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The first asymmetric total syntheses of 3((1*R*,2*R*)- and 3((1*S*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid

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ABSTRACT

The first efficient total syntheses of 3((1*R*,2*R*)- and 3((1*S*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid have been achieved following a chelation controlled modified Simmon–Smith cyclopropanation, Wittig reaction, Horner–Wadsworth–Emmons olefination, and *p*-toluenesulfonyl hydrazide catalyzed hydrogenation as key reactions in good overall yield.

The cyclopropyl ring can be found in a range of naturally occurring biologically active compounds including those present in bacterial fatty acids.[1] The cyclopropane fatty acids, 3-(2-(12-methyltridecyl)-4,5-*trans*-cyclopropyl)propanoic acid, 3-(2-(13-methyltetradecyl)-4,5-*trans*-cyclopropyl)propanoic acid, and 3-(2-(12-methyltetradecyl)-4,5-*trans*-cyclopropyl)propanoic acid, were recently isolated and characterized for the first time in nature in the phospholipids of the hermit-crab sponge *Pseudospongosorites suberitoides* which was collected from the Mona island, Puerto Rico in 2007.[2] These marine fatty acids are quite interesting since they incorporate an unusual *trans* 4,5-cyclopropane in addition to isomethyl branching (**1a–1d**) (Fig. 1). Pyrrolidine derivatization combined with spectral analysis was the key in identifying position of the cyclopropyl, methyl group, and trans-stereochemistry of the cyclopropyl group. Recently, Carballeira et al. reported the total synthesis of (±)-3-(2-(12-methyltridecyl)-4,5-*trans*-cyclopropyl) propanoic acid and its corresponding cis analog.[3] As per our knowledge, there is no information concerning the asymmetric total synthesis of these fatty acids. Because of our interest to synthesize cyclopropyl bearing biologically active natural products,[4] herein, we disclose the first asymmetric synthesis of 3((1*R*,2*R*)- and 3((1*S*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid (**1a**) and (**1b**), respectively.

From retrosynthetic perspective, we envisioned that the *trans* cyclopropane fatty acid **1a** could be derived from the cyclopropane derivative diene ester **2** via *p*-toluenesulfonyl hydrazide catalyzed hydrogenation which in turn would come from the acetonide protected diol **3**. The diol could be prepared from the aldehyde **4** and TPP salt of long chain compound **5**. The salt **5** could be obtained from the long chain iodo compound **7** where as the aldehyde **4** could be synthesized from (*R*)-2,3-*O*-isopropylidine glyceraldehyde (**6**) via chelation controlled modified Simmon–Smith cyclopropanation reaction (Scheme 1).

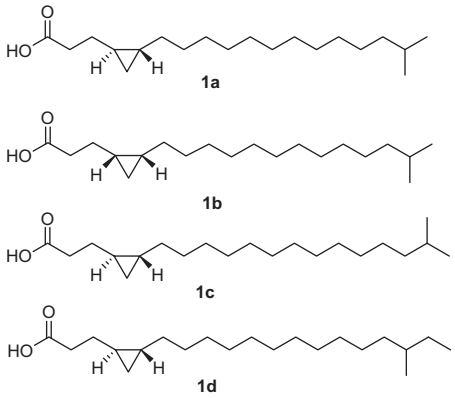

Figure 1. Structures of cyclopropyl fatty acids **1a**, **1b**, **1c**, and **1d**.

The synthesis of **1a** was commenced from (*R*)-2,3-*O*-isopropylidine glyceraldehyde[5] (**6**) which was converted into cyclopropyl alcohol **4** following a well known protocol via Wittig reaction to obtain (*E*)-α,β-unsaturated ester, DIBAL-H reduction, TBDPS ether

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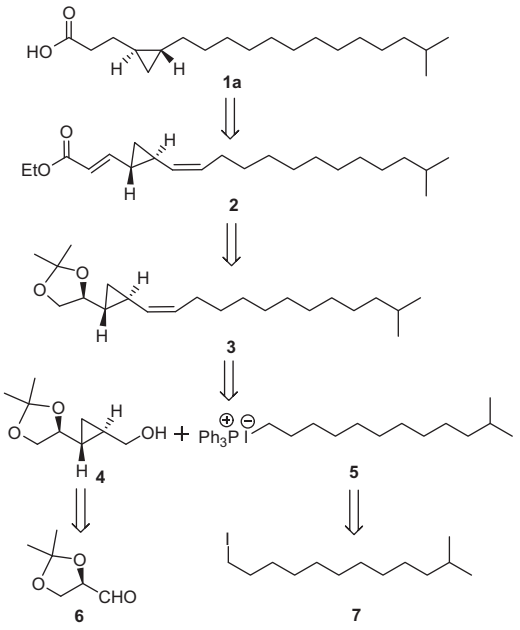
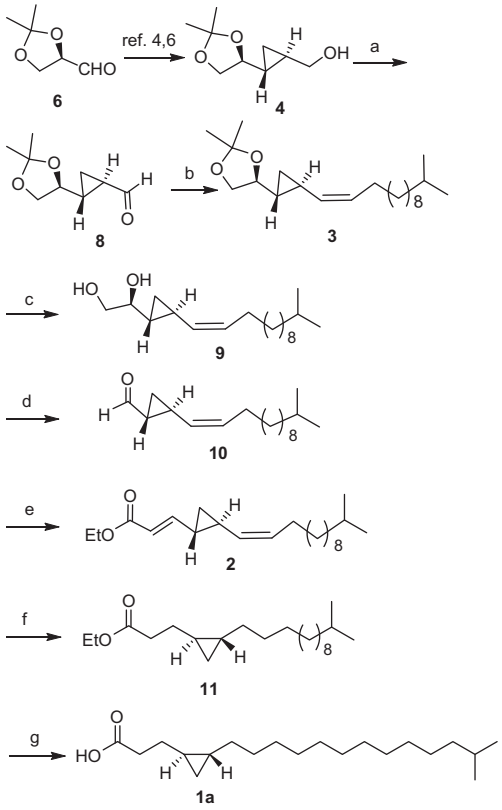


Scheme 1. Retrosynthetic analysis of **1a**.

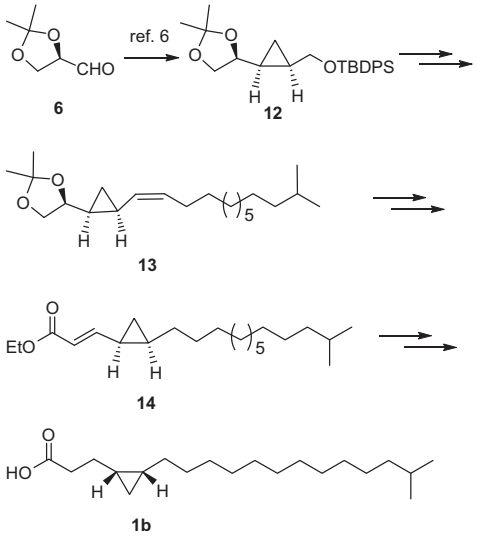
formation followed by chelation–controlled Simmon–Smith cyclopropanation[6] and cleavage of the silyl protective group. The resulting primary alcohol **4** was oxidized to the corresponding aldehyde **8** with Dess–Martin periodinane[7] in CH_2Cl_2 in 90% yield. The carbon–carbon bond formation at C7–C8 was achieved by performing the Wittig reaction[8] of 11-methyldodecyl)triphenylphosphonium iodide[9] with the resulting aldehyde **8** in the presence of NaHMDS at −78 °C to supply **3** as a single *Z*-isomer in 89% yield which on treatment with PPTS in MeOH at room temperature afforded the diol **9** in 91% yield. Oxidative cleavage of the resulting diol **9** followed by two carbon homologation via Horner–Wadsworth–Emmons[10] olefination with ethyl diethyl phosphonoacetate and sodium hydride gave the α,β-unsaturated ester **2** in 85% yield over two steps. Initially, hydrogenation of both the double bonds with Pd/C, Pd/OH, and Raney Ni in different solvents like MeOH, EtOH, and toluene ended up with an intractable mixture of products. Finally, when compound **2** was treated with *p*-toluenesulfonyl hydrazide[11] and sodium acetate in THF/H_2O (1:1) mixture, reaction went smoothly providing saturated cyclopropyl ester **11** in 92% yield. Saponification of ester group present in **11** with KOH in EtOH:H_2O (3:1) provided the desired target molecule **1a** in 91% yield (Scheme 2).

Similarly, total synthesis of 3((1*S*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid (**1b**) was achieved in good overall yield starting from the cis-olefination of the aldehyde **6** to obtain (*Z*)-α,β-unsaturated ester followed by DIBAL-H reduction, TBDPS protection and cyclopropanation afforded known cyclopropyl TBDPS ether **12** (Scheme 3). Silyl group deprotection, oxidation followed by Wittig reaction furnished olefin compound **13**. Double bond reduction under *p*-toluenesulfonyl hydrazide catalyzed hydrogenation conditions, acetonide deprotection, oxidative cleavage of diol, Horner–Wadsworth–Emmons olefination with ethyl diethyl phosphonoacetate, reduction of double bond under *p*-toluenesulfonyl hydrazide catalyzed hydrogenation conditions followed by saponification gave 3((1*S*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid (**1b**).

In conclusion, the first asymmetric total synthesis of 3((1*R*,2*R*)-2-(12-methyltridecyl)cyclopropyl)propanoic acid (**1a**) was accomplished in seven steps with 51.6% overall yield starting from a known cyclopropyl alcohol intermediate **4**. Similarly, 3((1*S*,2*R*)-2-



Scheme 2. Reagents and conditions: (a) DMP, CH_2Cl_2, $NaHCO_3$, rt, 2 h, 90%; (b) (11-methyldodecyl) triphenylphosphonium iodide, NaHMDS, THF, 1 h, −78 to 0 °C, 89%; (c) PPTS, MeOH, 0 °C to rt, 3 h, 91%; (d) $NaIO_4$ impregnated over silica gel, CH_2Cl_2, 0 °C to rt, 10 min, 94%; (e) triethylphosphonoacetate, NaH, THF, 30 min, 0 °C to rt, 90%; (f) *p*-$TsNHNH_2$, NaOAc, THF:H_2O (1:1), reflux, 12 h, 92%; (g) KOH, EtOH:H_2O (3:1), 0 °C to rt, 2 h, 91%.



Scheme 3. Total synthesis of **1b**.

(12-methyltridecyl)cyclopropyl)propanoic acid (**1b**) was achieved in nine steps with 43% overall yield starting from a known intermediate **12**. The key steps are a highly diastereoselective Simmon–Smith cyclopropanation reaction and a *p*-toluenesulfonyl hydrazide catalyzed hydrogenation reaction. Following the same protocol, other related natural products are in the process of synthesis and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.133.

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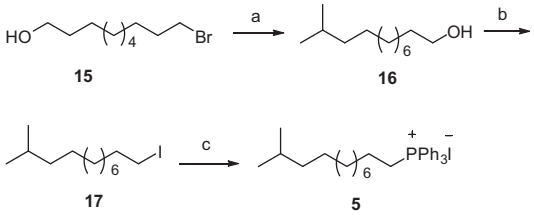
9. The reaction between commercially available 10-bromo decanol **15** and the Grignard[10] reagent prepared from 2-bromopropane with Li_2CuCl_4 afforded the long chain hydroxy compound **16** in 89% yield. Subsequent iodination of the primary hydroxyl group with iodine, TPP and imidazole furnished the iodo compound **17** in 94% yield. The iodo compound **17** was converted to the corresponding TPP salt **5** by refluxing the compound in acetonitrile in 90% yield.



Reagent conditions: (a) 2-bromo propane, Mg, Li_2CuCl_4, THF, −78 °C to 0 °C, 89%; (b) I_2, TPP, Imidazole, THF, 0 °C to rt, 94%; (c) TPP, MeCN, reflux, 90%.
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