New Approach to Bicyclo[5.3.0]decanes : Stereoselective Guaiane Synthesis

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Supporting Information

General

Merck 40-60 silica gel 60 was employed for column flash chromatography. A Nicolet 400 spectrophotometer was used to record IR spectra. A Brucker Avance 300 or a Varian Unity+ 500 spectrometer was employed for the NMR spectra ($CDCl_3$ solutions with TMS as the reference for ^1H, and $CDCl_3$ as the reference for ^{13}C). Melting points were taken on a Büchi-Tottoli apparatus and not corrected. Mass spectra were obtained on an AEI MS-30 or a Thermo Finnigan PolarisQ mass spectrometer. HRMS and microanalyses were performed by the Central Service of the CNRS. THF and ether were distilled from sodium benzophenone ketyl, and dichloromethane, DMF, HMPA, DMPU, and toluene from calcium hydride. Reactions were generally carried out under an argon atmosphere in dried glassware and stirred magnetically.

(±)-(1*R*,10*S*)-4-Chloro-10-methyl-1,10-dihydroazulen-3-one (3). To a solution of **1** (7.54 g, 71.0 mmol) in 200 mL of ether containing Zn-Cu couple (9.84 g, ca. 145 mmol) was added dropwise over 1 h a solution of freshly distilled $POCl_3$ (7.25 mL, 77.8 mmol) and trichloroacetyl chloride (8.70 mL, 78.0 mmol) in 55 mL of ether. The mixture was stirred at 20 ˚C for an additional 13 h, filtered over celite to remove excess couple, and then partially concentrated (ca. 150 mL) before 500 mL of hexane was added in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with water, sat. $NaHCO_3$ (twice), water, and brine and then dried over anhydrous Na_2SO_4. Filtration and concentration of the solution under reduced pressure left 12.46 g of cyclobutanone **2** (IR: 1804 cm^{-1}), containing ca. 3% of diastereomer [δ 1.10 (d, J = 5.8 Hz)] and 10% of double-addition product.[1] To 7.05 g of this mixture in 13 mL of ether was added 153 mL of an ethereal solution of diazomethane (ca. 0.3 M) and then 13 mL of methanol. The solution was stirred

slowly for 35 min and then concentrated under vaccum, in order to remove solvents and excess diazomethane (caution!), to yield the α,α-dichlorocyclopentanone (IR: 1767 cm^{-1}) as a viscous brown oil, which was used immediately. The crude α,α-dichlorocyclopentanone was dissolved in 130 mL of DMF and stirred at 20 ˚C for 24 h, whereupon water was added and the aqueous layer was extracted three times with ether-pentane (1:1). The combined organic layers were washed four times with water and then with sat. NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the resulting crude product on silica gel with 12% ethyl acetate in pentane afforded 3.44 g (44% overall) of pure **3**: mp 102 °C (dichloromethane); IR 1709 cm^{-1}; ^{1}H NMR (300 MHz) δ 6.62 (ABX, δ_A = 6.84, δ_B = 6.41, J_{AB} = 11.6 Hz, J_{AX} = 0.4 Hz, J_{BX} = 7.0 Hz, 2 H), 6.01 (A'B'X'Y'Z', $\delta_{A'}$ = 6.06, $\delta_{B'}$ = 5.97, $J_{A'B'}$ = 11.6 Hz, $J_{A'X'}$ = 7.0 Hz, $J_{A'Y'}$ = 2.6 Hz, $J_{A'Z'}$ = 0.4 Hz, $J_{B'X'}$ = 2.8 Hz, $J_{B'Y'}$ = 0.8 Hz, $J_{B'Z'}$ = 0.8 Hz, 2 H), 2.87-2.73 (m, 2 H), 2.51-2.34 (m,1 H), 2.32-2.18 (m, 1 H), 1.26 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 198.4, 164.1, 144.1, 135.3, 130.4, 125.4, 124.2, 43.2, 40.0, 36.8, 20.7; MS (DCI) *m/z* 195 (MH^+, 100%). Anal. Calcd for $C_{11}H_{11}OCl$: C, 67.87; H, 5.70. Found: C, 67.88; H, 5.56.

4-Chloro-10-methylazulen-2-yl Acetate (4). mp 79-80 °C; IR 1774 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.38 (d, *J* = 9.5 Hz, 1 H), 7.55 (ps t, *J* = 10.1 Hz, 1 H), 7.32 (s, 1 H), 7.18-7.28 (m, 2 H), 2.86 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (75 MHz) δ 167.9, 151.1, 147.3, 136.4, 134.2, 133.8, 131.8, 128.4, 123.1, 105.9, 104.3, 24.2, 21.2; MS (DCI) *m/z* 235 (MH^+, 100%). Anal. Calcd for $C_{13}H_{11}O_2Cl$: C, 66.53; H, 4.72. Found: C, 66.24; H, 4.67.

Tricarbonyl(iron) complexes 5a and 5b. For **5a**: mp 99-101 °C; IR 2058, 1990, 1694 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.78 (ddd, *J* = 5.3, 5.3, 1.0 Hz, 1 H), 5.50 (ddd, *J* = 8.2, 5.3, 1.0 Hz, 1 H), 3.71 (d, *J* = 6.4 Hz, 1 H), 3.17 (ps d, *J* = 8.1 Hz, 1 H), 2.46 (dd, *J* = 18.7, 6.8 Hz, 1 H), 2.17 (dqd, *J* = 10.4, 6.5, 1.5 Hz, 1 H), 2.10-1.99 (m, 2 H), 1.20 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 208.8 (br), 196.7, 175.5, 124.7, 90.0, 88.8, 67.2, 51.4, 48.8, 42.2, 39.4, 25.0; HRMS *m/z* calcd for $C_{14}H_{12}O_4ClFe^+$: 334.9774. Found: 334.9786. Anal. Calcd for $C_{14}H_{11}O_4ClFe$: C, 50.26; H, 3.31. Found: C, 49.92; H, 3.23. For **5b**: mp 149-151 °C

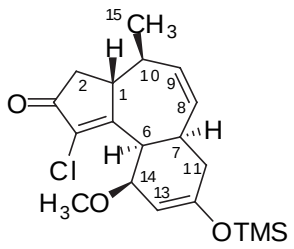
[1] Coquerel, Y.; Blanc, A.; Deprés, J.-P.; Greene, A. E.; Averbuch-Pouchot, M.-T.; Philouze, C.; Durif, A. *Acta Cryst.* **2000**, *C56*, 1480-1481.

(chloroform); IR 2057, 1990, 1707 cm^{-1}; ^1H NMR (500 MHz) δ 5.65 (ddd, *J* = 8.3, 4.6, 1.2 Hz, 1 H), 5.54 (dd, *J* = 8.3, 4.9 Hz, 1 H), 3.77 (d, *J* = 8.3 Hz, 1 H), 2.99 (d, *J* = 8.0 Hz, 1 H), 2.65 (dd, *J* = 18.4, 6.2 Hz, 1 H), 2.30 (ddd, *J* = 10.5, 6.2, 4.0 Hz, 1 H), 1.96 (dd, *J* = 18.2, 3.7 Hz, 1H), 1.35-1.43 (m, 1 H), 1.16 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz) δ 209.5 (br), 198.1, 171.2, 132.5, 90.4, 89.2, 68.0, 55.6, 50.1, 39.7, 31.6, 22.3; HRMS *m/z* Calcd for $C_{14}H_{12}O_4ClFe^+$: 334.9774. Found: 334.9784.

Epoxide 6. mp 133-134 ˚C (dichloromethane-hexane); IR 1710, 1637, 1560 cm^{-1}; ^1H NMR (300 MHz) δ 6.86 (dd, *J* = 11.9, 0.6 Hz, 1 H), 6.47-6.38 (m, 1 H), 3.44-3.38 (m, 2 H), 3.09 (ddd, *J* = 10.9, 7.2, 4.4 Hz, 1 H), 2.55 (ABX, δ_A = 2.76, δ_B =2.34, J_{AB} = 18.5 Hz, J_{AX} = 6.8 Hz, J_{BX} = 3.7 Hz, 2 H), 2.18-2.05 (m, 1 H), 1.37 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 199.1, 162.5, 135.0, 133.5, 128.4, 66.0, 52.1, 40.1, 39.6, 35.8, 20.2; HRMS *m/z* Calcd for $C_{11}H_{12}O_2Cl^+$: 211.0526. Found: 211.0538.

Epoxide 7. mp 131-132 ˚C (diethyl ether-pentane); IR 1713, 1635, 1561 cm^{-1}; ^1H NMR (300 MHz) δ 6.60 (ABX, δ_A = 6.75, δ_B = 6.46, J_{AB} = 11.5 Hz, J_{AX} = 0.8 Hz, J_{BX} = 3.0 Hz, 2 H), 3.39 (dd, *J* = 4.1, 4.1 Hz, 1 H), 3.20 (ddd, *J* = 11.0, 6.7, 4.1 Hz, 1 H), 3.15 (ddd, *J* = 6.0, 4.1, 1.0 Hz, 1 H), 2.55 (A'B'X', $\delta_{A'}$ = 2.71, $\delta_{B'}$ = 2.38, $J_{A'B'}$ = 18.4 Hz, $J_{A'X'}$ = 6.8 Hz, $J_{B'X'}$ = 4.1 Hz, 2 H), 1.73-1.88 (m, 1 H), 1.30 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ; 198.6, 163.7, 134.8, 133.6, 125.2, 64.0, 50.9, 42.4, 38.1, 37.3, 18.4; HRMS *m/z* Calcd for $C_{11}H_{12}O_2Cl^+$: 211.0526. Found: 211.0546. Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.72; H, 5.26. Found: C, 62.29; H, 5.16.

Diels-Alder Adduct 8. mp 146-147 ˚C (diethyl ether-pentane); IR 1712, 1660, 1592 cm^{-1}; ^1H NMR (500 MHz) see Table 1; ^{13}C NMR (75 MHz) δ 199.5, 176.8, 152.6, 136.6, 134.2, 132.6, 103.0, 75.6, 57.3, 46.2, 42.9, 39.4, 36.7, 35.0, 31.7, 20.5, 0.5; HRMS *m/z* Calcd for $C_{19}H_{28}O_3ClSi^+$-H_2: 365.1340. Found: 365.1340.



8

Table 1. ^{1}H NMR data (500 MHz) for **8** ($CDCl_3$)

Proton	δ (ppm)	Pattern	J (Hz)	nOe(%)[a]
1	3.00	ddd	10.3, 6.3, 3.6	2β(7.0), 8(1.8), 9(2.3), 15(2.2)
2α	2.26	ABX	18.6, 3.3	2β(35.7), 15(6.1)
2β	2.66	ABX	18.6, 6.3	1(13.0), 2α(35.4)
6	3.36	dd	3.8, 3.8	7(6.0), 11α(4.7), 14(12.7)
7	2.89-2.94	m	-	6(8.5), 10(<19.3), 11α(<19.3), 11β(3.6), 8(<3.8)
8	5.65	A'B'X'Y'	10.3, 5.0, 2.1	7(2.2), 9(5.6), 11β(5.5), 1(nd)
9	5.49	A'B'X'Y'	10.3, 4.7, 2.3	1(2.5), 8(5.4), 10(2.7), 15(6.3)
10	2.37-2.48	m	-	7(nd), 9(>1.7), 15(>3.3)
11α	2.42	A''B''X''	17.3, 5.6	6(nd), 7(nd), 11β(>17.9)
11β	2.09	A''B''X''	17.3, 1.5	7(5.3), 8(12.8), 11α(32.6)
13	5.23	dd	4.7, 1.8	14(9.4), OCH_3(4.9), OTMS(nd)
14	3.90	ddd	4.6, 4.6, 1.2	6(12.6), 13(12.8), OCH_3(7.1)
15	1.14	d	6.9	1(3.3), 2α(4.1), 9(8.5), 10(6.7)
OTMS	0.26	s	-	8(2.2), 13(5.5), 11α(nd), 11β(nd)
OCH_3	3.18	s	-	13(2.4), 14(3.0)

[a]In some cases, the nOe enhancement could not be measured due to overlapping signals. nd = not determined.

1,6 Adduct 9a. mp 83-84 ˚C (dichloromethane-hexane); IR 1712, 1611 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.87 (dddd, *J* = 11.4, 7.6, 5.5, 2.4 Hz, 1 H), 5.48 (m, 1 H), 3.04-2.86 (m, 2 H), 2.49 (ABX, δ_A = 2.69, δ_B = 2.27, J_{AB} = 18.7 Hz, J_{AX} = 6.3 Hz, J_{BX} = 2.0 Hz, 2 H), 2.63 (ddd, *J* = 17.6, 8.1, 2.6 Hz, 1 H), 2.53-2.38 (m, 1 H), 2.09-2.29 (m, 2 H), 1.16 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 199.5, 176.5, 136.7, 131.0, 129.5, 45.6, 40.0, 39.2, 30.8, 23.6, 21.7; HRMS *m/z* Calcd for $C_{11}H_{14}OCl^+$: 197.0733. Found: 197.0743.

1,6 Adduct 9b. mp 73 ˚C (dichloromethane); IR 1716, 1608 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.70 (ABXY, δ_A = 5.81, δ_B = 5.58, J_{AB} = 11.4 Hz, J_{AX} = 5.8 Hz, J_{AY} = 2.6 Hz, J_{BX} = 3.5 Hz, J_{BY} = 1.9 Hz, 2 H), 4.86 (ps d, *J* = 3.8 Hz, 2 H), 3.07 (dd, *J* = 14.6, 2.0 Hz, 1 H), 3.02-2.92 (m, 1 H), 2.82-2.58 (m, 3 H), 2.36-2.20 (m, 2 H), 1.80 (br s, 3 H), 1.17 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 199.2, 174.8, 147.0, 136.6, 134.0, 131.2, 111.5, 45.7, 43.0, 39.4, 37.2, 34.5, 21.3,

20.9; HRMS *m/z* Calcd for $C_{14}H_{17}OCl^+$: 237.1046. Found: 237.1051. Anal. Calcd for $C_{14}H_{17}OCl$: C, 71.03; H, 7.24. Found: C, 70.81; H, 7.09.

1,6 Adduct 9c. Mixture of stereoisomers at C-10. ^{1}H NMR (300 MHz, selected resonances) δ 1.26 (d, *J* = 6.9 Hz, CH_3(C-13), major isomer), 1.25 (d, *J* = 6.8 Hz, CH_3(C-13), minor isomer), 1.18 (d, *J* = 6.9 Hz, CH_3(C-14)); ^{13}C NMR (75 MHz) major isomer: δ 199.3, 175.4, 174.3, 137.3, 134.2, 131.7, 52.0, 46.0, 43.8, 39.2, 38.7, 36.9, 33.2, 21.3, 14.1. Minor isomer: δ 199.2, 175.5, 173.9, 137.5, 133.7, 131.8, 52.1, 45.9, 44.3, 39.1, 38.7, 36.6, 34.2, 21.2, 14.3. HRMS *m/z* Calcd for $C_{15}H_{20}O_3Cl^+$: 283.1101. Found: 283.1097. C-7 β configuration in **9c** was established by chemical correlation with **9b** (see **10b** → **14b**).

Enone 10b. IR 1702, 1639 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.67 (ABXY, δ_A = 5.78, δ_B = 5.56, J_{AB} = 11.3 Hz, J_{AX} = 5.8 Hz, J_{AY} = 2.4 Hz, J_{BX} = 3.3 Hz, J_{BY} = 1.8 Hz, 2 H), 4.83 (ps s, 2 H), 2.96-2.82 (m, 2 H), 2.65-2.43 (m, 3 H), 2.25-2.08 (m, 2 H), 1.79 (ps s, 3 H), 1.70 (ps s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz) δ 207.0, 174.1, 146.7, 136.1, 134.9, 133.1, 110.0, 45.6, 42.8, 39.6, 36.6, 33.7, 20.9, 19.7, 6.9; HRMS *m/z* Calcd for $C_{15}H_{21}O^+$: 217.1592. Found: 217.1578. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.27; H, 9.08.

(±)-1-Epi-hydroxycolorenone (11). mp 58-59 °C; IR 3580, 1693, 1633 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.97 (dd, *J* = 12.4, 2.2 Hz, 1 H), 2.60 (dd, *J* = 18.2, 5.9 Hz, 1 H), 2.34-2.28 (m, 1 H), 2.10 (ps t, *J* = 11.7 Hz, 1 H), 2.02 (dd, *J* = 18.5, 2.5 Hz, 1 H), 1.71 (d, *J* = 1.5 Hz, 3 H), 1.73-1.55 (m, 5 H), 1.25 (s, 3 H), 1.23 (s, 3 H), 1.30-1.20 (m, 2 H), 1.04 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz) δ 209.2, 176.9, 135.6, 73.7, 51.0, 46.7, 42.2, 39.9, 32.5, 29.1, 27.9, 27.2, 25.9, 23.2, 7.8; HRMS *m/z* calcd for $C_{15}H_{25}O_2^+$: 237.1855. Found: 237.1847. The ^{1}H NMR and IR spectral data are in full agreement with those reported for (-)-**11**.

(±)-8-Desangeloyloxytorilin (13). IR 1729, 1698, 1641 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.84 (ps d, *J* = 9.9 Hz, 1 H), 2.60 (dd, *J* = 18.4, 6.3 Hz, 1 H), 2.36-2.25 (m, 1 H), 2.19-2.10 (m, 2 H), 2.03 (dd, *J* = 18.4, 2.6 Hz, 1 H), 2.00 (s, 3 H), 1.70 (d, *J* = 1.9 Hz, 3 H), 1.68-1.58 (m, 4 H), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.35-1.24 (m, 1 H), 1.03 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 208.8, 175.8, 170.3, 135.7, 85.3, 50.8, 43.8, 41.9, 39.3, 32.4, 28.6, 26.4, 23.6, 23.1, 22.6,

22.0, 7.7; MS (EI) *m/z* 278 (M^+, 1%), 218 (100%), 203 (27%), 175 (63%), 161 (47%), 147 (45%), 133 (30%), 121 (12%), 119 (38%), 105 (28%), 91 (26%); MS (DCI) *m/z* 279 (MH^+, 100%), 219 (51%). The ^1H and ^{13}C NMR, Mass, and IR spectral data are in complete accord with those reported for natural (-)-**13**.

(±)-6-Deoxygeigerin (15b). mp 120-121 ˚C (diethyl ether-hexane); IR 1771, 1698, 1649 cm^{-1}; ^1H NMR (500 MHz) δ 4.43 (ddd, *J* = 11.1, 8.0, 3.4 Hz, 1 H), 3.05 (dd, *J* = 13.0, 5.3 Hz, 1 H), 2.36 (ABX, δ_A = 2.63, δ_B = 2.08, J_{AB} = 18.5 Hz, J_{AX} = 6.2 Hz, J_{BX} = 1.5 Hz, 2 H), 2.47-2.36 (m, 2 H), 2.33 (ps t, *J* = 8.3 Hz, 1 H), 2.24 (ps t, *J* = 11.7 Hz, 1 H), 2.00-1.88 (m, 2 H), 1.73 (d, *J* = 1.5 Hz, 3 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.32-1.24 (m, 1 H), 1.15 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 207.9, 178.0, 170.1, 137.7, 80.8, 50.4, 43.0, 42.1, 40.9, 39.7, 37.1, 31.3, 22.9, 14.4, 7.9; HRMS *m/z* calcd for $C_{15}H_{21}O_3^+$: 249.1491. Found: 249.1485. The ^1H and ^{13}C NMR and IR spectral data are in complete accord with those reported for natural (-)-**15b**.