Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting information

Synthesis of fluorinated catharanthine analogues and investigation of their biomimetic coupling with vindoline

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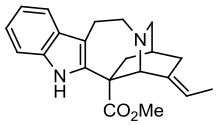
General

Unless otherwise specified, chemicals were purchased from Sigma-Aldrich and used without further purification. Catharanthine was provided by "Les laboratoires Pierre Fabre" (Gaillac, France). Reactions were carried out under nitrogen using dry solvent, unless otherwise noted. THF and Et_2O were distilled from sodium/benzophenone, and CH_2Cl_2, from calcium hydride. Flash chromatography was carried out on Kieselgel 60 (230-240 mesh, Merck) and analytical TLC was performed on Merck precoated silica gel (60 F_{254}); visualization was carried out with UV and/or heating with a solution of 5-7 wt.% phosphomolybdic acid in ethanol. Melting points were determined using open-ended capillary tubes on a Büchi 535 apparatus and are uncorrected. Mass spectra were recorded on an ESI-TOF Mariner spectrometer. HRMS were recorded at the "Service de Spectrométrie de Masse de l'Institut des Substances Naturelles" in Gif-sur-Yvette (France). ^{1}H ($CHCl_3$/7.26 ppm), ^{13}C ($CDCl_3$/77.0 ppm), and ^{19}F ($CFCl_3$/0.0 ppm) NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer at 400, 100 and 376 MHz respectively. Chemical shifts (δ) are expressed in ppm, coupling constants (J) in hertz, and the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dq (doublet of quartets), dqd (doublet of quartet of doublets), qd (quartet of doublets), qdd (quartet of doublet of doublets), m (multiplet), l (enlarged) and app. (apparent). IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR. Optical rotations were determined using the sodium D line (589 nm) on a Perkin Elmer 341 polarimeter.

Difluorocatharanthine synthesis – Isomerization strategy

Isocatharanthine ((4*E*)-$\Delta^{4,20}$-*exo*-isocatharanthine, 13)



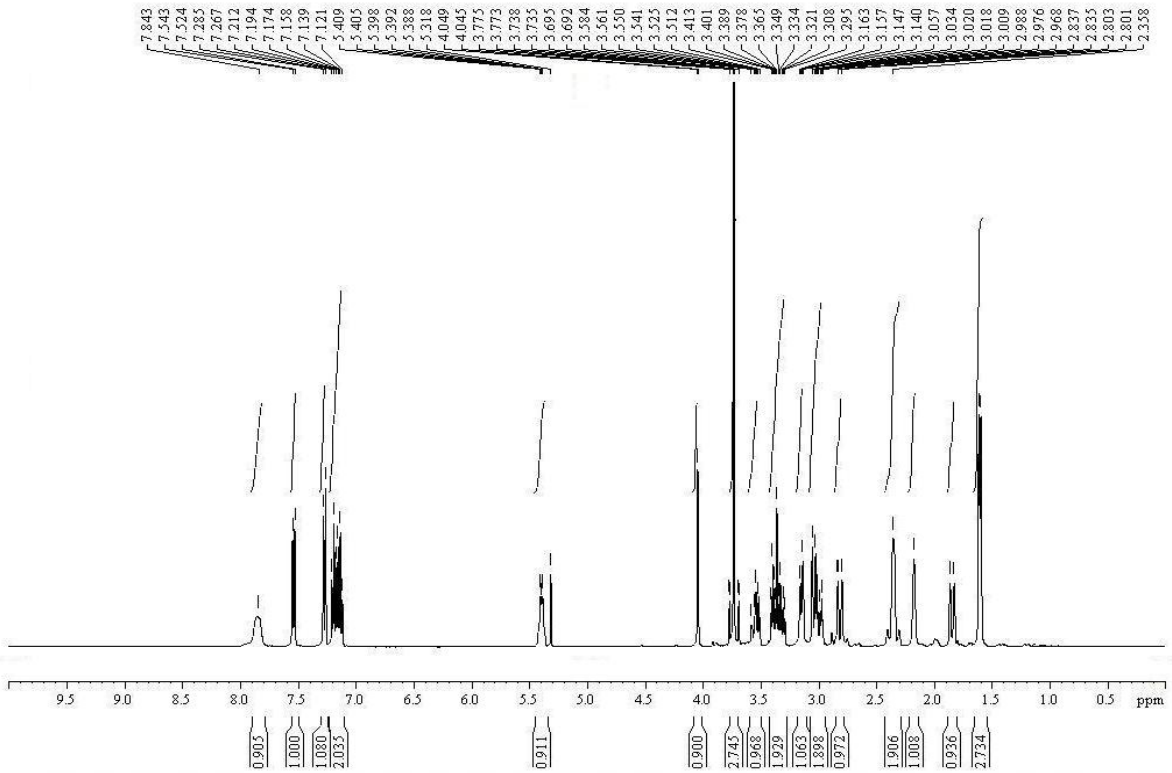
Pd (10 wt.% on carbon, 2.61 g, 0.2 equiv.) in 60 mL of MeOH was stirred under a 1-bar atmosphere of H_2 for 1 h. The gas was evacuated and replaced by N_2. Catharanthine **6** (3.88 g, 11.53 mmol, 1 equiv.) in 75 mL of MeOH was added, the gas was evacuated, and a pressure of 0.3 bar of H_2 was set. The reaction was gently stirred under 0.3 bar of H_2 for 2 h (progress of the reaction was monitored by ^{1}H NMR). The mixture was then filtered on a pad of celite, washed thoroughly with CH_2Cl_2/MeOH 1/1 (v/v), and the filtrate was evaporated to dryness. The crude product was recrystallized from MeOH to give compound **13** (2.82 g, 73%) as colorless crystals.

R_f 0.35 (CH_2Cl_2/MeOH 98/2).
mp = 78-81 °C.

^{1}H NMR ($CDCl_3$): δ 7.58 (sl, 1H), 7.49 (d app., J = 7.5 Hz, 1H), 7.25 (d app., J = 8.0 Hz, 1H), 7.16 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.10 (ddd, J = 7.5 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 5.35 (qdd, J = 6.5 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 4.00 (s, 1H), 3.70 (s, 3H), 3.56-3.46 (m, 1H), 3.39-3.25 (m, 2H), 3.12 (ddd, J = 9.5 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 3.02 (d app., J = 9.5 Hz, 1H), 3.00-2.93 (m, 1H), 2.78 (ddd, J = 13.5 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 2.35 (d app., J = 18.5 Hz, 1H), 2.30 (d app., J = 18.5 Hz, 1H), 2.19-2.08 (m, 1H), 1.82 (ddd, J = 13.5 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H), 1.56 (d, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 174.6, 137.2, 137.1, 135.2, 128.8, 121.9, 119.3, 118.5, 118.3, 110.5, 110.4, 63.6, 55.5, 53.0, 52.7, 50.2, 37.3, 29.7, 27.2, 21.3, 12.7.

IR (KBr): 3368, 2916, 2855, 1714, 1461, 1264, 740 cm^{-1}.
MS (ESI+ TOF): 337 $[M+H]^+$ (100), 359 $[M+Na]^+$ (2).
$[\alpha]_D^{20}$ = + 35 (*c* 2.3, $CHCl_3$).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7.212
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7.121
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5.398
5.392
5.388
5.318
4.049
4.045
3.775
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3.525
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3.401
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3.378
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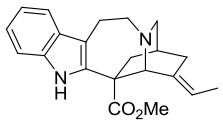
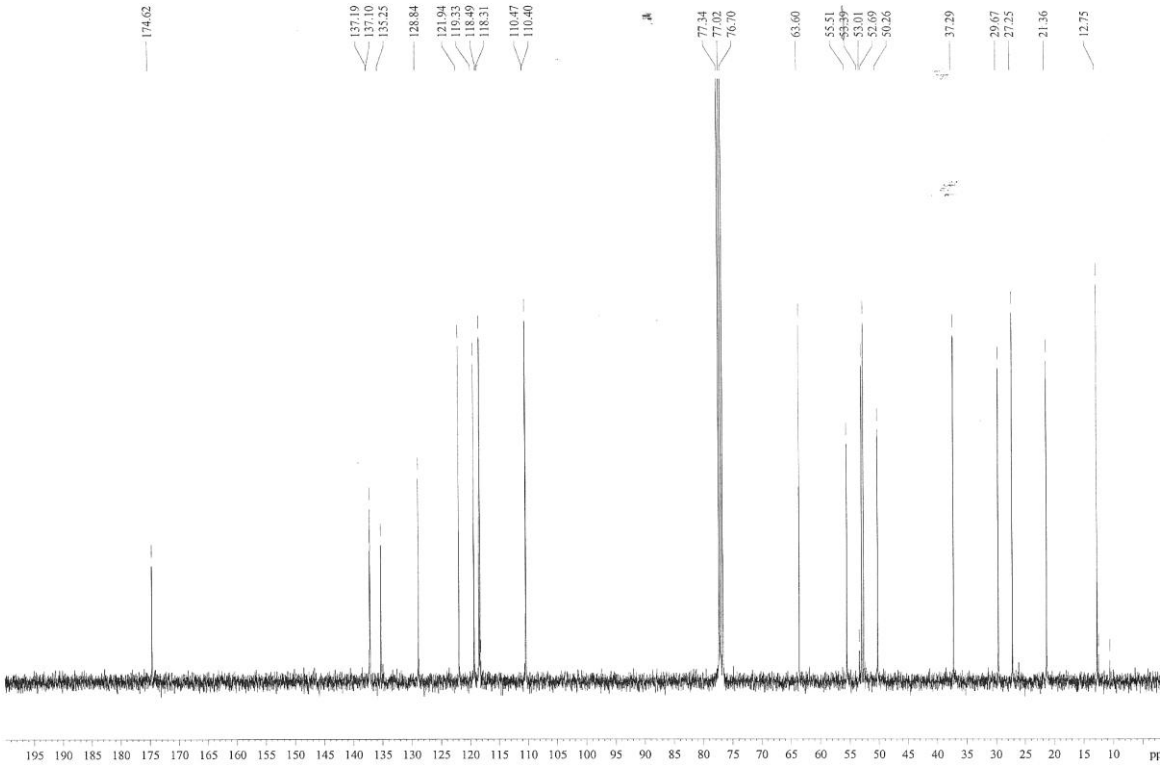
3.334
3.321
3.308
3.295
3.163
3.157
3.147
3.140
3.057
3.034
3.020
3.018
3.009
2.988
2.976
2.968
2.837
2.835
2.803
2.801
2.358
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.905
1.000
1.080
2.035
0.911
0.900
2.745
0.968
1.929
1.063
1.898
0.972
1.906
1.008
0.936
2.734


N
H
CO2Me

13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118.31
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110.40
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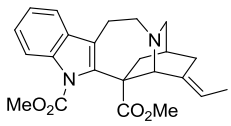
77.02
76.70
63.60
55.51
53.39
53.01
52.69
50.26
37.29
29.67
27.25
21.36
12.75
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10

Synthesis of N_a-methoxycarbonyl-19-oxoisocatharanthine (14)

- **Protection of the indole: N_a-methoxycarbonylisocatharanthine**



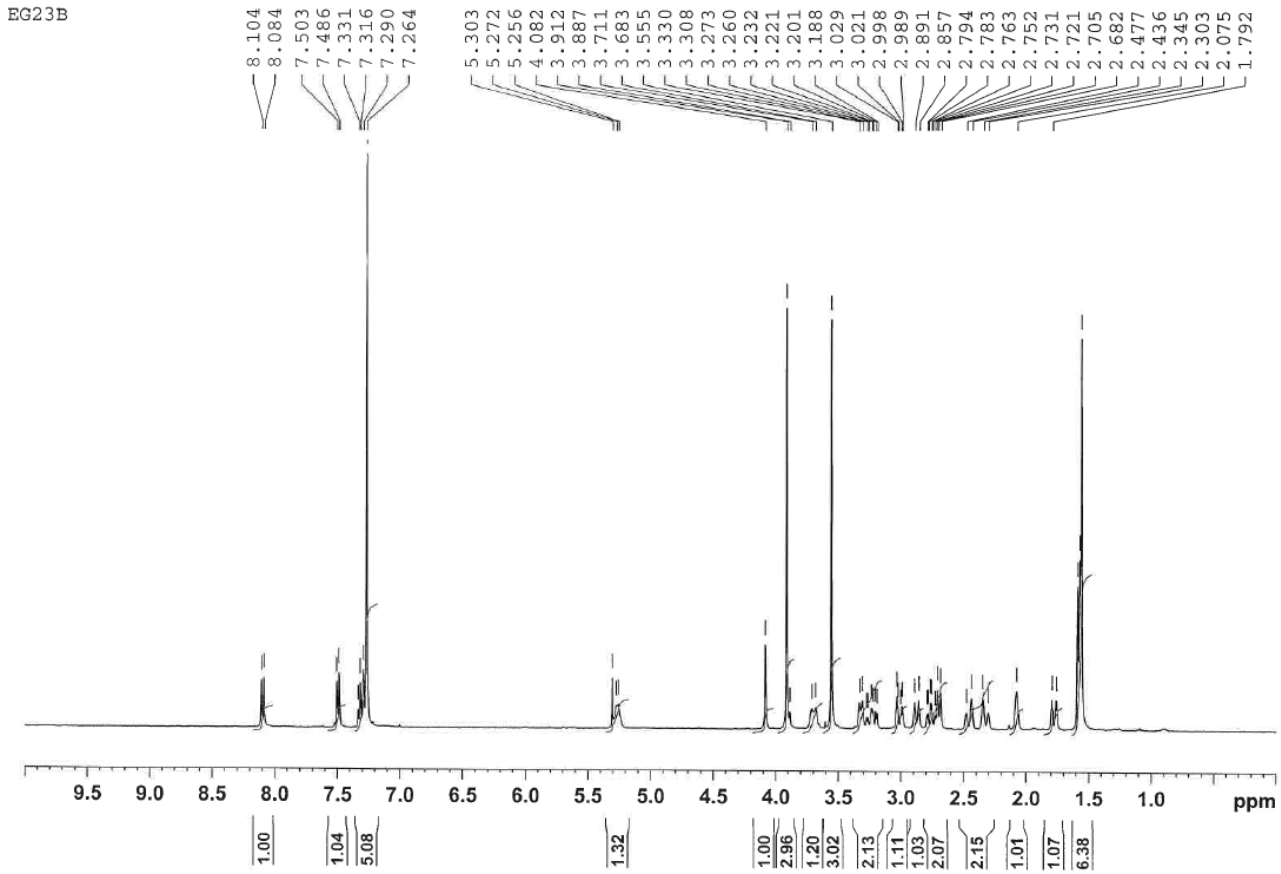
KH (0.72 g of a 35 wt.% suspension in oil, 1.6 equiv.) was washed three times with hexane, and suspended in 10 mL of anhydrous THF. To this suspension was added dropwise, at 0 °C, a solution of isocatharanthine **13** (1.34 g, 3.98 mmol, 1 equiv.) in 20 mL of anhydrous THF. The mixture was stirred 30 min at 0 °C before methyl chloroformate (500 µL, 1.6 equiv.) was added dropwise. The mixture was further stirred for 1 h at 0 °C and for 18 h at rt. The reaction was then quenched by addition of 10 mL of sat. K_2CO_3 and 10 mL of brine. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×20 mL) and CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 97/3) to give isocatharanthine methylcarbamate (1.30 g, 83%) as a white solid.

R_f 0.48 (CH_2Cl_2/MeOH 95/5).
mp = 62-64 °C.

^{1}H NMR ($CDCl_3$): δ 8.12 (d app., J = 8.0 Hz, 1H), 7.48 (dd, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.33 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.29 (ddd, J = 7.5 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 5.29 (qdd, J = 6.5 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 4.11 (s, 1H), 3.93 (s, 3H), 3.72 (ddd, J = 12.0 Hz, J = 5.0 Hz, J = 3.0 Hz, 1H), 3.58 (s, 3H), 3.34 (ddd, J = 9.0 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 3.25 (ddd, J = 16.0 Hz, J = 13.0 Hz, J = 5.0 Hz, 1H), 3.03 (ddd, J = 16.0 Hz, J = 4.0 Hz, J = 4.0 Hz, 1H), 2.90 (ddd, J = 14.0 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 2.78 (ddd, J = 13.0 Hz, J = 12.0 Hz, J = 4.0 Hz, 1H), 2.71 (d app., J = 9.0 Hz, 1H), 2.48 (d app., J = 16.5 Hz, 1H), 2.35 (d app., J = 16.5 Hz, 1H), 2.12-2.08 (m, 1H), 1.79 (ddd, J = 14.0 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 1.60 (d, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 173.4, 151.8, 138.1, 137.4, 135.7, 129.5, 124.6, 122.7, 119.7, 118.2, 117.4, 115.4, 60.5, 57.9, 56.5, 54.0, 53.1, 52.0, 37.5, 29.7, 27.9, 21.8, 12.7.

IR (KBr): 2943, 2849, 1738, 1460, 1441, 1360, 1332, 747 cm^{-1}.
MS (ESI+ TOF): 395 $[M+H]^+$ (100), 789 $[2M+H]^+$ (22).
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{27}N_2O_4]^+$: 395.1971, Found: 395.1956.
$[\alpha]_D^{20}$ = + 48 (*c* 1.0, $CHCl_3$).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7.331
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7.290
7.264
5.303
5.272
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4.082
3.912
3.887
3.711
3.683
3.555
3.330
3.308
3.273
3.260
3.232
3.221
3.201
3.188
3.029
3.021
2.998
2.989
2.891
2.857
2.794
2.783
2.763
2.752
2.731
2.721
2.705
2.682
2.477
2.436
2.345
2.303
2.075
1.792
9.5 9.0 8.5 8.0 7.5 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 ppm
1.00
1.04
5.08
1.32
1.00
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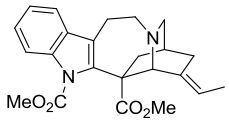
3.02
2.13
1.11
1.03
2.07
2.15
1.01
1.07
6.38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N
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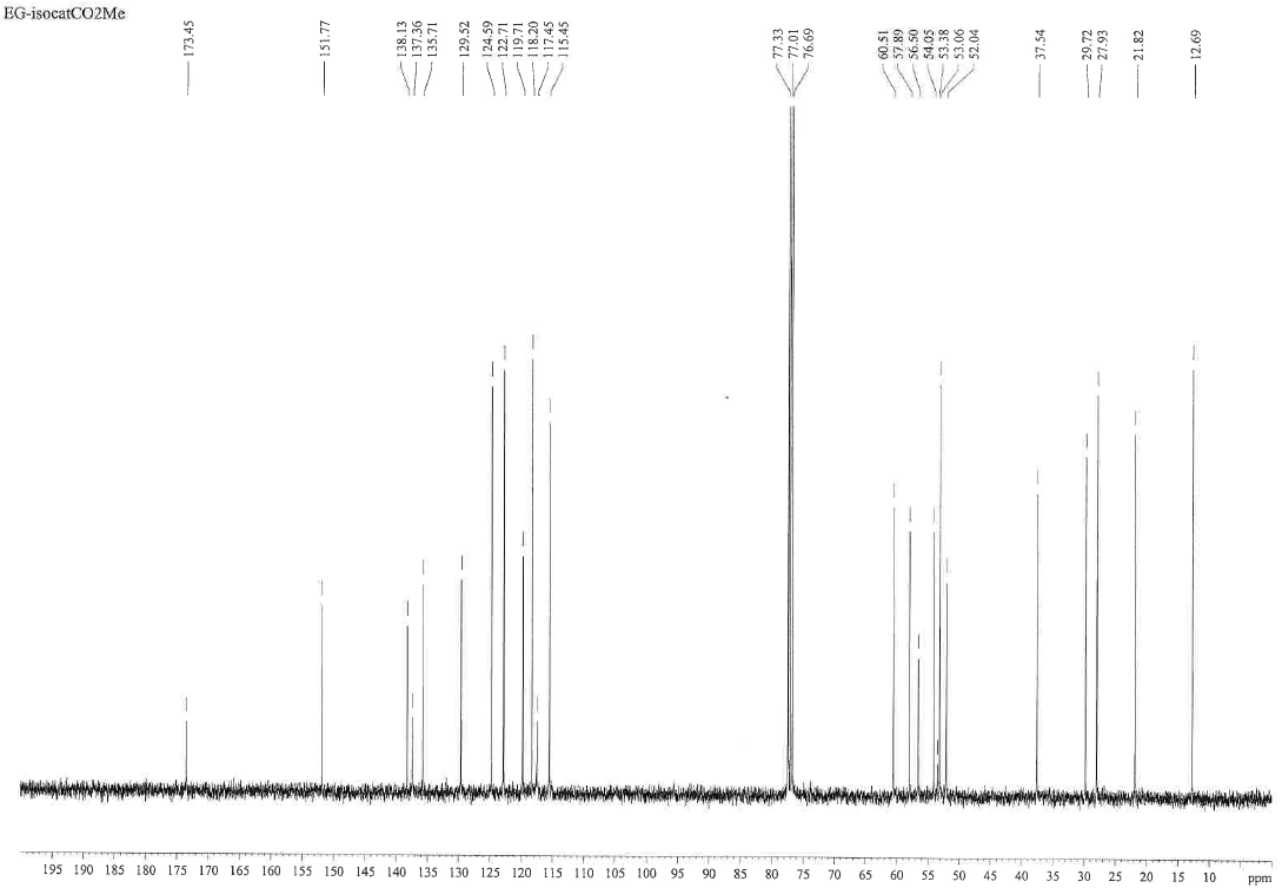
CO2Me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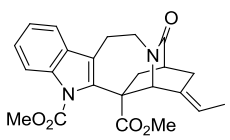
151.77
138.13
137.36
135.71
129.52
124.59
122.71
119.71
118.20
117.45
115.45
77.33
77.01
76.69
60.51
57.89
56.50
54.05
53.38
53.06
52.04
37.54
29.72
27.93
21.82
12.69
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

N_a-methoxycarbonyl-19-oxoisocatharanthine (14)



Isocatharanthine methylcarbamate (1.22 g, 3.09 mmol, 1 equiv.) dissolved in 30 mL of THF was added to 15 mL of 2 M aq. Na_2CO_3 at 0 °C. Iodine (3.62 g, 4.6 equiv.) in 25 mL THF was then added dropwise. The dark mixture was stirred at rt for 18 h before 50 mL of sat. $Na_2S_2O_3$ were added. The pale yellow solution was further stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 97/3) to give **14** (1.25 g, 99%) as a white solid.

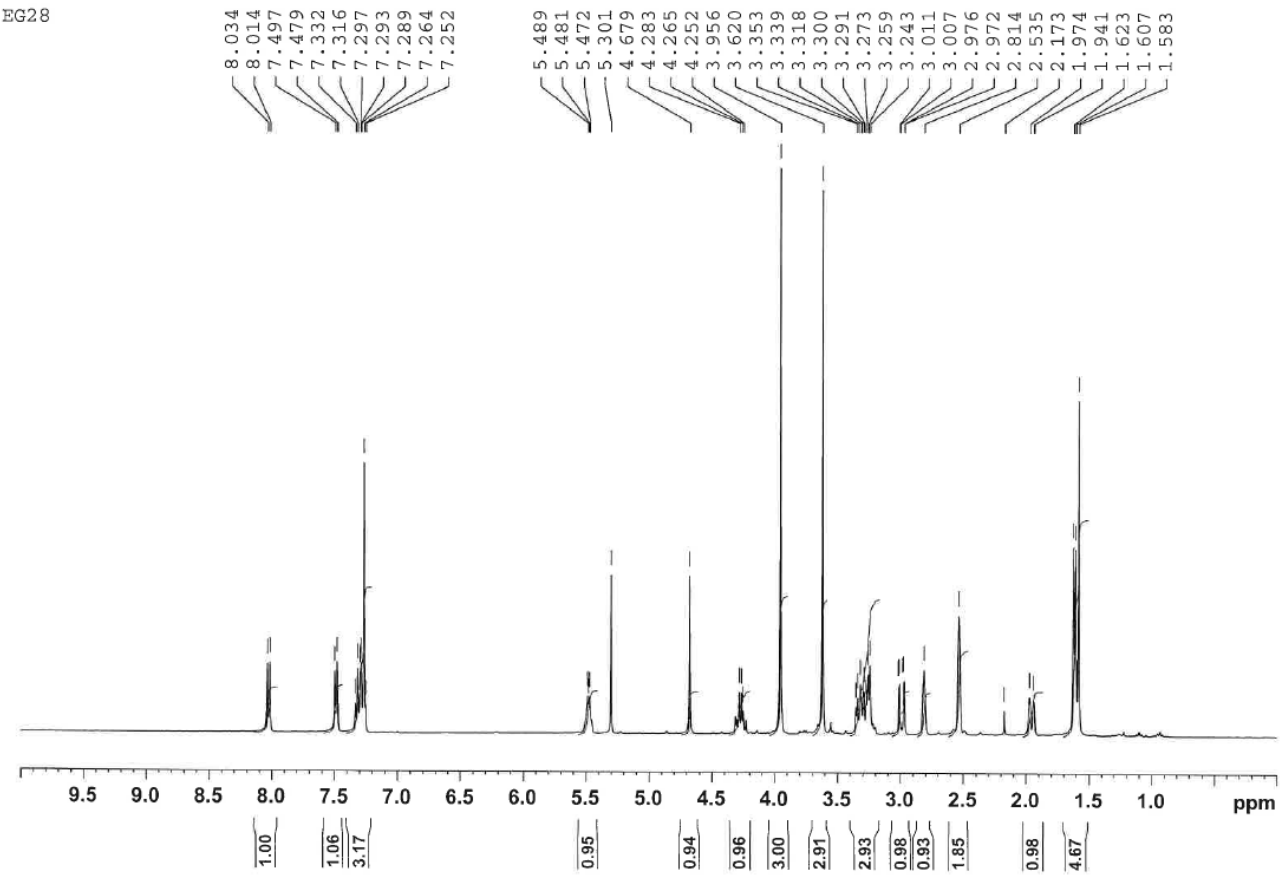
R_f 0.52 (CH_2Cl_2/MeOH 95/5).
mp = 94-96 °C.

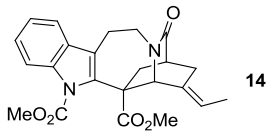
^{1}H NMR ($CDCl_3$): δ 8.03 (d app., J = 8.0 Hz, 1H), 7.49 (dd, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.35-7.24 (m, 2H), 5.48 (qdd, J = 6.5 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 4.68 (s, 1H), 4.33-4.22 (m, 1H), 3.96 (s, 3H), 3.62 (s, 3H), 3.38-3.20 (m, 3H), 2.99 (dd, J = 14.0 Hz, J = 2.0 Hz, 1H), 2.84-2.79 (m, 1H), 2.59-2.47 (m, 2H), 1.96 (d app., J = 14.0 Hz, 1H), 1.62 (d app., J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 174.8, 172.1, 151.7, 136.6, 135.2, 132.6, 129.3, 125.0, 122.9, 121.1, 118.2, 117.1, 115.7, 61.6, 58.8, 53.4, 52.3, 40.5, 39.0, 37.3, 28.6, 21.3, 13.2.

IR (KBr): 3461, 2951, 1742, 1674, 1460, 1361, 1329, 1254, 1208, 1143, 747 cm^{-1}.
MS (ESI+ TOF): 409 $[M+H]^+$ (100), 817 $[2M+H]^+$ (34).
$[\alpha]_D^{20}$ = + 255 (c 0.4, $CHCl_3$).

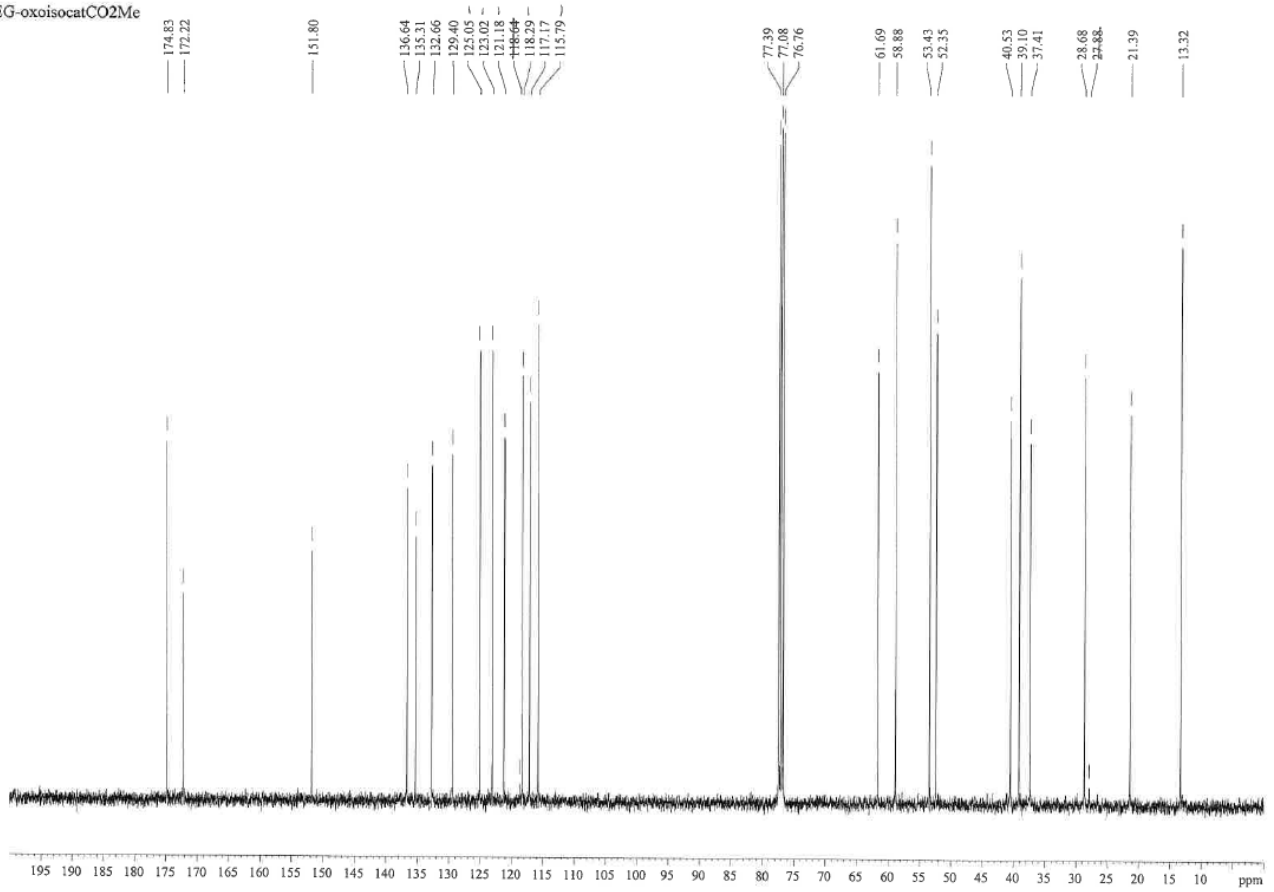
EG28



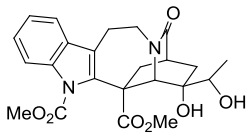


14

EG-oxoisocatCO2Me



N_a-methoxycarbonyl-3-hydro-4,20-dihydroxy-19-oxocatharanthine (15)



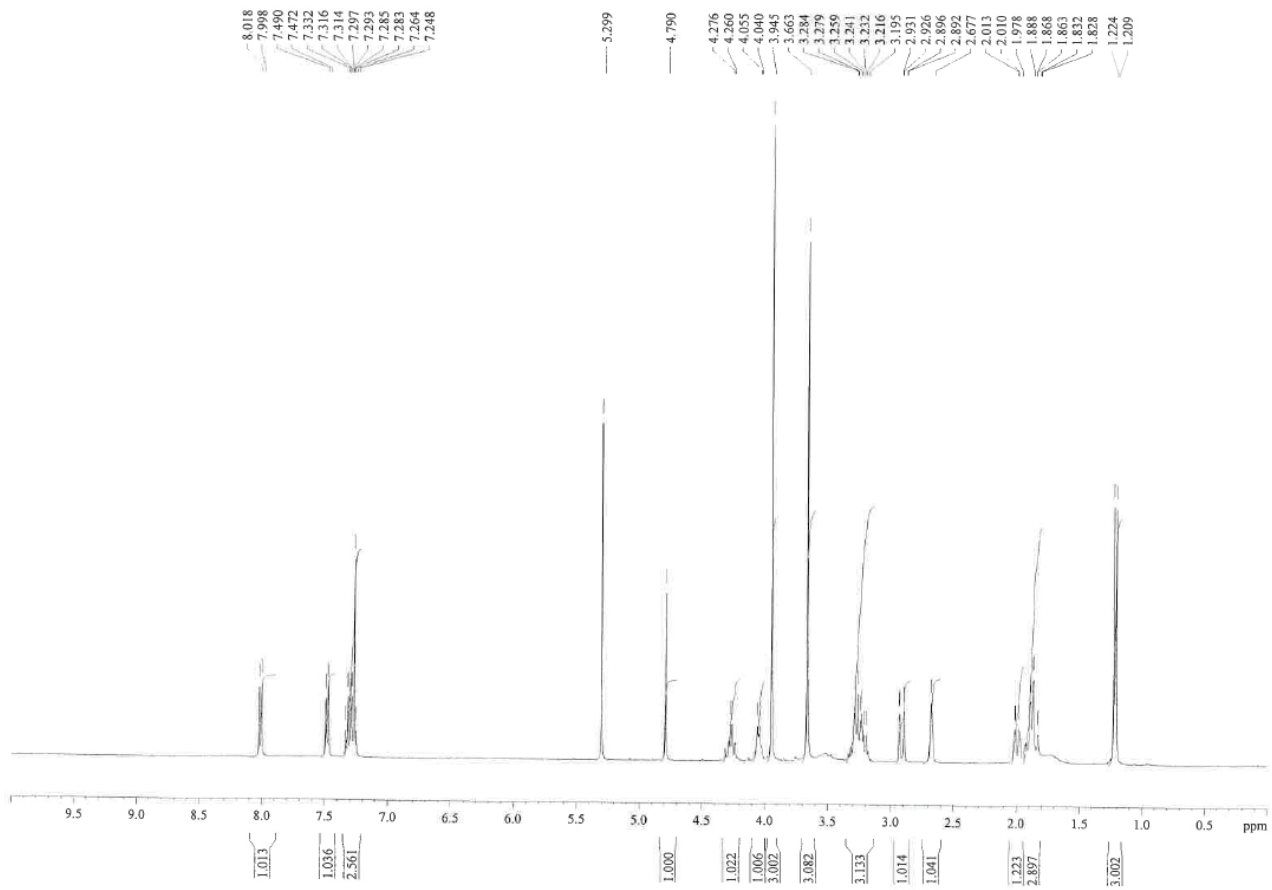
To a solution of bis-protected isocatharanthine **14** (1.24 g, 3.04 mmol, 1 equiv.) in 27 mL of acetone/water 8/1 (v/v) at 0 °C were added OsO_4 (1.9 mL of a 2.5 wt.% soln. in *t*-BuOH, 0.05 equiv.) and NMO (0.72 g, 2 equiv.) in portions. After 15 min at 0 °C, the mixture was further stirred for 18 h at rt. The reaction was stopped by adding sat. $Na_2S_2O_3$ (15 mL) and water (15 mL), and stirred for 20 min. The solution was extracted with CH_2Cl_2 (4×30 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was then purified by chromatography on silica (CH_2Cl_2/MeOH, 97/3) to give diol **15** (1.18 g, 88%) as a white solid.

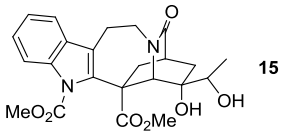
R_f 0.5 (CH_2Cl_2/MeOH 9/1).
mp = 102-104 °C.

^{1}H NMR ($CDCl_3$): δ 8.00 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.34-7.23 (m, 2H), 4.79 (s, 1H), 4.31-4.19 (m, 1H), 4.05 (q, J = 6.0 Hz, 1H), 3.95 (s, 3H), 3.67 (s, 3H), 3.34-3.15 (m, 3H), 2.91 (dd, J = 14.0 Hz, J = 1.5 Hz, 1H), 2.69-2.64 (m, 1H), 1.99 (d app., J = 13.5 Hz, 1H), 1.91 (d app., J = 14.0 Hz, 1H), 1.83 (d app., J = 14.0 Hz, 1H), 1.22 (d, J = 6.0 Hz, 3H).

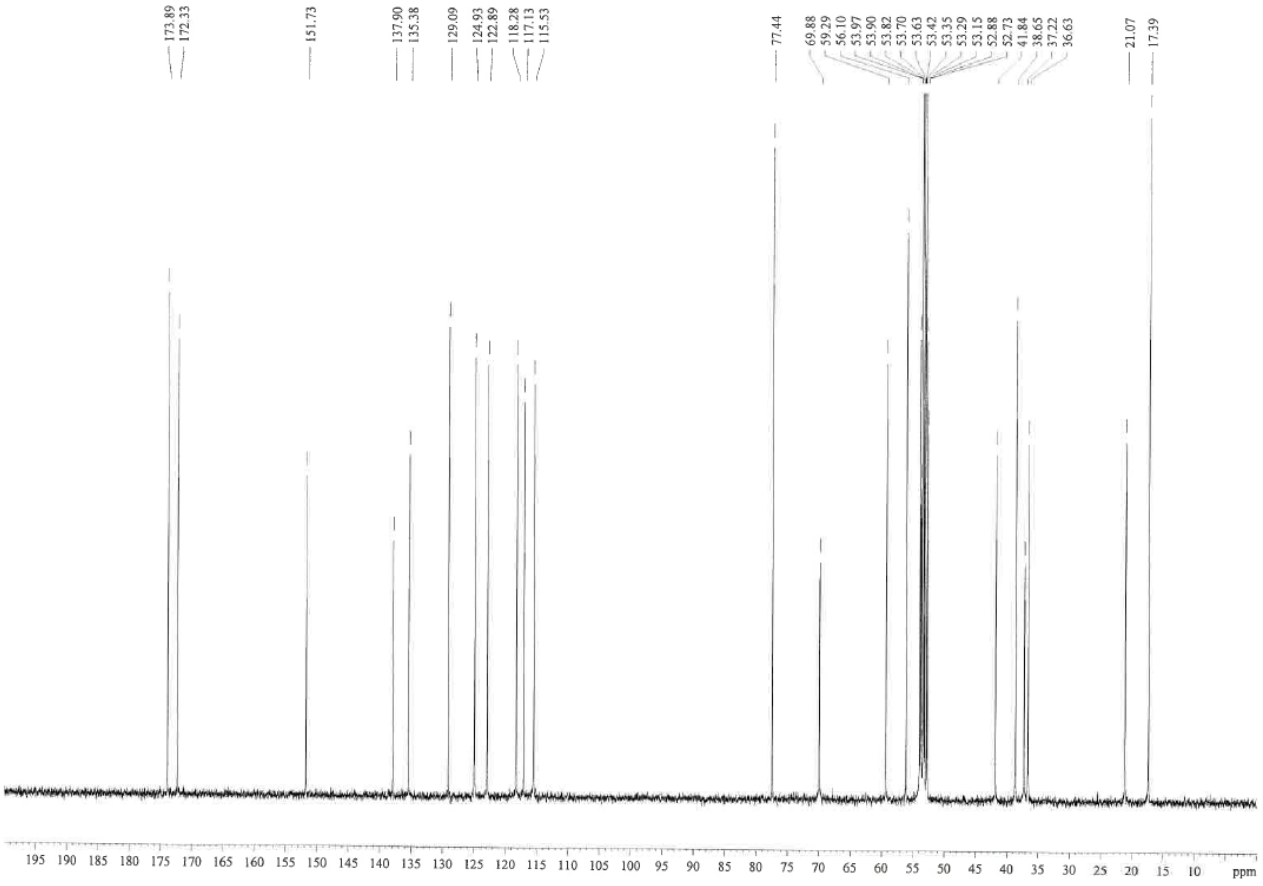
^{13}C NMR ($CDCl_3$): δ 174.0, 172.5, 151.7, 137.6, 135.2, 129.0, 125.0, 123.0, 118.2, 117.1, 115.6, 77.3, 69.9, 59.2, 55.9, 53.4, 52.8, 42.0, 38.5, 37.2, 36.7, 21.0, 17.6.

IR (KBr): 3402, 2954, 1741, 1657, 1458, 760 cm^{-1}.
MS (ESI+ TOF): 443 $[M+H]^+$ (11), 465 $[M+Na]^+$ (100), 907 $[2M+Na]^+$ (36).
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{26}N_2NaO_7]^+$: 465.1638, Found: 465.1631.
$[\alpha]_D^{20}$ = + 97 (*c* 0.5, $CHCl_3$).

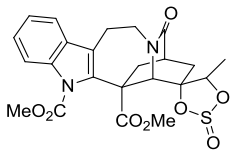




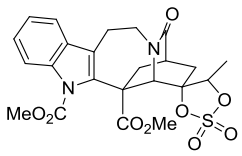
15



N_a-methoxycarbonyl-3-hydro-4,20-dihydroxy-19-oxocatharanthine cyclic sulfate (17)



To a solution of diol **15** (473 mg, 1.07 mmol, 1 equiv.) in 20 mL of CH_2Cl_2 at 0 °C was added NEt_3 (350 µL, 2.3 equiv.), followed by dropwise addition of $SOCl_2$ (100 µL, 1.3 equiv.). After 30 min at 0 °C, the reaction was stopped by adding brine (20 mL) and water (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum.



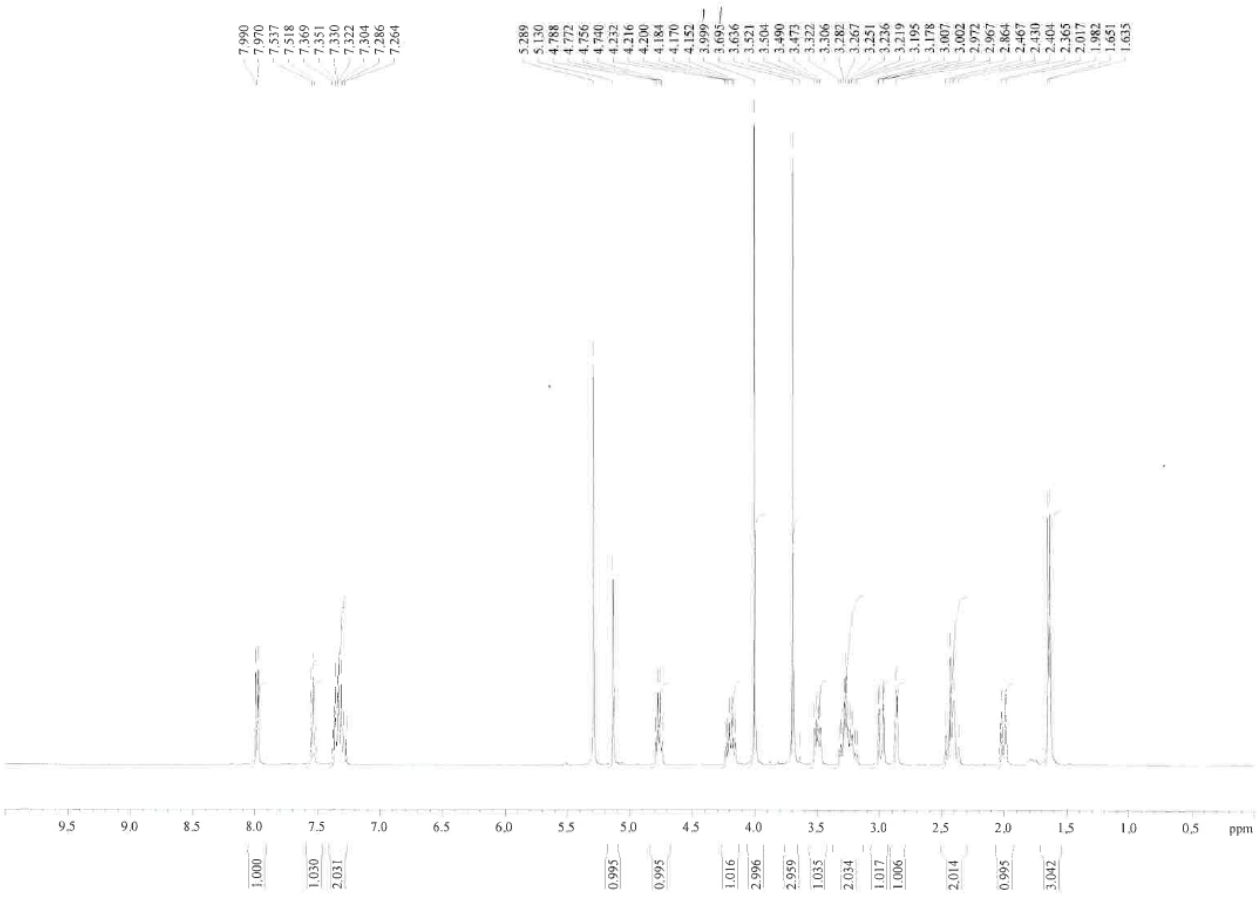
The crude residue was dissolved in 28 mL of CH_3CN/H_2O 15/13 v/v and the solution was stirred vigorously at rt. $NaIO_4$ (572 mg, 2.5 equiv.) and $RuCl_3$ (11 mg, 0.05 equiv.) were then added. After 90 min, Et_2O (30 mL) was added and stirring was continued for another 10 min. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were washed with water (50 mL), sat. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2) to give cyclic sulfate **17** (338 mg, 63%) as a white solid.

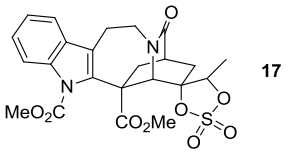
R_f 0.49 (CH_2Cl_2/MeOH 95/5).
mp = 140-142 °C.

^{1}H NMR ($CDCl_3$): δ 7.98 (d app., J = 8.0 Hz, 1H), 7.53 (d app., J = 7.5 Hz, 1H), 7.39-7.27 (m, 2H), 5.13 (s, 1H), 4.77 (q, J = 6.5 Hz, 1H), 4.19 (ddd, J = 13.0 Hz, J = 12.5 Hz, J = 6.5 Hz, 1H), 4.00 (s, 3H), 3.70 (s, 3H), 3.50 (dd, J = 12.5 Hz, J = 6.5 Hz, 1H), 3.34-3.16 (m, 2H), 2.99 (dd, J = 14.0 Hz, J = 2.0 Hz, 1H), 2.89-2.84 (m, 1H), 2.45 (d app., J = 15.5 Hz, 1H), 2.39 (d app., J = 15.5 Hz, 1H), 2.00 (d app., J = 14.0 Hz, 1H), 1.64 (d, J = 6.5 Hz, 3H).

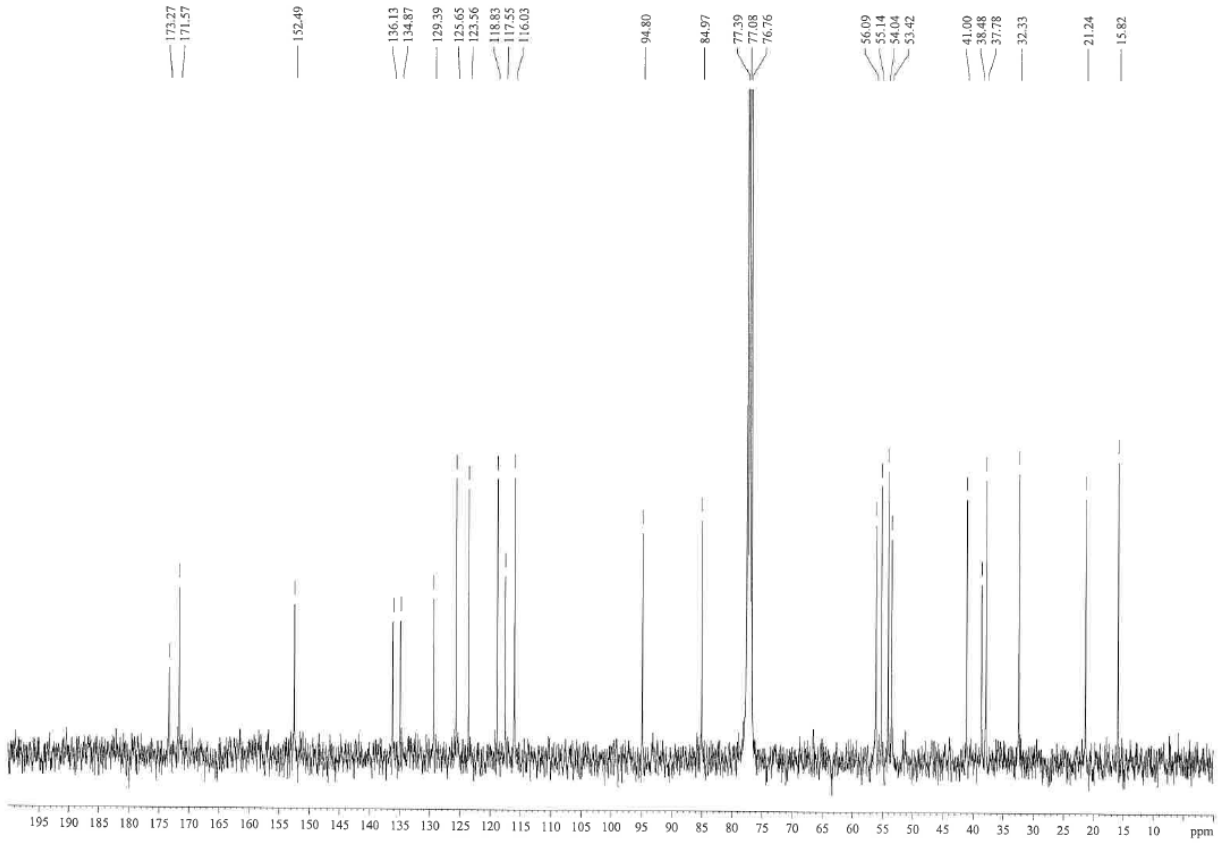
^{13}C NMR ($CDCl_3$): δ 173.2, 171.5, 152.4, 136.1, 134.8, 129.3, 125.6, 123.5, 118.8, 117.5, 116.0, 94.7, 84.9, 56.0, 55.1, 54.0, 53.3, 40.9, 38.4, 37.7, 32.3, 21.2, 15.7.

IR (KBr): 1735, 1687, 1459, 1382, 1215, 904 cm^{-1}.
MS (ESI+ TOF): 505 $[M+H]^+$ (100), 1009 $[2M+H]^+$ (13).
$[\alpha]_D^{20}$ = + 165 (c 0.3, $CHCl_3$).





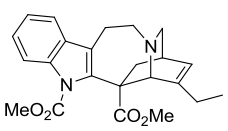
17



Difluorocatharanthine synthesis – Allylic oxidation strategy

Synthesis of N_a-methoxycarbonyl-19-oxocatharanthine (23)

- **Protection of the indole: N_a-methoxycarbonylcatharanthine**



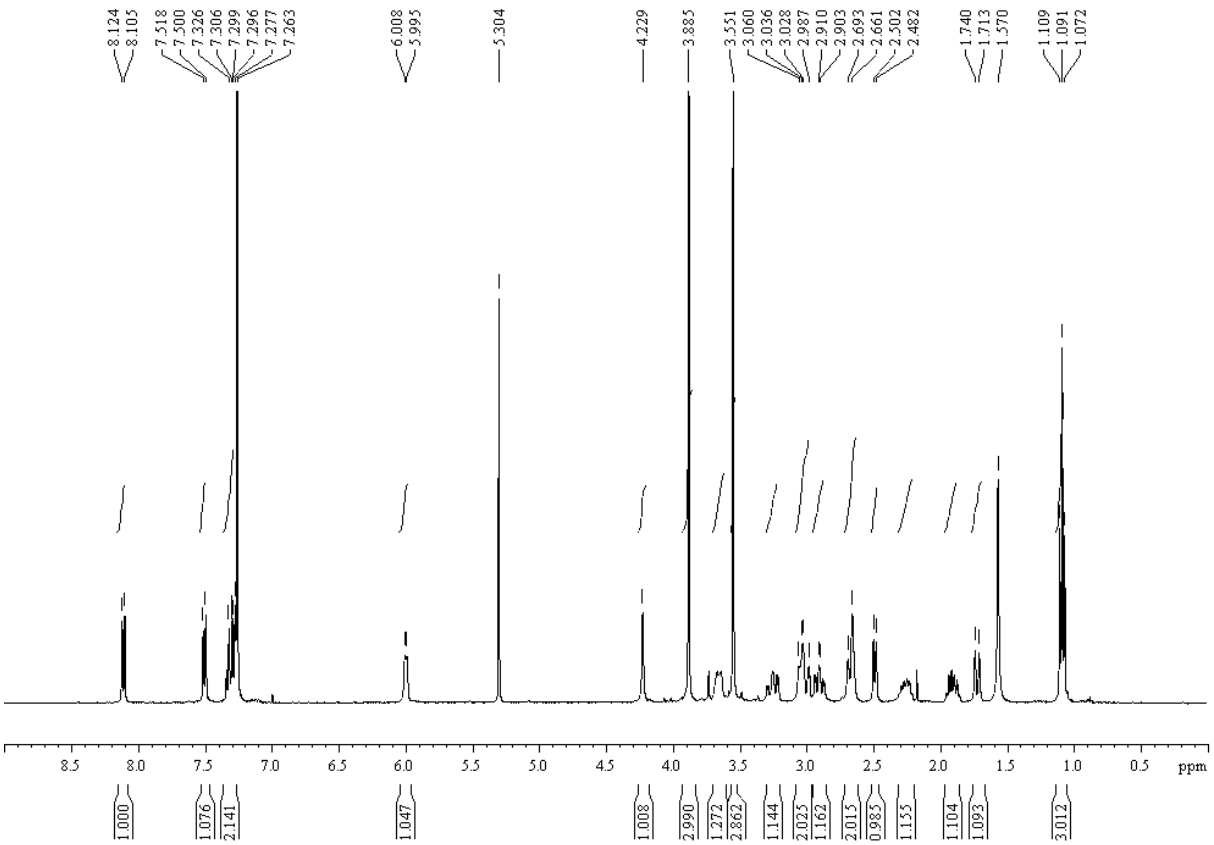
KH (5.00 g of a 30 wt.% suspension in oil, 2.5 equiv.) was washed three times with hexane, and suspended in 30 mL of anhydrous THF. To this suspension was added dropwise at 0 °C a solution of catharanthine **6** (5.00 g, 14.8 mmol, 1 equiv.) in 50 mL of anhydrous THF. The mixture was stirred 30 min at 0 °C before methyl chloroformate (2.9 mL, 2.5 equiv.) was added dropwise. The medium was further stirred for 1 h at 0 °C and for 18 h at rt. The reaction was then quenched by addition of 30 mL of sat. K_2CO_3 and 30 mL of brine. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×40 mL) and CH_2Cl_2 (2×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by chromatography on silica (CH_2Cl_2/MeOH, 97/3) to give catharanthine methylcarbamate (5.04 g, 86%) as a white solid.

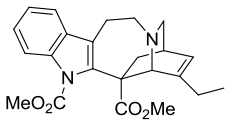
R_f 0.47 (CH_2Cl_2/MeOH, 95/5).

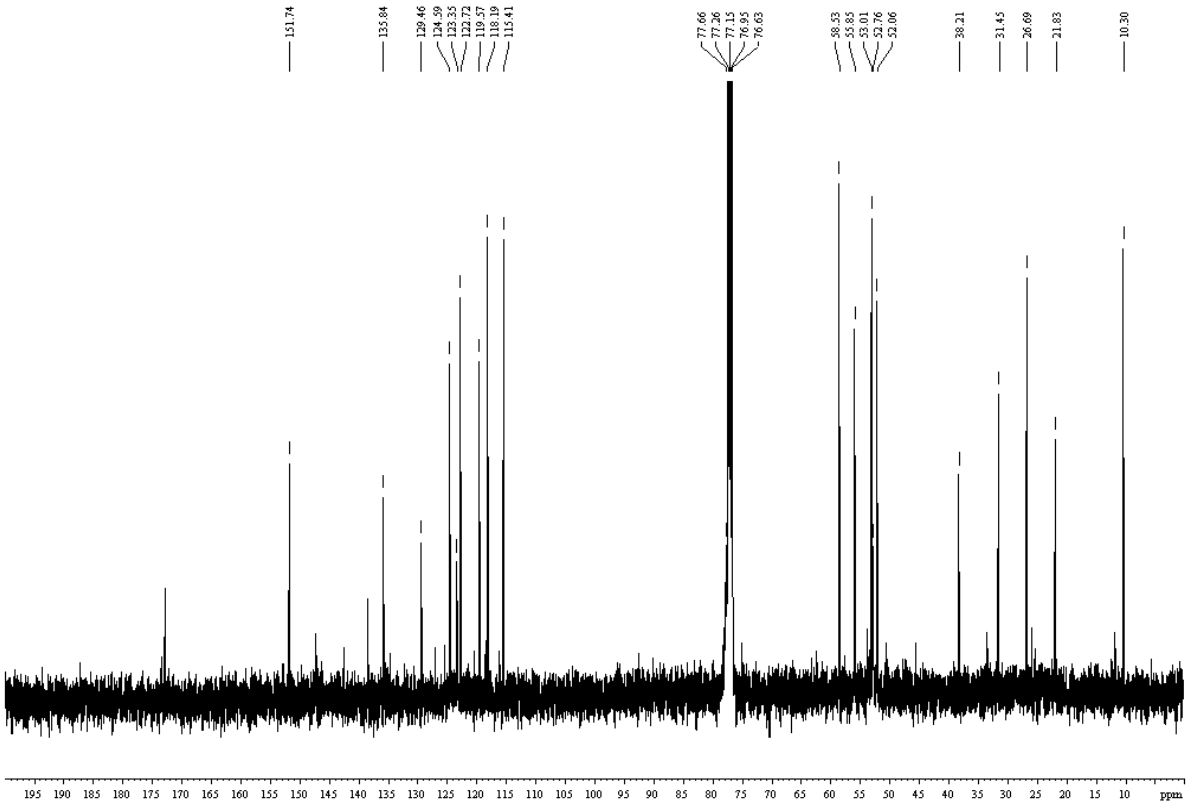
^{1}H NMR ($CDCl_3$): δ 8.12 (d app., J = 8.0 Hz, 1H), 7.51 (d app., J = 7.0 Hz, 1H), 7.35-7.25 (m, 2H), 6.00 (d app., J = 5.5 Hz, 1H), 4.23 (s, 1H), 3.89 (s, 3H), 3.66 (ddd, J = 12.0 Hz, J = 5.0 Hz, J = 3.0 Hz, 1H), 3.55 (s, 3H), 3.25 (ddd, J = 16.0 Hz, J = 13.5 Hz, J = 5.0 Hz, 1H), 3.05 (ddd, J = 8.0 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H), 3.01 (ddd, J = 16.0 Hz, J = 4.0 Hz, J = 3.0 Hz, 1H), 2.91 (ddd, J = 13.5 Hz, J = 12.0 Hz, J = 4.0 Hz, 1H), 2.69 (ddd, J = 10.5 Hz, J = 3.0 Hz, J = 3.0 Hz, 1H), 2.68-2.62 (m, 1H), 2.49 (d app., J = 8.0 Hz, 1H), 2.26 (dqd, J = 17.0 Hz, J = 7.5 Hz, J = 2.0 Hz, 1H), 1.92 (dqd, J = 17.0 Hz, J = 7.5 Hz, J = 2.0 Hz, 1H), 1.73 (d app., J = 10.5 Hz, 1H), 1.09 (dd, J = 7.5 Hz, J = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 172.9, 151.8, 147.3, 138.5, 135.9, 129.5, 124.6, 123.4, 122.8, 119.6, 118.2, 115.5, 58.6, 55.9, 55.8, 53.1, 52.7, 52.1, 38.3, 31.5, 26.7, 21.9, 10.4.

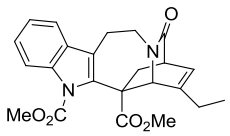
MS (ESI+ TOF): 395 $[M+H]^+$ (100).







N_a-methoxycarbonyl-19-oxocatharanthine (23)



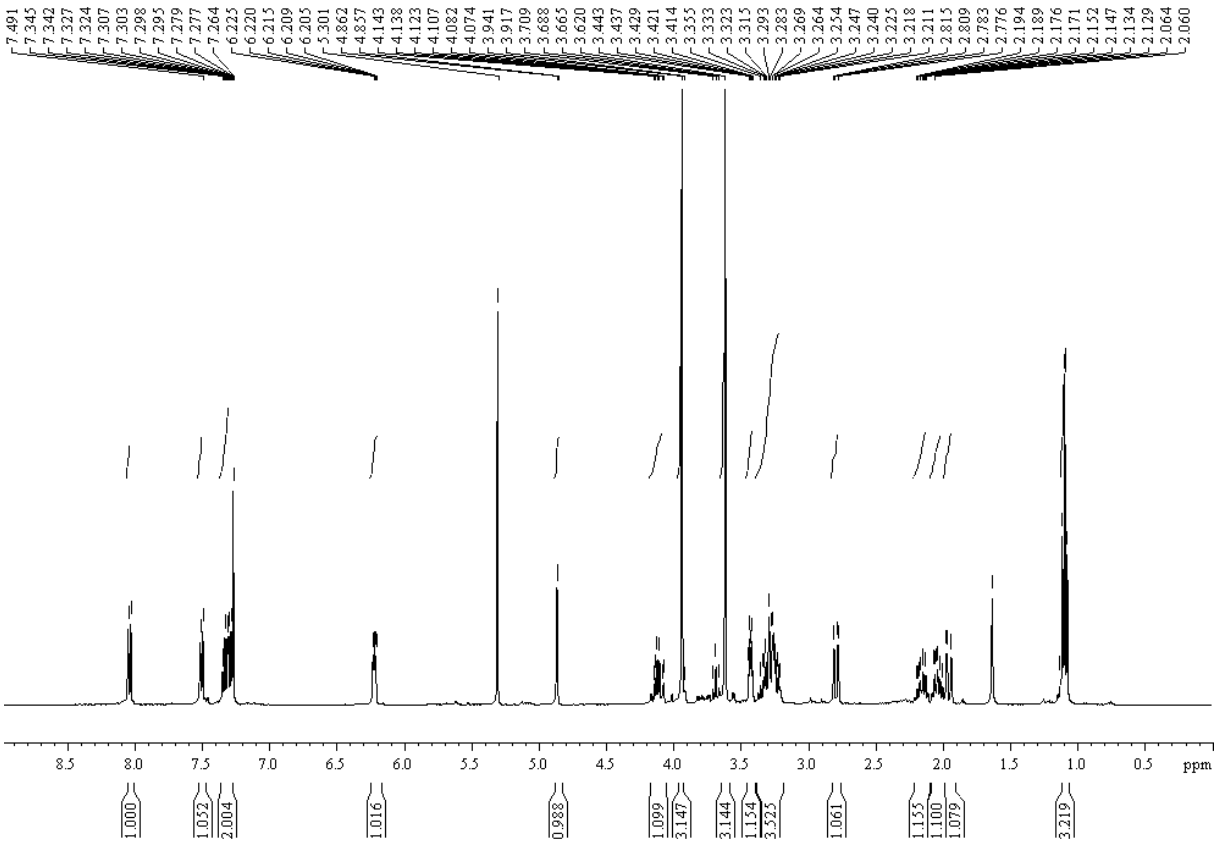
Catharanthine methylcarbamate (2.68 g, 6.8 mmol, 1 equiv.) dissolved in 30 mL of THF was added to 30 mL of 2 M aq. Na_2CO_3 at 0 °C. Iodine (8.0 g, 4.6 equiv.) in 40 mL THF was then added dropwise. The dark mixture was stirred for 18 h at rt, and 50 mL of sat. $Na_2S_2O_3$ were added. The pale yellow solution was further stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2) to give **23** (2.56 g, 92%) as a white solid.

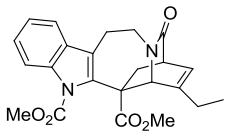
R_f 0.53 (CH_2Cl_2/MeOH, 95/5).
mp = 154-156 °C.

^{1}H NMR ($CDCl_3$): δ 8.05 (d app., J = 8.0 Hz, 1H), 7.51 (dd, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.34 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.29 (ddd, J = 7.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H), 6.23 (dddd, J = 6.5 Hz, J = 2.0 Hz, J = 2.0 Hz, J = 1.5 Hz, 1H), 4.88 (d, J = 2.0 Hz, 1H), 4.18-4.08 (m, 1H), 3.95 (s, 3H), 3.63 (s, 3H), 3.44 (ddd, J = 6.5 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 3.39-3.20 (m, 3H), 2.81 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 2.18 (dqd, J = 17.0 Hz , J = 7.5 Hz, J = 2.0 Hz, 1H), 2.04 (dqd, J = 17.0 Hz, J = 7.5 Hz, J = 1.5 Hz, 1H), 1.97 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 1.11 (dd, J = 7.5 Hz, J = 7.5 Hz, 3H).

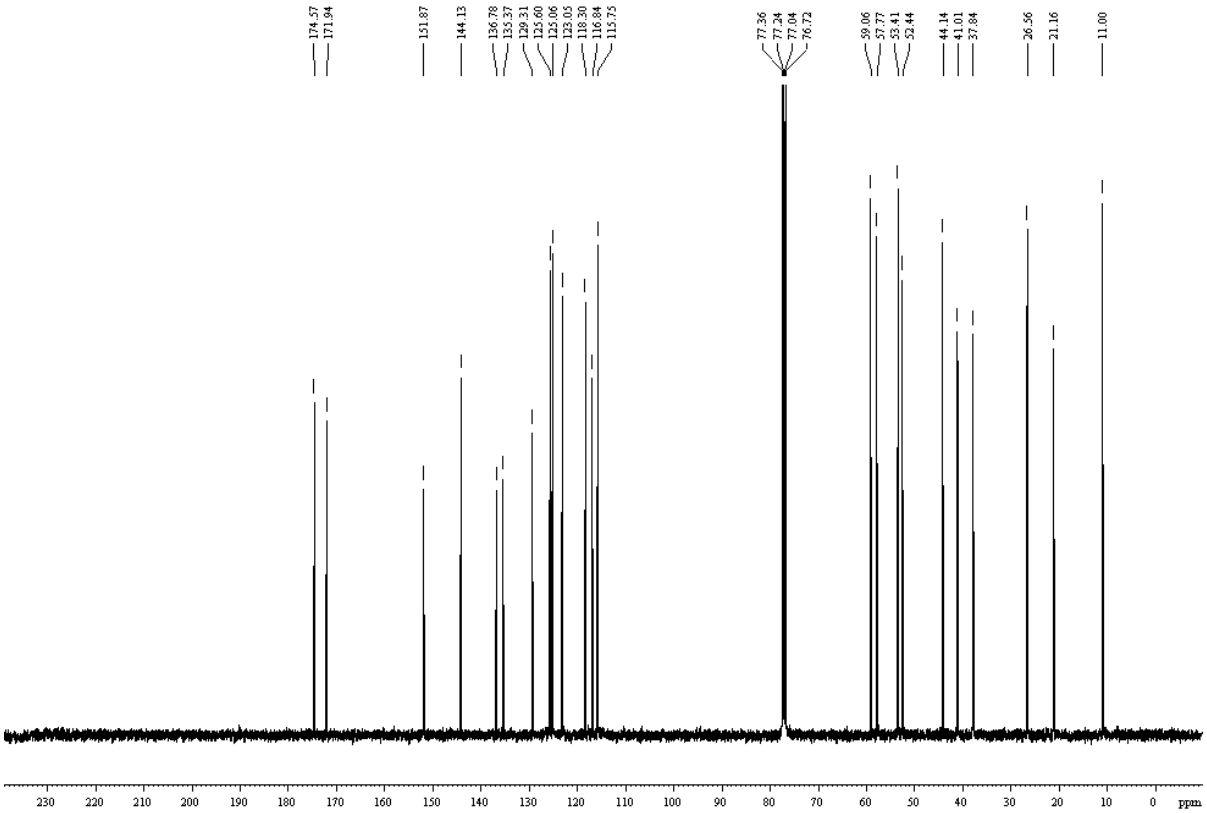
^{13}C NMR ($CDCl_3$): δ 174.5, 171.9, 151.8, 144.1, 136.7, 135.3, 129.3, 125.6, 125.0, 123.0, 118.3, 116.8, 115.7, 59.0, 57.7, 53.4, 52.4, 44.1, 41.0, 37.8, 26.5, 21.1, 11.0.

IR (neat): 2996, 2959, 2881, 1739, 1681, 1461, 1443, 1256, 751 cm^{-1}.
MS (ESI+ TOF): 431 $[M+Na]^+$ (100), 839 $[2M+Na]^+$ (14).
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{24}N_2NaO_5]^+$: 431.1583, Found: 431.1365.
$[\alpha]_D^{20}$ = + 141 (c 1.9, $CHCl_3$).





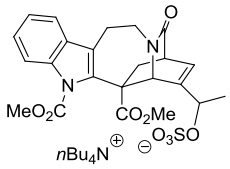
23



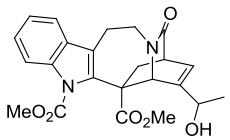
Difluorocatharanthine synthesis – Products common to both strategies

***N*$_a$-methoxycarbonyl-20-hydroxy-19-oxocatharanthine (19)**

- **Isomerization strategy: β-elimination and hydrolysis of cyclic sulfate 17**

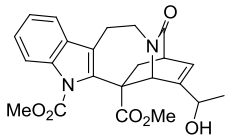


To a solution of sulfate **17** (300 mg, 0.59 mmol, 1 equiv.) in 5 mL of THF was added dropwise a solution of *n*Bu$_4$NF (1 M in THF, 1.2 mL, 2 equiv.), and the reaction was stirred for 18 h at rt.



10 mL of a 2 M solution of H_2SO_4 in THF and 1 mL of water were added. The reaction was stirred for another 48 h and sat. $NaHCO_3$ (40 mL) was added. The aqueous phase was extracted with AcOEt (4×10 mL); the organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2 → 95/5) to give allylic alcohol **19** (155 mg, 62%, 2 steps) as a white solid.

- **Allylic oxidation strategy: allylic oxidation of bis-protected catharanthine 23**



In a 30-mL-pressure tube, selenium dioxide (2.72 g, 5 equiv.) was added in one portion to a solution of bis-protected catharanthine **23** (2.0 g, 4.90 mmol, 1 equiv.) in 20 mL of 95% ethanol. The tube was sealed with a Teflon stopper and heated to 120 °C (temperature of the oil bath) under stirring. After 24 h, temperature was lowered to rt, and another portion of SeO_2 (1.64 g, 3 equiv.) was added and the medium was heated at 120 °C under pressure. This operation was repeated again after 24 h. After 72 h of reaction (overall), the starting material was fully consumed (progress of the reaction was monitored by ^{1}H NMR). The medium was cooled to rt, diluted with 90 mL of Et_2O, and washed with 100 mL of brine. The aqueous phase was extracted by Et_2O (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2 → 95/5) to give allylic alcohol **19** (1.26 g, 61%) as a white solid.

R_f 0.32 (CH_2Cl_2/MeOH, 95/5).

mp = 188-190 °C.

^{1}H NMR ($CDCl_3$): δ 8.02 (d app., J = 8.0 Hz, 1H), 7.51 (dd, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.34 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.29 (ddd, J = 7.5 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.42 (dd, J = 6.5 Hz, J = 2.0 Hz, 1H), 5.26 (d, J = 2.0 Hz, 1H), 4.39 (qd, J = 6.5 Hz, J = 3.5 Hz, 1H), 4.17-4.06 (m, 1H), 3.96 (s, 3H), 3.58 (s, 3H), 3.45 (ddd, J = 6.5 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H), 3.41-3.20 (m, 3H), 2.80 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 2.04 (dd, J = 13.0 Hz, J = 3.0 Hz, 1H), 1.88 (d, J = 3.5 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H).

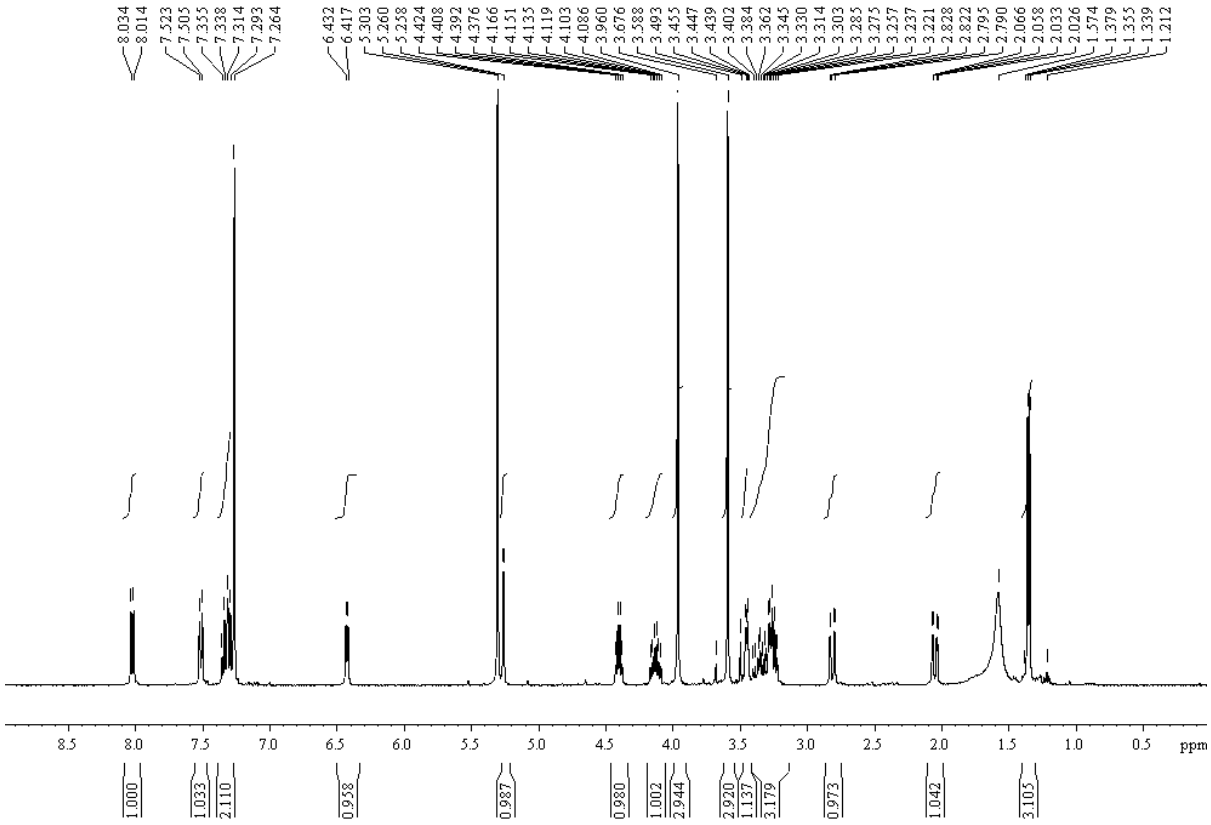
^{13}C NMR ($CDCl_3$): δ 174.2, 173.8, 152.1, 145.3, 136.6, 135.3, 129.4, 128.6, 125.2, 123.2, 118.4, 116.7, 115.8, 67.1, 58.0, 54.4, 53.6, 52.9, 44.1, 40.7, 38.4, 21.4, 21.2.

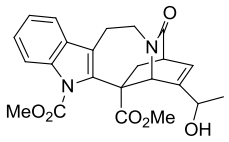
IR (KBr): 3414, 2944, 1743, 1653, 1458, 1437, 1327, 1242, 1208, 1069, 754 cm^{-1}.

MS (ESI+ TOF): 425 $[M+H]^+$ (6), 447 $[M+Na]^+$ (100), 871 $[2M+Na]^+$ (64).

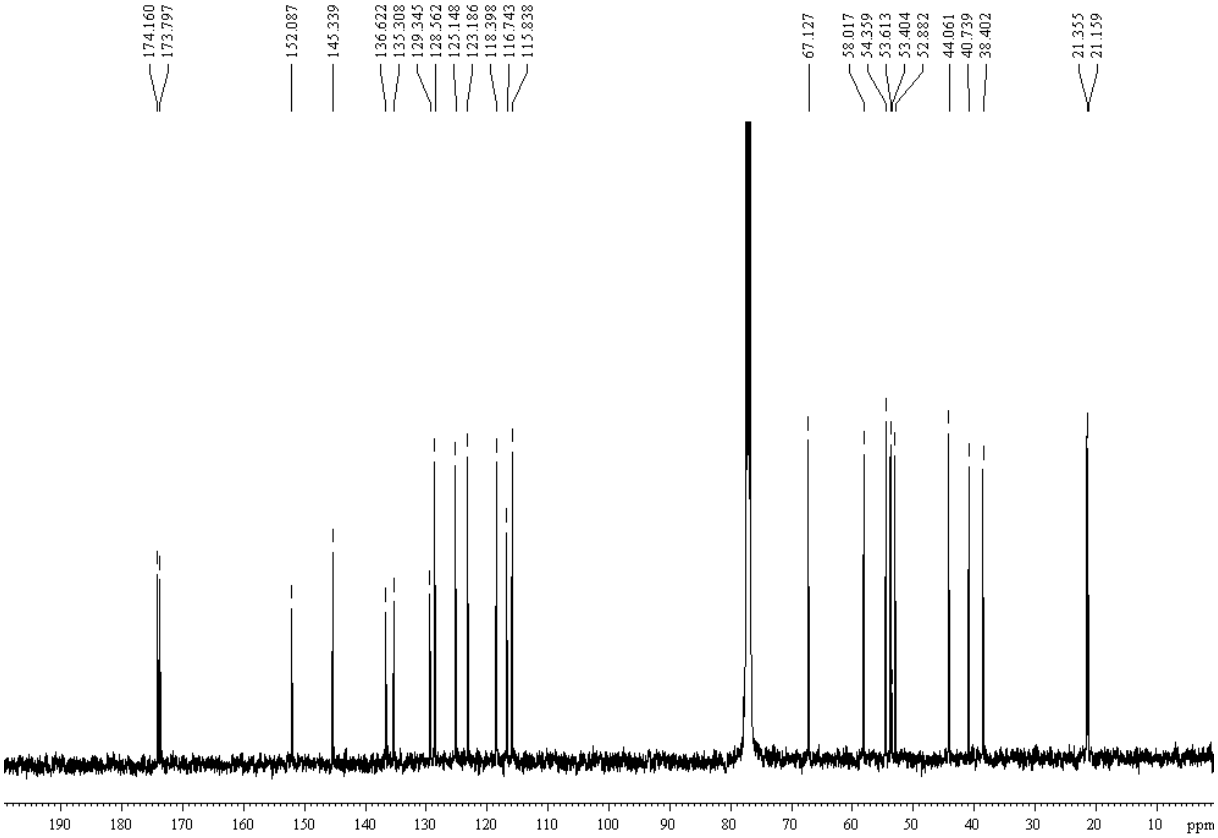
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{24}N_2NaO_6]^+$: 447.1532, Found 447.1532.

$[\alpha]_D^{20}$ = + 181 (*c* 0.7, $CHCl_3$).

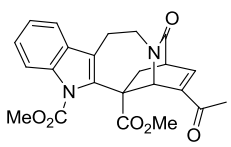




19



N_a-methoxycarbonyl-19,20-dioxocatharanthine (20)



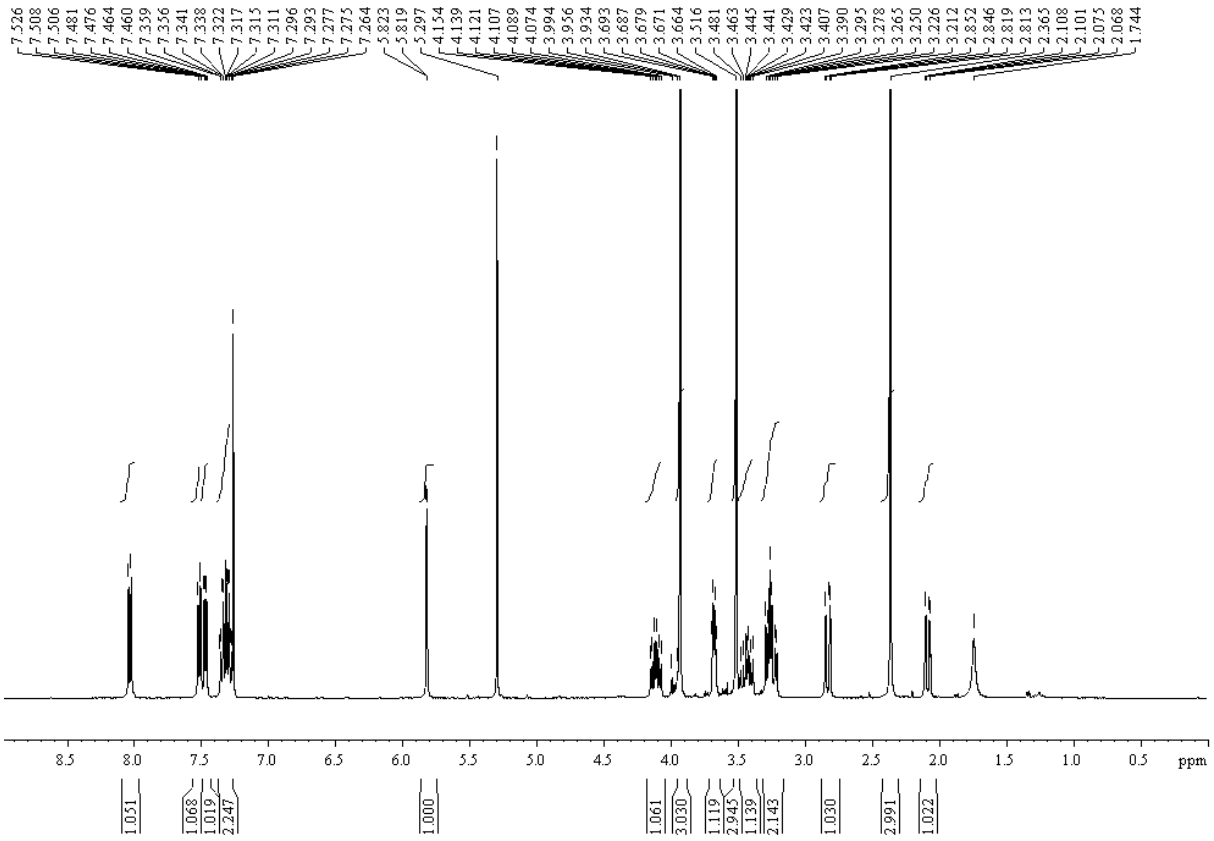
At 0 °C, to a solution of protected catharanthine allylic alcohol **19** (500 mg, 1.18 mmol, 1 equiv.) in 30 mL CH_2Cl_2 was added activated MnO_2 (85 wt.%, 7.0 g, 58 equiv.) in one portion. The black suspension was stirred at 0 °C for 3 h. The mixture was filtered on a pad of celite, washed thoroughly with CH_2Cl_2, and the filtrate was concentrated under vacuum to give enone **20** (425 mg, 85%) as a white solid.

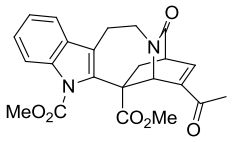
R_f 0.36 (CH_2Cl_2/MeOH, 95/5).
mp = 108-110 °C.

^{1}H NMR ($CDCl_3$): δ 8.04 (d app., J = 8.0 Hz, 1H), 7.52 (dd, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.47 (dd, J = 6.5 Hz, J = 1.5 Hz, 1H), 7.34 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.30 (ddd, J = 7.5 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 5.82 (d, J = 1.5 Hz, 1H), 4.12 (ddd, J = 13.5 Hz, J = 12.5 Hz, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.68 (ddd, J = 6.5 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H), 3.52 (s, 3H), 3.44 (ddd, J = 15.5 Hz, J = 13.5 Hz, J = 7.0 Hz, 1H), 3.31-3.20 (m, 2H), 2.83 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 2.37 (s, 3H), 2.09 (dd, J = 13.0 Hz, J = 3.0 Hz, 1H).

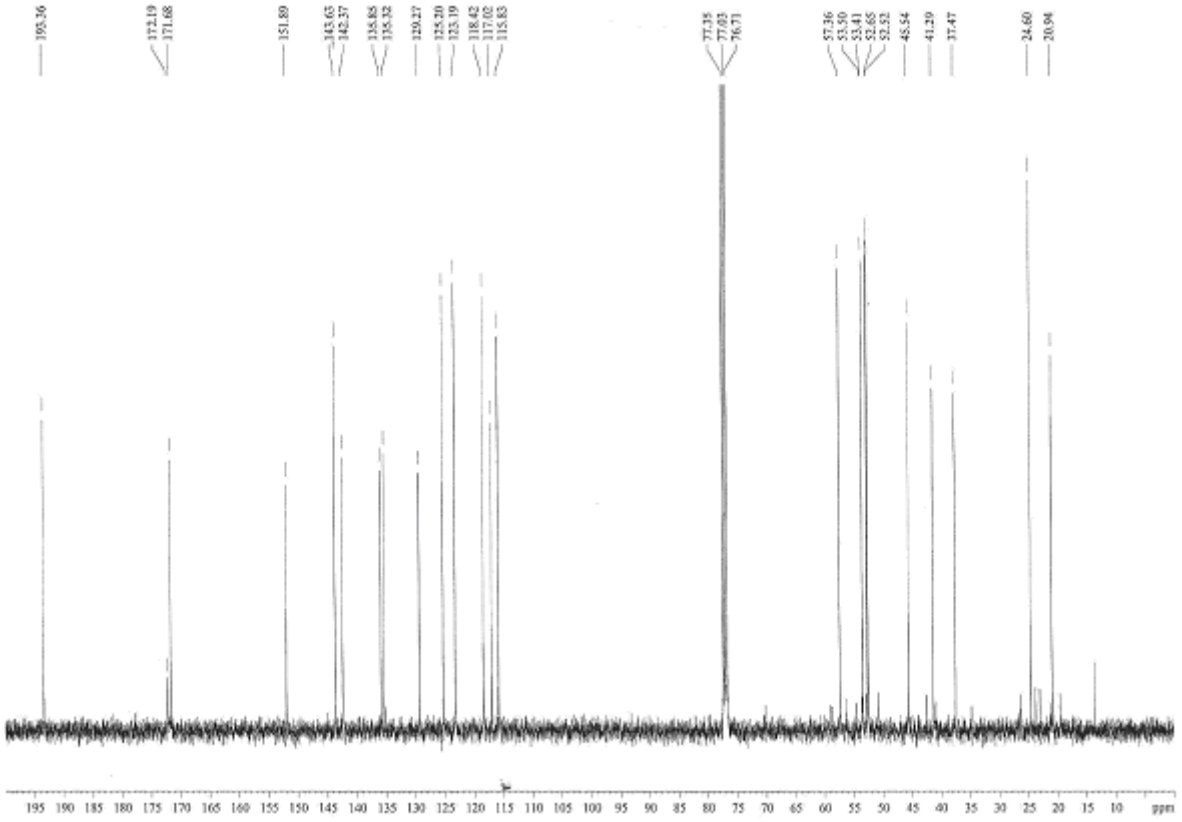
^{13}C NMR ($CDCl_3$): δ 193.3, 172.2, 171.7, 151.9, 143.6, 142.3, 135.8, 135.3, 129.2, 125.2, 123.2, 118.4, 117.0, 115.8, 57.3, 53.5, 52.6, 52.5, 45.5, 41.3, 37.4, 24.6, 20.9.

IR (KBr): 2953, 1740, 1668, 1459, 1442, 1252, 751 cm^{-1}.
MS (ESI+ TOF): 423 $[M+H]^+$ (10), 445 $[M+Na]^+$ (100), 867 $[2M+Na]^+$ (32).
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{22}N_2NaO_6]^+$: 445.1376, Found 445.1357.
$[\alpha]_D^{20}$ = + 183 (c 1.8, $CHCl_3$).

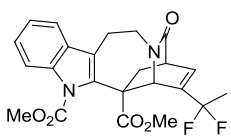




20



N_a-methoxycarbonyl-20,20-difluoro-19-oxocatharanthine (21)



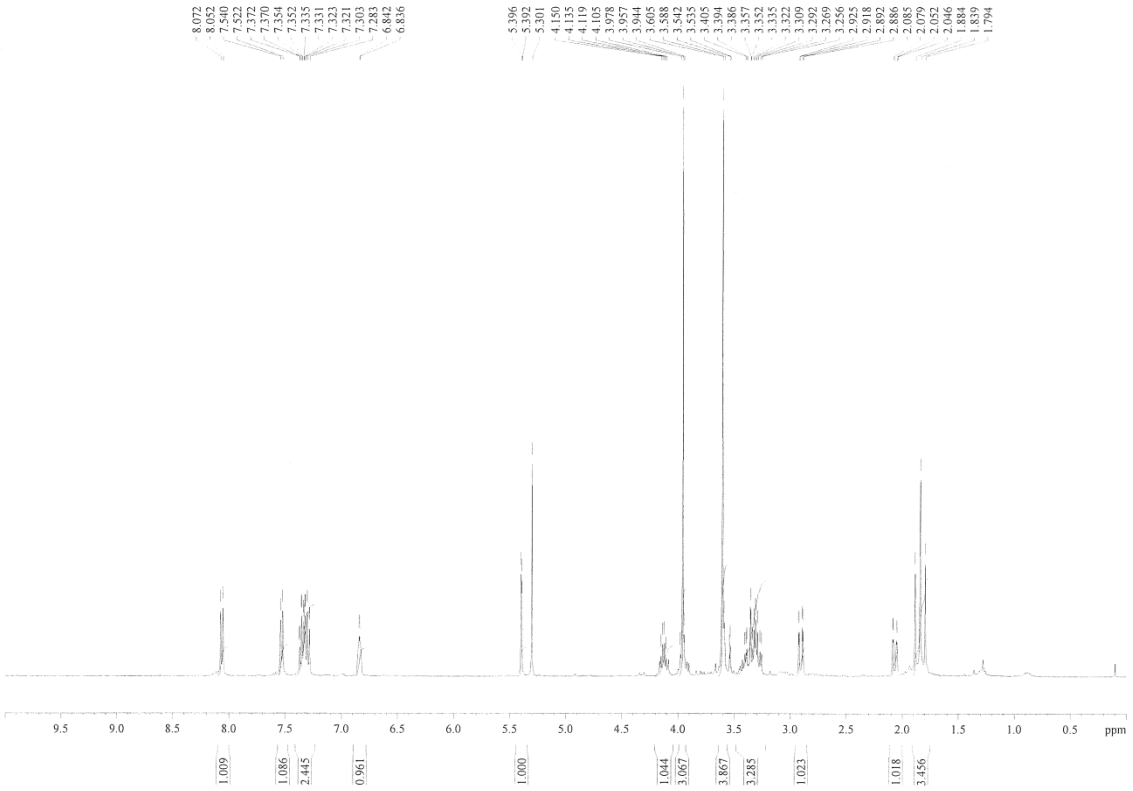
Enone **20** (302 mg, 0.71 mmol, 1 equiv.) was dissolved in neat Deoxofluor™ (3.0 mL, 22.9 equiv.) before three drops of EtOH were added. The mixture was stirred for 24 h at 70 °C. Deoxofluor™ (0.6 mL, 4.6 equiv.) and two drops of ethanol were again added and the reaction was further stirred for 48 h at 70 °C (progress of the reaction was monitored by ^{1}H NMR). The medium was diluted with 200 mL of CH_2Cl_2 and 100 mL of sat. K_2CO_3 were added. The mixture was stirred for 15 min at rt and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2 → *c*-Hex/AcOEt, 6/4) to give *gem*-difluorinated **21** (152 mg, 48%) as a white solid.

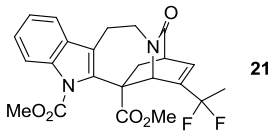
R_f 0.33 (*c*-Hex/AcOEt, 4/6).

^{1}H NMR ($CDCl_3$): δ 8.05 (d app., J = 8.0 Hz, 1H), 7.52 (d app., J = 7.5 Hz, 1H), 7.34 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.29 (ddd, J = 7.5 Hz, J = 7.5 Hz, J = 1.0 Hz, 1H), 6.86-6.80 (m, 1H), 5.38 (d, J = 2.0 Hz, 1H), 4.16-4.06 (m, 1H), 3.95 (s, 3H), 3.60 (s, 3H), 3.62-3.56 (m, 1H), 3.45-3.24 (m, 3H), 2.90 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 2.06 (dd, J = 13.0 Hz, J = 2.5 Hz,1H), 1.83 (dd, J = 18.0 Hz, J = 18.0 Hz, 3H).

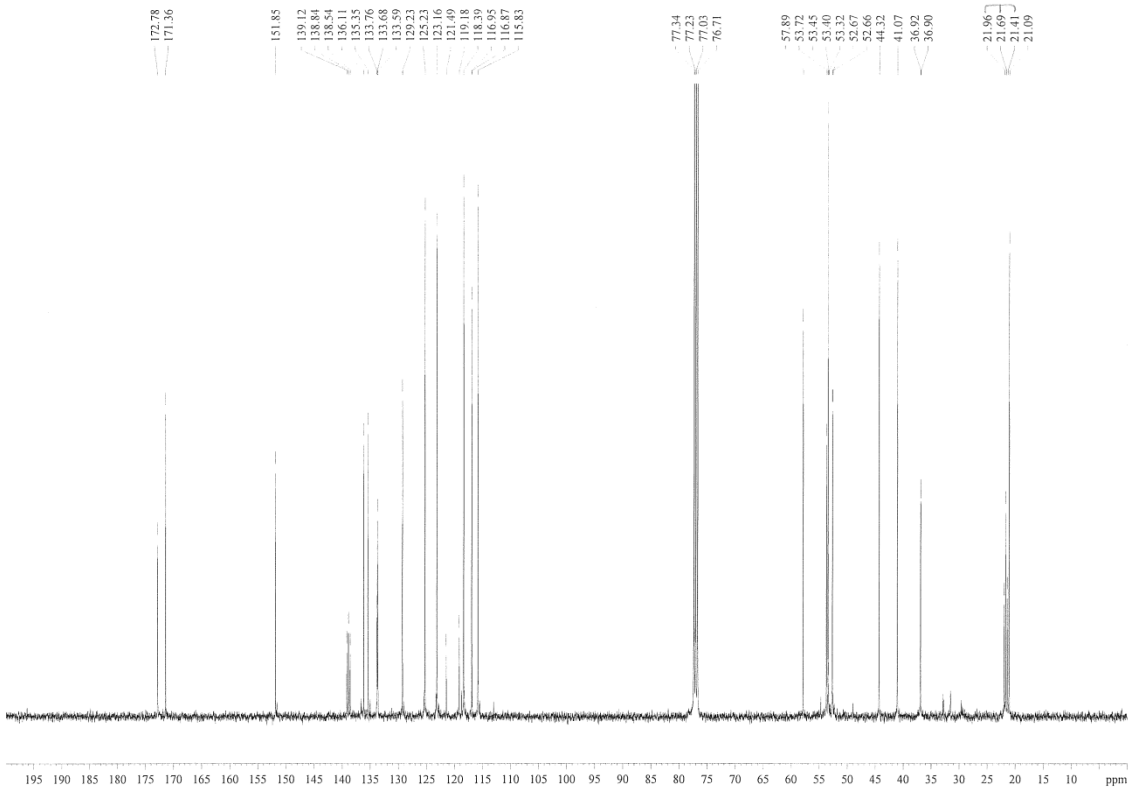
^{13}C NMR ($CDCl_3$): δ 172.8, 171.3, 151.8, 138.8 (t, J = 29 Hz), 136.1, 135.3, 133.7 (t, J = 9 Hz), 129.2, 125.2, 123.1, 119.2 (t, J = 231 Hz), 118.4, 116.9, 115.8, 57.9, 53.7, 53.4, 52.6, 44.3, 41.0, 36.9, 21.7 (t, J = 28 Hz), 21.1.

IR (KBr): 2955, 1743, 1685, 1665, 1460, 1442, 1327, 1256, 751 cm^{-1}.
MS (ESI+ TOF): 445 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{23}H_{22}F_2N_2NaO_5]^+$: 467.1394, Found 467,1385.

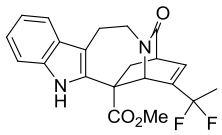




21



20,20-difluoro-19-oxocatharanthine (22)



To a solution of bis-protected difluorocatharanthine **21** (130 mg, 0.29 mmol, 1 equiv) in 100 mL of MeOH was added K_2CO_3 (2 g, 50 equiv.). The suspension was stirred at rt for 18 h, before 50 mL of H_2O were added. The aqueous phase was extracted with CH_2Cl_2 (4×50 mL); the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was precipitated in *c*-Hex/AcOEt (8/2) to afford carbamate-free difluorocatharanthine analogue **22** (101 mg, 90%) as a white solid.

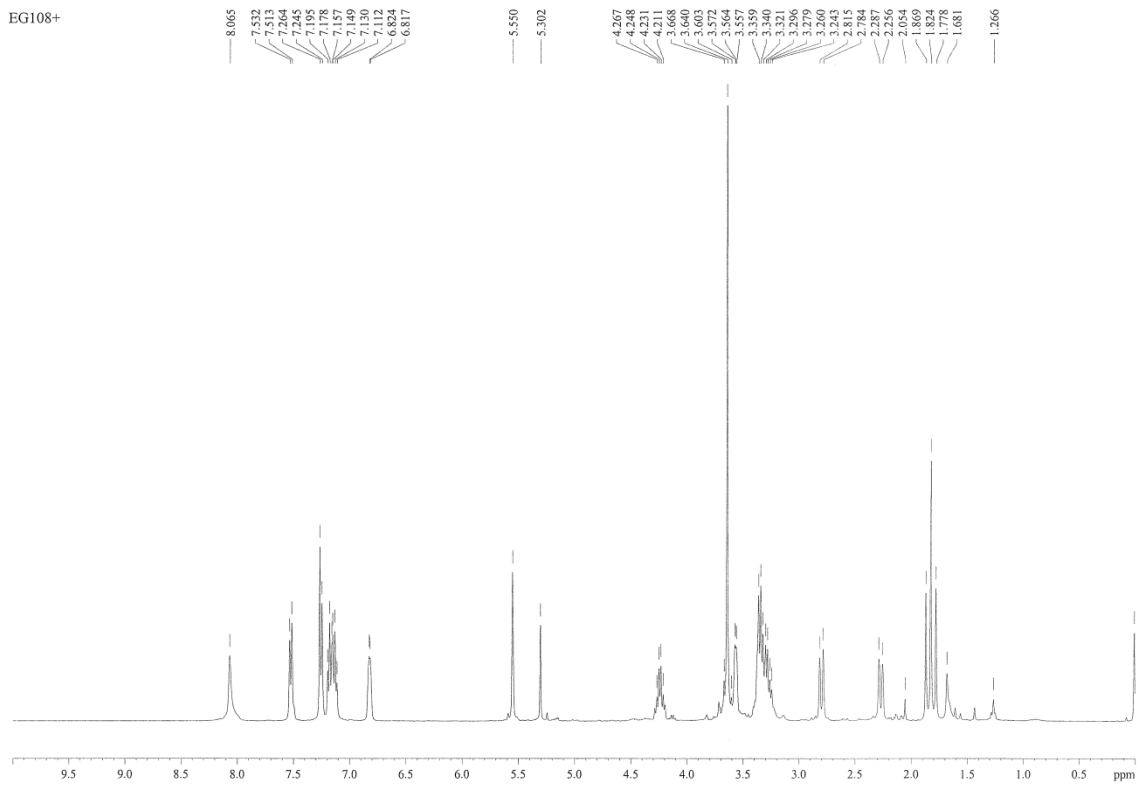
R_f 0.62 (CH_2Cl_2/MeOH, 95/5).

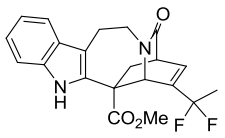
^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.52 (d app., J = 7.5 Hz, 1H), 7.26 (d app., J =7.5 Hz, 1H), 7.21-7.10 (m, 2H), 6.86-6.79 (m, 1H), 5.55 (d, J = 1.5 Hz, 1H), 4.30-4.19 (m, 1H), 3.65 (s, 3H), 3.62-3.55 (m, 1H), 3.42-3.22 (m, 3H), 2.82 (dd, J = 13.0 Hz, J = 2.0 Hz, 1H), 2.28 (dd, J = 13.0 Hz, J = 2.5 Hz, 1H), 1.83 (dd, J = 18.0 Hz, J = 18.0 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 172.8, 171.6, 139.5 (t, J = 30 Hz), 135.8, 135.2 (t, J = 9 Hz), 133.8, 127.7, 122.4, 119.7, 119.1 (t, J = 233 Hz), 118.4, 110.6, 108.7, 56.3, 53.6, 53.0, 44.0, 42.8, 35.5, 22.4 (t, J = 28 Hz), 20.7.

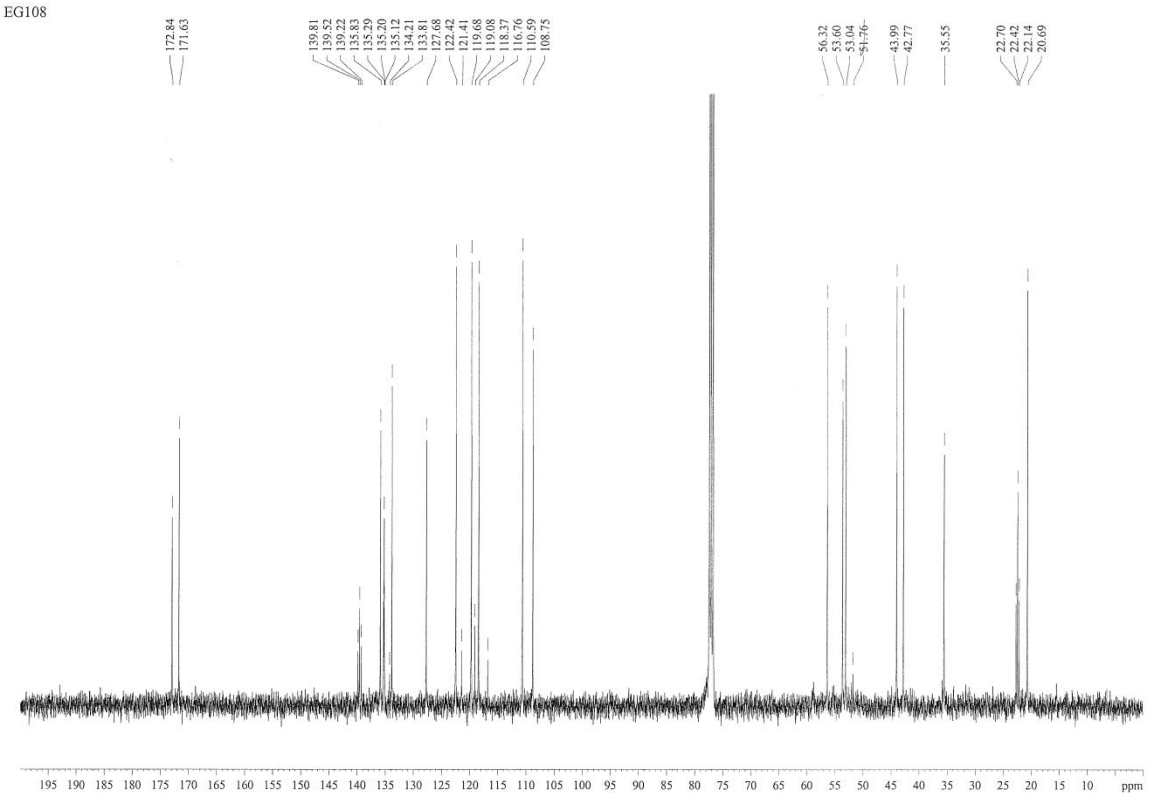
MS (ESI+ TOF): 387 $[M+H]^+$ (100).

$[\alpha]_D^{20}$ = + 155 (*c* 0.4, $CHCl_3$).

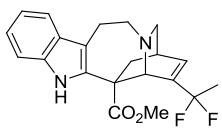

EG108+
8.065
7.532
7.513
7.264
7.245
7.195
7.178
7.157
7.149
7.130
7.112
6.824
6.817
5.550
5.302
4.267
4.248
4.231
4.211
3.668
3.640
3.605
3.572
3.564
3.557
3.359
3.340
3.321
3.296
3.279
3.260
3.243
2.815
2.784
2.287
2.256
2.054
1.869
1.824
1.778
1.681
1.266
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


O
N
N
H
CO2Me
F
F

22


EG108
172.84
171.63
139.81
139.52
139.22
135.83
135.29
135.20
135.12
134.21
133.81
127.68
122.42
121.41
119.68
119.08
118.37
116.76
110.59
108.75
56.32
53.60
53.04
43.99
42.77
35.55
22.70
22.42
22.14
20.69
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

20,20-difluorocatharanthine (10)



To a solution of **22** (70 mg, 0.18 mmol, 1 equiv.) in 40 mL of dry THF was added $NaBH_4$ (180 mg, 26 equiv.) in one portion. The suspension was cooled to 0 °C before BF_3•OEt_2 (0.95 mL, 42 equiv.) was added dropwise. The yellow mixture was stirred at rt for 7 h. The solvent was then evaporated under vacuum and MeOH (25 mL), water (5 mL) and 10 wt.% HCl (5 mL) were added. The resulting mixture was stirred for 15 h at rt. MeOH was evaporated and the residue was taken up in 75 mL of CH_2Cl_2. The solution was neutralized with 75 mL of sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL); the combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2) to give difluorocatharanthine **10** (39 mg, 58%) as a white solid.

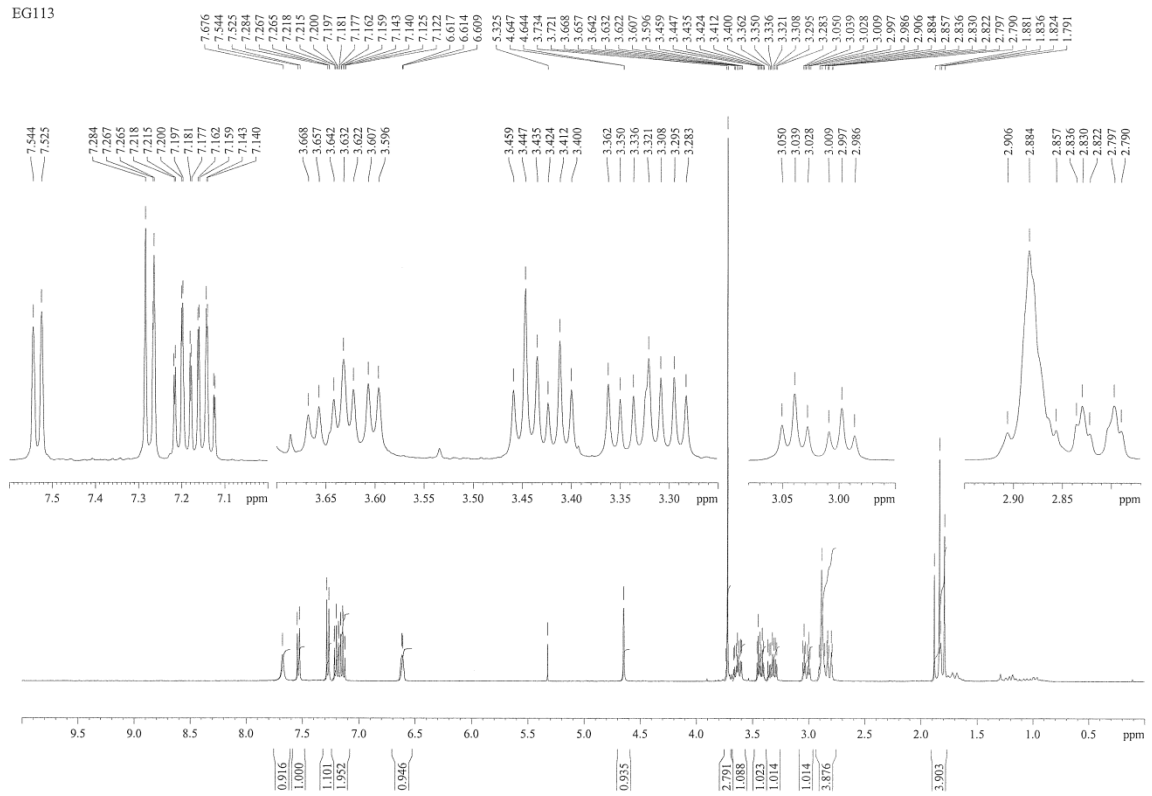
R_f 0.54 (CH_2Cl_2/MeOH, 95/5).
mp = 70-72 °C.

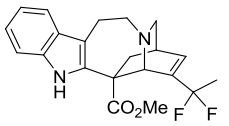
^{1}H NMR ($CDCl_3$): δ 7.68 (s, 1H), 7.52 (d app., J = 8.0 Hz, 1H), 7.26 (d app., J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.12 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.63-6.58 (m, 1H), 4.63 (d, J = 1.0 Hz, 1H), 3.70 (s, 3H), 3.61 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 4.5 Hz, 1H), 3.41 (ddd, J = 14.0 Hz, J = 5.0 Hz, J = 4.5 Hz, 1H), 3.30 (ddd, J = 16.5 Hz, J = 10.5 Hz, J = 5.0 Hz, 1H), 3.00 (ddd, J = 16.5 Hz, J = 4.5 Hz, J = 4.5 Hz, 1H), 2.90-2.83 (m, 3H), 2.79 (ddd, J = 13.0 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H), 1.82 (dd, J = 18.0 Hz, J = 18.0 Hz, 3H), 1.79 (d app., J = 13.0 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ 173.5, 143.3 (t, J = 28 Hz), 136.2, 135.3, 132.1 (t, J = 9 Hz), 128.8, 122.1, 119.8 (dd, J = 232 Hz), 119.5, 118.4, 110.6, 110.4, 57.1, 55.3, 52.8, 52.4, 47.1, 37.0, 30.8, 22.6 (t, J = 28 Hz), 21.6.

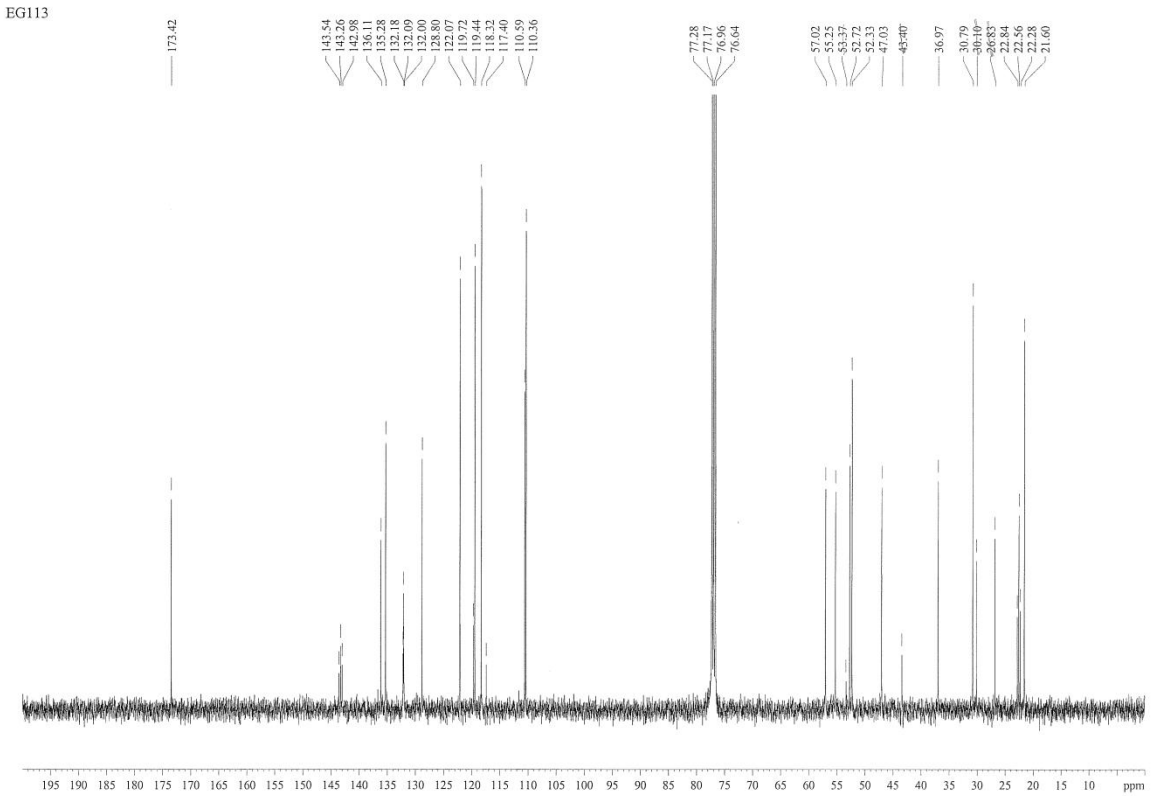
^{19}F NMR (H-decoupled, $CDCl_3$): δ – 88.3 (d, J = 262 Hz, 1F), – 90.7 (d, J = 262 Hz, 1F).

IR (KBr): 3373, 2849, 1714, 1461, 1275, 1172, 743 cm^{-1}.
MS (ESI+ TOF): 353 $[M-HF+H]^+$ (4), 373 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{21}H_{23}F_2N_2O_2]^+$: 373.1728, Found 373.1728.
$[\alpha]_D^{20}$ = + 43 (c 0.4, $CHCl_3$).

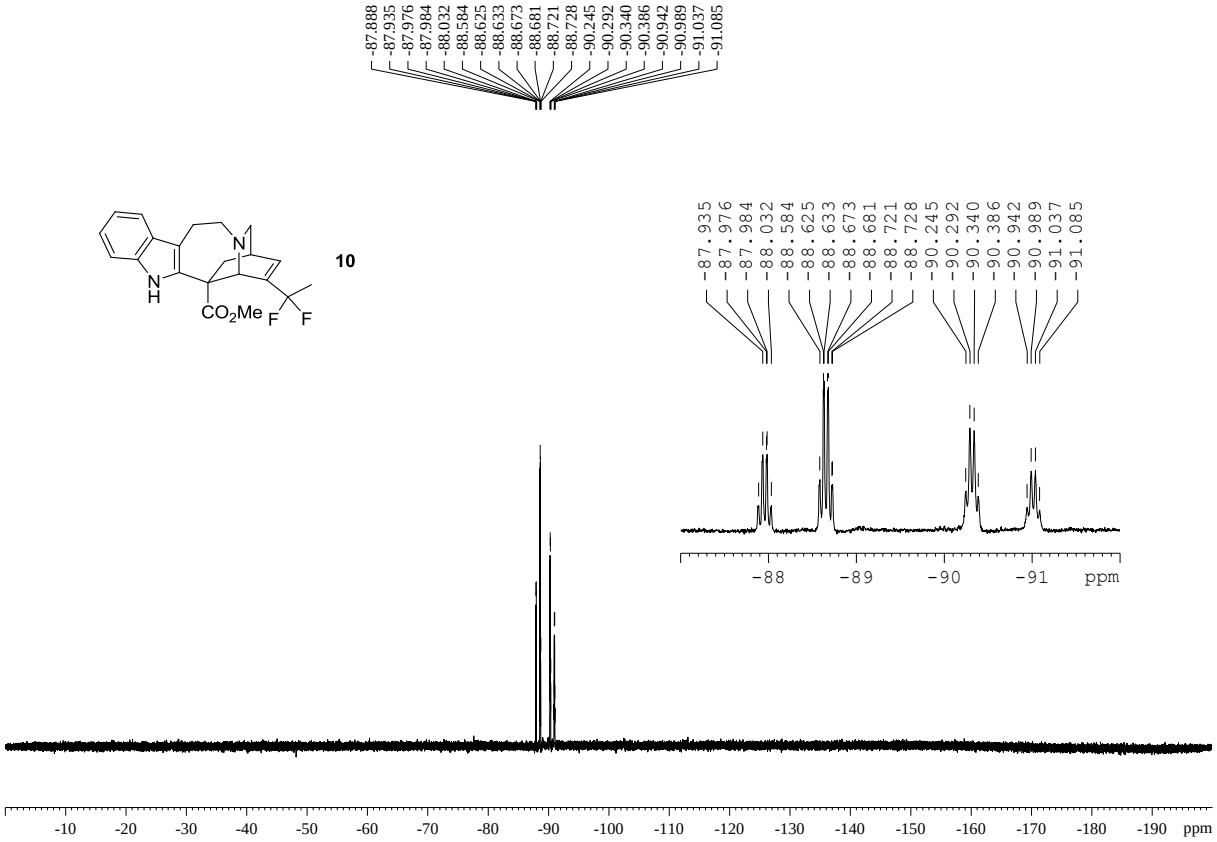




10

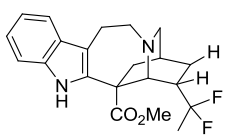


^{19}F NMR spectrum of difluorocatharanthine 10 (inset: zoom in the – 87 / – 92 ppm region, H-coupled)



Hydrogenated derivatives of difluorocatharanthine

20,20-difluoro-3,4-dihydrocatharanthine (32)



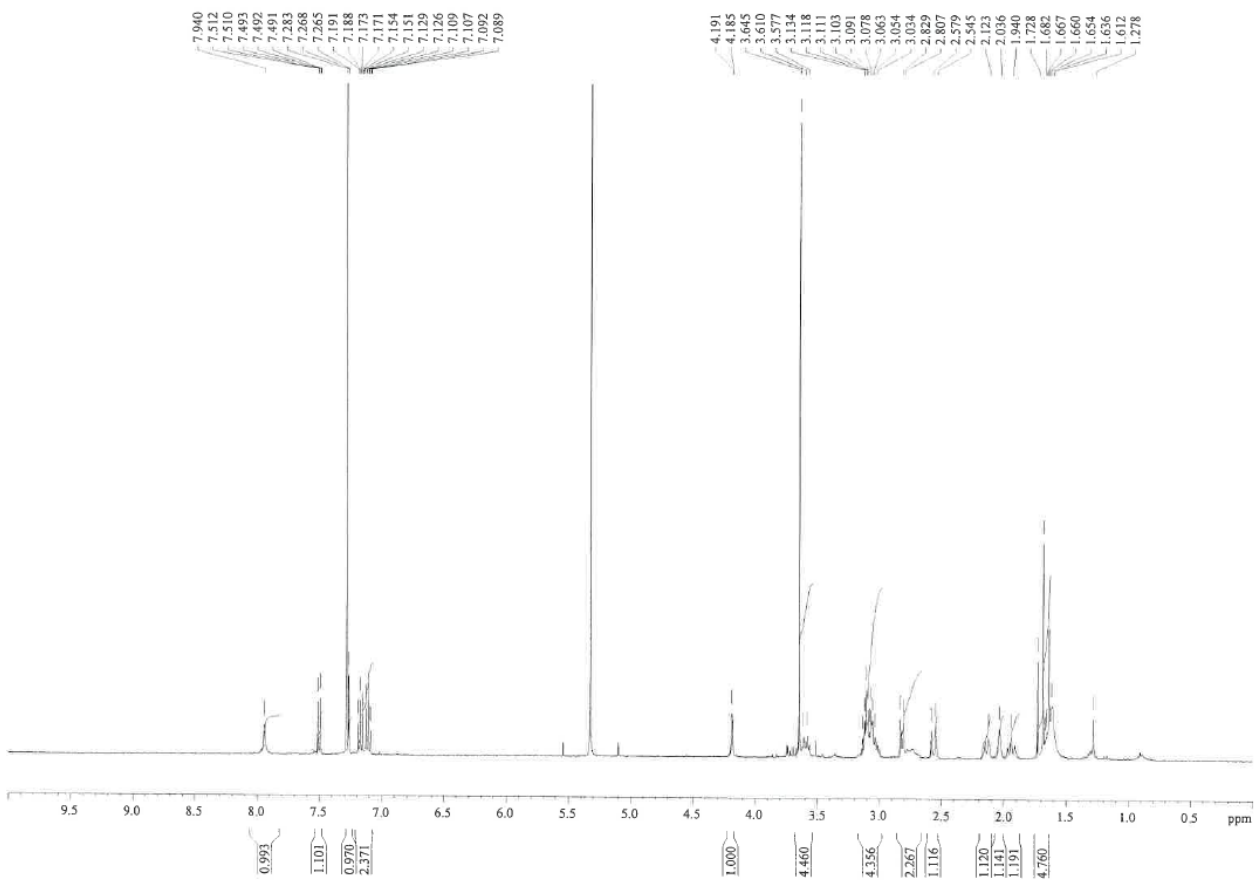
PtO_2 (160 mg, 1.3 equiv.) was suspended in 4 mL of MeOH and stirred for 1 h under hydrogen gas. To this suspension was added a solution of 20,20-difluorocatharanthine **10** (200 mg, 0.537 mmol, 1 equiv.) in 4 mL of MeOH and a few drops of CH_2Cl_2. The mixture was stirred under 1 bar of hydrogen for 24 h. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica (*c*-Hex/AcOEt, 4/1) to give hydrogenated difluorocatharanthine **32** (16 mg, 8%), and isomerized flurocatharanthines **33** (81 mg, 43%) and **34** (46 mg, 24%) as white solids.

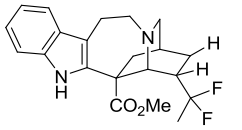
R_f 0.62 (CH_2Cl_2/MeOH, 95/5).

^{1}H NMR ($CDCl_3$): δ 8.00 (sl, 1H), 7.49 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.27 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.16 (ddd, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 3.63 (s, 3H), 3.61-3.54 (m, 1H), 3.13-2.98 (m, 4H), 2.81 (d, *J* = 9.0 Hz, 1H), 2.80-2.67 (m, 1H), 2.55 (d, *J* = 13.5 Hz, 1H), 2.13 (ddd, *J* = 13.0 Hz, *J* = 2.5 Hz, *J* = 2.5 Hz, 1H), 2.02 (s app., 1H), 1.93 (t app., *J* = 12.5 Hz, 1H), 1.67 (dd, *J* = 18.5 Hz, *J* = 18.5 Hz, 3H), 1.67-1.61 (m, 1H).

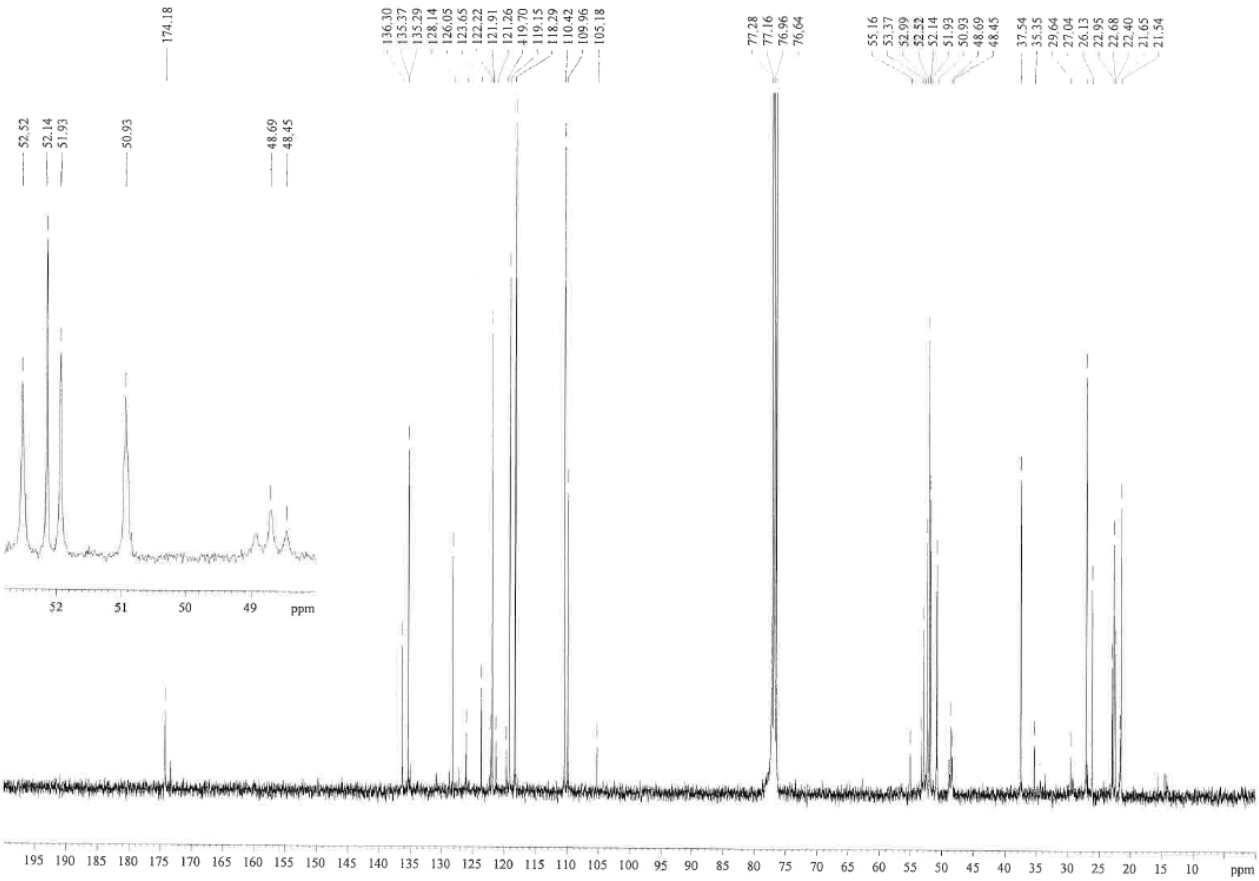
^{13}C NMR ($CDCl_3$): δ 174.2, 136.3, 135.3, 128.1, 123.7 (t, *J* = 240 Hz), 121.9, 119.2, 118.3, 110.4, 110.0, 53.0, 52.5, 52.1, 51.9, 50.9, 48.7 (t, *J* = 24 Hz), 37.5, 27.0, 26.1, 22.7 (t, *J* = 28 Hz), 21.5.

IR (KBr): 3371, 2949, 2855, 1717, 1462, 1434, 1265, 1123, 908, 744, 730 cm^{-1}.
MS (ESI+ TOF): 375 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{21}H_{25}F_2N_2O_2]^+$: 375.1884, Found: 375.1886.

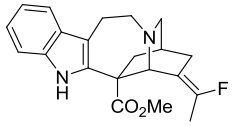




32



(4*E*)-20-fluoro-$\Delta^{4,20}$-*exo*-isocatharanthine (33)

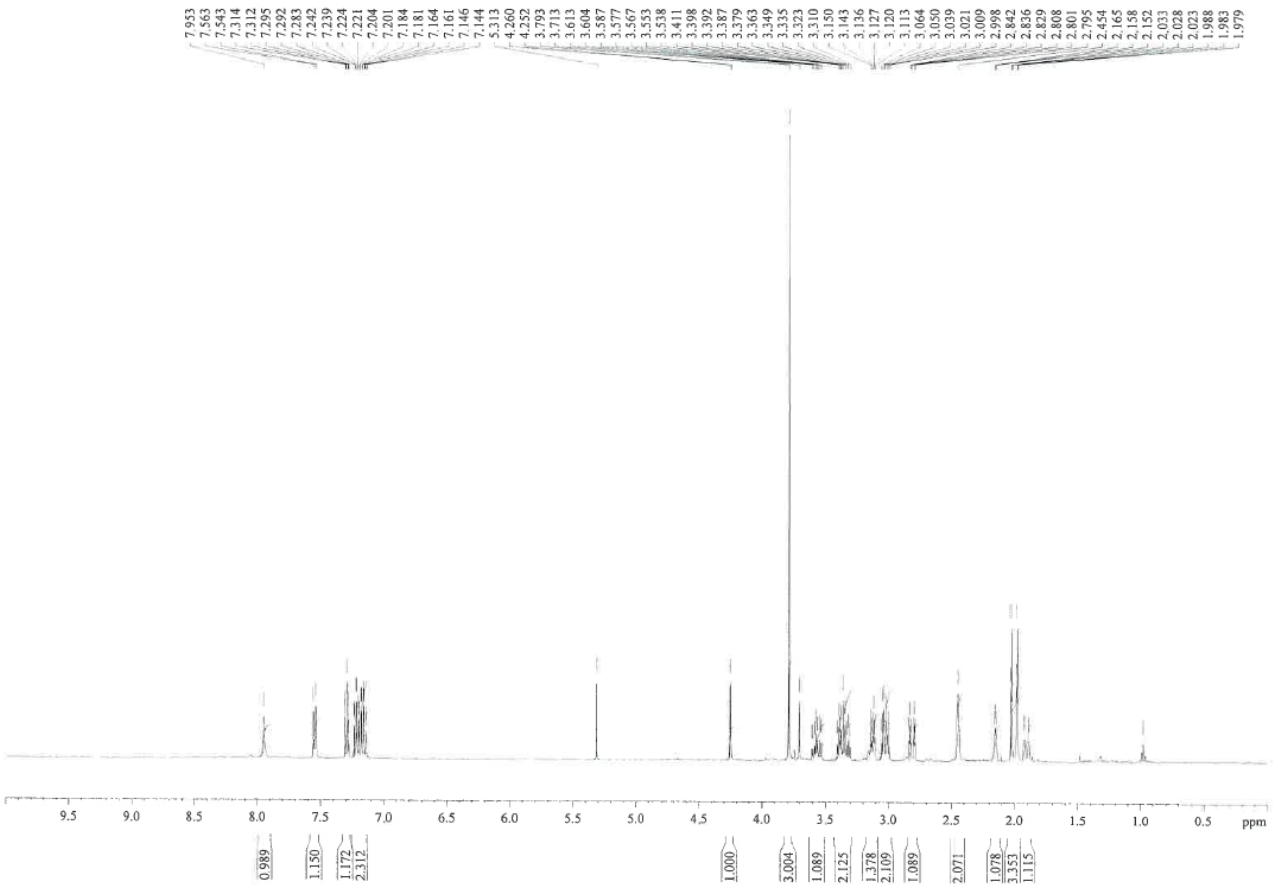


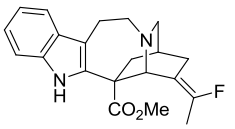
R_f 0.34 (CH_2Cl_2/MeOH, 95/5).

^{1}H NMR ($CDCl_3$): δ 7.95 (sl, 1H), 7.56 (d app., *J* = 8.0 Hz, 1H), 7.30 (d app., *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 4.26 (d, *J* = 3.0 Hz, 1H), 3.79 (s, 3H), 3.61-3.54 (m, 1H), 3.42-3.30 (m, 2H), 3.13 (ddd, *J* = 9.5 Hz, *J* = 3.0 Hz, *J* = 3.0 Hz, 1H), 3.07-2.99 (m, 2H), 2.82 (ddd, *J* = 13.5 Hz, *J* = 2.5 Hz, *J* = 2.5 Hz, 1H), 2.47-2.44 (m, 2H), 2.18-2.14 (m, 1H), 2.00 (ddd, *J* = 18.0 Hz, *J* = 2.0 Hz, *J* = 2.0 Hz, 3H), 1.91 (d app., *J* = 13.5 Hz, 1H).

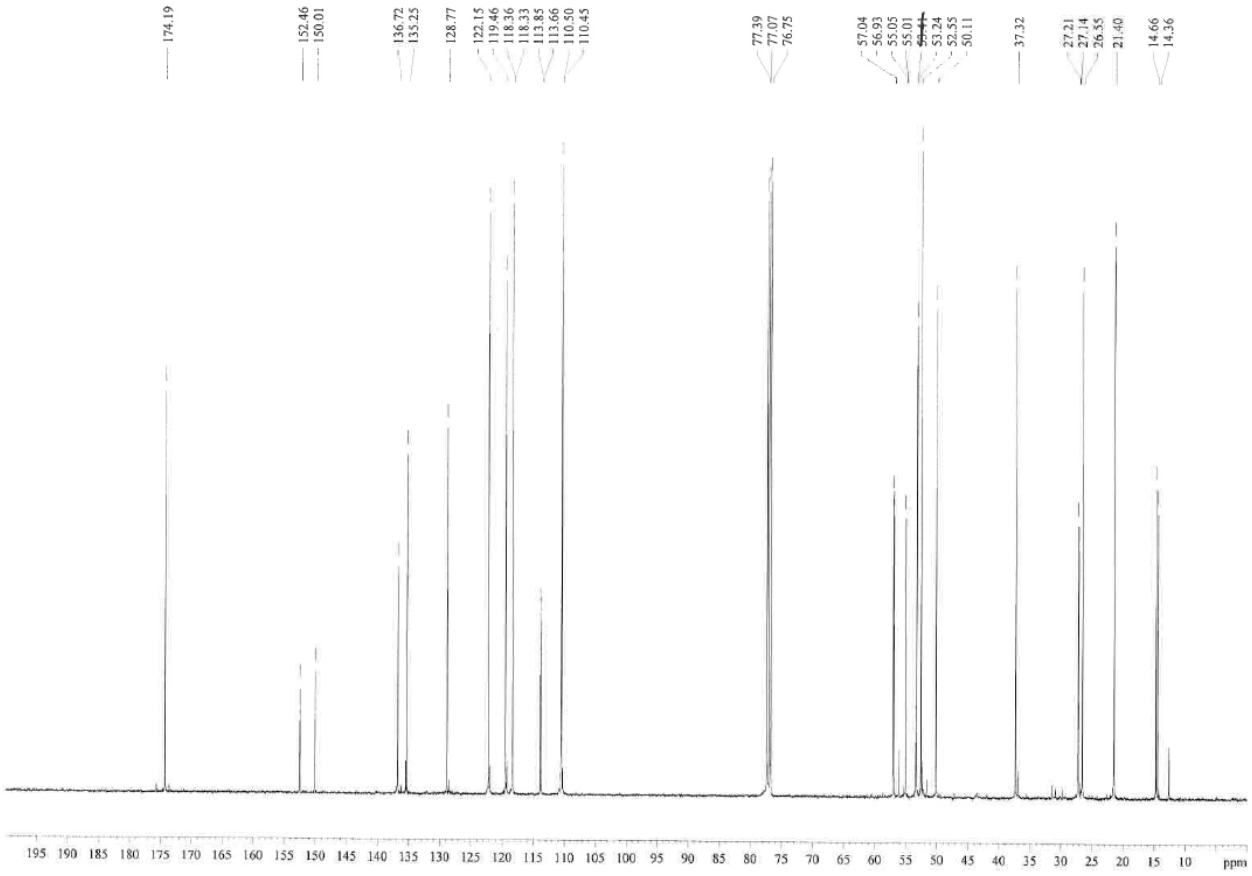
^{13}C NMR ($CDCl_3$): δ 174.2, 151.2 (d, *J* = 245 Hz), 136.7, 135.3, 128.8, 122.2, 119.5, 118.3, 113.8 (d, *J* = 11 Hz), 110.5 (2C), 57.0 (d, *J* = 11 Hz), 55.0 (d, *J* = 4 Hz), 53.2, 52.6, 50.1, 37.3, 27.2 (d, *J* = 7 Hz), 26.6, 21.4, 14.5 (d, *J* = 30 Hz).

IR (KBr): 3376, 2923, 2845, 1722, 1460, 1434, 1246, 1170, 1155, 1085, 742 cm^{-1}.
MS (ESI+ TOF): 355 $[M+H]^+$ (100).

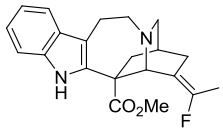




33



(4*Z*)-20-fluoro-$\Delta^{4,20}$-*exo*-isocatharanthine (34)

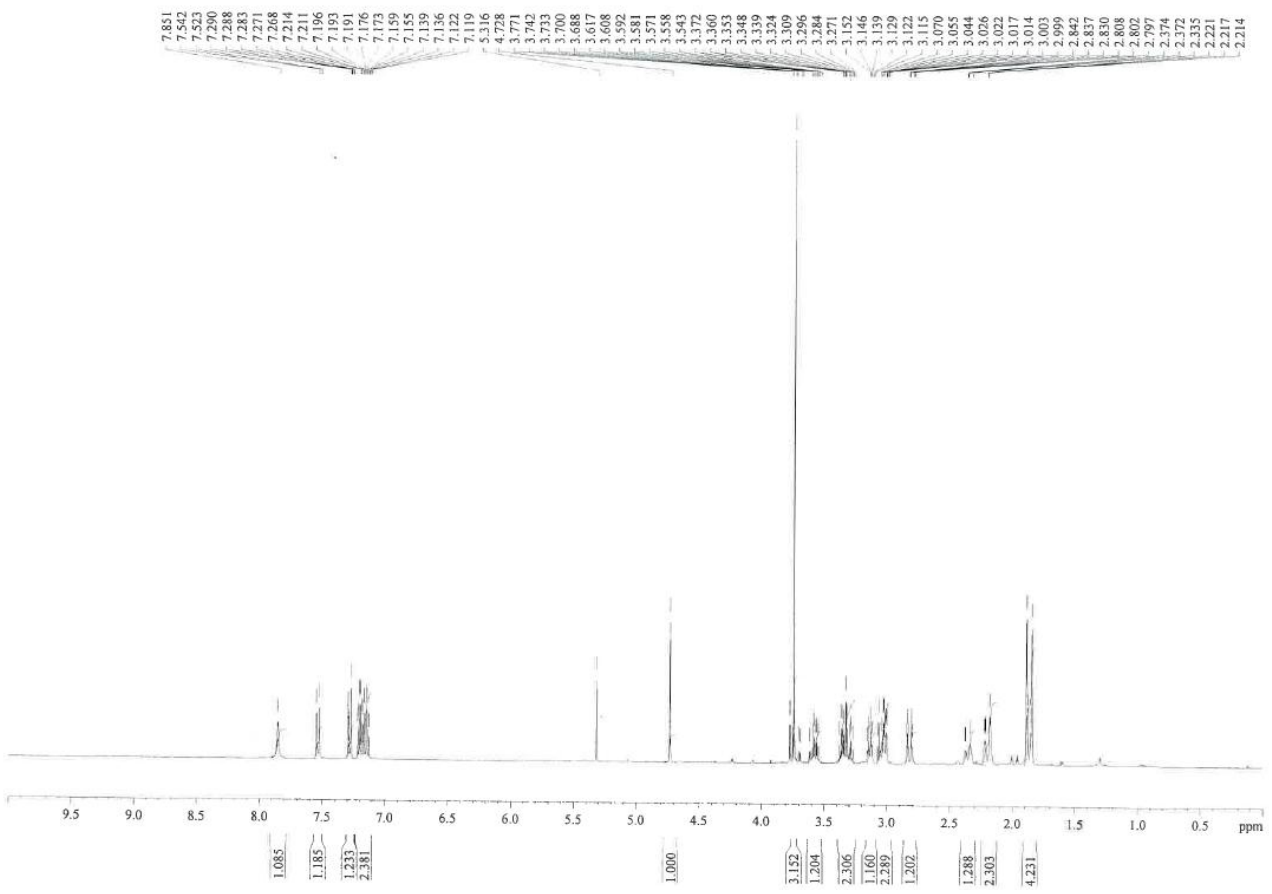


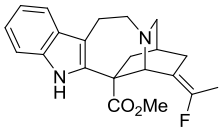
R_f 0.22 (CH_2Cl_2/MeOH, 95/5).

^{1}H NMR ($CDCl_3$): δ 7.85 (sl, 1H), 7.53 (d app., *J* = 8.0 Hz, 1H), 7.28 (d app., *J* = 8.0 Hz, 1H), 7.20 (ddd, *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 4.73 (s, 1H), 3.74 (s, 3H), 3.62-3.54 (m, 1H), 3.38-3.26 (m, 2H), 3.13 (ddd, *J* = 9.5 Hz, *J* = 2.5 Hz, *J* = 2.5 Hz, 1H), 3.08-2.99 (m, 2H), 2.82 (dd, *J* = 13.5 Hz, *J* = 2.5 Hz, *J* = 2.5 Hz, 1H), 2.35 (d app., *J* = 15.0 Hz, 1H), 2.20 (d app., *J* = 15.0 Hz, 1H), 2.20-2.16 (m, 1H), 1.87 (d app., *J* = 13.0 Hz, 1H), 1.86 (d app., *J* = 17.0 Hz, 3H).

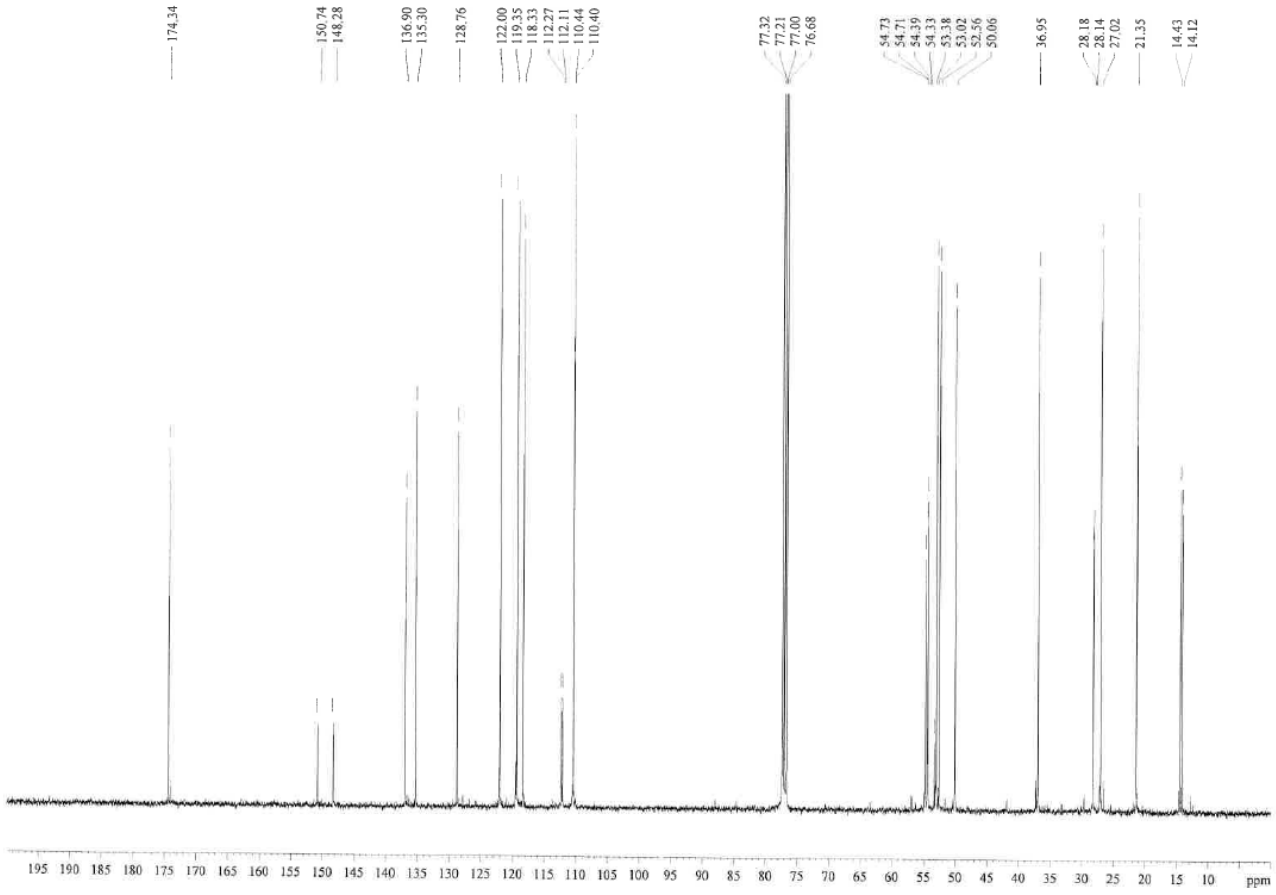
^{13}C NMR ($CDCl_3$): δ 174.3, 149.5 (d, *J* = 246 Hz), 136.9, 135.3, 128.8, 122.0, 119.4, 118.3, 112.2 (d, *J* = 16 Hz), 110.4 (2C), 54.7 (d, *J* = 2 Hz), 54.4 (d, *J* = 6 Hz), 53.0, 52.6, 50.1, 37.0, 28.2 (d, *J* = 4 Hz), 27.0, 21.4, 14.3 (d, *J* = 31 Hz).

IR (KBr): 3369, 2921, 2844, 1717, 1461, 1434, 1258, 1155, 1087, 742 cm^{-1}.
MS (ESI+ TOF): 355 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{21}H_{24}FN_2O_2]^+$: 355.1822, Found: 355.1828.



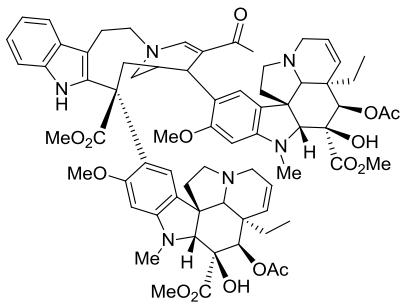


34



Coupling products

4′,5′-anhydro-20′-oxo-3′-vindolin-15″-ylvinblastine (26)



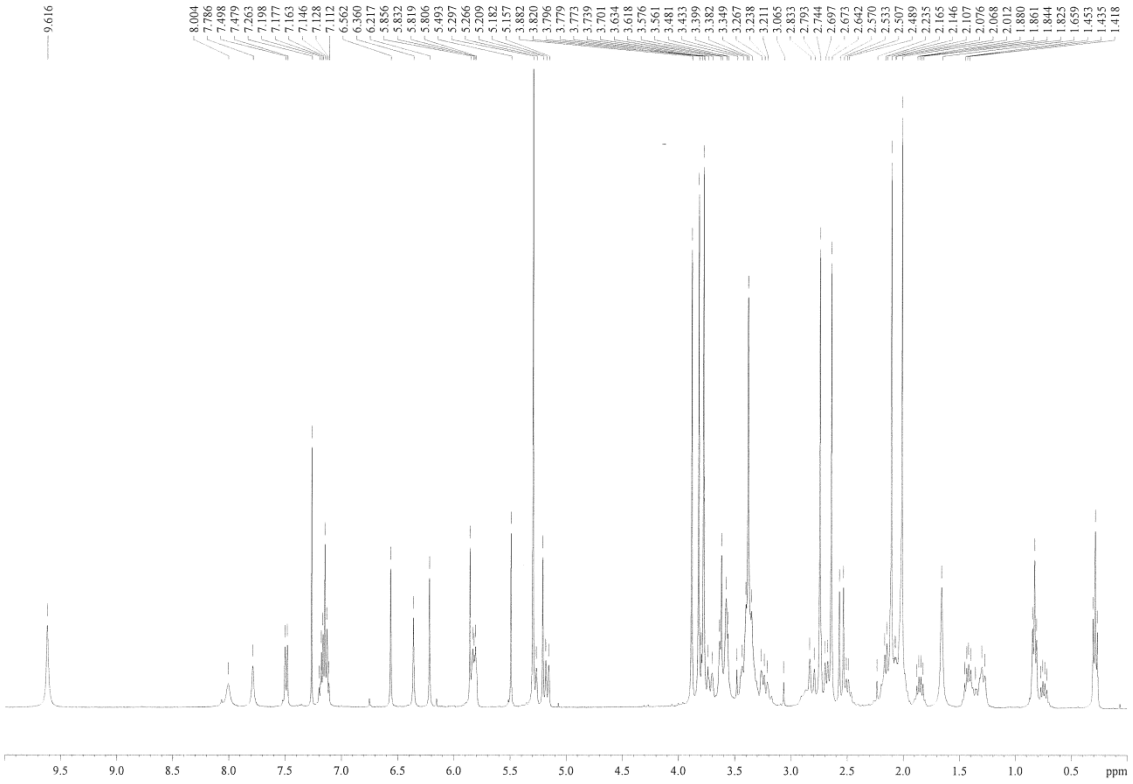
20,20-difluorocatharanthine **10** (100 mg, 0.269 mmol, 1 equiv.) was added in one portion to a mixture of 10 mL of glycine buffer (0.75 g of glycine and 0.585 g of NaCl in 100 mL of water) and 20 mL of 0.1 M aq. HCl. After dissolution of **10**, vindoline **7** (124 mg, 1 equiv.) and $FeCl_3$ (220 mg, 5 equiv.) were added in one portion. The reaction mixture was stirred for 30 min at rt, before 2 mL of 28 wt.% aq. NH_3 were added dropwise. After 10 min at rt, 20 mL of CH_2Cl_2 and 20 mL of sat. Rochelle's salt were added and the mixture was stirred vigorously for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 98/2) to give trimer **26** (96 mg, 57%) as a pale yellow solid and dimer **27** (35 mg, 16%) as an off-white solid.

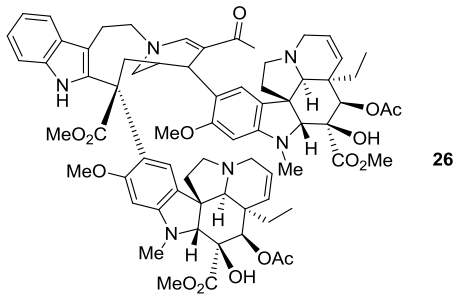
R_f 0.43 (CH_2Cl_2/MeOH, 9/1).

^{1}H NMR ($CDCl_3$): δ 9.73-9.55 (m, 2H), 8.02 (sl, 1H), 7.81 (sl, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.22-7.11 (m, 3H), 6.58 (s, 1H), 6.38 (s, 1H), 6.24 (s, 1H), 5.88 (s, 1H), 5.87-5.80 (m, 2H), 5.51 (s, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.23 (s, 1H), 5.19 (d, J = 10.5 Hz, 1H), 3.92-3.55 (m, 14H), 3.50-3.18 (m, 13H), 2.87-2.48 (m, 13H), 2.23-1.96 (m, 14H), 1.87 (dq, J = 14.5 Hz, J = 7.5 Hz, 1H), 1.49-1.26 (m, 4H), 0.85 (dd, J = 7.5 Hz, J = 7.5 Hz, 3H), 0.76 (dq, J = 14.5 Hz, J = 7.5 Hz, 1H), 0.31 (dd, J = 7.5 Hz, J = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 194.8, 171.8, 171.6, 171.0, 170.3, 158.1, 157.2, 152.8, 151.7, 147.4, 141.4, 138.2, 134.6, 132.8, 130.1, 129.7, 128.7, 125.4, 124.5, 124.0, 122.6, 122.4, 119.3, 117.8, 114.2, 110.9, 94.5, 92.7, 83.4 (2C), 79.6, 79.3, 76.3, 76.2, 66.0, 65.9, 56.1, 55.6, 55.3, 53.1, 53.0, 52.3, 52.2, 52.1, 51.1, 50.6 (2C), 50.4, 44.8, 44.4, 44.0, 42.7, 42.6, 38.9, 37.6, 35.8, 34.7, 33.5, 30.9, 29.8, 28.2, 24.8, 21.1, 21.0, 8.6, 7.9.

MS (ESI+ TOF): 631 $[M+2H]^{2+}$ (12), 1261 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{71}H_{84}N_6NaO_{15}]^+$: 1283.5892, Found 1283.5918.





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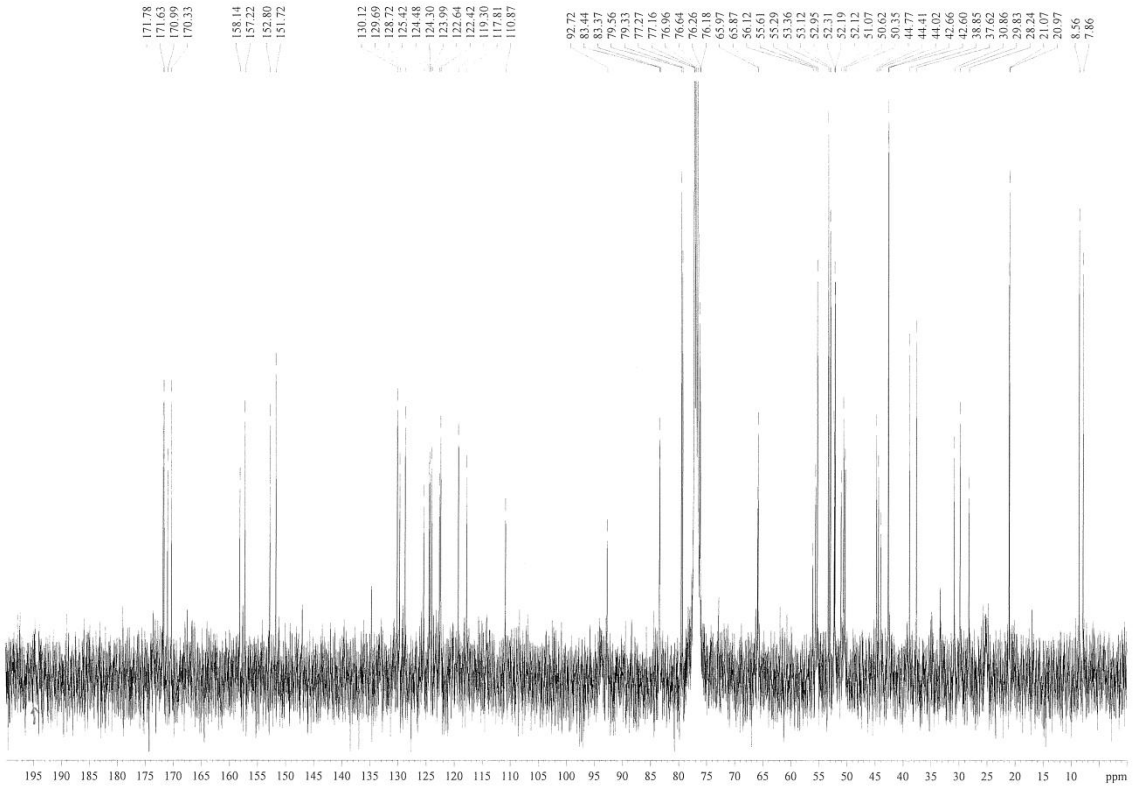
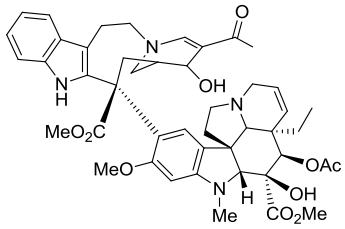


4′,5′-anhydro-3′-hydroxy-20′-oxovinblastine (27)

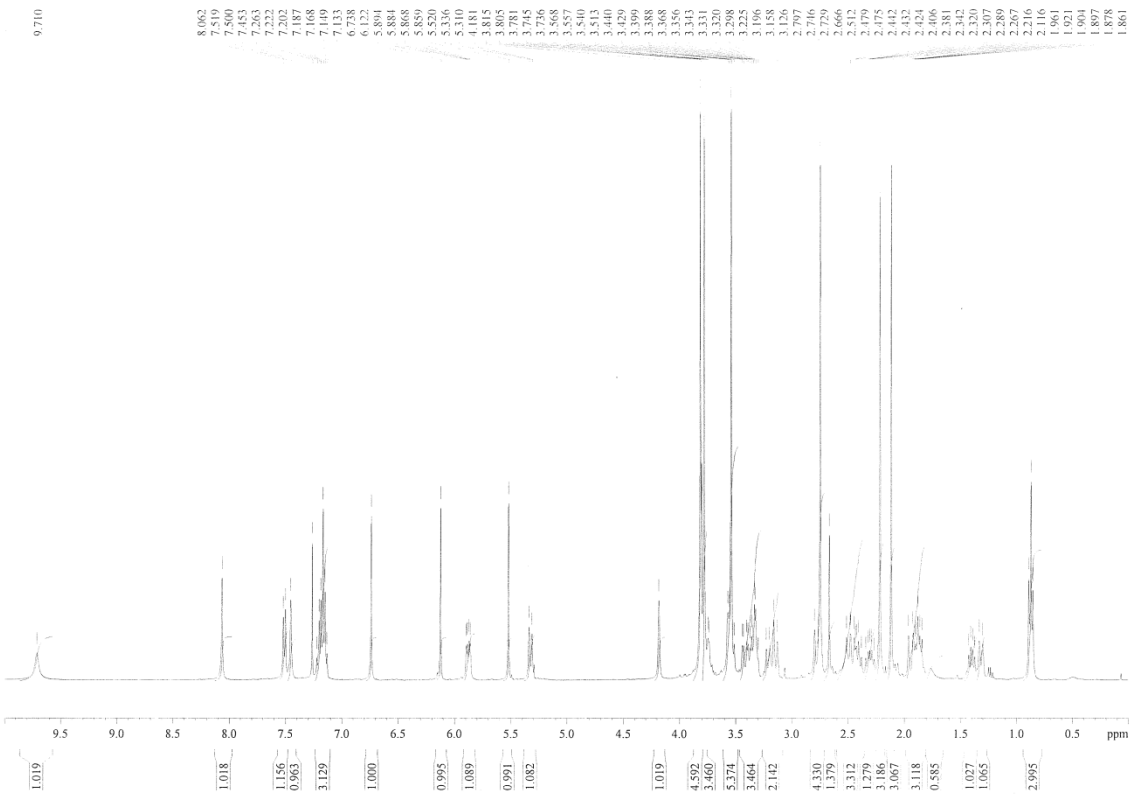


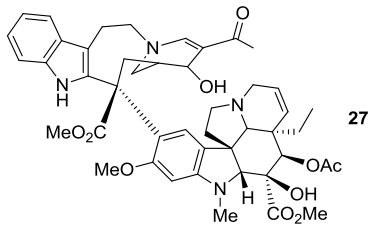
R_f 0.40 (CH_2Cl_2/MeOH, 9/1).

^{1}H NMR ($CDCl_3$): δ 9.71 (sl, 1H), 8.06 (sl, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 7.24-7.11 (m, 3H), 6.74 (s, 1H), 6.12 (s, 1H), 5.88 (dd, *J* = 10.5 Hz, *J* = 4.0 Hz, 1H), 5.52 (s, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.18 (s, 1H), 3.78 (s, 3H), 3.75 (s, 1H), 3.74 (s, 3H), 3.75-3.71 (m, 1H), 3.54 (s, 3H), 3.58-3.50 (m, 2H), 3.45-3.28 (m, 3H), 3.24-3.18 (m, 1H), 3.14 (d, *J* = 12.5 Hz, 1H), 2.75 (s, 3H), 2.81-2.71 (m, 1H), 2.67 (s, 1H), 2.53-2.37 (m, 2H), 2.36-2.25 (m, 1H), 2.21 (s, 3H), 2.11 (s, 3H), 1.97-1.82 (m, 3H), 1.40 (dq, *J* = 14.5 Hz, *J* = 7.0 Hz, 1H), 1.31 (d, *J* = 12.5 Hz, 1H), 0.87 (dd, *J* = 7.0 Hz, *J* = 7.0 Hz, 3H).

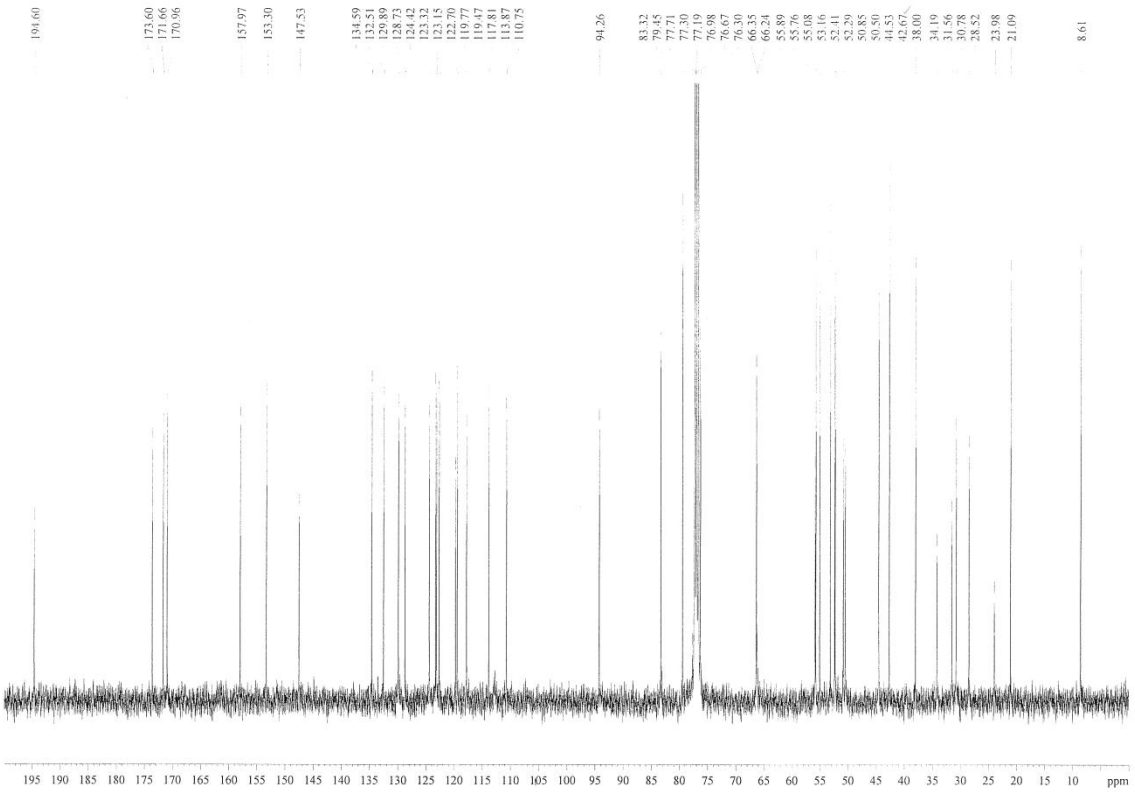
^{13}C NMR ($CDCl_3$): δ 194.6, 173.6, 171.7, 171.0, 158.0, 153.3, 147.5, 134.6, 132.5, 129.9, 128.7, 124.4, 123.3, 123.2, 122.7, 119.8, 119.5, 117.8, 113.9, 112.8, 110.8, 94.3, 83.3, 79.5, 76.3, 66.4, 66.2, 55.9, 55.8, 55.1, 53.2, 52.4, 52.3, 50.9, 50.5, 44.5 (2C), 42.7, 38.0, 34.2, 31.6, 30.8, 28.5, 24.0, 21.1, 8.6.

MS (ESI+ TOF): 823 $[M+H]^+$ (100).
HRMS (ESI+ TOF): Calc. for $[C_{46}H_{55}N_4O_{10}]^+$: 823.3918, Found: 823.3920.

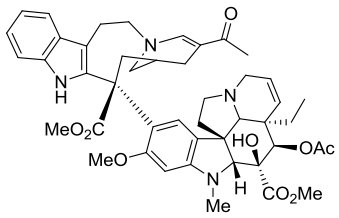




27



4′,5′-anhydro-20′-oxovinblastine (35)



20,20-difluoro-3,4-dihydrocatharanthine **32** (4.0 mg, 10.7 µmol, 1 equiv.) was added in one portion to a mixture of 0.5 mL of a glycine buffer (0.75 g of glycine and 0.585 g of NaCl in 100 mL of water) and 1 mL of 0.1 M aq. HCl. After complete solubilization, vindoline **7** (5 mg, 1 equiv.) and $FeCl_3$ (10 mg, 5.6 equiv.) were added in one portion successively. The reaction mixture was stirred for 30 min at rt, before 200 µL of 28 wt.% aq. NH_3 were added dropwise. After 10 min at rt, 2 mL of CH_2Cl_2 and 2 mL of sat. Rochelle's salt were added, and the mixture was stirred vigorously for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×3 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica (CH_2Cl_2/MeOH, 95/5) to give dimer **35** (5 mg, 58%) as an off-white solid.

Alternative protocol

Preceding protocol was applied to a mixture of fluorinated isomers **33** and **34** (50 mg, 0.141 mmol, 1 equiv.) in a glycine buffer (5 mL) and 0.1 M aq. HCl (10 mL). Vindoline (64 mg, 1 equiv.) and $FeCl_3$ (115 mg, 5 equiv.) were added and the mixture was stirred for 1 h. The reaction was quenched by addition of 1.5 mL of aq. 28 wt.% NH_3. After 10 min at rt, 20 mL of CH_2Cl_2 and 20 mL of sat. Rochelle's salt were added, and the mixture was stirred vigorously for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica afforded dimer **35** (88 mg, 77%) as an off-white solid.

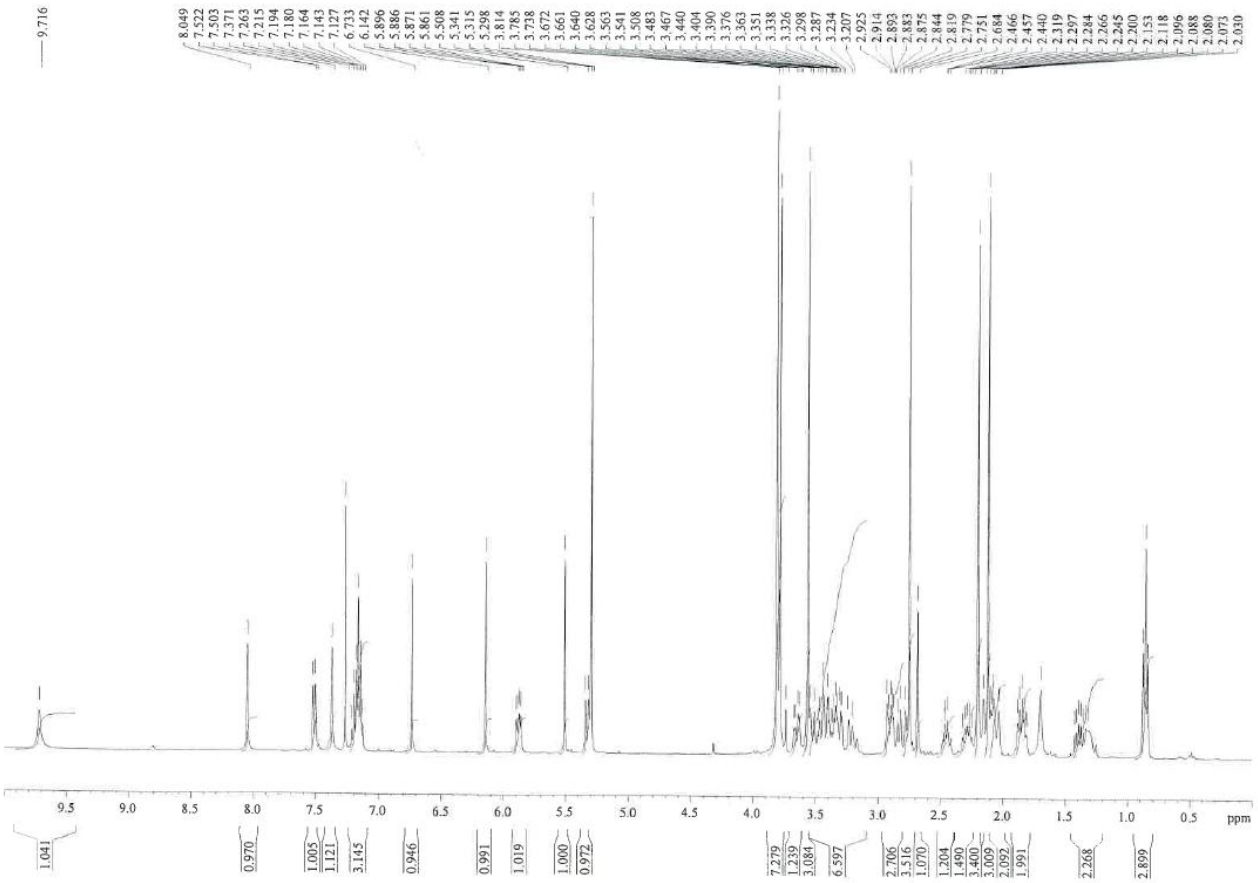
$\mathbf{R_f}$ 0.45 (CH_2Cl_2/MeOH, 9/1).

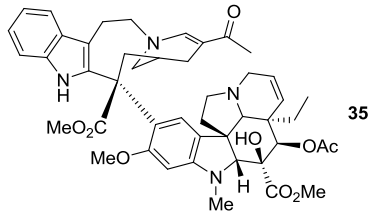
^{1}H NMR ($CDCl_3$): δ 9.72 (sl, 1H), 9.08 (sl, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.38 (s, 1H), 7.20-7.08 (m, 3H), 6.73 (s, 1H), 6.14 (s, 1H), 5.87 (dd, J = 10.5 Hz, J = 4.5 Hz, 1H), 5.50 (s, 1H), 5.32 (d, J = 10.5 Hz, 1H), 3.81 (s, 3H), 3.78 (m, 4H), 3.70-3.61 (m, 1H), 3.55 (s, 3H), 3.55-3.49 (m, 1H), 3.48-3.15 (m, 5H), 2.94-2.74 (m, 3H), 2.74 (s, 3H), 2.68 (s, 1H), 2.49-2.40 (m, 1H), 2.32-2.23 (m, 1H), 2.18 (s, 3H), 2.19-2.13 (m, 1H), 2.11 (s, 3H), 2.11-2.04 (m, 2H), 1.88-1.79 (m, 2H), 1.38 (dq, J = 14.5 Hz, J = 7.5 Hz, 1H), 1.34-1.28 (m, 1H), 0.85 (dd, J = 7.5 Hz, J = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 193.7, 173.7, 171.5, 170.7, 157.9, 153.0, 146.8, 134.5, 132.0, 129.8, 128.7, 124.3, 122.9, 122.8, 122.4, 120.5, 119.2, 117.8, 114.2, 110.6, 108.9, 94.1, 83.2, 79.4, 76.1, 66.0, 55.7, 55.5, 55.2, 53.1, 52.2, 52.1, 50.5, 50.3, 48.3, 44.5, 42.5, 38.0, 33.3, 30.6, 28.7, 28.2, 26.5, 23.9, 20.9, 8.4.

MS (ESI+ TOF): 807 $[M+H]^+$ (100).

HRMS (ESI+ TOF): Calc. for $[C_{46}H_{55}N_4O_9]^+$: 807.3969, Found: 807.3950.





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