

Use of Fluoroalkyl as a Latent Group for Internal Alkylation – Application to the Synthesis of Bridged Tetrahydrofluorenones

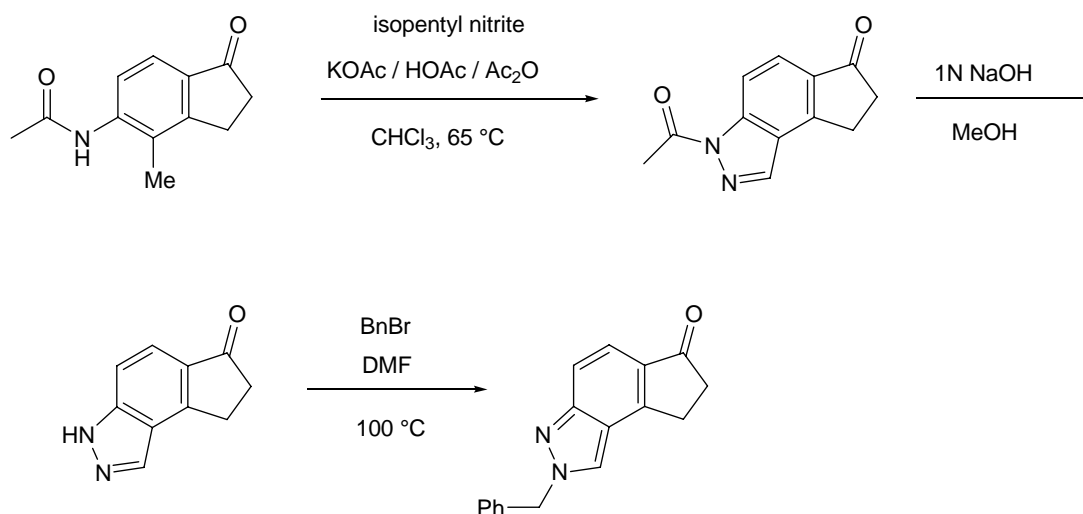
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Supporting Information

Anhydrous dimethyl acetamide (DMAC), dimethyl formamide (DMF) and tetrahydrofuran (THF) were used straight from the AcroSeal™ bottle without further purification. Column chromatographies were performed using Biotage columns as noted. NMR spectra were obtained on either a Varian INOVA500 or Varian INOVA600. Chemical shifts (δ) are reported in ppm using the solvent as the internal standard – CDCl₃ (7.26 for ¹H and 77.00 for ¹³C), CD₃OD (3.30 for ¹H and 49.00 for ¹³C). Exact mass analysis was performed on a Waters Micromass (Milford, MA) LCT time of flight mass spectrometer with electrospray ionization. Mass was determined using leucine enkephalin (m/z 556.2771) for lock mass reference.

Preparation of 2-benzyl-7,8-dihydrocyclopenta[e]indazol-6(2H)-one (**10**).



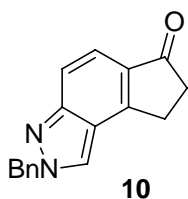
Step 1: 3-acetyl-7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one

A stirred mixture of N-(4-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)acetamide (20.00 g, 98.40 mmol), potassium acetate (19.32 g, 197 mmol), acetic acid (11.3 mL, 197 mmol), acetic anhydride (18.6 mL, 197 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (5.20 g, 19.7 mmol) in 600 mL of chloroform was heated at 65 °C and isopentyl nitrite (33.0 mL, 246 mmol) was added during 10 minutes. The mixture was stirred at 65 °C for 23 hours and was then allowed to cool to room temperature. The reaction mixture was diluted with chloroform and washed successively with saturated sodium bicarbonate (2x), water and brine. After drying over sodium sulfate, the solution was concentrated to low volume under vacuum and flash chromatographed on silica gel eluting with ethyl acetate/dichloroethane (0:100 to 10:90) to give 3-acetyl-7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one as a yellow solid.

Step 2: 7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one

To a suspension of 3-acetyl-7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one (9.19 g, 42.9 mmol) in methanol (250 mL) was added 1N aqueous sodium hydroxide (55.6 mL, 55.6 mmol). The resulting brown solution was stirred at room temperature for 1 hour. The methanol was evaporated under vacuum and the residue was diluted with water (250 mL) and adjusted to pH 4 with 6N aqueous HCl. The resulting precipitate was isolated by filtration, washed thoroughly with water and dried under vacuum to give 7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one as a yellow solid.

Step 3: 2-benzyl-7,8-dihydrocyclopenta[*e*]indazol-6(2*H*)-one (**10**)

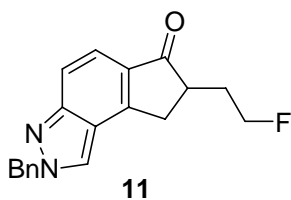


To a suspension of 7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one (6.00 g, 34.8 mmol) in 60 mL of dimethylformamide was added benzyl bromide (5.40 mL, 45.5 mmol) and the mixture was heated to 100 °C. After 15 hours, the solution was cooled to room temperature and partitioned between chloroform and saturated aqueous NaHCO₃. The organic phase was washed with water (3x) and brine and dried over Na₂SO₄. The solution was concentrated to low volume under vacuum and flash chromatographed on silica gel eluting with ethyl acetate/dichloroethane (0:100 to 20:80) which removed a minor amount (~10%) of the faster eluting regioisomer 3-benzyl-7,8-dihydrocyclopenta[*e*]indazol-6(3*H*)-one and gave 2-benzyl-7,8-dihydrocyclopenta[*e*]indazol-6(2*H*)-one as a pale yellow solid.

^1H NMR (CDCl_3 , 600 MHz): δ 8.09 (s, 1H), 7.66 (d, 1H), 7.59 (d, 1H), 7.3-7.4 (m, 5H), 5.64 (s, 2H), 3.22 (m, 2H), 2.76 (m, 2H).

Mass spectrum: m/z = 263.1 ($\text{M}+\text{H}$), 285.1 ($\text{M}+\text{Na}$).

2-benzyl-7-(2-fluoroethyl)-7,8-dihydrocyclopenta[*e*]indazol-6(2*H*)-one (**11**):

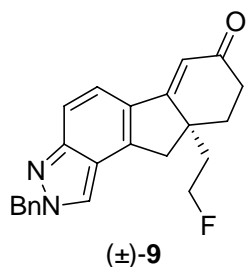


To a suspension of compound **10** (10.3 g, 39.3 mmol) in anhydrous THF (180 mL) at -70°C under nitrogen, was added a solution of LiHMDS in THF (86 mL, 1.0 M, 86mmol, 2.2 eq) via syringe pump over 20 minutes. The resulting reddish-brown solution was allowed to warm (by melting of dry ice/acetone bath) to -33°C over 30 minutes, at which time it was cooled back to -70°C . Ethyl cyanoformate (5.9 mL, 60 mmol, 1.5 eq) was added over one minute, then the reaction mix was allowed to warm to 15°C over 2.75 hours. Aqueous HCl (1 N, 100 mL) was added, followed by ethyl acetate (200 mL) and additional 1 N HCl (200 mL). The two phases were separated and the organic phase was washed sequentially with water, 1 N HCl, water, 5% aq. NaHCO_3 , and then brine (extracting with ethyl acetate where necessary). The organic phase was dried with sodium sulfate, filtered through silica gel and concentrated in vacuo, then placed under high vacuum overnight to give a brown oil.

The crude brown oil (14 g, max. of 39.1 mmol) was dissolved in dimethyl acetamide (DMAC, 160 mL) to give a dark brown solution. To this solution was added K_2CO_3 (11g, 80 mmol, 2 eq.), KI (13.3 g, 80 mmol, 2 eq.) and 1-bromo-2-fluoroethane (3.8 mL, 51 mmol, 1.3 eq.). The reaction was heated to 65°C under nitrogen for 19 hours at which point LCMS indicated that the alkylation was complete. The reaction mixture was cooled to room temperature, then 160 mL water, 160 mL THF, and 24 mL 5N sodium hydroxide were added. After three hours LCMS indicated that the decarboxylation was not complete, so 5 mL 5N NaOH were added. After an additional hour had passed the reaction was found to be complete, and aqueous HCl (1N, 150 mL) was added. The reaction was diluted with ethyl acetate (400 mL) and the two phases were separated. The aqueous phase was extracted with ethyl acetate seven times (100 mL each time) until the 7th extract was judged by TLC to be devoid of product. All the ethyl acetate fractions were combined and then washed with 5% aq. $NaHCO_3$, followed by brine, before drying with $MgSO_4$, filtration and concentration by rotary evaporation to give a dark brown oil. To this oil was added diethyl ether (50mL) and rotary evaporation repeated to give 11.8 g solid 2-benzyl-7-(2-fluoroethyl)-7,8-dihydrocyclopenta[*e*]indazol-6(2*H*)-one **11** which was carried forward without purification.

1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (s, 1H), 7.66 (d, J = 9.1Hz, 1H), 7.57 (d, J = 8.9Hz, 1H), 7.3 – 7.42 (m, 2H), 1.84 – 1.9 (m, 1H), 4.6-4.76 (m, 2H), 3.5 (dd, J = 17.8, 7.4 Hz, 1H), 3.0 (dd, J = 17.8, 3.4 Hz, 1H), 2.85-2.93 (m, 1H), 2.35-2.45 (m, 1H),

(±)-2-benzyl-9a-(2-fluoroethyl)-8,9,9a,10-tetrahydroindeno[2,1-*e*]indazol-7(2*H*)-one (9):



Compound **11** (2-benzyl-7-(2-fluoroethyl)-7,8-dihydrocyclopenta[*e*]indazol-6(2*H*)-one) (11.8 g, 38.3 mmol) was dissolved in anhydrous THF (100 mL) and DBU (1.2 mL, 7.7 mmol, 0.2 eq.) followed by MVK (6.4 mL, 77 mmol, 2 eq.) were added. The reaction was heated at 55°C under nitrogen for 24 hours, at which point NMR analysis of an aliquot indicated complete conversion. The reaction was cooled to room temperature before being partitioned between 5% MeOH/DCM and water. The organic phase was washed with 5% aq. NaHCO₃, then dried and concentrated in vacuo. Column chromatography on a Biotage FLASH 75TMS column, eluting with 6L of 2/1 Hexane/Ethyl acetate, followed by 3L of 1/1 Hex/EA was performed. The product containing fractions (product R_f of approximately 0.3 with 1:1 Hex/EA) were divided into two portions: those that contained a relatively non-polar spot (R_f of approximately 0.6), and those that did not. The contaminated fractions were repurified using a Biotage FLASH 40TMM column. All product containing fractions were combined and concentrated to an orange foam (10.8g, 75% yield.)

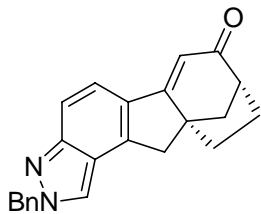
The orange foam (10.8 g, 28.6 mmol) was dissolved in toluene (300 mL) and pyrrolidine (2.4 mL, 28.6 mmol) and acetic acid (1.64 mL, 28.6 mmol) were added. The reaction was heated at 90°C under nitrogen for 15 hours at which time LCMS analysis indicated complete reaction. The reaction was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous phase was extracted as necessary and the combined organic phase was washed with 5% aq. NaHCO₃ then brine, before drying with MgSO₄ and filtration and concentration. The crude product was purified by Biotage FLASH 75TMS eluting with 6L of 2/1 Hexane/Ethyl acetate, followed by 2L of 1/1 Hex/EA collecting 400 mL fractions. The product-containing fractions were concentrated to a sticky orange solid (7.5g) which was diluted with 100 mL Heptane (which it is not soluble in) followed by 150 mL DCM to give a solution. This solution was placed on the rotovap under 210 mm Hg vacuum and rotated slowly to encourage precipitation of a white solid. Once it appears that the dichloromethane was removed the solid was filtered (washing with heptane) to give 5.75 g white solid (40% yield from compound **9**). The filtrate was concentrated and repurified by column chromatography to give 1g of orange solid which contained a 2:1 mixture of compound **9** (thus an additional 5%) and compound **13**).

¹H NMR (CDCl₃, 600 MHz): δ 7.91 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.32 – 7.41 (m, 5H), 6.23 (s, 1H), 5.6 (br s, 2H), 4.49 (dt, *J* = 47.3, 5.8 Hz, 2H), 3.28 (d, *J* = 16.7 Hz, 1H), 2.93 (d, *J* = 16.8 Hz, 1H), 2.63 (ddd, *J* = 18.4, 13.4, 5.2 Hz, 1H), 2.52 (dd, *J* = 18.3, 4.3 Hz, 1H), 2.40 (ddd, *J* = 13.3, 5.2, 4.0 Hz, 1H), 2.06-2.16 (m, 2H), 1.92-2.01 (m, 1H).

^{13}C NMR (CDCl_3 , 150 MHz) δ 198.46, 172.87, 150.80, 141.44, 135.16, 131.22, 129.11, 128.71, 123.15, 120.22, 119.82, 118.07, 115.74, 82.09, 80.99, 57.82, 45.98, 45.96, 42.71, 38.04, 37.92, 33.96, 32.17

High Res. Mass Spectrum: m/z calc. 361.1716 found 361.1710 ($\text{M}+\text{H}$)

(\pm)-2-benzyl-2,9,10,11-tetrahydro-8,10a-methanoazuleno[2,1-*e*]indazol-7(8*H*)-one (**13**)



(\pm)-**13**

Two step Procedure:

To solution of **7** (3.2 g, 8.9 mmol) in dichloromethane (90 mL) cooled to -78°C under an atmosphere of N_2 , was added BBr_3 (1M in CH_2Cl_2 , 27 mL, 27 mmol) dropwise over 15 min. After warming to 0°C over 30 min, the reaction mixture was partitioned between 5% aq. NaHCO_3 and EtOAc (with a small % MeOH to affect solution). The organic phase was washed with H_2O then brine, then dried over MgSO_4 , filtered and concentrated to 3.8 g of a crude orange-brown solid.

The crude product was dissolved in anhydrous THF (175 mL) and cooled to -78°C under an atmosphere of N_2 . KHMDS (0.5 M solution in toluene, 22 mL, 11.5 mmol) was added

dropwise over 20 minutes. After 25 minutes of warming to -5°C the reaction was judged to be 95% completed by LC-MS analysis, so additional KHMDS solution was added (1 mL) and the cooling bath was removed. After 15 minutes the reaction was quenched with 1 N HCl (30 mL) and the reaction mixture was partitioned between EtOAc and H_2O . The organic phase was washed with 5% aq. NaHCO_3 then brine, then dried over MgSO_4 filtered and concentrated to in vacuo to approximately half volume at which point a large amount of precipitate has formed. Filtration yielded 2.05 g yellow solid. This procedure was repeated to give an additional 200 mg of solid. The remaining product was chromatographed on silica gel with hexane/EtOAc to give 450 mg yellow solid. Thus 2.7 g of **13** were produced in 88% yield for two steps.

One Pot LiCl Procedure:

Compound 7 (1.59 g, 4.4 mmol) was dissolved in anhydrous DMF (40 mL) and LiCl (1.85 g, 44 mmol) was added. The resulting suspension was heated at 150°C under nitrogen for 24 hours. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate and water and the organic phase washed with water then brine. Drying (MgSO_4), filtration and concentration in vacuo provided a faintly brown solid (1.42 g), with sufficient purity by NMR for use in further chemistry. A small sample was purified for analysis.

^1H NMR (CDCl_3 , 600 MHz): δ 7.94 (s, 1H), 7.66 (d, $J = 8.9\text{Hz}$, 1H), 7.3-3.4 (m, 6H), 6.10 (d, 0.9Hz, 1H), 5.61 (AB, $J = 15.3\text{ Hz}$, 2H), 3.33 (d, $J = 17.5\text{ Hz}$, 1H), 3.20 (d, $J =$

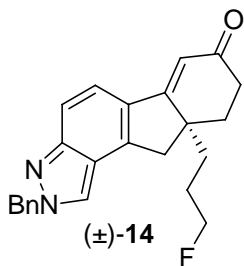
17.6 Hz, 1H), 3.03 (dd, $J = 6.7, 4.4$ Hz, 1H), 2.25-2.32 (m, 1H), 1.93-2.04 (m, 3H), 1.85-1.91 (m, 1H), 1.7-1.76 (m, 1H).

^{13}C NMR (CDCl_3 , 150 MHz) δ 203.80, 175.14, 150.61, 143.52, 135.25, 129.76, 129.04, 128.62, 128.07, 123.25, 120.69, 119.93, 117.77, 112.55, 57.72, 53.1, 51.24, 43.44, 39.37, 36.87, 26.25.

High Res. Mass Spectrum: m/z calc. 341.1654, found 341.1467 ($\text{M}+\text{H}$)

(\pm)-2-benzyl-9a-(3-fluoropropyl)-8,9,9a,10-tetrahydroindeno[2,1-*e*]indazol-7(2*H*)-one

(**14**):

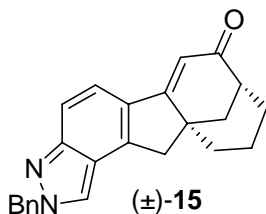


Compound **10** was converted to compound **14** following the procedures for the conversion for **10** to **9**, using 1-bromo-3-fluoro-propane.

^1H NMR (CDCl_3 , 500 MHz): δ 7.91 (s, 1H), 7.66 (d, $J = 8.9$ Hz, 1H), 7.42 (d, $J = 9.2$ Hz, 1H), 7.3 – 7.4 (m, 5H), 5.6 (s, 2H), 4.33 (dt, $J = 47.2, 5.8$ Hz, 2H), 3.13 (d, $J = 16.9$ Hz, 1H), 2.89 (d, $J = 16.7$ Hz, 1H), 2.61 (ddd, $J = 18.5, 13.3, 5.3$ Hz, 1H), 2.50 (m, 1H),

2.31 (ddd, $J = 13.1, 5.3, 1.4$ Hz, 1H), 2.08 (ddd, $J = 13.3, 13.3, 5.5$ Hz, 1H), 1.46 – 1.84 (m, 4H).

(±)-6-benzyl-6,7-diazapentacyclo[13.3.1.0^{1,12}.0^{3,11}.0^{4,8}]nonadeca-3(11),4,7,9,12-pentaen-14-one (**15**):

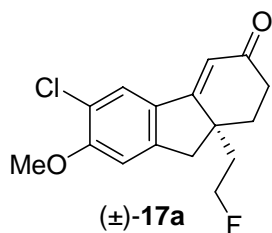


¹H NMR (CDCl₃, 600 MHz): δ 7.90 (s, 1H), 7.65 (d, $J = 9.0$ Hz, 1H), 7.43 (d, $J = 9.1$ Hz, 1H), 7.3 -7.4 (2m, 5H), 6.41 (s, 1H), 5.60 (AB, $J = 5.1$ Hz, 2H), 3.20 (d, $J = 16.3$ Hz, 1H), 2.99 (d, $J = 16.7$ Hz, 1H), 2.66 (br, s, 1H), 2.28 (dd, $J = 11.1, 1.7$ Hz, 1H), 2.04 (dd, $J = 12.0, 2.3$ Hz, 1H), 1.5 – 1.6 (m, 3H), 1.84 (dd, $J = 11.9, 1.3$ Hz, 1H), 1.72 - 1.78 (m, 1H), 1.64 (ddd, $J = 16.6, 12.7, 3.9$ Hz, 1H).

¹³C NMR (CDCl₃, 150 MHz) δ 202.75, 170.46, 150.66, 142.34, 135.27, 130.84, 129.04, 128.62, 128.09, 123.05, 120.69, 120.14, 118.03, 117.60, 57.73, 45.61, 44.99, 43.93, 39.80, 34.69, 27.27, 19.05.

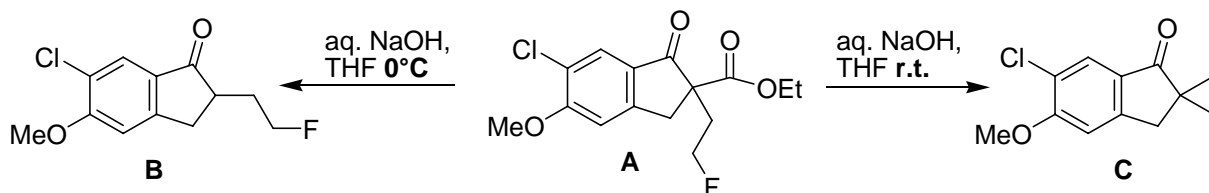
High Res. Mass Spectrum: m/z calc. 355.1810 found 355.1800 (M + H)

(±)-6-chloro-9a-(2-fluoroethyl)-7-methoxy-1,2,9,9a-tetrahydro-3H -fluoren-3-one (**17a**):



Compound **19a** was prepared using the procedures for the conversion of **10** to **9** . One important modification. The decarboxylation of the fluoroalkyl keto-ester **A** to give **B** with 5N NaOH must be run at 0°C to avoid the formation of spirocyclopropane **C**. (see NOTE)

NOTE:

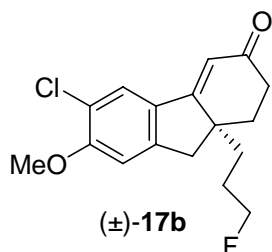


^1H NMR (CDCl_3 , 600 MHz): δ 7.55 (s, 1H), 6.87 (s, 1H), 6.13 (s, 1H), 4.48 (dt, J = 47.2, 5.8 Hz, 2H), 3.94 (s, 3H), 3.13 (d, J = 16.3 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H), 2.58 (ddd, J = 18.4, 13.4, 5.2 Hz, 1H), 2.49 (ddd, J = 18.4, 5.3, 1.3 Hz, 1H), 2.36 (ddd, J = 13.3, 5.0, 1.5 Hz, 1H), 2.01 – 2.09 (m, 2H), 1.85 – 1.94 (m, 1H).

^{13}C NMR (CDCl_3 , 150 MHz) δ 198.30, 170.29, 158.16, 147.14, 130.61, 124.50, 122.84, 116.42, 108.47, 81.84, 80.73, 56.35, 46.05, 46.04, 43.48, 37.57, 37.44, 33.78, 32.20.

High Res. Mass Spectrum: m/z calc. 295.0901 found 295.0906 ($M + H$)

(±)-6-chloro-9a-(3-fluoropropyl)-7-methoxy-1,2,9,9a-tetrahydro-3H-fluoren-3-one (17b):



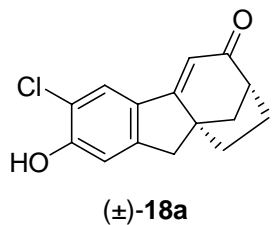
Compound **17b** was prepared using the analogous procedures for conversion of **10** to **9**.

¹H NMR (CDCl₃, 600 MHz): δ 7.54 (s, 1H), 6.87 (s, 1H), 6.12 (s, 1H), 4.35 (dt, *J* = 47.0, 5.5 Hz, 2H), 2.99 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.3 Hz, 1H), 2.47 (dd, *J* = 8.3, 4.6 Hz, 1H), 2.26 (ddd, *J* = 13.2, 5.2, 1.5 Hz, 1H), 2.30 (ddd, *J* = 13.5, 13.5, 5.5 Hz, 1H), 1.6-1.78 (m, 3H), 1.46 – 1.59 (m, 1H),

¹³C NMR (CDCl₃, 150 MHz) δ 198.40, 170.82, 158.09, 147.44, 130.98, 124.41, 122.76, 116.12, 108.37, 84.23, 83.13, 56.34, 46.54, 43.21, 33.66, 33.50, 33.47, 32.19, 26.54, 26.41.

High Res. Mass Spectrum: *m/z* calc. 309.1058 found 309.1060 (M + H)

(±)-3-chloro-2-hydroxygibba-1,3,4a(10a),4b-tetraen-6-one - methane (1:2) (18a):

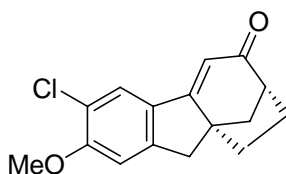


^1H NMR (CD_3OD , 600 MHz): δ 7.64 (s, 1H), 6.92 (s, 1H), 6.04 (d, $J = 1.2$ Hz, 1H), 3.17 (d, $J = 17.1$ Hz, 1H), 3.02 (d, $J = 17.3$ Hz, 1H), 2.93 (dd, $J = 6.9, 4.5$ Hz, 1H), 2.30-2.38 (m, 1H), 1.92 – 2.02 (m, 3H), 1.74 – 1.8 (m, 1H), 1.56- 1.64 (m, 1H),

^{13}C NMR (CD_3OD , 150 MHz) δ 206.90, 177.00, 158.59, 151.42, 126.29, 122.45, 113.76, 112.70, 54.80, 52.33, 44.43, 40.47, 37.52, 27.31

High Res. Mass Spectrum: m/z calc. 261.0682 found 261.0685 ($\text{M} + \text{H}$)

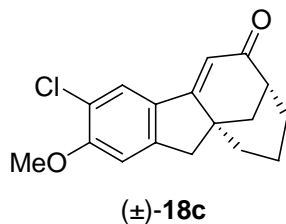
(\pm)-3-chloro-2-methoxygibba-1,3,4a(10a),4b-tetraen-6-one - methane (1:2) (**18b**):



Compound **17a** (55 mg, 0.19 mmol) was dissolved in anhydrous THF (0.4 mL) and cooled to -78°C under nitrogen. To this solution was added KHMDS in toluene (0.5 M, 0.6 mL, 0.3 mmol, 1.5 eq) which gave the reaction mixture an orange color. After 15 minutes the cooling bath was replaced with an ice-water bath at 0°C . After an additional 50 minutes the bath temp was 10°C and the reaction was quenched by addition of 1 N HCl. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with 5% NaHCO_3 then brine then dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude reaction mixture was purified by prep-TLC eluting

with 2:1 Hex:EA to give compound (39 mg, 75%) which appears by NMR to be a 93:7 mixture of desired product and starting material.

(±)-3-chloro-2-methoxy-7,8,9,10-tetrahydro-7,10a-methanocycloocta[*a*]inden-6(11*H*)-one (18c):



¹H NMR (CDCl₃, 600 MHz): δ 7.55 (s, 1H), 6.87 (s, 1H), 6.32 (s, 1H), 3.93 (s, 3H), 2.88 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.2 Hz, 1H), 2.63 (m, 1H), 2.22 (m, 1H), 1.99 (dd, *J* = 12.2, 2.2 Hz, 1H), 1.8 (m, 1H), 1.44 – 1.50 (m, 5H).

¹³C NMR (CDCl₃, 150 MHz) δ 202.63, 167.94, 157.82, 148.08, 130.42, 122.43, 118.67, 108.74, 60.36, 56.32, 45.74, 45.67, 43.74, 39.70, 34.16, 27.27, 18.96,

High Res. Mass Spectrum: *m/z* calc 289.0995 found 289.1001 (M + H)