JOC Article

A New Method for the Preparation of 1,5-Diynes. Synthesis of (4*E*,6*Z*,10*Z*)-4,6,10-Hexadecatrien-1-ol, the Pheromone Component of the Cocoa Pod Borer Moth *Conopomorpha cramerella*

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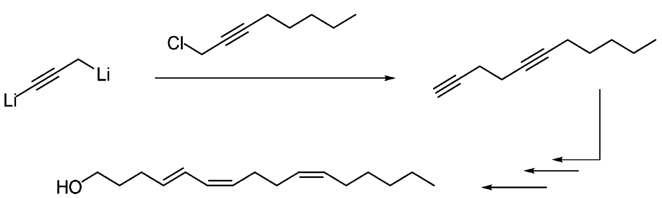

A new method for the synthesis of 1,5-diynes, from the reaction of 1,3-dilithiopropyne and propargyl chlorides, was developed. This new methodology was used to prepare (4*E*,6*Z*,10*Z*)-4,6,10-hexadecatrien-1-ol, one of the pheromone components of the cocoa pod borer moth *Conopomorpha cramerella*, in 51% overall yield.

Introduction

1,5-Unsaturated compounds such as 1,5-dienes are widely spread in nature and many of them have important biological activity. It is possible to find these structural units in terpenoids,[1] juvenile hormones,[2] and insect pheromones.[3] Many methods for the synthesis of 1,5-dienes have been reported.[4] Attractive synthetic precursors of (*Z*,*Z*)-1,5-dienes are the corresponding 1,5-diynes.

Some methods for the preparation of functionalized 1,5-diynes have been reported; however, they are cumbersome.[5] Dai and co-workers reported[5c,d] the synthesis of some functionalized 1,5-diynes from the palladium-catalyzed reaction of (*Z*)-2-bromocinnamaldehyde with terminal acetylenes to obtain the corresponding 2-alkynyl cinnamaldehyde, which upon reaction with lithium acetylides afforded the functionalized 1,5-diyne-3-ol. This method required the preparation of the starting material (*Z*)-2-bromocinnamaldehyde.

An attractive alternative for the synthesis of 1,5-diynes is a three-carbon homologation (propagylation) of propargyl halides. Negishi and co-workers reported[6] the preparation of 1,5-enynes in good yields, from the coupling reaction of 1,3-dilithio-3-thiophenylpropyne (prepared from 3-thiophenyl-1-propyne and *n*-BuLi) with allylic bromides, followed by reductive elimination (Li/$NH_3(l)$) of the thiophene group. Although this procedure allows the preparation of 1,5-enynes in good yields, it is incompatible with groups sensitive to the lithium reduction conditions such as disubstituted acetylenes, thus its application in the preparation of 1,5-diynes is restricted.

We have previously reported an easy preparation of 1,3-dilithiopropyne **1** (also known as propargylide), from allene, and its regioselective reaction with allylic halides[7] and carbonyl compounds,[8] and recently we reported a new preparation of this dianion **1**, from propargyl bromide[9] (Scheme 1). We envisioned that regioselective reaction of this dianion (**1**) with propargyl halides (**2**) could represent an easy access to 1,5-diynes (**3**), according to Scheme 1. Thus, we are reporting herein an efficient, one-pot reaction for the preparation of 1,5-diynes, from the coupling of 1,3-dilithiopropyne **1**, with propargyl halides. We applied this new methodology to develop an efficient synthesis of (4*E*,6*Z*,10*Z*)-4,6,10-hexadecatrien-

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[3] Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845.

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10.1021/jo048019y CCC: $30.25

SCHEME 1. Synthesis of 1,5-Undecadiyne 3

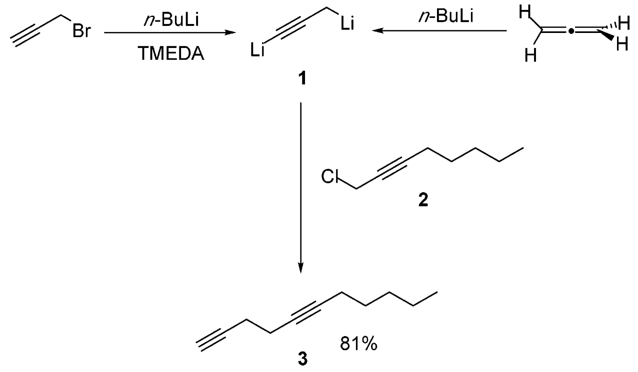


TABLE 1. Reaction of 1 with 2 (see Scheme 1) under Different Reaction Conditions

entry	method[a]	concn of **1** (mol/L)	**1**:**2** ratio	% yield of **3**
1	A	0.33	2.1	8[b]
2	B	0.34	1.7	27[c]
3	B	0.34	2.4	71[c]
4	B	0.48	2.4	81[c]

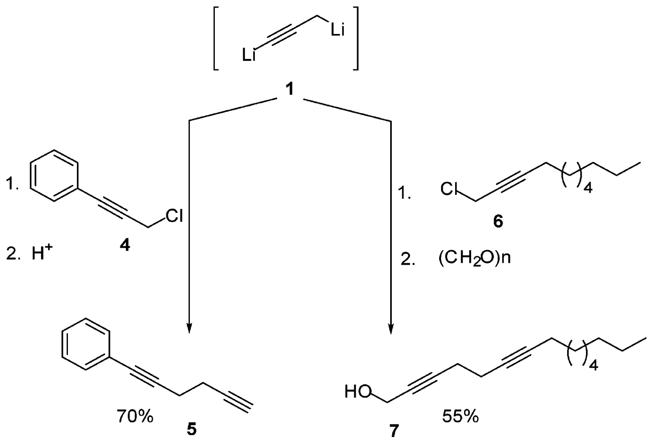
[a] Method of preparation of **1** (Scheme 1): (A) propargyl bromide + *n*-BuLi (TMEDA);[9] (B) allene + *n*-BuLi.[7] [b] Calculated by ^{1}H NMR. [c] Percent yield of chromatographically isolated compound.

1-ol (**13**), one of the pheromone components of the cocoa pod borer moth *Conopomorpha cramerella*.

Results and Discussion

Preliminary reactions involved treatment, at −78 °C, of 1-chloro-2-octyne (**2**) with 1,3-dilithiopropyne (**1**), which was prepared by the treatment of propargyl bromide with 2 equiv of *n*-butyllithium in the presence of TMEDA[9] (Scheme 1). In this case, ^{1}H NMR analysis of the crude reaction mixture showed the presence of traces of the expected product 1,5-undecadiyne (**3**) (Table 1, entry 1), and several unidentified byproducts, including allene derivatives, whose formation might have been favored by the presence of TMEDA. It has been reported that when alkylation (with *n*-heptyl iodide) of metalated allene (from allene and *n*-butyllithium) is performed in a polar coordinating media such as THF and TMEDA, a mixture of the corresponding substituted allene and acetylene products (1.2:1 ratio) is obtained in poor yields,[10] and as the polarity of the solvent increases the allene derivative is favored at the expense of the corresponding acetylene product. It is also known that coordinating agents such as ethylenediamine diminish the reactivity of carbanions as lithium acetylide.[11] Because of these results, the reaction was next undertaken in a less polar solvent system, and 1,3-dilithiopropyne (**1**) was prepared by the reaction of allene and *n*-butyllithium in a solvent mixture of ether:hexanes (1:1) as previously reported.[7] Thus, allene was treated with *n*-BuLi (0.7 equiv) at −78 °C, and the reaction mixture was allowed to warm to −15 °C, at which temperature a heavy precipitate, presumably 1,3-dilithipropyne (**1**), formed (Cn $\sim$ 0.34 mol/L), and it was reacted with 1-chloro-2-octyne (**2**) and stirred at room temperature for 12 h. After the usual workup and purification by column chromatography, 1,5-undecadiyne **3** was obtained in 27% yield (Table 1, entry 2). In this experiment a significant amount of unreacted starting material **2** was detected (70% by ^{1}H NMR), thus the molar ratio between dianion **1** and halide **2** was increased from 1.7 to 2.4; in this case the yield of diyne **3** increased to 71% (Table 1, entry 3). When the reaction was repeated increasing the molar concentration of 1,3-dilithiopropyne (**1**), from 0.34 M to 0.48 M, diyne **3** was isolated in 81% yield with a very high purity (Table 1, entry 4). In this case all the starting material **2** was consumed.

SCHEME 2. Synthesis of Functionalized 1,5-Diynes



To show the versatility of this new methodology, diynes **5** and **7** were prepared (Scheme 2). Reaction of 1,3-dilithiopropyne (**1**) with 3-chloro-1-phenylpropyne (**4**), under the same optimized conditions described before (Table 1, entry 4), afforded, after protonolysis, 1-phenyl-1,5-hexadiyne (**5**) in 70% isolated yield (Scheme 2).

Coupling reactions of propargylide **1** are highly regioselective. Depending on the "hardness" of the electrophile, it is possible to react 1,3-dilithiopropyne (**1**) selectively by its sp^{3} or sp carbon, or through the sp^{2} carbon of the rearranged allene species.[8,9] To show the selectivity of this methodology, functionalized diyne **7** was prepared (Scheme 2). Thus, dianion **1** was reacted with 1-chloro-2-undecadiyne **6** followed by addition of paraformaldehyde to obtain, after the usual workup and column chromatography purification, 2,6-pentadecadiyne-1-ol (**7**) in 55% yield and in a one-pot reaction.

We decided to apply this new methodology to the synthesis of (4*E*,6*Z*,10*Z*)-hexadecatrien-1ol (**13**), one of the pheromone components of the cocoa pod borer moth *Conopomorpha cramerella*. This insect constitutes the most serious pest of cocoa plantations in Southeast Asia.[12] Its life cycle starts when the eggs are laid on the pod surface of the cocoa plantations (this cycle lasts for 2−7 days), and once in the larva stage, it tunnels the pod surface until it reaches the sclerotic layer of the husk, where it feeds, causing scarification and sticking of the beans. Damage to the funicles of pods results in beans that are malformed and under sized, significantly reduc-

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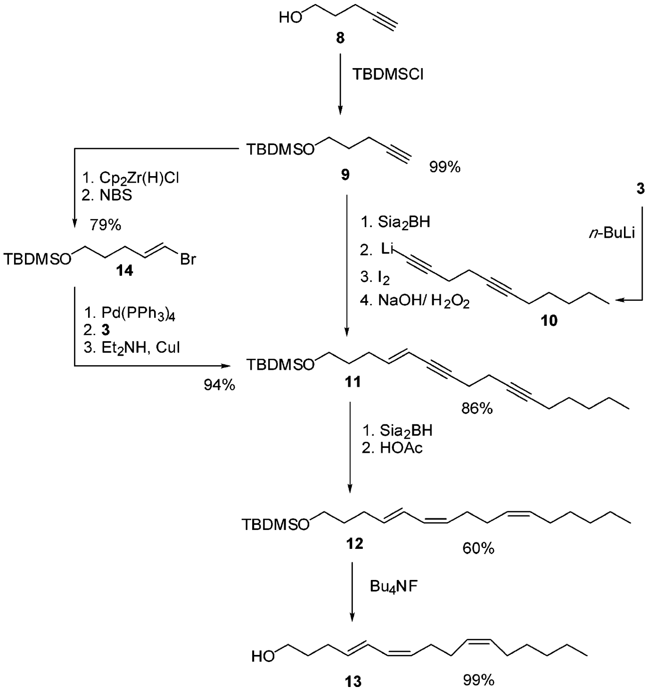
(10) Calzada, J. G. Ph.D. Thesis, The University of Alberta, Canada, 1974, p 8.

(11) Stowell, J. C. *Carbanions in Organic Synthesis*; John Willey & Sons: New York, 1979; p 78.

(12) Beevor, P. S.; Cork, A.; Hall, D. R.; Nesbitt, B. F.; Day, R. K.; Mumford, J. D. *J. Chem. Ecol.* **1986**, *12*, 1.

SCHEME 3. Synthesis of (4*E*,6*Z*,10*Z*)-4,6,10-Hexadecatrien-1-ol (13)



ing quality and thus the value of processed beans. Feeding in pods also causes them to yellow or ripen unevenly and prematurely, confusing ripeness standards for harvesting.[13] Losses can be in excess of 50% of the crop.[12]

In 1985 Beevor and co-workers[12] isolated, identified, and synthesized the pheromone components of *Conopomorpha cramerella*. Here, a very long, nonstereospecific synthesis was used. Later, in 1992, Yen and co-workers[14] reported a shorter synthesis for this compound, in eight steps and with an overall yield of 32%.

We considered that the crucial step for the synthesis of trienol **13** is the stereospecific formation of the bond between carbons 5 and 6, thus we decided to perform this synthesis coupling two unit fragments with 5 and 11 carbon atoms (Scheme 3). Our synthesis started with the commercially available 4-pentyn-1-ol (**8**) (5 carbon unit), which was treated with *tert*-butyldimethylsilyl chloride to obtain the corresponding silyl ether **9**, in quantitative yield.[15] The silyl ether **9** was hydroborated with disiamylborane, followed by sequential treatment with 1-lithio-1,5-undecadiyne (**10**) (11 carbon unit; from 1,5-undecadiyne **3** and n-BuLi), iodine at −78 °C, and sodium hydroxide to afford stereospecifically the coupling product **11** in 86% yield.[16] Hydroboration of triple bonds of **11**, with disiamylborane at −20 °C, followed by treatment with acetic acid produced the corresponding triene **12**, in 60%, which upon treatment with Bu_4NF gave the desired (4*E*,6*Z*,10*Z*)-hexadecatrien-1-ol (**13**) quantitatively and with a very high stereochemical purity (>99%). Using this sequence, the trienol **13** was stereospecifically synthesized in 4 steps and with an overall yield of 51%.

Alternatively, product **11** was prepared by the Sonogashira's palladium cross coupling reaction[17] between (*E*)-5-bromo-4-pentenyl *tert*-butyldimethylsilyl ether (**14**) and 1,5-undecadiyne **3** (previously prepared, Scheme 1), using copper(I) as catalyst,[18] in 94% yield (Scheme 3). Vinyl bromide **14** was stereospecifically prepared by hydrozirconation of 4-pentynyl *tert*-butyldimethylsilyl ether (**9**) with Schwartz's reagent followed by treatment with NBS. With this alternative route, trienol **13** was obtained in 45% overall yield.

In conclusion, we reported herein a new procedure for the preparation of 1,5-diynes and functionalized derivatives in good yields. This new method allowed us to developed a new synthesis of (4*E*,6*Z*,10*Z*)-hexadecatrien-1-ol (**13**), one of the pheromone components of the cocoa pod borer moth *Conopomorpha cramerella*, in only 4 steps and with higher overall yield (51%) than those previously reported.[12,14]

Experimental Section

Typical Procedure for the Synthesis of 1,5-Diynes. Preparation of 1,5-Undecadiyne (3).[19] A dry 250-mL three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing addition funnel, and a dry ice condenser was charged with 50 mL of dry ethyl ether and 20 mL of dry hexanes and cooled to −78 °C. On a separate assembly, allene gas (density at −40 °C = 0.67 g/mL) from a compressed gas cylinder was condensed into a 10 mL graduated cylinder (cooled to −40 °C) equipped with a 14/20 standard taper joint attached to a Claisen adapter, a bubbler, and a dry ice condenser. After 9.0 mL (150 mmol) of allene had been collected, the adapter, bubbler, and condenser were removed and the graduated cylinder was capped with a rubber septum, the cooling bath was removed from the graduated cylinder, and allene was distilled into the reaction flask, using a double tipped needle. n-BuLi in hexanes (45.6 mL, 110 mmol) was added dropwise, from the addition funnel in 30 min, to the reaction flask and the reaction mixture was allowed to warm to −15 °C, where a white precipitate was formed and stirred at this temperature for 15 min. After this time, the reaction was cooled to −78 °C, 1-chloro-2-octyne (**2**; 3.3 g, 22.8 mmol) in ether (10 mL) was added, and the reaction mixture was allowed to warm to room temperature overnight. The mixture was added over ice, extracted with ether (3 × 30 mL), and dried ($MgSO_4$). After the desiccant was removed, the solvent was distilled using a Vigreaux column and the residue was purified by column chromathography, using hexane as eluent. The column chromatography fractions were concentrated by distillation using a 10 cm Vigreaux column to obtain 2.73 g (18.4 mmol) of diyne **3** (81% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, $J = 7.4$ Hz), 1.26−1.40 (m, 4H), 1.48 (tt, 2H, $J = 7.4, 7.4$ Hz), 2.00 (t, 1H, $J = 2.0$ Hz), 2.14 (tt, 2H, $J = 2.0, 7.4$ Hz), 2.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.5, 19.1, 19.4, 19.6, 22.7, 29.1, 31.4, 69.3, 78.4, 81.9, 83.4; IR (film) 3306, 2957, 2930, 2860, 2121, 1434, 1338, 1260, 1111, 727, 637 cm^{-1}; MS *m/e* (rel intensity) 148 (M^+, 0.1), 147 ($M^+ - H$, 0.7), 133 (5), 120 (2), 199 (11), 117 (4), 109 (15), 105 (31), 91 (100), 79 (17), 77 (16), 67 (22), 65 (13), 55 (10), 53 (9), 52 (7), 51 (7). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 87.24; H, 11.33.

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[15] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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[18] Ratovelama, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.

[19] The preparation of 1,5-undecadiyne (**3**) already has been described: (a) Ward, J. P.; van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 117. (b) Gunstone, F. D.; Lie Ken Jie, M. *Chem. Phys. Lipids* **1970**, 1.

(*E*)-4-Hexadecen-6,10-diynyl *tert*-Butyldimethylsilyl Ether (11): Procedure A (from 9). BH_3·THF (1 M solution, 5 mL, 5 mmol) was added into a 50 mL dry flask, cooled to 0 °C and under nitrogen. 2-Methyl-2-butene (2 M solution, 5 mL, 10 mmol) was added dropwise and the solution was stirred at this temperature for 1 h. After this time, the flask was cooled to −30 °C and a THF solution (5 mL) of 4-pentynyl *tert*-butyldimethylsilyl ether (**9**; 0.99 g, 5 mmol) was added dropwise, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 1 h. After this time the reaction mixture was cooled to −78 °C and treated with a THF solution of 1-lithio-1,5-undecadiyne (**10**) [prepared at −50 °C, from 1,5-undecadiyne (**3**; 0.741 g, 5 mmol) and *n*-BuLi (2.65 M, 1.9 mL, 5 mmol) in 7 mL of THF]. The mixture was allowed to warm from −78 °C to −50 °C and stirred at this temperature for 1.5 h. The mixture was cooled to −78 °C and a THF solution (10 mL) of I_2 (1.3 g, 5 mmol) was added and the solution was allowed to warm to 0 °C in 2.5 h. The mixture was treated with NaOH (3 M, 2 mL) and H_2O_2 (30%, 2 mL), stirred for 15 min, and extracted with ether (3 × 25 mL), and the organic extracts were washed with $NaHSO_3$ and dried (Na_2SO_4). The crude was purified by column chromathography, using Al_2O_3 as the stationary phase and mixtures of ether:hexane as eluant, to obtain 1.68 g of the product (86% yield).

Procedure B (from 14). A benzene solution (3 mL) of (*E*)-5-bromo-4-pentenyl *tert*-butyldimethylsilyl ether (**14**; 0.279 g, 1 mmol) was added to $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol), previously dissolved in benzene (5 mL), and the resulting mixture was stirred at room temperature for 30 min. After this time, the mixture was treated with 1,5-undecadiyne (**3**; 0.148 g, 1 mmol) dissolved in diethylamine (3 mL), followed by addition of CuI[20] (0.041 g, 0.2 mmol), and the resulting reaction mixture was stirred at room temperaure overnight. The crude reaction was treated with NH_4Cl solution, extracted with ether (3 × 25 mL), and dried (Na_2SO_4). After the solvent was evaporated in vacuo the product was purified by column chromatography to obtain 0.325 g of **11** (94% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 6H), 0.85 (m, 12H), 1.20−1.36 (m, 4H), 1.44 (tt, 2H, $J = 6.1, 6.1$ Hz), 1.55 (tt, 2H, $J = 6.9, 6.9$ Hz), 2.10 (m, 4H), 2.33 (tt, 2H, $J = 6.1, 2.1$ Hz), 2.43 (tt, 2H, $J = 6.5, 1.8$ Hz), 3.56 (t, 2H, 6.5 Hz), 5.42 (dtt, 1H, $J = 15.6, 1.8, 1.8$ Hz), 6.03 (dt, 1H, $J = 15.6, 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.1, 14.1, 18.4, 18.8, 19.3, 20.2, 22.4, 26.0, 28.8, 29.4, 31.1, 32.0, 62.3, 78.4, 79.8, 81.4, 87.1, 109.8, 143.1; IR (film) 2956, 2930, 2858, 1463, 1362, 1255, 1104, 954, 836, 776 cm^{-1}; HRMS (EI) mass calcd for $C_{22}H_{38}SiO$ 369.2590, found 369.2588.

(*E*)-5-Bromo-4-pentenyl *tert*-Butyldimethylsilyl Ether (14). A THF solution of acetylene (**9**; 0.495 g, 2.5 mmol) was added dropwise to a THF (15 mL) solution of $Cp_2Zr(H)Cl$ (1.03 g, 4 mmol), at room temperature under nitrogen, and the solution was stirred at this temperature for 30 min. After this time, NBS (0.66 g, 3.75 mmol) was added through a solid addition funnel[20] and stirring was continued for 50 min. The mixture was quenched by the addition of water, extracted with ether, and dired (Na_2SO_4). The solvent was evaporated in vacuo and the residue purified by column chromatography, using hexanes, to obtain 0.55 g of **14** (79%). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.61 (tt, 2H, $J = 7.2, 6.0$ Hz), 2.11 (tdd, 2H, $J = 7.2, 7.2, 1.2$ Hz), 3.61 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.3, 18.3, 25.9, 29.3, 31.6, 62.0, 104.4, 137.7; HRMS (EI) mass calcd for $C_{11}H_{23}SiOBr$ 279.0780, found 279.0779.

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Supporting Information Available: Copies of ^1H NMR and (or) ^{13}C NMR spectra of all compounds, and experimental procedures for the preparation of compounds **7**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] CuI (or NBS) was added under nitrogen using a solids addition funnel: Shriver, D. F.; Drezdon, M. A. *The Manipulation of Air-Sensitive Compounds*; John Wiley & Sons: New York, 1986; p 30.