ORGANIC LETTERS

2009
Vol. 11, No. 15
3286−3289

Total Synthesis of (+)-Bourgeanic Acid Utilizing *o*-DPPB-Directed Allylic Substitution

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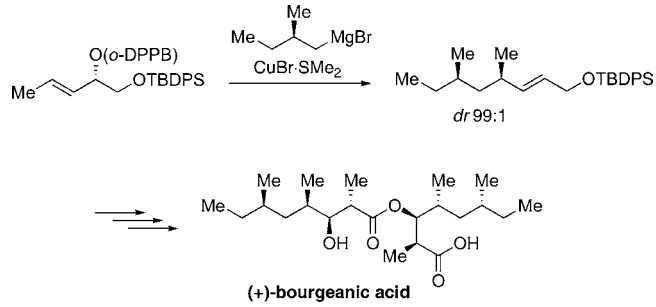
Received May 25, 2009

ABSTRACT



The lichen metabolite (+)-bourgeanic acid has been synthesized utilizing a new strategy for the construction of propionate motifs relying on the *o*-DPPB-directed copper-mediated allylic substitution. This synthesis features the *o*-DPPB-directed allylic substitution employing a chiral Grignard reagent, Sharpless asymmetric epoxidation, and reductive epoxide ring opening with a higher order dimethylcuprate to set the four stereogenic centers of the aliphatic depside.

Reactions which allow for stereospecific construction of a carbon skeleton through carbon−carbon bond formation are of particular value for organic synthesis. In this context, we recently reported on the development of the *o*-diphenylphosphanylbenzoyl (*o*-DPPB)-directed allylic substitution with Grignard-derived organocopper reagents which occurs with complete control of chemo-, regio-, and stereochemistry delivering the corresponding S_N2' substitution products with either a tertiary or a quarternary stereogenic center with perfect syn-1,3-chirality transfer (figure 1).[1,2] Interestingly, this reaction requires only a stoichiometric amount of the Grignard reagent to achieve quantitative transformation. This allows us to employ valuable functionalized Grignard reagents and may be employed even in a fragment coupling step in the course of a total synthesis.[3] Furthermore, based on the directed allylic substitution, a new methodology for the iterative construction of deoxypropionates has been developed, and the strength and reliability of this methodology has been proven.[4,5]

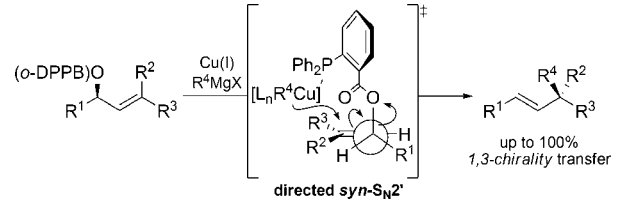


Figure 1. *o*-DPPB-directed allylic substitution with Grignard-derived organocopper reagents.

We herein report on the total synthesis of the aliphatic depside bourgeanic acid (**1**), which relies on our newly developed

(1) Demel, P.; Keller, M.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6669. Breit, B.; Demel, P.; Grauer, D.; Studte, C. *Chem. Asian J.* **2006**, *1*, 586. Breit, B.; Demel, P.; Studte, C. *Angew. Chem.* **2004**, *116*, 3874; *Angew. Chem., Int. Ed.* **2004**, *43*, 3786. Breit, B.; Demel, P. *Adv. Synth. Catal.* **2001**, *343*, 429.

10.1021/ol9011635 CCC: $40.75
Published on Web 07/07/2009

strategy for the stereospecific construction of propionate and acetate−propionate motifs based on the *o*-DPPB-directed allylic substitution with allylic *o*-DPPB ester **2**.[6,7]

(+)-Bourgeanic acid (**1**) was isolated as a metabolite from several *Ramalina* species of lichen (Figure 2).[8] The relative

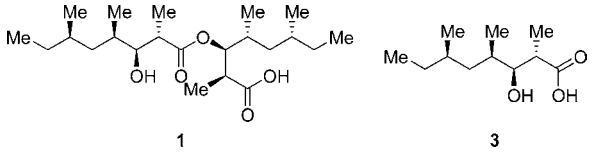


Figure 2. Structure of (+)-bourgeanic acid (**1**) and (−)-hemibourgeanic acid (**3**).

configuration of **1** was established by degradation and spectroscopic analysis; hence, Bodo concluded that **1** was an esterification product of two molecules of 3-hydroxy-2,4,6-trimethyloctanoic acid. The absolute configuration was determined by X-ray crystallographic analysis of the degradation product (−)-hemibourgeanic acid (**3**), as its *p*-bromophenacyl ester.[9] In 1990, White reported the first enantioselective synthesis of **1**.[10]

Figure 3 illustrates our synthesis plan for **1**. Since **1** is a self-esterification product of hemibourgeanic acid (**3**), dis-

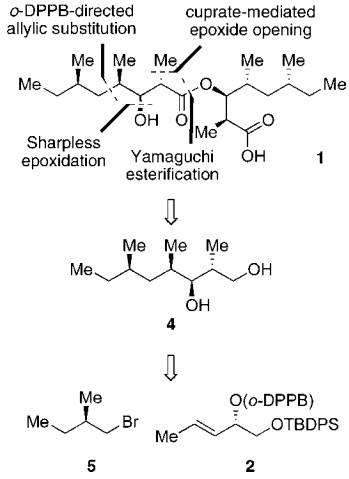
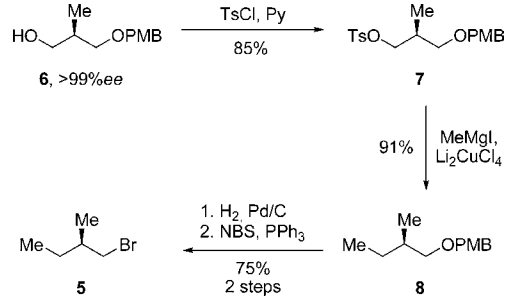


Figure 3. Synthesis plan.

connection of the ester linkage traces back to an appropriate carboxylic acid and a complementary alcohol component. Both of them could originate from the same diol **4**. As the key step for the preparation of **4**, we envisioned an *o*-DPPB-directed allylic substitution of allylic *o*-DPPB ester **2** with the chiral Grignard reagent, derived from bromide **5**.

The synthesis of bromide **5** began with tosylation of the (*R*)-3-(4-methoxybenzyloxy)-2-methylpropan-1-ol (**6**) (>99% ee) (available in two steps from Roche ester)[11] with tosyl chloride in pyridine to provide **7** (Scheme 1).

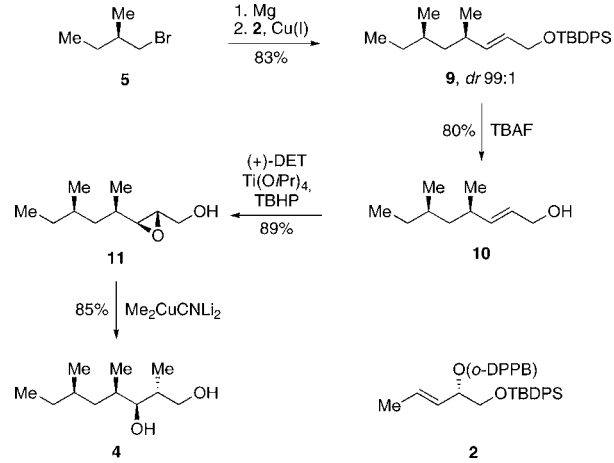
Scheme 1



The missing methyl group was introduced utilizing a copper-catalyzed sp^3-sp^3 cross-coupling reaction between **7** and methylmagnesium iodide to furnish **8** in a very good yield.[12] Subsequently, the PMB ether was cleaved by catalytic hydrogenation with palladium on charcoal, and the obtained alcohol was converted into the desired bromide **5** employing a Mukaiyama redox-condensation protocol.[13]

The bromide **5** was transformed with magnesium into the corresponding Grignard reagent and subjected to the conditions of the directed allylic substitution with allylic *o*-DPPB ester **2** (99% ee, $E/Z > 99:1$), in the presence of 0.5 equiv of copper bromide-dimethyl sulfide to give the protected allylic alcohol **9** (dr syn/anti = 99:1) with complete 1,3-chirality transfer (Scheme 2). Liberation of the alcohol function

Scheme 2



occurred upon treatment with tetra-*n*-butylammonium fluoride. A subsequent Sharpless asymmetric epoxidation[14] with

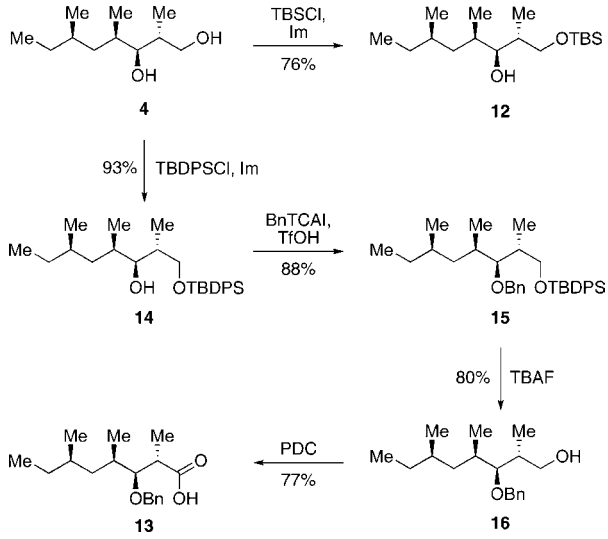
(2) For other recent important contributions, see: Kioyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719. Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F. *Angew. Chem.* **2005**, *117*, 4703; *Angew. Chem., Int. Ed.* **2005**, *44*, 4627. Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. Spino, C.; Beaulieu, C. *Angew. Chem.* **2000**, *112*, 2006; *Angew. Chem., Int. Ed.* **2000**, *39*, 1930. Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055.

(3) Rein, C.; Demel, P.; Outten, R. A.; Netscher, T.; Breit, B. *Angew. Chem.* **2007**, *119*, 8824; *Angew. Chem., Int. Ed.* **2007**, *46*, 8670.

catalytic amounts of titanium(IV) isopropoxide and L-(+)-diethyl tartrate as chiral ligand at −20 °C delivered the *syn*-epoxide **11** in a diastereomer ratio of 93:7. Nucleophilic epoxide ring-opening occurred upon reaction with the higher order cuprate $Me_2CuCNLi_2$[15] introducing the missing methyl substitutent to furnish the diol **4** with all four stereogenic centers in place.[16]

In order to avoid problems with potential epimerization during the final esterification to form bourgeanic acid from hemibourgeanic acid, we decided to couple a protected hemibourgeanic acid with a complementary alcohol component at the oxidation state of the diol **4**. Thus, the primary alcohol of the common diol intermediate **4** was transformed to the TBS ether **12** upon reaction with TBSCl and imidazole (Scheme 3). The synthesis of the acid **13**

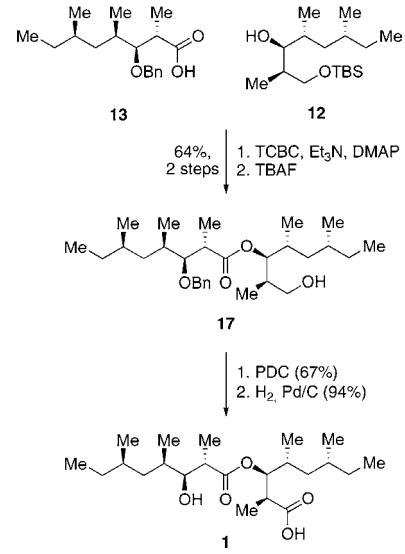
Scheme 3



commenced with selective protection of the primary alcohol function as a TBDPS ether to furnish **14**. Subsequently, the secondary alcohol was orthogonally protected as the benzyl ether **15** upon reaction with benzyl trichloroacetimidate in the presence of TfOH at 0 °C.[17] Cleavage of the TBDPS ether with TBAF, and oxidation of the corresponding alcohol **16** with PDC[18] furnished the desired carboxylic acid **13**.

Completion of the synthesis began with a Yamaguchi−Yonemitsu esterification of carboxylic acid **13** with alcohol **12**.[19] Subsequent cleavage of the silyl ether with TBAF furnished the hydroxy ester **17** in 64% yield over two steps (Scheme 4).[20] It is worthy of note that applying the same

Scheme 4



esterification conditions toward acid **13** and alcohol **14** did not give any esterification product at all, which is presumably caused by steric reasons. Oxidation of the primary alcohol function of **17** to the carboxylic acid occurred smoothly applying PDC as the oxidant. Finally, catalytic reductive cleavage of the benzyl ether liberated (+)-bourgeanic acid (**1**) in a 94% yield. Spectroscopic and analytical data of **1** were identical to those reported previously.[10]

The total synthesis of the aliphatic depside (+)-bourgeanic acid (**1**) has been achieved in 12 steps with an overall yield of 10% starting from **5**. The synthesis displays the efficiency of methodology relying on the on the *o*-DPPB-directed allylic substitution for stereoselective construction of propionate structural motifs and thus complements more traditional strategies relying on aldol and enolate alkylation chemistry.

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(19) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikotam, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
(20) Under the basic conditions, a slight epimerization at the α-position of the carboxylic ester function was observed, and the diastereomeric ratio could be determined as 92:8.

Acknowledgment. This work was supported by the DFG including the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038) and the Krupp foundation (fellowship to T.R.). We thank Novartis, BASF, and Wacker for generous gifts of chemicals.

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

OL9011635