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A Concise Li/liq. NH₃ Mediated Synthesis of (4*E*,10*Z*)-Tetradeca-4,10-dienyl Acetate: The Major Sex Pheromone of Apple Leafminer Moth, *Phyllonorycter ringoniella*

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Apple, originated from central Asia and Europe, is one of the widely cultivated tree fruit around the world that has become very important in both human diet and health aspects due to its exceptional nutrition and biological significance.[1] The commercial outcome of apple orchards is greatly affected by various insect pests like tufted apple bud moth (*Platynota idaeusalis* (Walker)), codling moth (*Cydia pomonella*) and light brown apple moth (*Epiphyas postvittana*) to name a few around the world. Even though, pesticides show efficient results in controlling these pests, they are having disadvantages owing to less nutrition and thus pheromones come in to more attention. Pheromones are chemical substances that secreted or excreted to elicit social response among the members of same species with opposite sex. To discover appropriate methods for the accurate estimation of insect numbers, development timing and control, the sex attractants have already been studied by several research groups. The apple leafminer moth, *Phyllonorycter ringoniella* (or *Lithocolletis ringoniella*), is a serious insect pest on apple trees with four to five generations a year in Korea, Japan and China.[2] The two components (4*E*,10*Z*)-tetradeca-4,10-dienyl acetate (*E*4,*Z*10-14:Ac; **1**) and (*Z*)-tetradec-10-enyl acetate (*Z*10-14:Ac; **1a**)[3] are identified in the female sex pheromone of apple leafminer moth (Figure 1). Major component in the blend of these two has found to be **1**, in examining male response (taxis, approach, and landing) of *P. ringoniella* that were observed in Korea, Japan and China.[4]

One needs to have good quantities of pheromones in order to understand the behavioral responses of insect pests that are studied in management programs, which is possible only by synthesis. The activity of such a synthetic pheromone is completely dependent on its stereochemical purity.[5] In general,
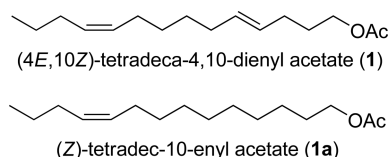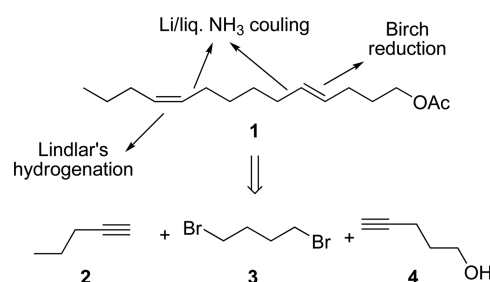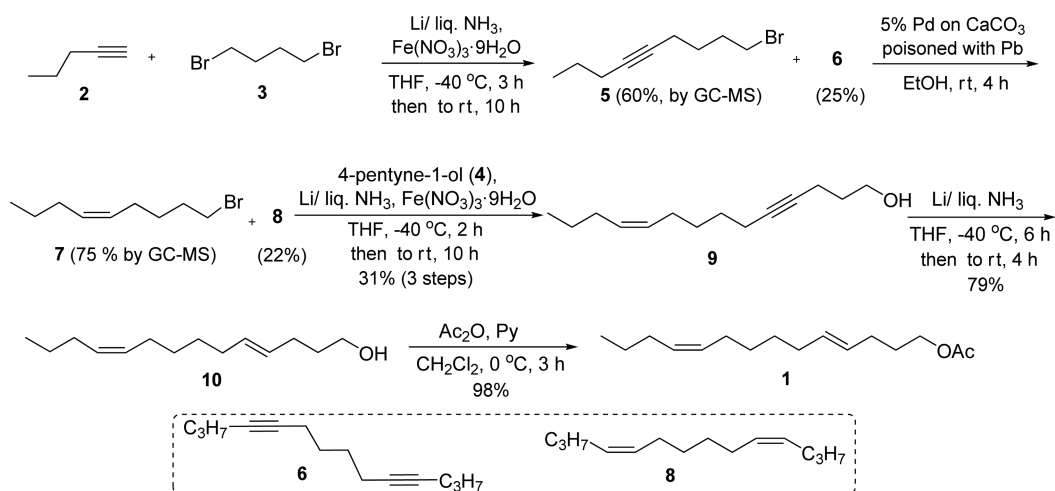
(*E*,*Z*)-diene structures are widespread in insect pheromones that are responsible for special functions,[6] but pose great challenges for their stereoselective synthesis. Only two direct reports are known to synthesize this pheromone and followed corresponding Wittig olefination methods and Claisen rearrangement to attain required stereochemistry of olefins.[2,7] However, these methods involve protections and de-protections that follow seven to ten step sequence to achieve target pheromone with not more than 10% overall yield. Thus, there is always been a demand for a new synthetic process that convene stereochemical outcome as well as good yields.

Our previous work on the synthetic studies towards various pheromones sex attractants[8] *etc.*, encouraged us to take up the synthesis of the title compound. As a part of our research on the synthesis of biologically and pharmacologically important chemical entities, we here in report a concise synthesis of the major component of sex pheromone **1**. Our synthetic strategy mainly deals with the metal based coupling reactions in liquid ammonia and stereoselective reduction reactions of corresponding alkynlinic precursors in to 'Z' and 'E' olefins. The retrosynthetic analysis of pheromone **1** starting from commercially available 1-pentyne (**2**), 1,4-dibromobutane (**3**) and 4-pentyne-1-ol (**4**) has been shown in scheme 1.

The unambiguous stereoselective synthesis of **1** involves a protection free five step synthesis as outlined in Scheme 2. Here, we would like to discuss an alternative way to the *ⁿ*BuLi based coupling reactions, which generally need longer

Figure 1. Major sex pheromone of *Phyllonorycter* δ

(4*E*,10*Z*)-tetradeca-4,10-dienyl acetate (**1**)

(*Z*)-tetradec-10-enyl acetate (**1a**)

Scheme 1. Retrosynthetic analysis of pheromone **1**.

Scheme 2. Synthesis of (4*E*,10*Z*)-tetradeca-4,10-dienyl acetate from 1-pentyne (**2**), 1,4-dibromo butane (**3**) and 4-pentyne-1-ol (**4**).

durations, co-solvents like DMPU/HMPA with low yields.[9] The metal (Li) dissolving reaction in liquid ammonia can be tuned for both coupling and stereoselective reduction reactions. Thus, we have carried out the selective mono coupling conversion by adding equiv molar amounts of **3** and of **2** along with lithium amide in liquid ammonia at −45 °C in presence of catalytic $Fe(NO_3)_3 \cdot 9H_2O$ for the first time, with relatively better yields when compared to *n*BuLi procedures. This reaction afforded successfully 9-bromonon-4-yne (**5**) as a major product along with byproduct tetradeca-4,10-diyne (**6**) and minor amounts of unreacted **3**. The products were non-separable and the yields described are from GC-MS analysis of crude reaction mixture. This mixture of non polar substrates was further preceded for hydrogenation using Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead) in presence of catalytic quinoline under H_2 gas atmosphere. The partial hydrogenation afforded the respective mixture of products (*Z*)-9-bromonon-4-ene (**7**), (4*Z*,10*Z*)-tetradeca-4,10-diene (**8**) and traces of **3** which were not separable by column chromatography and again confirmed by GC-MS analysis. The above crude reaction mixture was directly used in the next conversion that involves another metal based coupling reaction.

In this regard the mixture of **3** (traces), **7** and **8** was treated with freshly generated lithium acetylide (from 1.2 equiv of 4-pentyne-1-ol and 3 equiv lithium) in liquid ammonia at −45 °C for 3 h with catalytic $Fe(NO_3)_3 \cdot 9H_2O$ and slowly warmed to room temperature during 10 h to give rise the desired compound (*Z*)-tetradec-10-en-4-yn-1-ol (**9**), which was easily purified by column chromatography.[10] The overall yield of **9** was calculated to be 31% for three steps. The purified compound **9** showed IR absorption bands at 1054 and 2206 cm^{−1} for *cis*-olefin (=C-H bending) and alkyne (stretching) respectively. The stereoselective Birch reduction of **9** in presence of lithium in liquid ammonia[11] at −45 °C for 6 h gave (4*E*,10*Z*)-tetradeca-4,10-dien-1-ol (**10**) in 79% yield. The same conversion was also performed by LAH reduction in THF to achieve compound **10** in 72% yield. The characteristic =C-H bending vibration at 969 cm^{−1} in IR

spectrum confirmed the formation of *trans*-olefin and two carbons appeared at δ 129.55 and 131.10 in ^{13}C NMR spectrum also confirmed the same. All the intermediates prepared in this approach and the procedures described so far are convenient and can be used in many other pheromone syntheses of similar structures from *Phyllonorycter* genus of moths (in the family Gracillariidae) and also from various insect families. Finally, acetylation[7,12] was performed on the primary alcohol **10** using acetic anhydride and pyridine in CH_2Cl_2 to afford final pheromone **1** in 98% yield and was confirmed by IR, GC-MS, ^{1}H NMR, ^{13}C NMR spectrometric analyses.

In summary, we have accomplished a protection free, concise, Li/liq. NH_3 mediated and gram scale synthesis of (4*E*,10*Z*)-tetradeca-4,10-dienyl acetate (**1**), the major sex pheromone of apple leafminer moth, *Phyllonorycter ringoniella* starting from commercially available 1-pentyne, 1,4-dibromobutane and 4-petyne-1-ol in 24% overall yield. The Li/liq. NH_3 based mono-alkynylation of dibromobutane has been introduced for the first time. The stereoselective formation of 10(*Z*) and 4(*E*) olefins are accomplished by partial hydrogenation (Lindlar's catalyst) and birch reduction respectively. The economy, efficiency, simplicity and high stereo chemical purity of this synthesis allow the potential use of pheromone **1** in integrated field studies to understand the behavioral responses of male apple leafminer moth.

Experimental

General. All the glassware was dried thoroughly in hot oven and streamed with nitrogen before use. Solvents were dried and purified by conventional methods prior to use. All the chemicals were purchased from Sigma Aldrich (USA). IR measurements of all the samples were performed on FTIR-6300 Spectrometer (JASCO, Japan). ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100MHz) spectroscopic data were recorded on an Avance 400 MHz spectrometer (BRUKER, Germany) in $CDCl_3$. Gas chromatography-mass spectrometric (GC-MS) analyses were carried out with a Hewlett-

Packard 6890 & 5973 system (AGILENT, USA).

9-Bromonon-4-yne (5). Ammonia (500 mL) was condensed in a 1 L 2-necked flask attached to a circulating condenser maintained below –45 °C. To the flask at –50 °C, $Fe(NO_3)_3 \cdot 9H_2O$ (713 mg, 1.76 mmol) was added to observe brown color at –50 °C and stirred it for 30 min. The lithium metal (2.47 g, 352.9 mmol) was added slowly to the mixture and the brown color was eventually turned into white-gray after additional 30 min stirring. Then, a solution of 1-pentyne (**2**) (17.4 mL, 176 mmol) in dry THF was added drop wise to the reaction mixture. The resulting solution was stirred for one hour, after which a solution of the 1,4-dibromobutane (**3**) (38.11 g, 176 mmol) in THF (70 mL) was added slowly. Stirring was continued for 2 h at –45 °C and the reaction mixture was left for stirring overnight at ambient temperature resulting in complete evaporation of ammonia. The residue was cautiously treated with saturated NH_4Cl (200 mL) and then extracted with ether (3×250 mL). The combined organic layers was washed with water and dried over anhydrous Na_2SO_4. Removal of volatiles afforded a crude residue (34.1 g, mixture of **3**, 9-bromonon-4-yne (**5**) and tetradeca-4,10-diyne (**6**)) under reduced pressure and these non-separable products were directly used in the next reaction. Products were confirmed by GC-MS analysis. GC-MS (*m/z*): 202 [M]$^+$ (**5**), 216 [M]$^+$ (**3**), and 190 [M]$^+$ (**6**).

(Z)-9-Bromonon-4-ene (7). To a suspension of crude compound **5** (34.1 g, nearly 167.9 mmol) and 5% Pd/CaCO$_3$ poisoned with lead (3.5 g, 1.67 mmol) was added quinoline (150 mg) in ethyl acetate (200 mL) and it was placed in Parr reaction bottle (500 mL). The reaction mixture was shaken under H$_2$ atmosphere at 40 psi for 4 h using Parr hydrogenation apparatus. After completion of the reaction it was filtered through Celite and volatiles were removed in rotary evaporator under reduced pressure. The crude residue (34.0 g) (with mixture of products **3**, (*Z*)-9-bromonon-4-ene (**7**) and (4*Z*,10*Z*)-tetradeca-4,10-diene (**8**)) that contain desired product was directly used in the next reaction. All the products were identified and confirmed by GC analysis. GC-MS (*m/z*): 204 [M]$^+$ (**7**), 216 [M]$^+$ (**3**), and 194 [M]$^+$ (**8**).

(Z)-Tetradec-10-en-4-yn-1-ol (9). Again, ammonia (400 mL) was condensed in a 1 L 2-necked flask attached to a circulating condenser maintained below –45 °C. To the flask, Fe (NO$_3$)$_3 \cdot$9H$_2$O (670 mg, 1.66 mmol) was added to observe brown color and stirred for 30 minutes at –50 °C. The lithium metal (4.17 g, 597 mmol) was added slowly to the mixture and the brown color was eventually turned into white-gray after additional 30 min stirring. Then, a solution of 4-pentyne-1-ol (**4**) (18.49 mL, 199 mmol) in dry THF (40 mL) was added drop wise to the reaction mixture. After an hour the mixture of compounds **3**, **7**, and **8** (34 g, 166 mmol) in dry THF (70 mL) was added drop wise to the flask. The reaction mixture was stirred for 1.5 h at –45 °C and then was left overnight at ambient temperature resulting in complete evaporation of the ammonia. The residue was cautiously treated with saturated NH_4Cl (200 mL) and then extracted with ether (3×250 mL). The combined organic layers were

washed with water and dried on anhydrous NaSO$_4$. The crude residue was purified using column chromatography (2:8 EtOAc/Hexane) to afford pure alkynol **9** (11.3 g, with overall yield 31% for three steps, purity by GC 99%) as a colorless liquid. IR ν_{max}/cm^{-1}: 3642 (w), 3011 (w), 2933 (s), 2849 (s), 2206 (s), 1552 (s), 1054 (s). ^{1}H NMR: δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.32-1.40 (m, 2H), 1.40-1.54 (m, 4H), 1.65 (br s, 1H), 1.70-1.77 (m, 2H), 1.97-2.08 (m, 4H), 2.12-2.18 (m, 2H), 2.25-2.31 (m, 2H), 3.76 (t, *J* = 5.0 Hz, 2H), 5.34-5.40 (m, 2H). ^{13}C NMR: δ 13.78, 15.50, 18.66, 22.89, 26.75, 28.71, 28.98, 29.35, 31.75, 62.15, 79.42, 81.12, 129.80, 130.00. GC-MS *m/z*: 208 [M]$^+$. Anal. Calcd. for C$_{14}$H$_{24}$O: C, 80.71; H, 11.61. Found: C, 81.02; H, 11.33.

(4E,10Z)-Tetradeca-4,10-dien-1-ol (10). Ammonia (200 mL) was condensed in a 500 mL 2-necked flask attached to a circulating condenser maintained below –45 °C. To the flask at –50 °C, it was added lithium metal (1.52 g, 217 mmol) giving a blue color on dissolution. The reaction mixture was kept under dry condition and stirred magnetically. After 30 min alkynol **9** (11.3 g, 54 mmol) in THF (50 mL) was added drop wise and stirred for 6 hours at –45 °C. The reaction was left stirring for 4 hours at ambient temperature resulting in complete evaporation of ammonia. The residue was cautiously treated with saturated NH_4Cl (100 mL) and then extracted with ether (3×100 mL). The combined organic layers were washed with water and dried with anhydrous NaSO$_4$. The crude residue obtained was purified by column chromatography (using 3:7 EtOAc/Hexane) gave pure dienol, **10** (9.05 g, 79% yield, purity by GC > 98%) as a colorless liquid. IR ν_{max}/cm^{-1}: 3645 (w), 3005 (w), 2931 (s), 2853 (s), 1556 (s), 1050 (s), 969 (m). ^{1}H NMR: δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.30-1.44 (m, 7H), 1.63 (m, 2H), 1.95-2.21 (m, 8H), 3.63-3.66 (m, 2H), 5.31-5.40 (m, 2H), 5.40-5.50 (m, 2H). ^{13}C NMR: δ 13.78, 22.9, 27.10, 28.94, 29.21, 29.28, 29.35, 32.44, 32.58, 62.61, 129.55, 129.81, 129.95, 131.13. GC-MS *m/z*: 210 [M]$^+$. Anal. Calcd. for C$_{14}$H$_{26}$O: C, 79.94; H, 12.46. Found: C, 80.22; H, 12.73.

(4E,10Z)-Tetradeca-4,10-dienyl acetate (1). To the dienol **10** (9.0 g, 43 mmol) in dry dichloromethane (100 mL), pyridine (6.78 mL, 85 mmol) was added at room temperature under nitrogen atmosphere. After stirring for 15 min., acetic anhydride (6 mL, 64 mmol) was added drop wise at 0 °C. Reaction temperature was allowed to warm at RT and stirred for 3 h. After which 100 mL of water was added to the reaction mixture and was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried over NaSO$_4$, filtered and concentrated under reduced pressure. Crude material was purified by column chromatography (using 1:9 EtOAc/Hexane) gave acetate **1** (10.5 g, 98% yield, purity by GC 96%) as a colorless liquid. IR ν_{max}/cm^{-1}: 3008 (w), 2931 (s), 2859 (s), 1742 (s), 1550 (s), 1239 (s), 1050 (s), 969 (m), 781 (m). ^{1}H NMR: δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.31-1.42 (m, 6H), 1.64-1.73 (m, 2H), 2.04 (s, 3H), 1.96-2.07 (m, 8H), 4.06 (t, *J* = 6.8 Hz, 2H), 5.33-5.37 (m, 2H), 5.37-5.50 (m, 2H). ^{13}C NMR: δ 13.77, 20.93, 22.92, 27.11, 28.62, 28.90, 29.19, 29.29, 29.37, 32.44, 64.03, 128.83, 129.80, 129.95, 131.46, 171.05. GC-

MS (*m/z*): 252 [M]$^+$. Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.40; H, 11.03.

Supporting Information. Supplementary data associated with this article can be found in the online version.

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