ORGANIC LETTERS

2009
Vol. 11, No. 21
4767−4769

Enantioselective Total Synthesis and Determination of Absolute Configuration of Vittatalactone

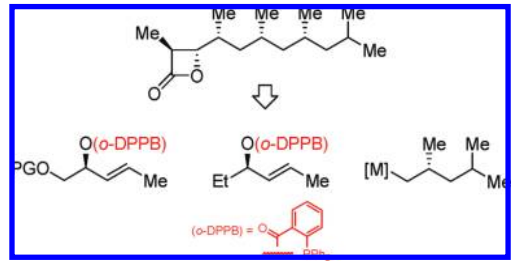
Yvonne Schmidt and Bernhard Breit*

Institut für Organische Chemie und Biochemie, Freiburg Institute for Advanced Studies (FRIAS), Albert-Ludwigs-Universität Freiburg, Alberstr. 21, 79104 Freiburg, Germany

bernhard.breit@chemie.uni-freiburg.de

Received July 13, 2009

ABSTRACT



The first asymmetric total synthesis of vittatalactone features the divergent synthesis of two diastereomers to assign the absolute configuration of the natural product. Its consecutive propionate and deoxypropionate stereogenic centers are established by enantioselective *o*-DPPB directed allylic substitution.

The striped cucumber beetle, *Acalymma vittatum*, is a cause of major damage to cucurbit crops in North America. To develop an environmentally benign plant protection strategy, recent research has focused on identifying sex pheromones of the cucumber beetle. In this context, vittatalactone (**1**) has been isolated by Morris and Francke, and its possible role as an aggregation pheromone was determined employing electrophysiological studies.[1] Structural investigations revealed the constitution of vittatalactone featuring a trideoxypropionate unit as well as a β-lactone derived from a propionate unit.

From spectroscopic analysis of the Mosher ester derivative, the absolute configuration on the β-lactone could be deduced to be 2*R*,3*R*, but the relative configuration of the trideoxypropionate side chain was not determined so far. However, after comparison of the chemical shifts of C^5H_2 and C^7H_2-hydrogens with known trideoxypropionate diastereomers, we presumed the methyl substituents to be all-*syn* configured (Figure 1).[1,2] Still, the relative configuration between the

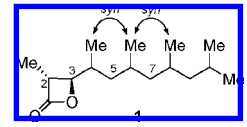


Figure 1. Known structural features of vittatalactone.

β-lactone (i.e., propionate) and deoxypropionate subunit remained unknown. We herein report on the total synthesis of the two diastereomers **1a** and **1b** in enantiomerically pure form, thus enabling the determination of the relative and

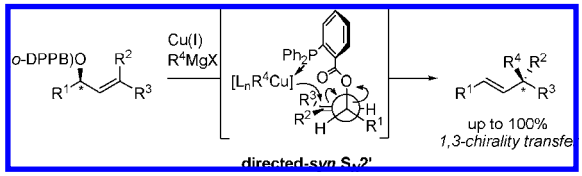
(1) Morris, B. D.; Smyth, R. R.; Foster, S. P.; Hoffmann, M. P.; Roelofs, W. L.; Franke, S.; Francke, W. *J. Nat. Prod.* **2005**, *68*, 26–30.

(2) By comparison of NMR data we found a strong splitting (0.2 and 0.3 ppm, respectively) for the chemical shift of the methylene protons, which has been shown to be typical for the internal methylene unit of a *syn*-deoxypropionate unit. In the case of the *anti*-configured diastereomers, the chemical shift differences decrease. For experimental data, see: (a) Herber, C.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6684–6691. (b) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, 3512–3519. (c) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784–13792. For a theoretical overview of conformation control, see: (d) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070, and references cited therein.

10.1021/ol901591t CCC: $40.75
Published on Web 09/30/2009

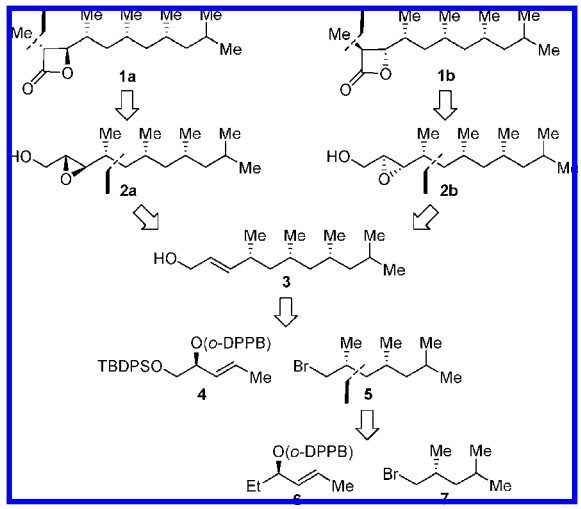
absolute configuration of vittatalactone. The synthesis employs our recently developed methodology for polyketide construction relying on the *o*-DPPB-directed copper-mediated allylic substitution, which allows for stereospecific 1,3-chirality transfer (Scheme 1).[3,4]

Scheme 1. *o*-DPPB-Directed Allylic Substitution with Grignard-Derived Organocopper Reagents



Our synthesis plan is outlined in Scheme 2. Thus, to enable a late-stage divergency toward both diastereomers **1a** and

Scheme 2. Retrosynthetic Analysis of Vittatalactone

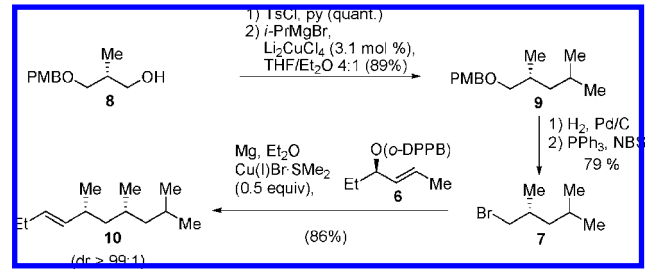


1b, we decided in favor of functionalized trideoxypropionate **3** as the common intermediate. A catalyst-controlled Sharpless epoxidation followed by methylcuprate epoxide ring opening, adjustment of oxidation state, and lactone formation would furnish both diastereomers of vittatalactone, **1a** and **1b**.

The common allylic alcohol **3** could be constructed stereospecifically employing our iterative copper-mediated *o*-DPPB-directed allylic substitution. The first disconnection leads to *o*-DPPB-ester **4** and the Grignard reagent derived from bromide **5** which in turn should be the coupling product of *o*-DPPB-ester **6** and the Grignard reagent obtained from bromide **7**.

Our synthesis started with monoprotected diol **8**,[5] which is available in two steps from the corresponding Roche ester through O-protection and hydride reduction. Alcohol **8** was activated as its tosylate and submitted to the conditions of a copper-catalyzed sp^3-sp^3-coupling reaction with *i*-PrMgBr (Scheme 3) to furnish PMB ether **9** in good yield. Trans-

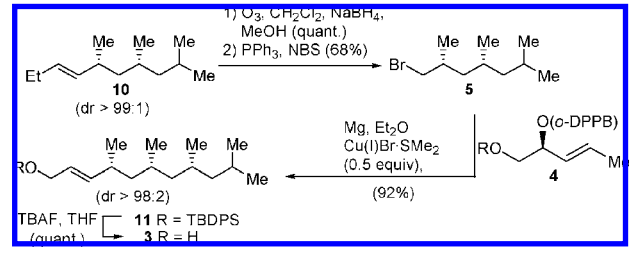
Scheme 3. Synthesis of Grignard Precursor **7** and *o*-DPPB-Directed Allylic Substitution



formation of **9** toward bromide **7** was conducted as a one-pot procedure due to the high volatility of both alcohol and bromide. Bromide **7** was converted into the corresponding Grignard reagent and subsequently subjected to the conditions of the directed allylic substitution with the unfunctionalized *o*-DPPB ester **6**.[3c,6] The S_N2' substitution product **10** was obtained in 86% yield with respect to ester **6** using 1.1 equiv of Grignard only. Analysis of the substitution product by capillary GC showed a diastereomeric ratio of >99:1.

Iteration for trideoxypropionate construction began with ozonolysis of alkene **10** and reductive workup to give the corresponding alcohol (Scheme 4). Mukaiyama redox con-

Scheme 4. Iteration of *o*-DPPB-Directed Allylic Substitution



densation[7] furnished bromide **5**. Transfer into the corresponding Grignard reagent occurred upon treatment with magnesium in diethylether, and subsequent subjection to the conditions of the directed allylic substitution with O-functionalized *o*-DPPB-ester **4** furnished the allylic silyl ether

(3) (a) For a recent review, see: Schmidt, Y.; Breit, B. *Chem. Rev.* **2008**, *108*, 2928–2952. (b) Reiss, T.; Breit, B. *Chem.—Eur. J.* **2009**, *15*, 6345–6348. (c) Herber, C.; Breit, B. *Angew. Chem.* **2005**, *117*, 5401−5403; *Angew. Chem., Int. Ed.* **2005**, *44*, 5267−5269.

(4) For a recent synthesis of bourgeanic acid employing this methodology, see: Reiss, T.; Breit, B. *Org. Lett.* **2009**, *11*, 3286–3289.

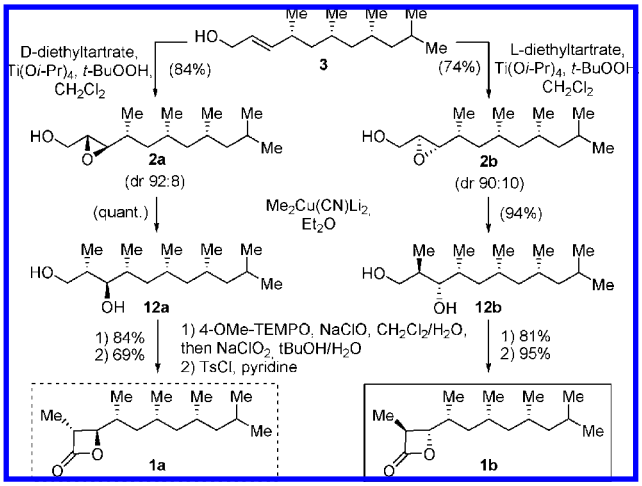
(5) Walkup, R. D.; Boatman, P. D., Jr.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1991**, *32*, 3937–3940.

(6) Herber, C.; Breit, B. *Angew. Chem.* **2004**, *116*, 3878−3880; *Angew. Chem., Int. Ed.* **2004**, *43*, 3790−3792.

(7) Mukaiyama, T. *Angew. Chem.* **1976**, *88*, 111−120; *Angew. Chem., Int. Ed.* **1976**, *15*, 94−103.

11 in excellent yield and stereoselectivity.[3b] Fluoride-mediated liberation of the key allylic alcohol **3** was quantitative.

Transformation of **3** toward the two diastereomeric target structures **1a** and **1b** started with the catalyst-controlled stereoselective Sharpless epoxidation employing D- and L-diethyl-tartrate, respectively.[8] Both diastereomeric epoxy-alcohols **2a** and **2b** were obtained in good yields and diastereoselectivity, even for the mismatched case toward **2b**.



The carbon skeleton of vittatalactone was completed by addition of cyanodimethylcuprate to give the 1,3-diols **12a** and **12b**, respectively, in good yield and stereoselectivity.[9] At this stage, the minor diastereomers could be separated by column chromatography. Selective oxidation of the primary alcohol function of diol **12** toward the β-hydroxy aldehyde was accomplished applying 4-methoxy-TEMPO/hypochlorite.[10] Pinnick oxidation then furnished the corresponding β-hydroxy acid.[11] Finally, ring closure with tosyl chloride in pyridine yielded the β-lactones **1a** and **1b** in good to high yields.[12]

Both diastereomeric lactones were subjected to NMR spectroscopic analysis. Comparison of the proton and carbon NMR data with those of the natural material isolated by the Francke group[1] showed a perfect match for β-lactone **1b**.[13] Hence, **1b** has the correct relative configuration of natural vittatalactone.

However, compared with the structure analysis by the Mosher ester method, lactone **1b** is 2*S*,3*S* configured and should therefore be the enantiomer of natural vittatalactone. Thus, by synthesis of the enantiomer, the absolute configuration of vittatalactone can be assigned to be 2*R*,3*R*,4*S*,6*S*,8*S*.[14]

In conclusion, the enantioselective total synthesis of *ent*-vittatalactone **1b** from *Acalymma vittatum* has been accomplished, thus enabling the relative and the absolute configuration of the natural product to be determined. The successful enantioselective synthesis of the two diastereomers **1a** and **1b** highlights the synthetic power of our recent methodology for deoxypropionate and propionate construction, which relies on the *o*-DPPB-directed allylic substitution by Grignard-derived organocopper reagents. Thus, this methodology complements more traditional strategies for polyketide synthesis relying on enolate alkylation and aldol addition reactions.[15]

Acknowledgment. This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038), the Fonds der Chemischen Industrie (Fellowship to YS), and Novartis and Wacker (Donation of Chemicals). We thank Prof. Dr. Wittcko Francke (Univ. Hamburg) for sharing preliminary results, as well as G. Fehrenbach and Dr. M. Keller for analytical assistance and J. Weipert for synthetic work (Univ. Freiburg).

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

OL901591T

(8) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) For a review, see: Katsuki, T. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. II, pp 621−677.

(9) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817–823.

(10) (a) Hu, T.; Takanaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 12806–12815. (b) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.

(11) Pinnick, H. W.; Balkrishna, S. B.; Childers, W. E., Jr. *Tetrahedron* **1981**, *37*, 2091–2096.

(12) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000–2006.

(13) See Supporting Information for details.

(14) Unfortunately, we could not compare the optical rotation of **1b** with the natural product since this has neither been reported (ref 1) nor determined.

(15) For recent reviews, see: (a) Paterson, I. *Asym. Synth.* **2007**, 278–282. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525. (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947. For Evans alkylation in ionomycin synthesis: (d) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313. For a review covering deoxypropionate synthesis, see: (e) Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, 1057–1076.