

## Synthesis of Hydroxy- $\alpha$ -sanshool

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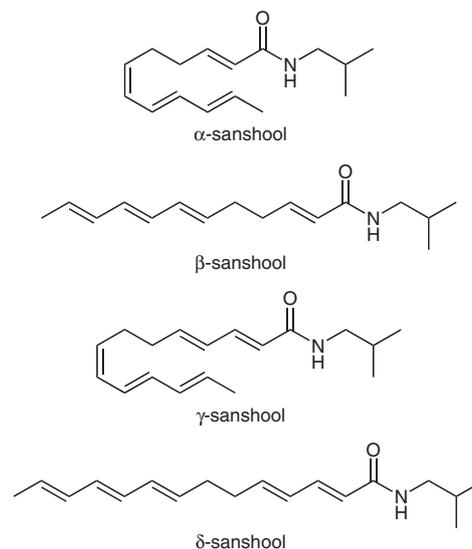
**Abstract:** The amide hydroxy- $\alpha$ -sanshool is responsible for the mild numbing sensation experienced when Sichuan (or Szechuan) peppercorns (*huajiao*) are eaten. It has been synthesized in six steps from simple commercially available starting materials using Wittig reactions as the key transformations for construction of the carbon skeleton. The penultimate synthetic intermediate was 2*E*,6*Z*,8*E*,10*E*-dodecatetraenoic acid, and its crystalline nature allowed it, and thus hydroxy- $\alpha$ -sanshool, to be purified to a very high level of stereochemical homogeneity.

**Key words:** natural products, isomers, alkenes, Wittig reaction, aldehydes

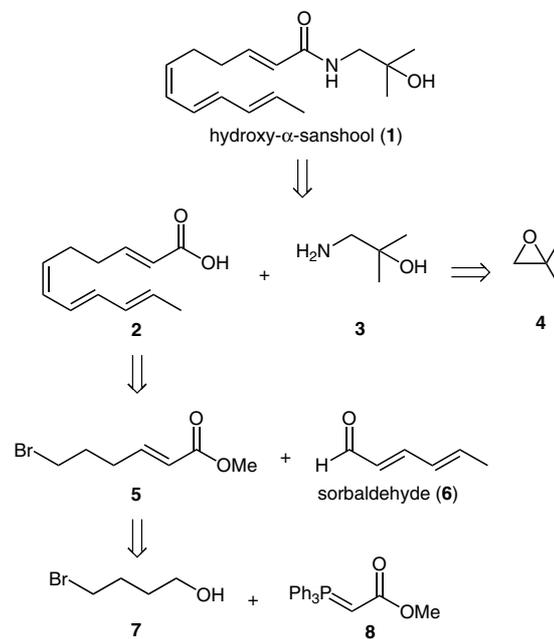
The sanshools are a group of polyunsaturated amides found in various *zanthoxylum* species (Figure 1).<sup>1</sup> Notably, hydroxy- $\alpha$ -sanshool (**1**; Scheme 1) is responsible for the mild numbing/tingling sensation one experiences when eating Sichuan (or Szechuan) peppercorns known as *huajiao*.<sup>2a</sup> Recently its mechanism of action has been studied, and it has been found to excite sensory neurons through inhibition of two-pore potassium channels.<sup>2</sup> This observation has generated interest in synthesizing and studying analogues of **1**,<sup>3</sup> since its isolation is tedious and low-yielding.<sup>4</sup> In light of the importance of such biological activity,<sup>5</sup> the interesting physiological effects of **1**,<sup>6</sup> and its potential utility in the cosmetics<sup>7</sup> and food<sup>8</sup> industries, we sought to develop an efficient synthesis that would allow for easy access to not only **1**, but also analogues for structure–activity relationship studies. Herein, we report the realization of this objective and describe what is, to the best of our knowledge, the first reported de novo synthesis of **1**.

Our retrosynthetic analysis for **1** is outlined in Scheme 1. Carboxylic acid **2**<sup>9</sup> was targeted as the key intermediate since it could be used to prepare not only **1**, but also a library of amide analogues. Thus, the final step would involve coupling acid **2** with amine **3**, which can be prepared by reaction of isobutylene oxide (**4**) with benzylamine followed by debenzylation,<sup>3</sup> to afford **1**. It was envisioned that a Wittig reaction could be used to synthesize an ester of **2** by reaction of a phosphorane derived from **5** with sorbaldehyde (**6**), and that ester **5** could, in turn, be prepared in two steps from commercially available building blocks 4-bromobutanol (**7**) and phosphorane **8**. Thus, our plan was to synthesize **2** from **6–8** using a pair

of stereoselective Wittig reactions as the key carbon-connecting steps.



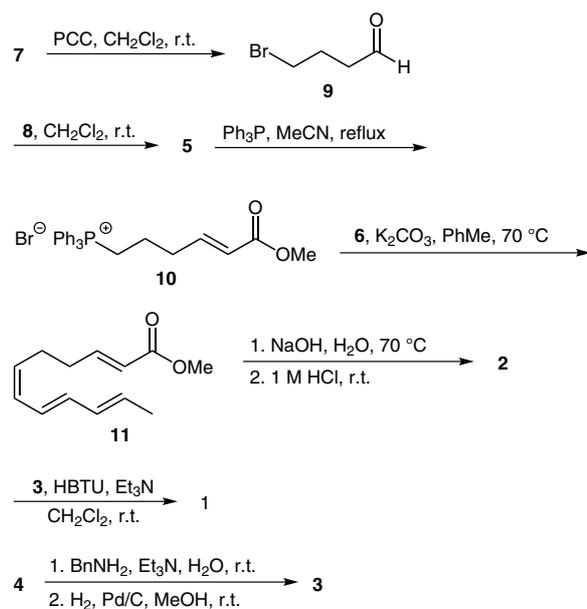
**Figure 1** Sanshool compounds



**Scheme 1** Retrosynthetic analysis for hydroxy- $\alpha$ -sanshool (**1**)

The successful realization of our synthetic plan is presented in Scheme 2.<sup>10</sup> Oxidation of alcohol **7** using PCC afforded aldehyde **9** in 76% yield, and subsequent reaction

of **9** with phosphorane **8** afforded enoate **5** in 91% yield with predominate *E*-stereoselectivity (92:8). This was followed by treatment of **5** with  $\text{Ph}_3\text{P}$  to afford the corresponding phosphonium salt **10** in 96% yield. Salt **10** was then mixed with  $\text{K}_2\text{CO}_3$  and aldehyde **6** to effect the second Wittig reaction, which afforded **11** in 80% yield with approximate 2:1 *Z/E*-stereoselectivity.<sup>11</sup> Ester **11** was then converted into **2** in 43% yield after recrystallization. Finally, coupling of **2** with **3** (prepared according to the literature procedure from **4**<sup>3</sup>) with HBTU and  $\text{Et}_3\text{N}$  afforded **1** in 92% yield. Thus, **1** was synthesized expediently in 21% overall yield in a process that required six reactions in the longest linear sequence.<sup>12</sup> It should be noted that commercially available **6** is labeled as being ‘predominantly *trans,trans*’, and is approximately a 5:1 mixture of isomers according to  $^1\text{H}$  NMR analysis. This is one of the major reasons for the relatively modest yield of **2**. Considering this fact and the amounts of undesired alkene isomers formed in the two Wittig reactions, our achieved yield of **2** is quite respectable. Fortunately, nearly all of the undesired stereochemical isomers due to the nature of **6** used as the starting material, and formed in the Wittig reactions, could be removed by the recrystallization of **2** (ca. 96% isomerically pure).



**Scheme 2** Synthesis of hydroxy- $\alpha$ -sanshool (**1**)

In conclusion, we report a short, high-yielding synthesis of **1** from four simple and inexpensive building blocks that involves two stereoselective Wittig reactions as the key transformations for construction of the carbon skeleton. Importantly, penultimate intermediate **2** can be recrystallized to a high level of stereochemical homogeneity, and thus the undesired diastereomers resulting from starting material **6** and formed in the Wittig reactions can be readily removed. We are currently investigating the application of our previously reported methodology for facilitating Wittig reactions<sup>13</sup> to the

synthesis of **1**, and envision that easy access to large quantities of **2** will allow the preparation of a broad range of amide analogues of **1** for use in structure–activity relationship studies. Results of this ongoing research program will be reported shortly.

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**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (10) See the Supporting Information for details.
- (11) This stereoselectivity is typical of such Wittig reactions involving unstabilized ylides, and we are currently exploring the purification of the *E*-isomer so that it can be used in the synthesis of  $\beta$ -sanshool derivatives.
- (12) Characterization data for synthetic **1**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.21 (s, 6 H), 1.75–1.77 (d,  $J$  = 7.2 Hz, 3 H), 2.23–2.35 (m, 4 H), 3.13 (s, 1 H), 3.29–3.31 (d,  $J$  = 6.0 Hz, 2 H), 5.31–5.37 (dt,  $J$  = 10.4, 7.4 Hz, 1 H), 5.67–5.75 (dq,  $J$  = 14.0, 7.2 Hz, 1 H), 5.83–5.87 (d,  $J$  = 15.2 Hz, 1 H), 5.97–6.03 (dd,  $J$  = 10.8, 10.8 Hz, 1 H), 6.19–6.06 (m, 2 H), 6.27–6.33 (m, 2 H), 6.80–6.87 (dt,  $J$  = 13.2, 6.4 Hz, 1 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 18.4, 26.5, 27.2, 32.1, 50.6, 70.8, 124.0, 125.2, 129.4, 129.7, 130.2, 131.8, 133.6, 144.1, 167.2. This matches the data previously reported for material isolated from natural sources.<sup>1a</sup>
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