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Chiral Arene-Cr(CO)$_3$ Complexes in Organic Synthesis: A Short Enantioselective Total Synthesis of Putative Helioporin D

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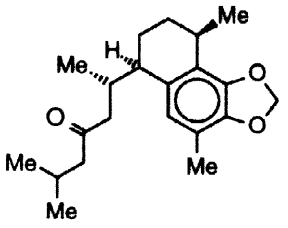
Abstract: The first total synthesis of a member of the helioporin class of marine diterpenes has been achieved. Starting from (4a*S*)-η^6-5,6-dimethoxytetralin-Cr(CO)$_3$ (≥ 99% *e.e.*) the target molecule (putative helioporin D) is obtained in a mere 8 steps in an excellent overall yield of 45%. The 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 6-methyl-5-hepten-2-yl sidechain is diastereoselectively introduced in a stereoconvergent manner by alkylation of a benzylic lithiated complex with the *in situ* generated triflate of (*R*)-6-methyl-5-hepten-2-ol. The relative configuration of the alkylation product was confirmed by X-ray crystal structure analysis. As the NMR data of the synthetic target compound are not in agreement with those of natural helioporin D, the stereostructure of the latter has to be revised.

In 1993, T. Higa and coworkers reported on the isolation and structure elucidation of a group of bioactive diterpenes from the blue coral *Heliopora coerulea* which they named the helioporins.[1] While some of these compounds, e.g. helioporin B (**1**), exhibited antiviral activity, others, e.g. helioporin D (**2**) and helioporin E (**3**), showed cytotoxicity. The helioporins are structurally related to the anti-inflammatory *seco*-pseudopterosins[2] and the pseudopterosins.[3] A characteristic feature of all helioporins is the benzodioxole substructure.



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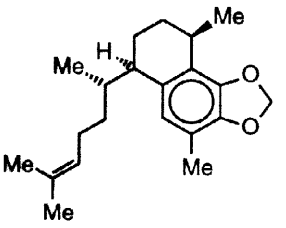

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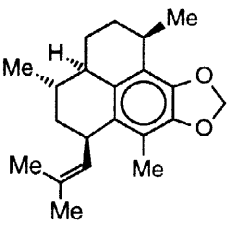

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In the course of our program[4] directed towards the application of chiral arene-Cr(CO)$_3$ complexes[5] as building blocks for the enantioselective total synthesis of biologically active compounds, we previously demonstrated that 5,6-dimethoxytetralin derivatives of type **4** (with two *cis*-configurated benzylic side-chains) are regio- and diastereoselectively accessible by successive deprotonation/alkylation of η^6-5,6-dimethoxytetralin-Cr(CO)$_3$ (**5**) (Scheme 1)[6]. We here report on the application of this general strategy for an efficient enantioselective total synthesis of **2**, and thereby on the first ever total synthesis of a helioporin.

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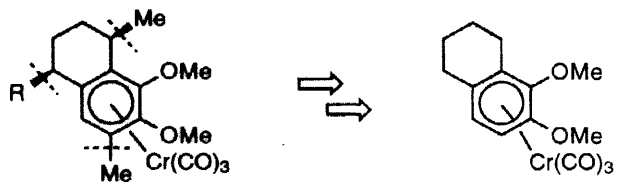


Scheme 1 **4** **5**

The overall course of our synthesis is depicted in Scheme 2. The planar-chiral starting complex **5** (≥ 99% *e.e.*) was prepared in ca. 60% yield from 5,6-dimethoxy-1-tetralone *via* enantioselective reduction, diastereoselective complexation and ionic hydrogenation as described earlier.[6,7] After protection of the acidic arylic position (*n*BuLi, THF, TMSCl), benzylic deprotonation/methylation (*n*BuLi, THF, MeI) afforded exclusively the 4-*exo*-methylated product **6**.[6] To control the configuration at the sidechain chirality center, a stereo-convergent strategy was developed. Thus, benzylic deprotonation (*s*BuLi) at the 1-position of **6** and alkylation of the lithiated intermediate with the *in situ* generated triflate **8** of (*R*)-sulcatol (**7**)[8] allowed the introduction of the (2*S*)-6-methyl-5-hepten-2-yl sidechain in a single synthetic step in 85% yield under stereoselective generation of two new chirality centers. Under the optimized reaction conditions for the *in situ* formation of **8** from **7** and the subsequent alkylation step (see Scheme 2) the preparation of **9** was achieved in a highly amenable manner. However, despite the fact that both starting materials (**5** and **7**) were employed with high enantiomeric purity (≥99% *e.e.*) the isolated coupling product (**9**) was contaminated with ca. 8% of an undesired diastereomer.[9] We believe that the observed loss of stereochemical information is due to the formation of an oxonium ion from **8** and THF which itself may act as an alkylating agent.[10] Nevertheless, after desilylation of **9** (TBAF) the undesired isomer could be separated by chromatography to afford **10**[11] as a pure diastereomer (oil), the relative configuration of which was unambiguously established by X-ray crystallography of crystalline *rac*-**10** (Figure 1).[12] After *ortho*-lithiation/methylation (*n*BuLi, MeI) and oxidative decomplexation (→ **11**)[13] the cleavage of the methoxy groups was achieved in very high yield employing LiSEt[14] which proved to be superior compared to a variety of other demethylation reagents. The formation of the methylenedioxy bridge (CsF, CH_2Cl_2)[15] finally yielded the target molecule **2**.[16] The overall yield of the 8-step sequence for the conversion of **5** to **2** was ca. 45% which demonstrates the competitiveness of the underlying strategy based on arene-$Cr(CO)_3$ chemistry.

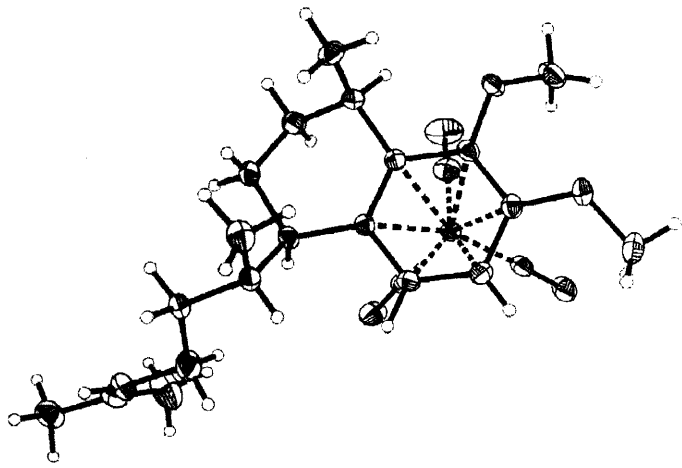
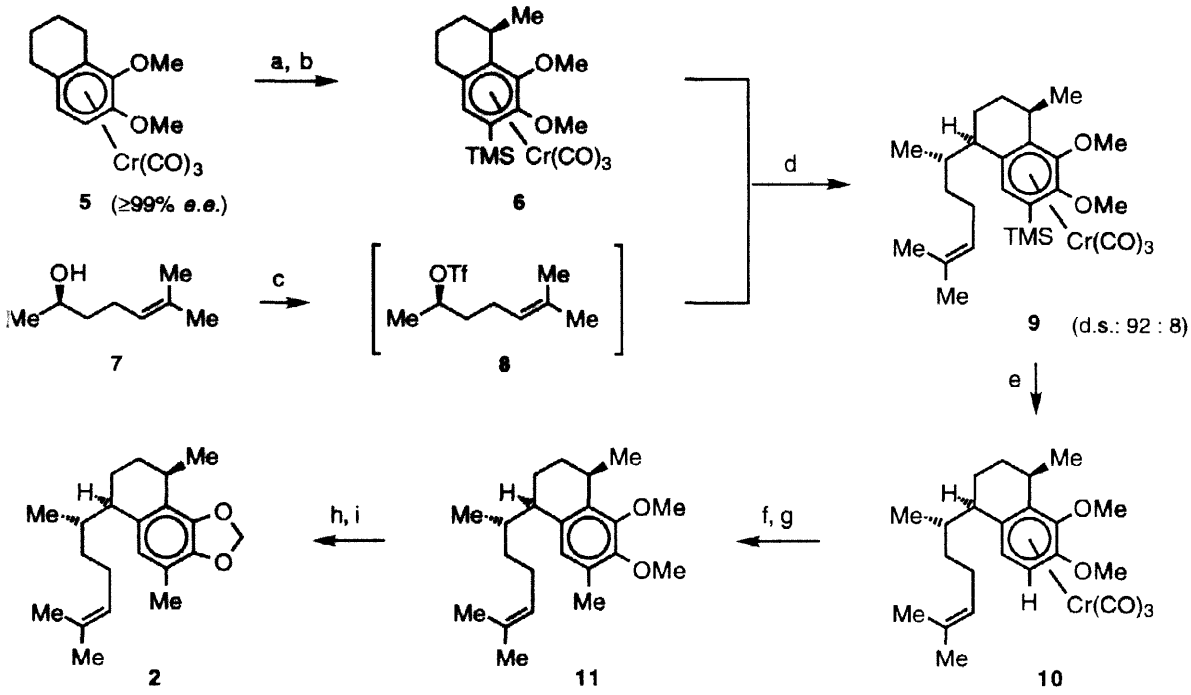


Figure 1: structure of *rac*-**10** in the crystalline state



Scheme2: a) *n*BuLi, THF, TMSCl (91%); b) *n*BuLi, THF, MeI (93%); c) *n*BuLi, hexane, 0°C; then slow addition of the resulting alkoxide solution to a solution of 0.99 eq. of Tf_2O in CH_2Cl_2 at -20°C; d) *s*BuLi, THF, -70°C → -20°C, 75 min, then addition of **8** in hexane/CH_2Cl_2 at -65°C → 25°C, 1.5 h (85%), e) TBAF, THF, 0°C (100%), then subsequent separation of the undesired diastereomer by flash chromatography (SiO_2, hexane/EtOAc, 50 + 1); f) *n*BuLi, THF, -70°C → -20°C, 70 min, then MeI, -40°C → 25°C, 1.5 h (95%); g) air, sunlight, Et_2O (100%); h) LiSEt, DMF, reflux, 2 h (95%); i) CsF, CH_2Cl_2, DMF, reflux 3 h (88%).

Having completed the synthesis of **2**, we were surprised to find that its NMR data did not match those of helioporin D.[1,17] Since the relative stereochemistry at all three chirality centers (of **2**) had been established by X-ray crystallography of *rac*-**10**, the original structural assignment of helioporin D was clearly proven to be wrong. The revised structure of helioporin D is described in the accompanying paper.[17]

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8. (R)-Sulcatol (**7**) ($[\alpha]_D^{23}$ = -15.4° (c = 5.0 in EtOH)) was prepared from *rac*-**7** by enzymatic resolution using porcine pancreas lipase following the protocol of Stokes and Oehlschlager: Stokes, T. M., Oehlschlager, A.C. *Tetrahedron Lett.***1987**, *28*, 2091.
9. This compound was shown to be the epimer of **9** at the sidechain chirality center as it evolved as the (slightly) dominating product on alkylation of **6** with *rac*-**8** (d.s.: 2 : 3).
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11. For **10**: yellow oil, $[\alpha]_D^{20}$ = -93.3° (c = 0.20 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.66 (d, 3H, *J* = 7.0 Hz), 1.18 - 1.76 (m, 5H), 1.25 (d, 3H, *J* = 7.0 Hz), 1,64 (s, 3H), 1.71 (s, 3H), 1.91 - 2.12 (m, 4H), 2.72 (ddd, 1H, *J* = 14.0, 4.0, 8.0 Hz), 3.06 - 3.16 (m, 1H), 3.84 (s, 3H), 3.90 (s, 3H), 5.12 (t, 1H, *J* = 7.0 Hz), 5.18 (d, 1H, *J* = 8.0 Hz), 5.45 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.6 (q), 15.7 (t), 17.7 (q), 19.9 (q), 25.7 (q), 25.9 (t), 27.4 (t), 28.0 (d), 34.5 (t), 37.0 (d), 38.7 (d), 55.9 (q), 65.6 (q), 74.5 (d), 89.4 (d), 105.3 (s), 117.0 (s), 124.1 (d), 128.7 (s), 131.9 (s), 134.3 (s), 234.6 (s).
12. X-ray crystal structure analysis of *rac*-**10**: Siemens Smart diffractometer, MoK_α radiation, 133 K, empirical absorption correction using program SADABS; $C_{24}H_{32}CrO_5$, triclinic, space group P-1 (no. 2), a = 6.7182(9) Å, b = 11.363(1) Å, c = 15.347(2) Å, α = 74.01(1)°, β = 81.645(9)°, γ = 85.60(1)°, V = 1113.5(3) $Å^3$, Z = 2, ρ_{calc} = 1.350 g/cm^3; 5692 independent reflections, of which 5508 with I > 0 were used, R = 0.049, R_w = 0.042. Crystallographic data (excluding structure factors) for *rac*-**10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100864. 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).
13. For **11**: Fp. 42 °C, $[\alpha]_D^{20}$ = +86.2° (c = 0.20 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 (d, 3H, *J* = 7.0 Hz), 1.18 - 1.36 (m, 1H), 1.22 (d, 3H, *J* = 7.0 Hz), 1.36 - 1.45 (m, 1H), 1.45 - 1.55 (m, 1H), 1.55 - 1.78 (m, 2H), 1.64 (s, 3H), 1.73 (s, 3H), 1.86 (tt, 1H, *J* = 14.0, 4.0 Hz), 1.94 - 2.14 (m, 3H), 2.21 (s, 3H), 2.88 (ddd, 1H, *J* = 14.0, 4.0, 8.0 Hz), 3.00 - 3.11 (m, 1H), 3.79 (s, 3H), 3.96 (s, 3H), 5.07 (s, 1H), 5.13 (t, br, 1H, *J* = 7.0 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (q), 15.6 (t), 16.0 (q), 17.7 (q), 20.0 (q), 25.7 (q), 26.0 (t), 27.6 (d), 28.0 (t), 34.6 (t), 37.2 (d), 38.7 (d), 62.2 (q), 63.2 (q), 88.4 (d), 103.1 (s), 109.8 (s), 111.2 (s), 124.1 (d), 131.2 (s), 131.8 (s), 135.4 (s), 234.3 (s).
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16. For **2**: colorless oil, $[\alpha]_D^{23}$ = +10.4° (c = 0.36 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 (d, 3H, *J* = 7.0 Hz), 1.22 (d, 3H, *J* = 7.0 Hz), 1.24-1.40 (m, 1H), 1.40 - 1.52 (m, 1H), 1.54-1.80 (m, 4H), 1.64 (s, 3H), 1.72 (s, 3H), 1.94-2.23 (m, 3H), 2.20 (s, 3H), 2.68-2.74 (m, 1H), 2.95-3.06 (m, 1H), 5.17 (tt, 1H, *J* = 7.0, 1.5 Hz), 5.90 (d, 1H, *J* = 1.0 Hz), 5.96 (d, 1H, *J* = 1.0 Hz), 6.56 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 14.4 (q), 14.7 (q), 17.7 (t), 17.7 (q), 20.5 (q), 25.8 (q), 26.3 (t), 27.2 (d), 28.5 (t), 35.1 (t), 35.7 (d), 41.1 (d), 100.5 (t), 116.2 (s), 121.6 (d), 123.3 (s), 124.8 (d), 131.3 (s), 133.3 (s), 142.7 (s), 144.4 (s).
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