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Synthesis of an Analog of the Cytotoxic Marine Diterpene Helioporin C Exploiting Arene-Cr(CO)$_3$ Chemistry

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Abstract: The total synthesis of a racemic analog of putative helioporin C has been achieved. Starting from η^6-5,6-dimethoxytetralin-Cr(CO)$_3$ the target molecule was obtained in 8 steps in an overall yield of ca. 17%. The synthesis is based on the specific reactivity and stereochemistry of the arene-Cr(CO)$_3$ substructure and involves highly regio- and diastereoselective benzylic deprotonation/alkylation steps. The sidechain stereocenter was diastereoselectively established under substrate control by Michael addition of a benzylic lithiated complex to ethylidene Meldrum's acid. The relative configuration of the addition product was confirmed by X-ray crystal structure analysis. By correlation of NMR spectroscopic data of the marine diterpene helioporin C with a number of stereochemically defined synthetic analogs it was shown that the original stereochemical assignment for this compound has to be revised. The configuration of helioporin C (**23**) was established to be identical with that of the *seco*-pseudopterosins.

The helioporins are a group of bioactive diterpenes isolated from the blue coral *Heliopora coerulea* by T. Higa and coworkers in 1993.[1] These metabolites, which all share a characteristic benzodioxole substructure, are structurally closely related to the anti-inflammatory pseudopterosins.[2,3] In contrast to the latter, the helioporins exhibit antiviral or cytotoxic properties.[1] While the constitution of these compounds clearly followed from their spectroscopic data (NMR, IR, HRMS) their stereochemistry could be assessed only by indirect means: (1) chemical correlation experiments showed that all helioporins belong to the same stereochemical series; (2) the relative configuration of helioporin E was judged by comparison of its NMR data with those of the pseudopterosins. The structures of helioporins A-G as originally assigned by Higa (**1**-**7**) are given in Figure 1.

We recently reported an enantioselective total synthesis of **4**.[4] By doing so, we were able to show that the marine diterpene helioporin D is not represented by structure **4** as the spectroscopic data of **4** did not match those of the natural product.[5,6] Nevertheless, the independently synthesized epimeric compound **8** was found to be identical with natural helioporin D.[5] It was thus unequivocally established that helioporin D (**8**) belongs to the same stereochemical series as the *seco*-pseudopterosins, both having a

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trans configuration of the two benzylic sidechains. The comparison of the molecular rotation of the synthetic compound **8** and natural helioporin D confirmed the presumed absolute configuration of the latter.[5] Of course, this result raised the question whether the structures proposed for the other helioporins have to be revised as well.

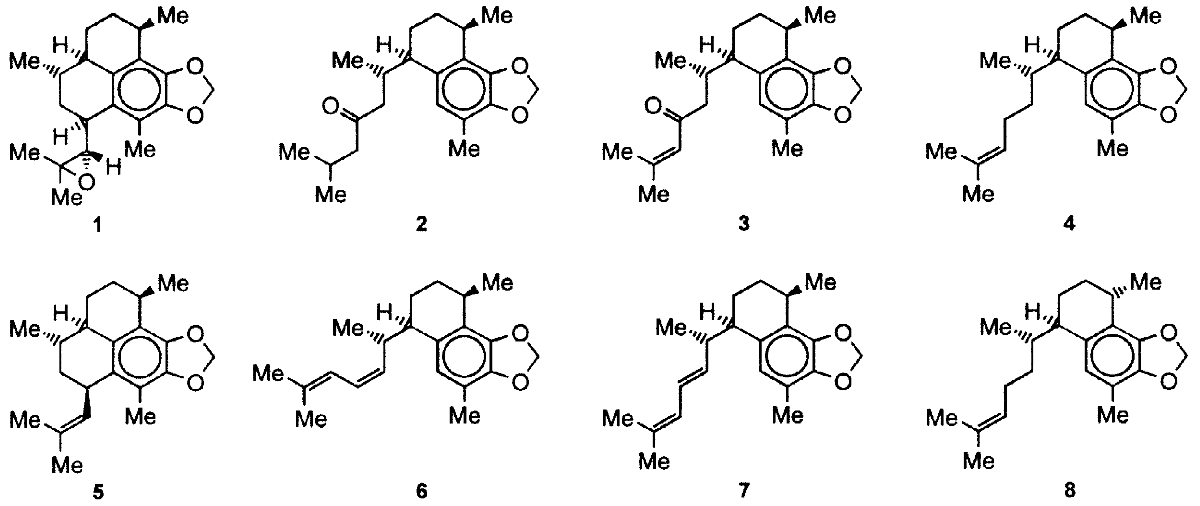
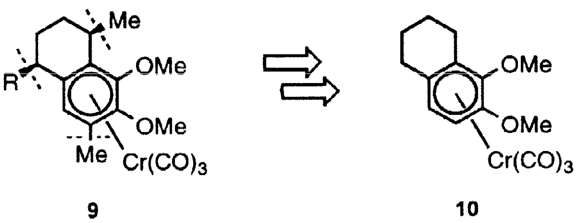


Figure 1: Structures of the helioporins A-G according to Higa (**1-7**) and the revised structure of helioporin D (**8**).

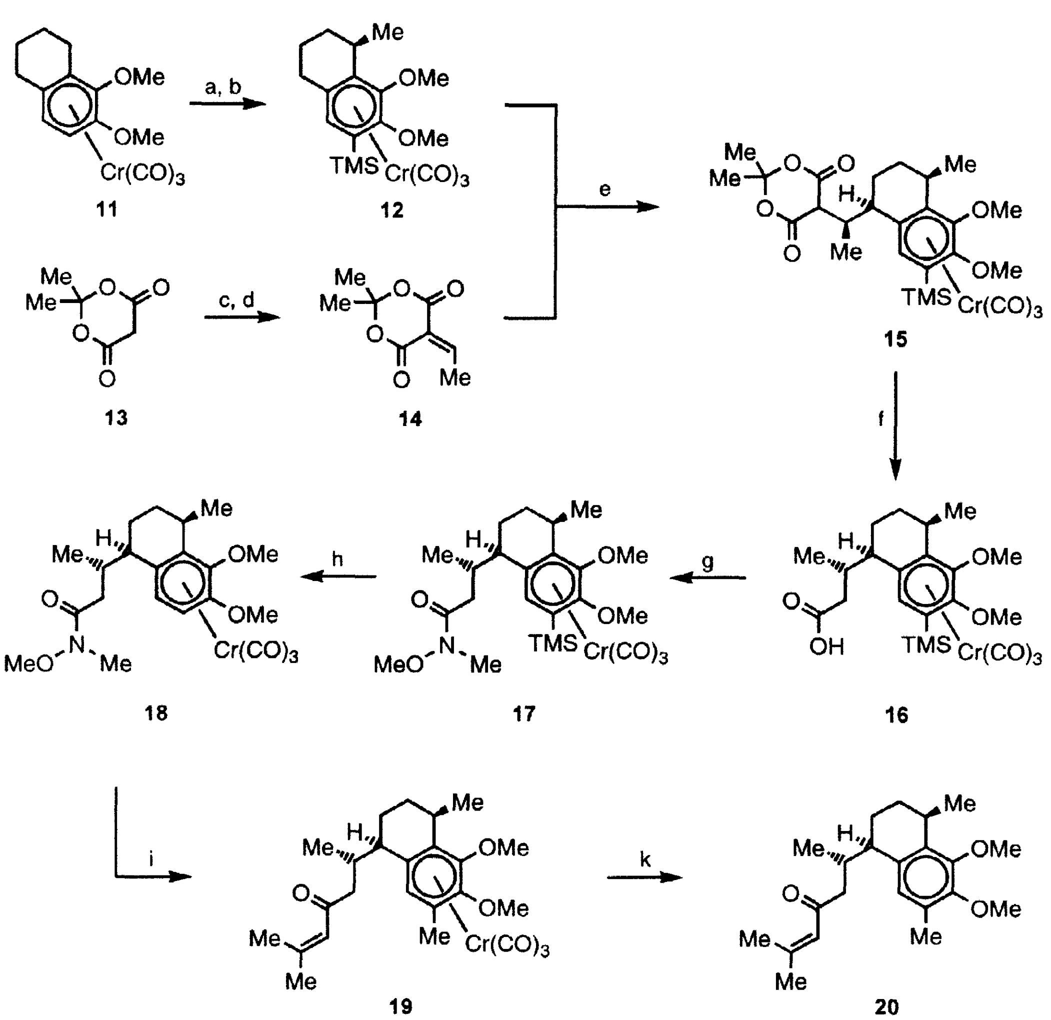
In this paper we report on an efficient diastereoselective synthesis of a compound closely related to **3**, the structure proposed for helioporin C. By correlation of NMR data we are able to show, that the stereostructure of helioporin C has also to be revised.

Our synthetic strategy is based on the utilization of the specific reactivity of arene-$Cr(CO)_3$ complexes.[7] As we previously described, 5,6-dimethoxytetralin derivatives of type **9** (with two *cis*-configurated benzylic sidechains) are regio- and diastereoselectively accessable from η^6-5,6-dimethoxytetralin-$Cr(CO)_3$ (**10**) by successive deprotonation/alkylation (Scheme 1).[4,8]



Scheme 1

The overall course of the synthesis is shown in Scheme 2.[9] The starting complex *rac*-**11** was obtained in 94% yield by direct complexation of 5,6-dimethoxytetralin. The conversion of *rac*-**11** to *rac*-**12** was carried out by arylic silylation followed by regio- and diastereoselective benzylic methylation as previously described.[4,8] Benzylic deprotonation of *rac*-**12** (*s*-BuLi, THF) and Michael addition of the lithiated intermediate to ethylidene Meldrum's acid (**14**)[10] gave complex *rac*-**15** in 40-60% yield as a single diastereomer. The relative configuration of *rac*-**15** was determined by X-ray crystal structure analysis (Figure 2). Thus, the two new chirality centers were established in a single transformation with the desired relative configuration. Acidic cleavage of the cyclic diester with concomitant monodecarboxylation, conversion of the resulting acid *rac*-**16** to the *Weinreb* amide *rac*-**17**,[11] and desilylation afforded complex *rac*-**18**. Treatment of *rac*-**18** with an excess of *iso*-butenyllithium followed by the addition of iodomethane gave the complex *rac*-**19** in good yield. This way, the completion of the helioporin C sidechain and the introduction of the arylic methyl group were efficiently achieved in a single step. Finally, oxidative decomplexation of *rac*-**19** afforded *rac*-**20**, the dimethoxy analog of putative helioporin C (**3**).



Scheme 2: a) *n*-BuLi, THF, TMSCl (94%); b) *n*-BuLi, THF, MeI (94%); c) $Me_2NCH(OMe)_2$, NaOMe, THF (75%); d) MeMgI, THF, Et_2O (97%); e) *s*-BuLi, THF, -65°C → -20°C, 45 min, then addition of **14** in THF at -60°C → 25°C, 1 h (40-60%); f) HCl, THF, H_2O, 65°C, 40 h (79%); g) MeONHMe·HCl, CBr_4, PPh_3, pyridine, CH_2Cl_2, 25°C, 35 min (76%); h) TBAF, THF, 0°C (94%); i) *iso*-butenyllithium (3.4 eq.), THF, -30°C → 10°C, 30 min, then MeI, -20°C → 0°C, 30 min (71%); k) air, sunlight, Et_2O (100%).

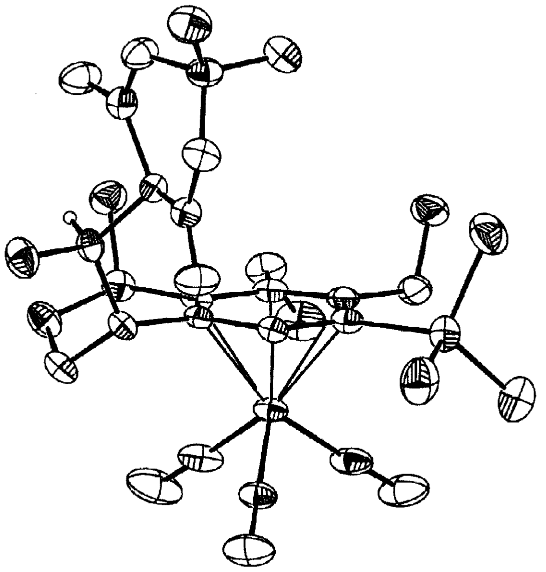


Figure 2: Structure of crystalline *rac*-**15**.

Within the above described synthetic sequence, the highly diastereoselective Michael addition (*rac*-**12** → *rac*-**15**) deserves particular attention. The stereoselectivity of this purely substrate controlled reaction cannot be explained using the common models for stereoselective Michael additions.[12] However, one can expect the two pro-chirality centers of the reactants to approach each other from parallel planes in such a fashion that repulsive steric interactions are minimized. While two transition states (**A** and **B**) should be possible based on the inspection of molecular models, only transition state **A** would lead to the product with the observed configuration (**15**). We postulate that the obvious preference of **A** is due to a secondary orbital interaction (attraction of two centers with opposite partial charges) as depicted in Figure 3.

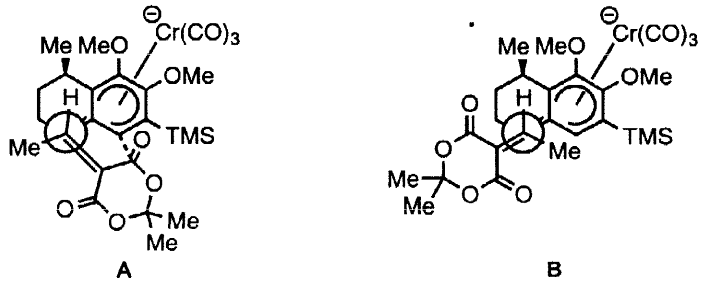
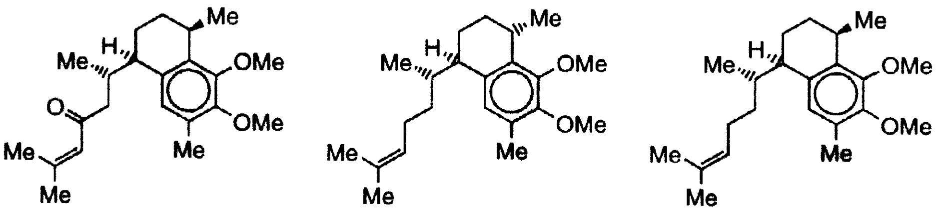


Figure 3: Possible transition states of the Michael addition.

Having achieved the synthesis of *rac*-**20**, a close analog of putative helioporin C, we were able to probe the stereochemistry of the natural product by correlation of NMR data. As the basis of our correlation we used the data of the synthetic compounds **4**,[4] **8**,[1,5] **20**,[10] **21**,[13] and **22**[4] (Figure 4). By analyzing the ^{1}H and ^{13}C NMR data of these compounds it became evident that the (selected) signals given in Table 1 are especially suited to distinguish the two stereochemical series.

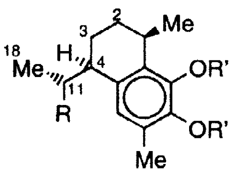
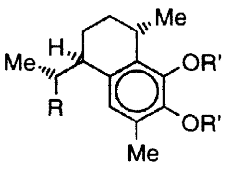


20 **21** **22**

Figure 4: Synthetic products **20**, **21** and **22**.

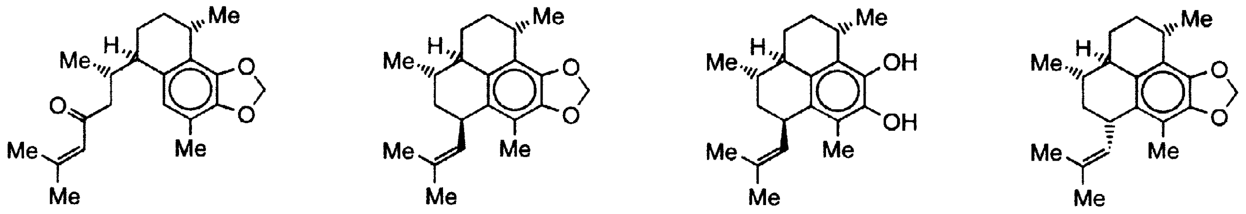
In the *cis* series (**4**, **20**, and **22**) the signal of the proton at C4[14] is always shifted to a lower field compared to the *trans* series (**8** and **21**). In addition, we found significant differences in the pattern of the ^{1}H NMR signals of the protons at C2 and C3: in the *cis* series these appear as a single multiplet in the range between 1.5 and 1.8 ppm, whereas in the *trans* series the signals of the protons at C2 show up above and below this area. The ^{13}C NMR spectra revealed three signals which are significantly shifted to a higher field in the *cis* series.

Table 1:
Selected ^{1}H and ^{13}C NMR data of natural helioporin C (**23**) and the synthesized compounds **4**, **8**, **20**, **21**, and **22**.

	cis series			*trans* series		
						
	22	**4**	**20**	**21**	helioporin D (**8**)	helioporin C (**23**)
H-C2	1.52 - 1.76	1.54 - 1.80	1.54 - 1.70	1.30 - 1.52	1.15 - 1.49	1.38
H'-C2				1.75 - 1.88	1.92 - 2.14	1.99
H-C3					1.74 - 1.84	1.76
H'-C3				1.64 - 1.67	1.50 - 1.62	1.60
H-C4	2.80	2.71	2.76	2.65	2.66	2.54
C3	16.5	17.7	17.3	18.3	20.5	21.1
C11	35.8	35.7	32.7	38.8	37.3	34.2
C18	15.9	14.7	15.8	16.3	15.6	16.4

As Table 1 suggests, these characteristics seem to be almost invariant to structural changes in the sidechain and the oxygen substituents. By comparing the NMR data of natural helioporin C[1,6] with those of the synthetic compounds discussed it became immediately apparent that helioporin C must belong to the *trans* series and is represented by structure **23** (Figure 5). This supports the assumption that all tricyclic helioporins have a *trans* configuration of the benzylic sidechains in common. However, the configuration at the additional stereocenter of the tetracyclic helioporins (A and E) remained open. As we previously proved, the spectroscopic data of **24**, which is derived from the pseudopterosin A aglycone

(**25**), do not match those of natural helioporin E.[5] Considering Higa's finding that all helioporins have the same relative configuration at the three stereocenters present in the tricyclic compounds, we postulate that helioporin E is correctly described by formula **26** which would be the only possible diastereomer left. This would be completely consistent with Higa's chemical correlation.[1] In addition, Corey and Lazerwith have recently demonstrated that the cyclization of helioporin G type substrates may lead to products having the same stereochemistry as **26**.[15]



23 **24** **25** **26**

Figure 5

In conclusion, we have achieved an efficient synthesis of the helioporin C analog *rac*-**20**. In contrast to our previous work, this synthesis relies on a remarkable substrate controlled process to introduce the stereocenter of the sidechain. As an additional outcome of this work, we have provided strong evidence that the stereostructure of helioporin C and probably of all other helioporins has to be revised. In contrast to the original assignment, the tricyclic helioporins all seem to have the same relative and absolute configuration as the *seco*-pseudopterosins.[2] It would be interesting to prove the suggested structure for helioporin E by means of total synthesis.

EXPERIMENTAL

General methods: Manipulations involving air sensitive compounds were carried out in anhydrous solvents under an argon atmosphere using *Schlenk* and syringe techniques. IR: *Nicolet* Magna FT-IR. ^{1}H NMR and ^{13}C NMR spectra: *Bruker* AM 270 or AM 400. Preparative thin layer chromatography (PTLC): Chromatotron *Harrison Research*.

(4aSR)-Tricarbonyl-(η^6-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene)-chromium(0) (*rac*-**11**): In a flame dried 250 ml *Schlenk* flask equipped with reflux condenser and Hg-bubbler 5,6-dimethoxytetralin (4.50 g, 23.4 mmol) and chromium hexacarbonyl (5.15 g, 23.4 mmol) were dissolved in 120 ml of anhydrous di-*n*-butyl ether. The apparatus was evacuated and flushed with argon several times and then 12 ml of anhydrous THF was added with a syringe. The mixture was stirred under reflux for 2 d. Carbon monoxide was removed from time to time by flushing the apparatus with argon. The yellow solution was cooled to room temp. and concentrated under reduced pressure. The residue was dissolved in EtOAc and filtered through silica gel. Evaporation of the solvent in vacuo and recrystallization from *n*-hexane/EtOAc gave 7.24 g (94 %) of the chromium complex *rac*-**11** in the form of yellow crystals. m.p.: 84°C; IR

(ATR) = 2942w, 2863w, 1944s, 1853s, 1533w, 1474m, 1449m, 1396m, 1277m, 1087m, 1037m, 999m, 834w, 670m; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.64 - 1.83 (m, 3H, H-C2, H-C3), 1.83 - 1.96 (m, 1H, H'-C3), 2.44 - 2.58 (m, 2H, H-C1), 2.73 (dt, 1H, J_1 = 18.0 Hz, J_2 = 6.5 Hz, H-C4), 2.82 (dt, 1H, J_1 = 18.0 Hz, J_2 = 6.5 Hz, H'-C4), 3.82 (s, 3H, ^1J(CH) = 120 Hz, OCH_3-C6), 3.88 (s, 3H, ^1J(CH) = 120 Hz, OCH_3-C5), 5.08 (d, 1H, J = 7.0 Hz, ^1J(CH) = 150 Hz, H-C7), 5.30 (d, 1H, J = 7.0 Hz, ^1J(CH) = 150 Hz, H-C8); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ = 21.5 (t, C2/C3), 21.7 (t, C2/C3), 23.5 (t, C4), 27.8 (t, C1), 56.1 (q, OCH_3-C6), 65.0 (q, OCH_3-C5), 74.0 (d, C7), 91.9 (d, C8), 101.7 (s, C8a), 110.1 (s, C4a), 128.4 (s, C5), 135.3 (s, C6), 234.6 (s, CO); $C_{15}H_{16}CrO_5$: calcd. C 54.88, H 4.91; found C 54.72, H 5.00.

(4RS,4aSR)-Tricarbonyl-(η^6-5,6-dimethoxy-7-trimethylsilanyl-1,2,3,4-tetrahydronaphthalene)-chromium(0): The complex *rac*-**11** (8.00 g, 24.3 mmol) was dissolved in 200 ml of anhydrous THF and cooled to -60°C. *n*-Butyllithium (16.0 ml, 25.6 mmol, 1.05 eq., 1.6 M in *n*-hexane) was added and the mixture was allowed to warm to -30°C over a period of 90 min. The solution turned from yellow to orange. Then TMSCl (6.0 ml, 47 mmol, 1.9 eq.) was added and the solution was stirred for 3 h at -30 to 0°C (TLC shows complete conversion). The mixture was diluted with *n*-hexane, transferred to a separatory funnel and washed with water and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (*n*-hexane/EtOAc = 10/1) to give 9.20 g (94 %) of the silylated complex as yellow crystals. m.p.: 90°C; IR (ATR) = 2946m, 2865w, 1948s, 1866s, 1506w, 1446m, 1374m, 1356m, 1316m, 1250m, 1238m, 1092w, 1029m, 840m, 660m; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.34 (s, $SiMe_3$), 1.62 - 1.78 (m, 3H, H-C2, H-C3), 1.82 - 1.95 (m, 1H, H'-C3), 2.42 - 2.58 (m, 2H, H-C1), 2.72 (dt, 1H, J_1 = 17.0 Hz, J_2 = 6.5 Hz, H-C4), 2.86 (dt, J_1 = 17.0 Hz, J_2 = 6.5 Hz, 1H, H'-C4), 3.81 (s, 3H, ^1J(CH) = 144 Hz, OCH_3-C5), 3.83 (s, 3H, ^1J(CH) = 144 Hz, OCH_3-C6), 5.17 (s, 1H, ^1J(CH) = 171 Hz, H-C8); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ = -0.2 (q, $SiMe_3$), 21.6, 21.8, 23.3 (each t, C2, C3, C4), 27.9 (t, C1), 61.3 (q, OCH_3-C6), 64.1 (q, OCH_3-C5), 91.6 (s, C7), 98.0 (d, C8), 103.6 (s, C8a), 110.0 (s, C4a), 130.9 (s, C5), 139.7 (s, C6), 234.4 (s, CO); $C_{18}H_{24}CrO_5Si$: calcd. C 53.99, H 6.04; found C 53.84, H 5.99.

(4RS,4aSR)-Tricarbonyl-(η^6-5,6-dimethoxy-4-methyl-7-trimethylsilanyl-1,2,3,4-tetrahydronaphthalene)-chromium(0) (*rac*-**12**): The silylated complex (9.20 g, 22.6 mmol) and HMPA (6 ml) were dissolved in 200 ml of anhydrous THF. *n*-Butyllithium (17.5 ml, 28 mmol, 1.2 eq., 1.6 M in *n*-hexane) was added at -50°C. The reaction mixture was stirred at -50°C for 10 min and then at 0°C for 1 h. After cooling the now orange mixture to -25°C iodomethane (3.0 ml, 48 mmol, 2.1 eq.) was added and the solution was allowed to warm to 0°C and stirred at this temp. for 2 h. The mixture was diluted with *n*-hexane/EtOAc = 1/1, transferred to a separatory funnel and washed with HCl (2N), water, and brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were then dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (*n*-hexane/EE = 10/1) to give 8.94 g (94 %) of *rac*-**12** as a single diastereomer in the form of yellow crystals. m.p.: 154°C; IR (ATR) = 2946m, 1948s, 1870s, 1507w, 1444m, 1371m, 1355w, 1308m, 1297m, 1251m, 1238m, 1021m, 867m, 842m, 672m; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.36 (s, 9 H, $SiMe_3$), 1.31 (d, 3H, J = 7.0 Hz, Me-C4), 1.63 - 1.79 (m, 3H, H-C2, H-C3), 1.90 - 2.04 (m, 1H, H'-C3), 2.45 - 2.54 (m, 2H, H-C1), 3.14 - 3.24 (m, 1H, H-C4), 3.76 (s, 3H, ^1J(CH) = 146 Hz, OCH_3-C6), 3.85 (s,

3H, ^1J(CH) = 146 Hz, OCH$_3$-C5), 5.25 (s, ^1J(CH) = 146 Hz, H-C8); ^{13}C NMR (67.7 MHz, CDCl$_3$) δ = -0.45 (q, SiMe$_3$), 16.8 (t, C2), 20.9 (q, Me-C4), 26.8 (t, C1), 27.8 (d, C4), 28.4 (t, C3), 60.5 (q, OCH$_3$-C6), 65.2 (q, OCH$_3$-C5), 90.7 (s, C7), 98.9 (d, C8), 101.8 (s, C8a), 117.3 (s, C4a), 131.9 (s, C5), 139.5 (s, C6), 234.0 (s, CO); $C_{19}H_{26}CrO_5Si$: calcd. C 55.06, H 6.32; found C 54.78, H 6.43.

(1RS,1'SR,4RS,4aSR)-Tricarbonyl-[η^6-1-(1-(2,2-dimethyl-[1,3]dioxane-4,6-dion-5-yl)-ethyl)-5,6-dimethoxy-4-methyl-7-trimethylsilanyl-1,2,3,4-tetrahydronaphthalene]-chromium(0) (*rac*-**15**): In a 10 ml *Schlenk* tube the complex *rac*-**12** (100 mg, 0.24 mmol) was dissolved in 2 ml of anhydrous THF and cooled to -65°C. *s*-Butyllithium (200 µl, 0.27 mmol, 1.1 eq., 1.35 M in cyclohexane/*n*-hexane) was added and the mixture was allowed to warm to -20°C over a period of 45 min. The initial yellow solution turned orange. A second *Schlenk* tube was charged with freshly *kugelrohr* distilled 5-ethylidene-2,2-dimethyl-[1,3]dioxane-4,6-dione (**14**) (50 mg, 0.29 mmol, 1.2 eq.) in 0.5 ml of anhydrous THF. The solution of **14** was transferred to the deprotonated complex via cannula at -60°C. The colour of the reaction mixture changed back to yellow. The solution was warmed to room temp. over a period of 1 h and then diluted with 25 ml of *n*-hexane/EtOAc = 4/1 and transferred to a separatory funnel. The mixture was washed with NH$_4$Cl (satd.), water, and brine, dried (MgSO$_4$), and concentrated in vacuo. The crude product was separated from remaining starting material by flash chromatography (*n*-hexane/EtOAc = 4/1, then MTB ether/dichloromethane = 4/1) to give 68 mg (48 %) of *rac*-**15** in the form of yellow crystals. m.p.: 140°C; IR (ATR) = 2954w, 2878w, 1945s, 1882s, 1854s, 1777w, 1744m, 1373m, 1294m, 1249w, 1209w, 1070w, 1024m, 1000w, 841m, 666m; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.31 (s, 9H, SiMe$_3$), 1.10 (d, 3H, J = 7.0 Hz, H-C2'), 1.37 (d, 3H, J = 7.0 Hz, Me-C4), 1.47 - 1.58 (m, 1H, H-C3), 1.69 (s, 3H, C(CH$_3$)$_2$), 1.77 (s, 3H, C(CH$_3$)$_2$), 1.75 - 1.84 (m, 1H, H-C2), 1.88 - 1.96 (m, 1H, H'-C2), 2.19 - 2.28 (m, 1H, H'-C3), 2.74 - 2.88 (m, 2H, H-C1, H-C1'), 3.25 (qd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz, H-C4), 3.53 (d, 1H, J = 2.0 Hz, H-C(COOR)$_2$), 3.79 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 5.44 (s, 1H, H-C8); ^{13}C NMR (67.7 MHz, CDCl$_3$) δ = 0.0 (q, SiMe$_3$), 14.3 (q, C2'), 24.4 (q, Me-C4), 24.9 (t, C2), 25.1 (t, C3), 26.7 (d, C4), 27.3 (q, CH$_3$-C(OCOR)$_2$), 28.1 (q, C'H$_3$-C(OCOR)$_2$), 36.8 (d, C1'), 39.1 (d, C1), 48.7 (d, C(COOR)$_2$), 60.2 (q, OCH$_3$-C6), 65.6 (q, OCH$_3$-C5), 88.7 (s, C7), 98.3 (d, C8), 104.8 (s, C8a), 106.8 (s, C(OCOR)$_2$), 117.6 (s, C4a), 131.1 (s, C5), 140.3 (s, C6), 164.4 (s, RCOOR'), 165.7 (s, RCOOR'), 233.6 (s, CO); HRMS calcd. for $C_{27}H_{36}CrO_9Si$: 584.1534; found: 584.1530; $C_{27}H_{36}CrO_9Si$: calcd. C 55.47, H 6.21; found C 55.34, H 6.07; X-ray crystal structure analysis of *rac*-**15**: STOE STADI 4 diffractometer, MoK$_\alpha$ radiation, 298 K; $C_{28}H_{38}Cl_2CrO_9Si$, triclinic, space group P-1, a = 7.6560(10) Å, b = 13.243(2) Å, c = 16.349(3) Å, α = 82.28(2)°, β = 89.593(14)°, γ = 87.12(2)°, V = 1640.6(5) Å^3, Z = 2, ρ_{calc} = 1.355 g/cm^3; 4283 independent reflections, of which 3853 were used, R = 0.0486, R$_W$ = 0.1066.[16]

(1RS,3'SR,4RS,4aSR)-Tricarbonyl-[η^6-3-(5,6-dimethoxy-4-methyl-7-trimethylsilanyl-1,2,3,4-tetrahydronaphthalen-1-yl)-butyric acid]-chromium(0) (*rac*-**16**): In a 100 ml flask equipped with a reflux condenser and a Hg-bubbler the complex *rac*-**15** (300 mg, 513 mmol) was dissolved in 30 ml of THF and 15 ml of HCl (2N). The mixture was stirred at 70°C for 40 h. The solution was diluted with *n*-hexane and transferred to a separatory funnel. It was washed with water and brine, dried (MgSO$_4$), and concentrated in vacuo. The crude product was purified by PTLC (*n*-hexane/EtOAc/HOAc = 5/5/0.1) and recrystallization from *n*-hexane/EtOAc to give 202 mg (79 %) of the carboxylic acid *rac*-**16**. m.p.: 136°C;

IR (ATR) = 2951m, 2876w, 1951s, 1870s, 1708m, 1453w, 1372m, 1356m, 1304m, 1251m, 1021m, 869w, 841m, 761w, 669m; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.36 (s, 9H, SiMe$_3$), 0.81 (d, 3H, J = 7.0 Hz, H-C4'), 1.28 (d, 3H, J = 7.0 Hz, Me-C4), 1.52 - 1.59 (m, 2H, H-C2, H-C3), 1.68 - 1.74 (m, 1H, H'-C3), 1.97 - 2.04 (m, 1H, H'-C2), 2.31 (dd, 1H, J_1 = 15.5 Hz, J_2 = 8.5 Hz, H-C2'), 2.42 (dd, 1H, J_1 = 15.5 Hz, J_2 = 6.0 Hz, H'-C2'), 2.51 - 2.60 (m, 1H, H-C3'), 2.68 (ψtd, 1H, J_1 = 9.0 Hz, J_2 = 5.0 Hz, H-C1), 3.12 - 3.19 (m, 1H, H-C4), 3.78 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 5.42 (s, 1H, H-C8); ^{13}C NMR (67.7 MHz, CDCl$_3$) δ = 0.0 (s, SiMe$_3$), 13.9 (q, C4'), 16.8 (t, C2), 20.6 (q, Me-C4), 27.1 (t, C3), 27.7 (d, C4), 34.3 (d, C3'), 39.0 (t, C2'), 39.1 (d, C1), 60.4 (q, OCH$_3$-C6), 65.1 (q, OCH$_3$-C5), 90.6 (s, C7), 96.0 (d, C8), 105.4 (s, C8a), 117.2 (s, C4a), 132.0 (s, C6), 139.1 (s, C5), 178.0 (s, COOH), 233.9 (s, CO); HRMS calcd. for $C_{23}H_{32}CrO_7Si$: 500.1322; found: 500.1317.

(1RS,3'SR,4RS,4aSR)-Tricarbonyl-[η^6-3-(5,6-dimethoxy-4-methyl-7-trimethylsilanyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-N-methoxy-N-methyl-butyramide]-chromium(0) (*rac*-**17**): The carboxylic acid *rac*-**16** (40 mg, 80 μmol), N,O-dimethyl-hydroxylamine hydrochloride (12 mg, 0.12 mmol), carbon tetrabromide (41 mg, 0.12 mmol), and anhydrous pyridine (10 μl, 0.12 mmol) were dissolved in 1 ml of anhydrous dichloromethane. Then triphenylphosphane (32 mg, 0.12 mmol) was added portionwise over a period of 5 min and the mixture was stirred at room temp. for 30 min. The solution was diluted with 5 ml of *n*-hexane/EtOAc = 1/1 and filtered through Celite to remove the formed white precipitate. After evaporating the solvent in vacuo the crude product was purified by PTLC (*n*-hexane/EtOAc = 7/3) to give 33 mg (76 %) of the *Weinreb* amide *rac*-**17**. m.p.: 132-133°C; IR (ATR) = 2961m, 2944m, 1950s, 1868s, 1655m, 1453m, 1373m, 1300m, 1251m, 1021m, 925w, 842m, 669m; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.35 (s, 9H, SiMe$_3$), 0.77 (d, 3H, J = 7.0 Hz, H-C4'), 1.28 (d, 3H, J = 7.0 Hz, Me-C4), 1.55 - 1.62 (m, 2H, H-C2, H-C3), 1.67 - 1.74 (m, 1H, H'-C3), 1.97 - 2.07 (m, 1H, H'-C2), 2.42 (d, 2H, J_2 = 6.0 Hz, H-C2'), 2.63 - 2.70 (m, 2H, H-C1, H-C3'), 3.10 - 3.17 (m, 1H, H-C4), 3.20 (s, 3H, NCH$_3$), 3.69 (s, 3H, OCH$_3$-N), 3.77 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 5.46 (s, 1H, H-C8); ^{13}C NMR (67.7 MHz, CDCl$_3$) δ = 0.0 (s, SiMe$_3$), 13.9 (q, C4'), 16.8 (t, C2), 20.5 (q, Me-C4), 27.2 (t, C3), 27.8 (d, C4), 33.9 (d, C3'), 36.7 (t, C2'), 39.6 (d, C1), 60.4 (q, OCH$_3$-C6), 61.2 (q, OCH$_3$-N), 65.0 (q, OCH$_3$-C5), 90.7 (s, C7), 96.2 (d, C8), 106.1 (s, C8a), 117.2 (s, C4a), 132.1 (s, C6), 139.0 (s, C5), 234.0 (s, CO); HRMS calcd. for $C_{25}H_{37}CrNO_7Si$: 543.1744; found: 543.1745.

(1RS,3'SR,4RS,4aSR)-Tricarbonyl-[η^6-3-(5,6-dimethoxy-4-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-N-methoxy-N-methyl-butyramide]-chromium(0) (*rac*-**18**): The *Weinreb* amide *rac*-**17** (27 mg, 50 μmol) and water (5 μl, 0.28 mmol) were dissolved in 1 ml of THF and cooled to 0°C. TBAF (60 μl, 60 μmol, 1.1 eq., 1.0 M in THF) was added and the solution was stirred for 30 min at room temp. The mixture was diluted with *n*-hexane/EtOAc = 1/1, transferred to a separatory funnel and washed with water and brine. The organic layer was dried (MgSO$_4$) and concentrated in vacuo. The crude product was purified by PTLC (*n*-hexane/EtOAc =1/1) to give 22 mg (94 %) of *rac*-**18** in the form of yellow crystals. m.p.: 133°C; IR (ATR) = 2962w, 2940w, 1948s, 1861s, 1660m, 1535w, 1471m, 1389m, 1278m, 1094w, 1049m, 1000m, 671m; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.74 (d, 3H, J = 7.0 Hz, H-C4'), 1.25 (d, 3H, J = 7.0 Hz, Me-C4), 1.50 - 1.63 (m, 2H, H-C2, H-C3), 1.68 - 1.76 (m, 1H, H'-C3), 1.94 - 2.04 (m, 1H, H'-C2), 2.42 (d, 2H, J = 6.0 Hz, H-C2'), 2.66 - 2.80 (m, 2H, H-C1, H-C3'), 3.09 - 3.16 (m, 1H,

H-C4), 3.20 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3-N), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.20 (d, 1H, J = 7.0 Hz, H-C7/C8), 5.59 (d, 1H, J = 7.0 Hz, H-C7/C8); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ = 13.5 (q, C4'), 16.2 (t, C2), 19.9 (q, Me-C4), 27.4 (t, C3), 27.9 (d, C4), 33.9 (d, C3'), 36.5 (t, C2'), 39.2 (d, C1), 56.0 (q, OCH_3-C6), 61.2 (q, OCH_3-N), 65.6 (q, OCH_3-C5), 74.5 (d, C7), 89.6 (d, C8), 104.2 (s, C8a), 116.8 (s, C4a), 128.6 (s, C6), 134.4 (s, C5), 234.4 (s, CO); $C_{22}H_{29}CrNO_7$: calcd. C 56.05, H 6.20, N 2.97; found C 55.96, H 6.63, N 3.26.

(1RS,2'SR,4RS,4aSR)-Tricarbonyl-[η^6-1-(6-methyl-5-hepten-4-on-2-yl)-5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydro-naphthalene]-chromium(0) (*rac*-**19**): The *Weinreb* amide *rac*-**18** (25 mg, 53 µmol) was dissolved in 0.5 ml of anhydrous THF and cooled to -30°C. A solution of 2-methyl-1-propenyllithium in diethyl ether (600 µl, 0.18 mmol, ca. 0.3 M) was added and the mixture was allowed to warm to 10°C over a period of 30 min. Then iodomethane (20 µl, 0.32 mmol) was added at -20°C and the solution was stirred at 0°C for 30 min. The reaction mixture was diluted with *n*-hexane and water and transferred to a separatory funnel. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by PTLC (*n*-hexane/EtOAc = 4/1) to give 18 mg (71 %) of *rac*-**19** as a yellow oil. IR (ATR) = 2962m, 2941m, 2876w, 1949s, 1864s, 1684m, 1619m, 1464m, 1388m, 1378m, 1305m, 1242w, 1067m, 911w, 671m; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.71 (d, 3H, J = 7.0 Hz, H-C1'), 1.21 (d, 3H, J = 7.0 Hz, Me-C4), 1.49 - 1.75 (m, 3H, H-C2, H-C3, H'-C3), 1.80 - 1.89 (m, 1H, H'-C2), 1.91 (s, 3H, H-C7'), 2.16 (s, 3 H, Me-C7/Me-C6'), 2.21 (s, 3H, Me-C7/Me-C6'), 2.38 (dd, 1H, J_1 = 16.0 Hz, J_2 = 9.0 Hz, H-C3'), 2.48 (dd, 1H, J_1 = 16.0 Hz, J_2 = 5.0 Hz, H-C3'), 2.63 - 2.73 (m, 1H, H-C1), 2.78 - 2.90 (m, 1H, H-C2'), 3.01 - 3.10 (m, 1H, H-C4), 3.78 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.20 (s, 1H, H-C8), 6.09 (s, 1H, H-C5'); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ = 13.5 (q, C1'), 15.9 (t, C2), 16.1 (q, Me-C7), 20.0 (q, Me-C4), 20.7 (q, Me-C6'), 27.5 (d, C4/q, C7'), 27.6 (d, C4/q, C7'), 27.8 (t, C3), 33.5 (d, C2'), 39.0 (d, C1), 48.7 (t, C3'), 62.1 (q, OCH_3-C6), 63.1 (q, OCH_3-C5), 88.5 (d, C8), 103.0 (s, C7), 108.5 (s, C8a), 111.0 (s, C4a), 123.8 (d, C5'), 131.3 (s, C6), 135.2 (s, C5), 156.1 (s, C6'), 199.5 (s, C4'), 234.0 (s, CO); HRMS calcd. for $C_{25}H_{32}CrO_6$: 480.1604; found: 480.1605.

2-Methyl-1-propenyllithium: In a flame dried *Schlenk* flask lithium (0.55 g, 79 mmol) was suspended in 16 ml of anhydrous diethyl ether. A solution of 1-bromo-2-methylpropene (3.0 ml, 29 mmol) in 4 ml of anhydrous diethyl ether was added at -25°C over a period of 10 min. The mixture was stirred at 0°C for 4 h and then filtered through a membrane filter (Minisart RC 25, 0.2 µm). The solution obtained was stored under an argon atmosphere at -18°C and titrated prior to use.

(1RS,2'SR,4RS)-1-(6-Methyl-5-hepten-4-on-2-yl)-5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydro-naphthalene (*rac*-**20**): The complex *rac*-**19** (18 mg, 37 µmol) was dissolved in 20 ml of diethyl ether and then exposed to sunlight until TLC showed no more starting material. The mixture was filtered through silica gel to remove the precipitate of chromium trioxide. The solvent was then removed in vacuo to give 13 mg (quantitative yield) of *rac*-**20** as a nearly colourless oil. IR (ATR) = 2959s, 2934s, 2827m, 1685s, 1619s, 1481s, 1446s, 1406s, 1376m, 1321s, 1276w, 1283m, 1072s, 1026m, 913m, 888w, 795w, 735w; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.68 (d, 3H, J = 6.5 Hz, H-C1'), 1.18 (d, 3H, J = 6.5 Hz, Me-C4), 1.54 - 1.70 (m, 4H, H-C2, H-C3), 1.91 (s, 3 H, H-C7'), 2.16 (s, 3H, Me-C6'), 2.21 (s, 3H,

Me-C7), 2.41 (dd, 1H, J_1 = 15.0 Hz, J_2 = 8.5 Hz, H-C3'), 2.52 (dd, 1H, J_1 = 15.5 Hz, J_2 = 6.0 Hz, H-C3'), 2.73 - 2.79 (m, 1H, H-C1), 2.80 - 2.88 (m, 1 H, H-C2'), 3.08 - 3.16 (m, 1H, H-C4), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.14 (s, 1H, H-C5'), 6.89 (s, 1H, H-C8); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 (q, C1'), 15.8 (q, Me-C7), 17.3 (t, C2), 20.8 (q, Me-C4), 21.5 (q, Me-C6'), 27.0 (q, C7'), 27.7 (d, C4), 29.0 (t, C3), 32.7 (d, C2'), 41.1 (d, C1), 49.6 (t, C3'), 59.7 (q, OCH_3-C6), 60.2 (q, OCH_3-C5), 124.2 (d, C8/C5'), 124.3 (d, C8/C5'), 129.1 (s, C7), 134.5 (s, C4a), 135.3 (s, C8a), 148.6 (s, C6), 150.2 (d, C5), 155.1 (s, C6'), 201.0 (s, C4'); HRMS calcd. for $C_{22}H_{32}O_3$: 344.2351; found: 344.2357.

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6. We are grateful to Prof. Higa, Nishihara, for providing us with copies of the original IR and ^{1}H NMR spectra of the helioporins B-F.
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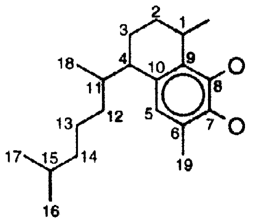
14. For the discussion (incl. Table 1) the general numbering scheme suggested by Fenical for the *seco*-pseudoudopterosins was used.[2]



Please note that the NMR assignments given in the experimental part are based on the systematic nomenclature of the individual compounds.

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16. Crystallographic data (excluding structure factors) for *rac*-**15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-117954. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223)336-033; e-mail: teched@ccdc.cam.ac.uk).