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Synthesis of Hydroxy-α-sanshool

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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 2E,6Z,8E,10E-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 pepper, 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.7 This observation has generated interest in studying analogues of 1, 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, and its potential utility in the cosmetics7 and food8 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.

Our retrosynthetic analysis for 1 is outlined in Scheme 1. Carboxylic acid 2 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, 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 enolate 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 44) with HBTU and Et3N afforded 1 in 92% yield. Thus, 1 was synthesized expeditiously 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 stereoc hemical 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 stereoc hemical 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 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.

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References and Notes


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


(9) For what is to our knowledge the only previously reported synthesis of 2 (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 unsaturated 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: 1H-NMR (400 MHz, CDCl3) 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, J1 = 10.4 Hz, J2 = 7.4 Hz, 1H), 5.67-5.75 (dq, J1 = 14.0 Hz, J2 = 7.2 Hz, 1H), 5.83-5.87 (d, J = 15.2 Hz, 1H), 5.97-6.03 (dd, J1 = 10.8 Hz, J2 = 10.8 Hz, 1H), 6.19-6.06 (m, 2H), 6.27-6.33 (m, 2H), 6.80-6.87 (dt, J1 = 13.2 Hz, J2 = 6.4 Hz, 1H); 13C-NMR (100 MHz, CDCl3) δ ppm 18.4, 26.5, 27.2, 32.1, 50.6, 70.8, 124.0, 1398-1409. 

Graphical abstract

Hydroxy-α-sanshool
numbing compound found
in Sichuan peppercorns

Commercially available building blocks