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Supporting Information

Diastereoselective Total Synthesis of (±)-Codeine

Marie Varin, Elvina Barré, Bogdan Iorga* and Catherine Guillou*

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse

91198 Gif-sur-Yvette, France.

guillou@icsn.cnrs-gif.fr

Supporting information

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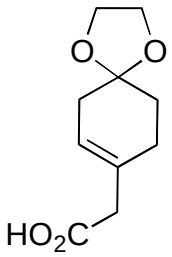
2-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)ethanoic acid **10**



2-(4-Methoxycyclohexa-1,4-dienyl)ethanoic acid

p-methoxyphenyl acetic acid (10.0 g; 60.2 mmol) and *t*-BuOH 15 mL, 156 mmol.) were placed in a tricol (1l, fitted with solid CO_2-ethanol condenser). About 500 mL of dried (over KOH) ammonia were directly condensed at -78°C under argon. Li wire (2.2 g, 317 mmol) was added in portion to the magnetically stirred mixture under argon. The deep blue mixture was stirred at -78°C for 6h. The excess of lithium was then destroyed at -78°C by cautiously addition of NH_4Cl (17.0g, 317 mmol) in portion. The blue colour was discharged and became white. The reaction mixture was allowed to heat to room temperature and then the NH_3 was distillated. The resulting salts were taken up in ice-cold water and the pH of the solution was adjusted to 5 by careful addition of aqueous solution HCl 3N. The aqueous solution was extracted with ether 3 times (3x150 mL) and the pH was adjusted to 5 by addition of aqueous solution HCl 1N after each extraction with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to dryness. 9.74 g of the crude acid were thus obtained as a white powder (97%). The product possesses the same ^{1}H NMR as that described (see Pearson, A.J.; Chandler, M. *J. Chem.. Soc. Perkin Trans 1* **1980**, 2238-2243).
The crude acid was immediately protected with ethylene glycol.

F.P. : 74 - 76°C

I.R. ($CHCl_3$) ν (cm^{-1}) : 3042 (OH), 1712 (C=O), 1667 (C=C), 1514 (Car-C), 1486 (Car-C).

S.M. (I.C., m/z) : 225 (M^+ + iBu), 169 (MH^+), 141 (M^+ - CO).

^{1}H NMR ($CDCl_3$, 250 MHz) :

10.59 (1H, s, OH), 5.60 (1H, s, H2), 4.62 (1H, s, H5), 3.55 (3H, s, OCH_3), 3.05 (2H, s, CH_2), 2.90-2.70 (4H, m, H3, H6).

^{13}C NMR ($CDCl_3$, 50 MHz) :

178.7 (C=O).153,2 (C4), 128.6 (C1), 123.2 (C2), 90.1 (C5), 54.5 (OCH_3), 42.3 (CH_2), 30.9 (C3), 29.7 (C6).

2-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)ethanoic acid

To a solution of 2-(4-methoxycyclohexa-1,4-dienyl)ethanoic acid (3.36 g, 20 mmol) and ethylen glycol (1.2 mL, 22 mmol) in diethyl ether was added dropwise $BF_3.OEt_2$ (0.5 mL, 4 mmol) at 0°C. After being stired 1h at 0°C, the reaction mixture was diluted with diethyl ether (20 mL), then hydrolysed with 30 mL of an acetic buffer solution (1M), acidified to pH 5 with an aqueous solution HCl (0.1M) and saturated with NaCl. The reaction mixture was extracted with AcOEt. The combined organic layer was washed with H_2O, brine, dried ($MgSO_4$) and evaporated. Silical gel flash-column chromatography (elution with Heptane/AcOEt/AcOH : 70/27,5/2,5) of the residue afforded as white crystals (3.20g, 81%).

P.F. : 69-71°C (litt.[1] : 71-74°C) (see Still, W. C., Lewis, A. J., Goldsmith, D. *Tetrahedron Lett.*, **1971**, 1421-1424)

Elemental analysis calc for $C_{10}H_{14}O_4$: C, 60.59, H, 7.12, O 32,29, found: C, 60.07, H, 7.31, O, 32.45

I.R. ($CHCl_3$) ν (cm^{-1}) : 3530 (OH) ; 1710 (C=O) ; 1588 (C=C).

M.S. (I.E., m/z): 198 ($M^{+\cdot}$) ; 153 ($M^{+\cdot}$ - CO_2H) ; 139 ($M^{+\cdot}$ - CH_2CO_2H) ; 86 ($M^{+\cdot}$ - $C_6H_8O_2$).

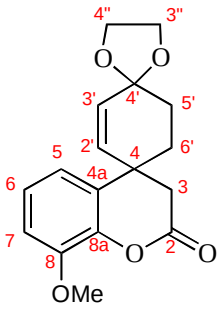
^{1}H NMR ($CDCl_3$, 250 MHz) :

9.60 (1H, s, OH), 5.53 (1H, s, H7), 3.99 (4H, s, H2, H3), 3.05 (2H, s, CH_2), 2.33-2.28 (4H, m, H6, H9), 1.81 (2H, t, $J_{10\text{-}9}$ = 6.7, H10).

^{13}C NMR ($CDCl_3$, 62,5 MHz) :

178,9 (C=O) ; 130,4 (C8) ; 124,1 (C7) ; 108,5 (C5) ; 65,2 (C2, C3) ; 42,1 (CH_2) ; 36,7 (C9) ; 31,6 (C10); 28,0 (C6).

8-Methoxydispiro[chromene-4,1'-cyclohex[2']ene-4',2"-[1,3]dioxolan]-2(3*H*)-one **11**



To a solution of **8** (2.96 g, 6.8 mmol) and tris(dibenzylideneacetone)dipalladium (63 mg, 0.068 mmol) in DMF (50 mL), was added triethylamine (2.87 mL, 20.6 mmol). The reaction mixture was stirred at 140°C for 5h, cooled to room temperature, quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : Heptane/AcOEt : 80/20) gave 1.2 g of **11** (yield 60%).

H.R.M.S. (ESI, m/z) : calcd for $C_{17}H_{18}O_5Na^+$: 325.1052, found : 325.1024

M.S. (ESI, m/z) : 303 $[M+H]^+$

I.R. ($CHCl_3$) ν (cm^{-1}) : 1766 (C=O), 1583 (C=C), 1481 (ArC-C), 1233 (ArC-O), 1090 (C-O).

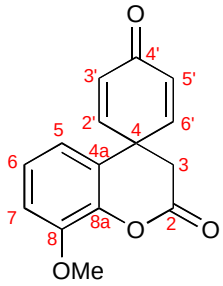
^{1}H NMR ($CDCl_3$, 300 MHz)

δ (ppm) : 7.08 (1H, dd, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 8.0, H6), 6.91 (1H, dd, $J_{7\text{-}6}$ = 8.0, $J_{7\text{-}5}$ = 1.5, H7), 6.81 (1H, dd, $J_{5\text{-}6}$ = 8.0, $J_{5\text{-}7}$ = 1.5, H5), 5.94 (1H, d, $J_{3'\text{-}2'}$ = 10.0, H3'), 5.68 (1H, d, $J_{2'\text{-}3'}$ = 10.0, H2'), 4.05-3.97 (4H, m, H3'', H4''), 3.90 (3H, s, OMe), 2.80 (1H, d, J_{gem} = 15.4, H3), 2.70 (1H, d, J_{gem} = 15.4, H3), 1.95-1.76 (4H, m, H6', H5').

^{13}C NMR ($CDCl_3$, 75 MHz)

δ (ppm) : 167.4 (C2), 148.8 (C8), 141.1 (C8a), 135.2 (C3'), 132.3 (C2'), 129.8 (C4a), 125.3 (C6), 119.4 (C5) 112.7 (C7), 105.5 (C5'), 65.8 and 65.6 (C3'', C4''), 57.1 (OMe), 41.5 (C3), 39.4 (C4), 33.0 (C5'), 30.4 (C6').

8-Methoxyspiro[chroman-4,1'-cyclohexa[2',5']diene]-2,4'-dione **7**



To a solution of **11** (1.58 g, 5.22 mmol) in dichloromethane (70 mL) was added triphenylcarbenium tetrafluoroborate (1.72 g, 5.22 mmol). After stirring 2 h at room temperature, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : Heptane/AcOEt : 80/20 to 60/40) gave 1.24 g of 8-methoxyspiro[chroman-4,1'-cyclohex[2']ene]-2,4'-dione (yield 92%).

To a solution of 8-methoxyspiro[chroman-4,1'-cyclohex[2']ene]-2,4'-dione (1.24 g, 4.8 mmol) in chlorobenzene (60 mL), was added $NaHCO_3$ (2.02 g, 24 mmol) and benzeneseleninic anhydride (1.73 g, 4.8 mmol). The reaction mixture was stirred at 120°C for 2 h and benzeneseleninic anhydride (1.73 g, 4.8 mmol) was added. After another 2 h at 120°C benzeneseleninic anhydride (864 mg, 2.4 mmol) was added and the heating was pursued until completion was checked by NMR (4 h). The reaction mixture was hydrolysed and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : Heptane/AcOEt : 80/20 to 60/40) gave 690 mg of **7** (yield 60%).

H.R.M.S. (ESI, m/z) : calcd for $C_{15}H_{11}O_4^-$: 255.0657, found : 255.0656

M.S. (ESI, m/z) : 255 $[M-H]^-$

I.R. ($CHCl_3$) ν (cm^{-1}) : 1778 (O-C=O), 1666 (C=O), 1477 (ArC-C), 1273, 1177.

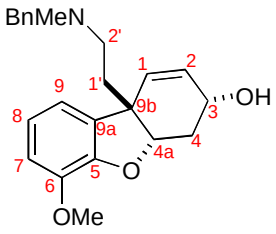
^{1}H NMR ($CDCl_3$, 300 MHz)

δ (ppm) : 7.08 (1H, dd, $J_{6-5} = J_{6-7} = 8.1$, H6), 6.96 (1H, d, $J_{7-6} = 8.1$, H7), 6.89 (2H, d, $J_{2'-3'} = J_{6'-5'} = 10.3$, H2', H6'), 6.54 (1H, d, $J_{5-6} = 8.1$, H5), 6.39 (2H, d, $J_{3'-2'} = J_{5'-6'} = 10.3$, H3', H5'), 3.90 (3H, s, OCH_3), 2.90 (2H, s, H3)

^{13}C NMR ($CDCl_3$, 75 MHz)

δ (ppm) : 184.5 (C4'), 164.6 (C2), 148.4 (C8), 148.0 (C2', C6'), 140.9 (C8a), 130.1 (C3', C5'), 125.5 (C6), 123.2 (C4a), 117.6 (C5), 113.0 (C7), 56.3 (OCH_3), 42.8 (C4), 38.6 (C3)

9b-(2'-(Benzyl(methyl)amino)ethyl)-6-methoxy-3,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-3a-ol **12**

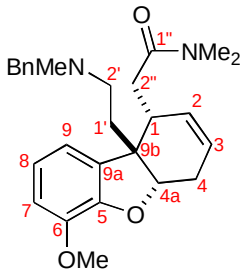


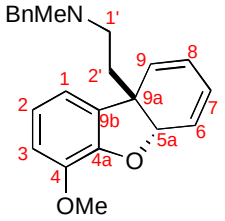
To a solution of **7** (1.82 g, 7.109 mmol) in THF (55 mL) was added de *N*-methylbenzylamine (5.2 mL, 42,99 mmol). The reaction mixture was stirred at room temperature for 16 h prior to concentration *in vacuo*. The residue was taken up in dichloromethane and washed with 1M aqueous HCl. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give 3 g of a pale yellow oil. The crude residue was directly taken up in THF (180 mL) at 0°C. $LiAlH_4$ 1M in THF (35 mL, 35 mmol) was added dropwise, the reaction mixture was stirred at 0°C for 1 h and refluxed for 1 h. After cooling at 0°C, potassium sodium tartrate tetrahydrate (5 spatula) was added and the mixture was cautiously treated with water, stirred for 30 min, diluted with saturated aqueous NH_4Cl and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : DCM/MeOH 100/0 to 94/6 with 1% NH_4OH) gave 2.0 g of **12** (yield 77%).

H.R.M.S. (ESI, m/z) : calcd for $C_{23}H_{28}NO_3^+$: 366.2069, found : 366.2057
M.S. (ESI, m/z) : 366 $[M+H]^+$, 388 $[M+Na]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 1616, 1590 (C=C), 1489, 1455, 1278, 1196.
^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 7.35-7.24 (5H, m, Bn), 6.90 (1H, dd, $J_{8\text{-}9}$ = 7.6, $J_{7\text{-}8}$ = 7.9, H8), 6.79 (1H, d, $J_{7\text{-}8}$ = 7.9, H7), 6.78 (1H, d, $J_{8\text{-}9}$ = 7.6, H9), 5.97 (1H, dd, $J_{1\text{-}2}$ = 10.1, $J_{2\text{-}3}$ = 4.7, H2), 5.60 (1H, d, $J_{1\text{-}2}$ = 10.1, H1), 4.89 (1H, t, $J_{4\text{-}4a}$ = 3.8, H4a), 4.18-4.13 (1H, m, H3), 3.89 (3H, s, OMe), 3.51 (2H, s, Bn), 2.55-2.36 (3H, m, H4. H2'), 2.20 (3H, s, NMe), 2.11 (1H, ddd, J_{gem} = 14.8, J = 4.9, J = 3.1, H4), 2.03 (2H, t, $J_{1'\text{-}2'}$ = 7.6, H1').
^{13}C NMR ($CDCl_3$, 125 MHz)
δ (ppm) : 146.2 (C5), 145.2 (C6), 139.0 (Bn), 134.9 (C9a), 131.4 (C1), 129.2 (Bn), 128.5 (C2 et Bn), 127.4 (Bn), 122.3 (C8), 115.4 (C9), 111.7 (C7), 86.4 (C4a), 62.5 (C3), 62.4 (Bn), 56.1 (OMe), 53.1 (C2'), 48.2 (C9b), 42.3 (NMe), 34.6 (C1'), 32.3 (C4).

2’’-(9b-(2’-(Benzyl(methyl)amino)ethyl)-6-methoxy-1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-*N*,*N*-dimethylacetamide **13**

N-Benzyl-2’-(4-methoxy-5a,9a-dihydrodibenzo[*b*,*d*]furan-9a-yl)-*N*-methylethanamine **14**





To a solution of **12** (560 mg, 1.53 mmol) in decalin (7.8 mL) was added *N*,*N*-dimethylacetamide dimethylacetal (1.5 mL, 9.20 mmol). The reaction mixture was heated for 2 h in a molten metal bath (T = 250°C), filtered on silica gel, washing with heptane (150 mL) followed by washing with a solution of dichloromethane/methanol : 80/20 (200 mL). This last fraction was concentrated and purified by flash chromatography on silica gel (elution : Heptane/AcOEt 100/0 to 0/100 with 1% NH_4OH) providing 170 mg of **14** (yield 32%) and 295 mg of **13** (yield 44%).

2’’-(9b-(2’-(benzyl(methyl)amino)ethyl)-6-methoxy-1,4,4a,9b-tetrahydrodibenzo [*b*,*d*]furan-1-yl)-*N*,*N*-dimethylacetamide **13**

H.R.M.S. (ESI, m/z) : calcd for $C_{27}H_{35}N_2O_3^+$: 435.2648, found : 435.2612

M.S. (ESI, m/z) : 435 $[M+H]^+$

I.R. ($CHCl_3$) ν (cm^{-1}) : 1644, 1489, 1454, 1268.

^{1}H NMR ($CDCl_3$, 500 MHz)

δ (ppm) : 7.32-23 (5H, m, Bn), 6.79 (1H, dd, J_{7-8} = 7.9, J_{8-9} = 7.3, H8), 6.73 (1H, d, J_{7-8} = 7.9, H7), 6.67 (1H, d, J_{8-9} = 7.3, H9), 5.84-5.77 (2H, m, H2 et H3), 4.96 (1H, dd, J_{4-4a} = 5.3, J_{4-4a} = 3.2, H4a), 3.87 (3H, s, OMe), 3.45 (2H, s, Bn), 2.91 (3H, s, CON$\underline{Me}_2$), 2.87 (3H, s, CON$\underline{Me}_2$), 2.86-2.82 (1H, m, H1), 2.75 (1H, dt, J_{gem} = 16.6, J = 4.2, H4), 2.53-2.45 (2H, m, H4 et H2’), 2.35 (2H, d, J = 7.3, H2’’), 2.29 (1H, td, J_{gem} = 10.8, $J_{1'-2'}$ = 4.3, H2’), 2.16 (3H, s, NMe), 2.14-2.01 (2H, m, H1’).

^{13}C NMR ($CDCl_3$, 125 MHz)

δ (ppm) : 172.0 (C1’’), 148.9 (C5), 144.4 (C6), 139.8 (Bn), 133.4 (C2), 132.7 (C9a), 129.2 (Bn), 128.4 (Bn), 127.2 (Bn), 124.8 (C3), 120.7 (C8), 117.2 (C9), 111.0 (C7), 87.8 (C4a), 62.5 (Bn), 55.9 (OMe), 53.6 (C2’), 52.3 (C9b), 42.4 (NMe), 39.5 (C1), 37.4 (CON$\underline{Me}_2$), 36.0 (C1’), 35.7 (CON$\underline{Me}_2$), 34.5 (C2’’), 28.5 (C4).

N-benzyl-2’-(4-methoxy-5a,9a-dihydrodibenzo[*b*,*d*]furan-9a-yl)-*N*-methylethanamine **14**

H.R.M.S. (ESI, m/z) : calcd for $C_{23}H_{26}NO_2^+$: 348.1964, found : 348.1959

M.S. (ESI, m/z) : 348 $[M+H]^+$

I.R. ($CHCl_3$) ν (cm^{-1}) : 1490, 1454, 1274, 1203.

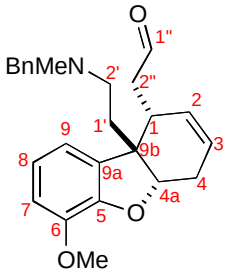
^{1}H NMR ($CDCl_3$, 500 MHz)

δ (ppm) : 7.33-7.23 (5H, m, Bn), 6.87 (1H, dd, J_{2-3} = 7.8, J_{1-2} = 7.6, H2), 6.79 (1H, dd, J_{1-2} = 7.6, J_{1-3} = 1.3, H1), 6.72 (1H, dd, J_{2-3} = 7.8, J_{1-3} = 1.3, H3), 6.14 (1H, dd, J_{6-7} = 9.7, J_{7-8} = 5.4, H7), 6.04 (1H, dd, J_{6-7} = 9.7, J_{5a-6} = 4.8, H6), 5.94 (1H, dd, J_{8-9} = 9.6, J_{7-8} = 5.4, H8), 5.72 (1H, d, J_{8-9} = 9.6, H9), 5.32 (1H, d, J_{5a-6} = 4.8, H5a), 3.88 (3H, s, OMe), 3.48 (2H, s, Bn), 2.52 (1H, ddd, J_{gem} = 12.5, $J_{1'-2'}$ = 10.2, $J_{1'-2'}$ = 4.9, H1’), 2.38 (1H, ddd, J_{gem} = 12.5, $J_{1'-2'}$ = 9.9, $J_{1'-2'}$ = 5.7, H1’), 2.18 (3H, s, NMe), 2.17 (1H, ddd, J_{gem} = 13.5, $J_{1'-2'}$ = 9.9, $J_{1'-2'}$ = 4.9, H2’), 2.02 (1H, ddd, J_{gem} = 13.5, $J_{1'-2'}$ = 10.2, $J_{1'-2'}$ = 5.7, H2’).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ (ppm) : 146.9 (C4a), 144.8 (C4), 139.0 (Bn), 134.2 (C9b), 132.2 (C9), 129.0 (Bn), 128.3 (Bn), 127.0 (Bn), 126.5 (C7), 121.6 (C2 et C6), 120.8 (C8), 115.5 (C1), 110.8 (C3), 84.4 (C5a), 62.3 (Bn), 55.9 (OMe), 52.1 (C1'), 48.3 (C9a), 42.3 (NMe), 38.2 (C2').

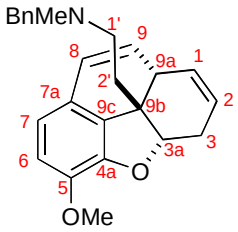
(9b-{2'-[Benzyl(methyl)amino]ethyl)-6-methoxy-1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-1-yl)acetaldehyde **15**



A rod tube was charged with **13** (355 mg, 0.828 mmol), Ti(O^iPr)$_4$ (477 µL, 1.63 mmol) and phenylsilane (260 µL, 2.04 mmol). After sonication and vortex stirring to mix the reagents, the reaction mixture was stirred neat for 35 min (a deep blue color was observed after stirring 5 min). The reaction mixture was diluted with THF (5 mL) and 10 mL of 1M aqueous HCl was added dropwise. After basification (pH 12) with aqueous NaOH 4M and extraction with dichloromethane, the combined organic layers were dried over $MgSO_4$ and evaporated to dryness, the crude product was used without purification for the next step because the aldehyde **15** was not stable by purification by flash chromatography on silica gel. For analytical purpose, aldehyde **15** can be purified by flash chromatography on silica gel (elution : DCM/MeOH : 97/3 with 1% NH_4OH).

H.R.M.S. (ESI, m/z) : calcd for $C_{25}H_{30}NO_3^+$: 392.2226, found : 392.2241
M.S. (ESI, m/z) : 392 $[M+H]^+$; 424 $[M+H+MeOH]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 1720 (C=O), 1616 (C=C), 1492 et 1455 (ArC-C), 1269, 1205.
^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 9.62 (1H, sl, H1''), 7.33-7.27 (5H, m, Bn), 6.78 (1H, dd, J_{7-8} = 7.6, J_{8-9} = 7.3, H8), 6.73 (1H, d, J_{7-8} = 7.6, H7), 6.63 (1H, d, J_{8-9} = 7.3, H9), 5.88-5.83 (1H, m, H3), 5.72 (1H, ddd, J_{2-3} = 9.0, J = 4.5, J = 1.6, H2), 4.92 (1H, dd, J_{4-4a} = 4.9, J_{4-4a} = 3.4, H4a), 3.85 (3H, s, OMe), 3.52 (2H, sl, Bn), 2.78-2.70 (2H, m, H1. H4), 2.59-2.40 (4H, m, H2', H2''et H4), 2.36-2.27 (1H, m, H2'), 2.21 (3H, s, NMe), 2.18-2.09 (1H, m, H1'), 2.05-1.98 (1H, m, H1').
^{13}C NMR ($CDCl_3$, 125 MHz)
δ (ppm) : 201.6 (C1''), 148.8 (C5), 144.5 (C6), 136.3 (Bn), 132.2 (C2), 131.7 (C9a), 129.5 (Bn), 128.7 (Bn), 127.8 (Bn), 126.1 (C3), 121.1 (C8), 116.9 (C9), 111.4 (C7), 87.3 (C4a), 62.3 (Bn), 56.0 (OMe), 53.3 (C2'), 52.3 (C9b), 45.7 (C2''), 42.2 (NMe), 37.3 (C1), 35.2 (C1'), 28.5 (C4).

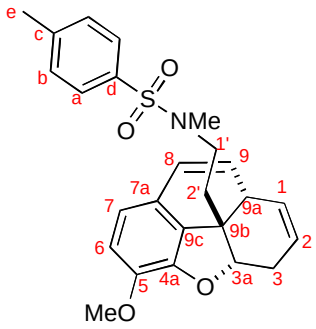
N-Benzyl-2'-[5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-9b(3a*H*)-yl]-*N*-methylethanamine **16**



To a solution of 520 mg of crude **15** (obtained from 0.828 mmol of **13**) in toluene (20 mL) was added APTS (360 mg, 2.09 mmol) and the reaction mixture was stirred 16 h at room temperature. Addition of saturated aqueous $NaHCO_3$ was followed by extraction with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : Heptane/AcOEt 90/10 to 40/60 with 1% NH_4OH) gave 168 mg of **16** as a pale yellow oil (yield 55% from **13**).

H.R.M.S. (ESI, m/z) : calcd for $C_{25}H_{28}NO_2^+$: 374.2110, found : 374.2115
M.S. (ESI, m/z) : 374 $[M+H]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 1633, 1506, 1451, 1436, 1279, 1163.
^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 7.33-24 (5H, m, Bn), 6.67 (1H, d, J_{6-7} = 8.1, H6), 6.61 (1H, d, J_{6-7} = 8.1, H7), 6.43 (1H, dd, J_{8-9} = 9.4, J_{8-9a} = 1.5, H8), 5.84 (1H, dd, J_{8-9} = 9.4; J_{9-9a} = 6.0, H9), 5.66 (1H, ddd, J_{1-2} = 10.1, J_{2-3} = 7.2, J_{2-9a} = 3.6, H2), 5.45 (1H, ddd, J_{1-2} = 10.2, J_{1-9a} = 4.6, J_{1-3} = 2.2, H1), 5.04 (1H, dd, J_{3-3a} = 7.7, J_{3-3a} = 4.7, H3a), 3.89 (3H, s, OMe), 3.45 (2H, sl, Bn), 3.09-3.04 (1H, m, H9a), 2.57-2.42 (3H, m, H3 et H1'), 2.20-2.13 (4H, m, H3 et NMe), 2.00-1.94 (2H, m, H2').
^{13}C NMR ($CDCl_3$, 125 MHz)
δ (ppm) : 145.3 (C4a), 145.1 (C5), 138.6 (Bn), 129.5 (C9c), 128.7 et 128.5 (C9. Bn et Bn), 126.3 (C1), 124.4 (C2), 124.1 (C7a), 123.8 (C8), 117.8 (C7), 112.5 (C6), 87.8 (C3a), 61.8 (Bn), 56.5 (OMe), 52.8 (C1'), 43.8 (C9b), 42.0 (NMe), 38.5 (C9a), 34.9 (C2'), 29.1 (C3).

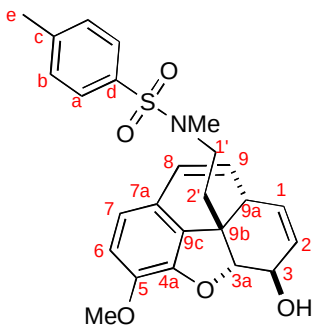
N-(2'-[5-Methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-9b(3a*H*)-yl]ethyl)-*N*,4-dimethylbenzenesulfonamide **17**



To a solution of **16** (141 mg, 0.374 mmol) in 1,2-dichloroethane (5 mL) at 0°C, was added 1-chloroethyl chloroformate (205 µL, 1.90 mmol). After stirring for 5 min at 0°C and 5 min at room temperature, the reaction mixture was refluxed for 1 h, evaporated, taken up in methanol (10 mL) and refluxed for 2 h. The removal of solvents under reduced pressure led to a white solid (128 mg) which was taken up in dichloromethane (5 mL), tosyl chloride (113 mg, 0.597 mmol) and triethylamine (167 µL, 1.19 mmol) were added. The reaction mixture was stirred for 16 h. The residue obtained after concentration under reduced pressure was purified by (elution : Heptane/ACOEt : 80/20 à 40/60) providing 137 mg of **17** (yield 83%).

H.R.M.S. (ESI, m/z) : calcd for $C_{25}H_{27}NO_4NaS^+$: 460.1559, found : 460.1571
M.S. (ESI, m/z) : 460 $[M+Na]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 1715, 1685, 1597, 1504, 1453, 1483, 1336 (SO_2), 1157 (SO_2).
^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 7.60 (2H, d, J_{a-b} = 7.9, Ha), 7.29 (2H, d, J_{a-b} = 7.9, Hb), 6.68 (1H, d, J_{6-7} = 8.1, H6), 6.62 (1H, d, J_{6-7} = 8.1, H7), 6.42 (1H, dd, J_{8-9} = 9.5, J_{8-9a} = 1.4, H8), 5.87 (1H, dd, J_{8-9} = 9.5, J_{9-9a} = 5.8, H9), 5.66 (1H, ddd, J_{1-2} = 10.1, J_{2-3} = 7.2, J_{2-3} = 4.0, H2), 5.46 (1H, ddd, J_{1-2} = 10.1, J_{1-9a} = 4.4, J_{1-3} = 1.9, H1), 4.98 (1H, dd, J_{3-3a} = 7.7; J_{3-3a} = 4.9, H3a), 3.88 (3H, s, OMe), 3.11-2.99 (3H, m, H9a et H1'), 2.64 (3H, s, NMe), 2.61-2.48 (1H, m, H3), 2.43 (3H, s, He), 2.18-2.08 (1H m, H3), 1.95 (2H, t, $J_{1'-2'}$ = 8.1, H2').
^{13}C NMR ($CDCl_3$, 75 MHz)
δ (ppm) : 145.4 et 144.9 (C4a et C5), 143.4 (Cc), 134.9 (Cd), 129.8 (Cb), 128.7 (C9c), 128.5 (C9), 127.6 (Ca), 126.0 (C1), 124.4 (C2), 124.0 (C7a), 123.8 (C8), 117.9 (C7), 112.7 (C6), 87.8 (C3a), 56.4 (OMe), 46.5 (C1'), 43.3 (C9b), 38.7 (C9a), 36.5 (C2'), 35.0 (NMe), 28.9 (C3), 21.7 (Ce).

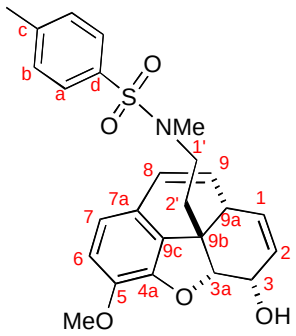
N-[2'-(3β-Hydroxy-5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-9b(3a*H*)-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide **18**



To a solution of SeO_2 (20 mg, 0.18 mmol) in dioxane (0.3 mL) was added $^tBuO_2H$ (80 µL, 0.83 mmol) and the reaction mixture was stirred for 30 min prior to addition of a solution of **17** (100 mg, 0.23 mmol) in dioxane (1 mL). The reaction mixture was stirred at 50°C and the same amounts of SeO_2 et $^tBuO_2H$ in solution in dioxane were added after 3 h and 6 h. After stirring at 50°C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to give 130 mg of **18**. The crude residue was used directly for the next step but for analytical purpose, it can be purified by flash chromatography on silica gel (elution : Heptane/AcOEt : 80/20 to 40/60).

^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 7.58 (2H, d, $J_{a\text{-}b}$ = 7.9, Ha), 7.28 (2H, d, $J_{a\text{-}b}$ = 7.9, Hb), 6.68 (1H, d, $J_{6\text{-}7}$ = 8.0, H6), 6.62 (1H, d, $J_{6\text{-}7}$ = 8.0, H7), 6.42 (1H, d, $J_{8\text{-}9}$ = 9.5, H8), 5.83 (1H, dd, $J_{8\text{-}9}$ = 9.5, $J_{9\text{-}9a}$ = 5.7, H9), 5.76-5.72 (1H, m; H1), 5.62-5.58 (1H, d, m, H2), 4.70 (1H, d, $J_{3\text{-}3a}$ = 4.4, H3a), 4.13-4.09 (1H, m, H3), 3.88 (3H, s, OMe), 3.23-3.19 (1H, m, H9a), 3.04 (2H, t, $J_{1'\text{-}2'}$ = 8.0, H1'), 2.63 (3H, s, NMe), 2.42 (3H, s, He), 2.03-1.94 (1H, m, H2'), 1.89-1.82 (1H, m, H2').
^{13}C NMR ($CDCl_3$, 125 MHz)
δ (ppm) : 145.4 (C4a), 144.2 (C5), 143.3 (Cc), 134.7 (Cd), 129.7 (Cb), 128.7 (C9c), 128.4 et 128.0 (C1 et C2), 127.4 (Ca), 127.3 (C9), 123.9 (C8), 123.3 (C7a), 118.2 (C7), 112.8 (C6), 95.0 (C3a), 68.6 (C3), 56.3 (OMe), 46.1 (C1'), 43.3 (C9b), 38.8 (C9a), 36.5 (C2'), 34.8 (NMe), 21.5 (Ce).

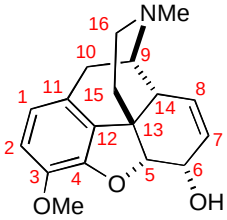
N-[2'-(3α-Hydroxy-5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-9b(3a*H*)-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide **20**



To a solution of crude alcool **18** (130 mg, obtained from 0.23 mmol of **17**) in dichloromethane (5 mL) was added Dess Martin reagent (200 mg, 0.46 mmol). After 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, stirred for 30 min and extracted with dichloromethane. The combined organic layers were, dried over $MgSO_4$ and evaporated to dryness. The resulting residue was taken up in methanol (10 mL) and cooled to 0°C. $NaBH_4$ (13 mg, 0.345 mmol) was added, the reaction was stirred for 1h and allowed to rise to room temperature, quenched with 1M aqueous HCl and exracted with dichloromethane. The combined organic layers were, dried over $MgSO_4$ and evaporated to dryness. Purification by preparative TLC (elution : Heptane/AcOEt : 50/50) gave 29 mg **20** (yield 28% from **17**).

H.R.M.S. (ESI, m/z) : calcd for $C_{25}H_{27}NO_5NaS^+$: 476.1508, found : 476.1517
M.S. (ESI, m/z) : 476 $[M+Na]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 1682, 1597, 1504, 1454, 1335 (SO_2), 1156 (SO_2).
^{1}H NMR ($CDCl_3$, 500 MHz)
δ (ppm) : 7.61 (2H, d, J_{a-b} = 8.2, Ha), 7.29 (2H, d, J_{a-b} = 8.2, Hb), 6.64 (1H, d, J_{6-7} = 7.9, H6), 6.59 (1H, d, J_{6-7} = 7.9, H7), 6.51 (1H, d, J_{8-9} = 9.5, H8), 6.01 (1H, dd, J_{8-9} = 9.5, J_{9-9a} = 6.4, H9), 5.84-5.79 (1H, d, m, H1), 5.28 (1H, dt, J_{1-2} = 10.1, J_{2-3} = 2.6, H2), 5.14 (1H, d, J_{3-3a} = 6.4, H3a), 4.30-4.25 (1H, m, H3), 3.85 (3H, s, OMe), 3.20 (1H, ddd, J_{gem} = 13.6, $J_{1'-2'}$ = 10.0, $J_{1'-2'}$ = 5.6, H1'), 2.96-2.94 (1H, m, H9a), 2.80 (1H, ddd, J_{gem} = 13.6, $J_{1'-2'}$ = 10.0, $J_{1'-2'}$ = 5.6, H1'), 2.66 (3H, s, NMe), 2.42 (3H, s, He), 2.16 (1H, ddd, $J_{1'-2'}$ = 10.0, $J_{1'-2'}$ = 5.6, H2'), 1.96 (1H, ddd, J_{gem} = 13.7, $J_{1'-2'}$ = 10.0, $J_{1'-2'}$ = 5.6, H2').
^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) : 146.3 (C4a), 144.1 (C5), 143.6 (Cc), 134.6 (Cd), 132.2 (C1), 129.9 (Cb), 129.2 (C9), 128.7 (C9c), 127.6 (C2 et Ca), 125.4 (C8), 123.8 (C7a), 118.3 (C7), 112.6 (C6), 90.2 (C3a), 66.0 (C3), 56.3 (OMe), 46.9 (C1'), 45.2 (C9b), 37.4 (C9a), 35.3 (NMe), 33.9 (C2'), 21.7 (Ce).

(±)-Codeine **1**



A 6 mg (0.85 mmol) amount of lithium metal was added to a solution of THF-anhydrous ammonia (10 mL) containing 27 µL (0.28 mmol) of *t*-BuOH at -78 °C. The resulting dark blue solution was stirred at -78 °C for 5 min, and 13 mg (0.029 mmol) of **20** en solution in THF (1 mL) was then added dropwise. The initial blue color was discharged after the addition of **20**, and an additional 3 mg (0.45 mmol) of lithium metal was added until the blue color became persistent. After stirring at -78 °C for 8 min the reaction was quenched with a MeOH/aqueous NH_4Cl solution, and the resulting mixture was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (elution : DCM/MeOH : 100/0 to 90/10 with 1% NH_4OH) gave 4.5 mg of (±)-codeine **1** (analysis are in concordance with description of litterature, yield 51%) and 2 mg of starting material **20**.

H.R.M.S. (ESI, m/z) : calcd for $C_{18}H_{22}NO_3^+$: 300.1600, found : 300.1598
M.S. (ESI, m/z) : 300 $[M+H]^+$; 322 $[M+Na]^+$
I.R. ($CHCl_3$) ν (cm^{-1}) : 2933, 1504, 1454, 1276.
^{1}H NMR ($CDCl_3$, 300 MHz)
δ (ppm) : 6.68 (1H, d, $J_{1\text{-}2}$ = 8.1, H1), 6.59 (1H, d, $J_{1\text{-}2}$ = 8.1, H2), 5.75-5.71 (1H, m, H7), 5.34-5.30 (1H, m, H8), 4.91 (1H, d, $J_{5\text{-}6}$ = 6.7, H5), 4.28-4.22 (1H, m, H6), 3.89 (3H, s, OMe), 3.39-3.35 (1H, m, H9), 3.07 (1H, d, J_{gem} = 18.3, H10), 2.71-2.67 (1H, m, H14), 2.61 (1H, dd, J_{gem} = 12.2, $J_{15\text{-}16}$ = 4.6, H16), 2.46 (3H, s, NMe), 2.41 (1H, dd, J_{gem} = 12.2, $J_{15\text{-}16}$ = 3.4, H16), 2.32 (1H, dd, J_{gem} = 18.6, $J_{9\text{-}10}$ = 6.4, H10), 2.12-2.05 (1H, m, H15), 1.92-1.88 (1H, m, H15).
^{13}C NMR ($CDCl_3$, 125 MHz)
δ (ppm) : 146.4 (C4), 142.3 (C3), 133.5 (C7), 131.2 (C12), 128.3 (C8), 127.3 (C11), 119.7 (C1), 113.0 (C2), 91.4 (C5), 66.5 (C6), 59.0 (C9), 56.4 (OMe), 46.5 (C16), 43.2 (NMe), 43.0 (C13), 40.9 (C14), 35.9 (C15), 20.5 (C10).