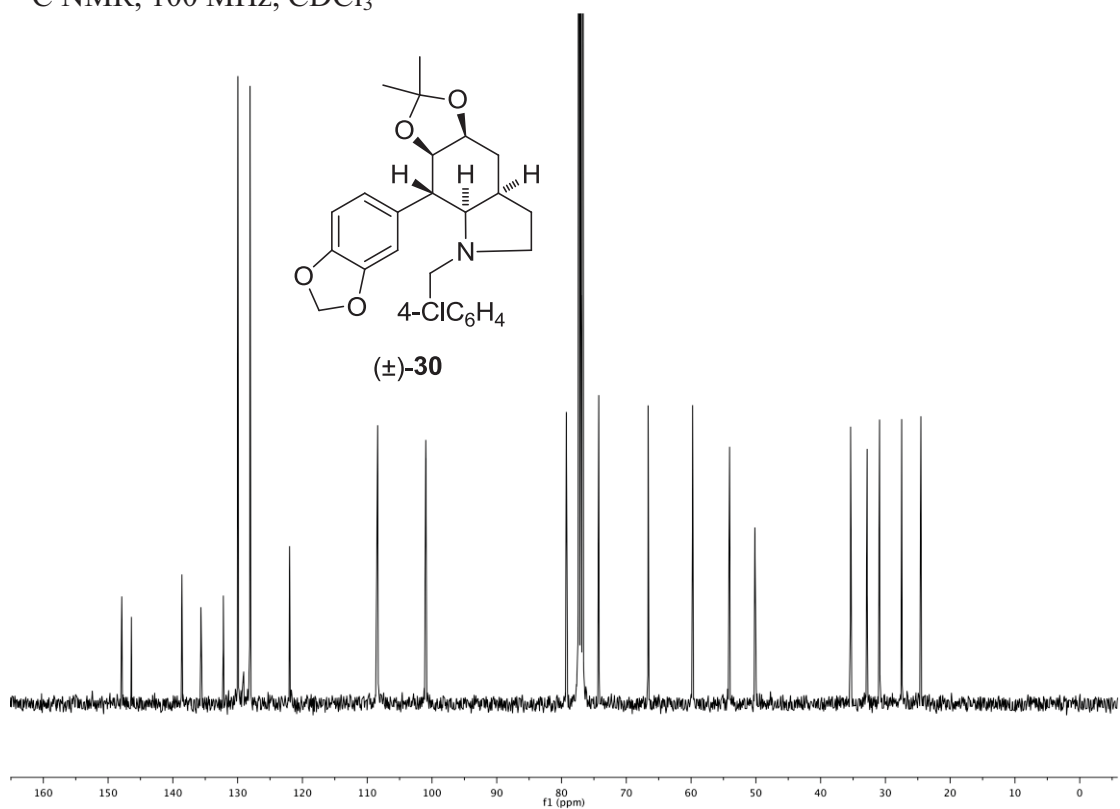
^{13}C NMR, 100 MHz, CDCl_3



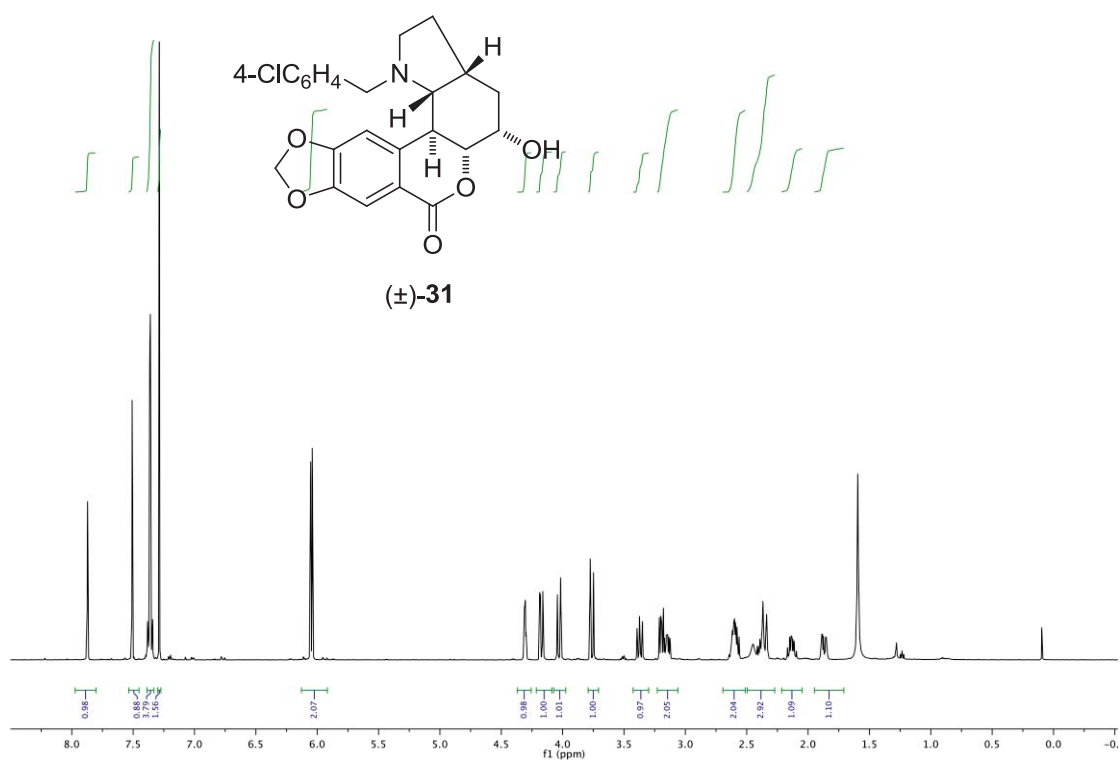
^1H NMR, 400 MHz, CDCl_3



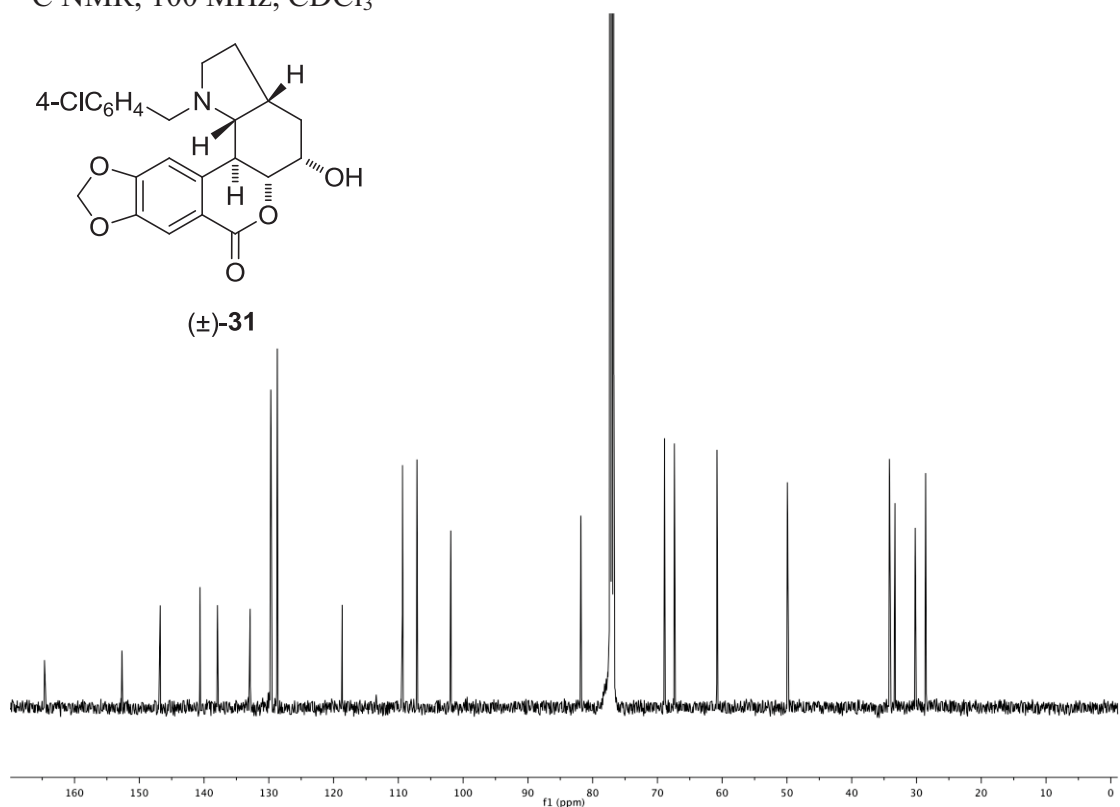
^{13}C NMR, 100 MHz, CDCl_3



^1H NMR, 400 MHz, CDCl_3



^{13}C NMR, 100 MHz, CDCl_3



Total Synthesis of the Amaryllidaceae Alkaloid Clivonine

Helmut Haning,^{a,b} Carles Giró Mañas,^c Victoria L. Paddock,^c Christian Bochet,^{d,b} Andrew J. P. White,^c Gerald Bernardinelli,^b Inderjit Mann,^e Wolfgang Oppolzer^b and Alan C. Spivey^{*c,b}

^a Bayer Schering Pharma AG, Müllerstr. 178, 13353 Berlin, Germany.

^b Department of Organic Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland.

^c Department of Chemistry, Imperial College London, South Kensington campus, London, SW7 2AZ, UK.

^d Department of Chemistry, University of Fribourg, 9 Ch. du Musée, CH-1700 Fribourg, Switzerland.

^e GSK Tonbridge, Old Powder Mills, Leigh, Tonbridge, Kent, TN11 9AN UK.

Supporting Information — X-Ray Crystallography

Crystal data for 13: C₂₀H₂₆O₆, *M* = 362.41, monoclinic, *P*2₁/*c* (no. 14), *a* = 14.5941(4), *b* = 9.4049(2), *c* = 13.8121(3) Å, β = 91.949(2)°, *V* = 1894.70(8) Å³, *Z* = 4, *D*_c = 1.270 g cm⁻³, μ(Mo-Kα) = 0.093 mm⁻¹, *T* = 173 K, colourless plates, Oxford Diffraction Xcalibur 3 diffractometer; 6105 independent measured reflections (*R*_{int} = 0.0455), *F*² refinement, *R*₁(obs) = 0.0448, *wR*₂(all) = 0.1191, 3310 independent observed absorption-corrected reflections [*|F*_o] > 4σ(*|F*_o), 2θ_{max} = 64°], 235 parameters. CCDC 792816.

Crystal data for 16: C₂₁H₂₇NO₅·H₂O, *M* = 391.45, monoclinic, *P*2₁/*n* (no. 14), *a* = 7.2818(1), *b* = 33.8728(3), *c* = 8.3252(1) Å, β = 104.148(1)°, *V* = 1991.17(4) Å³, *Z* = 4, *D*_c = 1.306 g cm⁻³, μ(Cu-Kα) = 0.784 mm⁻¹, *T* = 173 K, colourless blocks, Oxford Diffraction Xcalibur PX Ultra diffractometer; 3808 independent measured reflections (*R*_{int} = 0.0259), *F*² refinement, *R*₁(obs) = 0.0424, *wR*₂(all) = 0.1248, 3426 independent observed absorption-corrected reflections [*|F*_o] > 4σ(*|F*_o), 2θ_{max} = 143°], 263 parameters. CCDC 792817.

The hydrogen atoms of the included water molecule in the structure of **16** were located from Δ*F* maps and refined freely subject to an O–H distance constraint of 0.90 Å. The methyl protons of the N=CMe₂ unit were added in idealised tetrahedral positions and, as they are on *sp*³ centres bonded to an *sp*² centre, the groups were allowed to rotate about the associated C–C bond to find the best fit with the electron density map (*i.e.* the SHELX HFIX/AFIX 137 command). *C*₁-related molecules are linked by O–H⋯O hydrogen bonding *via* the included water molecule (Fig. S3).

Crystal data for 20: C₁₉H₂₃NO₄, $M = 329.38$, hexagonal, $P6_1$ (no. 169), $a = b = 10.695(1)$, $c = 25.134(4)$ Å, $V = 2489.7(5)$ Å³, $Z = 6$, $D_c = 1.318$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.092$ mm⁻¹, $T = 298$ K, colourless prisms, Stoe Stadi-4 diffractometer; 2331 independent measured reflections ($R_{\text{int}} = 0.0$), F^2 refinement, $R_1(\text{obs}) = 0.0446$, $wR_2(\text{all}) = 0.0846$, 1415 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{\text{max}} = 46^\circ$], 218 parameters. The absolute structure of **20** could not be determined by either an R -factor test [$R_1^+ = 0.0446$, $R_1^- = 0.0446$] or by use of the Flack parameter [$x^+ = 0.0(17)$, $x^- = 2.6(17)$], and so was assigned by internal reference on C(7), C(8), C(12), C(14) and C(22). CCDC 792818.

Crystal data for 28: C₂₅H₂₆ClNO₅, $M = 455.92$, triclinic, $P-1$ (no. 2), $a = 6.0988(2)$, $b = 11.8551(4)$, $c = 16.3205(5)$ Å, $\alpha = 102.804(3)$, $\beta = 98.740(3)$, $\gamma = 102.130(3)^\circ$, $V = 1100.31(6)$ Å³, $Z = 2$, $D_c = 1.376$ g cm⁻³, $\mu(\text{Cu-K}\alpha) = 1.854$ mm⁻¹, $T = 298$ K, colourless plates, Oxford Diffraction Xcalibur PX Ultra diffractometer; 4218 independent measured reflections ($R_{\text{int}} = 0.0256$), F^2 refinement, $R_1(\text{obs}) = 0.0368$, $wR_2(\text{all}) = 0.1087$, 3060 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{\text{max}} = 143^\circ$], 290 parameters. CCDC 792819.

Figures

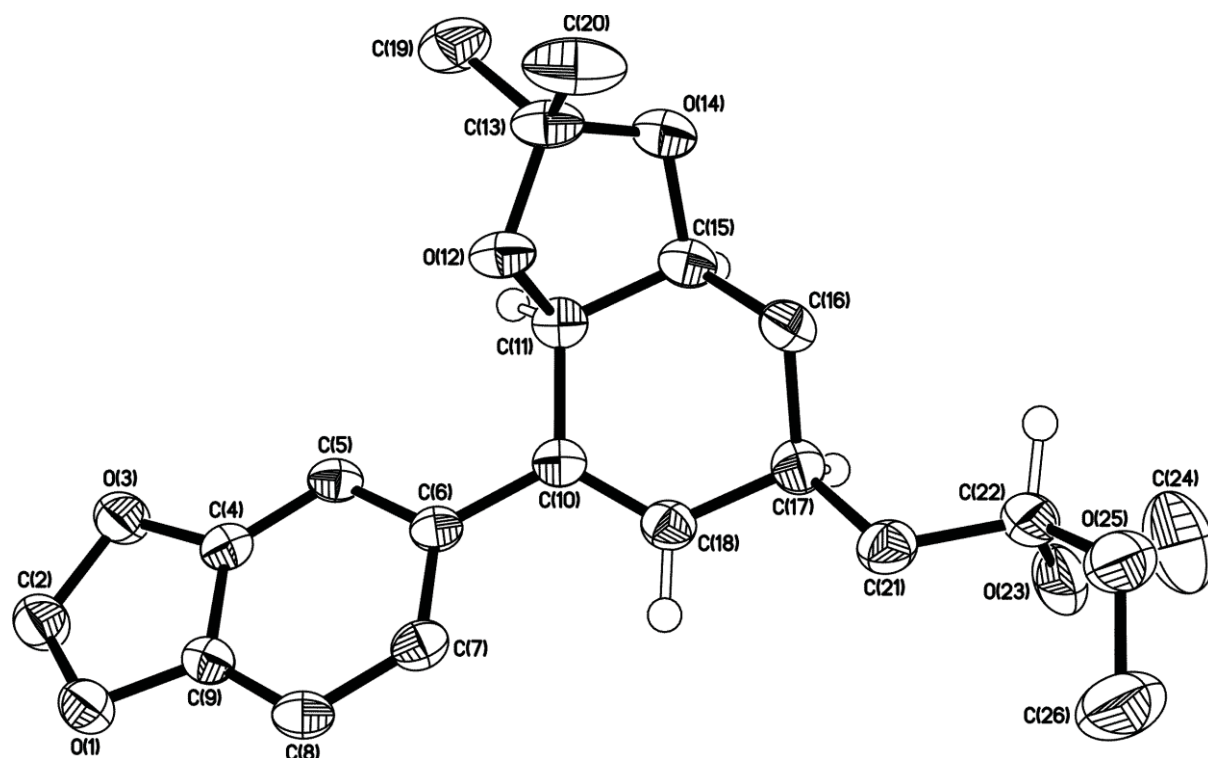


Fig. S1 The molecular structure of 13 (50% probability ellipsoids).

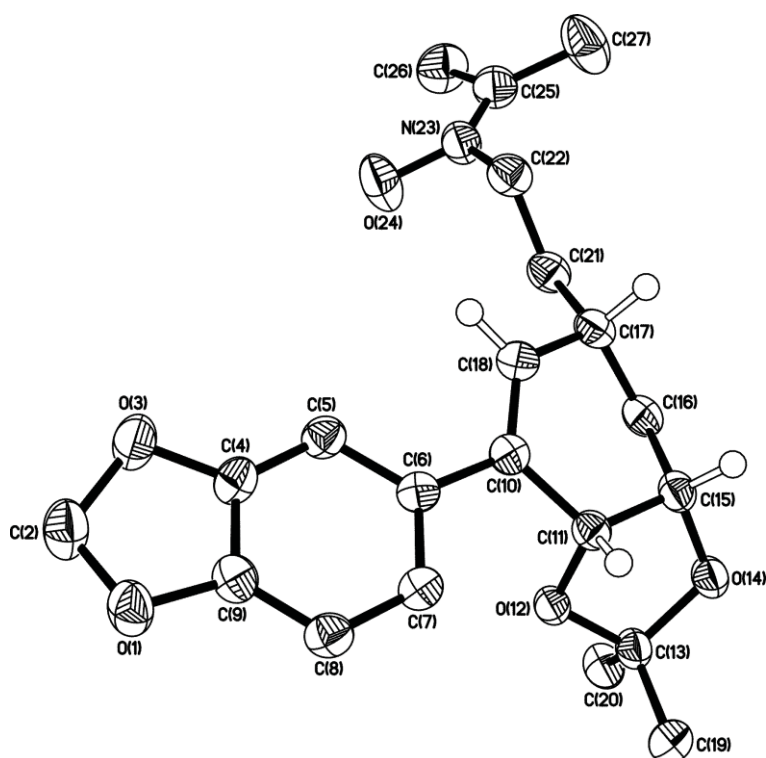


Fig. S2 The molecular structure of 16 (50% probability ellipsoids).

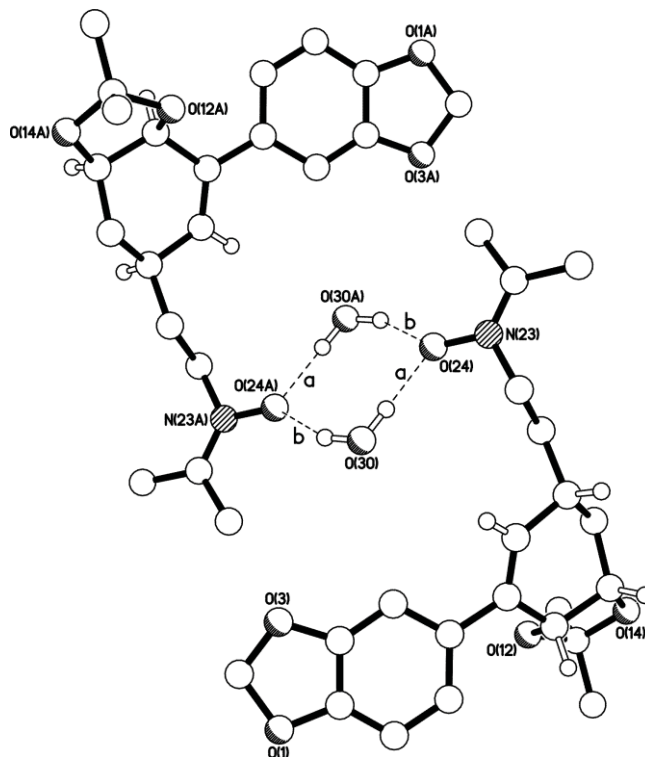


Fig. S3 The molecular structure of **16** showing the C_i -symmetric dimer formed by hydrogen bonding to the included water molecule. The O–H···O hydrogen bonds have [O···O], [H···O] distances (Å) and [O–H···O] angles (°) of **a**) 2.794(2), 1.90, 175, and **b**) 2.811(2), 1.98, 153.

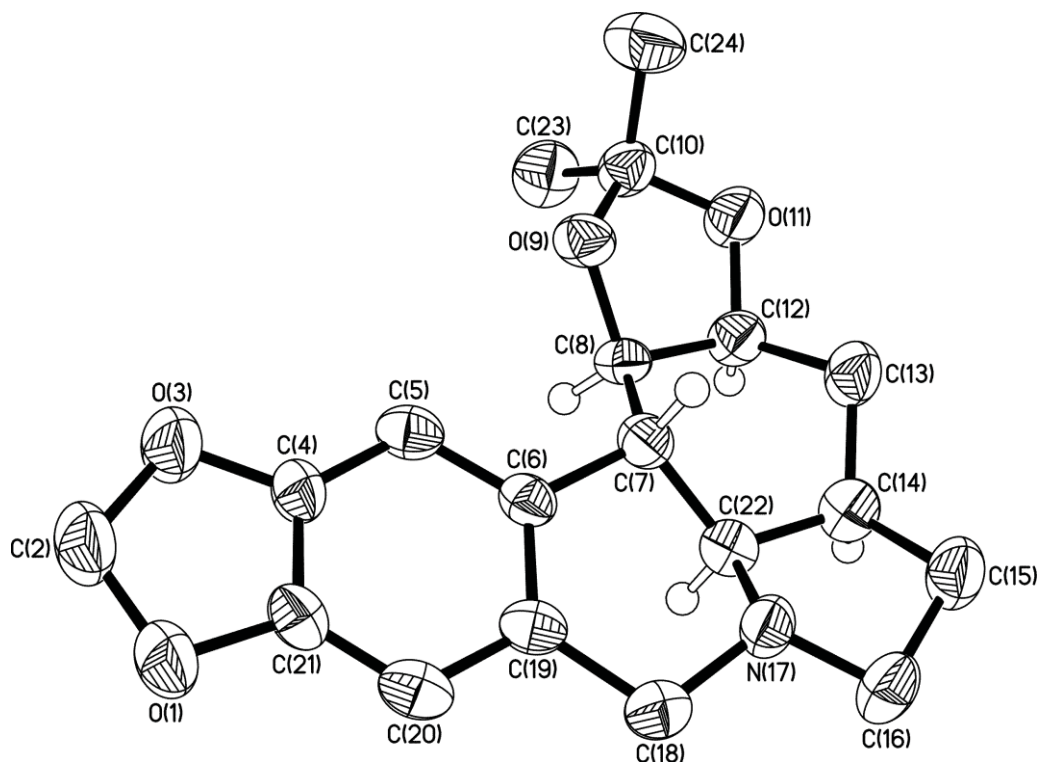


Fig. S4 The molecular structure of **20** (50% probability ellipsoids).

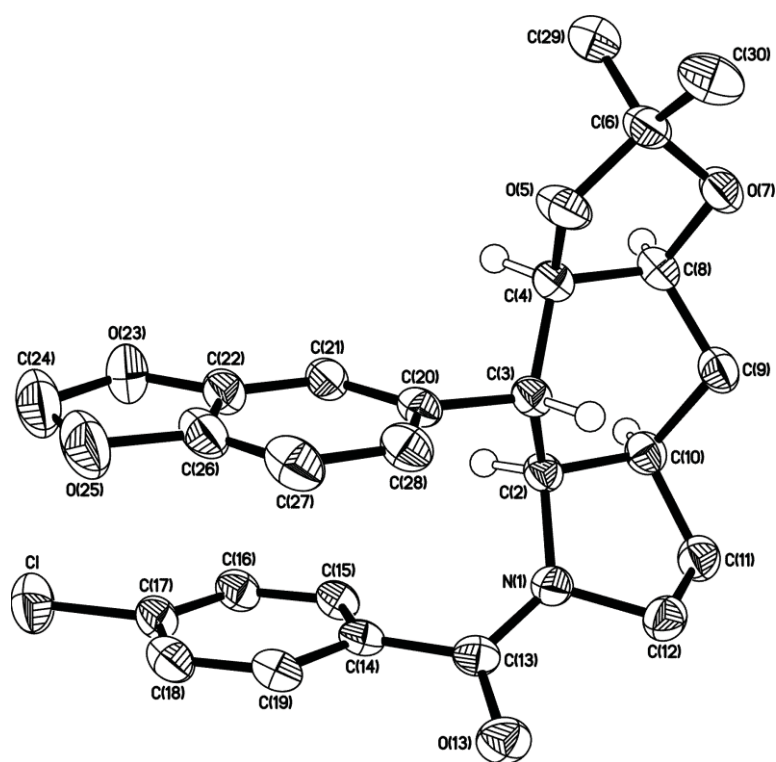


Fig. S5 The molecular structure of **28** (30% probability ellipsoids).