ORGANIC LETTERS

2012
Vol. 14, No. 23
5996–5999

An Enantioselective Total Synthesis of Helioporins C and E

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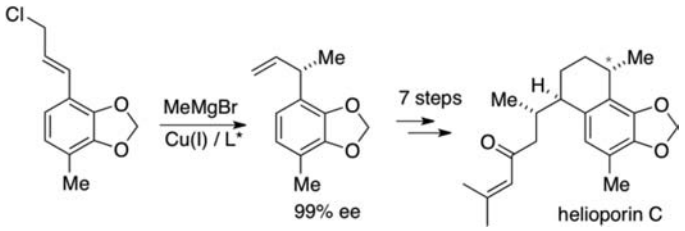
Received October 21, 2012

ABSTRACT



A short and enantioselective total synthesis of helioporins C and E, which are bioactive marine diterpenes containing a serrulatane or amphilectane skeleton, was elaborated. The chirogenic step, i.e. a Cu(I)-catalyzed allylic alkylation of a cinnamyl chloride with methylmagnesium bromide, proceeded with virtually complete enantioselectivity (99% *ee*) in the presence of a chiral phosphine-phosphite ligand. The other stereocenters were diastereoselectively established through Me_2AlCl-mediated cationic cyclization and Ir-catalyzed hydrogenation.

The helioporins, for instance helioporin C (**1**) and helioporin E (**2**), are marine metabolites isolated by Higa and co-workers from the blue coral *heliopora coerulae* and were found to exhibit antiviral and cyctotoxic activities.[1] These polycyclic diterpenes possess a serrulatane or an amphilectane skeleton and closely resemble the aglycones of the earlier discovered seco-pseudopterosins[2] and pseudopterosins,[3] respectively.

Some years ago, in the course of our work on the use of chiral arene–$Cr(CO)_3$ complexes as synthetic building blocks we revised the initial stereochemical assignments of helioporins C and D through stereorational total synthesis of the proposed structures and by chemical correlation with the seco-pseudopterosin aglycone.[4] Our stereostructural proposal was later confirmed by Corey and co-workers in a total synthesis of helioporin E.[5]

We here describe a novel, short, and enantioselective synthetic approach toward the helioporins (C and E) exploiting various metal-catalyzed transformations and, in particular, an asymmetric Cu-catalyzed allylic substitution reaction to set up the first chirality center.

Our synthetic strategy (Scheme 1) implies a late stage divergence toward either **1** or **2**. We envisaged that the central allylic alcohol intermediate **3** could be prepared from calamenene **4**, which in turn might be accessible by Lewis acid initiated diastereoselective cyclization of **5**, in analogy to a transformation previously described.[6]

Furthermore, we intended to assemble the cyclization precursor **5** through hydroboration/Suzuki coupling from the terminal olefin **6**. This first chiral intermediate was projected to be prepared from the cinnamyl chloride **7** applying our recently developed protocol[7] for Cu(I)-catalyzed asymmetric allylic alkylation.

The synthesis of the cinnamyl chloride **7**, i.e. the projected substrate for the enantioselective allylic alkylation, started with the directed *ortho*-metalation of 2,3-dimethoxy-toluene (**8**) with *tert*-BuLi/TMEDA

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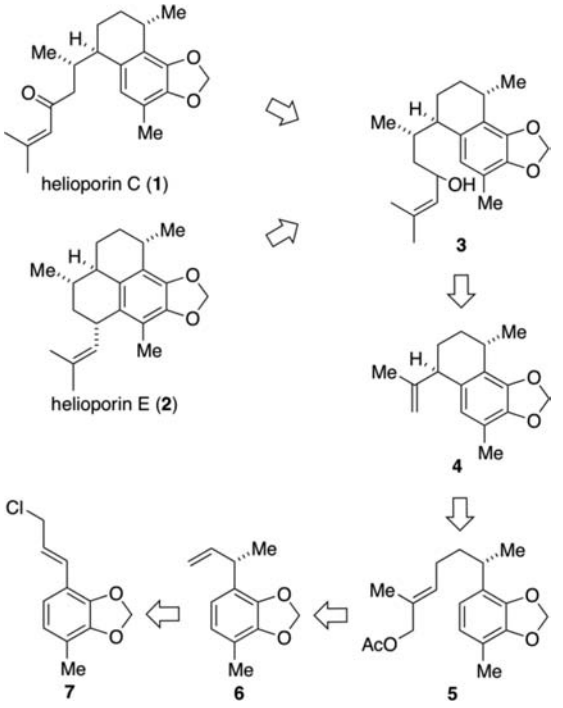
10.1021/ol302898h
Published on Web 11/13/2012

Scheme 1. Retrosynthetic Analysis

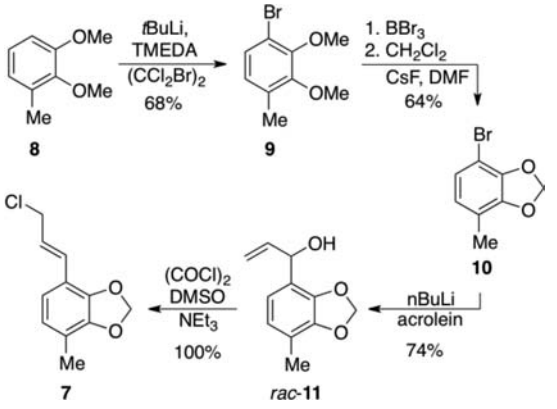


under apolar solvent conditions (pentane/Et_2O = 10:1) followed by bromination of the aryllithium intermediate. Cleavage of the methoxy groups of **9** with BBr_3 and subsequent methylenation of the resulting catechol with CH_2Cl_2/CsF[8] afforded the benzodioxole **10**, which turned out to be rather volatile. Treatment of **10** with *n*-BuLi (Br−Li exchange) followed by 1,2-addition of the intermediate aryl lithium species to acrolein gave the allylic alcohol *rac*-**11**. Chlorination (under allylic rearrangement) was achieved under Moffat−Swern conditions[9] to yield the cinnamyl chloride **7** in quantitative yield (Scheme 2).

Noteworthy, a direct *ortho*-functionalization of (nonbrominated) benzodioxoles (e.g., debrominated **10** or benzodioxole itself) through lithiation (with *n*-BuLi or *tert*-BuLi) could not be achieved.

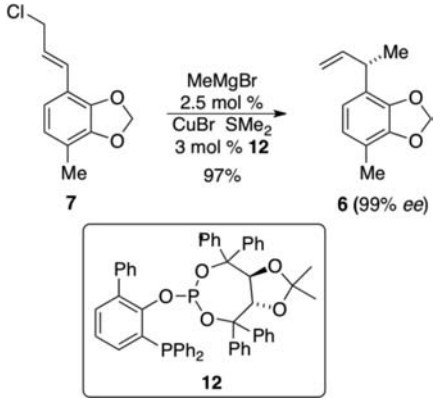
The enantioselective conversion of **7** into the chiral building block **6** was performed under the previously reported conditions[7] for the Cu-catalyzed allylic alkylation[10] of cinnamyl chlorides using Grignard reagents as nucleophiles (Scheme 3). Thus, **7** was reacted with Me-MgBr in the presence of catalytic amounts of the (*S*,*S*)-TADDOL-derived chiral phosphine-phosphite ligand **12**[11] and CuBr•SMe_2 under appropriate cooling (−78 °C). Much to our satisfaction, the desired product **6** was obtained in excellent yield (97%),

Scheme 2. Preparation of Cinnamyl Chloride **7**



with high regioselectivity (≥99:1) and in virtually enantiopure form (99% *ee*) even on a multigram scale.[12]

Scheme 3. Cu(I)-Catalyzed Asymmetric Alkylation of **7** with MeMgBr in the Presence of the Phosphine-Phosphite Ligand **12**



The absolute configuration of **6** was confirmed (to be *S*) by comparison of the TDDFT-calculated[13] and measured circular dichroism (CD) spectra.[14]

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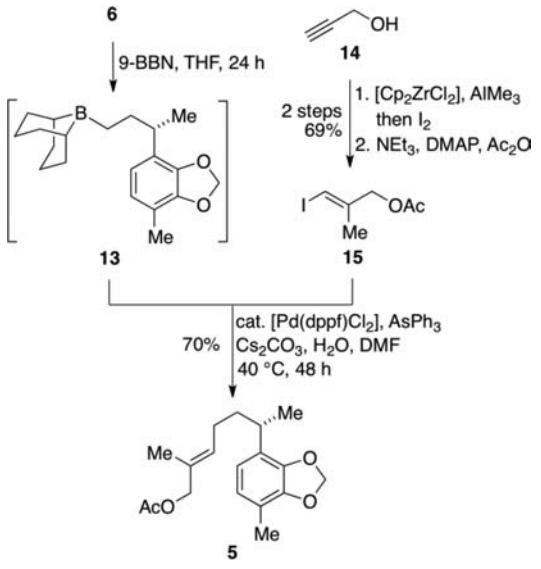
(12) For the synthesis of a compound related to **6** through asymmetric hydrovinylation, see: Mans, D. J.; Cox, G. A.; RajanBabu, T. V. *J. Am. Chem. Soc*. **2011**, *133*, 5776.

(13) (a) Calculation of the CD spectrum in MeOH was performed with: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, revision d.02; Gaussian, Inc.: Pittsburgh, PA, 2003. (b) A B3LYP functional with TZVP (triple-ζ basis set with polarisation functions) basis set was applied.

The cyclization precursor **5** was prepared from olefin **6** by Suzuki coupling of the in situ formed borane **13** with the vinyl iodide **15**, which in turn was synthesized from propargylic alcohol **14** in 69% yield through Zr-catalyzed methyl-alumination/iodination[15] followed by acetylation of the alcohol functionality (Scheme 4).[16]

Scheme 4. Synthesis of the Cyclization Precursor **5**



The use of the iodo-allyl acetate **15** (instead of the corresponding bromo-allyl-TBS-ether)[6] in the Pd-catalyzed Suzuki coupling was not trivial. However, this reaction was achieved in 70% yield employing 10 mol % of $Pd(dppf)Cl_2/AsPPh_3$ at slightly elevated temperatures (40 °C) for 48 h. Under these comparably mild conditions, the direct introduction of the allylacetate moiety was possible without much loss associated with the formation of reactive π-allyl-Pd intermediates.

According to the devised strategy (Scheme 1), the (diastereoselective) Friedel–Crafts-type cyclization of the allylic acetate **5** was investigated next (Scheme 5). Using Me_2AlCl (2.5 equiv), as reported earlier for a similar system,[6] the reaction proceeded smoothly to give preferentially the *trans*-calamenene **4**; however, the diastereoselectivity did not exceed a 4:1 ratio even at −15 °C in CCl_4. Thus, in comparison to the related veratrol-derived substrate, the (more electron rich) benzodioxole **5** reacted faster but with lower diastereoselectivity. Variation of both the solvent and the Lewis acid did not lead to an improvement. Also, attempts to achieve the cyclization by intramolecular arylation of an electrophilic Pd-allyl intermediate[17] (in the presence of catalytic amounts of a Pd^0 source with or without addition of a base) only led to the formation of uncyclized products with an isomerized double bond.

Since the steroisomers of **4** were not separable, the synthesis was continued with the 4:1 mixture. The side chain was elongated through Lewis acid mediated carbonyl-ene reaction[18] employing the silyl-protected glycolaldehyde **16**, which was prepared from ethylene glycol in two steps.[19] This way, the alcohol **17** was obtained in 68% yield (as a 1:1 mixture of epimers) besides 16% of reisolated starting material.[20] The *homo*-benzylic stereocenter was then set up in a highly diastereoselective manner by hydrogenation of the exocyclic double bond using the iridium catalyst **18** developed by Pfaltz and co-workers.[21] In the presence of 2 mol % of **18** at 50 bar of H_2 a full conversion of **17** was achieved within 96 h. After purification by flash column chromatography a mixture (ca. 1:1) of **19a** and its desilylated congeneer **19b** was isolated in 78% yield. In a one-pot procedure, the desilylation was completed by treatment with tetrabutylammonium fluoride followed by oxidative cleavage of the glycole **19b** with periodic acid to afford the aldehyde **20** in quantitative yield (Scheme 5). At this stage, ^1H NMR analysis allowed determination of the selectivity of the previous hydrogenation step as >95:5 in favor of the desired diastereoisomer. To complete the carbon skeleton the aldehyde **20** was reacted with isobutenylmagnesium bromide to afford a 1:1 epimeric mixture of the acid-sensitive intermediate **3** in 85% yield after purification on Celite.

Having successfully prepared the key allylic alcohol **3** we next investigated its oxidation to helioporin C (**1**) as a first target structure (Scheme 6). Using either Jones reagent or Dess-Martin periodinane (DMP) the product was contaminated with major amounts of **2** (and its diastereomer) resulting from acid-triggered cyclization. However, this side reaction could be suppressed by using DMP in the presence of 3 equiv of pyridin. This way, helioporin C (**1**) was obtained in 86% yield.

Next, the cationic cyclization of **3** to helioporin E (**2**) was investigated. While this transformation takes place readily in the presence of a Brønsted or Lewis acid, the challenge was to achieve a significant level of diastereoselectivity. By employing $MeSO_3H$ (30 mol %) as an acid at very low temperatures in CH_2Cl_2/pentane (3/1), the product, i.e. helioporin E (**2**), was formed in 98% yield, however, as a 3:1 mixture of epimers, which could not be separated by chromatography.

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(16) The expected (*E*) configuration of **15** was confirmed by a NOESY experiment.

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(18) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

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(20) For unknown reasons, the conversion of **4** was never complete even after prolonged reaction times even using an excess of Me_2AlCl.

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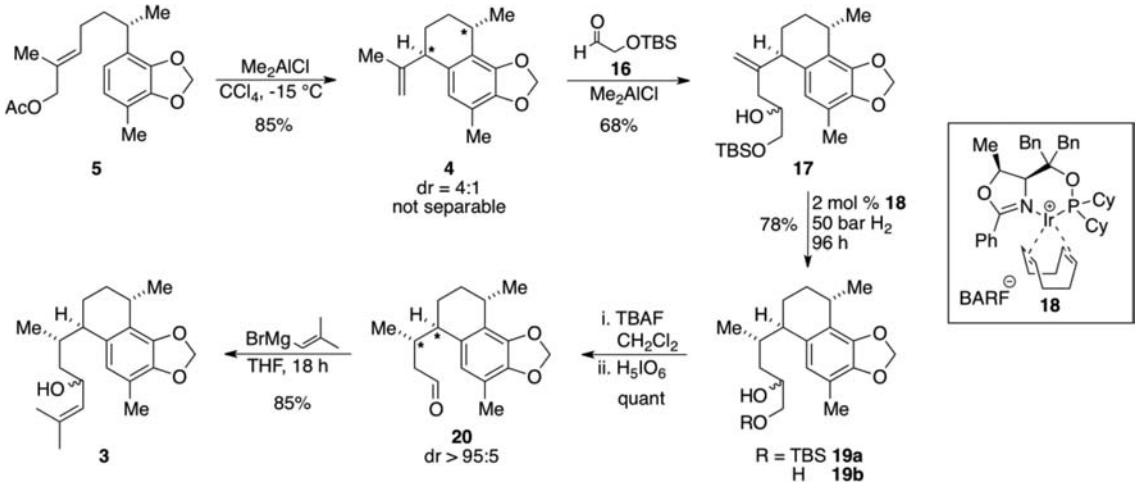
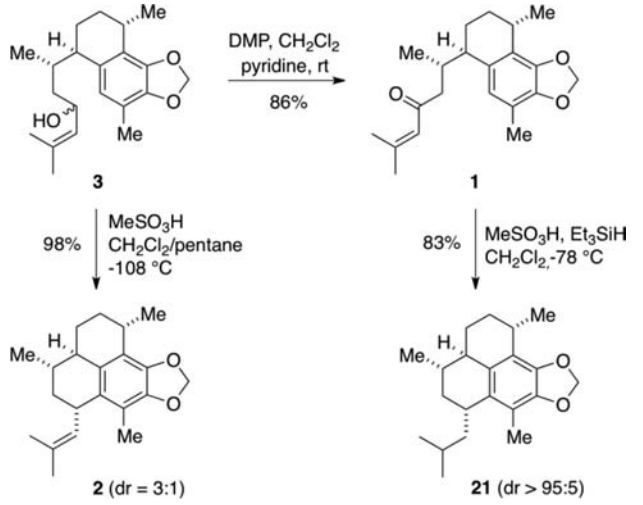
Scheme 5. Conversion of **5** into the Allylic Alcohol **3** as a Late Key Intermediate

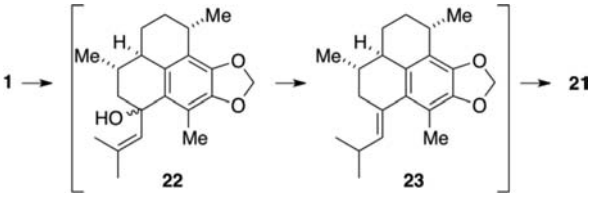


Scheme 6. Preparation of the Helioporins C (**1**) and E (**2**) from Allylic Alcohol **3** and Derivative **21** from Helioporin C (**1**)



Interestingly, dihydro-helioporin E (**21**) was obtained with excellent diastereoselectivity (> 95:5) by treatment of **1** with $MeSO_3H$ in the presence of Et_3SiH (Scheme 6). We assume this transformation to proceed via **22** as an intermediate, which is converted to **23** and further to **21** in two subsequent ionic hydrogenation steps (Scheme 7). Thus, the configuration at the new stereocenter is established in this case through diastereoselective hydride transfer from Et_3SiH to a benzylic carbenium ion.

Scheme 7. Proposed Intermediates in the Conversion of **21** to **1**



To conclude, we have elaborated a short total synthesis of helioporins C and E exploiting a series of catalytic steps. We are currently trying to improve the diastereoselectivity of the cyclization step and to apply the strategy to the synthesis of structurally related marine diterpenoids and analogs, which are of high pharmacological interest.

Acknowledgment. This work was supported by the University of Cologne. We thank the Chemetall GmbH for valuable gifts of organolithium and Grignard reagents.

Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.