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Synthesis of hydroxy-substituted unsaturated fatty acids and the amino-acid insect-derivative volicitin

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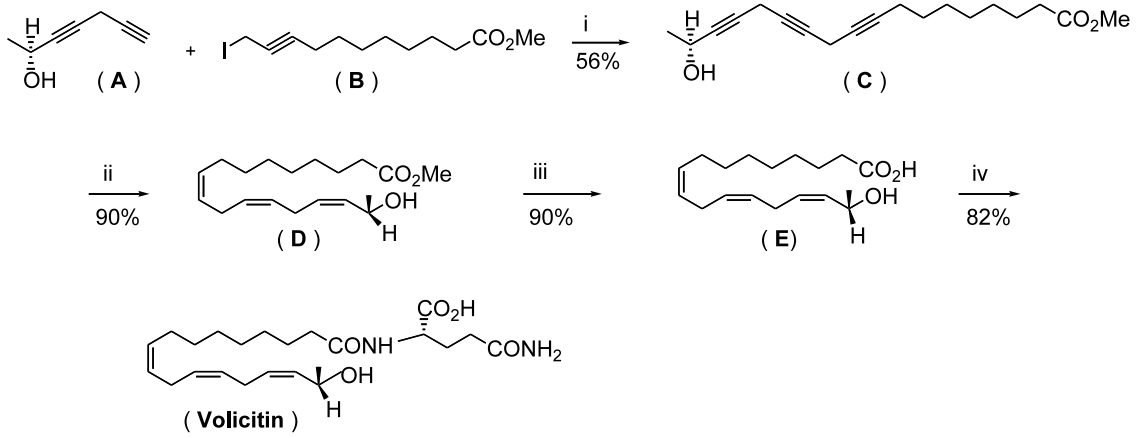
Abstract—An efficient synthesis of *N*-(17*S*-hydroxylinolenoyl)-L-glutamine (volicitin), a chemical elicitor from the herbivore-pest beet armyworm is presented. The synthesis, which utilizes a copper-catalyzed acetylene coupling, links (*S*)-3,6-heptadiyne-2-ol with a C-8 propargylic iodine methyl ester to form the (*S*)-17-hydroxylinolenate skeleton. By substituting different heptadiyne-2-ol groups, a series of methylene interrupted polyacetylene analogues were generated. © 2003 Elsevier Science Ltd. All rights reserved.

N-(17*S*-Hydroxylinolenoyl)-L-glutamine is the first biochemical elicitor to be isolated and characterized from insects that triggers defense responses in plants.[1] It was originally isolated from the regurgitant of the herbivore-pest beet armyworm (*Spodoptera exigua*) and since has been found in other Lepidopteran species.[2] This fatty acid derivative, referred to as volicitin, activates genes in corn seedlings (*Zea may*) for the synthesis of terpenoids and the nitrogen containing metabolite indole, as well as the subsequent release of C-10 and C-15 volatile components from the aerial portion of insect-damaged plants.[3]

Several synthetic schemes have been reported for volicitin, with the goal to synthesize sufficient material for structural confirmation.[4] In each case, the preparation of the methylene-interrupted polyacetylene α-linolenic acid backbone was based on either Grignard reagent coupling of propargylic bromides followed by catalytic hydrogenation to form unconjugated double bonds units and/or (*Z*)-selective Wittig olefination.[4] The coupling of the fatty acid moiety to the amino acid took place in the final step. These literature procedures gave over-all yields of ca. 0.1–33% or complex product mixtures.[4] In our experience, such synthetic routes are not



Scheme 1. *Reagents and conditions*: (i) 2 equiv. (A), 2 equiv. EtMgBr, 10% CuCl, THF, rt, 15 h; (ii) P_2–Ni, H_2, EtOH, rt, 6 h; (iii) 10 equiv. LiOH, THF–H_2O (1:1, v/v), rt, 12 h; (iv) NEt_3, THF, $ClCO_2Et$, −10°C 20 min, then Gln, NaOH, rt, 25 min.

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well suited for gram scale synthesis, nor appropriate for modifying the length or terminal group of the fatty acid backbone for studying structure–reactivity relationships.

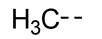
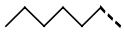
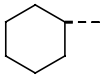
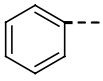
We report here an efficient protocol for the preparation of ω-hydroxy unsaturated fatty acids based on a cuprous chloride-catalyzed coupling of 3,6-heptadiyne-2-ol derivatives with a C-8 propargylic iodine methyl ester to form 17-hydroxylinolenate skeletons. The general synthetic route outlined in Scheme 1, allows for facile modifications to the fatty acid skeleton and an overall yield for the four-step procedure at ca. 37%.

The key step in this synthetic strategy was the coupling of (**A**) with C-8 propargylic iodide (**B**) to form the C-17 triynol (**C**). The most common coupling approach for forming such a methylene-interrupted polyacetylene carbon chain is based on cuprous chloride-catalyzed Grignard coupling of a protected diynol with a unit containing propargylic bromine[7,8] or other similar methods.[9] However, we found that such protocols were not well suited for gram-scale synthesis. We then examined Becker's procedure,[10] in which similar triacetylene alcohols were obtained in ca. 55% yield through the condensation of a C-9 propargylic iodine with 2,5-hexadiyne-1-ol.

Since the experimental protocol was not provided, we tested several conditions before establishing that with 10 mol% of CuCl as catalyst, our key intermediate, C-17 triynol liquid (**C**) was obtained in 56% yield (the off red color may have been to a contamination of a conjugated product. This step relies on the coupling of the Grignard reagent derived from 3,6-heptadiyne-2-ol (**A**)[11] with a C-8 propargylic iodine (**B**).[12] Catalytic hydrogenation of (**C**) using P_2–Ni as the catalyst,[13] yielded the corresponding (*Z*,*Z*,*Z*)-trienol (**D**) as a yellowish liquid and that product was then converted to 17-hydroxylinolenic acid (**E**) in 90% yield using aqueous LiOH in THF. Coupling of (**E**) with L-glutamine to give volicitin was achieved by a modified ethylcarbonate mixed anhydride method[14] in 82% yield for this final step.

With this successful procedure in hand, a series of analogues of (**C**) were synthesized by the same Grignard coupling reaction as shown in Scheme 2. Results shown in Table 1 indicate that increasing the carbon chain length R-group from methyl to isopropyl, *sec*-butyl, isobutyl, or *n*-hexyl (entries 2–5) did not significantly effect the coupling reaction albeit, the adding of the benzyl or cyclohexyl unit did slightly decrease the yields (entries 6–7). It is noteworthy that the yield of (**C**) was diminished to less then 30% if the C-8 propargylic iodine was substituted with the C-8 propargylic bromine while the other reaction parameters were unchanged.

Table 1.

Entry	R-Group [a]	Yield %
1		56[b]
2		55
3		55
4		54
5		58
6		51
7		50

[a] Hatched lines indicate the site of connection to the side chain.
[b] Racemic and S-isomer substrates resulted in equal yields.

By using commercially available (*S*)-(−)-3-butyn-2-ol as the substrate in the formation of 3,6-heptadiyne-2-ol, optically active 17-hydroxylinolenic acid was generated in the natural-product *S*-configuration originally isolated from beet armyworms.[15] In conclusion, a simple synthesis of volicitin[16] in four steps is presented here which proceeds with an overall yield of 37%.

Acknowledgements

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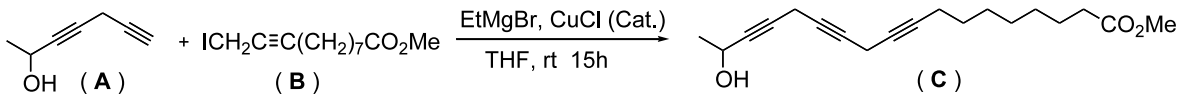

Scheme 2.

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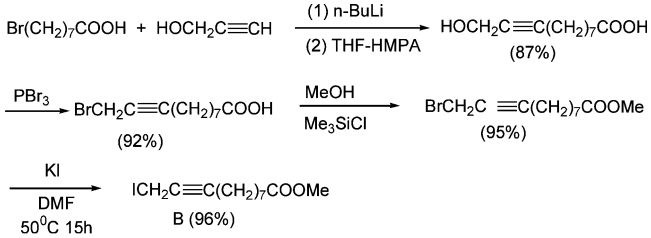
11. Several methods have been reported for the synthesis of diynol species.[5,6,10] all of which are based on the coupling reaction of alkynes and propargylic halides with a copper salt as the catalyst. However, low yields (less then 20%) served as the impetus to develop this new procedure. Our increased yield of (**A**) turned out to be a critical step in an overall increased yield. After exploratory experimentation, it was found that the yield of (**A**) (Table 1, entry 1) was largely dependent on the concentration of EtMgBr. Namely, when the concentration of EtMgBr was lower that 0.8 M in THF, product (**A**) was generated in more than 40% yield, while when the EtMgBr solution was more than 1.4 M, the yield of (**A**) was less than 20%. An explanation of this result could be ascribed to the solubility of the Grignard dianion of 3-butyn-2-ol in THF which results in poor stirring in the viscous concentrated mixtures. From the commercial available ynols, the other analogues of (**A**) were prepared in reasonable yield in the same way with 'dilute' EtMgBr solution. Yields for different R-groups include: methyl 41%, isopropyl 44%, *sec*-butyl 44%, isobutyl 43%, *n*-hexyl 46%, cyclohexyl 42%, and benzyl 38%. For the generation of (*S*)-3,6-heptadiyne-2-ol, (*S*)-(−)-3-butyn-2-ol was substituted for racemic 3-butyn-2-ol with the same overall yield.
12. Preparation of (**B**).



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16. Selected date for intermediates and volicitin: (**B**):^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (t, $J=2.4$ Hz, 2H), 3.66 (s, 3H), 3.30 (t, $J=9$ Hz, 2H), 2.18 (m, 2H), 1.63 (m, 2H), 1.46 (m, 2H), 1.32 (m, 6H); (**D**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.34–5.43 (m, 6H), 4.69 (m, 1H), 3.66 (s, 3H), 2.82–2.86 (m, 4H), 2.31 (t, $J=7.4$ Hz, 2H), 2.02–2.05 (m, 2H), 1.60–1.66 (m, 2H), 1.29–1.40 (m, 8H), 1.20 (d, $J=7.2$ Hz, 3H); (**E**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.32–5.45 (m, 6H), 4.64–4.72 (m, 1H), 2.78–2.89 (m, 4H), 2.32 (t, $J=7.4$ Hz, 2H), 2.04–2.11 (m, 2H), 1.60–1.69 (m, 2H), 1.28–1.39 (m, 8H), 1.20 (d, $J=7.2$ Hz, 3H). **Volicitin**: ^{1}H NMR (CD_3OD, 500 MHz): δ 1.06 (d, $J=6.5$ Hz, 3H), 1.18–1.28 (m, 10H), 1.49 (t, $J=7.2$ Hz, 2H), 1.77–1.87 (m, 1H), 1.96 (q, $J=6.5$ Hz, 2H), 1.96–2.07 (m, 1H), 2.12 (t, $J=7.2$ Hz, 2H), 2.20–2.17 (m, 2H), 2.69–2.75 (m, 4H), 4.25 (dd, $J=4.8$, 4.0, 1H), 4.48 (dq, $J=6.8$, 6.2), 5.15–5.32 (m, 6H); ^{13}C NMR (CD_3OD, 125 MHz): δ 22.9, 25.4, 25.8, 25.9, 63.2, 127.7, 127.8 128.1, 128.7, 130.2, 134.3, 174.1, 175.4, 176.8