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Planar Chiral (η^6-arene)$Cr(CO)_3$ Containing Carboxylic Acid Derivatives: Synthesis and Use in the Preparation of Organometallic Analogues of the Antibiotic Platensimycin

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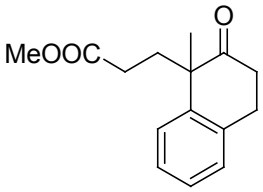
1) Materials. All chemicals were of reagent grade quality or better, obtained from commercial suppliers and used without further purification. Solvents were used as received or dried over molecular sieves. 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate was prepared following a literature procedure.[1] All preparations were carried out using standard Schlenk techniques. All the reaction of (η^6-arene)$Cr(CO)_3$ containing compounds were carried out in dark.

2) Instrumentation and methods. *^1H and ^{13}C NMR spectra* were recorded in deuterated solvents on Bruker DRX 200, 250, 400, or 600 spectrometers at 30°C. The chemical shifts, δ, are reported in ppm (parts per million). The residual solvent peaks have been used as an internal reference. The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). *Infrared spectra* were recorded on an ATR unit using a Bruker Tensor 27 FTIR spectrophotometer at 4 cm^{-1} resolution. Signal intensity is abbreviated br (broad), s (strong), m (medium), and w (weak). *ESI mass spectra* were recorded on a Bruker Esquire 6000. *Crystallographic data* for **7** and **8** were collected using a Rigaku Mercury 375 R/M CCD (XtaLAB mini) diffractometer. The structures were solved by direct methods (SHELXS-97[2]) and refined against F^2 with all measured reflections (SHELXL-97[2], Palton-Squeeze[3]). *Elemental microanalyses* were performed using a Fisons Carlo Erba EA1108 instrument (CHNS version).

3) Antimicrobial activity test. The antimicrobial activity tests were performed in a microtiter plate assay containing 0.2 mL of Luria Broth medium and appropriate compound concentrations up to 180 µg/mL. The tubes were inoculated with 10^5 cells/mL and incubated at 37 °C for 18 h. The compounds did not inhibit the visible growth of the bacteria.

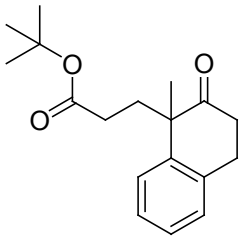
4) Synthesis of the compounds.



4a

Methyl 3-(1,2,3,4-tetrahydro-1-methyl-2-oxonaphthalen-1-yl)propanoate (4a). 1-Methyl-2-tetralone (**3**) (500 mg, 3.12 mmol) in 2 mL of Et_2O was added drop wise by a syringe to a stirred solution of KO^{t}Bu (23.3 mg, 0.21 mmol) in 1/1 (v/v) mixture of ^{t}BuOH and Et_2O (40 mL) under N_2 atmosphere. Methyl acrylate (268 mg, 3.12 mmol) was then added dropwise by a syringe while maintaining the temperature below 30 °C. After stirring for 5 h at room temperature, 40 mL of distilled water and 10 mL of 2M H_2SO_4 were added. The reaction mixture was then extracted with Et_2O (2×50 mL). The combined organic phase was washed with distilled water (2×50 mL), brine (1×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatogryphy (silica gel, hexane/EtOAc 5/1) gave the desired product **4a** as light yellow oil (yield: 392 mg, 51%).

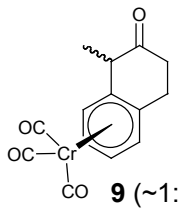
Data for 4a: R_f = 0.33 (silica gel, hexanes/EtOAc 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.35 (s, 3H, CH_3), 1.78-1.90 (m, 1H, CH_2), 1.94-2.02 (m, 2H, CH_2), 2.34-2.40 (m, 1H, CH_2), 2.48-2.57 (m, 1H, CH_2), 2.62-2.68 (m, 1H, CH_2), 2.97-3.03 (m, 2H, CH_2), 3.47 (s, 3H, OCH_3), 7.08-7.13 (m, 2H, *benzene ring proton*), 7.17-7.23 (m, 2H, *benzene ring proton*). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 27.2, 28.4, 29.9, 34.3, 37.8, 51.1, 51.4, 126.4, 126.6, 127.2, 128.2, 135.9, 140.9, 173.4, 213.7. IR bands(ν): 2951w, 1735s, 1709s, 1436m, 1377w, 1298w, 1235m, 1048w, 944w, 891w, 761s, 735m cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 269.04 (100) $[M+Na]^+$.



4b

***Tert*-butyl 3-(1,2,3,4-tetrahydro-1-methyl-2-oxonaphthalen-1-yl)propanoate (4b).** A similar experimental procedure as described for **4a** was followed. 1-Methyl-2-tetralone (3 g, 18.7 mmol), KO^{t}Bu (140 mg, 1.25 mmol), 1/1 (v/v) mixture of ^{t}BuOH and Et_2O (100 mL), *tert*-butyl acrylate (2.6 g, 20.6 mmol), reaction time 6 h, flash column chromatogryphy (silica gel, hexane/EtOAc 10/1→8/1), compound **4b** was obtained as colourless oil (yield: 3.2 g, 61%).

Data for 4b: R_f = 0.35 (silica gel, hexane/EtOAc 8/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.31 (s, 9H, C(C*H*$_3$)$_3$), 1.36 (s, 3H, C*H*$_3$), 1.74-2.02 (m, 3H, C*H*$_2$), 2.24-2.37 (m, 1H, C*H*$_2$), 2.50-2.67 (m, 2H, C*H*$_2$), 2.94-3.06 (m, 2H, C*H*$_2$), 7.08-7.13 (m, 2H, *benzene ring proton*), 7.17-7.26 (m, 2H, *benzene ring proton*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 27.2, 28.0, 28.4, 31.1, 34.3, 37.8, 50.9, 80.1, 126.4, 126.5, 127.2, 128.2, 135.9, 141.1, 172.2, 213.6. IR bands(ν): 2975w, 1713s (br), 1489w, 1453w, 1366m, 1246w, 1210w, 1146s, 983w, 917w, 761m, 666w cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 298.06 (80) [M–CH_2+Na]$^+$, 311.02 (100) [M+Na]$^+$, 326.99 (60) [M+K]$^+$.

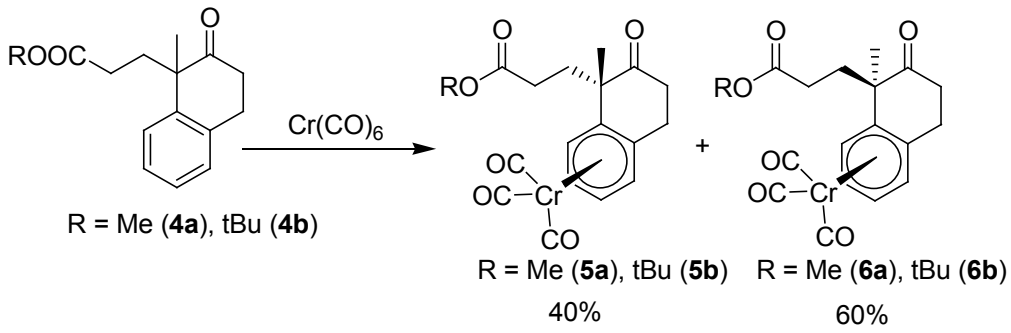


9 (~1:1 mixture of two diastereomers)

Compound 9. To a stirred solution of **3** (1.5 g, 9.4 mmol) in 60 mL of degassed Bu_2O/THF 9/1 (v/v), $Cr(CO)_6$ (2.6 g, 14 mmol) was added at room temperature and the mixture was heated for 36 h at 140°C under a N_2 atmosphere in dark. The reaction mixture was then

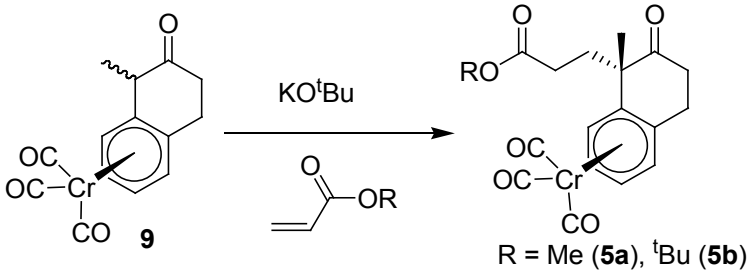
cooled to room temperature, filtered and concentrated. Flash column chromatography (silica gel, hexane:EtOAc 2/1→1/1) yielded of **9** (ca. 1:1 mixture of two diastereomers**)** as yellow-orange solid (yield: 1.8 g, 68%).

Data for 9 (1:1 mixture of two diastereomers): R_f = 0.17 and 0.08 for two diatereomers (silica gel, hexane/EtOAc 3/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.43 (d, 3H); 1.51 (d, 3H), 2.66-2.77 (m, 6H), 3.01-3.11 (m, 3H), 3.26-3.36 (m, 1H), 3.40-3.49 (m, 2H), 5.19-5.43 (m, 8H). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) 11.1, 18.9, 26.2, 26.4, 36.8, 37.6, 44.8, 46.3, 89.4, 90.7, 91.1, 91.2, 91.6, 92.6, 93.5, 94.1, 106.4, 107.6, 108.7, 109.3, 205.6, 207.5, 232.5. IR bands(ν): 1948s, 1844s (br), 1712s,1532w, 1453m, 1306w, 1229w, 1111w, 1053w, 954w, 763w, 664s, 625s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 284.21 (50) [M–2H_2O–H+Na]$^+$, 318.83 (100) [M+Na]$^+$. Anal. calcd. for $C_{14}H_{12}CrO_4$: C 56.76, H 4.08. Found: C 56.78, H 4.14.



Synthesis of 5a and 6a from 4a. To a stirred solution of **4a** (1 g, 4.06 mmol) in 70 mL of degassed Bu_2O/THF 9/1 (v/v), $Cr(CO)_6$ (1.34 g, 6.09 mmol) was added at room temperature and the mixture was heated for 36 h at 140 °C under N_2 atmosphere in dark. The reaction mixture was then cooled to room temperature, filtered and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 4/1→3/1) yielded the diasteriomeric mixture of **5a** and **6a** in a ratio of 2:3, respectively (combined yield: 1.2 g, 77%).

Synthesis of 5b and 6b from 4b. The same procedure as used for the preparation of diastereomeric mixture of **5a** and **6a** was followed. **4b** (1 g, 3.47 mmol), $Cr(CO)_6$ (1.14 g, 5.2 mmol), 70 mL of degassed Bu_2O/THF 9/1 (v/v), reaction time 36 h at 140 °C. Flash column chromatography (silica gel, hexane:EtOAc 4/1→3/1) yielded the diasteriomeric mixture of **5b** and **6b** in a ratio of 2:3, respectively (combined yield: 1.3 g, 88%).

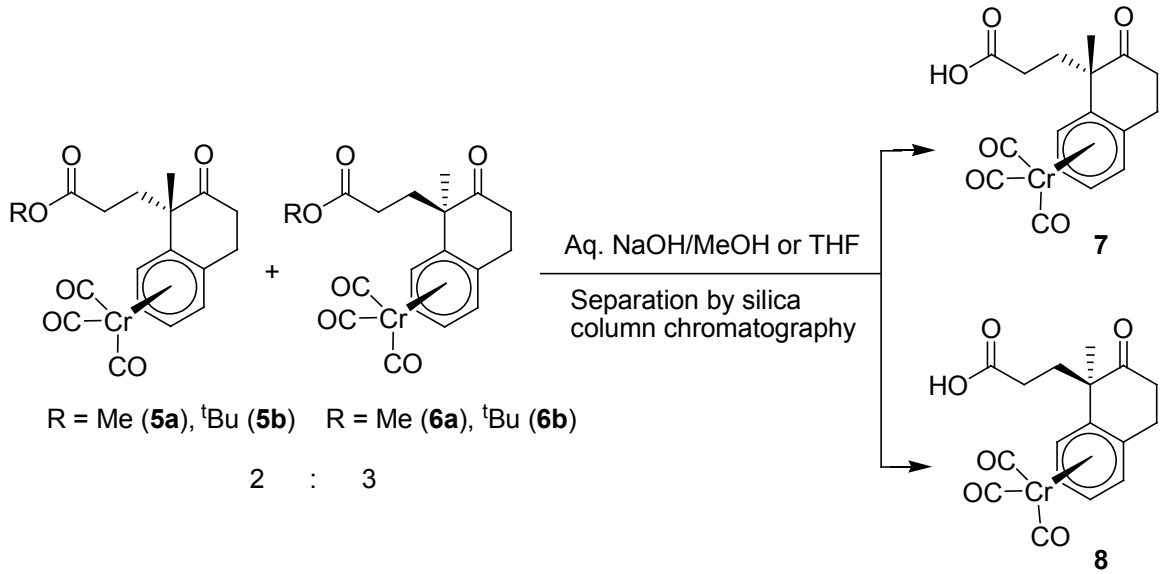


Diastereoselective synthesis of 5a. A suspension of **9** (500 mg, 1.69 mmol) in 15 mL of Et_2O was added slowly to a stirred solution of KO^{t}Bu (16 mg, 0.14 mmol) in 2/1 (v/v) mixture of ^{t}BuOH and Et_2O (45 mL) under N_2 atmosphere. After 20 min, methyl acrylate (159 mg, 1.85 mmol) was added dropwise while maintaining the temperature below 30 °C. After stirring for 6 h at room temperature, the reaction mixture was diluted with 100 mL Et_2O, washed with distilled water (2×100 mL) and brine (80 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatogryphy (silica gel, hexane/EtOAc 2/1→1/1) gave compound **5a** as yellow solid (yield: 551 mg, 85%).

Data for 5a: R_f = 0.19 (silica gel, hexane/EtOAc 1/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.53 (s, 3H, C*H*$_3$), 1.85-1.98 (m, 1H, C*H*$_2$), 2.09-2.24 (m, 3H, C*H*$_2$), 2.69-2.85 (m, 3H, C*H*$_2$), 3.14-3.26 (m, 1H, C*H*$_2$), 3.61 (s, 3H, OC*H*$_3$), 5.25-5.32 (m, 2H, *benzene ring proton*), 5.38-5.45 (m, 2H, *benzene ring proton*). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 22.7, 26.5, 29.4, 35.3, 36.3, 49.5, 51.7, 90.2, 90.8, 91.9, 93.0, 109.1, 112, 172.8, 208.7, 232.7. IR bands(ν): 1952s, 1859s (br), 1731s, 1712s, 1489m, 1437w, 1298w, 1196m, 1081w, 1018w, 764w, 664s, 626s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 404.88 (100) $[M+Na]^+$. Anal. calcd. for $C_{18}H_{18}CrO_6$: C 56.55, H 4.75. Found: C 56.31, H 4.82.

Diastereoselective synthesis of 5b. A similar procedure as described for the diastereoselctive preparation of **5a** was followed. Compound **9** (1 g, 3.37 mmol) in 25 mL of Et_2O, KO^tBu (31 mg, 0.28 mmol), 2/1 (v/v) mixture of ^tBuOH and Et_2O (75 mL), *tert*-butyl acrylate (475 mg, 3.7 mmol), reaction time 6.5 h, Flash column chromatogryphy (silica gel, hexane/EtOAc 5/1) gave **5b** as light yellow solid (yield: 1.17 g, 82%).

Data for 5b: R_f = 0.11 (silica gel, hexane/EtOAc 5/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H, $(CH_3)_3$), 1.52 (s, 3H, CH_3), 1.83-1.95 (m, 1H, CH_2), 2.01-2.18 (m, 3H, CH_2), 2.67-2.88 (m, 3H, CH_2), 3.16-3.29 (m, 1H, CH_2), 5.25-5.33 (m, 2H, *benzene ring proton*), 5.38-5.45 (m, 2H, *benzene ring proton*). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 22.2, 26.6, 28.1, 30.4, 35.4, 36.3, 49.9, 80.9, 90.5, 90.8, 92.1, 92.9, 109.1, 112, 171.5, 208.4, 232.7. IR bands(ν): 1941s, 1865s, 1715s (br), 1448w, 1326w, 1289w, 1147m, 984w, 961w, 848w, 779w, 666s, 626s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 424.01 (20) $[M]^+$, 447.01 (40) $[M+Na]^+$, 452.97 (45) $[M+K]^+$, 561.04 (100) $[M+TFA+Na]^+$. Anal. calcd. for $C_{21}H_{24}CrO_6$: C 59.43, H 5.70. Found: C 59.53, H 5.67.



Ester hydrolysis of 5a/6a mixture and 5b/6b mixture. To a stirred solution of the mixture **5a** and **6a** (1.5 g, 3.92 mmol) in MeOH (40 mL), 40 mL of aqueous 1M NaOH was added.

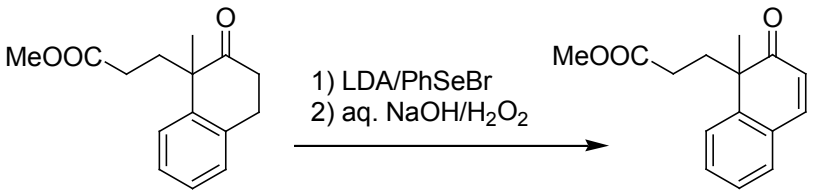
The mixture was de-oxygenated by bubbling N_2 for 10 min and stirred 3 h at room temperature. The reaction mixture was then diluted with distilled water (50 mL) and the aqueous layer was washed with Et_2O (2×30 mL). The aqueous layer was acidified with 1M HCl up to ~P^H 2 and extracted with EtOAc (2×60 mL). The combined organic phase was washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel. Using EtOAc/MeOH mixture (25/1→20/1) as eluent, **8** (650 mg) was obtained as yellow crystalline solid. Then using EtOAc/MeOH/AcOH mixture (20:1:0.02) as eluent **7** (340 mg) was obtained as light yellow solid. Combined yield after flash column chromatography was 990 mg, 69%.

For the ester hydrolysis of **5b** and **6b** mixture, similar procedure as used for **5a** and **6a** mixture was followed accept instead of only MeOH, 1/1 (v/v) mixture of MeOH/THF was used and the reaction time was 12 h at room temperature. Combined yield of **7** and **8** was 305 mg (88%) from 400 mg of **5b** and **6b** mixture.

Ester hydrolysis of the diastereomerically pure **5a** and **5b** were carried out following the same procedure as described for the ester hydrolysis of their corresponding disatereomeric mixtures.

Data for carboxylic acid 7: R_f = 0.38 (silica gel, EtOAc/MeOH/AcOH 20/1/0.03). ^{1}H NMR (250 MHz, Acetone-d_6): δ (ppm) 1.53 (s, 3H, C*H*$_3$), 1.95-2.01 (m, 1H, C*H*$_2$), 2.12-2.25 (m, 3H, C*H*$_2$), 2.69-2.84 (m, 3H, C*H*$_2$), 3.34-3.45 (m, 1H, C*H*$_2$), 5.62-5.71 (m, 2H, *benzene ring proton*), 5.75-5.86 (m, 2H, *benzene ring proton*), 10.56 (s, br, 1H, COO*H*). ^{13}C NMR (400 MHz, Acetone-d_6): δ (ppm) 21.1, 25.9, 28.7, 34.8, 35.8, 49.9, 92.1, 92.5, 93.6, 94.4, 110.9, 113.7, 172.8, 207.6, 233.5. IR bands(ν): 2920w, 1959s, 1855s, 1702s, 1445w, 1421m, 1300w, 1217m, 1172m, 1065w, 990w, 831m (br), 670s, 631s cm^{-1}. ESI-MS (pos. detection mode): *m/z* (%): 390.88 (100) [M+Na]$^+$. Anal. calcd. for $C_{17}H_{16}CrO_6 \cdot H_2O$: C 52.85, H 4.70. Found: C 53.01, H 4.77.

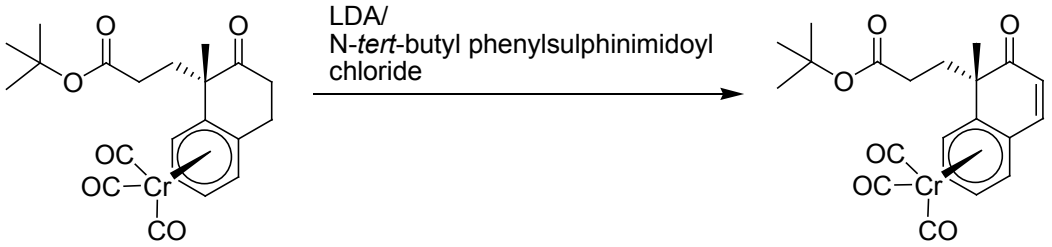
Data for carboxylic acid 8: R_f = 0.52 (silica gel, EtOAc). ^{1}H NMR (250 MHz, Acetopne-d_6): δ (ppm) 1.38 (s, 3H, C*H*$_3$), 2.20-2.44 (m, 3H, C*H*$_2$), 2.50-2.69 (m, 2H, C*H*$_2$), 2.79-2.99 (m, 2H, C*H*$_2$), 3.21-3.33 (m, 1H, C*H*$_2$), 5.51-5.57 (m, 2H, *benzene ring proton*), 5.79-5.85 (m, 1H, *benzene ring proton*), 5.94 (m, 1H, *benzene ring proton*), 10.55 (s, br, 1H, COO*H*). ^{13}C NMR (400 MHz, Acetone-d_6): δ (ppm) 25.2, 27.5, 33.4, 36.1, 49.1, 90.4, 91.6, 93.6, 95.7, 110.7, 115.4, 173.1, 208.1, 233.6. IR bands(v): 2941w, 1945s, 1846s (br), 1701s, 1313w, 1124w, 978w, 718w, 660s, 629s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 390.91 (100) $[M+Na]^+$. Anal. calcd. for $C_{17}H_{16}CrO_6$: C 55.44, H 4.38. Found: C 55.17, H 4.67.



4a **10**

Methyl ester 10. To a stirred solution of **4a** (250 mg, 1.01 mmol) in 20 mL of THF, lithium diisopropy amide (LDA) (0.76 mL of 2M solution in THF, 1.51 mmol) was added at –78 °C under N_2 atmosphere. After 30 min, PhSeBr (358 mg, 1.51 mmol) in 5 mL THF was added and the mixture was allowed to stir for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2×70 mL). The combined organic phase was washed with brine (1×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was dissolved in 15 mL of CH_2Cl_2, 0.24 mL of pyridine and 1.5 mL of 30% H_2O_2 was added successively and the mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with 150 mL of EtOAc. The organic phase was washed with 1M aqueous HCl, distilled water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 3/1) gave **10** as colourless oil (yield: 129 mg, 52%).

Data for 10: R_f = 0.29 (silica gel, hexane/EtOAc 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44 (s, 3H, C*H*$_3$), 1.75-1.85 (m, 1H, C*H*$_2$), 1.96-2.06 (m, 1H, C*H*$_2$), 2.18-2.25 (m, 1H, C*H*$_2$), 2.46-2.56 (m, 1H, C*H*$_2$), 3.52 (s, 3H, OC*H*$_3$), 6.17 (d, 1H, C*H*), 7.27-7.35 (m, 2H, *benzene ring protons*), 7.41-7.47 (m, 3H, C*H* and *benzene ring protons*). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 28.4, 29.7, 36.3, 50.7, 51.4, 125.3, 126.3, 129.6, 129.7, 130.3, 145.1, 145.2, 173.2, 203.3. IR bands(ν): 2950w, 1732s, 1654s, 1597w, 1436m, 1375w, 1296m, 1241m, 1195m, 1088w, 915w, 878s, 758s, 731m cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 266.97 (100) $[M+Na]^+$.

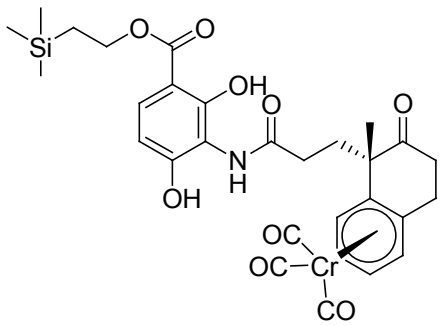


5b **12**

***tert*-Butyl ester 12.** To a solution of diisopropyl amine (116 mg, 1.15 mmol) in 2 mL THF, *n*-BuLi (0.57 mL of 1.6 M solution in hexane) was added slowly at −78 °C under N_2 atmosphere. The resulting mixture was stirred for 20 min. A solution of **5b** (350 mg, 0.82 mmol in 1.5 mL of THF) was added and the mixture was stirred further 20 min. Finally a solution of N-*tert*-butyl phenylsulfinimidoyl chloride (230 mg, 1.06 mmol) in 1.5 mL of THF was added to the reaction mixture and the color changed immediately to deep red. After 40 min, the reaction was quenched with aqueous *sat.* NH_4Cl solution and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 5/1→4/1) provided **12** as red colour liquid (yield: 146 mg, 42%).

Data for 12: R_f = 0.28 (silica gel, hexane/EtOAc 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H, C(C*H*$_3$)$_3$), 1.54 (s, 3H, C*H*$_3$), 1.92-2.20 (m, 4H, C*H*$_2$), 5.39-5.51 (m, 4H, *benzene*

ring protons), 6.17 (d, 1H, C*H*), 7.01 (d, 1H, C*H*). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 22.3, 28.2, 30.6, 41.1, 49.2, 80.7, 89.5, 90.7, 91.3, 92.5, 95.3, 115.4, 125.7, 142.3, 171.5, 199.3, 231.6. IR bands(ν): 2979w, 1957s, 1870s, 1719s, 1665m, 1613w, 1523w, 1455w, 1366m, 1241w, 1149s, 1129s, 912w, 839w, 656s, 619s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 444.94 (100) $[M+Na]^+$.

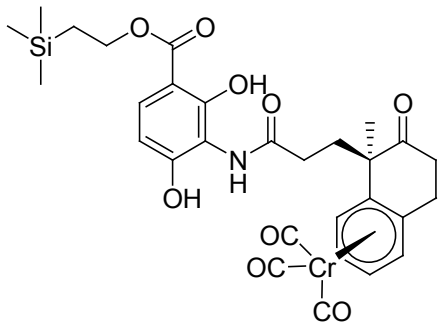


14a

Amide 14a. To a stirred solution of the carboxylic acid **7** (250 mg, 0.67 mmol) in 4 mL degassed DMF, HATU (645 mg, 2.10 mmol) and DIPEA (259 mg, 2.10 mmol) were added and the mixture was allowed to stir for 30 min under an argon atmosphere. 2-(trimethylsilyl)ethyl 3-amino-2,4-dihydroxybenzoate[1] (450 mg, 1.67 mmol) in 4 mL degassed DMF was then added and the mixture was stirred for 20 h at room temperature. The reaction mixture was then diluted with 30 mL of EtOAc and washed with 1M HCl, H_2O and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatography (silica gel, hexane/EtOAc 3/1→2/1) gave **14a** as yellow sticky solid (yield: 270 mg, 64%).

Data for 14a. R_f = 0.20 (silica gel, hexane/EtOAc 2.5/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.13 (m, 2H, CH$_2$-C*H*$_2$-Si), 1.55 (s, 3H, C*H*$_3$), 2.01-2.10 (m, 1H, C*H*$_2$), 2.26-2.42 (m, 3H, C*H*$_2$), 2.66-2.88 (m, 3H, C*H*$_2$), 3.17-3.25 (m, 1H, C*H*$_2$), 4.43 (m, 2H, C*H*$_2$-CH$_2$-Si), 5.20-5.28 (m, 2H, *benzene-Cr(CO)$_3$ protons*), 5.34-5.44 (m, 2H, *benzene-Cr(CO)$_3$ protons*), 6.47 (d, 1H, *benzene ring proton*), 7.55 (d, 1H, *benzene ring*

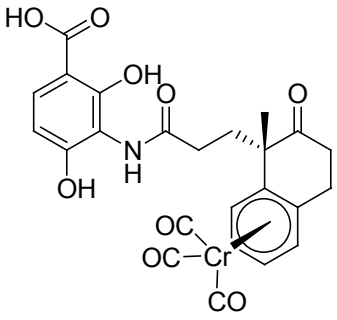
proton), 7.86 (s, 1H, N*H*), 10.71 (s, br, 1H, O*H*), 11.87 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) -1.46, 17.3, 23.1, 26.8, 32.1, 35.5, 36.3, 50.1, 63.9, 90.2, 91.1, 91.6, 93.2, 104.5, 109.1, 111.1, 111.9, 113.9, 127.6, 153.8, 154.4, 170.4, 172.1, 208.7, 232.5. IR bands(ν): 2956w, 1958s, 1870s, 1714m, 1652m, 1595m, 1535m, 1454w, 1385m, 1328m, 1250s, 1146m, 1059w, 857m, 788w, 663m, 626s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 642.09 (40) $[M+Na]^+$, 626.30 (60) $[M+Na-H_2O]^+$.



14b

Amide 14b. A similar procedure as used for the synthesis of **14a** was followed except carboxylic acid **8** was used instead of **7**. Flash column chromatography (silica gel, hexane/EtOAc 1/1) gave **14b** as yellow sticky solid (yield: 240 mg, 57%).

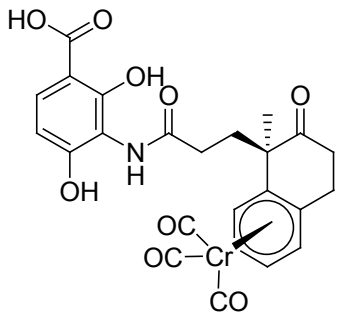
Data for 14b. R_f = 0.35 (silica gel, hexane/EtOAc 1/1). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.13 (m, 2H, CH_2-C*H*$_2$-Si), 1.38 (s, 3H, C*H*$_3$), 2.20-2.53 (m, 2H, C*H*$_2$), 2.64-2.84 (m, 3H, C*H*$_2$), 2.92-3.27 (m, 3H, C*H*$_2$), 4.43 (m, 2H, C*H*$_2$-CH_2-Si), 5.17-5.34 (m, 2H, *benzene-Cr(CO)$_3$ protons*), 5.49-5.64 (m, 2H, *benzene-Cr(CO)$_3$ protons*), 6.51 (d, 1H, *benzene ring proton*), 7.56 (d, 1H, *benzene ring proton*), 8.07 (s, 1H, N*H*), 10.94 (s, br, 1H, O*H*), 11.82 (s, 1H, O*H*). ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) -1.3, 17.3, 26.7, 27.3, 32.1, 33.1, 36.2, 49.1, 63.8, 89.7, 90.5, 91.8, 94.1, 104.6, 108.7, 111.1, 113.1, 114.1, 127.4, 153.9, 154.6, 170.4, 172.9, 209.1, 232.6. IR bands(ν): 2953w, 1957s, 1866s, 1713w, 1652m, 1595w, 1530m, 1457w, 1385m, 1328m, 1250s, 1145m, 1060w, 857m, 787w, 663m, 626s cm^{-1}. ESI-MS (pos. detection mode): *m*/*z* (%): 642.26 (60) $[M+Na]^+$.



15a

Bioorganometallic 15a. To a stirred solution of amide **14a** (270 mg, 0.43 mmol) in DMF (5 mL), tris(dimethylamino)sulfonium difluorotrimethyl-silicate (TASF) (240 mg, 0.87 mmol) was added at room temperature and the mixture was heated at 40 °C for 40 min. The reaction mixture was then cooled to room temperature; brine was added and extracted with EtOAc (3×40 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. Flash column chromatography of the resulting residue (silica gel, EtOAc/MeOH/AcOH 20/1/0.05) gave compound **15a** as yellow solid (yield: 178 mg, 79%).

Data for 15a. R_f = 0.40 (silica gel, EtOAc/MeOH/AcOH 20/1/0.05). ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.45 (s, 3H, C*H*$_3$), 1.87-1.94 (m, 1H, C*H*$_2$), 2.07-2.18 (m, 3H, C*H*$_2$), 2.54-2.83 (m, 3H, C*H*$_2$), 3.21-3.36 (m, 1H, C*H*$_2$), 5.68-6.01 (m, 4H, *benzene-Cr(CO)$_3$ protons*), 6.40 (d, 1H, *benzene ring proton*), 7.54 (d, 1H, *benzene ring proton*), 9.01 (s, 1H, N*H*), 10.12 (s, br, 1H, O*H*). ^{13}C NMR (250 MHz, DMSO-d_6): δ (ppm) 21.5, 26.5, 31.1, 35.4, 35.8, 50.3, 93.5, 94.1, 94.8, 95.7, 106.1, 108.7, 111.9, 112.9, 114.1, 129.8, 159.1, 159.5, 171.2, 172.6, 209.1, 234.3. IR bands(ν): 1958s, 1867s, 1709m, 1648m, 1536m, 1377w, 1236m, 1150w, 1058w, 789w, 665s, 627s cm^{-1}. ESI-MS (neg. detection mode): *m*/*z* (%): 517.89 (100) [M–H]$^-$. Anal. calcd. for $C_{24}H_{21}CrNO_9$: C 55.50, H 4.08, N 2.70. Found: C 55.77, H 4.23, N 2.54.



15b

Bioorganometallic 15b. A similar procedure as used for the synthesis of **15a** was followed. Flash column chromatography (silica gel, EtOAc/MeOH/AcOH 20/1/0.04) gave compound **15b** as yellow sticky solid (yield: 120 mg, 62%).

Data for 15b. R_f = 0.26 (silica gel, EtOAc/MeOH/AcOH 20/1/0.04). ^{1}H NMR (250 MHz, Acetone-d_6): δ (ppm) 1.41 (s, 3H, C*H*$_3$), 2.32-2.39 (m, 2H, C*H*$_2$), 2.62-2.97 (m, 5H, C*H*$_2$), 3.16-3.29 (m, 1H, C*H*$_2$), 5.53 (m, 2H, *benzene-Cr(CO)$_3$ protons*), 5.78 (m, 1H, *benzene-Cr(CO)$_3$ protons*), 5.99 (m, 1H, *benzene-Cr(CO)$_3$ protons*), 6.46 (d, 1H, *benzene ring proton*), 7.54 (d, 1H, *benzene ring proton*), 9.01 (s, 1H, N*H*), 10.51 (s, br, 1H, O*H*), 11.95 (s, br, 1H, O*H*). ^{13}C NMR (250 MHz, Acetone-d_6): δ (ppm) 24.9, 27.5, 31.4, 34.2, 35.9, 48.8, 90.3, 91.4, 93.9, 95.9, 103.8, 110.3, 110.8, 114.1, 115.2, 127.8, 155.6, 156.2, 171.7, 173.8, 208.5, 233.5. IR bands(ν): 2926w, 1953s, 1861s, 1712m, 1650s (br), 1533m, 1381m, 1296w, 1237m (br), 1152w, 1057w, 791w, 664s, 627s cm^{-1}. ESI-MS (neg. detection mode): *m*/*z* (%): 517.85 (100) [M–H]$^-$. Anal. calcd. for $C_{24}H_{21}CrNO_9 \cdot 0.5H_2O$: C 54.54, H 4.19, N 2.65. Found: C 55.01, H 3.97, N 2.89.

5) H-bonding interactions and conformational difference in the cyclohexanone ring in 7 and 8.

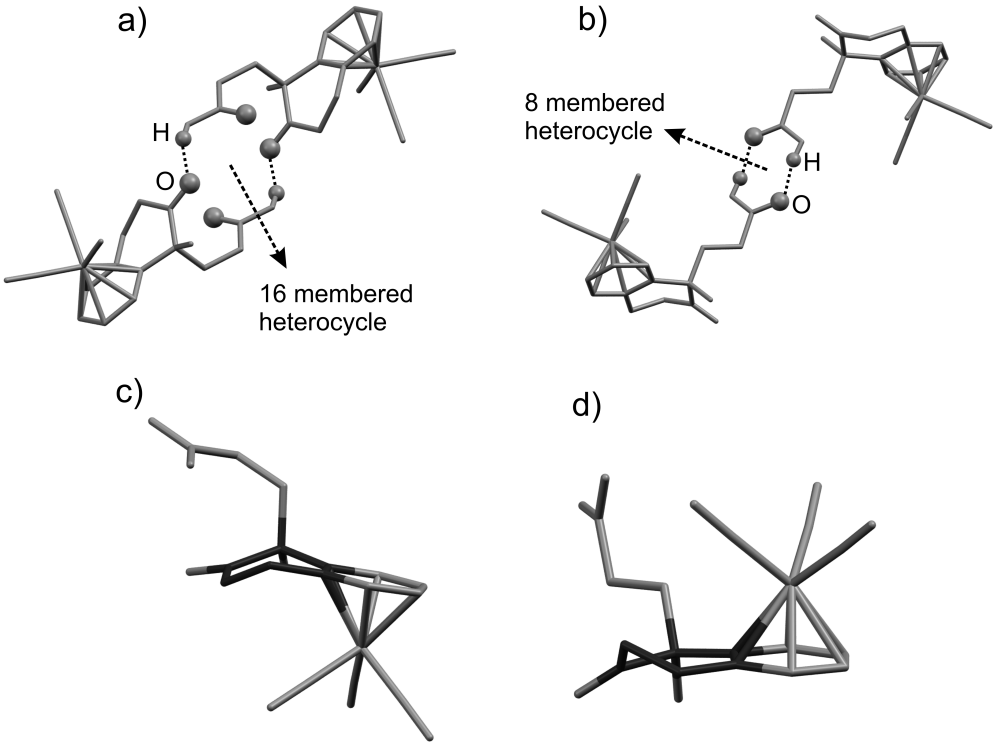
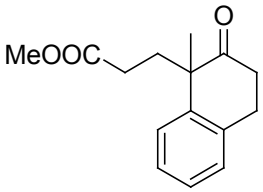


Figure S1. Dimeric arrangements of carboxylic acids **7** (a) and **8** (b), showing the intermolecular H-bonding interactions. Conformational difference of the cyclohexanone ring in carboxylic acid **7** (c) and **8** (d). Except OH, hydrogen atoms are omitted for clarity.

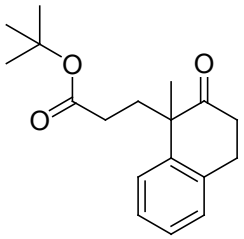
6) NMR Spectra of compounds.



4a

^{1}H, $CDCl_3$, 400MHz

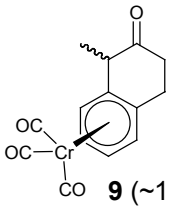
^{13}C, $CDCl_3$, 400MHz



4b

^{1}H, $CDCl_3$, 250 MHz

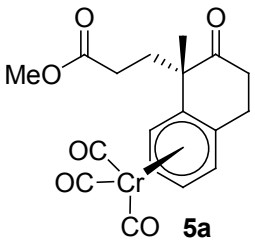
^{13}C, $CDCl_3$, 250 MHz



9 (~1:1 mixture of two diastereomers)

^{1}H, $CDCl_3$, 250 MHz

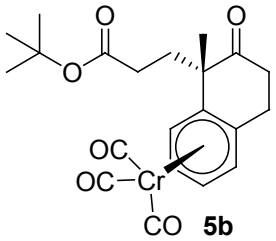
^{13}C, $CDCl_3$, 250 MHz



5a

^{1}H, $CDCl_3$, 250 MHz

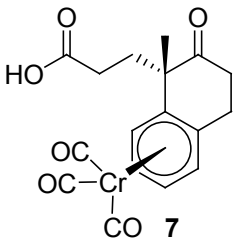
^{13}C, $CDCl_3$, 250 MHz



5b

^{1}H, $CDCl_3$, 250 MHz

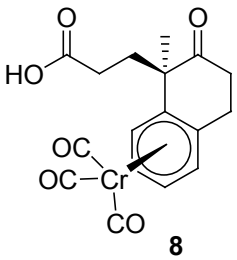
^{13}C, $CDCl_3$, 250 MHz



7

^{1}H, Acetone-d_6, 250 MHz

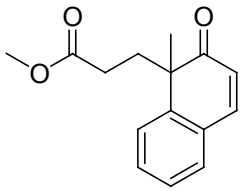
^{13}C, Acetone-d_6, 250 MHz



8

^{1}H, Acetone-d_6, 250 MHz

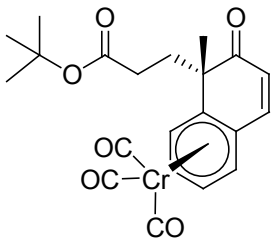
^{13}C, Acetone-d_6, 250 MHz



10

^{1}H, $CDCl_3$, 400MHz

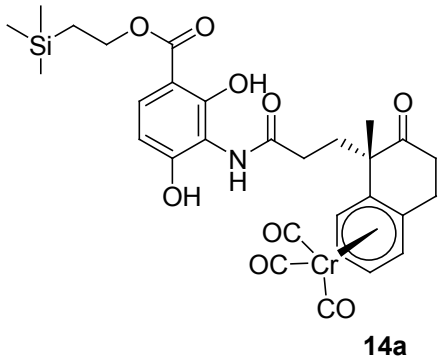
^{13}C, $CDCl_3$, 400MHz



12

^{1}H, $CDCl_3$, 400MHz

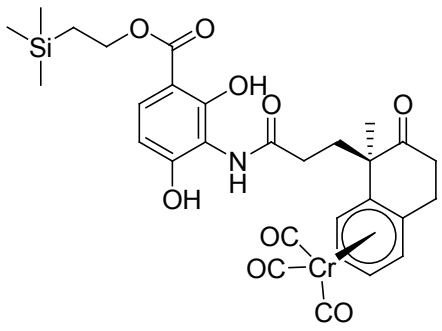
^{13}C, $CDCl_3$, 400MHz



14a

^{1}H, $CDCl_3$, 400MHz

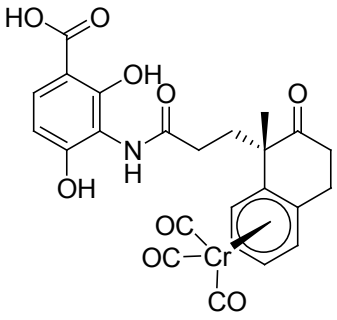
^{13}C, $CDCl_3$, 400MHz



14b

^{1}H, $CDCl_3$, 400MHz

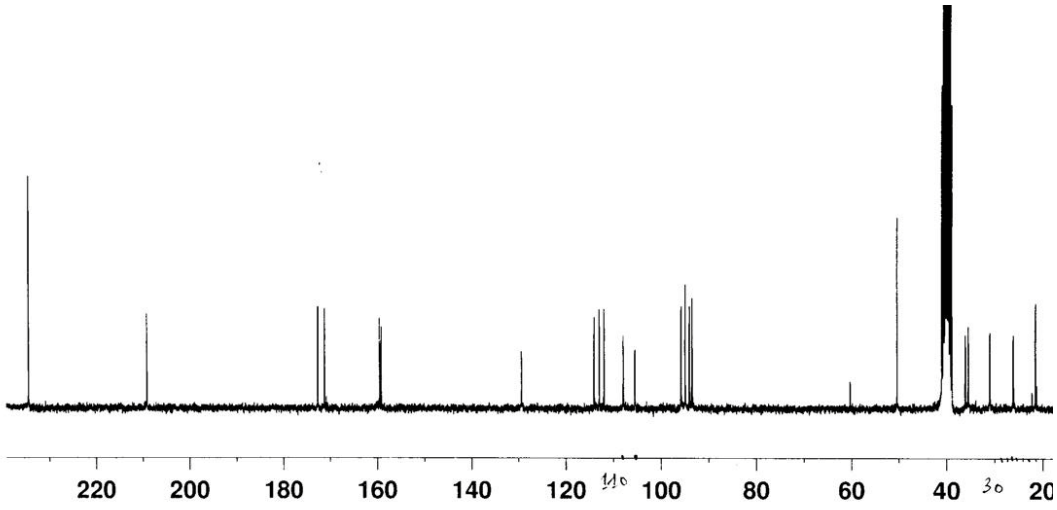
^{13}C, $CDCl_3$, 400MHz

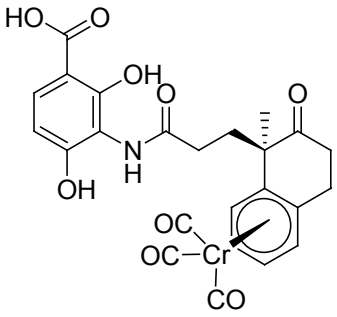


15a

^{1}H, DMSO-d$_6$, 250 MHz

^{13}C, DMSO-d$_6$, 250 MHz





15b

^{1}H, Acetone-d_6, 250 MHz

^{13}C, Acetone-d_6, 250 MHz

7) References.

1. K. C. Nicolaou, G. S. Tria and D. J. Edmonds, *Angew. Chem. Int. Ed.*, 2008, **47**, 1780-1783.
2. G. M. Sheldrick, (1997), University of Göttingen, Germany.
3. A. L. Spek, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1990, **46**, C34.