The HKU Scholars Hub   The University of Hong Kong   香港大學學術庫

Title	**Synthesis of Hydroxy- -sanshool**
Author(s)	**Wu, B; Li, K; Toy, PH**
Citation	**Synlett, 2012, v. 23 n. 17, p. 2564-2566**
Issued Date	**2012**
URL	**http://hdl.handle.net/10722/185711**
Rights	**Synlett. Copyright © Georg Thieme Verlag**

Synthesis of Hydroxy-α-sanshool

Bo Wu, Kun Li and Patrick H. Toy*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. of China
Fax +852 28571586; E-mail: phtoy@hku.hk
Received:

Abstract: The amide hydroxy-α-sanshool is responsible for the mild numbing sensation experienced when Sichuan (or Szechuan) peppercorns (*huajiao*) are eaten. It has been synthesized in 6 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-α-sanshool, to be purified to a very high level of stereochemical homogeneity.

Key words: hydroxy-α-sanshool, Sichuan peppercorn, Wittig reaction, sorbaldehyde

The sanshools are a group of polyunsaturated amides found in various *zanthoxylum* species (Figure 1).[1] Notably hydroxy-α-sanshool (**1**, Scheme 1) is responsible for the mild numbing/tingling sensation one experiences when eating Sichuan (or Szechuan) peppercorns known as *huajiao*.[2a]   Recently its mechanism of action has been studied, and it has been found to excite sensory neurons through inhibition of two-pore potassium channels.[2] This observation has generated interest in studying analogues of **1**,[3] since its isolation is tedious and low-yielding.[4] In light of the importance of such biological activity,[5] the interesting physiological effects of **1**,[6] and its potential utility in the cosmetics[7] and food[8] 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 our knowledge the first reported de novo synthesis of **1**.
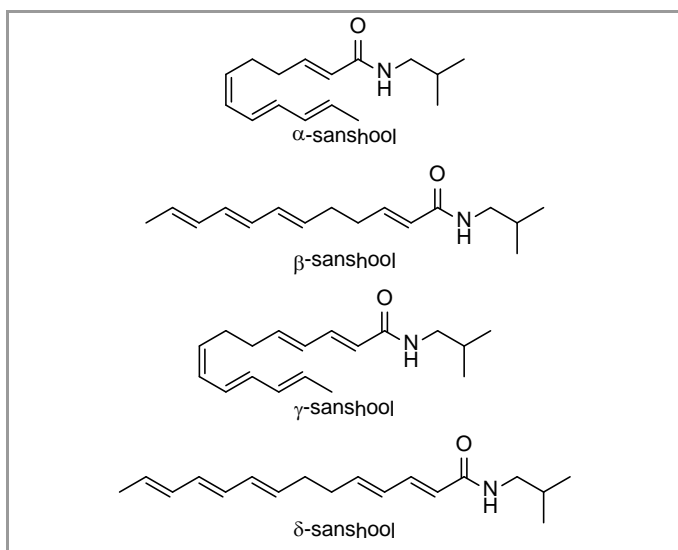

Figure 1 Sanhool compounds

Our retrosynthetic analysis for **1** is outlined in Scheme 1. Carboxylic acid **2**[9] was targeted as the key intermediate since it could be used to prepare not only **1**, but a library of amide

analogues as well. 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,[3] 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 in key the carbon connecting steps.
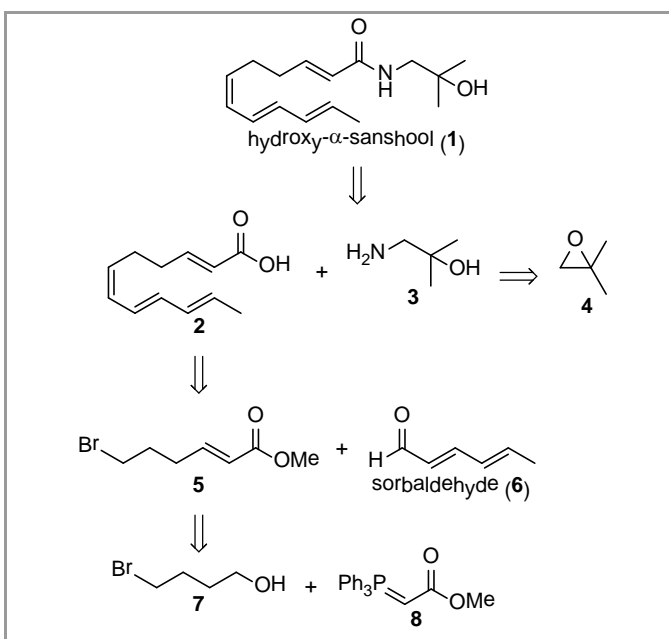
Scheme 1 Retrosynthetic analysis for hydroxy-α-sanshool (**1**)

The successful realization of our synthetic plan is presented in Scheme 2.[10] 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 PPh₃ to afford corresponding phosphonium salt **10** in 96% yield. Salt **10** was then mixed with K₂CO₃ and aldehyde **6** to effect the second Wittig reaction, which afforded **11** in 80% yield with approximate 2:1 *Z*:*E*-stereoselectivity.[11] 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**[3]) with HBTU and Et₃N afforded **1** in 92% yield. Thus, **1** was synthesized expediently in 21% overall yield in a process that required 6 reactions in the longest linear sequence.[12] 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 ¹H 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).
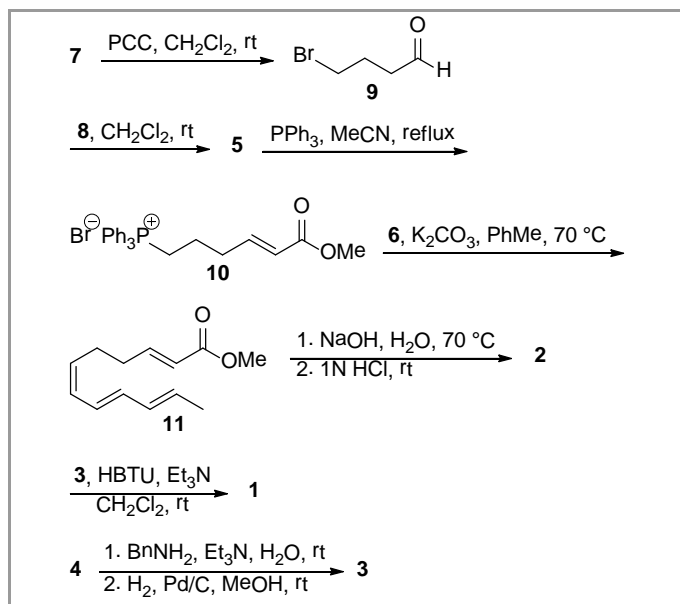
Scheme 2 Synthesis of hydroxy-α-sanshool (**1**)

In conclusion, we report a short, and high-yielding synthesis of **1** from 4 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[13] to the synthesis of **1**, and envision that easy access to large quantities of **2** will allow for 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.

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

Acknowledgement

References and Notes

(1)   (a) Yasuda, I.; Takeya, K.; Itokawa, H. *Phytochemistry* **1982**, *21*, 1295-1298 and references cited therein. (b) Mitzutani, K.; Fukunaga, Y.; Tanaka, O.; Takasugi, N.; Saruwatari, Y.-I.; Fuwa, T.; Yamauchi, T.; Wang, J.; Jia, M.-R.; Li, F.-Y.; Ling, Y.-K. *Chem. Pharm. Bull.* **1988**, *36*, 2362-2365. (c) Kashiwada, Y.; Ito, C.; Katagiri, H.; Mase, I.; Komatsu, K.; Namba, T.; Ikeshiro, Y. *Phytochemistry* **1997**,

44, 1125-1127. (d) Xiong, Q.; Shi, D.; Yamamoto, H.; Mizuno, M. *Phytochemistry* **1997**, *46*, 1123-1126. (e) Chen, I.-H.; Chen, T.-L.; Lin, W.-Y.; Tsai, I.-L.; Chen, Y.-C. *Phytochemistry* **1999**, *52*, 357-360. (f) Jang, K. H.; Chang, Y. H.; Kim, D.-D.; Oh, K.-B.; Oh, U.; Shin, J. *Arch. Pharm. Res.* **2008**, *31*, 569-572.

(2)   (a) Sugai, E.; Morimitsu, Y.; Iwasaki, Y.; Morita, A.; Watanabe, T.; Kubota, K. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1951-1957. (b) Koo, J. Y.; Jang, Y.; Cho, H.; Lee, C.-H.; Jang, K. H.; Chang, Y. H.; Shin, J.; Oh, U. *Eur. J. Neurosci.* **2007**, *26*, 1139-1147. (c) Bautista, D. M.; Sigal, Y. M.; Milstein, A. D.; Garrison, J. L.; Zorn, J. A.; Tsuruda, P. R.; Nicoll, R. A.; Julius, D. *Nature Neurosci.* **2008**, *11*, 772-779. (d) Riera, C. E.; Menozzi-Smarrito, C.; Affolter, M.; Michlig, S.; Munari, C.; Robert, F.; Vogel, H.; Simon, S. A.; le Coutre, J. *Br. J. Pharmacol.* **2009**, *157*, 1398-1409.

(3)   Menozzi-Smarrito, C.; Riera, C. E.; Munari, C.; Le Coutre, J.; Robert, F. *J. Agric. Food Chem.* **2009**, *57*, 1982-1989.

(4)   According to reference 2c, 50 g of dried seeds from *Zanthoxylum piperitum* afforded 55.2 mg of crude **1** after preparative HPLC. Repetitive chromatographic separation was required to further purify **1** to homogeneity.

(5)   (a) Baraldi, P. G.; Preti, D.; Materazzi, S.; Geppetti, P. *J. Med. Chem.* **2010**, *53*, 5085-5107. (b) Mathie, A. *J. Pharm. Pharmacol.* **2010**, *62*, 1089-1095. (c) Es-Salah-Lamoureux, Z.; Steele, D. F.; Fedida, D. *Trends Pharmacol. Sci.* **2010**, *31*, 587-595.

(6)   (a) Sawyer, C. M.; Carstens, M. I.; Simons, C. T.; Slack, J.; McCluskey, T. S.; Furrer, S.; Carstens, E. *J. Neurophysiol.* **2009**, *101*, 1742-1748. (b) Lennertz, R. C.; Tsunozaki, M.; Bautista, D. M.; Stucky, C. L. *J. Neurosci.* **2010**, *30*, 4353-4361. (c) Albin, K. C.; Simons, C. T. *PLoS One* **2010**, *5*, e9520. (d) Klein, A. H.; Sawyer, C. M.; Zanotto, K. L.; Ivanov, M. A.; Cheung, S.; Carstens, M. I.; Furrer, S.; Simons, C. T.; Slack, J. P.; Carstens, E. *J. Neurophysiol.* **2011**, *105*, 1701-1710.

(7)   Artaria, C.; Maramaldi, G.; Bonfigli, A.; Rigano, L.; Appendino, G. *Int. J. Cosmetic Sci.* **2011**, *33*, 328-333.

(8)   Starkenmann, C.; Cayeux, I.; Birkbeck, A. A. *Chimia* **2011**, *65*, 407-410.

(9)   For what is to our knowledge the only previously reported synthesis of **2** (and α-sanshool) by a different route, see: Sonnet, P. E. *J. Org. Chem.* **1969**, *34*, 1147-1149.

(10)   See 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 β-sanshool derivatives.

(12)   Characterization data for synthetic **1**: ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm 1.21 (s, 6H), 1.75-1.77 (d, J = 7.2 Hz, 3H), 2.23-2.35 (m, 4H), 3.13 (s, 1H), 3.29-3.31 (d, J = 6.0 Hz, 2H), 5.31-5.37 (dt, J_1 = 10.4 Hz, J_2 = 7.4 Hz, 1H), 5.67-5.75 (dq, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1H), 5.83-5.87 (d, J = 15.2 Hz, 1H), 5.97-6.03 (dd, J_1 = 10.8 Hz, J_2 = 10.8 Hz, 1H), 6.19-6.06 (m, 2H), 6.27-6.33 (m, 2H), 6.80-6.87 (dt, J_1 = 13.2 Hz, J_2 = 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm 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 what has been previously reported for material isolated from natural sources in reference 1a.

(13)   (a) Leung, P. S.-W.; Teng, Y.; Toy, P. H. *Synlett* **2010**, 1997-2001. (b) Leung, P. S.-W.; Teng, Y.; Toy, P. H. *Org. Lett.* **2010**, *12*, 4996-4999. (c) Teng, Y.; Lu, J.; Toy, P. H. *Chem. Asian J.* **2012**, *7*, 351-359.

Graphical abstract

hydroxy-α-sanshool
*numbing compound found
in Sichuan peppercorns*

commercially available building blocks