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# Unexpected *endo* Selectivity of Conjugate Nucleophilic Addition to an Arene–$Cr(CO)_3$ Complex: Enantioselective Synthesis of the Diterpene 11-*epi*-Helioporin B

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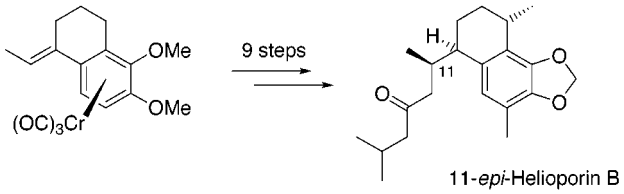
## ABSTRACT




**Starting from a nonracemic planar–chiral arene tricarbonyl chromium complex, an epimer of the bioactive marine diterpene helioporin B was synthesized in a highly stereoselective fashion. The stereostructure of the product (11-*epi*-helioporin B) corresponds to that of other serrulatane-type natural products. In a key step of the synthesis, 2-lithioacetonitrile undergoes conjugate nucleophilic addition to an unsaturated complex. Remarkably, this addition occurs in an *endo* mode, i.e., from the complexed face of the $\pi$-ligand.**

Since the discovery of the highly antiinflammatory pseudopterosins[1] and *seco*-pseudopterosins,[2] several other new bioactive diterpenoids with related structures have been isolated from marine organisms. These include, for instance, the antiviral and cytotoxic helioporins (e.g., **1**, **2**, and **3a**)[3] as well as the antimycobacterial pseudopteroxazoles (e.g., **4**).[4] Due to their interesting structural and biological features, these compounds have attracted the attention of several synthetic laboratories.[5]

Recently, we reported stereorational syntheses of the structure originally proposed for helioporin D[6a] and of a derivative of putative helioporin C.[6b] On the basis of this work, we suggested a revised stereostructure for the helioporins (Figure 1) which was subsequently confirmed by the total syntheses of helioporin D (**1**)[7] and helioporin E (**2**).[5d]

In continuation of our research program aimed at the use of arene−$Cr(CO)_3$ chemistry[8] in enantioselective synthesis, we here disclose a study which was originally targeted at the synthesis of helioporin B (**3a**).

(1) (a) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140. (b) Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S. A.; Van Duyne, G.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916.

(2) Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363.

(3) Tanaka, J.-i.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D. G. *Tetrahedron* **1993**, *49*, 811.

(4) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527.

(5) Selected recent work: (a) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem.* **2001**, *113*, 2543. (b) Corey, E. J.; Johnson, T. W. *J. Am. Chem. Soc.* **2001**, *123*, 4475. (c) Harrowven, D. C.; Wilden, J. D.; Tyte, M. J.; Hursthouse, M. B.; Coles, S. J. *Tetrahedron Lett.* **2001**, *42*, 1193. (d) Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389. (e) LeBradidec, J.-Y.; Kocienski, P. J.; Connolly, J. D.; Muir, K. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475. (f) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777. (g) Majdalani, A.; Schmalz, H.-G. *Synlett* **1997**, 1303. (h) McCombie, S. W.; Ortiz, C.; Cox B.; Ganguly, A. K. *Synlett* **1993**, 541.

(6) (a) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537. (b) Hörstermann, D.; Schmalz, H.-G.; Kociok-Köhn, G. *Tetrahedron* **1999**, *55*, 6905.

(7) (a) Geller, T.; Jakupovic, J.; Schmalz, H.-G. *Tetrahedron Lett.* **1998**, *39*, 1541.

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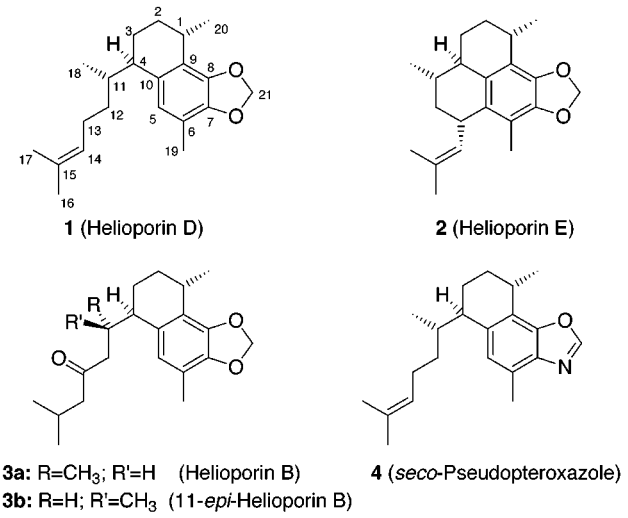
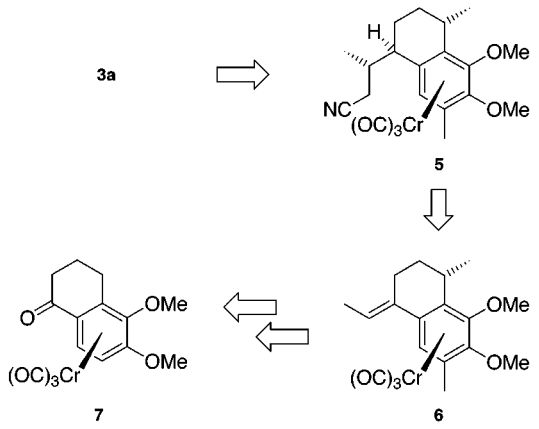



**Figure 1.** Structures of selected helioporins and of *seco*-pseudopteroxazole with revised configuration at C1.[5b,d,7]

Our retrosynthetic analysis (Scheme 1) is related to a strategy we had previously used for the synthesis of the nor-*seco*-pseudopterosin aglycone.[9] We considered the nitrile **5**

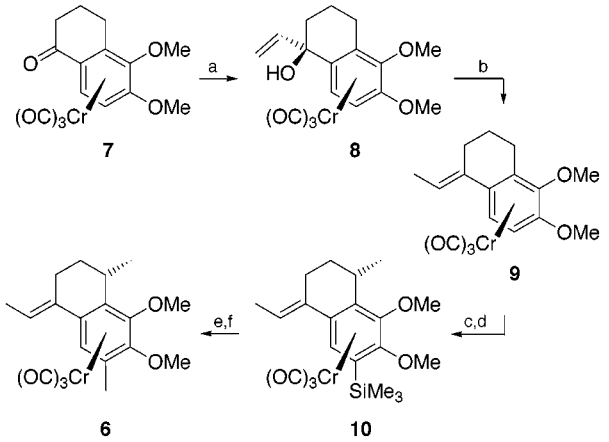
**Scheme 1.** Retrosynthetic Analysis




to be a suitable pre-target compound, which we intended to prepare by nucleophilic conjugate addition of the acetonitrile anion to the unsaturated complex **6**.[10] Due to the steric bulk of the $Cr(CO)_3$ fragment, we expected both the nucleophile attack and the subsequent protonation step to occur diastereoselectivly from the less shielded (*exo*) face of the arene. Complex **6** in turn was considered to be obtainable from the planar−chiral building block **7**.

The early part of our synthesis is shown in Scheme 2: Starting from the enantiomerically pure complex **7**[5g,9,11]

**Scheme 2**[a]




[a] Reagents and conditions: (a) $CH_2$=CHMgCl (3 equiv), $CeCl_3$ (4 equiv), THF, −55 to −30 °C, 1 h; (b) $Et_3SiH$ (3 equiv), $Me_2AlCl$ (2 equiv), $EtAlCl_2$ (1 equiv), $CH_2Cl_2$, −78 to 0 °C, 4 h, 67% (two steps); (c) *n*-BuLi (1.1 equiv), THF, −78 °C, 0.5 h, then TMSCl (2.0 equiv), 0.5 h, 96%; (d) *n*-BuLi (2.2 equiv), THF/HMPA (10:1), −40 to 0 °C, 1.5 h, then MeI (3.0 equiv), −40 °C, 0.5 h, 99%; (e) TBAF (1.5 equiv), THF, 0 °C, 1.5 h, 92%; (f) *n*-BuLi (1.3 equiv), THF, −78 °C, 1.5 h, then MeI (2.0 equiv), 98%.

($[\alpha]^{20}_D = -403$, $c = 0.12$ in $CHCl_3$), the first goal was the introduction of the ethylidene group. Initial attempts to achieve the direct olefination of **7** by standard methods failed. However, we found that $CeCl_3$ supported[12] addition of vinylmagnesium chloride to the ketone **7** and (vinylogous) ionic hydrogenation[13] of the resulting tertiary alcohol **8** with $Et_3SiH$ in the presence of a mixture of $Me_2AlCl$ and $EtAlCl_2$ as a Lewis acid gave the desired olefin **9** in 67% overall yield. The use of other Lewis acids ($BF_3{\cdot}Et_2O$, $EtAlCl_2$) or protic acids (TFA) resulted in the formation of inseparable mixtures of **9** and the corresponding hydrogenated (ethyl substituted) complex. Possibly, overreduction is suppressed by $Me_2AlCl$ because it serves as a proton scavenger.[14] The conversion of **9** to **6** (Scheme 2) was then performed in analogy to a synthetic sequence we had elaborated earlier for a related system.[9] After protecting the most acidic (arylic) position of **9** by silylation, deprotonation occurred regioselectively at the benzylic position, allowing the diastereoselective introduction of the methyl substituent at C1. Removal of the TMS group from complex **10** was followed by another deprotonation/methylation sequence to afford the

(8) Recent reviews on arene−$Cr(CO)_3$ chemistry: (a) Schmalz, H.-G.; Siegel, S. In *Transition Metals for Fine Chemicals and Organic Synthesis*; Bolm, C., Beller, M., Eds.; VCH: Weinheim, 1998. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; Chapter 10.

(9) Majdalani, A.; Schmalz, H.-G. *Tetrahedron Lett.* **1997**, *38*, 4545.

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(11) Schmalz, H.-G.; Millies, B.; Bats, J. W.; Dürner, G. *Angew. Chem.* **1992**, *104*, 640; Angew. *Chem., Int. Ed. Engl.* **1992**, *31*, 631.

(12) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747.

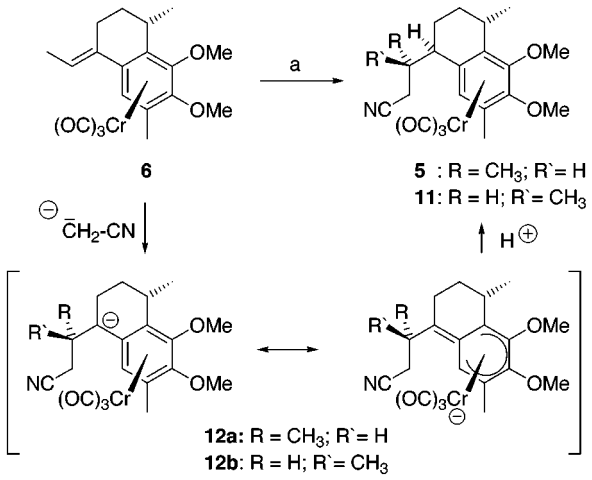
(13) (a) Semmelhack, M. F.; Bisaha, J.; Czarny, M. *J. Am. Chem. Soc.* **1979**, *101*, 768. For a review, see: (b) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

(14) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

desired intermediate **6** as a clean stereoisomer (85% overall yield from **9**).

In the crucial step of the synthesis (Scheme 3), complex **6** was treated with 2-lithioacetonitrile (prepared from MeCN

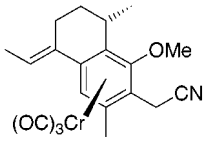
**Scheme 3**[a]




[a] Reagents and conditions: (a) $LiCH_2CN$, 1,4-dioxane/HMPA (10:1), 10 °C, 1 h, then saturated $NH_4Cl/H_2O$, 0 °C, 51% of **5**/**11** (dr = 8:92); 33% of pure **11** (dr > 99:1) after recrystallization from hexane/EtOAc.

and LDA in THF at −78 °C) in a mixture of dioxane/HMPA (10:1) at 10 °C.

The immediate appearance of a dark red color indicated the formation of a resonance-stabilized benzylic anion (**12**). After quenching the reaction mixture with saturated aqueous $NH_4Cl$, a mixture of the diastereomeric conjugate addition products **5**/**11** (dr = 8:92; HPLC) was isolated in 51% yield. Interestingly, significant amounts (33%) of complex **13**[15] were also obtained as an unexpected byproduct obviously formed from **6** by nucleophilic aromatic *ipso* substitution of a methoxy group (Figure 2).[16]




**13**

**Figure 2.** Structure of the byproduct **13** resulting from **6** by nucleophilic substitution of a methoxy group.

NMR investigation of the mixture of the conjugate addition products (**5**/**11**) proved the *trans* orientation of the two benzylic side chains (NOE between C4-H and C1-Me) in both diastereomers. This indicated that the protonation of the anionic intermediate (**12**) had occurred from the uncomplexed *exo* face, as expected.[9]

After recrystallization from hexanes/EtOAc (1:1), the diastereomerically pure main product was obtained in 33% yield and its configuration was determined by X-ray crystallography. To our surprise, the crystal structure (Figure 3)[17]

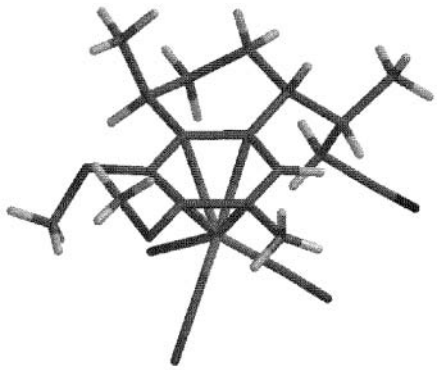


**Figure 3.** Structure of complex **11** in the crystalline state.

unambiguously showed that, instead of the expected complex **5** (vide supra), the diastereomeric compound **11** had been formed as the main product of the reaction shown in Scheme 3.

The formation of **11** as the main diastereomer indicates that the stabilized anion **12b** (and not **12a**) was formed as the primary intermediate. This means that *the acetonitrile anion attacks at the double bond of* **6** *preferentially from the endo face and not, as originally expected, from the exo face*. This fact deserves special recognition because it contradicts one of the basic paradigms in arene−$Cr(CO)_3$ chemistry, i.e., the rule that nucleophiles (usually) attack the ligand from the *exo*-face.[10,16,18]

However, the observed selectivity can be understood in terms of a more subtle analysis of the substrate geometry. The X-ray crystal structure of complex **10** (Figure 4)[17,19] shows the saturated ring of the tetralin system adopting a conformation in which the *exo* attack is hindered by the pseudoaxial methyl substituent at C1. In addition, *endo* attack is facilitated due to a significant deviation of the ethylidene unit out of the plane.

While the unexpected stereochemical outcome of the key reaction thwarted our original plans to synthesize helioporin B, we were well aware that several other natural products

(15) The constitution of **13** was secured by NOE measurements.

(16) For reviews on $S_NAr$ reactions on complexed arenes, see: (a) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II, Vol. 12*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; p 979. (b) Rose-Munch, F.; Gagliardini, V.; Renard, C.; Rose, E. *Coord. Chem. Rev.* **1998**, *178*−*180*, 249.

(17) For details of the X-ray analysis, see Supporting Information.

(18) For rare exceptions, see: (a) Schmalz, H.-G.; Jope, H. *Tetrahedron* **1998**, *54*, 3457. (b) Sarkar, A.; Ganesh, S.; Sur, S.; Mandal, S. K.; Swamy, V. M.; Maity, B. C.; Kumar, T. S. *J. Organomet. Chem.* **2001**, *624*, 18.

(19) The crystal structure was actually obtained from a sample of *ent*-**10**. Comparison of NMR data allowed the assumption that the preferred conformation of **10** resembles that of **6**.

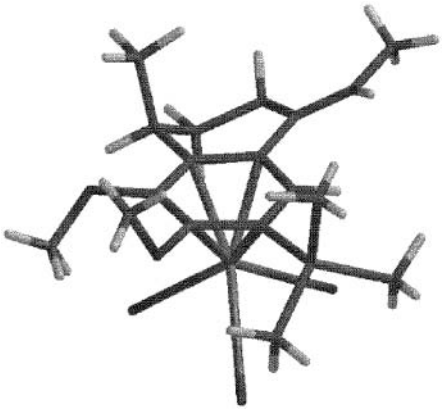


**Figure 4.** Structure of **10** in the crystalline state.[17,19]

of the serrulatane class possess exactly the relative configuration as compound **11**.[20] Thus, to demonstrate the feasibility of our synthetic concept, we decided to transform **11** into 11-*epi*-helioporin B (**3b**). This was accomplished in a sequence of four steps (Scheme 4): Oxidative decomplexation of **11** yielded the free ligand **14**. After cleavage of both methyl ether functions using LiSEt as the reagent of choice,[6a,21] the benzodioxole substructure was established by reacting the catechol intermediate with $CH_2Cl_2$ and CsF.[22] Finally, the conversion of nitrile **15** into 11-*epi*-helioporin B (**3b**) was achieved by addition of isobutylmagnesium bromide in benzene and subsequent aqueous workup.[23]

In conclusion, we have elaborated a highly stereoselective synthesis of 11-*epi*-helioporin B (**3b**) by exploiting the unique chemical and stereochemical opportunities of arene−chromium chemistry. The synthesis needs 11 steps (8% overall yield) starting from enantiomerically pure complex **7**. In addition, the work has led to the discovery of a rare

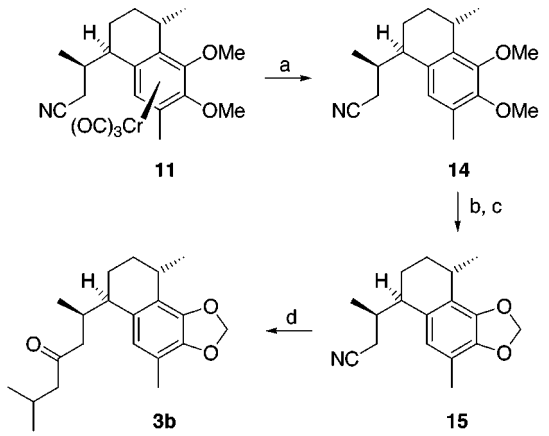
(20) (a) Forster, P. G.; Ghisalberti, E. L.; Jefferies, P. R.; Poletti, V. M.; Whiteside, N. J. *Phytochemistry* **1986**, *25*, 1377. (b) Ghisalberti E. L. *Phytochemistry* **1994**, *35*, 7; and references cited therein.

(21) LiSEt was prepared from HSEt and *n*-BuLi in hexane at 0 °C followed by solvent evaporation.

(22) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, 3361.

(23) Krafft, M. E.; Dasse, O. A.; Fu, Z. *J. Org. Chem.* **1999**, *64*, 2475.

**Scheme 4**[a]




[a] Reagents and conditions: (a) air/sunlight, $Et_2O$, 0 °C, 24 h, 99%; (b) LiSEt (10 equiv), DMF, 160 °C, 2 h, 99%; (c) $CH_2Cl_2$ (6 equiv), CsF (6 equiv), DMF, 130 °C, 4.5 h, 60%; (d) *i*-BuMgBr (6 equiv), benzene, 80 °C, 3 h, 73%.

case of nucleophilic *endo* addition to an arene−$Cr(CO)_3$ complex. We are optimistic that the strategy can be used for the synthesis of potentially bioactive compounds (helioporin and *seco*-pseudopterosin analogues) with varying benzylic side chains and substituents at the aromatic part of the tetralin core.

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**Supporting Information Available:** Characteristic data for all new compounds. Details of the X-ray analysis of compounds **11** and *ent*-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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