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Radical Cyclization of η^6-Arene-$Cr(CO)_3$ Complexes: A Regio- and Stereoselective Entry to Functionalized Pseudopterosin Precursors

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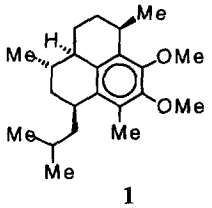
Abstract: The chiral 6,7-dimethoxytetralin-$Cr(CO)_3$ derivative *rac*-**10**, containing both a ketone and an olefin sidechain, was prepared from *rac*-**4** through a sequence of two successive benzylic deprotonation / alkylation steps. On treatment with samarium(II)iodide, *rac*-**10** selectively cyclized to the mono-demethoxylated hydrophenalene-$Cr(CO)_3$ derivative *rac*-**11**, a highly functionalized precursor for the synthesis of antiinflammatory pseudopterosins. This result displays the synthetic power of intramolecular radical additions to arene-$Cr(CO)_3$ complexes followed by single electron transfer (SET). Copyright © 1996 Elsevier Science Ltd

As part of our program directed towards the use of chiral arene-$Cr(CO)_3$ complexes[1] as building blocks for the enantioselective total synthesis of biologically active compounds[2], we recently reported on a short and highly stereoselective synthesis of the substituted hydrophenalene derivative **1**[2c], which is structurally closely related to the dihydro-analogues of pseudopterosin G (**2**)[3] and helioporin E (**3**)[4]. We here disclose new experimental results concerning the synthesis of compounds containing the unsaturated (isobutenyl) sidechain. As a prelusive exploratory study, the work described herein was performed, for economic reasons, employing racemic compounds[5]



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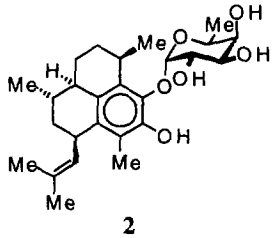

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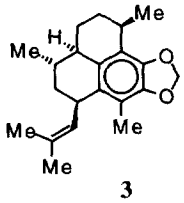
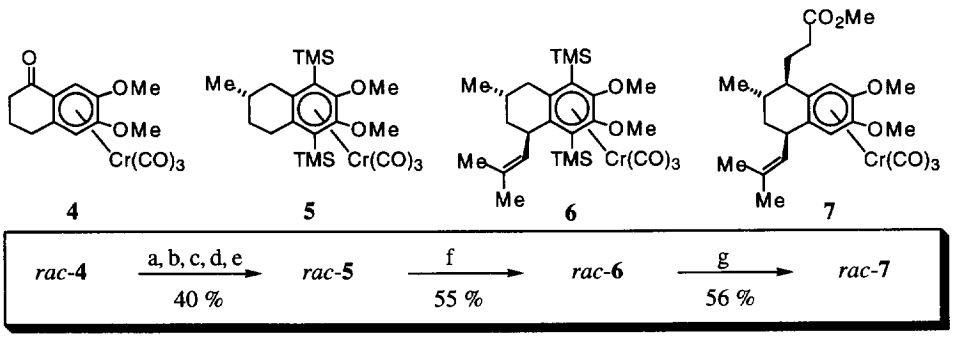


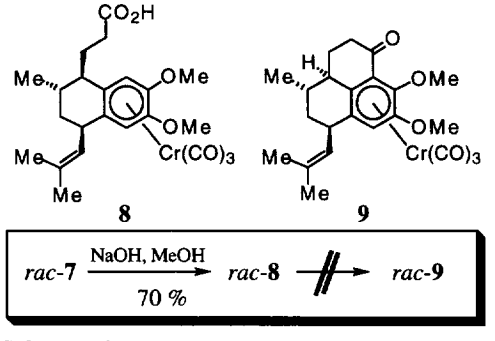
3

According to our general strategic scheme[2d], we started from 6,7-dimethoxy-1-tetralone-$Cr(CO)_3$ (*rac*-**4**) which was converted to *rac*-**5** (scheme 1)[6] through the same five step sequence we had previously applied in the nonracemic series[2c]. The regio- und diastereoselective introduction of the isobutenyl sidechain (*rac*-**5** → *rac*-**6**) was then achieved by (regioselective) deprotonation[2c,7] of *rac*-**5** with *n*-BuLi and Ni-mediated coupling[8] of the benzylic lithiated intermediate with 2-methyl-1-propenylbromide. The attachment of the second benzylic sidechain (*rac*-**6** → *rac*-**7**) in turn was accomplished by renewed deprotonation, Michael addition[9] (employing methyl α-trimethylsilyl acrylate[10]) and fluoride-induced desilylation.

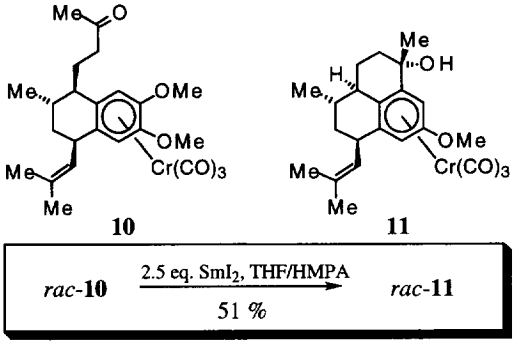


Scheme 1. a) LHDMS, THF, -78 °C then MeI, HMPT; b) $NaBH_4$, $MeOH/CH_2Cl_2$, rt.; c) *p*-TsOH on SiO_2, C_6H_6, rt.; d) H_2, cat. Rh/Al_2O_3, AcOEt/AcOH (50:1), rt.; e) LTMP, TMSCl, THF, - 40 °C → rt.; f) *n*-BuLi, THF/HMPT (20 : 1), -78 °C → 0 °C, 3 h, then Br-CH=CMe_2, Ni(0), THF, -78 °C → 0 °C, 2 h; g) *n*-BuLi, THF/HMPT (20:1), -55 °C → 0 °C, 2 h, then CH_2=C(TMS)CO_2Me, -78 °C → 0 °C, 30 min, then 2 N HCl, 0 °C, 5 min, then TBAF, THF, rt., 15 h;

To prepare for the attempted Friedel-Crafts-type cyclization, the ester *rac*-**7**[11] was hydrolysed to the carboxylic acid *rac*-**8**. To our disappointment (and in sharp contrast to the behaviour of its dihydro derivative[2c]), *rac*-**8** did not afford any of the desired ketone *rac*-**9** (s. scheme 2) under a variety of reaction conditions (e.g. PPA, rt.→ 50 °C)[12].



Scheme 2.

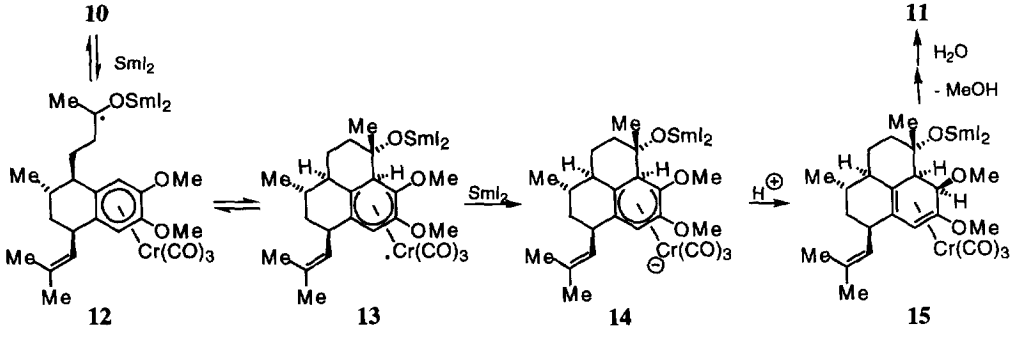


Scheme 3.

The cyclization problem was finally solved by applying our new protocol for the samarium(II)iodide mediated intramolecular radical addition to arene-$Cr(CO)_3$ complexes[13]. Thus, when *rac*-**10**[14] was subjected to samarium(II)iodide (2.5 eq.) in THF in the presence of HMPA and *t*-BuOH (-78 °C, 2 h → room temp., 1 h.) followed by aqueous workup, a single major new product was formed besides small amounts of unchanged starting material according to TLC analysis. After flash chromatography, the crystalline complex *rac*-**11**[15] was isolated in 51 % yield as a single regio- and diastereomer (scheme 3).

This result is remarkable for various respects: Firstly, while the unsaturated sidechain does not survive acidic reagents, it is completely uneffected under the conditions of the radical cyclization. Secondly, from a synthetic point of view, *rac*-**11** can be considered being a very promising precursor for the synthesis of the pseudopterosins. Thirdly, the formation of *rac*-**11** does not only involve the regio- and diastereoselective formation of a new C-C bond but also the completely regioselective loss of one methoxy group.

Mechanistically, the formation of *rac*-**11** can be rationalized in terms of the following picture (scheme 4)[16]. In the first step, a (nucleophilc) ketyl radical (**12**) is generated[17,18], which adds to the complexed arene ring from the face opposite to the $Cr(CO)_3$ fragment[19]. The transfer (SET) of a further electron from samarium(II)iodide to the resulting 17-electron complex (**13**) then gives an anionic η^5-complex (**14**). *Endo*-protonation (via primary protonation at the chromium atom[20]) leads to the η^4-intermediate **15**, from which the stable η^6-arene-$Cr(CO)_3$ substructure can now easily be restored by elimination of methanol.



Scheme 4.

In conclusion, we have performed a series of highly selective transformations of arene-$Cr(CO)_3$ complexes. In particular, we have demonstrated the synthetic power of our cyclization protocol involving radical addition to arene-$Cr(CO)_3$ complexes[13]. We are now going to prepare compound **11** in non-racemic form and to employ this material for the completion of our pseudopterosin synthesis.

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11. For *rac*-**7**: Fp. 147-148 °C; IR (KBr): ν = 1944, 1868, 1847, 1725, 1493, 1274; ^{1}H NMR: (250 MHz, $CDCl_3$): δ = 1.17 (d, 3 H, J = 6.8 Hz), 1.55-1.61 (m, 2 H), 1.72-1.80 (1 H), 1.76 (d, 3 H, J = 1.1 Hz), 1.79 (d, 3 H, J = 1.2 Hz), 1.92-2.08 (m, 2 H), 2.31-2.40 (m, 3 H), 3.43-3.51 (m, 1 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3H), 5.06 (m, 1 H), 5.15 (s, 1 H), 5.29 (s, 1 H); ^{13}C NMR: (62.90 MHz, $CDCl_3$): δ = 18.0 q, 20.6 q, 25.9 q, 28.1 d, 31.1 t, 31.5 t, 34.2 t, 34.7 d, 42.3 d, 51.8 q, 56.9 q, 57.0 q, 77.1 d, 78.6 d, 104.7 s, 106.8 s, 127.0 d, 132.6 s, 132.6 s, 134.1 s, 173.6 s, 233.7 s; Calc. for $C_{24}H_{30}O_7Cr$: 59.74 % C, 6.27 % H; found: 59.60 % C 6.29 % H
12. Mixtures of unidentified and majorly decomplexed products were obtained. ^{1}H NMR analysis of the crude product mixture indicated the absence of the typical olefinic proton of the isobutenyl sidechain.
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14. In analogy to *rac*-**7**, compound *rac*-**10** can be prepared from *rac*-**6** by deprotonation, Michael addition (employing α-trimethylsilyl methylvinylketone[10c]) and desilylation.
15. For *rac*-**11**: IR (CCl_4): ν = 3592, 2959, 1892, 1865, 1538, 1461; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (d, 3 H, J = 6.5 Hz), 1.22 - 1.35 (m, 2 H), 1.44 - 1.52 (m, 1 H), 1.55 (s, 3 H), 1.60 - 1.69 (m, 1 H), 1.73 (s, 3 H), 1.79 (d, 3 H, J = 1 Hz), 1.78 - 1.86 (m, 1 H), 1.95 - 2.2 (m, 4 H), 3.66 (s, 3 H), 3.67 - 3.73 (m, 1 H), 4.97 (d, 1 H, J = 2.5 Hz), 5.29 (d, 1 H, J = 10 Hz), 5.4 (d, 1 H, J = 2.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 234.4 s ($Cr(CO)_3$), 142.2 s, 132.0 s, 129.2 d, 121.5 s, 115.5 s, 101.0 s, 80.1 d, 74.8 d, 70.9 s, 55.5 q, 43.2 d, 38.8 t, 37.9 t, 37.2 d, 32.5 q, 30.7 d, 26.1 t, 25.8 q, 25.7 q, 19.3 q; HRMS: calc. for $C_{23}H_{28}O_5Cr$: 436.13418, found 436.13418.
16. This reaction resembles to some respect a nucleophilic aromatic (*cine*-) substitution with methoxide as a leaving group. Although there are several known examples for nucleophilic *tele*- and *cine*-substitutions at $Cr(CO)_3$-complexed arenes[19], only in very few cases a methoxy group acts as a leaving group: See, for instance, ref.[2b], as well as: a) Rose-Munch, F.; Bellot, O.; Mignon, L.; Semra, A.; Robert, F.; Jeannin, Y. *J. Organomet. Chem.* **1991**, *402*, 1; b) Djukic, J.P.; Rose-Munch, F.; Rose, E.; Simon, F.; Dromzee, Y. *Organometallics* **1995**, *14*, 2027; c) Schmalz, H.-G.; Schellhaas, K. *Tetrahedron Lett.* **1995**, *36*, 5511.
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