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Improved syntheses of methyl (14*E*)- and (14*Z*)-dehydrocrepenynate: key intermediates in plant and fungal polyacetylene biosynthesis

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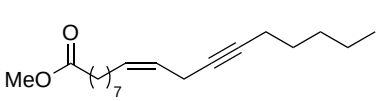
Abstract—Efficient syntheses of the (14*E*)- and (14*Z*)-isomers of methyl dehydrocrepenynate have been achieved. The key steps involve Pd-catalyzed cross-coupling reactions furnishing the C=C double bonds between C14 and C15, followed by Wittig reactions to construct the (*Z*)-alkene at C9. High overall yields and stereoselectivities were achieved for both isomers.

Secondary metabolism commencing from polyunsaturated fatty acids leads to many bioactive natural products such as the polyacetylenes and the prostaglandins. The formation of crepenynic (**1**) and dehydrocrepenynic acid (**2**) constitutes the branchpoint between primary and secondary metabolism for the biosynthesis of most polyacetylenic natural products.[1]

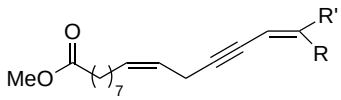
Crepenynic acid is widely produced by plants, particularly those of the families Umbelliferae and Compositae, Basidiomycetes (which include the gilled fungi), and certain bryophytes. It has been reported that crepenynic acid (**1**) is a potentially toxic constituent in *Ixiolaena brevicompta* (a plant responsible for causing acute muscular degeneration in sheep in western New South Wales and Queensland).[2] Biological activity studies have shown that crepenynic acid has significant inhibitory effects on prostanoid synthesis in sheep and rats at concentrations of 40–45 μM.[3,4] In contrast, the biological activity of the dehydrocrepenynates **2a** and **2b** is essentially unknown.[5]

Few organisms appear to accumulate substantial amounts of the early acetylenic metabolites **1** and **2b**. Dehydrocrepenynic acid was present in trace amounts in the fungus *Tricholoma grammopodium* examined by Bu'Lock and Smith.[6] Powell and co-workers subsequently examined *Afzelia cuanzensis* seed oil as a better source of this acid.[7] The common edible fungi *Cantharellus cibarus* (golden chanterelle) and *Craterellus cornucopiodes* (horn of plenty) accumulate up to 66% (14*Z*)-dehydrocrepenynate-containing triacylglycerols in their fruiting bodies.[8] Nevertheless, the susceptibility of **2** to decomposition during isolation procedures makes the purification of **2** from natural sources inconvenient.[7] Alternatively, chemical preparation can be used to provide both isomers conveniently in gram scale.

Existing syntheses for the [^{14}C]-labeled isomers of **2** have been used in experiments to probe the conversion of **2b** to more highly unsaturated polyacetylenes in certain Basidiomycetes.[9] In the reported example, much lower incorporations of **2a** compared to **2b** point to the (14*Z*)-compound as the biologically relevant isomer.[9] The reported syntheses have several drawbacks including difficult distillations to purify crucial diastereomeric intermediates, low diastereoselectivity and yields, and poor adaptability for other acetylenic regioisomers. To prepare substrates **2a** and **2b** for studies of fatty acid desaturating enzymes and to examine the microbicidal activity of these isomers, we have developed an improved synthesis of (*E*)- and (*Z*)-**2**.



1, Methyl Crepenynate



2a: R = H, R' = $CH_2CH_2CH_3$
2b: R = $CH_2CH_2CH_3$, R' = H

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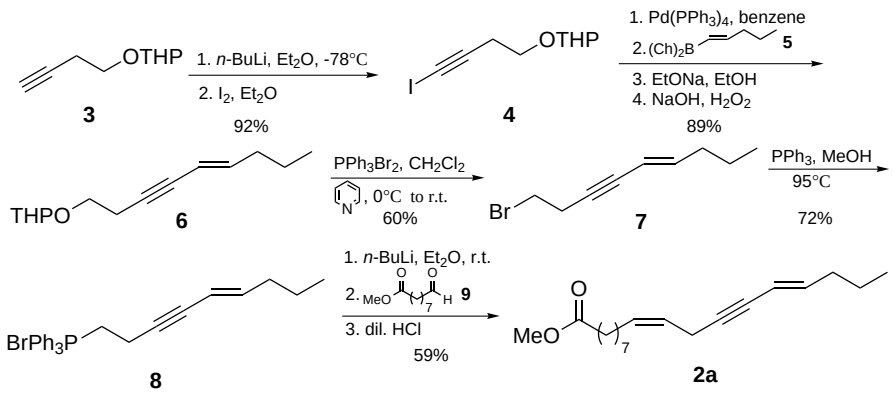
Results and discussion

The synthesis of methyl (14*E*)-dehydrocrepenynate **2a** began with the iodination of tetrahydro-2*H*-pyran-2-yl (THP)-protected 3-butyn-1-ol **3** with *n*-butyl lithium and iodine to afford the iodoalkyne **4** (Scheme 1). (*E*)-Dicyclohexyl-1-pentenylborane **5**, formed in situ by adding 1-pentyne to dicyclohexylborane, was cross-coupled with **4** by a Suzuki reaction.[10] This Pd-catalyzed coupling reaction stereospecifically produced the (*E*)-enynyl THP ether **6** in 89% yield. After treatment with triphenylphosphine dibromide, compound **6** was converted directly to bromide **7**.[11,12] Heating **7** in a sealed tube with PPh_3 and methanol produced the corresponding phosphonium salt **8**. Compound **8** smoothly underwent a Wittig reaction with methyl 9-oxononanate **9** in ether at room temperature to give the desired methyl 14(*E*)-dehydrocrepenynate **2a**.[9] $NaN(SiMe_3)_2$ and NaH were also tested as bases to generate the ylide for this reaction. BuLi, which used in earlier syntheses, gave the best yield after purification (59% isolated yield, *Z*:*E*= 85:15 by GC), whereas NaH in THF gave the best *Z*:*E* ratio (33% isolated yield, *Z*:*E*=97:3 by GC). When $NaN(SiMe_3)_2$ was used to generate the ylide in ether prior to adding the aldehyde, no product was obtained. However, adding the disilylamide to the mixture of **8** and the aldehyde **9** in THF provided **2b** in 30% isolated yield (*Z*:*E*>96:4, by GC).

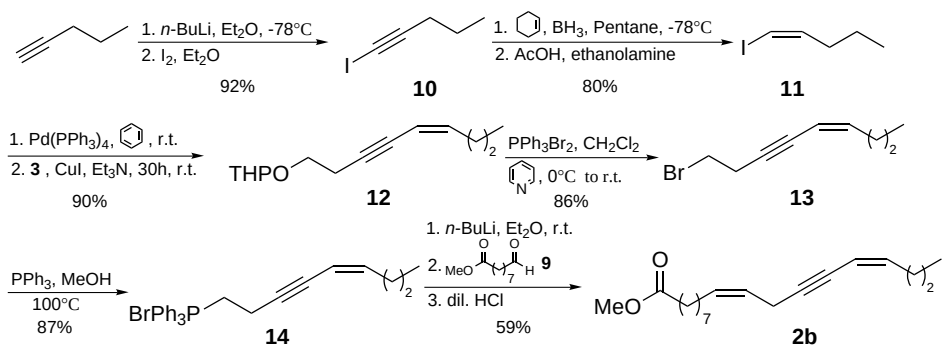
For the synthesis of methyl (14*Z*)-dehydrocrepenynate **2b**, a Pd-catalyzed coupling reaction was used to introduce the *cis*-alkene at C14 (Scheme 2). Iodination of 1-pentyne gave 1-iodo-1-pentyne **10** in excellent yield and the crude product was directly subjected to the stereospecific hydroboration without any further purification to generate (*Z*)-1-iodo-1-pentene **11** in 80% yield.[13] A Pd-catalyzed cross-coupling reaction furnished the THP-protected (*Z*)-enynol **12** in 90% yield.[14] Under the same conditions used for the (*E*)-isomer, **12** was brominated to form **13** in 86% yield. Bromoenyne **13** was readily converted to the white crystals of phosphonium salt **14**. Finally, the synthesis of **2b** was completed using a Wittig reaction to connect **14** with aldehyde **9** at room temperature. Good stereoselectivity (*Z*:*E*=95.5:4.5 by GC) was achieved using BuLi to generate the ylide. When NaH and $NaN(SiMe_3)_2$ were used for this reaction in THF, yields dropped to 30% (*Z*:*E*=97:3) and 29% (*Z*:*E*=96:4), respectively.

During the course of these studies, we found that the (*E*)-isomers **6** and **7** were surprisingly less stable than their corresponding (*Z*)-isomers **12** and **13**. The (*Z*)-isomers **12** and **13** were stored as pure liquids at 4°C for 2 months resulted in no significant changes as detected by ^{1}H NMR. After storage as neat liquids at 4°C for 3 weeks, the (*E*)-isomers had partially isomerized to the (*Z*)-isomers (25% by ^{1}H NMR).

Disk diffusion assays were used to test the bacteriostatic activity of the dehydrocrepenynate isomers against *Enterococcus faecalis* (ATCC 29212), *Staphylococcus aureus* (ATCC 29213), *Pseudomonas aeruginosa*



Scheme 1.



Scheme 2.

(ATCC 27853) and *Escherichia coli* (ATCC 25922). Levels up to 810 μg/disk for each isomer had negligible activity. In the case of *P. aeurginosa*, changes in the growth characteristics resulting in yellowish pigmentation and a flattened bacterial lawn surrounding the disk were observed for **2a** at loadings above 27 μg/disk.

In summary, a stereoselective synthesis of methyl (14*Z*)- and (14*E*)-dehydrocrepenynate was achieved in five to six steps and utilized a Pd-catalyzed cross-coupling reaction to construct the double bond between C14 and C15. Compared with the earlier methods, the improved syntheses are more convinent (no spinning band distillations or GLC separation of diastereomers were necessary) and higher *Z*:*E* ratios were obtained. The overall percent yield for (14*E*)-isomer is 20.8% and 29.2% for the (14*Z*)-isomer.

Supplementary material

GC–MS traces for esters **2a** and **2b**, combustion analysis for enyne **6**, and infrared, ^{1}H, ^{13}C NMR and electron impact HRMS spectra for compounds **2a**, **2b**, **6**, **7** and **13** are available from the authors.

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