Asymmetric Synthesis

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Enantioselective Total Synthesis and Determination of the Absolute Configuration of the 4,6,8,10,16,18-Hexamethyldocosane from *Antitrogus parvulus***

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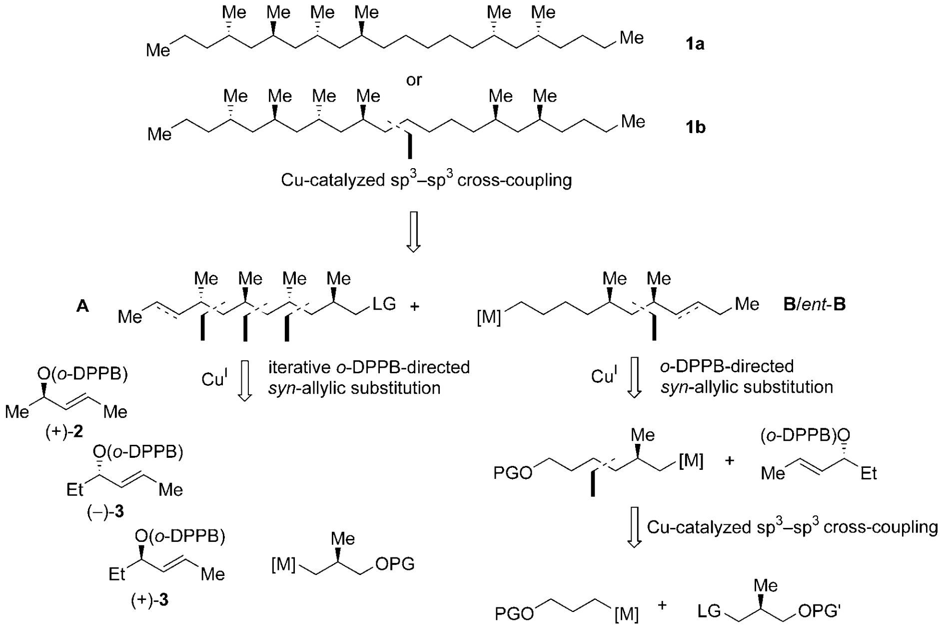
The larvae of the cane beetle *Antitrogus parvulus* (known as cane grubs) are a source of major damage in sugar-cane crops in Australia.[1] On searching for an environmentally benign plant-protection strategy, recent research has focused on the identification of sex pheromones of the cane beetle. As a result hydrocarbons, such as 4,6,8,10,16-penta- and 4,6,8,10,16,18-hexamethyldocosanes (**1**), that feature an unprecedented *anti-anti-anti* stereochemistry in the 4,6,8,10-methyl tetrad have been discovered.[2] However, the small amount of material isolated from the natural source has not yet allowed the determination of their biological role. Combined spectroscopic and synthetic efforts have elucidated the relative *anti* configuration of the four methyl-bearing stereocenters in the tetrad unit of **1** and the relative *syn* configuration within the methyl diad region. However, so far the stereochemical relation between the all-*anti* tetrad and the *syn* diad remains unknown (**1a** or **1b**), as does the absolute configuration (Scheme 1).[2]

We herein report on the total synthesis of both diastereomers **1a** and **1b** in enantiomerically pure form, thus enabling the determination of the relative and absolute configurations of the natural product. The synthesis relies heavily on our recently developed copper-mediated and *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB)-directed *syn*-allylic substitution with Grignard reagents for iterative deoxypropionate synthesis.[3] Additionally, we demonstrate the power of copper-catalyzed sp^3–sp^3 cross coupling by employing it for building-block construction and as the fragment-coupling step in a convergent total synthesis.



Scheme 1. Retrosynthesis for **1a** and **1b**. PG = protecting group, LG = leaving group, M = metal.

Our synthetic plan is outlined in Scheme 1. Fragment coupling of the methyl tetrad and the methyl diad by employing a catalytic sp^3–sp^3 cross-coupling reaction[4] was envisioned as an attractive final step of the synthesis to allow the flexible construction of both diastereomers **1a** and **1b**.

The corresponding tetradeoxypropionate building block should be assembled by our iterative deoxypropionate synthetic strategy employing enantiomerically pure allylic *o*-DPPB building blocks **2** and **3** as propionate acetate and propionate units, respectively.[3] The two optical antipodes of the methyl diad building block should be readily accessible by similar chemistry.

The synthesis began with construction of the tetrad building block **A** (Scheme 2). Thus, iodide (+)-**4** (available

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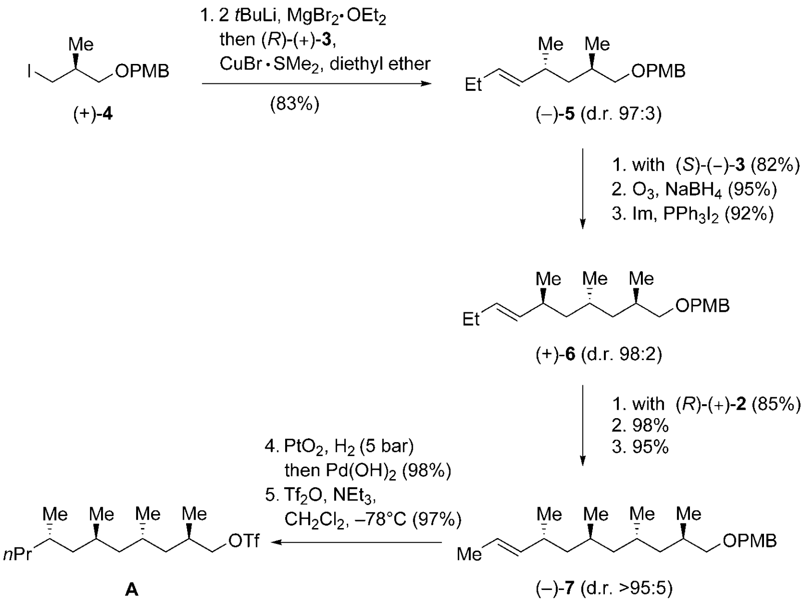
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

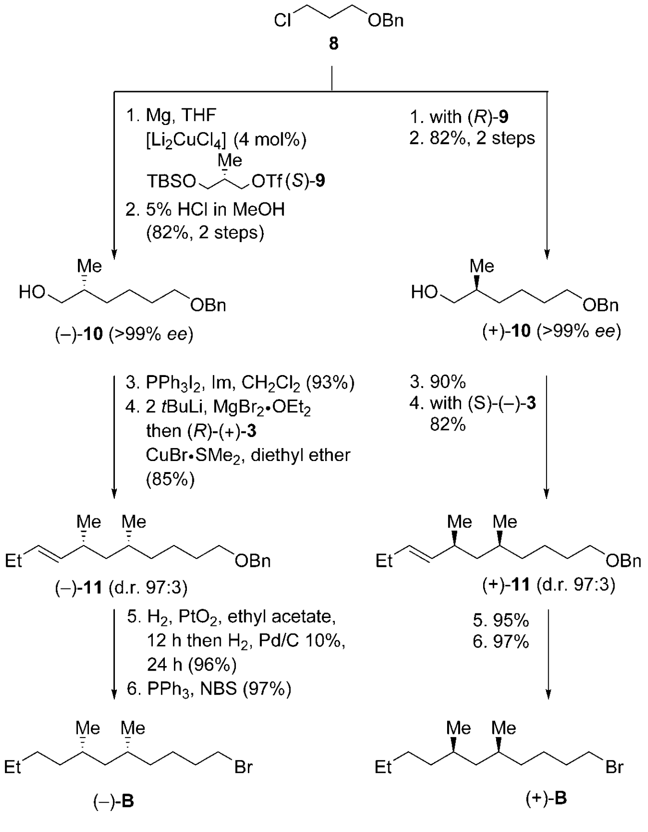


Scheme 2. Synthesis of tetradeoxypropionate building block **A**. Im = imidazole, Tf = trifluoromethanesulfonyl.

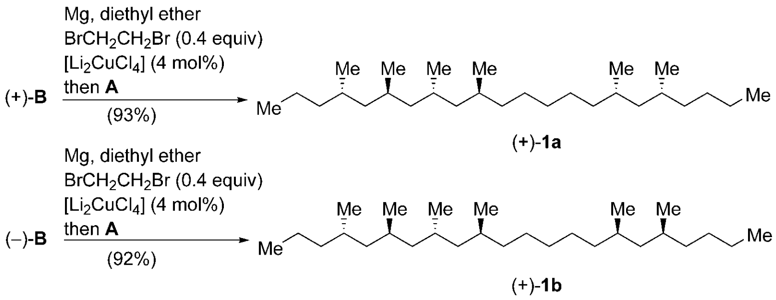
in three steps from the Roche ester)[5] was transformed into a Grignard reagent and subjected to *o*-DPPB-directed *syn*-allylic substitution with allylic *o*-DPPB ester (*R*)-(+)-**3** in the presence of 0.5 equivalents of copper bromide·dimethyl sulfide to give the dideoxypropionate (−)-**5** with a complete 1,3-chirality transfer.[3] Two separate iterations consisting of three steps (alkene ozonolysis with a reductive workup (NaBH$_4$), transformation to the iodide, and directed *syn*-allylic substitution with (*S*)-(−)-**3** and (*R*)-(+)-**2**, respectively) furnished the tetradeoxypropionate (−)-**7** with all the carbon atoms and stereocenters in place. Alkene hydrogenation and reductive cleavage of the *para*-methoxybenzyl (PMB) ether group occurred upon heterogenous catalytic hydrogenation. The thus-derived building block **A** was stored as the alcohol and activated prior to fragment coupling as the corresponding triflate.

Synthesis of the dideoxypropionate building blocks **B** commenced from chloride **8** (Scheme 3).[6] For the expansion of the carbon skeleton, we chose a copper-catalyzed sp^3–sp^3 cross-coupling reaction with a three-carbon electrophile of type **9** derived from the Roche ester.[7] Orientating experiments with the corresponding bromide and iodide derivatives, however, showed that significant chemoselectivity problems occurred because of elimination and reduction processes. These problems could be circumvented by employing the triflates (+)-**9** and (−)-**9** at −20 °C. In these cases, clean cross coupling in the presence of 4 mol % of [Li$_2$CuCl$_4$] was observed. Exposure of the crude coupling product to methanolic hydrogen chloride gave the primary alcohols (−)-**10** and (+)-**10** in 82 % yield (two steps). The Mukaiyama redox condensation furnished the corresponding iodides, which were subjected to the above protocol for the directed *syn*-allylic substitution with (*R*)-(+)-**3** and (*S*)-(−)-**3**, respectively, to furnish the dideoxypropionates (−)-**11** and (+)-**11** in excellent yield and complete diastereoselectivity. Minimal, standard functional-group manipulation led to building blocks (−)-**B** and (+)-**B**.

The final fragment-coupling step (Scheme 4) employing a copper-catalyzed sp^3–sp^3 cross coupling of the Grignard reagent derived from (−)/(+)-**B** with triflate **A** required some optimization because of problems that arose from the small scale of the reaction (0.1 mmol). It was found that generation of a Grignard reagent on this small scale was successful in the presence of an excess of dibromoethane. However, the thus-formed excess of magnesium bromide also reacted with the triflate electrophile to yield the corresponding bromide as a by-product (which unfortunately did not undergo further cross coupling). This problem could be circumvented by the addition of an ethereal solution of triflate **A** together with 4 mol % of the catalyst [Li$_2$CuCl$_4$] to an ethereal solution of the Grignard-reagent-derived form of **B**. Excellent yields of both diastereomers **1a** and **1b** were obtained under these conditions. Purification of the final product was achieved through kugelrohr distillation, which, as an additional benefit, allowed the boiling points of **1a** and **1b** (210 °C/20 mbar) to be determined.



Scheme 3. Synthesis of the enantiomeric dideoxypropionate building blocks (−)-**B**/(+)-**B**. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, NBS = *N*-bromosuccinimide.



Scheme 4. Fragment coupling through Cu-catalyzed sp^3–sp^3 cross coupling. Synthesis of (+)-**1a** and (+)-**1b**.

To prove the identity of the natural and synthetic material ^{13}C NMR spectra of **1a** and **1b** were recorded in the presence of an internal glass-capillary tube containing a solution of the natural product in $CDCl_3$.[8] Comparison of these spectra showed a perfect match for diastereomer **1b**. Finally, comparison of the optical-rotation studies of the natural material ($[\alpha]_D^{20}$ +10.7 ($c = 0.44$, $CHCl_3$)) and the synthetic product **1b** ($[\alpha]_D^{20}$ +8.5 ($c = 1.21$, $CHCl_3$)) determined the absolute configuration of the natural product as that depicted in Scheme 4.

In conclusion, the enantioselective total synthesis of the (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-hexamethyldocosane from *Antitrogus parvulus* has been accomplished, thus enabling the relative and the absolute configuration of the natural product to be determined. The successful enantioselective synthesis of **1b** (and its diastereomer **1a**) highlights the synthetic power of our recent methodology for deoxypropionate construction, which relies on an *o*-DPPB-directed and copper-mediated allylic substitution by Grignard reagents. Furthermore, the synthetic utility of copper-catalyzed sp^3–sp^3 cross-coupling for fragment coupling in a total synthesis has been demonstrated.

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[1] P. G. Allsopp, K. J. Chandler, *Proc. Int. Soc. Sugar-Cane Technol.* **1989**, *20*, 810–816.

[2] a) M. T. Fletcher, S. Chow, L. K. Lambert, O. P. Gallagher, B. W. Cribb, P. G. Allsopp, C. J. Moore, W. Kitching, *Org. Lett.* **2003**, *5*, 5083–5086; b) S. Chow, M. T. Fletcher, L. K. Lambert, O. P. Gallagher, C. J. Moore, B. W. Cribb, P. G. Allsopp, W. Kitching, *J. Org. Chem.* **2005**, *70*, 1808–1827.

[3] B. Breit, C. Herber, *Angew. Chem.* **2004**, *116*, 3878–3880; *Angew. Chem. Int. Ed.* **2004**, *43*, 3790–3792.

[4] For previous reports on copper-catalyzed sp^3–sp^3 cross-coupling reactions, see: a) M. Tamura, J. Kochi, *Synthesis* **1971**, 303–305; b) G. Fouquet, M. Schlosser, *Angew. Chem.* **1974**, *86*, 82–83; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 701–702; c) H. Kotsuki, I. Kadota, M. Ochi, *J. Org. Chem.* **1990**, *55*, 4417–4422; d) T. Netscher, *Chimia* **1996**, *50*, 563–567; e) G. Cahiez, C. Chaboche, M. Jezequel, *Tetrahedron* **2000**, *56*, 2733–2737.

[5] Prepared analogously to (*R*)-**3**, see: T. J. Heckrodt, J. Mulzer, *Synthesis* **2002**, 1857–1866.

[6] E. Dimitriadis, R. A. Massy-Westropp, *Aust. J. Chem.* **1984**, *37*, 619–627.

[7] G. F. Solberghe, I. E. Marko, *Tetrahedron Lett.* **2002**, *43*, 5061–5066.

[8] A comparison of the analytical data of the natural material and synthetic compounds **1a** and **1b** can be found in the Supporting Information.