Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6861-6864, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01455-8

Chiral η^6-Arene-$Cr(CO)_3$ Complexes as Synthetic Building Blocks: An Enantio- and Diastereoselective Approach to Substituted Hydrophenalenes Related to Helioporin E and Pseudopterosin G

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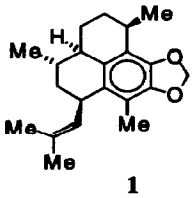
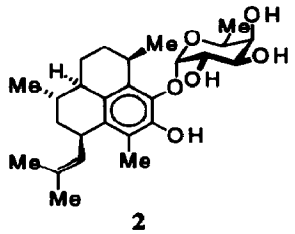
Abstract: The enantioselective total synthesis of compound **14**, an analogue of dihydro-helioporin E and dihydro-pseudopterosin G, is accomplished by a strategy which centrally relies on the reactivity of arene-$Cr(CO)_3$ complexes. The chiral synthetic building block **6** (> 97 % e.e.) is converted in 12 steps regio- and diastereoselectively into complex **12**, from which **14** is obtained by decomplexation and methylation. Key steps of the synthesis are two succesive regio- and diastereoselective benzylic deprotonation/alkylation reactions.

Recently, *Tanaka* et al. reported on the isolation of the helioporins, a group of bioactive diterpenes from the blue coral *Heliopora coerulea*.[1] One of these compounds, the cytotoxic helioporin E (**1**), is structurally closely related to pseudopterosin G (**2**), an antiinflammatory active compound isolated from an other octocoral, the gorgonian *Pseudopterogorgia elisabethae*.[2]



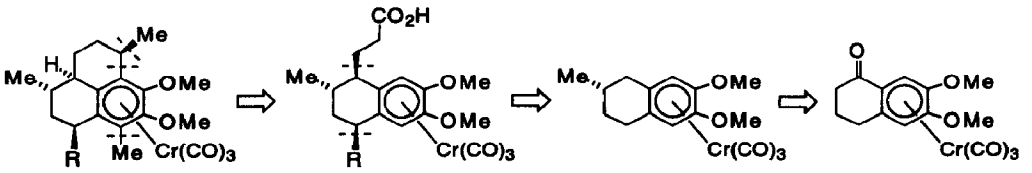
1



2

In this paper we wish to disclose a synthetic strategy which opens up an efficient and completely stereoselective total synthesis of substituted hydrophenalenes related to the above-mentioned compounds[3]. Our approach is centrally based on the reactivity of arene-$Cr(CO)_3$ complexes.[4] As a unique feature, *almost the complete synthesis is carried out at the complexed ligand.* The absolute stereochemical information is brought into the synthetic route by means of a chiral π-complex of an achiral arene ligand.

Our retrosynthetic analysis is shown in Scheme 1: Following a technique worked out with the aid of model compounds,[5] pre-target molecules of type **3** derive from substituted tetralin complexes of type **4**, which in turn should be accessible from the structurally much simpler complex **5** *via* establishing the two benzylic substituents at the tetralin skeleton by successive deprotonation/alkylation steps.[6] The $Cr(CO)_3$ group thereby serves as an activating group by enhancing the acidity at the benzylic positions[7] and furthermore acts as a stereodirecting group by blocking one π-face of the arene ligand. Therefore, the *exo*-configuration of the two benzylic substituents of **4** is guaranteed.



3 **4** **5** **6**

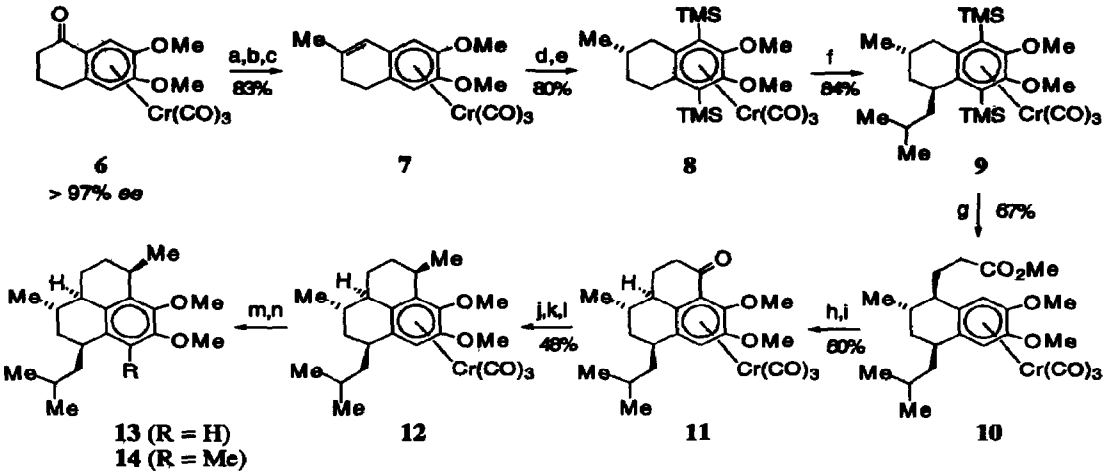
Scheme 1

The actual synthesis (Scheme 2)[8] starts with the nonracemic 1-tetralone-$Cr(CO)_3$ derivative **6**[9] which is obtained in ca. 60 % overall yield and with high enantiomeric purity[10] from 6,7-dimethoxy-1-tetralone *via* diastereoselective complexation of the temporarily chirally modified ligand[9]. This chiral synthetic building block is then converted to the dihydronaphthalene derivative **7** by α-methylation, reduction, and dehydration. Rh-catalyzed hydrogenation of **7** (from the face opposite to the metal) completely diastereoselectively gives the *endo*-complex **5**.[10] After protecting the two more acidic aryl positions by silylation using a one-pot procedure[11], benzylic deprotonation of the bis-silylated complex **8** is achieved with *n*-BuLi at 0 °C. Treatment of the lithiated intermediate with isobutyl iodide then furnishes the alkylated product **9**[12] as a pure regio- and diastereoisomer[13]. The introduction of the second benzylic sidechain is accomplished by a lithiation/Michael addition[14] sequence employing methyl-α-trimethylsilyl-acrylate[15]. After fluoride-induced desilylation, the ester **10**[16] is obtained as a single diastereomer.

The concluding steps of the synthesis are performed employing procedures worked out in the model series[5]. Hydrolysis of the ester function and Friedel-Crafts-type cyclization of the resulting carboxylic acid furnished the tricyclic complex **11**[17]. The benzylic methyl substituent is diastereoselectively introduced according to Uemura[18] by boranate reduction of the ketone, acetylation, and treatment of the resulting *endo*-acetate with trimethylaluminum. This way, the *exo*-methylated product **12** is obtained, from which the free ligand **13**[19] is liberated by oxidative decomplexation. Thus, the transformation of **6** to **13** is achieved in 12 steps with 10% overall yield.

As preliminary experiments have shown, the final methylation of **13** to **14**[20] is possible under the conditions given in Scheme 2 – albeit significant amounts of the mono-O-demethylated (phenolic) byproducts were obtained.

In conclusion, we have demonstrated that the chemistry of arene-$Cr(CO)_3$ complexes opens up a new powerful (and potentially flexibel) strategy for the stereoselective total synthesis of substituted hydrophenalenes – with the complex **6** as chiral synthetic building block.



Scheme 2: a) $(TMS)_2N$-Li, THF, -78 °C, 15 min, then MeI, HMPT, rt., 2.5 h; b) $NaBH_4$, MeOH/CH_2Cl_2, rt., 1 h; c) 3 % *p*-TsOH on SiO_2, C_6H_6, rt., 4 h; d) 5 bar H_2, cat. Rh/Al_2O_3, AcOEt/AcOH (50:1), rt., 30 h; e) lithium-2,2,6,6-tetramethyl-piperidide, TMSCl, THF, - 40 °C → rt., 1 h; f) *n*-BuLi, THF/ HMPT (25 : 1), -50 °C → 0 °C, 3 h, then I-CH_2-$CHMe_2$, THF, -30 °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, -75 °C → 0 °C, 30 min, then 2 N HCl, 0 °C, 5 min, then TBAF, THF, rt., 15 h; h) NaOH, MeOH/H_2O, rt., 20 h; i) PPA, rt., 3 h, 70 °C, 3h; j) $NaBH_4$, MeOH/CH_2Cl_2, rt., 3 h; k) Ac_2O, py, cat. DMAP, rt., 18 h; l) Me_3Al, CH_2Cl_2, -78 °C → 0 °C, 3 h; m) h·ν, air, ether, rt.; n) *n*-BuLi, TMEDA, hexane, 0 °C → 40 °C, 2 h, then MeI, 0 °C → rt, 17 h.

Acknowledgement. This work was supported by the Volkswagen-Stiftung and the Fonds der Chemischen Industrie. We wish to thank Prof. Dr. G. Quinkert, Frankfurt, for generous support and the Chemetall GmbH for gifts of butyllithium. A.S. acknowledges the Deutsche Forschungsgemeinschaft for a graduate fellowship within the Graduiertenkolleg "Chemische and biologische Synthese von Wirkstoffen".

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8. Compounds **6**, **7**, **5**, **8**, **9**, **10**, **11** and **13** were fully characterized by the usual spectroscopic methods and gave correct elemental analyses; yields refer to the analytically pure samples.
9. a) Schmalz, H.-G.; Millies, B.; Bats, J.W.; Dürner, G. *Angew. Chem.* **1992**, *104*, 640; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 631; b) Schmalz, H.-G.; Schwarz, A.; Dürner, G.; Bats, J.W. (manuscript submitted for publication).
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12. For **9**: Fp. 161-162 °C, $[\alpha]_D^{20}$ = -17.3° (c = 0.39 in $CHCl_3$); IR(KBr): ν [cm^{-1}] = 1942, 1867; ^{1}H-NMR (270 MHz, $CDCl_3$): δ = 0.47 (s, 9H), 0.49 (s, 9H), 0.93 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.3 Hz), 0.99 (d, 3H, J = 6.6 Hz), 2.29 (dd, 1H, J_1 = 10.5 Hz, J_2 = 16.9 Hz), 2.62 (dd, 1H, J_1 = 8.0 Hz, J_2 = 16.8 Hz), 2.90 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 3.5 q, 3.8 q, 21.5 q, 22.0 d, 22.3 q, 24.4 q, 25.5 d, 31.5 t, 34.1 d, 38.7 t, 45.4 t, 61.5 q, 61.9 q, 93.7 s, 96.1 s, 108.7 s, 119.6 s, 138.4 s, 234.6 s.
13. The high regioselectivity of the deprotonation of **6** will be discussed in ref.[9b].
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16. For **10**: Fp. 108 -109 °C, $[\alpha]_D^{20}$ = -83.5° (c = 0.619 in $CHCl_3$); IR(KBr): ν [cm^{-1}] = 1936, 1857; ^{1}H-NMR (270 MHz, $CDCl_3$): δ = 0.97 (d, 6H, J = 6.7 Hz), 1.09 (d, 3H, J = 5.7 Hz), 1.98-2.15 (m, 2H), 2.16-2.41 (m, 2H), 2.43-2.50 (m, 2H), 3.67 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.15 (s, 1H), 5.27 (s, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 21.6 q, 21.7 q, 23.5 q, 25.7 d, 27.2 d, 30.37 t, 30.44 t, 33.7 t, 35.2 d, 42.3 d, 45.6 t, 51.8 q, 57.0 q, 57.1 q, 76.3 d, 78.8 d, 104.9 s, 109.1 s, 132.2 s, 133.0 s, 173.6 s, 233.7 s.
17. For **11**: red oil, $[\alpha]_D^{20}$ = -301° (c = 0.084 in $CHCl_3$); IR(KBr): ν [cm^{-1}] = 1954, 1875, 1698; ^{1}H-NMR (270 MHz, $CDCl_3$): δ = 0.96 (d, 3H, J = 6.6 Hz), 1.01 (d, 3H, J = 6.5 Hz), 1.07 (d, 3H, J = 6.2 Hz), 2.08-2.26 (m, 2H), 2.51-2.73 (m, 2H), 2.81 (ddd, 1H, J_1 = 18.7 Hz, J_2 = 5.0 Hz, J_3 = 2.1 Hz), 3.79 (s, 3H), 3.91 (s, 3H), 5.14 (s, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 19.9 q, 21.4 q, 23.7 q, 25.9 d, 27.1 t, 28.6 d, 33.1 t, 35.7 d, 39.9 t, 42.9 d, 47.9 t, 56.7 q, 65.8 q, 77.5 d, 103.8 s, 110.5 s, 197.7 s, 233.0 s.
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19. For **13**: colourless oil, $[\alpha]_D^{20}$ = +9.0° (c = 0.20 in $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.94 (d, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 6.9 Hz), 1.05 (d, 3H, J = 5.9 Hz), 1.19 (d, 3H, J = 6.9 Hz), 2.72 (m, 1H), 3.20 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 6.53 (s, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 20.5 q, 21.6 q, 22.7 t, 22.9 q, 24.0 q, 25.6 d, 28.0 d, 30.5 d, 30.5 t, 35.3 d, 36.3 t, 44.0 d, 47.3 t, 55.7 q, 60.5 q, 109.7 d, 128.9 s, 135.3 s, 137.7 s, 144.7 s, 150.2 s.
20. For **14**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, 3H, J = 6.6 Hz), 0.99 (d, 3H, J = 6.5 Hz), 1.04 (d, 3H, J = 6.3 Hz), 1.17 (d, 3H, J = 6.9 Hz), 2.17 (s, 3H), 2.91 (m, 1H), 3.77 (s, 3H), 3.86 (s, 3H).

(*Received in Germany* 8 *July* 1994; *accepted* 27 *July* 1994)