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Polyunsaturated Alkyl Amides from *Echinacea*: Synthesis of Diynes, Enynes, and Dienes

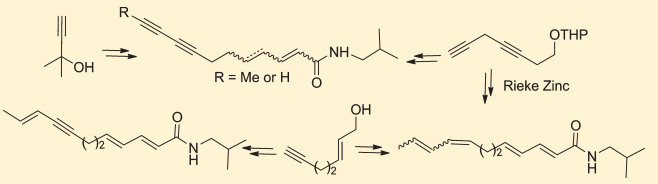
Nicholas J. Matovic,[†] Patricia Y. Hayes,[†] Kerry Penman,[‡] Reginald P. Lehmann,[‡] and James J. De Voss*[,†]

[†]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane 4072, Australia

[‡]Integria Healthcare, 35 Miles Platting Road, Eight Mile Plans Queensland 4113, Australia

Supporting Information

ABSTRACT: The synthesis of 20 alkyl amides, including 15 naturally occurring polyunsaturated alkyl amides previously identified from *Echinacea* spp. (**1**−**13** and **62**) or from *Achilla* sp. (**55**) and five previously unknown geometric isomers (**23**, **28**, **67**, **73**, and **80**), is described. Importantly, these amides include all of the major alkyl amides present in commercially used *Echinacea* extracts. The syntheses demonstrate methodology used for constructing alkyl amides containing conjugated diyne and isomerically pure enyne and diene moieties and may be adapted easily for the preparation of other alkyl amides present in *Echinacea* spp. Terminal-conjugated diynes were prepared by a Cadiot−Chodkiewitz coupling/deprotection sequence utilizing a protected bromoacetylene, and methyl-substituted diynes were made via a base-catalyzed rearrangement of terminal-skipped diynes. Conjugated dienes were prepared conveniently and with high stereoselectivity by the reduction of enynes or diynes with Rieke zinc. With the exception of **1**−**2** and **11**−**12**, the alkyl amides are synthesized here for the first time, and their NMR data are consistent with that of the reported isolated natural compounds.



INTRODUCTION

Echinacea sp. is a perennial herb from the Composite family, which is native to the central plains of the United States. The Native Americans first documented its use as a phytomedicine, and today, extracts from the plant's leaves, roots, or flowers are frequently used as a nonspecific immunostimulant for the treatment of bacterial and viral infection,[1] attracting significant scientific and economic interest. *E. purpurea*, *E. angustifolia*, and *E. pallida* are the three medicinally preferred *Echinacea* species which may show potential biological activity,[2] and ethanolic extracts of the roots, leaves, and flowers are among the most popular form of the commercial preparations. In 2002, the Echinacea industry was reported to be worth US$500 million in the United States of America alone.[3] Despite its widespread use for attempting to reduce the severity and duration of the common cold, the efficacy of *Echinacea* preparations is controversial, with clinical trials reporting negative results.[4] This might be caused to some degree by the erratic phytochemical profile of many *Echinacea* products, which depends on the species, the part of the plant used, the method of extraction, and even the geographic location of the plant's origin.[5,6] Thus, there is a need for chemically pure, authentic reference compounds, both for the standardization of the natural extracts and for biological evaluation. Ethanol/aqueous extracts commonly contain mostly polysaccharides and caffeic acid derivatives, whereas pure ethanolic extracts and extracts with less polar solvents are rich in alkyl amides. There is a growing belief that the alkyl amides are indeed the active constituents, owing to their anti-inflammatory properties[7] and their ability to cross the intestinal barrier,[8] which is an important factor for the efficacy of orally administered remedies. To date, the number of alkyl amides identified from extracts is about 20, comprising mostly isobutyl amides as well as some 2-methylbutyl alkyl amides (see Figure 1). We have recently reported that the (8*E*,10*Z*)-tetraene **9** is a previously unreported component of *Echinacea* extracts.[6] Typically, alkyl amides of *E. purpurea* contain a dienamide moiety,[9] and alkyl amides from *E. angustifolia* contain a monenamide moiety,[10] but the tetraene isomers **5** and **8** are the major constituents in both species.

The lipophilic extract from *E. pallida* has been shown to contain alkyl amides but in lower quantities and also contains significant amounts of acetylenic ketones **16** and **17**.[11] As part of our investigation of various *Echinacea* preparations, we required authentic alkyl amide standards in quantities ranging from 100 mg to several grams. Herein we report efficient and cost-effective total syntheses of the major alkyl amides that have been used as authentic standards and for biological assays.[6,8,12]

The alkyl amides from *Echinacea* sp. (Figure 1) present two areas of functionality that need to be addressed: the enamide or dienamide moiety with differing stereochemistries and the diyne, diene, or enyne unsaturations distal to the amide functionality. Robust, modular methods for construction of all of these structural motifs and the total synthesis of 14 naturally occurring alkyl amides from *Echinacea* sp. are presented.

RESULTS AND DISCUSSION

Enamides and Dienamides via Wittig Condensation. An (*E*)-enamide or dienamide is common to most of the alkyl amides found in *Echinacea* spp. (**1**−**10**). The phosphonium salt

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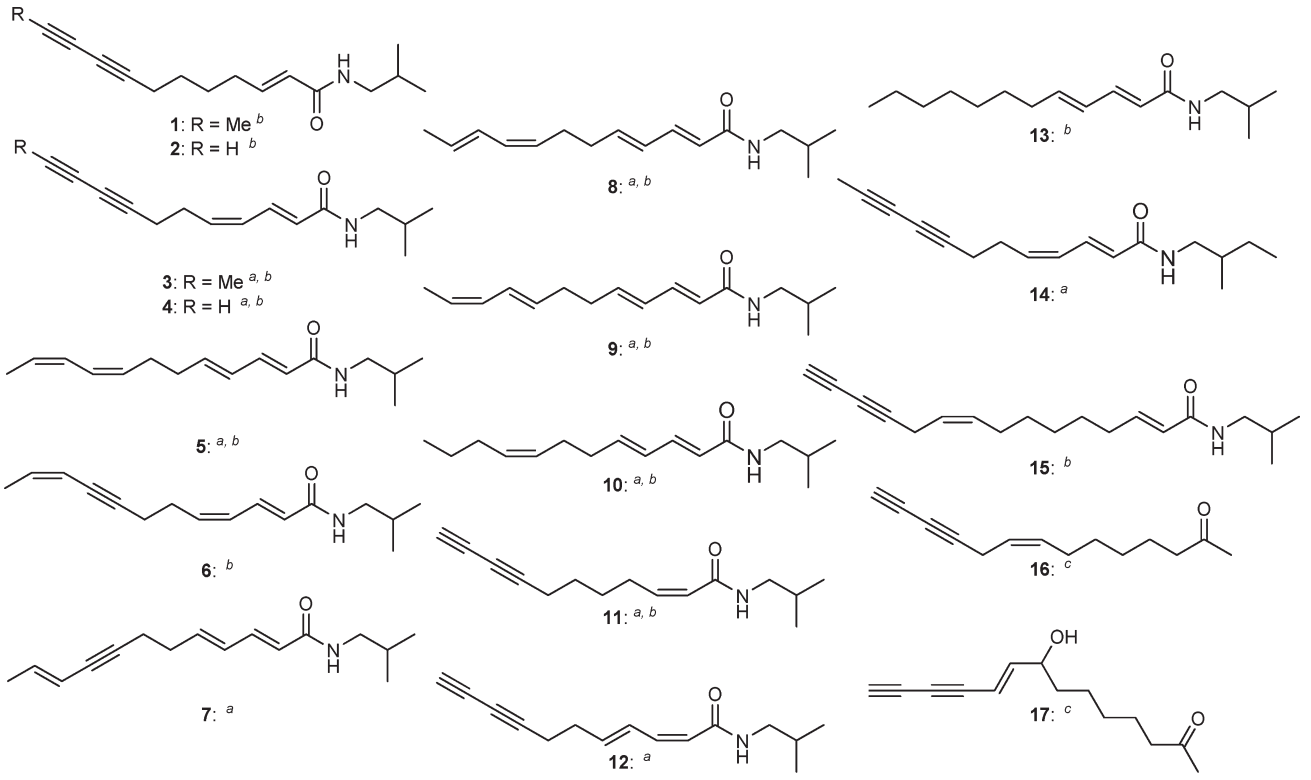


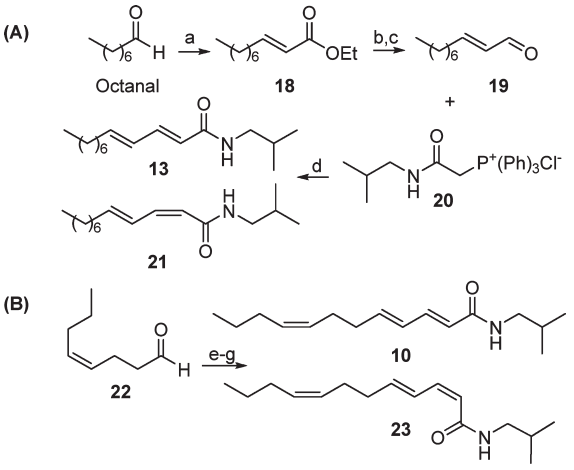
Figure 1. Some examples of the major liphophillic compounds isolated from extracts of (a) *E. purpurea*, (b) *E. angustifolia*, and (c) *E. pallida*.

20 has previously been used mainly for the construction the (*E*)-enamide alone[13] but surprisingly only once in the synthesis of dienamides.[14] A number of methods have been reported for the preparation of this dienamide moiety, some of which have been used to prepare the amide **13**, but most required a somewhat elaborate reaction scheme.[15] We established through the synthesis of the known **13** that the (*E*,*E*)-diene amide moiety could be robustly constructed from an appropriate aldehyde by a sequence of four reactions, including a final Wittig reaction that utilized phosphonium salt **20** to install the amide moiety (Scheme 1). Initially, the final Wittig condensation was conducted employing the literature method of NaOMe/methanol,[14] giving the (2*E*,4*E*)- and (2*Z*,4*E*)-isobutyl amides **13** and **21** in 42 and 22% yields, respectively. By exploring different solvents for this reaction, it was found that using KO*t*-Bu as the base in THF at 0 °C resulted in the highest yield and greatest *E*/*Z* ratio (approx 10:1) for the newly formed olefin, providing **13** in 66% yield (as well as 6.6% of **21**). We then used this methodology to synthesize for the first time the trienamide **10**, previously isolated from the roots of *E. purpurea*.[9] **10** was synthesized in four steps from known aldehyde **22**[16] in an overall yield of 20% (along with 3% of previously unknown minor 2*Z*-isomer **23**).

^{1}H NMR data obtained for this crystalline trienamide are consistent with that of the reported (2*E*,4*E*,8*Z*)-*N*-isobutyldeca-2,4,8-trienamide (**10**) which had previously been isolated as a yellow oil.[9]

Conceivably the (2*E*,4*E*)-*N*-isobutyl dienamide moiety could also be installed in a single step by adopting a more complex Wittig precursor, reducing the number of linear synthetic steps and hopefully increasing the overall yield. Preparation of the phosphonium salt **26** was achieved simply from crotonic acid, via bromoacid **24**[17] and bromoamide **25**[18] (Scheme 2). Phosphonate

Scheme 1. Preparation of the (*E*,*E*)-Diene Amide Moiety[a]



[a] (A) Synthesis of amides **13** and **21**. Reagents and conditions: (a) $(EtO)_2POCH_2COOEt$, NaH, Et_2O, 0 °C, 94%; (b) DIBAL, Et_2O, 0 °C, 91%; (c) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (di) **20**, KO^{t}Bu, THF, 66% (**13**) and 6.6% (**21**). (B) Synthesis of amides **10** and **23**. Reagents and conditions: (e) $(EtO)_2POCH_2COOEt$, NaH, Et_2O, 0 °C, 74%; (f) DIBAL, Et_2O, 0 °C, 80%; (g) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (dii) **20**, KO^{t}Bu, THF, 31% (**10**) and 3% (**23**).

ester **27** was also prepared from bromoamide **25**. However, preliminary results obtained from the reaction of **26** or **27** with octanal (Scheme 2) were disappointing. When reacted with octanal, both reagents gave moderate yields of diene amide product as an approximately 5:1 mixture of the *E*- and *Z*-isomers at the newly formed olefin (**13** and **28**). Separation of these

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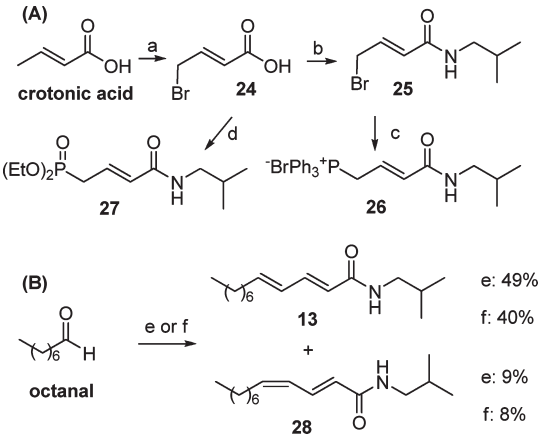
Scheme 2. Synthesis of 13 via Wittig Reagents 26 and 27[a]



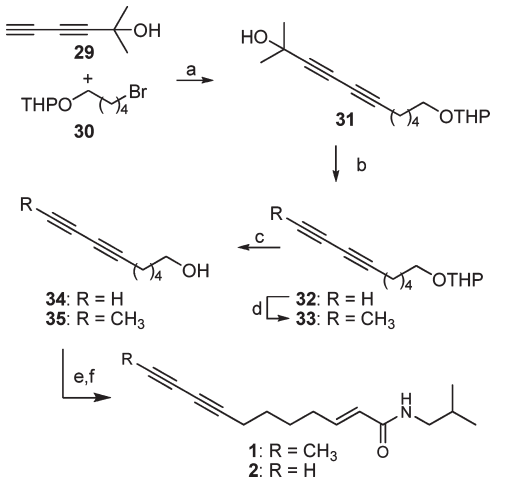
[a] (A) Reagents and conditions: (a) NBS, BzOOH, benzene, reflux, 80%; (b) (i) $SOCl_2$, (ii) *i*-$BuNH_2$, ether, 61%; (c) Ph_3P, benzene, 25 °C, 52%; (d) $P(OEt)_3$, 100 °C, 76%. (B) Reagents and conditions: (e) **26**, THF, KO*t*-Bu, 0 °C; (f) **27**, ether, NaH, 0 °C.

isomers by chromatography was difficult, and thus these reagents were not pursued for larger scale syntheses. Previously unknown **28** was isolated here as a colorless oil and fully characterized for the first time.

Preparation of Diyne Containing Alkyl Amides. With methodology for installation of the dienamides in hand, we turned to the construction of the unsaturations at the end of the long acyl chain in **1**−**9** and **11**−**12**. Reasoning that a diyne would provide a useful precursor for various dienes, our initial targets became **1** and **2** for investigating diyne construction. Initial trials were based on a modification of the protocol developed by Kraus.[19] This had employed the addition of the anion of a TMS-protected terminal diyne to an aldehyde, with the formed propargyl alcohol able to undergo tin-mediated deoxygenation and elaboration into the alkyl amides **1** and **2**. We explored the use of a preformed diyne to generate an anion that might be alkylated directly, thus avoiding the tin-mediated deoxygenation step (Scheme 3). Attempts at alkylating the protected diyne **29**, available via a two-step procedure from commercially available 2-methylbut-3-yn-2-ol,[20] with bromide **30**[21] were only successful when 10% HMPA was used as cosolvent. Refluxing the product **31** in toluene in the presence of NaOH effectively liberated the terminal diyne **32**. This **32** was either used directly for the preparation of **2** or methylated (methyl iodide) giving the methyl diyne **33** required for preparing alkyl amide **1**. After acid-catalyzed cleavage of the THP ethers **32** or **33**, the diyne containing alcohols **34** and **35** were subjected to Swern oxidation and subsequent Wittig condensation with the anion derived from phosphonium salt **20**. We found purification of the aldehydes after Swern oxidation unnecessary, and higher overall yields of alkyl amide were obtained simply by treating the crude oxidation product with the Wittig reagent. While the synthesis was successful, we found this scheme was not easily adapted to large-scale work in our laboratory. The use of large quantities of HMPA, which required rigorous drying prior to use and poses health and safety concerns, was unattractive. In addition, the synthesis of the diyne precursor **29** was somewhat tedious, and it had to be freshly prepared as required.

In searching for more general methodology for the syntheses of these diynes, we noted that the isomerization of terminal

Scheme 3. Preparation of 1 and 2[a]



[a] Reagents and conditions: (a) *n*BuLi, THF, HMPA, 0 °C, 64%; (b) NaOH, PhMe, reflux, 91%; (c) TsOH, MeOH, 93%; (d) *n*BuLi, THF, MeI, 0 °C, 91%; (e) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (f) **20**, KO^{t}Bu, THF, **1**: 53%, **2**: 51%.

acetylenes to methyl-substituted alkynes with KO^{t}Bu in DMSO had previously been reported.[22] We postulated that the isomerization of terminal-skipped diynes such as **42** might provide a unique, practical method for preparation of methyl-substituted, conjugated diynes. Thus, we investigated the synthesis of methyl diyne **33** via rearrangement of skipped diyne **42**.

As the doubly propargylic methylene of a skipped diyne is considerably more acidic than the corresponding hydrogens of a simple terminal acetylene, increased reactivity to the reported isomerization conditions (20 mol % of KO*t*-Bu, DMSO) was expected. Potential side reactions included the formation of allenes or isomerization of the internal triple bond.[23] Thus a model system easily derived from propargyl alcohol **36** was examined initially (Scheme 4A). After considerable optimization of the reaction conditions, it was found that by using low concentrations of DMSO in THF as solvent at lower temperatures (−40 °C, 10% DMSO in THF, 20 mol % of KO*t*-Bu, 10 min) the skipped diyne **37** smoothly isomerized to the methyl-substituted diyne **38** in 90% yield. We therefore applied this methodology to the synthesis of **1** (Scheme 4B).

Synthesis of the required **42** (Scheme 4B) began with treatment of 1-hexyne with butyllithium followed by reaction with paraformaldehyde to give **39**.[24] Isomerization of **39** under conditions for the modified "zipper" reaction[25] (NaH/ethylene-1,2-diamine, 60 °C) gave hept-6-yn-1-ol (**40**)[22] in excellent overall yield. Protection of the primary alcohol **40** as a THP ether gave **41** which, following deprotonation with EtMgBr in THF, underwent cuprate-catalyzed coupling with propargyl bromide[26] to yield **42**. Attempts to avoid the use of a protecting group and prepare the skipped diyne directly from **40** using 2 equiv of EtMgBr were unsuccessful, resulting in allene impurities that were inseparable from the desired product. Treatment of the skipped diyne **42** with KO*t*-Bu/DMSO under the conditions reported for alkyne isomerization (20 °C, DMSO, 20 mol % of KO*t*-Bu) instantly returned only black polymeric material. However, when the conditions developed for the model system above were employed (−40 °C, 10% DMSO in THF, 20 mol % of KO*t*-Bu, 10 min), the skipped diyne **42** smoothly isomerized

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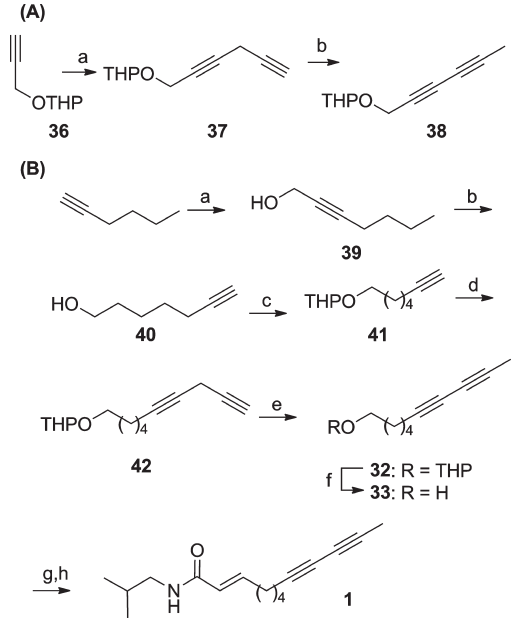
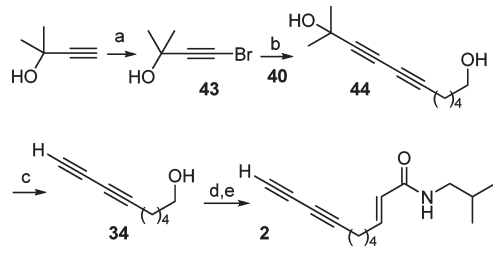
Scheme 4[a]



[a] (A) Model system based on propargyl alcohol, used for developing a method for the conversion of skipped diynes to methyl diynes. Reagents and conditions: (a) (i) EtMgBr, THF, (ii) propargyl bromide, CuCl, 50 °C, 75%; (b) KO*t*-Bu (20 mol %), THF/DMSO (10:1), −40°C, 90%. (B) Improved synthesis of methyl diyne **33** and alkyl amide **1**. Reagents and conditions: (a) BuLi, Et_2O, $(CHO)_n$, 0 °C, 89%; (b) $(NH_2CH_2)_2$, NaH, 60°C, 88%; (c) TsOH, DHP, CH_2Cl_2, 86%; (d) (i) EtMgBr, THF, 50 °C, (ii) propargyl bromide, CuCl, 50 °C, 75%; (e) KO^{t}Bu, THF, DMSO, −40 °C, 88%; (f) TsOH, MeOH, 93%; (g) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (h) **20**, KO^{t}Bu, THF, 59%.

Scheme 5. Revised Synthesis of Rerminal Diynes[a]

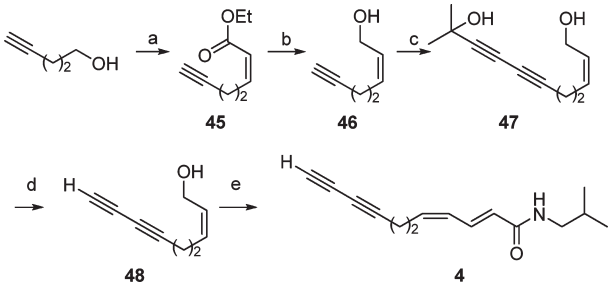


[a] Reagents and conditions: (a) KOH, H_2O, Br_2, 0 °C, 71%; (b) **40**, *n*-$PrNH_2$, H_2O, CuCl, $NH_2OH\cdot HCl$, 90%; (c) NaOH, PhMe, reflux, 85%; (d) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (e) **20**, KO^{t}Bu, THF, 53%.

and the methyl-substituted diyne **33** could be isolated in 88% yield. Methanolic cleavage of the THP protecting group procured the alcohol **22**, which was subjected to the usual Swern oxidation/Wittig sequence employing phosphonium salt **20**. This completed the synthesis of **1** in eight steps and 22% overall yield from 1-hexyne. We have found that this methodology, which avoids the use of HMPA, is easily scaled in our laboratory, and we have synthesized alkyl amide **1** in multigram quantities.

Alternative methodology was also devised for the synthesis of conjugated terminal diynes (Scheme 5), such as **34** required for the synthesis of **2**. The protected diyne **44** was made directly by coupling bromoalkyne **43** with alkyn-ol **40** under

Scheme 6. Preparation of Alkyl Amide 4[a]



[a] Reagents and conditions: (a) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) $(PhO)_2POCH_2CO_2Et$, NaH, Et_2O, 0 °C, 91%; (b) DIBAL, Et_2O, 0 °C, 92%; (c) **43**, *n*-$PrNH_2$, H_2O, CuCl, $NH_2OH\cdot HCl$, 88%; (d) NaOH, PhMe, reflux, 83%; (e) (i) TPAP, NMO, DCM, 3 Å mol sieves, (ii) **20**, KO^{t}Bu, THF, 56%.

Cadiot−Chodkiewicz conditions.[27] The diyne alcohol **34** was then released from **44** by treatment with NaOH in refluxing toluene and secured in only two steps and 76% overall yield from **40**. The usual Swern/Wittig protocol then delivered **2** in good yield from **34** and in 42% overall yield from **43** in four steps. We have found that bromoalkyne **43** is easy and inexpensive to prepare, gives very good yields of coupled products, and can be stored at −20 °C for extended periods.

Preparation of the (2*E*,4*Z*)-Diene Amide Moiety. Alkyl amides **3** and **4** occur in both *E. purpurea* and *E. angustifolia* and are analogous to **1** and **2** but contain the (2*E*,4*Z*)-dienamide moiety. By incorporating the methodology established for the preparation of terminal and methyl-substituted diynes, both compounds were synthesized from commercial pent-4-yn-1-ol (Scheme 6). Swern oxidation of this alcohol gave the corresponding aldehyde which underwent, without purification, Wittig condensation under *cis*-selective Horner−Wadsworth−Emmons conditions.[28] This generated the α,β-unsaturated ester **45** as an 89:11(*Z*/*E*) mixture, with the pure *cis*-isomer (*Z*)-**45** available in 69% overall yield after flash chromatography. DIBAL reduction of (*Z*)-**45** gave desired alkynol **46**. The allylic alcohol **46** was then subjected to the conditions developed above for the preparation of terminal conjugated diynes. Thus, Cadiot−Chodkiewicz coupling of **46** with bromoalkyne **43** to yield **47** followed by deprotection (toluene/NaOH/reflux) gave the terminal diyne **48** in 73% over the two steps. With the immediate precursor to alkyl amide **4** now in hand, the transformation of the (*Z*)-allyl alcohol **48** to the (*E*,*Z*)-dienamide **4** by the Swern oxidation/Wittig reaction protocol was attempted. However, treatment of the (*Z*)-allyl alcohol **48** under Swern conditions resulted in considerable *Z*/*E* isomerization of the newly formed α,β-unsaturated aldehyde. A number of other oxidants were investigated for the oxidation of the allyl alcohol **48**, including Dess−Martin periodinane, MnO_2, and PCC, but these also resulted in significant isomerization. Pleasingly, however, the TPAP oxidation/Wittig sequence suggested by Ley for the transformation of sensitive aldehydes[29] produced negligible *Z*/*E* isomerization and gave **4** in 56% yield from **48** (Scheme 6).

For the synthesis of alkyl amide **3**, pent-4-yn-1-ol was first converted to the corresponding THP ether and thence to skipped diyne **49** via copper-mediated alkylation with propargyl bromide. The methyl-substituted diyne **50** was subsequently smoothly produced via isomerization (89%), adopting the protocol developed previously (*vide supra*). The key (*Z*)-allyl

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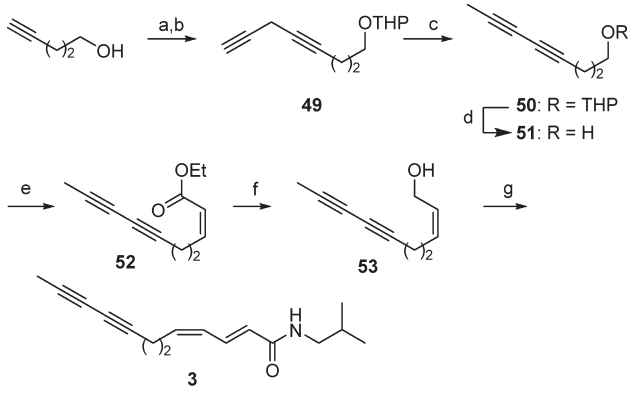
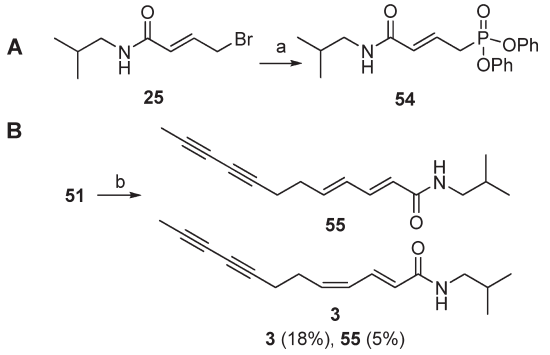
Scheme 7. Preparation of Alkyl Amide 3[a]



[a] Reagents and conditions: (a) DHP, TsOH, DCM, 78%; (b) (i) EtMgBr, THF, 50°C, (ii) propargyl bromide, CuCl, 50 °C, 77%; (c) KO^{t}Bu, THF, DMSO, −40 °C, 89%; (d) TsOH, MeOH, 90%; (e) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) $(PhO)_2POCH_2CO_2Et$, NaH, Et_2O, 0 °C, 78%; (f) DIBAL, Et_2O, 0 °C, 92%; (g) (i) TPAP, NMO, DCM, 3 Å mol sieves, (ii) **20**, KO^{t}Bu, THF, 60%.

Scheme 8. Use of a Phosphonate 54 for the Attempted Preparation of Alkyl Amide 3[a]



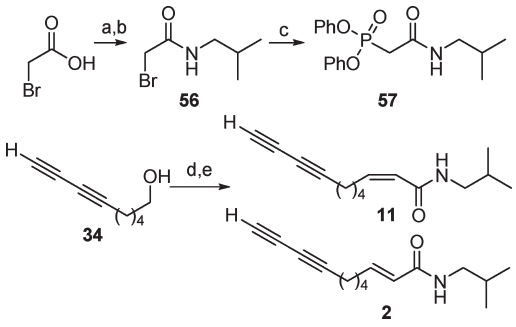
[a] Reagents and conditions: (A) (a) $(OEt)P(OPh)_2$, 100 °C, 8 h, 46%; (B) (b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) **54**, NaH, THF, −20 °C.

alcohol precursor **53** was available in three operational steps from **50**. THP cleavage to **51** was followed by Swern oxidation and *cis*-selective Horner−Wadsworth−Emmons methodology to yield **52**. The 9:1 (*Z*:*E*) mixture of α,β-unsaturated esters **52** was separated by flash chromatography to yield 73% of the pure *cis*-isomer (*Z*)-**52**, which underwent DIBAL reduction to **53**. TPAP-mediated oxidation and Wittig condensation with the anion of **20** in a manner identical to that developed for the synthesis of **4** gave **3** in 60% yield (Scheme 7).

Prior to the success with the TPAP oxidation/Wittig procedure for the preparation of the 4*Z* isomers **3** and **4**, we also investigated the previously unreported diphenylphosphonate reagent **54** (Scheme 8).

It was expected that substitution of the ethoxy substituents in the *trans*-selective diethylphosphonate reagent **27**, by the phenoxy groups, would provide high *Z*-selectivity in the newly formed double bond. This was based upon the same empirical principles which account for the high *Z*-selectivity seen in the (diphenylphosphono)acetate reagent developed by Ando.[30] This reagent **54** offered the possibility of a one-step synthesis

Scheme 9. Synthesis of Alkyl Amides 11 (and 2)[a]



[a] Reagents and conditions: (a) $SOCl_2$, Δ, 2 h, 64%; (b) *i*-$BuNH_2$, THF, −10 °C, 94%; (c) $(OEt)P(OPh)_2$, 100 °C, 12 h, 52%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (e) **57**, NaHMDS, THF, −20 °C, 64%.

of amide **3** from the methyl diyne precursor **51**, avoiding the isomerization problems experienced with **48** and **53**. Thus, reaction of an equimolar mixture of bromoamide **25** with ethyldiphenylphosphite (purified by distillation from the crude mixture prepared from triphenylphosphite) at 100 °C for 8 h produced the desired phosphonate reagent **54** in 46% yield (Scheme 7). Following deprotonation of phosphonate **54** with sodium hydride in THF, and subsequent reaction with the crude aldehyde obtained from Swern oxidation of **51** (Scheme 8), a 23% yield of amides **3** and **55** was obtained as a mixture in the ratio 3.6:1, respectively. The *Z*-selectivity exhibited by the reagent **54** was acceptable, but the relatively poor yield of product, coupled with the additional steps required to prepare **54**, meant this methodology was not competitive with the TPAP/Wittig route developed above. Although **55** has not been isolated from *Echinacea* sp., it has been identified from *Achillea* species[31] and from *Chrysanthemum frutescе*,[32] and full characterization is reported here for the first time.

Synthesis of (2*Z*)-Enamide and Dienamide Alkyl Amides. A number of alkyl amides have been reported from *Echinacea* sp. which possess a 2*Z*-configured unsaturation, such as **11** and **12** (see Figure 1).

We sought to access these via the synthesis of a *Z*-selective Wittig reagent, (diphenylphosphonato)acetamide reagent **57** (Scheme 9), successfully employed by Kraus[33] in the synthesis of **12**. Swern oxidation of alcohol **34** was followed by a Wittig reaction employing (diphenylphosphonato)acetamide reagent **57** (synthesized in two steps from bromoacetic acid via bromoamide **56**)[34] (Scheme 9). Pleasingly, the desired (2*Z*)-alkyl amide **11** (isolated from *E. angustifolia*)[10] was obtained predominantly (39%) along with the corresponding (2*E*)-alkyl amide **2** (25%) in an overall yield of 64% from **34**.

Alkyl amide **12** occurs in *E. purpurea* and *E. pallida* and contains a (2*Z*,4*E*)-dienamide moiety. **12** was synthesized from commercial pent-4-yn-1-ol (Scheme 10) using similar methodology to that employed for the synthesis of **4** (2*E*,4*E*-isomer of **12**). Thus, pent-4-yn-1-ol underwent Swern oxidation followed by the classical *trans*-selective Horner−Wadsworth−Emmons protocol to give **58**; subsequent DIBAL reduction delivered **59**[35] (Scheme 10). The Cadiot−Chodkiewicz coupling of **59** with bromoalkyne **43** followed by deprotection gave the terminal diyne **61** in 57% from **59**. A Swern oxidation/Wittig condensation sequence with phosphonate **57** afforded alkyl amides **12** (62%) and **62** (21%). Alkyl amide **12** has previously been synthesized by Kraus[29] from

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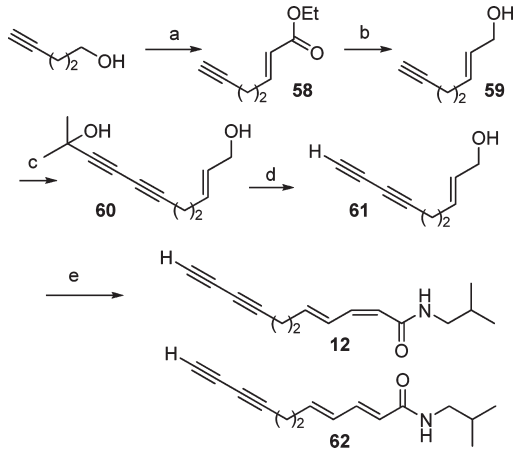
Scheme 10. Synthesis of Alkyl Amide 12[a]



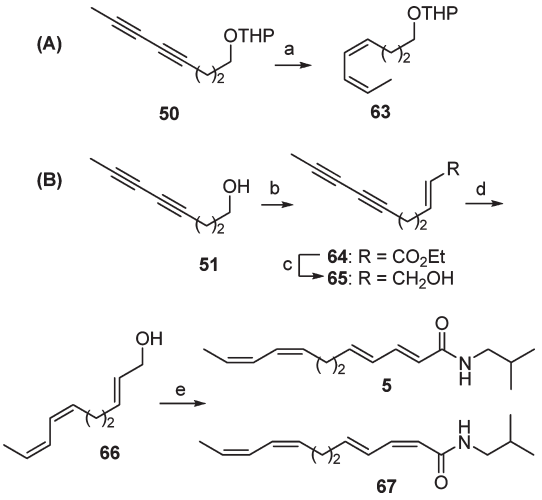
[a] Reagents and conditions: (a) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) $(EtO)_2POCH_2COOEt$, NaH, Et_2O, 0 °C, 89%; (b) DIBAL, Et_2O, 0 °C, 85%; (c) **43**, $^nPrNH_2$, H_2O, CuCl, $NH_2OH\cdot HCl$, 76%; (d) NaOH, PhMe, reflux, 75%; (e) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) **57**, NaHDMS, THF, −20 °C, 83%.

pent-4-yn-1-ol in nine steps in 24% overall yield. The synthesis reported here is comparable (seven steps in 27% yield) and can easily be conducted on a multigram scale. Although alkyl amide **62**, synthesized here for the first time, has not been reported from the three medicinally preferred *Echinacea* sp., it has been identified from the dried roots of *E. atrorubens* Nutt.[36]

Selective Reduction of the Methyl Diyne Unit to a (*Z*,*Z*)-Diene. With a practical route to methyl-substituted diynes such as **50** developed, we sought to utilize it as a precursor of alkyl amide **5** via selective reduction to the conjugated (*Z*,*Z*)-diene. There was literature precedent for partial *cis*-selective hydrogenation of conjugated enynes using Lindlar's catalyst[37] or P-2 nickel.[38] However, we found that, despite much experimentation, hydrogenation of the diyne **50** with either of these catalysts did not cleanly yield the corresponding (*Z*,*Z*)-diene, but instead resulted in a mixture of over and under reduced products with mixed stereochemistry. Turning our attention to other metal-mediated reductions, we obtained moderate yields (40−50%) of the desired diene **63** albeit with excellent *Z*,*Z*-selectivity by reduction of **50** using a Ti^{II}-based procedure developed by Kitching[39] (Scheme 11A). However, in our laboratory, we found this reaction difficult to scale up due to both the very large quantities of isopropylmagnesium bromide required and the careful temperature control needed.

We were intrigued by a report in which Rieke zinc was shown to reduce some alkynes to the corresponding (*Z*)-alkenes.[40] Chou et al. found that Rieke zinc successfully reduced conjugated and nonconjugated propargylic alcohols in excellent yields with as little as 2 equiv of zinc, whereas other zinc reductions require upwards of 25 equiv. This highly activated zinc is prepared by electrochemical reduction of anhydrous zinc chloride with lithium metal in THF, with approximately 10 mol % of naphthalene added as an electron transfer reagent.[41] Rieke zinc reduction of conjugated diynes that were not part of a propargylic alcohol system had not been reported in the literature. Using an analogous procedure, we found that the conjugated diyne moiety was also sufficiently active toward Rieke zinc reduction and produced the (*Z*,*Z*)-diene in excellent yields. Unfortunately, a

Scheme 11. Reduction of Diynes to (*Z*,*Z*)-Dienes[a]



[a] Reagents and conditions: (A) (a) $Ti(O^iPr)_4$ (4 equiv), ^iPrMgBr (11 equiv), Et_2O, −70 °C to −30 °C, 50%. (B) Preparation of alkyl amides **5** and **67**. Reagents and conditions: (b) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (ii) $(EtO)_2POCH_2COOEt$, NaH, Et_2O, 0 °C, 84%; (c) DIBAL, Et_2O, 0 °C, 90%; (d) $ZnCl_2$ (4 equiv), Li (6 equiv), naphthalene (0.1 equiv), THF, MeOH, 60 °C, 91%; (e) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) **20**, KO^tBu, THF, 55%.

THP group was incompatible with the reduction conditions, and therefore, we opted to perform the reduction at a more advanced stage of the synthesis to overcome any volatility issues associated with the reduction product of **51** (Scheme 11B). Thus, the desired diyne **65** was available in three steps from alcohol **51** via a standard Swern, stabilized Wittig, DIBAL reduction sequence. Pleasingly, we found that stereoselective reduction of **65** with 4 equiv of freshly prepared Reike zinc in THF/MeOH (4:1) at 60 °C for 8 h proceeded smoothly and resulted in >91% yield of diene **66**. ^1H NMR analysis confirmed the *Z*,*Z* geometry of the product and the isomeric purity was judged to be >95%, based on integration of the signals corresponding to the methyl terminus. In our hands, Reike zinc was superior for this reduction compared to other zinc reagents such as Zn(Cu/Ag) couple[42] and zinc dust activated by $(CH_2Br)_2$,[20] returning higher yields, and requiring shorter reaction times. Completion of the synthesis of **5** by standard Swern oxidation/Wittig condensation gave the desired alkyl amide **5** (51%) yield and new amide **67** (4%) in 55% overall yield. This constitutes the first reported synthesis of tetraene amide **5**, which was spectroscopically identical to the natural material isolated by Bauer.[9]

A number of other syntheses of key intermediate **65** were also explored. It was envisioned that enyne **59** would be a valuable intermediate for the preparation of not only **65** but also alkyl amides **7** and **8**. We investigated the conversion of the enyne **59** to the conjugated methyl diyne **65** via the KO*t*-Bu/DMSO catalyzed isomerization of skipped diyne **69** (Scheme 12). However, deprotonation of precursor **68** (THP derivative of **59**) with EtMgBr followed by copper-catalyzed addition to propargyl bromide in the usual manner returned approximately 20% of unreacted starting material, which could not be separated from the product. Attempts to circumvent this by the number of increasing equivalents of EtMgBr or propargyl bromide used were unsuccessful. Carrying the mixture forward through the base-catalyzed isomerization protocol prior to separation was

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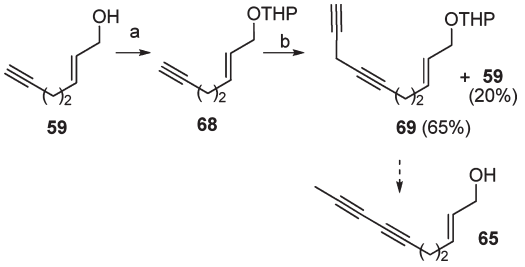
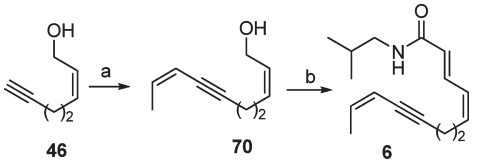
Scheme 12. Attempted Synthesis of 65 from 59[a]



[a] Reagents and conditions: (a) DHP, TsOH, CH_2Cl_2, 78%; (b) (i) EtMgBr, THF, 60 °C, (ii) propargyl bromide, CuCl, 50 °C, 65% (+20% of unreacted **59**).

Scheme 13. Preparation of Alkyl Amide 6[a]



[a] Reagents and conditions: (a) *cis*-1-bromopropene, $PdCl_2(PhCN)_2$, CuI, morpholine, 25 °C, 91%; (b) (i) TPAP, NMO, DCM, 3 Å mol sieves, (ii) **20**, KO^{t}Bu, THF, 56%.

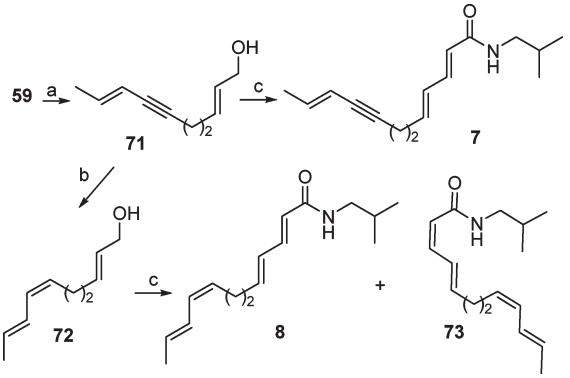
similarly unsuccessful. Thus, the route developed previously (Schemes 5 and 11) was employed for the synthesis of **65**.

Preparation and Selective Reduction of Enynes. Several of the alkyl amides found in *Echinacea* spp. such as **6** and **7** contain a methyl-substituted enyne moiety. We wished to synthesize these compounds and to use the (*E*)-enyne moiety as a precursor for a conjugated (*E*,*Z*)-diene, which is present in the other major alkyl amide **8** found in *Echinacea* sp. We proposed that selective Rieke zinc reduction of the enyne **71** would yield the desired precursor for alkyl amide **8**. The requisite enynes are readily available from coupling the appropriate alkyne and bromoalkene precursors. Thus, the key enyne precursor **70** of alkyl amide **6** was synthesized directly in 92% yield by coupling alkyne-ol **46** with (*Z*)-1-bromopropene under modified Sonagashira conditions.[43] Conversion to the amide **6** was then accomplished in 56% overall yield employing the TPAP oxidation/Wittig condensation sequence used for the synthesis of amide **4** (Scheme 13).

Synthesis of amide **7** (Scheme 14) was accomplished by a similar strategy that utilized the (*E*)-alkenynol precursor **59** (see Scheme 10). Sonagashira coupling of alkynol **59** with (*E*)-1-bromopropene afforded the key enyne **71**, which was subjected to the Swern oxidation/Wittig reaction sequence employing phosphonium salt **20**, completing the synthesis of amide **7** (Scheme 14). The proton NMR data for our synthetic product **7** compare well with that reported by Bauer for the isolated material.[9]

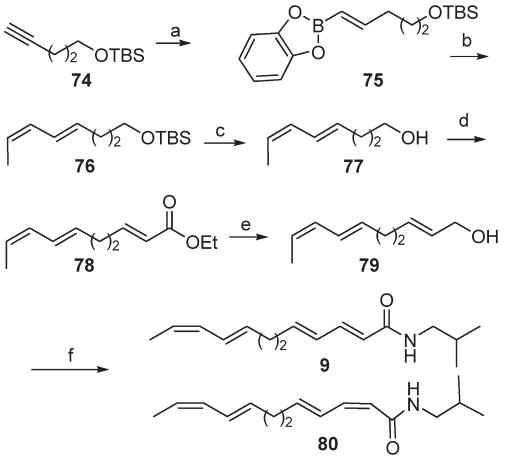
Treatment of enyne **71** with an excess of Zn dust (30 equiv) in methanol in the presence of 1,2-dibromoethane afforded **72** in 88% yield. In this case, we also found that 2 equiv of Rieke zinc smoothly reduced the triple bond, securing the required key (*Z*,*E*)-diene precursor **72** in 92% yield. ^{1}H NMR analysis of **72** indicated that isomeric impurities amounted to less than 1% based on integration of the signals corresponding to the methyl terminus. When **72** was subjected to the standard Swern/Wittig

Scheme 14. Preparation of Alkyl Amides 7 and 8[a]



[a] Reagents and conditions: (a) *trans*-1-bromopropene, $PdCl_2(PhCN)_2$, CuI, morpholine, 25 °C, 87%; (b) $ZnCl_2$ (2 equiv), Li (3 equiv), naphthalene (0.1 equiv), THF, MeOH, 60 °C, 92% or Zn/1,2-dibromoethane, MeOH, Δ, 4 days, 88%; (c) (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, (ii) **20**, KO^{t}Bu, THF, **7** = 52%; **8** = 50%.; **73** = 4%.

Scheme 15. Synthesis of Alkyl Amides 9 and 80[a]



[a] Reagents and conditions: (a) catechol borane, 60 °C, 4 h, 92%; (b) $Pd(PPh_3)_4$, *cis*-1-bromopropene, NaOEt, benzene, 60 °C, 2 h, 77%; (c) MeOH, conc HCl, 25 °C, 91%; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C, (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, ether, 0 °C, 71%; (e) DIBAL, ether, 0 °C, 96%; (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C, (ii) **20**, KO*t*-Bu, THF, 0 °C, 63%.

sequence, we secured **8** in 50% isolated yield (along with 4% of the previously unknown 2*Z*-isomer **73**). This constitutes the first synthesis of **8** which has been previously isolated as a solid from *E. purpurea*,[9] *E. angustifolia*,[10] and *Asarum forbesii Maxim*.[44]

Synthesis of Alkyl Amides 9 and 80. We recently identified **9** in *E. purpurea* and *E. angustifolia* extracts by stereospecific synthesis of **9** and GCMS co-injection studies.[6] Two different routes were developed to **9**, both of which started from pent-4-yn-1-ol. The less specific proceeded via a 1:1 mixture of (2*E*,6*E*,8*Z*)-deca-2,6,8-trien-1-ol **79** and its (2*E*,6*E*,8*E*)-isomer to yield, after separation, **9** in 11% yield.[6] To supply larger quantities of **9**, a stereospecific synthesis was developed (Scheme 15) with the key step being a Suzuki coupling[45] of the boronate ester **75** with *cis*-1-bromopropene to provide alcohol intermediate **77**. This route also yielded the previously unreported alkyl amide **80** in 11% yield.

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CONCLUSION

In summary, 14 alkyl amides which occur naturally in *Echinacea* sp. and one from *Achilla* sp. have been synthesized by direct and flexible routes as well as five previously unreported geometric isomers of naturally occurring alkyl amides. The procedures offer methodology for convenient and cost-effective multigram production of these and analogous alkyl amides in research laboratories. Alkyl amides containing methyl diyne moieties were prepared utilizing new methodology which involves the isomerization of terminal-skipped diynes. Alkyl amides containing terminal diyne moieties were prepared via Cadiot−Chodkiewicz coupling of an appropriate alkyn-1-ol with a common protected bromoacetylene precursor **43**, followed by deprotection of the coupled bisacetylene product. The two major alkyl amides (containing conjugated methyl (*Z*,*Z*)- and (*Z*,*E*)-diene moieties) **5** and **8** have been successfully synthesized by selective *cis*-reduction of the corresponding conjugated diyne or enyne respectively utilizing Rieke zinc. The requisite enynes were prepared by Sonagashira coupling of appropriate alkyn-1-ols with either *cis*- or *trans*-1-bromopropene. Considering the ready availability of alkyn-1-ols, these procedures are expected to be valuable to researchers who require pure synthetic standards of these and analogous alkyl amides from *Echinacea* sp.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on 300, 400, or 500 MHz spectrometers. ^{1}H and ^{13}C signals were recorded in parts per million (ppm) on the δ scale, with the residual solvent peaks ($CDCl_3$: δ_H 7.24 and δ_C 77.0; C_6D_6: δ_H 7.15 and δ_C 128.0) as internal references. Flash chromatography separations were performed with silica gel. Melting points were performed on a melting-point apparatus (Dr. Tottoli) and are uncorrected.

General Procedure A: THP protection. Alcohol (94 mmol) and 3,4-dihydro-2*H*-pyran (8.4 g, 100 mmol) were dissolved in dichloromethane (300 mL), and the mixture was cooled to 0−5 °C using an external ice bath. *p*-Toluene sulfonic acid monohydrate (180 mg, 0.94 mmol) was then added, and the reaction was stirred for 30 min at 0 °C. Then, 1 M NaOH solution (50 mL) was added, and the mixture was vigorously stirred for an additional 30 min. After separation of the two layers, the dichloromethane solution was dried ($MgSO_4$) and stripped of solvent. The crude material was then purified by distillation of flash chromatography.

General Procedure B: THP deprotection. THP-protected alcohol (0.63 mmol) was dissolved in 5 mL of methanol to which *p*-toluene sulfonic acid monohydrate (24 mg, 0.12 mmol) was added. The mixture was stirred at room temperature for 2 h, then 5 mL of 1 M NaOH solution was added followed by water (20 mL). The mixture was extracted into ether (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The crude oil obtained after evaporation of the ether was sufficiently pure to carry on to the next step. A small quantity was purified for analysis using column chromatography (silica gel, 20% ethyl acetate in hexane).

General Procedure C: DIBAL Reduction. DIBAL (9.6 g, 66 mmol) was dissolved in ether (150 mL) and the solution cooled to 0 °C. Next, the ester (30 mmol) dissolved in ether (15 mL) was added dropwise. After stirring at 0 °C for 1 h, the mixture was carefully quenched by the addition of water (20 mL), followed by 1 M HCl (100 mL). The mixture was stirred for a further 90 min, then the organic layer was separated and the aqueous phase extracted with ether (100 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), and evaporated, and the crude material was purified by flash chromatography.

General Procedure D: Terminal-Skipped Diyne Preparation. In a 500 mL round-bottom flask equipped with reflux condenser and pressure equalizing dropping funnel, a solution of ethyl magnesium bromide was prepared in the usual manner from ethyl bromide (13.1 g, 120 mmol), Mg (3.14 g, 130 mmol), and a small crystal of iodine in a total of 240 mL of THF. The mixture was warmed to 50 °C, and the alkyne (100 mmol) was added dropwise (ethane evolution). After complete addition, the reaction was stirred for a further 60 min at this temperature before cooling to room temperature. Next, CuCl (320 mg, 3.2 mmol) was added, and the mixture was stirred at room temperature for a further 15 min. Then the mixture was warmed to 50 °C again, and propargyl bromide (11.9 g, 100 mmol) was added dropwise. After complete addition, the reaction was stirred for a further 45 min, by which time a heavy bright yellow precipitate had developed. The mixture was then cooled using an external water/ice bath and quenched by the slow addition of saturated NH_4Cl solution (200 mL). The organic phase was collected, and the aqueous layer was extracted with hexanes (2 × 100 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), and stripped of solvent. The pure skipped diynes were obtained by flash chromatographic purification.

General Procedure E: Isomerization of Skipped Diynes. Skipped diyne (54.2 mmol) was dissolved in THF (200 mL) to which DMSO (20 mL) had been added, and the solution was cooled to −40 °C. With good stirring, KO*t*-Bu (1.21 g, 10.8 mmol) was then added portionwise, and the resulting dark brown mixture was stirred for 20 min at this temperature before dilution with hexanes (200 mL) and addition of water (100 mL). The organic layer was separated, washed with brine (2 × 150 mL), dried ($MgSO_4$), and stripped of solvent. Flash chromatographic purification of the residue gave the pure methyl-substituted diyne.

General Procedure F: Cadiot−Chodkiewicz Coupling. CuCl (238 mg, 2.4 mmol) was added to 75 mL of a stirred solution consisting of 30% w/v *n*-$PrNH_2$ in H_2O at 0 °C. After a few min of stirring, hydroxylamine hydrochloride (100 mg, 1.4 mmol) was added (this discharged the blue color). Terminal alkyne (55 mmol) was then added neat, and the mixture was stirred at 0 °C for 10 min by which time the formation of a bright yellow precipitate (probably the alkynyl cuprate) was observed. **43** (10.6 g, 65 mmol) dissolved in THF (12 mL) was then added dropwise, and the mixture was stirred at 0 °C for 1 h before addition of saturated NH_4Cl (125 mL). The mixture was extracted into ether (3 × 100 mL), and the combined ether layers were then washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated to give an oil which was purified by column chromatography giving the pure coupling product.

General Procedure G: Diyne Deprotection. The protected diyne (7.9 mmol) was dissolved in toluene (35 mL) to which freshly ground sodium hydroxide (32 mmol) had been added. The mixture was then refluxed with stirring for 25 min by which time TLC indicated the reaction was complete. After cooling, the mixture was washed with water (100 mL), then brine (100 mL), then stripped of toluene and purified using flash chromatography yielding the corresponding deprotected diyne.

General Procedure H: Sonagashira Coupling. $PdCl_2(PhCN)_2$ (76 mg, 0.2 mmol) and CuI (76 mg, 0.4 mmol) were suspended in freshly distilled morpholine (10 mL) at 0 °C with stirring. Then *cis*-1-bromopropene [or *trans*-1-bromopropene] (0.58 g, 4.8 mmol) was added in one portion followed by the slow addition of alkyne (4.1 mmol) dissolved in THF (2 mL). After complete addition of the alkyne, the ice bath was removed and the resulting pale green solution was stirred at room temperature for 3 h over which time the color had changed to a pale brown and a light precipitate had formed. The mixture was quenched with saturated ammonium chloride solution (40 mL) and extracted into ether (3 × 25 mL). The organic layers were washed with 0.5 M HCl (50 mL) then brine (50 mL) and dried

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($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography (20% EtOAc in hexanes, silica gel 60).

General Procedure I: Reike Zinc Reduction. Naphthalene (1.92 g, 15 mmol) was dissolved in THF (30 mL), and lithium (3.1 g, 450 mmol) was cut with a pair of scissors into thin slithers (approx 1 mm wide × 5 mm long) which fell directly into the THF solution. After stirring for 30 min at 25 °C, the deep green color indicative of lithium naphthalide was observed. Then, anhydrous zinc chloride (20.5 g, 150 mmol) dissolved in THF (150 mL) was added dropwise over 30 min, and after complete addition, the gray/black mixture was stirred for a further hour at 25 °C. Next, the mixture was heated to 50 °C, and the alkyne (37 mmol) dissolved in methanol (40 mL) was added dropwise with good stirring. Stirring was continued at 50 °C for 12 h, then the mixture was cooled to room temperature and water (500 mL) was added. The mixture was extracted into ether (3 × 100 mL), and the combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and stripped of solvent. Flash chromatographic purification gave the corresponding alkene.

General Procedure J: Consecutive Swern Oxidation/*cis*-Selective Horner−Wadsworth−Emmons Protocol. Oxalyl chloride (3.81 g, 30 mmol) was added to CH_2Cl_2 (100 mL), and the solution was cooled to −78 °C. Next, DMSO (3.9 g, 50 mmol) was added dropwise, and after complete addition, the solution was stirred for a further 2 min before the dropwise addition of the alcohol (23 mmol). Stirring was continued at −78 °C for 30 min, and then the reaction was warmed to −10 °C for 5 min. The mixture was recooled to −78 °C, and Et_3N (14.1 g, 140 mmol) was added. The reaction was allowed to return to room temperature and washed with water (100 mL), then 1 M HCl (100 mL) and then once more with water (100 mL). The organic layer was dried ($MgSO_4$) and the dichloromethane removed to give the crude aldehyde which was diluted with THF (10 mL) and used in the next step without delay. $(PhO)_2POCH_2CO_2Et$ (8 g, 25 mmol)[46] was added dropwise to a suspension of NaH (1.0 g, 25 mmol, 60% dispersion in mineral oil) in THF (100 mL) at 0 °C (H_2 evolution). After stirring a further 20 min, the mixture was cooled to −78 °C and the crude aldehyde solution prepared above was added to the reaction dropwise. After complete addition, the reaction was stirred for 30 min, then the dry ice bath was removed and water (200 mL) was slowly added. The mixture was extracted with petroleum spirit, bp 40−60 °C (2 × 150 mL), and the combined organic layers were washed with water (4 × 150 mL) then with brine (150 mL), dried ($MgSO_4$), and evaporated to give the crude product which was purified by flash chromatography.

General Procedure K: Consecutive Swern Oxidation/*trans*-Selective Horner−Wadsworth−Emmons Protocol. Oxalyl chloride (11.4 g, 90 mmol) was added to CH_2Cl_2 (300 mL), and the solution was cooled to −78 °C. Next, DMSO (12.5 g, 160 mmol) was added dropwise, and after complete addition, the solution was stirred for a further 2 min before the dropwise addition of alcohol (70 mmol). Stirring was continued at −78 °C for 30 min, and then the reaction was warmed to −10 °C for 5 min. The mixture was recooled to −78 °C, and Et_3N (34.8 g, 345 mmol) was added. The reaction was allowed to return to room temperature and washed with water (150 mL), then 1 M HCl (100 mL) and then once more with water (100 mL). The organic layer was dried ($MgSO_4$) and the dichloromethane removed to give the crude aldehyde which was diluted with ether (25 mL) and used in the next step without delay. Ethyl 2-(diethoxyphosphoryl)acetate (15.6 g, 69.6 mmol) was added dropwise to a suspension of NaH (3.0 g, 75 mmol, 60% dispersion in mineral oil) in ether (280 mL) at 0 °C (H_2 evolution). After stirring a further 15 min, the crude aldehyde solution prepared above was added slowly to the reaction mixture. After complete addition, the reaction was stirred for 10 min, then the ice bath was removed and water (200 mL) was slowly added. The mixture was extracted with petroleum spirit (200 mL), and the combined organic layers were washed with water (2 × 150 mL) then with brine (150 mL), dried ($MgSO_4$), and stripped of solvent and the crude material purified by distillation or by flash chromatography.

General Procedure L: Consecutive Swern Oxidation/Wittig Protocol Employing Phosphonium Salt 20. Oxalyl chloride (3.8 g, 30 mmol) was added to CH_2Cl_2 (200 mL), and the solution was cooled to −78 °C. Next, DMSO (5.49 g, 70 mmol) was added dropwise, and after complete addition, the solution was stirred for a further 2 min before the dropwise addition of alcohol (19.7 mmol). Stirring was continued at −78 °C for 30 min, and then the reaction was warmed to −10 °C for 5 min. The mixture was recooled to −78 °C, and Et_3N (15.1 g, 150 mmol) was added. The reaction was allowed to return to room temperature and washed with water (100 mL) then 1 M HCl (100 mL) and then once more with water (100 mL). The organic layer was dried ($MgSO_4$) and the dichloromethane removed to give the crude aldehyde which was diluted with tetrahydrofuran (15 mL) and used in the next step without delay. Meanwhile, KO*t*-Bu (2.24 g, 20 mmol) was added in one portion to a stirred suspension of **20** (9.0 g, 22 mmol) in tetrahydrofuran (100 mL) at room temperature. Stirring was continued for a further 30 min, then the mixture was cooled to 0 °C and the crude aldehyde solution prepared from the previous step was added in one portion. Stirring was continued at 0 °C for 2 h, then saturated NH_4Cl solution (100 mL) was added and the organic phase was separated. The aqueous phase was extracted into ether (2 × 100 mL), and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and stripped of solvent. Flash chromatographic purification (20% EtOAc in hexanes, silica) yielded the corresponding alkyl amide.

General Procedure M: Consecutive TPAP Oxidation/Wittig Protocol Employing Phosphonium Salt 20. The 3 Å powdered molecular sieves (300 mg) were added to a solution of *cis*-allylic alcohol (0.72 mmol) and NMO (93 mg, 0.8 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 15 min at room temperature, and then tetrapropylammonium perruthenate (12 mg, 0.036 mmol) was added. After stirring for 15 min, the reaction was added via syringe to a stirred mixture of the ylide generated from **20** (411 mg, 1.0 mmol) and KO^{t}Bu (112 mg, 1.0 mmol) in THF (5 mL) (see general procedure L for details). After stirring for 30 min at room temperature, saturated NH_4Cl solution (6 mL) was added followed by ether (6 mL). The organic layer was separated and the aqueous phase extracted once more with ether (6 mL), then the combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$), and stripped of solvent. Flash chromatographic purification (20% EtOAc in hexanes, silica gel 60) yielded the corresponding (4*Z*)-alkyl amide.

(2*E*,4*E*,8*Z*)-*N*-Isobutyldodeca-2,4,8-trienamide (10) and (2*Z*,4*E*,8*Z*)-*N*-Isobutyldodeca-2,4,8-trienamide (23). The title compounds were obtained in 31.4% (**10**, white solid) and 3% (**23**, colorless oil) yields from (*Z*)-oct-4-enal (**22**)[17] according to the general procedure L. **10**: Mp = 56−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 0.90 (d, J = 6.8 Hz, 6H), 1.29−1.40 (m, 2H), 1.72−1.80 (m, 2H), 1.92−2.00 (m, 2H), 2.12−2.18 (m, 3H), 3.13 (dd, J = 6.7, 6.7 Hz, 2H), 5.28−5.40 (m, 2H), 5.55 (brs, 1H), 5.74 (d, J = 15.0 Hz, 1H), 6.00−6.15 (m, 2H), 7.15 (dd, J = 10.4, 15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.1, 22.7, 26.5, 28.6, 29.3, 33.0, 46.9, 122.0, 128.4, 128.5, 130.7, 141.1, 142.2, 166.3; GC-MS EI m/z (%) 249 (4.4) [M^+], 234 (2), 206 (3), 177 (21), 166 (18), 152 (16), 110 (16), 66 (61), 57 (74), 55 (100), 41 (99); HR-MS m/z calcd $[M + Na]^+$ for $C_{16}H_{27}NONa$ 272.1990, found 272.1985. **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.6 Hz, 3H), 0.89 (d, J = 6.5 Hz, 6H), 1.28−1.37 (m, 2H), 1.72−1.82 (m, 2H), 1.92−2.00 (m, 2H), 2.10−2.22 (m, 3H), 3.10 (dd, J = 6.2, 6.8 Hz, 2H), 5.29−5.38 (m, 2H), 5.46 (d, J = 11.0 Hz, 1H), 5.63 (brs, 1H), 5.92 (dt, J = 6.5, 13.3 Hz, 1H), 6.34 (t, J = 11.3 Hz, 1H), 7.43 (ddq, J = 1.4, 11.3, 15.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 20.1, 22.7, 26.6, 28.5, 29.2, 33.0, 46.7, 118.7, 127.2, 128.6, 130.5, 141.3, 142.8, 166.5; GC-MS EI m/z (%) 249 (M^+ 0.4), 220 (6),

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206 (10), 166 (15), 152 (54), 110 (14), 66 (50), 57 (54), 55 (70), 41 (100); HR-MS m/z calcd $[M + Na]^+$ for $C_{16}H_{27}NONa$ 272.1990, found 272.1985.

(*E*)-4-Bromobut-2-enoic acid (24). Crotonic acid (10 g, 116 mmol) was dissolved in benzene (150 mL), and then *N*-bromosuccinimide (31.4 g, 120 mmol) was added followed by benzoyl peroxide (0.2 g, 1.4 mmol). The mixture was refluxed with stirring for 4 h, and after that, it was allowed to cool to room temperature, which resulted in precipitation of large succinimide crystals. The crystals were filtered and the filtrate was stripped of solvent. The crude product was recrystallized from the minimum amount of hexane yielding 15.4 g (80%) of the title compound as a white solid: mp = 69−70 °C; lit[47] mp = 72−73 °C. Spectroscopic data were consistent with a literature report:[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (dd, J = 1.2, 7.2 Hz, 2H), 6.04 (dt, J = 1.2, 15.0 Hz, 1H), 7.11 (dt, J = 7.2, 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 123.8, 144.4, 171.1.

(*E*)-4-Bromo-*N*-isobutylbut-2-enamide (25). **24** (15.0 g, 90.5 mmol) and thionyl chloride (16.0 g, 135 mmol) were mixed together and stirred at 25 °C overnight. The reaction was then setup for vacuum distillation, and after removal of excess thionyl chloride, the acid chloride was collected at 68−69 °C (3 mmHg), yielding 12.0 g of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, J = 1.2, 7.2 Hz, 2H), 6.27 (dt, J = 1.2, 15.0 Hz, 1H), 7.20 (dt, J = 7.2, 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 128.9, 147.8, 165.2. The acid chloride prepared above was then added to a solution of isobutylamine (12.5 g, 170 mmol) in ether (300 mL). After complete addition, water (100 mL) was added and the mixture was stirred vigorously for 2 min. The ether layer was washed with brine (100 mL), dried ($MgSO_4$), and evaporated to yield 12.1 g (61%) of the title compound as a white solid: mp = 90−91 °C; lit[48] mp = 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 6H), 1.80 (sept, J = 6.8 Hz, 1H), 3.15 (d, J = 6.4, 6.4 Hz, 2H), 4.0 (dd, J = 1.2, 7.2 Hz, 2H), 5.92 (brs, 1H), 6.03 (d, J = 14.8 Hz, 1H), 6.90 (dt, J = 7.2, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 28.5, 29.8, 47.0, 127.1, 137.7, 164.7.

(*E*)-(4-(Isobutylamino)-4-oxobut-2-enyl)triphenylphosphonium bromide (26). **25** (1.8 g, 8.2 mmol) and Ph_3P (2.62 g, 10.0 mmol) were dissolved in toluene (15 mL) and heated to 80 °C for 2 h with stirring. After cooling to room temperature, large crystals of the product had formed, which were collected by vacuum filtration giving 2.7 g (88%) of **26** that was used without further purification: mp = 198−200 °C; lit[49] = 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 6H), 1.92 (sept, J = 6.4 Hz, 1H), 3.12 (dd, J = 6.8 Hz, 2H), 4.92 (dd, J = 7.5, 15.8 Hz, 2H), 6.48 (dd, J = 15.8, 4.8 Hz, 1H), 6.85 (m, 1H), 7.8−7.95 (m, 15H).

(*E*)-Diethyl 4-(isobutylamino)-4-oxobut-2-enylphosphonate (27). **25** (2.0 g, 9.05 mmol) and triethyl phosphite (1.66 g, 10.0 mmol) were mixed together and stirred at 100 °C for 2 h. After cooling to room temperature, the mixture was purified by flash chromatography (silica gel, 50% EtOAc in hexane) yielding 1.9 g (76%) of the title compound **27** as a white solid: mp = 44−46 °C; ^{1}H NMR (500 M Hz, $CDCl_3$) δ 0.91 (d, J = 7.0 Hz, 6H), 1.31 (t, J = 7.0 Hz, 6H), 1.79 (sept, J = 7.0 Hz, 1H), 2.70 (ddd, J = 1.5, 8.0, 22.5 Hz, 2H), 3.16 (dd, J = 6.5, 6.5 Hz, 2H), 4.05−4.15 (m, 4H), 5.68 (brs, 1H), 6.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4 (d, J = 6.0 Hz), 20.1, 28.5, 30.1(d, J = 138.0 Hz), 46.9, 62.2 (d, J = 7.0 Hz), 128.4 (d, J = 1.0 Hz), 132.5 (d, J = 1.0 Hz), 164.9. Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.98; H, 8.72; N, 5.05. Found: C, 51.45; H, 8.69; N, 5.20.

(*E*)-Ethyl dec-2-enoate (18). (Diethoxyphosphoryl)acetic acid ethyl ester (13 g, 58 mmol) was added dropwise to a suspension of NaH (2.79 g, 58 mmol, 50% dispersion in mineral oil) in ether (250 mL) at 0 °C. After hydrogen evolution was complete (5 min), octanal (6.4 g, 50 mmol) was added dropwise with good stirring. Fifteen minutes later, the reaction was quenched by the addition of 100 mL of saturated ammonium chloride solution. The ether layer was separated and washed with water (2 × 100 mL) then with brine (100 mL), dried ($MgSO_4$), and evaporated. Purification by flash chromatography (silica gel 60/5% EtOAc in hexane) yielded 9.5 g (96%) of the title compound as a colorless oil. Spectroscopic data were consistent with a literature report:[50] ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.1 Hz, 3H), 1.20−1.36 (m, 8H), 1.27 (t, J = 6.8 Hz), 3H, 1.39−1.47 (m, 2H), 2.16 (dtd, J = 7.1, 7.1, 1.5 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 5.78 (dt, J = 15.6, 1.6 Hz, 1H), 6.94 (dt, J = 15.6, 6.9 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.6, 28.0, 29.0, 29.1, 31.7, 32.1, 60.0, 121.5, 149.4, 166.7; GC-MS EI m/z (%) 198 (M^+, 0.5), 169 (1), 153 (19), 152 (11), 141 (2), 127 (7), 110 (15), 101 (29), 84 (24), 69 (32), 55 (92), 43 (100).

(2*E*,4*E*)-*N*-Isobutyldodeca-2,4-dienamide (13) and (2*E*,4*Z*)-*N*-Isobutyldodeca-2,4-dienamide (28). The title compounds were obtained (after purification by column chromatography using 20% EtOAc in hexanes, silica gel 60) in 40% (**13**, white solid) and 8% (**28**, colorless oil) yields from octanal according to a procedure adapted from general procedure K [using (*E*)-diethyl 4-(isobutylamino)-4-oxobut-2-enylphosphonate (**27**) instead of ethyl 2-(diethoxyphosphoryl)acetate (**20**)]. **13**: Mp = 74−75 °C; lit[15a] mp = 76−77 °C. Spectroscopic data were consistent with a literature report:[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.0 Hz, 3H), 0.90 (d, J = 6.9 Hz, 6H), 1.22−1.30 (m, 8H), 1.34−1.42 (m, 2H), 1.77 (sept, J = 6.9 Hz, 1H), 2.11 (brq, J = 6.7 Hz, 2H), 3.13 (dd, J = 6.5, 6.5 Hz, 2H), 5.59 (brs, 1H), 5.74 (d, J = 15.1 Hz, 1H), 5.99−6.13 (m, 2H), 7.16 (dd, J = 9.9, 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.1, 22.6, 28.6, 28.8, 29.0, 29.1, 31.7, 32.9, 46.9, 121.7, 128.2, 141.2, 143.1, 166.4; GC-MS EI m/z (%) 251 (17) [M^+], 236 (10), 222 (1), 208 (4), 196 (3), 180 (16), 179 (65), 166 (9), 152 (39), 138 (7), 126 (9), 113 (21), 96 (100), 81 (93), 68 (42), 55 (86), 41 (96); HR-MS m/z calcd M^+ for $C_{16}H_{29}NONa$ 274.2147, found 274.2149. **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.9 Hz, 3H), 0.90 (d, J = 66 Hz, 6H), 1.20−1.31 (m, 8H), 1.33−1.40 (m, 2H), 1.78 (sept, J = 6.7 Hz, 1H), 2.26 (dq, J = 1.5, 6.7 Hz, 2H), 3.15 (dd, J = 6.2, 6.9 Hz, 2H), 5.54 (brs, 1H), 5.73−5.78 (m, 1H), 5.80 (d, J = 14.9 Hz, 1H), 6.05 (brt, J = 11.3 Hz, 1H). 7.53 (ddd, J = 1.1, 11.6, 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.1, 22.6, 28.2, 28.6, 29.1, 29.2, 29.5, 31.8, 46.9, 123.7, 126.3, 136.0, 140.3, 166.3; GC-MS EI m/z (%) 251 (26) [M^+], 236 (11), 208 (5), 179 (78), 152 (20), 113 (24), 81 (100), 55 (50), 41 (52); HR-MS m/z calcd M^+ for $C_{16}H_{29}NONa$ 274.2147, found 274.2141.

(2*E*,4*E*)-*N*-Isobutyldodeca-2,4-dienamide (13) and (2*Z*,4*E*)-*N*-Isobutyldodeca-2,4-dienamide (21). The title compounds were obtained in 66% (**13**, white solid) and 6.68% (**21**, colorless oil) yields from (*E*)-dec-2-enal (**19**)[51] according to the general procedure L. **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 6.8 Hz, 3H), 0.91 (d, J = 6.4 Hz, 6H), 1.18−1.43 (m, 10H), 1.78 (sept, J = 6.4 Hz, 2H), 3.11 (dd, 6.8, 6.8 Hz, 2H), 5.46 (d, J = 11.2 Hz, 1H), 5.65 (m, 1H), 5.93 (dt, J = 15.2, 6.8 Hz, 1H), 6.35 (dd, J = 10.8, 11.2 Hz, 1H), 7.43 (dd, J = 10.8, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.1, 22.6, 28.5, 28.9, 29.1, 29.2, 31.7, 32.9, 46.7, 118.4, 126.9, 141.5, 143.7, 166.6; HR-MS m/z calcd M^+ for $C_{16}H_{29}NONa$ 274.2147, found 274.2141.

2-Methyl-11-(tetrahydro-2*H*-pyran-2-yloxy)undeca-3,5-diyn-2-ol (31). A quantity of 5.3 mL (7.4 mmol) of *n*-BuLi in hexanes (1.4M) was slowly added to a well-stirred solution of **29**[18] (0.41 g, 3.7 mmol) in THF (10 mL) and HMPA (2.5 mL) at 0 °C. After complete addition, a heavy white precipitate had formed and the mixture was stirred for a further 5 min. **30**[52] (0.93 g, 3.7 mmol) was then added, and the mixture was stirred at 0 °C for 5 h. Saturated LiCl solution (30 mL) was then added, and the mixture was extracted into ether. The ether layers were washed with brine (100 mL), dried ($MgSO_4$), and stripped of solvent. Purification of the residue by flash chromatography (silica, 30% EtOAc in hexane) yielded 0.86 g (65%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40−1.84 (m, 12H), 1.49 (s, 6H), 2.01 (s, 1H), 2.27 (t, J = 6.7 Hz, 2H), 3.35 (dt, J = 6.5, 9.6 Hz,

1H), 3.50 (m, 1H), 3.72 (dt, J = 6.7, 9.6 Hz, 1H), 3.85 (m, 1H), 4.56 (dd, J = 3.1, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 19.7, 25.57, 25.60, 28.1, 29.3, 30.8, 31.3, 62.4, 64.6, 65.3, 67.38, 67.39, 80.1, 81.7, 98.9; HR-MS m/z calcd M^+ for $C_{17}H_{26}O_3$ 278.1882, found 278.1888.

2-(Nona-6,8-diynyloxy)tetrahydro-2*H*-pyran (32). The title compound was obtained in 85% yield (1.42 g, colorless oil) from **31** (2.2 g, 7.9 mmol) according to the general procedure G. The crude product was purified using flash chromatography (20% EtOAc in hexanes, silica): ^{1}H NMR (500 MHz, C_6D_6) δ 1.25−1.50 (m, 8H), 1.62−1.67 (m, 2H), 1.72 (t, J = 0.9 Hz, 1H), 1.76−1.85 (m, 2H), 1.92 (dt, J = 0.9, 6.7 Hz, 2H), 3.25 (dt, J = 6.5, 9.6 Hz, 1H), 3.44 (m, 1H), 3.73 (dt, J = 6.7, 9.6 Hz, 1H), 3.83 (m, 1H), 4.59 (dd, J = 3.1, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 17.9, 18.7, 24.8, 24.9, 27.0, 28.4, 30.0, 60.5, 64.3, 64.7, 66.1, 68.0, 77.4, 97.5; GC-MS EI m/z (%) 191 (0.3), 177 (1), 149 (2), 131 (2), 117 (14), 103 (9), 91 (33), 85 (100), 76 (18), 55 (38). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.05; H, 9.53.

2-(Deca-6,8-diynyloxy)tetrahydro-2*H*-pyran (33). Method A: 1.1 mL (1.54 mmol) of *n*-BuLi in hexanes (1.4 M) was slowly added to a solution of **32** (340 mg, 1.54 mmol) in THF (12 mL) at 0 °C. MeI (310 mg, 2.2 mmol) was then added in one portion, and the mixture was stirred at 0 °C for 3 h. Water (20 mL) was then added, and the mixture was extracted into hexanes. The organic layers were washed with water (50 mL) then brine (50 mL), dried ($MgSO_4$), and stripped of solvent. Purification of the residue by flash chromatography (silica, 5% EtOAc in hexane) yielded 330 mg (91%) of the title compound as a colorless oil. Method B: The title compound was obtained in 88% yield (11.8 g, colorless oil) from **42** (12.7 g, 54.2 mmol) according to the general procedure E. Purification: flash chromatography (10% ether in hexanes, silica): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36−1.66 (m, 12H), 1.72−1.80 (m, 1H), 1.82 (t, J = 1.2 Hz, 3H), 2.19 (dt, J = 1.2, 6.8 Hz, 2H), 3.31 (dt, J = 6.7, 9.7 Hz, 1H), 3.40−3.46 (m, 1H), 3.65 (dt, J = 6.7, 9.7 Hz, 1H), 3.76−3.82 (m, 1H), 4.50 (t, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.9, 18.9, 19.5, 25.3(2), 28.0, 29.0, 30.6, 62.1, 64.4, 65.3, 67.1, 72.7, 76.4, 98.6. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.17; H, 9.83.

Nona-6,8-diyn-1-ol (34). The title compound was obtained in 89% yield (11.8 g, colorless oil) from **32** (140 mg, 0.12 mmol) according to the general procedure B: purification by flash chromatography (20% ether in hexanes, silica); ^{1}H NMR (500 MHz, C_6D_6) δ 1.18−1.33 (m, 6H), 1.57 (s, 1H), 1.63 (s, 1H), 1.90 (t, J = 6.7 Hz, 2H), 3.36 (brt, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 18.9, 25.2, 27.9, 32.3, 62.2, 65.3, 65.8, 68.9, 78.4; GC-MS EI m/z (%) 136 (M^+, 0.5), 135 (4), 117 (25), 103 (31), 91 (47), 76 (100), 63 (80), 51(42). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.27; H, 8.65.

Deca-6,8-diyn-1-ol (35). The title compound was obtained in 93% yield from **33**, according to the general procedure B: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38−1.45 (m, 2H), 1.47−1.56 (m, 4H), 1.65 (s, 1H), 1.85 (t, J = 1.2 Hz, 3H), 2.21 (dt, J = 1.2, 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.0, 19.9, 24.9, 28.0, 32.1, 62.6, 64.4, 65.5, 73.0, 76.5; GC-MS EI m/z (%) 149 (2), 135 (9), 115 (25), 103 (11), 91 (65), 79 (36), 77 (65), 65 (29), 51(100). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.97; H, 9.62.

(*E*)-*N*-Isobutyldodeca-2-en-8,10-diynamide (1). The title compound was obtained in 58% yield from **34**, according to the general procedure L: white solid; mp = 102−104 °C; lit[10] mp = 104 °C, which gave spectroscopic data consistent with a literature report;[17] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.7 Hz, 6H), 1.45−1.54 (m, 4H), 1.75 (sept, J = 6.7 Hz, 1H), 1.85 (s, 3H), 2.10−2.24 (m, 4H), 3.10 (t, J = 6.7 Hz, 2H), 5.80 (d, J = 15.2 Hz, 1H), 5.98 (brs, 1H), 6.74 (dt, J = 6.9, 15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.0, 18.8, 20.0, 27.2, 27.6, 28.5, 31.2, 46.8, 64.4, 65.6, 73.1, 76.2, 124.1, 143.4, 166.0; GC-MS EI m/z (%) 245 (3) [M^+], 244 (4), 230 (3), 216 (11), 202 (9), 188 (7), 174 (9), 160 (13), 145 (30), 130 (27), 117 (48), 105 (26), 91 (33), 77 (39), 41 (100). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.44; H, 9.39; N, 5.94.

(*E*)-*N*-Isobutylundeca-2-en-8,10-diynamide (2). The title compound was obtained in 55% yield from **34**, according to the general procedure L: white solid; mp = 74−75 °C; lit[10] mp = 69 °C. Spectroscopic data were consistent with a literature report:[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 6H), 1.52−1.60 (m, 4H), 1.79 (sept, J = 6.8 Hz, 1H), 1.97 (t, J = 0.8 Hz, 1H), 2.15−2.30 (m, 4H), 3.14 (t, J = 6.5 Hz, 2H), 5.54 (br s, 1H), 5.77 (dt, J = 1.2, 15.2 Hz, 1H), 6.80 (dt, J = 6.8, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 20.1, 27.2, 27.3, 28.6, 31.3, 46.8, 64.7, 65.0, 68.4, 77.9, 124.1, 143.7, 165.9; GC-MS EI m/z (%) 231 (2) [M^+], 230 (3), 216 (3), 202 (8), 188 (7), 174 (6), 160 (8), 146 (10), 131 (20), 116 (28), 103 (26), 91 (100), 79 (13). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.94; H, 9.59; N, 5.68.

2-(Deca-6,9-diynyloxy)-tetrahydro-2*H*-pyran (42). The title compound was obtained in 75% yield from **41**[22,23,53] according to the general procedure D: flash chromatographic purification with 10% Et_2O in hexanes, silica gel; ^{1}H NMR (500 MHz, C_6D_6) δ 1.20−1.64 (m, 12H), 1.70−1.79 (m, 1H), 1.74 (t, J = 2.7 Hz, 1H), 1.91−1.97 (m, 2H), 2.81−2.84 (q, J = 2.5 Hz, 2H), 3.24 (dt, J = 6.4, 9.6 Hz, 1H), 3.35−3.50 (m, 1H), 3.70−3.81 (m, 2H), 4.54 (t, J = 3.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 9.6, 18.8, 19.6, 25.8, 25.9, 28.8, 29.6, 31.9, 61.5, 67.3, 68.8, 73.7, 79.0, 81.2, 98.5; GC-MS EI m/z (%) 195 (0.2), 167 (0.4), 125 (1), 111 (1.8), 101 (17), 85 (100), 79 (10), 67 (49), 55 (47). **42** was converted to the corresponding methyl-substituted diyne **33** (88% yield, purification with 10% Et_2O in hexanes, silica gel) according to the general procedure E.

10-Methylundeca-6,8-diyne-1,10-diol (44). The title compound was obtained in 90% yield from **43**[25] according to the general procedure F. The crude product was purified by column chromatography (silica gel, 30% ethyl acetate in hexane) to give **44** as a white solid: mp = 55−56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.60 (m, 6H), 1.51 (s, 6H), 2.18 (s, 1H), 2.29 (t, J = 6.8 Hz, 2H), 3.64 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.9, 27.9, 31.2, 32.1, 62.7, 64.5, 65.5, 67.3, 79.8, 81.5. Anal. Calcd: C, 74.19; H, 9.34. Found: C, 73.96; H, 9.42. **44** was converted to the corresponding **34** in 85% yield according to the general procedure E.

(*Z*)-Ethyl hept-2-en-6-ynoate (45). The title compound was obtained in 69% yield from pent-4-yn-1-ol, according to the general procedure J. Spectroscopic data were consistent with a literature report.[54]

(*Z*)-Hept-2-en-6-yn-1-ol (46). The title compound was obtained in 92% yield from **45**, according to the general procedure C. Spectroscopic data were consistent with a literature report.[55]

(*Z*)-10-Methylundeca-2-en-6,8-diyne-1,10-diol (47). The title compound was obtained in 88% yield from **46** (silica gel, 25% ethyl acetate in hexane), according to the general procedure F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 6H), 2.08 (s, 1H), 2.28−2.39 (m, 4H), 4.18−4.26 (m, 2H), 5.52−5.60 (m, 1H), 5.68−5.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 26.1, 31.1, 58.5, 64.9, 65.5, 67.0, 80.4, 80.8, 130.1, 130.5; GC-MS EI m/z (%) 173 (1), 159 (2), 131 (5), 115 (7), 91 (9), 77 (7), 43 (100). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.86; H, 8.68.

(*Z*)-Nona-2-en-6,8-diyn-1-ol (48). The title compound was obtained in 83% yield from **47**, according to the general procedure G and was used in the next step without delay: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 1H), 1.98 (s, 1H), 2.30−2.35 (m, 4H), 4.21 (brd, J = 4.4 Hz, 2H), 5.51−5.60 (m, 1H), 5.72 (dt, J = 6.8, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 25.9, 58.4, 65.0, 65.2, 68.1, 77.4, 129.8, 130.6; GC-MS EI m/z (%) 134 (0.2) [M^+], 133 (6), 115 (70), 103 (16), 91 (32), 77 (24), 63 (68), 41 (100); HR-MS m/z calcd $[M + Na]^+$ for $C_9H_{10}ONa$ 134.1751, found 134.1751.

(2*E*,4*Z*)-*N*-Isobutylundeca-2,4-dien-8,10-diynamide (4). The title compound was obtained in 56% yield from **48**, according to the general procedure L: white solid; mp = 58−60 °C; lit[9] mp = 61 °C. Spectroscopic data were consistent with a literature report:[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 6H), 1.78 (sept, J = 6.4 Hz, 1H), 1.95 (t, J = 1.2 Hz, 1H), 2.32−2.38 (m, 2H), 2.50−2.56 (m, 2H), 3.15 (t, J = 6.4 Hz, 2H), 5.54 (brs, 1H), 5.79 (dt, J = 7.2, 10.8 Hz, 1H), 5.85 (d, J = 14.8 Hz, 1H), 6.15 (t, J = 10.8 Hz, 1H), 7.46 (ddd, J = 1.2, 11.6, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.1, 26.5, 28.6, 46.9, 64.9, 65.5, 68.2, 76.9, 124.9, 128.0, 135.1, 136.2, 166.0; GC-MS EI m/z (%) 229 (3), 228 (4), 214 (4), 128 (100), 115 (32), 96 (27), 66 (60), 57 (74), 41 (50). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.15; H, 8.41; N, 6.09.

2-(Octa-4,6-diynyloxy)-tetrahydro-2*H*-pyran (50). **49** was obtained in 77% yield from THP-protected pent-4-yn-1-ol,[56] according to the general procedure D: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47−1.84 (m, 8H), 2.04 (t, J = 2.5 Hz, 1H), 2.26−2.31 (m, 2H), 3.13 (q, J = 2.5 Hz, 2H), 3.43−3.53 (m, 2H), 3.77−3.89 (m, 2H), 4.59 (dd, J = 3.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.5, 15.6, 19.5, 25.5, 28.8, 30.7, 62.1, 65.9, 68.4, 73.3, 78.9, 80.5, 98.8; GC-MS EI m/z (%) 205 (0.5), 167 (12), 135 (5), 122 (7), 103 (11), 85 (100), 77 (26). The title compound **50** was obtained in 89% yield from **49**, according to the general procedure E: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48−1.60 (m, 4H), 1.66−1.73 (m, 1H), 1.77−1.83 (m, 3H), 1.89 (t, J = 1.0 Hz, 3H), 2.37 (tq, J = 1.0, 6.5 Hz, 2H), 3.43−3.53 (m, 2H), 3.77−3.87 (m, 2H), 4.58 (dd, J = 3.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1, 16.1, 19.5, 25.5, 28.6, 30.6, 62.2, 64.5, 65.6, 65.8, 73.0, 76.1, 98.8; GC-MS EI m/z (%) 206 (0.2) [M^+], 191 (5), 161 (6), 149 (8), 135 (12), 122 (20), 103 (31), 85 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.81; H, 8.99.

Octa-4,6-diyn-1-ol (51). The title compound was obtained in 90% yield from **50**, according to the general procedure B: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (quint, J = 1.2 Hz, 2H), 1.89 (t, J = 1.2 Hz, 3H), 2.36 (tq, J = 1.2, 6.7 Hz, 2H), 3.72 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.0, 15.5, 30.8, 61.2, 64.2, 65.6, 73.2, 75.8. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.85; H, 4.49.

(*Z*)-Ethyl deca-2-en-6,8-diynoate (52). The title compound was obtained in 90% yield from **51**, according to the general procedure J: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.88 (s, 3H), 2.38 (t, J = 7.0 Hz, 2H), 2.85 (dq, J = 1.7, 7.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 5.82 (dt, J = 1.7, 11.5 Hz, 1H), 6.27 (dt, J = 7.2, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 14.3, 18.9, 27.6, 60.0, 64.4, 66.2, 73.5, 75.4, 121.2, 147.2, 166.2; GC-MS EI m/z (%) 190 (0.2) [M^+], 189 (1), 175 (0.2), 162 (8), 161 (17), 145 (25), 133 (9), 117 (60), 115 (79), 105 (9), 91 (36), 77 (54), 51 (100). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.06; H, 7.41.

(*Z*)-Deca-2-en-6,8-diyn-1-ol (53). The title compound was obtained in 91% yield from **52**, according to the general procedure C: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.22−2.40 (m, 4H), 4.13−4.18 (m, 2H), 5.50−5.59 (m, 1H), 5.66−5.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1, 19.4, 26.2, 58.3, 64.2, 65.9, 73.6, 75.8, 130.0, 130.4; GC-MS EI m/z (%) 148 (1) [M^+], 147 (7), 129 (21), 128 (17), 115 (41), 105 (18), 91 (25), 77 (45), 63 (15), 5 1(100). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.02; H, 8.18.

(2*E*,4*Z*)-*N*-Isobutyldodeca-2,4-dien-8,10-diynamide (3). Method A: The title compound was obtained in 60% yield from **53**, according to the general procedure M: white solid; mp = 74−76 °C; lit[9] mp = 74 °C. Method B: **3** was obtained in 18% yield (and 5% of **55**) from **51** according to a procedure adapted from general procedure J using (*E*)-diphenyl 4-(isobutylamino)-4-oxobut-2-enylphosphonate (**54**). **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.8 Hz, 6H), 1.80 (sept, J = 6.8 Hz, 1H), 1.89 (t, J = 1.2 Hz, 3H), 2.32−2.38 (m, 2H), 2.48−2.55 (m, 2H), 3.17 (t, J = 6.4 Hz, 2H), 5.56 (brs, 1H), 5.81 (dt, J = 7.6, 10.8 Hz, 1H), 5.83 (d, J = 14.8 Hz, 1H), 6.15 (t, J = 11.6 Hz, 1H), 7.49 (ddd, J = 0.8, 11.6, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.2, 19.4, 20.1, 26.8, 28.6, 46.7, 64.4, 66.2, 73.5, 75.3, 124.8, 127.8, 135.3, 136.8, 166.1; GC-MS EI m/z (%): 148 (6) [M^+], 242 (9), 215 (3), 186 (5), 171 (19), 152 (4), 143 (22), 128 (62), 115 (20), 77 (54), 57 (100). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.46; H, 8.70; N, 5.61. **55**: ^{1}H NMR (400 MHz, C_6D_6) δ 0.81 (d, J = 6.7 Hz, 6H), 1.35 (s, 3H), 1.71 (sept, J = 6.7 Hz, 1 H), 1.90−1.94 (m, 4H), 3.13 (dd, J = 6.5, 6.5 Hz, 2H), 5.60 (dt, J = 15.2, 6.5 Hz, 1H), 5.78 (d, J = 15.0 Hz, 1H), 5.98 (dd, J = 11.0, 15.1 Hz, 1H), 6.04 (t, J = 5.8 Hz, 1H), 7.41 (dd, J = 11.0, 15.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 3.2, 18.6, 19.9, 28.7, 31.5, 46.8, 65.3, 66.9, 73.4, 75.4, 123.9, 138.7, 138.9, 165.7; HR-MS m/z calcd M^+ for $C_{16}H_{21}NO$ 243.1623, found 243.1620.

(*Z*)-*N*-Isobutylundeca-2-en-8,10-diynamide (11). Oxalyl chloride (0.99 g, 0.78 mmol) was added to CH_2Cl_2 (10 mL), and the solution was cooled to −78 °C. Next, DMSO (0.80 g, 10.2 mmol) was added dropwise, and after complete addition, the solution was stirred for a further 2 min before the dropwise addition of alcohol (0.35 g, 2.6 mmol) in CH_2Cl_2 (5 mL). Stirring was continued at −78 °C for 30 min, and then the reaction was warmed to −10 °C for 5 min. The mixture was recooled to −78 °C, and Et_3N (4.96 g, 49 mmol) was added. The reaction was allowed to return to room temperature and washed with water (20 mL), then 1 M HCl (20 mL), and then once more with water (20 mL). The organic layer was dried ($MgSO_4$), and the dichloromethane removed to give the crude aldehyde which was diluted with tetrahydrofuran (5 mL) and used in the next step without delay. Meanwhile, a 1 M solution of NaHMDS in tetrahydrofuran (2.77 mL, 2.77 mmol) was slowly added to a stirred suspension of (diphenylphosphonato)acetamide reagent **57** (0.98 g, 2.8 mmol) in tetrahydrofuran (25 mL) at −78 °C. Stirring was continued for a further 20 min, and then the crude aldehyde solution prepared from the previous step was slowly added. Stirring was continued at −78 °C for 1 h, then saturated NH_4Cl solution (20 mL) was added and the organic phase was separated. The aqueous phase was extracted into ethyl acetate (2 × 50 mL), and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and stripped of solvent. Flash chromatographic purification (20% EtOAc in hexanes, silica) yielded alkyl amides **11** (230 mg, 39%) and **2** (20 mg, 25%). Spectroscopic data were consistent with a literature report.[17] **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 6H), 1.48−1.60 (m, 4H), 1.77 (sept, J = 6.8 Hz, 1H), 1.93 (t, J = 1.3 Hz, 1H), 2.26 (dt, J = 1.3, 6.8 Hz, 2H), 2.66 (dt, J = 1.9, 7.6 Hz, 2H), 3.10 (ddt, J = 6.2, 6.4 Hz, 2H), 5.47 (brs, 1H), 5.67 (dt, J = 1.6, 11.5 Hz, 1H), 5.94 (dt, J = 7.6, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 20.1, 27.5, 27.9, 28.3, 28.5, 46.6, 64.5, 64.8, 68.5, 78.2, 122.7, 144.6, 166.5; GC-MS EI m/z (%) 231 (0.6) [M^+], 202 (6), 131 (58), 117 (73), 104 (24), 91 (85), 68 (35), 63 (55), 57 (72), 55 (60), 41 (100); HR-MS m/z calcd $[M + Na]^+$ for $C_{15}H_{21}NONa$ 254.1521, found 254.1515.

(*E*)-Ethyl hept-2-en-6-ynoate (58). The title compound was obtained in 89% yield from pent-4-yn-1-ol, according to the general procedure K: purification by distillation (95−97 °C, 10 mmHg), colorless oil. Spectroscopic data were consistent with a literature report.[51] **(*E*)-hept-2-en-6-yn-1-ol (59)**: The title compound was obtained in 91% yield from **58**, according to the general procedure C. Spectroscopic data were consistent with a literature report.[33]

(*E*)-10-Methylundeca-2-en-6,8-diyne-1,10-diol (60). The title compound was obtained in 76% yield from **59**, according to the general procedure F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 6H), 1.94 (brs, 1H), 2.22−2.28 (m, 2H), 2.32−2.37 (m, 2H), 4.07−4.10 (m, 2H), 5.67−5.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 30.7, 31.1, 63.3, 64.9, 65.4, 67.1, 80.2, 80.7, 130.1, 130.7; GC-MS EI m/z (%) 173 (1), 159 (2), 131 (5), 115 (7), 91 (9), 77 (7), 43 (100); HR-MS m/z calcd $[M + Na]^+$ for $C_{12}H_{16}O_2Na$ 215.1048, found 215.1043. Anal. Calcd for $C_{12}H_{16}O_2$: C, 80.56; H, 7.51. Found: C, 80.45; H, 7.35.

(*E*)-Nona-2-en-6,8-diyn-1-ol (61). The title compound was obtained in 75% yield from **60**, according to the general procedure F,

and was used in the next step without delay: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (brt, J = 1.1 Hz, 1H), 2.28−2.35 (m, 4H), 4.11 (brs, 2H), 5.71−5.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.0, 20.9, 30.5, 60.3, 63.3, 64.7, 129.8, 130.8; GC-MS EI m/z (%) 134 (M^+ 3), 133 (30), 115 (51), 103 (37), 91 (60), 77 (56), 63 (100).

(2*Z*,4*E*)-*N*-Isobutylundeca-2,4-dien-8,10-diynamide (12) and (2*E*,4*E*)-*N*-Isobutylundeca-2,4-dien-8,10-diynamide (62). Following a procedure similar to that for **11**, the title compounds were obtained in 83% yield from **61** (**12**, 62% and **62**, 21%). **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 6H), 1.78 (sept, J = 6.8 Hz, 1H), 1.95 (brs, 1H), 2.34−2.41 (m, 4H), 3.10 (dd, J = 6.8, 6.8 Hz, 2H), 5.51 (d, J = 11.3 Hz, 1H), 5.61 (brs, 1H), 5.94 (dt, J = 6.3, 15.4 Hz, 1H), 6.35 (t, J = 11.4 Hz, 1H), 7.49 (dd, J = 11.2, 15.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.1, 28.5, 29.7, 31.2, 46.7, 64.9, 65.3, 68.3, 77.2, 119.7, 128.3, 139.5, 140.6, 166.3; ^{1}H NMR (400 MHz, C_6D_6) δ 0.72 (d, J = 6.7 Hz, 6H), 1.46 (t, J = 1.2 Hz, 1H), 1.54 (sept, J = 6.7 Hz, 1H), 1.74−1.78 (m, 2H), 1.84−1.90 (m, 2H), 2.96 (dd, J = 6.3, 6.8 Hz, 2H), 4.61 (brs, 1H), 5.06 (brd, J = 11.3 Hz, 1H), 5.69 (ddt, J = 0.8, 7.0, 15.4 Hz, 1H), 6.12 (dt, J = 0.8, 11.3 Hz, 1H), 8.00 (ddq, J = 1.4, 11.3, 15.4 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.8, 20.1, 28.9, 31.1, 46.6, 65.3, 66.1, 68.9, 77.6, 120.2, 129.3, 139.2, 140.7, 165.4; GC-MS EI m/z (%) 229 (1) [M^+], 214 (3), 186 (5), 172 (6), 166 (40), 152 (59), 128 (100), 115 (30), 96 (24), 66 (93), 57 (60), 41 (58); HR-MS m/z calcd [M + Na]$^+$ for $C_{15}H_{19}NONa$ 252.1364, found 252.1359. **62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.7 Hz, 6H), 1.78 (sept, J = 6.7 Hz, 1H), 1.96 (brs, 1H), 2.36−2.38 (m, 4H), 3.14 (dd, J = 6.7, 6.7 Hz, 2H), 5.54 (brs, 1H), 5.79 (d, J = 15.1 Hz, 1H), 5.99−6.06 (m, 2H), 6.17 (dd, J = 10.8, 15.1 Hz, 1H), 7.15 (dd, J = 10.8, 15.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 20.1, 28.6, 31.2, 47.0, 65.0, 65.5, 68.2, 77.3, 123.1, 128.8, 139.1, 140.4, 166.2; GC-MS EI m/z (%) 229 (4), 228 (7), 214 (5), 157 (55), 128 (83), 110 (13), 66 (100), 41 (58); HR-MS m/z calcd [M + Na]$^+$ for $C_{15}H_{19}NONa$ 252.1364, found 252.1359.

(*E*)-Ethyl deca-2-en-6,8-diynoate (64). The title compound was obtained in 78% yield from **51**, according to the general procedure K: colorless oil; ^{1}H NMR (400 MHz, C_6D_6) δ 1.05 (t, J = 7.0 Hz, 3H), 1.41 (s, 3H), 1.82−1.97 (m, 4H), 4.10 (q, J = 7.0 Hz, 2H), 5.84 (d, J = 15.4 Hz, 1H), 6.93 (dt, J = 6.2, 15.4 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 3.2, 13.9, 17.7, 30.5, 59.7, 65.1, 67.1, 73.6, 74.7, 122.6, 145.6, 166.4; GC-MS EI m/z (%) 190 (0.8) [M^+], 161 (39), 145 (20), 133 (10), 115 (41), 105 (8), 91 (26), 77 (77), 51 (100). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.40; H, 6.97.

(*E*)-Deca-2-en-6,8-diyn-1-ol (65). The title compound was obtained in 90% yield from **64**, according to the general procedure C: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (s, 1H), 1.88 (t, J = 2.3 Hz, 3H), 2.22−2.33 (m, 4H), 4.09 (d, J = 5.0 Hz, 2H), 5.67−5.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1, 19.1, 30.9, 63.3, 64.3, 65,8, 73.3, 75.7, 130.2, 130.6; GC-MS EI m/z (%) 148 (1.5) [M^+], 147 (12), 133 (16), 115 (29), 105 (29), 91 (41), 77 (65), 51 (100). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.94; H, 8.26.

(2*E*,6*Z*,8*Z*)-Deca-2,6,8-trien-1-ol (66). The title compound was obtained in 91% yield from **65**, according to the general procedure I: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 1H), 1.75 (d, J = 8.4 Hz, 3H), 2.12−2.19 (m, 2H), 2.24−2.32 (m, 2H), 4.08 (d, J = 4.3 Hz, 2H), 5.45 (dt, 1H, J = 7.1, 10.4 Hz), 5.55 (dq, 1H, J = 7.0, 10.4 Hz), 5.63−5.74 (m, 2H), 6.22−6.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 27.0, 32.1, 63.5, 123.8, 124.4, 126.4, 129.4, 130.5, 132.3; GC-MS EI m/z (%) 152 (1) [M^+], 134 (1), 119 (4), 105 (2), 81 (100), 80 (63), 53 (48), 41 (94). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.70; H, 10.87.

(2*E*,4*E*,8*Z*,10*Z*)-*N*-Isobutyldodeca-2,4,8,10-tetraenamide (5). The title compound was obtained in 51% yield from **66**, according to the general procedure L: white solid; mp = 74−76 °C. Spectroscopic data were consistent with a literature report:[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 6H), 1.74 (dd, J = 1.6, 7.2 Hz, 3H), 1.78 (sept, J = 6.8 Hz, 1H), 2.20−2.33 (m, 4H), 3.16 (t, J = 6.8 Hz, 2H), 5.42 (dt, J = 6.8, 11.4 Hz, 1H), 5.50−5.60 (m, 2H), 5.77 (d, J = 15.2 Hz, 1H), 6.06 (dt, J = 6.9, 15.2 Hz, 1H), 6.15 (dd, J = 10.4, 15.2 Hz, 1H), 6.24 (ddq, J = 1.6, 11.0, 11.0 Hz, 1H), 6.30 (dd, J = 11.0, 11.0 Hz, 1H), 7.18 (dd, J = 10.8, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 20.1, 26.7, 28.6, 32.8, 46.9, 122.2, 124.1, 124.2, 126.7, 128.7, 130.0, 141.0, 141.8, 166.3. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.66; H, 10.31; N, 5.58. The minor (2*Z*,4*E*,8*Z*,10*Z*)-isomer **67** was also obtained in 4% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 6H), 1.72 (dd, J = 1.6, 7.2 Hz, 3H), 1.78 (sept, J = 6.4 Hz, 1H), 2.20−2.30 (m, 4H), 3.10 (dd, J = 6.4, 6.4 Hz, 2H), 5.38−5.56 (m, 2H), 5.49 (d, J = 10.8 Hz, 1H), 5.69 (brs, 1H), 5.93 (dt, J = 6.0, 15.2 Hz, 1H), 6.18−6.30 (m, 2H), 6.34 (dd, J = 11.0, 11.0 Hz, 1H), 7.48 (ddd, J = 1.2, 10.8, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 20.1, 26.9, 28.5, 32.8, 46.7, 118.8, 123.9, 124.3, 126.4, 127.4, 130.3, 141.2, 142.3, 166.5; HR-MS m/z calcd [M + Na]$^+$ for $C_{16}H_{25}NONa$ 270.1834, found 270.1828.

(2*Z*,8*Z*)-Deca-2,8-dien-6-yn-1-ol (70). The title compound was obtained in 91% yield from **45**, according to the general procedure H: ^{1}H NMR (300 MHz, C_6D_6) δ 0.8 (s, 1H), 1.79 (dd, J = 0.6, 6.4 Hz, 3H), 1.98−2.18 (m, 4H), 3.91 (brd, J = 6.0 Hz, 2H), 5.32−5.70 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 15.8, 20.0, 27.0, 58.4, 78.3, 94.5, 110.9, 130.0, 131.0, 137.0. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.45; H, 9.00.

(2*E*,4*Z*,10*Z*)-*N*-Isobutyldodeca-2,4,10-trien-8-ynamide (6). The title compound was obtained as a colorless oil in 54% yield from **70**, according to the general procedure L. Spectroscopic data were consistent with a literature report:[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, 6H, J = 6.8 Hz), 1.80 (sept, J = 6.8 Hz, 1H), 1.83 (dd, J = 1.5, 7.2 Hz, 3H), 2.43−2.59 (m, 4H), 3.16 (t, J = 6.5 Hz, 2H), 5.43 (dq, J = 1.6, 10.8 Hz, 1H), 5.56 (br s, 1H), 5.84 (d, J = 15.0 Hz, 1H), 5.84−5.91 (m, 2H), 6.16 (dd, J = 10.5, 10.5 Hz, 1H), 7.53 (ddd, J = 1.2, 14.8, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 19.7, 20.1, 27.5, 28.6, 46.9, 78.0, 93.4, 110.1, 124.5, 127.5, 135.6, 137.4, 137.6, 166.1. ^{1}H NMR in C_6D_6 enabled complete resolution of all alkene protons: ^{1}H NMR (400 MHz, C_6D_6) δ 0.73 (d, J = 6.8 Hz, 6H), 1.58 (sept, J = 6.8 Hz, 1H), 1.79 (dd, J = 1.6, 6.8 Hz, 3H), 2.07−2.20 (m, 4H), 3.02 (dd, J = 6.4, 6.8 Hz, 2H), 4.84 (brs, 1H), 5.45 (d, J = 15.0 Hz, 1H), 5.51 (dq, J = 1.6, 10.8 Hz, 1H), 5.64 (dq, J = 6.8, 10.8 Hz, 1H), 5.73 (dt, J = 7.2, 10.8 Hz, 1H), 6.07 (dd, J = 11.0, 11.0 Hz, 1H), 7.85 (ddd, J = 1.2, 11.6, 14.8 Hz, 1H); HR-MS m/z calcd [M + Na]$^+$ for $C_{16}H_{23}NONa$ 268.1677, found 268.1677.

(2*E*,8*E*)-Deca-2,8-dien-6-yn-1-ol (71). The title compound was obtained as a colorless oil in 87% yield from **59**, according to the general procedure H: ^{1}H NMR (500 MHz, C_6D_6) δ 0.89 (s, 1H), 1.51 (dd, J = 1.7, 6.8 Hz, 3H), 2.14−2.20 (m, 2H), 2.26−2.32 (m, 2H), 3.89 (d, J = 5.0 Hz, 2H), 5.52−5.66 (m, 3H), 6.14 (dq, J = 6.4, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 17.2, 18.7, 30.9, 62.3, 79.3, 86.9, 110.9, 128.8, 130.2, 136.9. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.09; H, 9.61.

(2*E*,6*Z*,8*E*)-Deca-2,6,8-trien-1-ol (72). The title compound was obtained in 92% yield from **71**, according to the general procedure I: colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.84 (s, 1H), 1.70 (ddd, J = 0.54, 1.0, 6.7 Hz, 3H), 2.06−2.11 (m, 2H), 2.22−2.30 (m, 2H), 3.92 (d, J = 4.1 Hz, 2H), 5.36 (dt, J = 6.9, 10.9 Hz, 1H), 5.57−5.60 (m, 2H), 5.65 (dq, J = 6.7, 14.1 Hz, 1H), 6.13 (t, J = 10.9 Hz, 1H), 6.42−6.49 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 18.1, 27.5, 32.4, 63.3, 127.4, 128.6, 129.2, 129.4, 130.4, 130.9; GC-MS EI m/z (%) 152 (1.0) [M^+], 134 (1), 121 (3), 105 (2), 81 (100), 79 (47), 55 (11), 53 (37); HR-MS m/z calcd [M + Na]$^+$ for $C_{10}H_{16}O$ 152.1201, found 152.1204.

(2*E*,4*E*,10*E*)-*N*-Isobutyldodeca-2,4,10-trien-8-ynamide (7). The title compound was obtained in 52% yield from **71**, according to the general procedure L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.8 Hz, 6H), 1.75 (dd, J = 1.5, 7.2 Hz, 3H), 1.85 (sept, J = 6.8 Hz, 1H), 2.30−2.50 (m, 4H), 3.18 (t, J = 6.8 Hz, 2H), 5.45 (dq, J = 2.0, 15.0 Hz, 1H), 5.49 (brs, 1H), 5.78 (d, J = 15.2 Hz, 1H), 6.05 (dq, J = 6.4, 15.0 Hz,

1H), 6.10 (dt, J = 6.0, 15.2 Hz, 1H), 6.19 (dd, J = 10.4, 15.2 Hz, 1H), 7.18 (dd, J = 10.4, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.1, 20.1, 28.6, 32.2, 46.9, 80.0, 86.9, 110.8, 122.6, 129.2, 138.5, 140.4, 140.8, 166.2; GC-MS EI m/z (%) 245 (4) [M^+], 244 (5), 230 (2), 173 (6), 167 (11), 145 (22), 117 (22), 91 (18), 77 (79), 57 (100). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.94; H, 9.59; N, 5.68.

(2*E*,4*E*,8*Z*,10*E*)-*N*-Isobutyldodeca-2,4,8,10-tetraenamide (8). The title compound was obtained in 50% yield from **72**, according to the general procedure L: white solid; mp = 66−68 °C. Spectroscopic data were consistent with a literature report:[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 6H), 1.78 (dd, J = 2.0, 6.8 Hz, 3H), 1.79 (sept, J = 6.8 Hz, 1H), 2.22−2.31 (m, 4H), 3.17 (t, J = 6.8 Hz, 2H), 5.25 (dt, J = 7.6, 10.8 Hz, 1H), 5.45 (brs, 1H), 5.70 (dq, J = 6.8, 15.2 Hz, 1H), 5.75 (d, J = 14.8 Hz, 1H), 5.97 (dd, J = 10.8, 10.8 Hz, 1H), 6.07 (dt, J = 6.4, 15.2 Hz, 1H), 6.16 (dd, J = 10.4, 15.2 Hz, 1H), 6.29 (ddt, J = 1.2, 11.2, 15.2 Hz, 1H), 7.19 (dd, J = 10.4, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 20.1, 26.9, 28.6, 33.0, 46.9, 122.1, 126.7, 127.9, 128.7, 129.3, 129.8, 141.1, 142.0, 166.3; GC-MS EI m/z (%) 247 (1) [M^+], 167 (16), 152 (5), 147 (2), 128 (8), 115 (12), 81 (100), 79 (43), 66 (45), 57 (36), 53 (29), 41 (55). Anal. Calcd: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.62; H, 10.44; N, 5.56. The minor (2*Z*,4*E*,8*Z*,10*E*)-isomer **76** was also obtained in 15% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6H), 1.74 (dd, J = 1.2, 6.7 Hz, 3H), 1.78 (sept, J = 6.6 Hz, 1H), 2.20−2.31 (m, 4H), 3.11 (dd, J = 6.2, 6.8 Hz, 2H), 5.25 (dt, J = 6.6, 10.6 Hz, 1H), 5.45 (d, J = 11.3 Hz, 1H), 5.51 (brs, 1H), 5.65 (dq, J = 7.0, 15.0 Hz, 1H), 5.90−5.98 (m, 2H), 6.23 −6.31 (m, 1H), 6.35 (t, J = 11.1 Hz, 1H), 7.19 (ddq, J = 1.4, 11.3, 15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 20.1, 27.1, 28.6, 33.0, 46.7, 118.7, 126.9, 127.4, 128.2, 129.2, 129.5, 141.3, 142.5, 166.5; GC-MS EI m/z (%) 247 (2) [M^+], 232 (2) 167 (11), 152 (24), 115 (18), 81 (100), 66 (55), 57 (54), 41 (64); HR-MS m/z calcd [M + Na]$^+$ for $C_{16}H_{25}NONa$ 270.1834, found 270.1828.

(2*E*,4*E*,8*E*,10*Z*)-*N*-Isobutyldodeca-2,4,8,10-tetraenamide (9). The title compound was obtained in 63% yield from **79**,[6] according to the general procedure L: white solid; mp =78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 6H), 1.73 (dd, J = 2.0, 6.8 Hz, 3H), 1.78 (sept, J = 6 0.8 Hz, 1H), 2.20−2.30 (m, 4H), 3.15 (t, J = 6.8 Hz, 2H), 5.39 (dq, J = 7.5, 11.0 Hz, 1H), 5.57−5.66 (m, 2H), 5.77 (d, J = 14.8 Hz, 1H), 5.95 (dd, J = 11.0, 11.5 Hz, 1H), 6.05 (dt, J = 6.7, 14.8 Hz, 1H), 6.15 (dd, J = 10.8, 15.2 Hz, 1H), 6.34 (dd, J = 10.8, 15.2 Hz, 1H), 7.18 (dd, 1H, J = 10.4, 14.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 20.1, 28.6, 32.1, 32.8, 46.9, 122.1, 124.6, 126.1, 128.7, 129.2, 132.6, 141.0, 141.8, 166.3; GC-MS EI m/z (%) 247 (2.4) [M^+], 167 (15), 152 (4), 128 (2), 115 (10), 81 (100), 79 (45), 66 (35), 57 (32). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66; O, 6.47. Found: C, 77.36; H, 10.13; N, 5.84. The minor (2*Z*,4*E*,8*E*,10*Z*)-isomer **80** was also obtained in 11% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 6H), 1.71 (dd, J = 1.5, 7.1 Hz, 3H), 1.78 (sept, J = 6 0.8 Hz, 1H), 2.19−2.30 (m, 4H), 3.11 (dd, J = 6.3, 6.8 Hz, 2H), 5.32−5.41 (m, 1H), 5.46 (d, J = 11.5 Hz, 1H), 5.52 (brs, 1H), 5.62 (dt, J = 6.7, 15.0 Hz, 1H), 5.90−5.97 (m, 2H), 6.28−6.36 (m, 1H), 6.35 (t, J = 11.4 Hz, 1H), 7.18 (ddq, 1H, J = 1.5, 11.3, 15.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 20.1, 28.6, 32.2, 32.7, 46.7, 118.8, 124.4, 126.0, 127.4, 129.3, 133.0, 141.3, 142.4, 166.4; GC-MS EI m/z (%) 247 (2) [M^+], 167 (8), 152 (15), 81 (100), 79 (12), 66 (71), 57 (48), 55 (19), 41 (96); HR-MS m/z calcd [M + Na]$^+$ for $C_{16}H_{25}NONa$ 270.1834, found 270.1828.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and for alkyl amides **1**−**13**, **21**, **23**, **28**, **55**, **62**, **67**, **73**, and **80**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +61 (7) 33653825. Fax: + 61 (7) 3365 4299. E-mail: j.devoss@uq.edu.au.

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