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# Synthesis of a new apiol-derived cyclotriveratrylene analog

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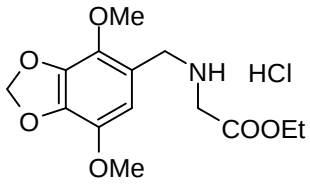
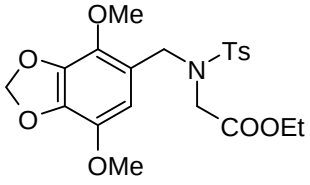
Melting points were measured using a Boetius melting point apparatus and were uncorrected. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DRX-500 instrument (working frequencies of 500.13 MHz ($^{1}$H) and of 125.76 MHz ($^{13}$C), respectively). Low resolution mass spectrum (*m*/*z*) was recorded on a Finnigan MAT/INCOS50 mass spectrometer at 70 eV using direct probe injection. High resolution mass spectrum (HRMS) was measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). All solvents and reagents were purified according to standard procedures.

***N*-[2,5-Dimethoxy-3,4-(methylenedioxy)benzyl]-*N*-tosylglycine 2**



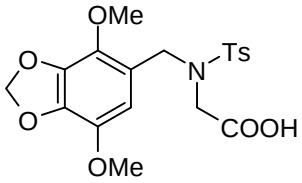

*N*-[2,5-Dimethoxy-3,4-(methylenedioxy)benzyl]glycine ethyl ester hydrochloride

*i*: To a suspension of apiolaldehyde **1** (6.25 g, 30 mmol) and glycine ethyl ester hydrochloride (12.5 g, 90 mmol) in EtOH (130 ml), $NaBH_3CN$ (1.87 g, 30 mmol) was added in one portion at room temperature. The mixture was stirred for 6 h, left overnight, and the solvent evaporated to dryness. To the residue 2M HCl (40 ml) was added, this was stirred for 1 h, extracted with EtOAc (2 x 50 ml), the aqueous layer was separated, neutralized with saturated aq. $K_2CO_3$ (40 ml) to pH 9, extracted with $CHCl_3$ (3 x 50 ml), dried and evaporated. The residue was dissolved in ether (80 ml), and into this solution gaseous HCl was passed at 0-10 °C. The resulting precipitate was filtered off, washed with ether, and dried *in vacuo* to yield 7.8 g (79%) of the amino ester hydrochloride.




*N*-[2,5-Dimethoxy-3,4-(methylenedioxy)benzyl]-*N*-tosylglycine ethyl ester

*ii*: To a suspension of the above hydrochloride (1.0 g, 3.3 mmol) in dry $CH_2Cl_2$ (30 ml), $Et_3N$ (0.67 g, 6.6 mmol) was added in one portion at 0 °C. In 5 min, tosyl chloride (0.63 g, 3.3 mmol) was added in one portion, the mixture stirred for 1 h at 0 °C, left overnight, and then poured into water (30 ml). The organic layer was separated, washed with brine, dried, and evaporated to yield 1.1 g (81%) of the crude *N*-tosylated amino ester. $^{1}$H NMR (DMSO-$d_6$) δ: 1.10 (t, J = 7.1 Hz, 3H, $CH_3$), 2.40 (s, 3H, Me), 3.66 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.92 (s, 2H, $NCH_2$), 3.98 (q, J = 7.1 Hz, 2H, $OCH_2$), 4.30 (s, 2H, $NCH_2$), 5.99 (s, 2H, $OCH_2O$), 6.35 (s, 1H, $H_{Ar}$), 7.40 (d, J = 8.2 Hz, 2H, $H_{Ts}$), 7.72 (d, J = 8.2 Hz, 2H, $H_{Ts}$). $^{13}$C NMR (DMSO-$d_6$) δ: 13.7, 20.8, 45.9, 47.7, 56.2, 59.5, 60.5, 101.6, 108.9, 120.1, 127.0 (2 C), 129.5 (2 C), 136.3, 136.7, 137.9, 138.5, 143.1, 168.5.

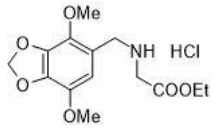



*N*-[2,5-Dimethoxy-3,4-(methylenedioxy)benzyl]-*N*-tosylglycine **2**

*iii*: To the above amino ester (3.4 g, 8.03 mmol), a solution of NaOH (1 g, 25 mmol) in MeOH (30 ml) was added, and this was stirred for 1 h at 50-55 °C. MeOH was evaporated, the residue dissolved in water (50 ml), washed with EtOAc (2×30 ml). The aqueous layer was acidified with 3N HCl, the resulting precipitate was filtered off, washed with water and dried to afford 2.88 g (91%) of compound **2**. M.p. 144-146 ºC. $^{1}$H NMR (DMSO-$d_6$) δ: 2.39 (s, 3H, Me), 3.65 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.84 (s, 2H, $NCH_2$), 4.32 (s, 2H, $NCH_2$), 5.98 (s, 2H, $OCH_2O$), 6.34 (s, 1H, $H_{Ar}$), 7.38 (d, J = 8.2 Hz, 2H, $H_{Ts}$), 7.71 (d, J = 8.2 Hz, 2H, $H_{Ts}$). $^{13}$C NMR (DMSO-$d_6$) δ: 20.8, 45.7, 47.6, 56.2, 59.5, 101.6, 108.7, 120.3, 126.9 (2 C), 129.5 (2 C), 136.1, 136.2, 137.0, 137.9, 138.5, 142.9, 170.0. Found C 54.15, H 5.07, N 3.04 $C_{19}H_{21}NO_8S$ Calc. C 53.89, H 5.00, N 3.31.

Characterization data for 1,4,6,9,11,14-hexamethoxy-2,3,7,8,12,13-tris(methylenedioxy)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*][9]annulene **4**: Colorless crystals, m.p. 182-184 °C $^{1}$H NMR (DMSO-$d_6$) δ: 3.69 (s, 6H, OMe), 3.81 (s, 2H, $CH_2$), 5.96 (s, 2H, $OCH_2O$). $^{1}$H NMR ($CDCl_3$) δ: 3.77 (s, 6H, OMe), 3.95 (s, 2H, $CH_2$), 5.87 (s, 2H, $OCH_2O$). $^{13}$C NMR ($CDCl_3$) δ: 23.2, 59.8, 101.0, 125.6, 137.1, 137.2. EIMS m/z: 582 ($[M]^+$, 8%), 551 (13), 387 (45), 356 (28), 341 (28), 195 (100), 180 (32), 45 (47). HRMS: exact mass $[M+H]^+$ 583.1792, $[M+NH_4]^+$ 600.2062, $[M+Na]^+$ 605.1618, $[M+K]^+$ 621.1362. $C_{30}H_{30}O_{12}$ Calc. $[M+H]^+$ 583.1810, $[M+NH_4]^+$ 600.2076, $[M+Na]^+$ 605.1629, $[M+K]^+$ 621.1369.

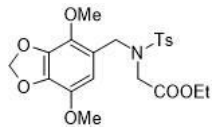
# NMR/50750522



# NMR/29330098

Found protons = 25 impurity* = 0.1 %





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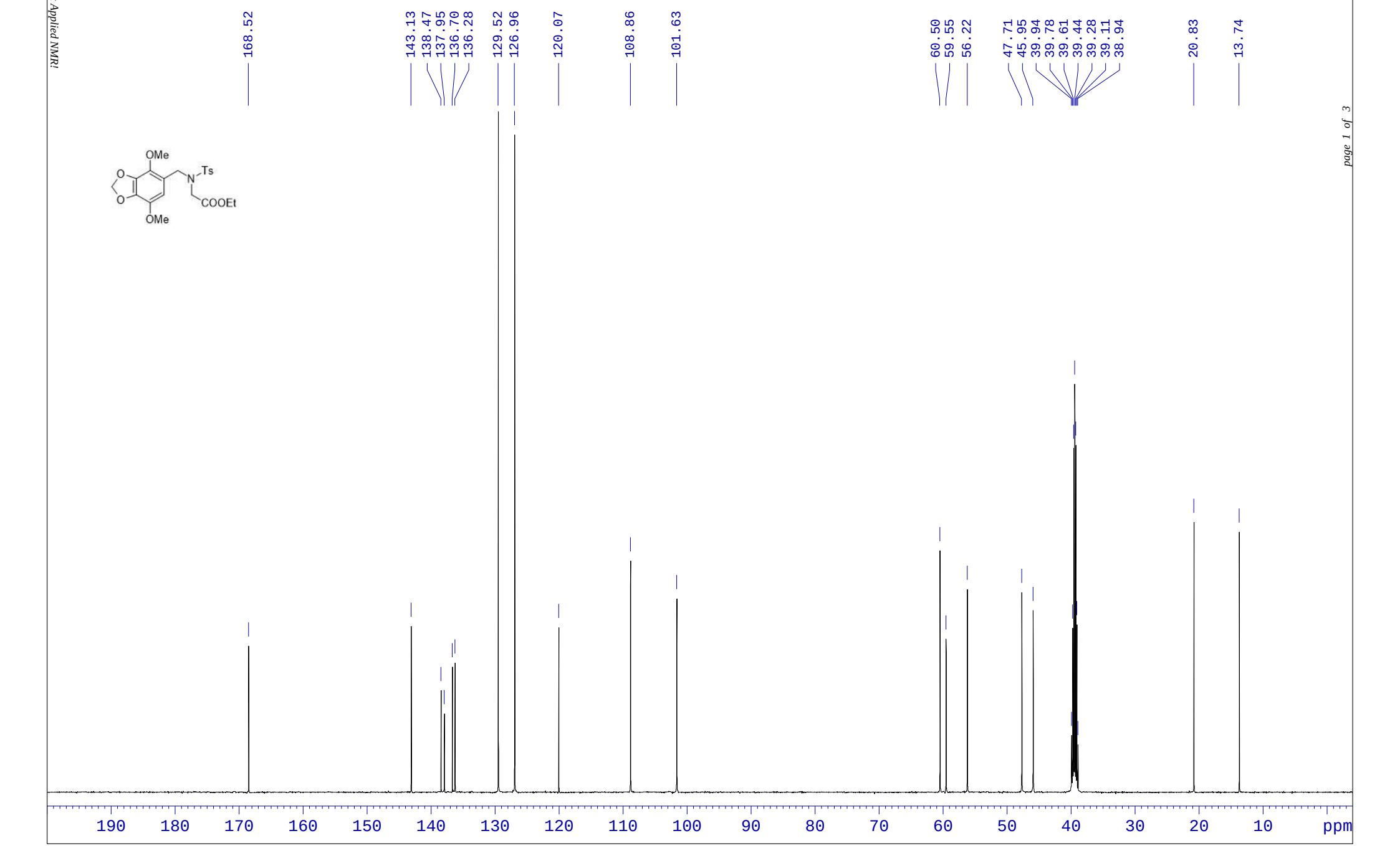
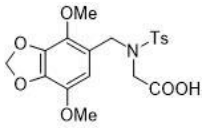


# NMR/29330099

Found protons = 25 impurity* = 0.1 %



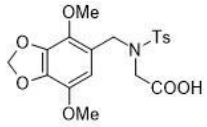



**2**

# NMR/29330099



169.98
142.95
138.45
137.94
137.04
136.22
136.15
129.46
126.92
120.33
108.66
101.61
59.55
56.19
47.56
45.71
39.92
39.75
39.58
39.42
39.25
39.08
38.92
20.82



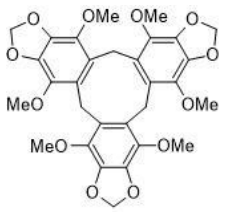

**2**

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

*The Best Applied NMR!*

# NMR/29330097

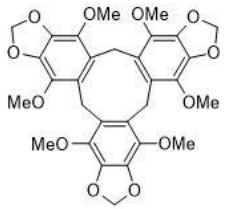





**4**

CDCl3

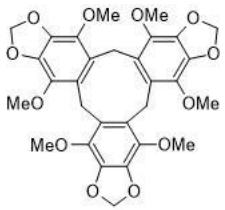
# NMR/50084447




4

DMSO-d6

# NMR/29357785




**4**

137.16
137.14
125.57
100.95
77.30
77.04
76.79
59.82
23.17
-0.00



180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

# Display Report

**Analysis Info**

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| Method | tune_low.m | Operator | BDAL@DE |
| Sample Name | /DVTS 1231 | Instrument / Ser# | micrOTOF 10248 |
| Comment | C30H30O12 mH 583.1810 clb added CH3CN | | |

**Acquisition Parameter**

| | | | | | |
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| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Not active | | | Set Dry Heater | 180 °C |
| Scan Begin | 50 m/z | Set Capillary | 4500 V | Set Dry Gas | 4.0 l/min |
| Scan End | 2000 m/z | Set End Plate Offset | -500 V | Set Divert Valve | Waste |