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Synthesis of *N*-(2-methylpropyl)-2*E*-undecene-8,10-diynamide, a novel constituent of *Echinacea angustifolia*

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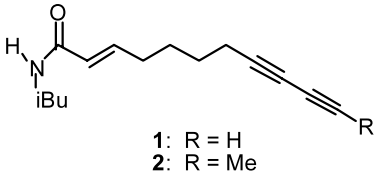
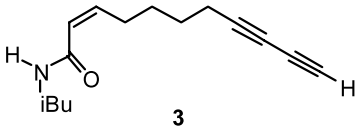
Abstract—The first synthesis of a diacetylenic amide from *Echinacea* is reported. The key steps included the reaction of an aldehyde with the monoanion of a diacetylene and the reductive removal of a propargylic alcohol.

Among the many novel natural products isolated from *Echinacea angustifolia* are a series of diacetylenic amides.[1,2] The structures of three members of the series are shown below. A complex mixture containing at least twelve different acetylenic amides can be obtained by supercritical fluid extraction of fresh dried roots.



1: R = H
2: R = Me



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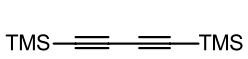

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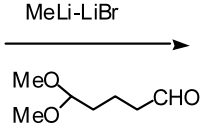

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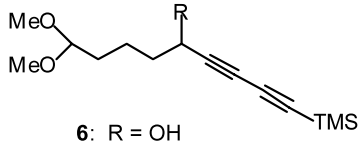
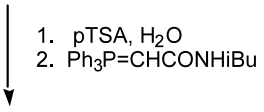
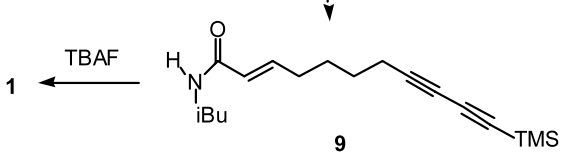


6: R = OH
7: R = OCSIm
8: R = H





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These amides have been shown to be active against *A. aegyptii* larvae and *H. zea* neonates at the microgram per milliliter level.[3] Authentic standards of these amides are important for metabolomics studies. In conjunction with a study of the metabolites of *Echinacea* and *St. John's wort*, we report the first synthesis of **1** by a direct synthetic route.

Our synthetic route to **1** began with acetal aldehyde **5** that was readily available from the ozonolysis of cyclopentene by the method of Schreiber.[4] Generation of the monoanion of commercially available bis-trimethylsilyldiacetylene (**4**) with methyl lithium–lithium bromide complex in THF at 0°C followed by reaction at −78°C with aldehyde **5** afforded propargylic alcohol **6** in 88% yield.[5] Deoxygenation by formation of the thiocarbonylimidazolide with thiocarbonyldiimidazole (CH_2Cl_2, rt)[6] followed by treatment with 2 equiv. of tributyltin hydride and AIBN at 80°C in toluene for

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one hour produced **8** in 51% yield over two steps. The use of larger quantities of tributyltin hydride should be avoided since addition to the acetylene occurred.[7] Hydrolysis of the acetal (*p*TSA, aqueous acetone) at ambient temperature gave almost a quantitative yield of aldehyde. The aldehyde reacted with the amide phosphorane[8] to afford *E*-isomer **9** in 73% yield.[9] Approximately 10% of the *Z*-isomer was also formed and was readily separable from the *E*-isomer by silica gel flash chromatography. The reaction of amide **9** with tetrabutylammonium fluoride (TBAF) in THF at 0°C produced **1** in 95% yield.

The proton and carbon NMR of our sample was identical to the spectra reported by Nair.[3] Diacetylene **1** has been synthesized in eight steps from cyclopentene by a direct and flexible synthetic route. Extension of this work to the synthesis of other members of this family is in progress.

Acknowledgements

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7. 5 equiv. of tributyltin hydride gave only the products of tin hydride addition.
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9. *Spec. for aldehyde*: 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.75 (1H, t, $J=1.8$ Hz), 2.45 (2H, td, $J=6.9$, 1.8 Hz), 2.30 (2H, t, $J=6.9$ Hz), 1.68–1.78 (2H, m), 1.50–1.60 (2H, m), 0.14 (9H, s); ^{13}C NMR ($CDCl_3$) δ 202.1, 88.5, 83.7, 79.3, 66.2, 43.4, 27.7, 21.4, 19.3, –0.1; IR (neat) cm^{-1} 2958, 2359, 2225, 2108, 1708, 1250, 846; HRMS m/z for $C_{12}H_{18}OSi$ calcd 206.1127, measured 206.1130.
Amide ***9***: 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.78 (1H, dt, $J=15.3$, 6.9 Hz), 5.78 (1H, d, $J=15.3$ Hz), 5.67 (1H, brs), 3.13 (2H, t, $J=6.3$ Hz), 2.25–2.29 (2H, m), 2.14–2.20 (2H, m), 1.74–1.83 (1H, m, $J=6.9$ Hz), 1.52–1.56 (4H, m), 0.91 (6H, d, $J=6.9$ Hz); ^{13}C NMR δ 166.1, 143.9, 124.3, 88.6, 83.5, 79.8, 66.0, 47.1, 31.5, 28.8, 27.7, 27.5, 20.4, 19.2, –0.2; IR (neat) cm^{-1} 3289, 2958, 2359, 2225, 2108, 1669, 1628, 844; HRMS m/z for $C_{18}H_{29}$ NOSi calcd 303.2018, measured 303.2023.