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Synthesis of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-Hexamethyldocosane from *Antitrogus parvulus* via Diastereoselective Hydrogenations

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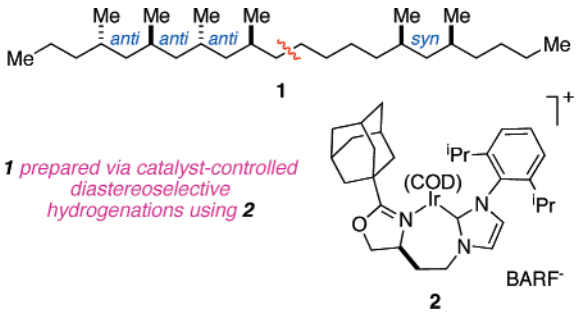
ABSTRACT



The hydrocarbon 1 was prepared via a series of catalyst-controlled diastereoselective hydrogenations beginning with fragments derived from the Roche ester.

Kitching and co-workers isolated hydrocarbon **1** (see Abstract) from female Australian melolonthine beetles.[1,2] The larvae of these insects are apparently significant pests, attacking sugar cane crops in that region.

Definitive elucidation of the structure emerged from a synthesis by Breit et al.[3] that built on work Kitching had done to eliminate many stereochemical possibilities. Kitching's group reported that the "Western fragment" (as drawn above) had *anti*,*anti*,*anti* relative stereochemistry and that the Eastern part had *syn* stereochemistry. They made several epimers of **1** in this process, but via routes based on existing methodologies that are not readily amenable to making all stereoisomers. Thus, the relative configurations of the Western and Eastern fragments and the absolute configuration of the whole molecule were not established. Breit was then able to make the particular *anti*,*anti*,*anti*/*syn* stereoisomer shown and proved that it corresponded to the natural product.

Breit's synthesis featured a methodology developed in his laboratory.[4] Briefly, it is an iterative approach beginning with the Roche ester to prepare two deoxypolyketide fragments. The essential feature of the iteration sequence is that organocuprates are prepared from Roche ester derived fragments, and these are added to an optically pure allylic ester formed from (2-diphenylphosphino)benzenoic acid. This particular ester directs a *syn*-S_N2' displacement. Other steps in the iteration are reductive ozonolysis and conversion of the product alcohol into an organoiodide, ready for the next cycle.

We saw a synthesis of the hydrocarbon **1** as an opportunity to test our catalyst-controlled diastereoselective hydrogena-

(1) Fletcher, M. T.; Chow, S.; Lambert, L. K.; Gallagher, O. P.; Cribb, B. W.; Allsopp, P. G.; Moore, C. J.; Kitching, W. *Org. Lett.* **2003**, *5*, 5083−5086.

(2) Chow, S.; Fletcher, M. T.; Lambert, L. K.; Gallagher, O. P.; Moore, C. J.; Cribb, B. W.; Allsopp, P. G.; Kitching, W. *J. Org. Chem.* **2005**, *70*, 1808−1827.

(3) Herber, C.; Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5267−5269.

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tion methodology for syntheses of deoxypolyketide chirons. Figure 1 outlines the approach that was envisaged.

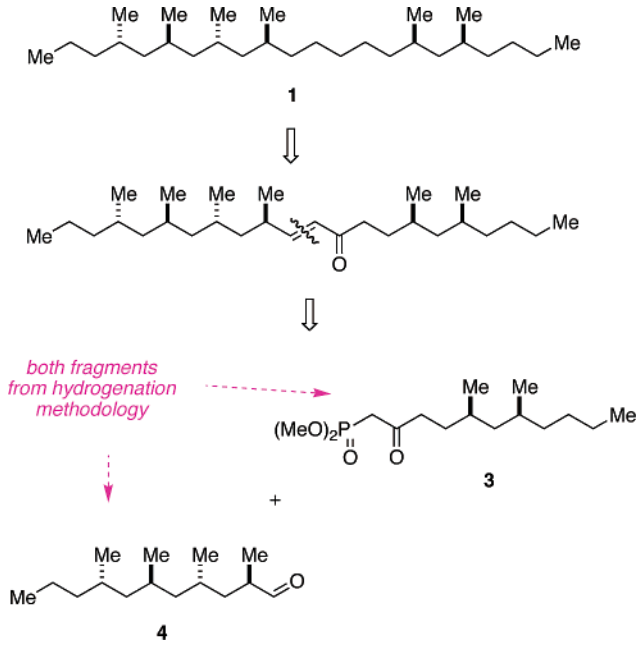
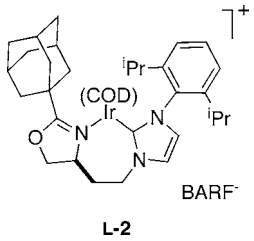


Figure 1. Conceptual synthesis of **1** from two C_{11} chains derived from catalyst-controlled diastereoselective hydrogenations.

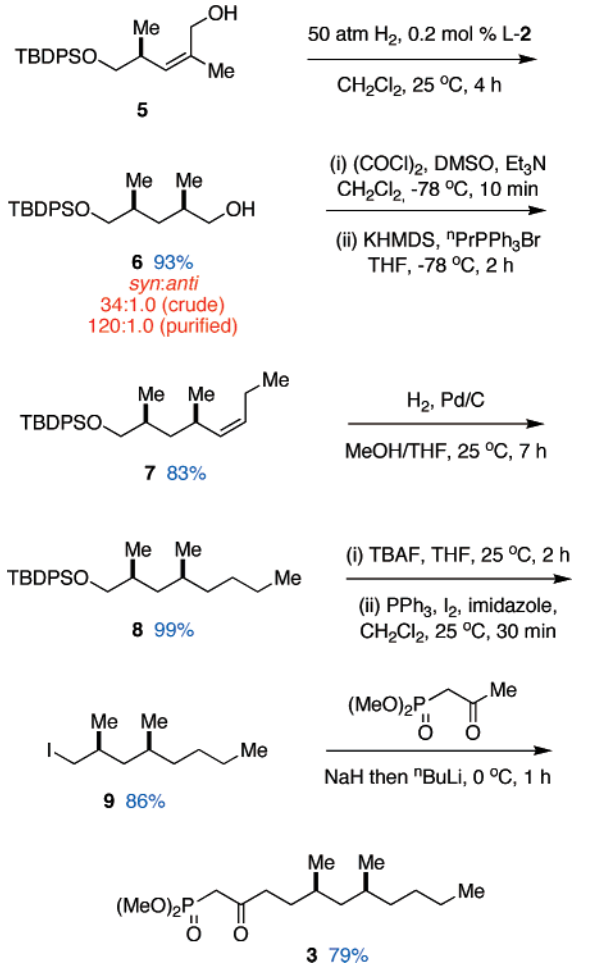
Comprehensive details of our catalyst-controlled diastereoselective hydrogenation methodology have been published.[5,6] In the work described here, it was only necessary to use catalyst L-**2**.[7,8]



L-2

Hydrogenation of **5** in the first step of Scheme 1 reiterates one of the several reactions we have used to prepare chiron **6**. This reaction is catalyst controlled, but there is a significant "substrate vector",[5] and the *Z*-allylic alcohol was used to optimize this. Crude material formed in this step had a 34:1.0 (via GC, throughout this paper) *syn*/*anti* diastereomeric ratio, and 93% yield of 120:1.0 *syn*/*anti* product was obtained after one chromatography. The Swern oxidation, Wittig, heterogeneous hydrogenation, deprotection, and iodination sequence shown in converting the alcohol **6** to the iodide **9** were straightforward transformations. The last step, alkylation of a ketophosphonate dianion, is also known,[9] if not so widely applied.

Scheme 1. Synthesis of the Eastern Part of **1**, i.e., Chiron **3**

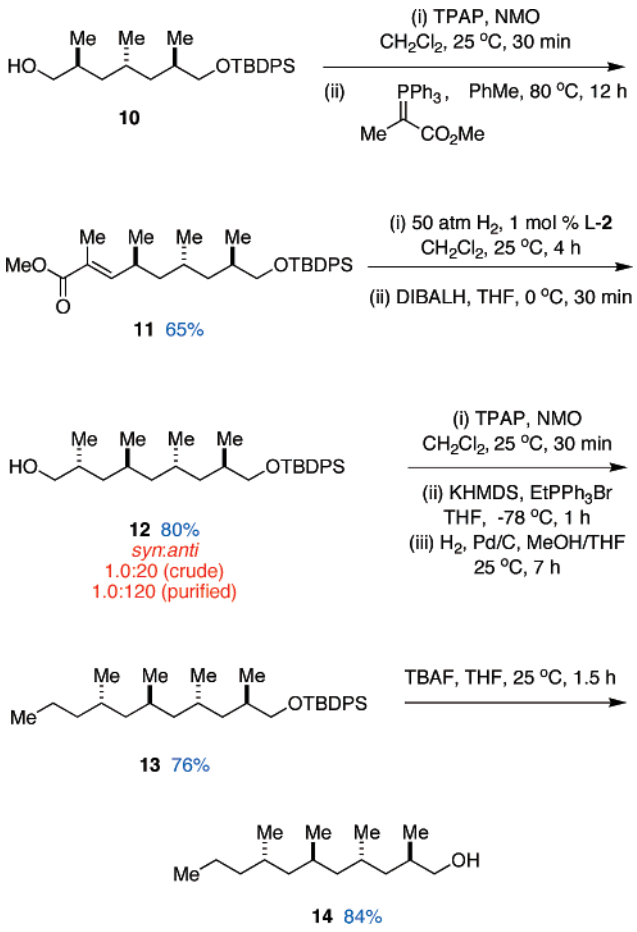


The challenge in this sequence was avoiding epimerization at the aldehyde stage. This was not a problem for the approach in Scheme 1, but it was for another approach that was abandoned for this reason (see Supporting Information).

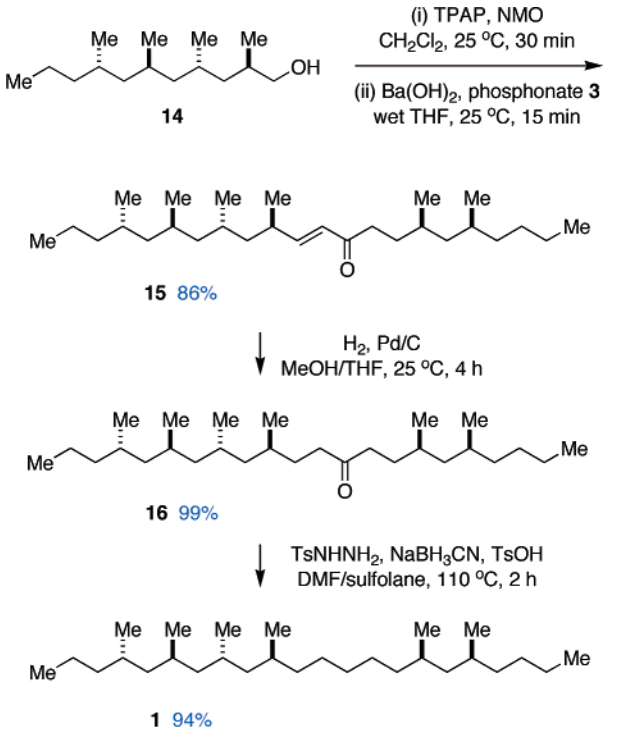
The Western part of **1**, derived from aldehyde **4**, contains a stereochemical tetrad. Our hydrogenation methodology had established a route to the *anti*,*anti*-stereochemical triad **10**,[5] so one further iteration was needed. Thus, alcohol **10** was converted to the ester **11**. Then, the material was reduced using L-**2**, and the crude material was reduced to the alcohol using DIBAL-H for ease of separation. Product **12** was obtained in 80% yield as one stereoisomer to within the limits of our GC detection after one chromatographic separation. The remaining oxidation, Wittig, heterogeneous hydrogenation, and deprotection steps gave the alcohol **14** (Scheme 2).

(5) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129−1131.
(6) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2007**, submitted.
(7) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961.
(8) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113−123.
(9) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071−3072.

Scheme 2. Synthesis of the Western Part of **1**, i.e., Precursor to Chiron **4**



Scheme 3. Completion of the Synthesis of **1**



Synthesis of the target molecule **1** from the alcohol **14**, via the aldehyde **4**, and the phosphonate **3** was accomplished as in Scheme 3. The Horner−Wadsworth−Emmons coupling[10] and heterogeneous hydrogenation steps were routine. Milder variants of the final Wolff−Kischner reduction were attempted briefly,[11] but the reductive modification gave better results.[12]

Proton and ^{13}C NMR spectra of the synthetic product **1** were essentially identical to those reported by both Kitching and Breit. Further, the optical rotation value for the synthetic material {$[\alpha]^{23}_D$ +12.1 (*c* 0.80, $CHCl_3$)} compares well with the value reported by Breit for natural material obtained from Kitching {$[\alpha]^{20}_D$ +10.7 (*c* 0.44, $CHCl_3$)}. Thus, we are confident that the relative and absolute configurations of product **1** match with those reports.

As a synthesis of compound **1**, the work described here is a very direct and convergent approach that uses only the two enantiomers of the Roche ester as starting materials. Further, it demonstrates that catalyst-controlled diastereoselective hydrogenation routes to deoxypolyketides have practical synthetic value. We feel that research on asymmetric hydrogenations of largely unfunctionalized alkenes is moving on from simple substrates[13−15] to ones that give useful chirons for organic synthesis.

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

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