Synthesis of γ-Sanshool and Hydroxy-γ-sanshool

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Abstract: Members of the family of polyunsaturated amide compounds known as the sanshools are found in various *Zanthoxylum* species such as Sichuan (or Szechuan) peppercorns (*huajiao*). γ-Sanshool and hydroxy-γ-sanshool have been synthesized from simple building blocks using an alkyne to *E,E*-1,3-diene isomerization reaction to stereoselectively install the *E,E*-2,4-diene group of the key synthetic intermediate 2*E*,4*E*,8*Z*,10*E*,12*E*-tetradecapentaenoic acid, which in turn was converted into both γ-sanshool and hydroxy-γ-sanshool by reaction with the appropriate amines.

Key words: alkenes, alkynes, isomerization reactions, natural products, Wittig reactions

The sanshools are a family of polyunsaturated fatty acid amides found in various *Zanthoxylum* species that has recently attracted the interest of a broad cross-section of the scientific community (Figure 1).[1] For example, hydroxy-α-sanshool (HAS) is responsible for the numbing/tingling sensation one experiences when eating Sichuan (or Szechuan) peppercorns (*huajiao*),[2] and this finding has led to interest in understanding the details of its mechanism of action,[3] and in developing various medicinal,[4] agricultural,[5] food,[6] and cosmetic[7] applications for it. However, while HAS has been relatively widely studied, it is rather difficult to obtain in pure form.[8] While much less is known regarding the other sanshools,[9] γ-sanshool (**1**) has been found to inhibit human acyl-CoA cholesterol acyltransferase-1, with an IC_{50} of 12 μM.[10] Thus, in order to increase the availability of the sanshools for wider study, we have initiated a program to synthesize them in stereochemically pure form, and have recently reported a synthesis of HAS that can be performed on a gram-scale.[11-14] In this report, we describe the synthesis of **1** and hydroxyl-γ-sanshool (**2**) from a common carboxylic acid intermediate.

The synthesis of **1** has been previously described by two groups, and in both syntheses a Horner-Wadsworth-Emmons (HWE) reaction was used to construct the 2,4-diene group (Scheme 1).[15,16] In the report published nearly 30 years ago by Crombie and Fisher, several synthetic strategies were described, but in the preferred route the C_2-C_3 double bond was formed from a HWE reaction.[15a] The authors did not discuss the stereoselectivity of this HWE reaction, but in the subsequent synthesis of **1** described by Igarashi et al., a similar HWE reaction used to form the C_4-C_5 double bond resulted in either a mixture of *E* and *Z* isomers, or only modest (40-56%) yield of the desired product.[16] Therefore, it seems that the synthesis by Crombie and Fisher possibly suffered from simi-

lar issues. Furthermore, both syntheses utilized amide functionalized phosphonate reagents in the HWE reactions, which resulted in dienamide products. Thus, these two routes only resulted in the synthesis of **1**, and do not involve an intermediate directly amenable to the synthesis of analogues of it in which the *N*-substituent varies, as it does in **2**. With these issues regarding this pervious work in mind, we felt that it would be useful to design a synthesis of **1** in which the issue of stereoisomers in the 2,4-diene group is eliminated, and that involves a carboxylic acid, which could also be used to generate not only **2**, but a library of other amide analogues as well.
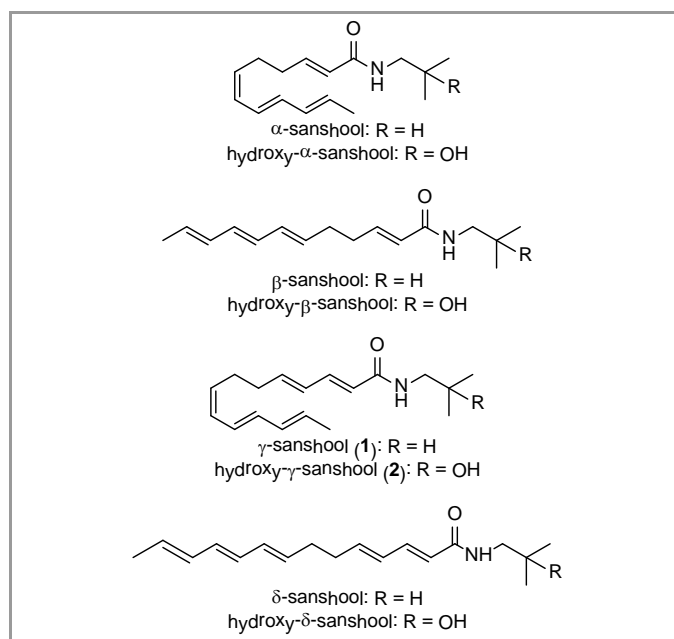

Figure 1 Sanshool compounds

Our retrosynthetic strategy for **1**, and thus **2**, is depicted in Scheme 2. As outlined above, carboxylic acid **3** was targeted as the key synthetic intermediate since it could conceivably be converted to a wide range of amides, and it might be prepared from alkynoate **4** using a stereoselective alkyne to *E,E*-1,3-diene isomerization reaction,[17,18] followed by saponification. The alkyne group of **4** could presumably be formed by a Corey-Fuchs reaction on aldehyde **5**, using methyl chloroformate to trap the acetylide intermediate to install the ester moiety. Aldehyde **5** in turn might be generated by adjusting the oxidation state of ester **6**, which itself might be synthesized via a *Z*-selective Wittig reaction between commercially available sorbaldehyde (**7**) and the phosphonium salt derived from **8**.
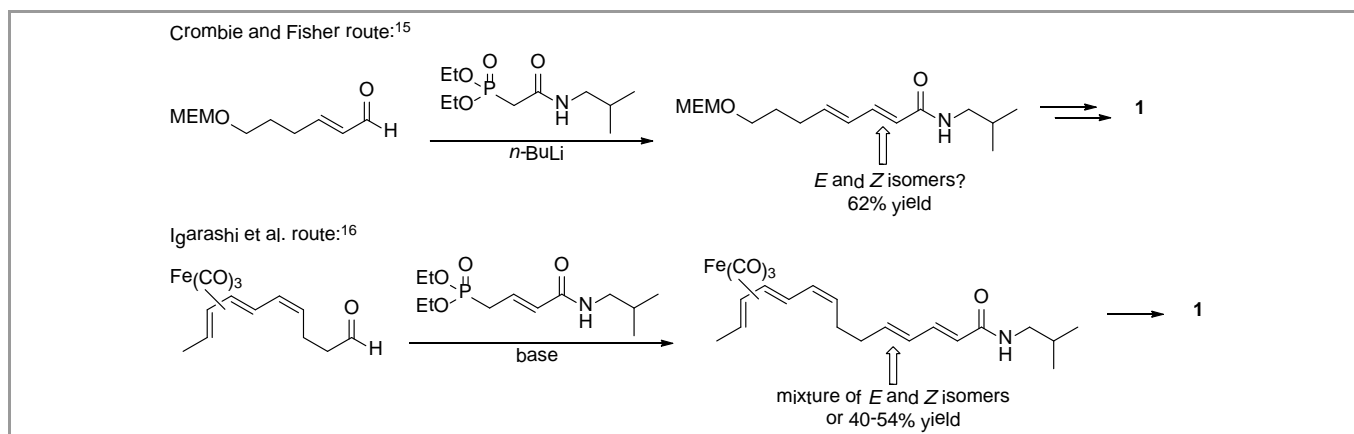
Scheme 1 Previous synthetic routes towards **1**
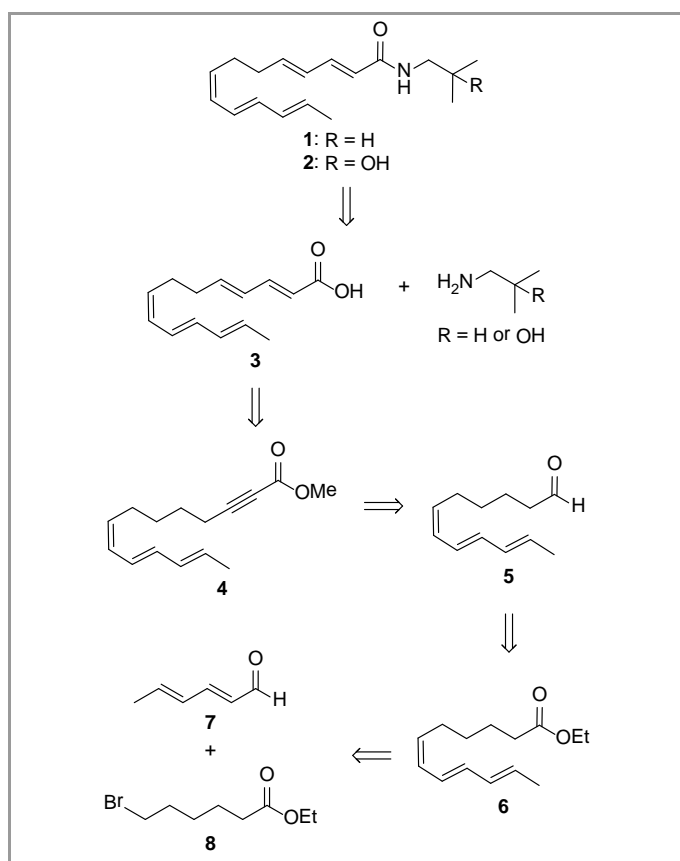
Scheme 2 Retrosynthetic analysis for **2** and **3**

The successful implementation of our synthetic plan is presented in Scheme 3.[19] Allkyl halide **8** was converted into the corresponding phosphonium salt **9** in high yield by reaction with PPh$_3$, and this in turn was used in a Wittig reaction with aldehyde **7** using excess Cs$_2$CO$_3$ in warm CH$_2$Cl$_2$ to afford ester **6** as a mixture of Z and E stereoisomers (ca. 3:1 ratio). These were not separated, and the mixture was directly reduced using DIBAL-H to afford aldehyde **5** in high yield. Next, conversion of aldehyde **5** into alkynoate **4** was achieved in a 3-stage Corey-Fuchs procedure using methyl chlorofor-

mate as the electrophile in good overall yield. Gratifyingly, the envisioned isomerization of **4** proceeded with high stereoselectivity in the presence of the combination of PPh$_3$ and PhOH in warm PhMe to afford penultimate intermediate **10** in high yield. Saponification of **10** afforded solid carboxylic acid **3**, which could be recrystallized to a high level of stereochemical homogeneity using a combination of CHCl$_3$ and hexane. Finally, amide formation using the appropriate amine afforded **1**[20] and **2**[21] in 28% and 29% overall yield, respectively, from **8**. It should be noted that commercially available **7** is labeled as being "predominantly *trans,trans*", and is approximately a 5:1 mixture of stereoisomers according to ^{1}H NMR analysis. Thus, the relatively modest 63% yield for the saponification of **10** to form carboxylic acid **3** is quite respectable since the isomers formed due to the impurity of **7** and during the Wittig reaction are removed during this step.

In summary, we report a concise, stereoselective, and high yielding route for the synthesis of both **1** and **2** from simple and commercially available building blocks. Notably, carboxylic acid **3** can be recrystallized to purity, and its use as the immediate precursor to **1** and **2** allows for the synthesis of amide analogues of these natural products. We are currently investigating the application of our previously reported methods for using polymer-supported reagents and catalysts in Wittig[22] and alkyne isomerization[23] reactions to the synthesis of **3**, and it is hoped that this work will further facilitate the study of the sanshools by making them and their analogues more easily available.
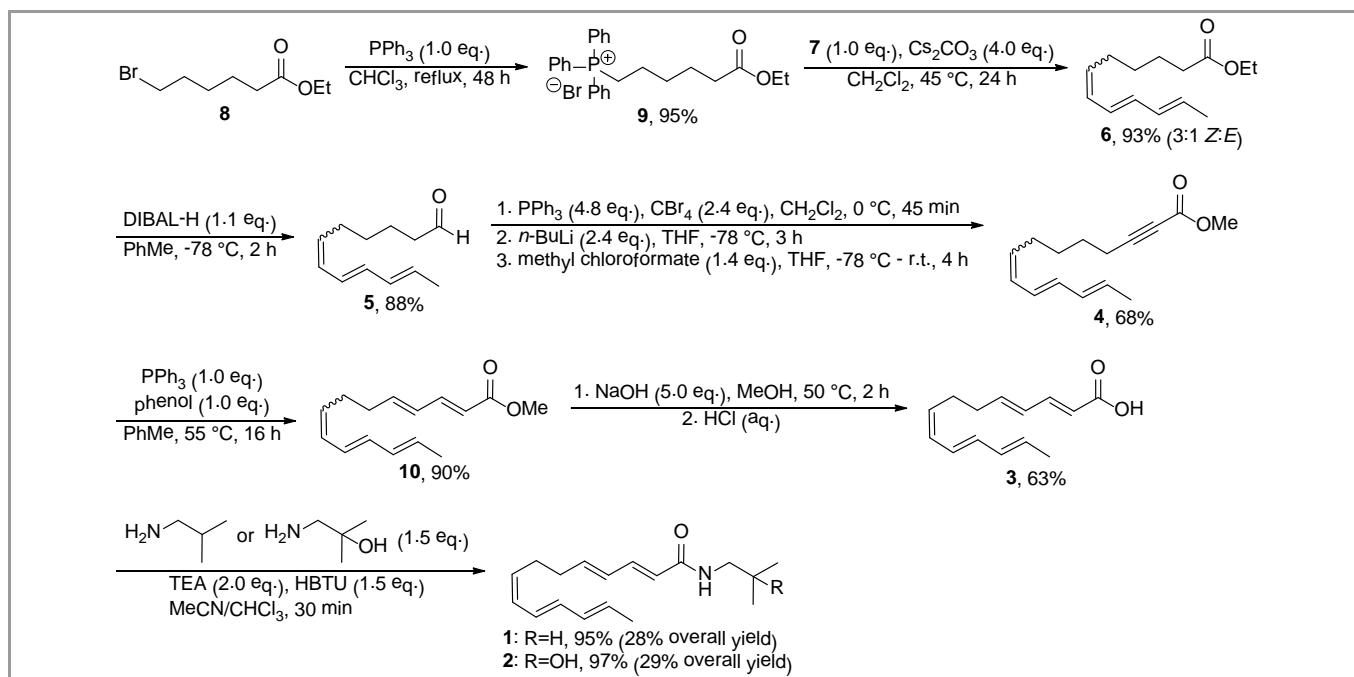
Scheme 3 Synthesis of **1** and **2**

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(20) Characterization data for **1**:[1c] ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.92 (d, 6H, J = 6.5 Hz), 1.78 (d, 3H, J = 6.5 Hz), 1.81 (q, 1H, J = 6.5 Hz), 2.25 (t, 2H, J = 6.7 Hz), 2.30 (t, 2H, J = 6.7 Hz), 3.15 (t, 2H, J = 6.5 Hz), 5.36 (dt, 1H, J_1 = 9.7 Hz, J_2 = 7.4 Hz), 5.72 (dt, 1H, J_1 = 14.0 Hz, J_2 = 7.0 Hz), 5.81 (d, 1H, J = 15.2 Hz), 5.85 (s, 1H), 5.99-6.20 (m, 5H), 6.29-6.33 (m, 1H), 7.17 (dd, 1H, J_1 = 14.6 Hz, J_2 = 10.7 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 18.4, 20.2, 27.2, 28.7, 33.0, 47.0, 122.4, 125.4, 128.9, 129.5, 130.0, 130.1, 132.0, 133.4, 141.0, 141.8, 166.5; MS for C$_{18}$H$_{27}$NO: calc 273.2, found 273.2.

(21) Characterization data for **2**:[1e] ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.22 (s, 6H), 1.78 (d, 3H, J = 6.7 Hz), 2.25 (t, 2H, J = 6.7 Hz), 2.30 (t, 2H, J = 6.7 Hz), 3.33 (d, 2H, J = 5.9 Hz), 5.35 (dt, 1H, J_1 = 10.1 Hz, J_2 = 7.5 Hz), 5.72 (dt, 1H, J_1 = 14.0 Hz, J_2 = 6.8 Hz), 5.84 (d, 1H, J = 15.0 Hz), 5.99-6.02 (m, 5H), 6.29-6.36 (m, 1H), 7.19 (dd, 1H, J_1 = 15.0 Hz, J_2 = 10.4 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 18.4, 27.1, 27.3, 33.0, 50.6, 71.0, 121.9, 125.4, 128.8, 129.6, 130.0, 130.1, 131.9, 133.5, 141.6, 142.4, 167.7; MS for C$_{18}$H$_{27}$NO$_2$: calc 289.2, found 289.2.

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Graphical abstract

γ-sanshool: R = H
hydroxy-γ-sanshool: R = OH

commercially available building blocks