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Chiral η^6-Arene-$Cr(CO)_3$ Complexes in Organic Synthesis: A Short and Highly Selective Synthesis of the 18-nor-*seco*-Pseudopterosin Aglycone

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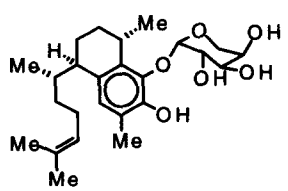
Abstract: The chiral synthetic building block 5,6-dimethoxy-1-tetralone-$Cr(CO)_3$ (**7**; >99% e.e.) was converted in only nine steps and with high regio- and diastereocontrol into the 18-nor-*seco*-pseudopterosin aglycone **3** (50 % overall yield). The synthesis is centrally based on the specific reactivity of the arene-$Cr(CO)_3$ substructure, especially on the stabilization of negative charge in benzylic position. The *trans*-configuration of the two benzylic substituents is secured by diastereoselective protonation of an anionic intermediate generated by conjugate addition of 4-methyl-3-pentenyl-lithium to complex **9**, prepared from **7** via Peterson olefination, *ortho*-silylation and benzylic deprotonation / methylation. © 1997 Elsevier Science Ltd.

In the course of our program directed towards the application of chiral nonracemic arene-$Cr(CO)_3$ complexes[1] as building blocks for the enantioselective total synthesis of biologically active compounds,[2] we recently demonstrated that 1,4-*cis*-disubstituted 5,6-dimethoxy-tetralin derivatives can efficiently be prepared by successive deprotonation / alkylation of both benzylic positions of the corresponding (nonracemic) $Cr(CO)_3$ complex.[3] Because a number of interesting natural products, e.g. the anti-inflammatory active sponge metabolite *seco*-pseudopterosin A (**1**)[4] or the serrulatane diterpene **2**,[5] represent 1,4-*trans*-disubstituted 5,6-dimethoxy-tetralins, we were searching for possibilities to exploit the specific chemical and stereochemical possibilities offered by the arene-$Cr(CO)_3$ chemistry also for the synthesis of *trans* configurated 1,4-disubstituted tetralins[6]. We here report on the results of a study which has culminated in an efficient synthesis of the 18-nor-*seco*-pseudopterosin aglycone (**3**).



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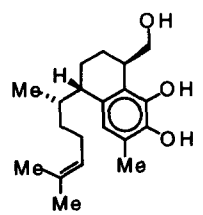

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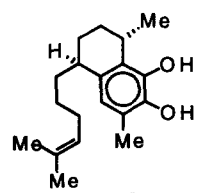

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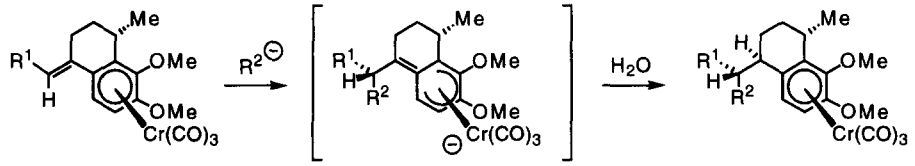
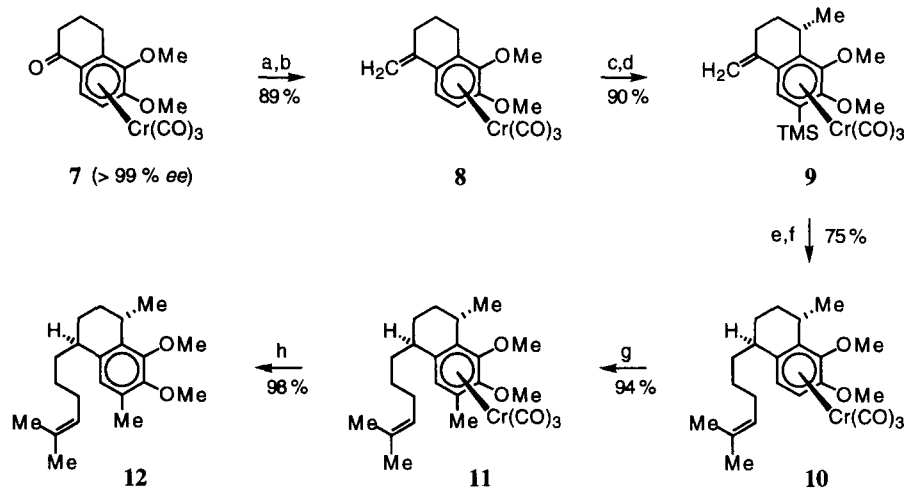
Our concept is briefly outlined in Scheme 1. It is based on the consideration that the addition of a nucleophile (e.g. R^2-Li) to the double bond[7] of a complex of type **4** should lead to an intermediate of type **5** which in turn would be diastereoselectively protonated from the unhindered π-face to afford preferentially a *trans*-configurated product of type **6**. In the case of $R^1 \neq H$, even the stereocenter in the sidechain should, in principle, be diastereoselectively generated because of the shielding effect of the bulky $Cr(CO)_3$ group.



4 5 6

Scheme 1

Our synthesis (Scheme 2)[8] starts with complex **7** (> 99% ee) which was enantioselectively prepared in 60 % overall yield from 5,6-dimethoxy-1-tetralone as described earlier.[9] Treatment of **7** with the reagent generated from trimethylsilylmethyllithium and cerium(III)cloride[10] followed by Peterson olefination (KH, THF)[11] of the intermediate *endo*-alcohol gave the methylenated product **8**[12] in excellent yield. Deprotonation of **8** (*n*-BuLi, THF, -78 °C) and subsequent addition of TMSCl furnished an *ortho*-silylated product, which in turn on treatment with *n*-BuLi (THF, -78 °C) gave rise to a benzylic deprotonated intermediate, as indicated by the red colour of the solution. After quenching with methyl iodide, complex **9**[13] was obtained in high yield. In the key step of the synthesis (compare Scheme 1), **9** was treated with 1.4 equivalents of 4-methyl-3-pentenyllithium (homoprenyllithium)[14] followed by aqueous workup to afford a 10 : 1-mixture of diastereomeric products. After desilylation (TBAF) the desired *trans*-configurated isomer **10**[15] was obtained in 75 % isolated yield (overall yield from **9**) besides 7 % of its *cis*-diastereomer after flash chromatography.

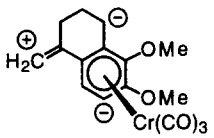


Scheme 2: a) TMS-CH_2-$CeCl_2$, THF, -75 °C → rt., 0.5 h, 96 %; b) KH, THF, rt., 10 min, 93 %; c) *n*-BuLi, THF, -78 °C, 0.5 h, then TMSCl (1.2 eq.), 94 %; d) *n*-BuLi, THF/ HMPT (70:1), -50 °C → 0 °C, 0.5 h, then MeI, -30 °C → 0 °C, 0.5 h, 96 %; e) homoprenyllithium (1.4 eq.), THF, -60 °C → 0 °C, 3 h, then 0.5 N HCl, 0 °C → rt., 94 % (10 : 1-mixture of diastereomers); f) TBAF, THF, H_2O, rt., 15 min, then separation of diastereomers by flash chromatography (SiO_2, hexane/EtOAc = 12 + 1), 80 % of **10**; g) *n*-BuLi, THF, -70 °C→ -40 °C, 2 h, then MeI, → 0 °C, 15 min, 94 %; h) h·ν, air, Et_2O, 98 %.

Having accomplished the crucial attachment of the sidechain, the concluding steps of the synthesis were performed in a straightforward manner as follows: Deprotonation / methylation of **10** furnished **11**[16]

which was submitted to photochemical decomplexation (Et_2O, air) to provide **12**[17] as a stable, storable compound (55 % overall yield from **7** !!). The conversion of **12** to the (air-sensitive) demethylated 18-nor-*seco*-pseudopterosin aglycone (**3**) was finally accomplished using boron trichloride (2 eq. BCl_3, CH_2Cl_2, 0 °C, 4 h)[18].

In conclusion, we have elaborated an extraordinary short, selective and efficient synthesis of the enantiopure *seco*-pseudopterosin analogue **3** starting from the chiral building block **7** thus demonstrating the power of the underlying arene-$Cr(CO)_3$ chemistry. As a particularly remarkable fact, we have shown that complex **8** represents an equivalent for the synthon **13** which can be threefold alkylated via sequential treatment with alkylithium reagents (deprotonation / alkylation, deprotonation / alkylation, conjugate addition / protonation). We are now trying to apply an analogous sequence towards the synthesis of the *seco*-pseudopterosin aglycone itself[6]. However, the direct ethylidenation of **7** to **14** seems to be rather difficult and we are therefore currently investigating other approaches to this key intermediate.



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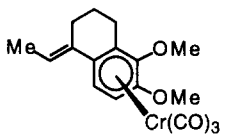

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REFERENCES AND NOTES

1. For the use of arene-$Cr(CO)_3$ chemistry in synthesis, see, for instance: a) Hegedus, L.S. *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley, **1994**, chapter 10; b) Semmelhack, M.F. in *Comprehensive Organometallic Chemistry II, Vol. 12*, Abel, E.W.; Stone, F.G.A.; Wilkinson, G., Eds.; Pergamon: Oxford, 1995, pp. 979-1015; c) Semmelhack, M.F., *ibid.*, pp. 1017-1038; d) Davies, S.G.; McCarthy, T.D.; *ibid.* pp. 1039-1070.
2. For some recent publications in this series, see: a) Schmalz, H.-G.; Schwarz, A.; Dürner, G. *Tetrahedron Lett.* **1994**, *35*, 6861; b) Schmalz, H.-G.; Majdalani, A.; Geller, T., Hollander, J. Bats, J. W. *Tetrahedron Lett.* **1995**, *36*, 4777; c) Schmalz, H.-G.; Siegel, S.; Schwarz, A. *Tetrahedron Lett.* **1996**, *37*, 2947; d) Schmalz, H.-G.; Schellhaas, K. *Angew. Chem.* **1996**, *108*, 2277; *Angew. Chem. Int. Ed. Engl.***1996**, *35*, 2146; e) see ref. 3.
3. a) Schmalz, H.-G.; Hollander, J.; Arnold, M.; Dürner, G. *Tetrahedron Lett.* **1993**, *34*, 6259; b) Schmalz, H.-G.; Arnold, M.; Hollander, J.; Bats, J.W. *Angew. Chem.* **1994**, *106*, 77; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 109.
4. a) Look, S.A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363; b) for a total synthesis of the racemic *seco*-pseudopterosin aglycone, see: McCombie, S.W.; Cox, B.; Lin, S.-I.; Ganguly, A.K.; McPhail, A.T. *Tetrahedron Lett.* **1991**, *32*, 2083; c) for a recent synthetic approach to the pseudopterosins via *seco*-intermediates, see: Gill, S.; Kociensky, P.; Kohler, A.; Pontiroli, A,; Qun, L. *J. Chem. Soc., Chem. Commun.* **1996**, 1743.
5. a) Tippet, L.M.; Massy-Westtropp, R.A. *Phytochem.* **1993**, *33*, 417; b) Croft, K.D.; Ghisalberti, E.L.; Jefferies, P.R.; Proudfoot, G.M. *Aust. J. Chem.* **34**, 1951.
6. We have recently completed a synthesis of the *seco*-pseudopterosin aglycone using a different strategy,

see: a) Majdalani, A.; Schmalz, H.-G. manuscript in preparation; b) for a synthesis of dihydroxyserrulatic acid employing racemic chromium arene complexes, see: Uemura, M.; Nishimura, M., Minami, T., Hayashi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 5402.

7. For the nucleophile addition to styrene-$Cr(CO)_3$ derivatives, see: a) Semmelhack, M.F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584; b) Uemura, M.; Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1193; c) see also ref. 1b and references cited therein.
8. All Compounds were fully characterized by the usual spectroscopic methods and gave correct elemental analyses and/or HRMS data; yields refer to the pure products after flash chromatography and/or recrystallization.
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) see ref. 2b.
10. Prepared in situ by addition of TMS-CH_2-Li to a preformed suspension of dry $CeCl_3$ in THF following the general procedure of Imamoto; for a review, see: Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747.
11. a) Peterson, D.J. *J. Org. Chem.* **1968**, *33*, 780; b) Ager, D.J. *Org. Reactions* **1990**, *38*, 1.
12. For **8**: Fp. 126 °C, $[\alpha]_D^{20}$ = -378.7° (c = 0.90 in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ = 1.82-1.89 (m, 2H), 2.27-2.38 (m, 1H), 2.43-2.53 (m, 1H), 2.79 (ddt, 1H, *J* = 17.6, 7.0, 1.6 Hz), 2.95 (dt, 1H, *J* = 17.6, 6.0 Hz), 3.87 (s, 6H), 4.97 (ψs, 1H), 5.16 (d, 1H, *J* = 7.3 Hz), 5.36 (ψs, 1H), 5.81 (d, 1H, *J* = 7.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.9 (t), 24.3 (t), 31.7 (t), 56.1 (q), 65.3 (q), 73.3 (d), 87.0 (d), 95.9 (s),109.5 (s), 109.6 (t), 127.6 (s), 135.8 (s), 139.6 (s), 233.8 (s).
13. For **9**: Fp. 110-111 °C, $[\alpha]_D^{20}$ = -438.7° (c = 0.49 in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ = 0.38 (s, 9H), 1.34 (d, 3H, *J* = 7.0 Hz), 1.70-1.80 (m, 1H), 2.04-2.17 (m, 1H), 2.34-2.57 (m, 2H), 3.26 (ψquin., 1H), 3.82 (s, 3H), 3.85 (s, 3H), 5.00 (ψd, 1H, *J* = 2.0 Hz), 5.38 (ψd, 1H, *J* = 2.0 Hz), 5.76 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = -0.1 (q), 20.2 (q), 26.2 (t), 28.0 (t), 28.1 (t), 60.6 (q), 65.2 (q), 90.3 (s), 93.3 (d), 95.8 (s), 110.0 (t), 115.2 (s), 131.3 (s), 138.9 (s), 139.6 (s), 233.6 (s).
14. Prepared from 4-methyl-3-pentenyl bromide and Li powder (suspension in hexane) in Et_2O at -25 °C.
15. For **10**: oil; $[\alpha]_D^{20}$ = +196.1° (c = 0.54 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, 3H, *J* = 7.0 Hz), 1.30-1.43 and 1.48-1.60 (m, together 6H), 1.62 (s, 3H), 1.70 (s, 3H), 1.72-1.80 and 1.93-2.04 (m, together 4H), 2.33-2.39 (m, 1H), 3.04 (ψquin., 1H), 3.81 (s, 3H), 3.85 (s, 3H), 4.93 (d, 1H, *J* = 7.0 Hz), 5.11-5.15 (m, 1H), 5.40 (d, 1H, J = 7.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.7 (q), 19.8 (t), 20.3 (q), 24.4 (t), 25.7 (q), 27.7 (t), 28.2 (d), 33.5 (d), 38.6 (t), 55.6 (q), 66.3 (q), 71.3 (d), 94.2 (d), 106.4 (s), 118.6 (s), 124.1 (d), 126.0 (s), 131.8 (s), 137.2 (s), 234.5 (s);
16. For **11**: oil; $[\alpha]_D^{20}$ = +13.9° (c = 0.74 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, 3H, *J* = 7.0 Hz), 1.47-1.69 (m, 6H), 1.64 (s, 3H), 1.71 (s, 3H), 1.76-1.83 (m, 1H), 1.86-1.93 (m, 1H), 2.01-2.09 (m, 2H), 2.17 (s, 3H), 2.36-2.42 (m, 1H), 3.02 (ψquin., 1H), 3.80 (s, 3H), 3.92 (s, 3H), 5.13-5.15 (m, 1H), 5.30 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.5 (q), 17.7 (q), 20.3 (q), 20.5 (t), 24.9 (t), 25.7 (q), 27.8 (t), 27.9 (d), 28.3 (t), 33.8 (d), 37.7 (t), 60.8 (q), 65.1 (q), 95.2 (d), 98.1 (s), 109.2 (s), 115.6 (s), 124.2 (d), 131.5 (s), 131.7 (s), 134.5 (s), 234.4 (s).
17. For **12**: oil; $[\alpha]_D^{20}$ = -5.7° (c = 0.65 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, 3H, *J* = 7.2 Hz), 1.35-1.55 (m, 6H), 1.61 (s, 3H), 1.70 (s, 3H), 1.85-1.90 and 1.96-2.05 (m, 2H), 2.22 (s, 3H), 2.59-2.64 (m, 1H), 3.09 (ψquin., 1H), 3.79 (s, 3H), 3.88 (s, 3H), 5.11-5.16 (m, 1H), 6.66 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.7 (q), 17.7 (q), 20.4 (t), 22.0 (q), 24.9 (t), 25.7 (q), 27.2 (d), 28.1 (t), 28.3 (t), 37.1 (d), 37.4 (t), 59.7 (q), 60.2 (q), 124.7 (d), 126.1 (d), 129.1 (s), 131.3 (s), 133.5 (s), 137.4 (s), 148.8 (s), 150.4 (s), 234.4 (s).
18. When the reaction of **12** with BCl_3 was run at higher temperatures (20 °C) a side-product resulting from hydrochlorination of the sidechain doublebond was formed in high yield.

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