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First enantioselective total synthesis of (−)-dysibetaine CPa and absolute configurations of natural product

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ABSTRACT

Here we report total synthesis of enantiomerically pure dysibetaine CPa, isolated from Micronesian marine sponge and expected to serve as a neuroactive agent. Starting from *meso*-cyclopropane triester, the synthesis was achieved in 12.8% overall yield over 10 steps including organocatalytic enantioselective solvolysis of *meso*-succinic anhydride as a key step. This work established the absolute configurations of the natural product as (3*R*,4*R*).

In 2004, a series of structurally interesting hydrophilic natural products, such as dysibetaine CPa (**1**) and dysibetaine CPb (**2**) (Fig. 1), have been isolated by Sakai et al. from Micronesian marine sponge, *Lendenfeldia chondrodes*.[1] The dysibetaines are trisubstituted cyclopropanes bearing carboxy and tetraalkylammonium groups, and thus contain γ-amino butyric acid (GABA) motif. Since Sakai group had discovered dysiherbaine from the same sponge in 1997[2] which was later identified as a potent agonist selective to GluK1, GluK2, and GluK3,[3] the dysibetaines **1** and **2** are also expected to serve as neuroactive agents. However, because of the limited availability from natural resources, their biological activities have not been studied well. In addition, the absolute stereochemistry of the natural products remains to be elucidated. While total synthesis is the strategy often employed toward elucidation of unknown configurations, two synthetic studies[4,5] previously reported for racemic dysibetaine CPa were not applicable to the enantioselective synthesis.

Here we report our preliminary results on the de novo asymmetric synthesis of (−)-dysibetaine CPa (**1**), which culminated in the structural determination of the natural product as (3*R*,4*R*).

As shown in Scheme 1, the asymmetric synthesis started with known *trans,meso*-cyclopropanetricarboxylic acid triethyl ester (**3**).[6] We expected that organocatalytic solvolysis of *meso* cyclic anhydride would discriminate between the anhydride carbonyl groups and allow us to synthesize enantiomerically pure dysibetaine CPa. Acidic hydrolysis of triethyl ester **3** (6 M aq HCl, 95 °C) followed by treatment with Ac_2O under microwave irradiation conditions gave dianhydride **5** in high yield (98%).

With succinic anhydride **5** in hand, we then investigated cinchona alkaloid-mediated methanolysis. After several experiments, it was found that Song's bifunctional quinine-sulfonamide catalyst[7] showed acceptable level of asymmetric induction (83–88% ee)[8] to give monomethyl ester **7** in moderate yield (54–62%).[9] The absolute stereochemistry was tentatively assigned as (3*S*,4*S*) (dysibetaine CPa numbering) on the basis of the empirical rule proposed by Bolm[10] and Oda,[11] and confirmed separately by single-crystal X-ray analysis of the 4-bromobenzoyl ester derivative (see the Supplementary data).

From dicarboxylic acid **7**, (−)-dysibetaine CPa (**1**) was synthesized as follows (Scheme 2). Esterification of **7** with *t*BuOH was performed by modified Takeda–Gooβen reaction (Boc_2O, DMAP,

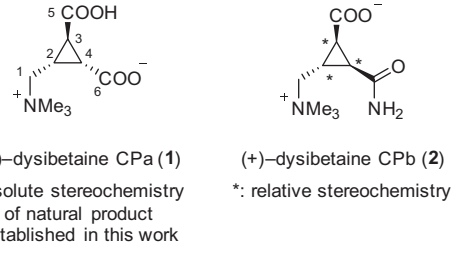

Figure 1. Cyclopropane-containing betaines from *Lendenfeldia chondrodes*.

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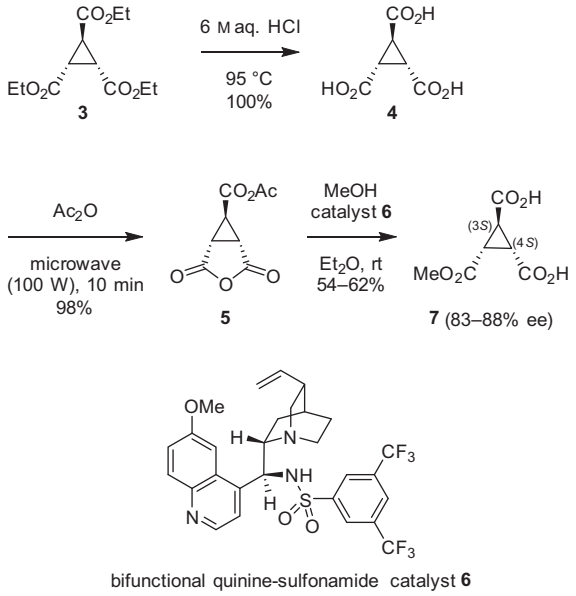
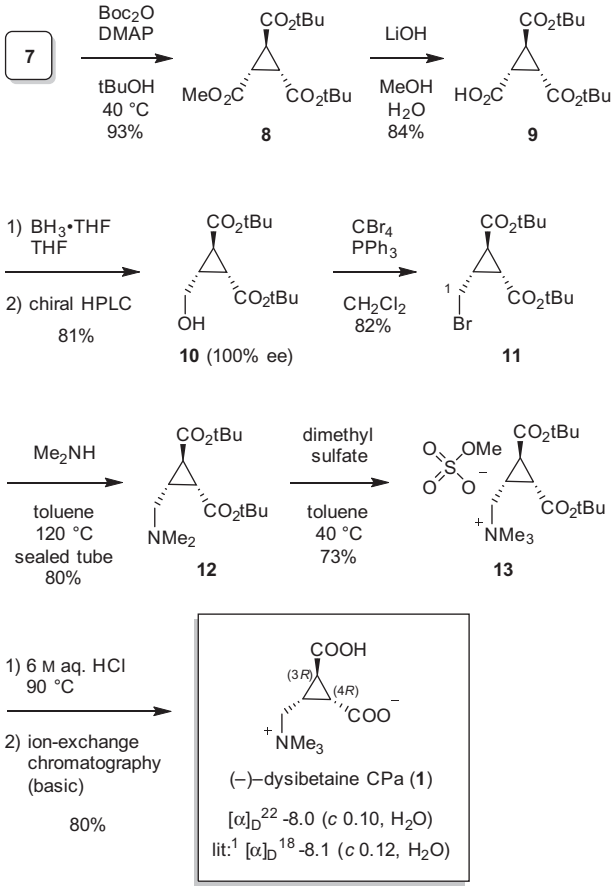


Scheme 1. Asymmetric synthesis of cyclopropane dicarboxylic acid **7** by organocatalytic methanolysis.



Scheme 2. Total synthesis of (−)-dysibetaine CPa (**1**) with natural configurations.

*t*BuOH)[12] to provide triester **8** in 93% yield. Selective hydrolysis of methyl ester **8** (LiOH, H_2O, 84%) and reduction of the carboxyl group furnished enantiomerically pure alcohol **10** in 81% yield after purification by chiral HPLC (Daicel CHIRALPAK IC column). Bromination (CBr_4, PPh_3) gave **11** in 82% yield, ready for introduction of the trimethylammonium group at the C1-position. According to our racemate synthesis,[5] we employed a stepwise reaction also here because of the poor reactivity of bromide **11** toward trimethylamine. Thus, amination with Me_2NH at 120 °C gave **12**, which, in turn, reacted with dimethyl sulfate to deliver trimethylammonium salt **13** successfully in 58% yield over two steps. For the N-methylation, other agents were impractical; MeI caused decomposition of the *tert*-butyl ester, and dimethyl carbonate was unreactive even at elevated temperature (50 °C). Finally, acidic hydrolysis (6 M aq HCl) followed by the removal of the monomethyl sulfate ion by ion-exchange chromatography (Dowex 1-X8) provided (3*R*,4*R*)-dysibetaine CPa, which was chromatographically and spectroscopically identical with natural product,[1] including the optical rotation data (−8.0 for synthetic, and −8.1 for authentic materials). Our total synthesis thus unequivocally established the absolute configurations of natural dysibetaine CPa as (3*R*,4*R*). Overall yield was 12.8% over 10 steps from *trans*,-*meso*-cyclopropanetricarboxylic acid triethyl ester (**3**). Evaluation of the bioactivity as well as syntheses of the analogs is currently underway in our laboratory.

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Supplementary data

Supplementary data (X-ray diffraction experiment of 4-bromobenzoate of **10**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.113.

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8. Enantiomeric purity was determined by chiral HPLC analysis of triester **8** later (0.46 × 25 cm Daicel CHIRALPAK IC column, EtOH/hexane = 10:90, 1.0 mL/min).
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