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# Syntheses of All-trans Acyclic Isoprenoid Pheromone Components

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**Abstract:** All-trans acyclic isoprenoid skeletons were made through a two-step iterative sequence. The method involves the Claisen rearrangement of allyl vinyl ethers formed from allylic alcohols and the dimethyl acetal of methyl isopropenyl ketone, followed by $LiAlH_4$ reduction of the α,β-unsaturated ketone formed by rearrangement. The α,β-unsaturated ketone was also transformed to the 2-methyl-1-propenyl group by using a one-pot deoxygenation reaction for the synthesis of *(E)*-β-farnesene, *(E)*-β-springene and dendrolasin

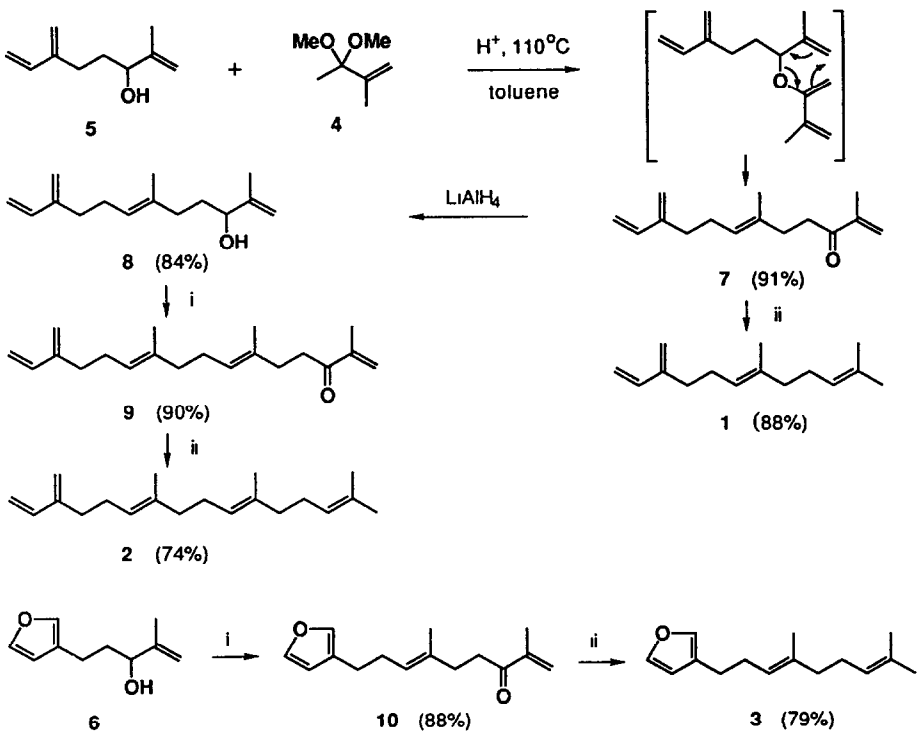
Many isoprenoids of biological importance have all-trans skeletons in their linear segments and are terminated by the 2-methyl-1-propenyl group, which we call "the fish tail ending". *(E)*-β-farnesene (**1**),[1] *(E)*-β-springene (**2**)[2] and dendrolasin (**3**),[3] pheromone components of aphids, the springbok antilope and ants, respectively, are challenging target molecules in this class of compounds. Different approaches to the synthesis of compounds **1**, **2** and **3** have been reported.[4] Here, we have addressed the problem of finding a general method to synthesize all-trans linear isoprenoids terminated by the very commonly occurring "fish tail ending".

Continuous efforts have been made by different investigators to establish general methods for the synthesis of this type of compound. One method for the synthesis of linear polyprenoids was published by Keinan et al.,[5] based on Pd(0)-catalyzed allylic couplings of monoterpene monomers. A different approach to produce isoprenoid homoallylic alcohols was reported by Kocienski et al.,[6] using the Ni(0)-catalyzed coupling of Grignard reagents with 5-alkyl-2,3-dihydrofurans.

In a recent comparative study of using acetals as precursors of vinyl allyl ethers in Claisen rearrangements,[7] it was shown that the rearrangement of vinyl ethers formed from isopropenyl methyl ketone dimethyl acetal (**4**) and secondary allylic alcohols containing an olefinic methylene group is the most useful reaction for constructing isoprenoid chains. The rearranged products are obtained under mild conditions, giving *E* isomers in high yields. The resulting α,β-unsaturated ketones can be reduced with $LiAlH_4$ without complications, and the corresponding allylic alcohols produced can then be used for an additional Claisen rearrangement. Thus, a convenient two-step iterative process to create all-trans isoprenoid

skeletons is available. To obtain a specific target molecule, the α,β-unsaturated ketone usually has to be modified. To achieve "the fish tail ending", we used a one-pot deoxygenation reaction with concomitant transposition of the double bond, which we previously introduced for the synthesis of the mealybug pheromone.[8]

It should be pointed out that the use of acetal **4** for Claisen rearrangements was introduced by Johnson and co-workers in the early seventies and was elegantly used for the synthesis of several isoprenoids.[9] In spite of its virtues as a building block for isoprenoids it has scarcely been used since then.[10]




**Scheme 1**

i) Acetal **4**, $H^+$, 110°C, toluene. ii) *p*-$TsNHNH_2$, AcOH, $NaBH_3CN$

Acetal **4** was prepared at room temperature from the corresponding ketone[11] according to a procedure similar to the one described by Johnson.[12] The starting alcohols **5** and **6** were obtained by photooxidation of myrcene.[13] The Claisen rearrangements were performed in the presence of one molar equivalent of 2,4-dinitrophenol in toluene. Thus, the Claisen

rearrangements with acetal **4** and allylic alcohols **5** and **6** gave the *E* ketones **7** and **10**, respectively. The workup was done in the simplest possible fashion by loading the whole reaction mixture on a silica gel column. In order to retain the large amount of dinitrophenol used in the reaction, the column was packed with a small amount of basic $Al_2O_3$ on the top. Allylic alcohol **8**, obtained by $LiAlH_4$ reduction of ketone **7** was subjected to a second Claisen rearrangement to give ketone **9**. The α,β-unsaturated carbonyl groups of compounds **7**, **9** and **10** were successfully converted to "the fish tail ending" of the final products **1**, **2** and **3** by the the one-pot deoxygenation method mentioned above (Scheme 1).

In this paper the use of acetal **4** was revitalized as a building block for linear all-trans isoprenoids by a two-step iterative method. The α,β-unsaturated ketone resulting from the rearrangement was converted to the 2-methyl-1-propenyl group to terminate the sequence, but the use of acetal **4** can obviously be expanded by using other terminating reactions.

## EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ using a Bruker AM 400 spectrometer. Analytical GC was performed on a PYE 204 instrument equipped with an FID detector and a 25 m DB-5 capillary column. All liquid chromatography was performed on silica gel (Merck 60, 0.040 – 0.063 mm) and eluted with a continuous gradient of increasing amounts of ethyl acetate in hexane.[14] TLC was performed on silica gel (Merck 60, precoated aluminum foil) eluted with 20 % ethyl acetate in hexane and developed with vanillin, sulfuric acid in ethanol.

**3-Methyl-3-buten-2-one dimethyl acetal (4).** In a three-neck flask equipped with a dropping funnel and a distillation set, $P_2O_5$ (5 g), $H_3PO_4$ (85%, 5 ml), Cu powder (0.5 g) and hydroquinone (0.5 g) were mixed. To this mixture 4-hydroxy-3-methyl-2-butanone (90 g, 0.88 mol) was added dropwise at 130 °C under a stream of nitrogen. The product was distilled out together with the formed water during the reaction period, separated and dried with $MgSO_4$. Removal of the drying agent by filtration gave pure 3-methyl-3-buten-2-one[11] in a yield of 69% (51 g). $^1H$ NMR δ 1.87 (3H, s, $-CH_3$), 2.33 (3H, s, $-CH_3$), 5.77 (1H, s, $=CH_2$) 5.93 (1H, s, $=CH_2$).

At room temperature, *p*-TsOH·$H_2O$ (190 mg, 0.001 mol) was added to a mixture of 3-methyl-3-buten-2-one (21 g, 0.25 mol), trimethyl orthoformate (26.5 g, 0.25 mol) and methanol (40 ml). After 15 min, the reaction was quenched by the addition of solid $Na_2CO_3$ (0.5 g) with stirring. After 30 min, the reaction mixture was poured into water (20 ml) and separated. The aqueous phase was extracted with pentane. The organic layers were combined and dried with $MgSO_4$. Distillation with a spinning band column gave product **4** at 24 °C/15 mmHg (lit. b.p. 54-56 °C /68 mmHg[12]) in 50% yield (16.3 g). $^1H$ NMR δ 1.34 (3H, s, $-CH_3$), 1.72 (3H, s, $-CH_3$), 3.14 (6H, s, $-OCH_3$), 5.00 (1H, s, small splits, $=CH_2$), 5.22 (1H, s, small splits, $=CH_2$).

**(*E*)-2,6-Dimethyl-10-methylene-1,6,11-dodecatrien-3-one (7).** To a mixture of alcohol **5** (1.07 g 7 mmol) and acetal **4** (2.73 g, 21 mmol) in toluene (10 ml) was added 2,4-dinitrophenol (1.29 g, 7 mmol) and the mixture was stirred and heated to 110 °C for 8 h, then cooled to room temperature. The crude product was separated by loading the entire reaction mixture on a silica gel column topped with approx. 3 cm of basic $Al_2O_3$ to adsorb the acid catalyst, and pure product was obtained in a yield of 87% (1.33 g) after a second purification by column chromatography . $^1$H NMR δ 1.62 (3H, s, -$CH_3$), 1.87 (3H, s, -$CH_3$), 2.20 (4H, s, -$CH_2$), 2.28 (2H, t, J = 8 Hz, -$CH_2$-), 2.78 (2H, t, J = 8 Hz, -$CH_2$-), 4.98-5.28 (5H, m, -CH=, $CH_2$=), 5.76 (1H, s, $CH_2$=), 5.95 (1H, s, $CH_2$=), 6.37 (1H, dd, J = 18, 11 Hz, -CH=). $^{13}$C NMR δ 16.19 ($CH_3$), 17.71 ($CH_3$), 26.63 ($CH_2$), 31.33 ($CH_2$), 34.39 ($CH_2$), 36.37 ($CH_2$), 113.13 ($CH_2$), 115.81 ($CH_2$), 124 38 ($CH_2$), 124.61 (CH), 134.40 (CH), 138.98 (C), 144.61 (C), 146.08 (C), 201.96 (CO).

**(*E*)-β-Farnesene (1).** Compound **7** (109 mg, 0.5 mmol) was mixed with *p*-toluenesulfonylhydrazide (93 mg, 0.5 mmol) in acetic acid (1 ml) and stirred at room temperature. The disappearance of **7** was monitored by TLC and after approximately 40 min, $NaBH_3CN$ (63 mg, 1 mmol) was added. After 4 h the reaction mixture was poured into ice-water, neutralized with 3N NaOH and extracted with hexane (10 ml x 3). The hexane solution was washed with water and dried with $MgSO_4$. Purification by column chromatography (elution with hexane) gave pure product in a yield of 88% (90 mg). $^1$H NMR δ 1.60 (6H, s, -$CH_3$), 1.68 (3H, s, -$CH_3$), 1.99 (2H, m, -$CH_2$-), 2.07 (2H, m, -$CH_2$-), 2.22 (4H, m, -$CH_2$-), 4.99-5.25 (6H, m, $CH_2$=, -CH=), 6.38 (1H, dd, J = 17, 10 Hz, -CH=). $^{13}$C NMR δ 16.02 ($CH_3$), 17.68 ($CH_3$), 25.68 ($CH_3$), 26.62 ($CH_2$), 26.71 ($CH_2$), 31.41 ($CH_2$), 39.70 ($CH_2$), 113.03 ($CH_2$), 115.70 ($CH_2$), 124.02 (CH), 124.35 (CH), 131.31 (CH), 138.38 (C), 139.00 (C), 146.14 (C).

**(*E*)-2,6-Dimethyl-10-methylene-1,6,11-dodecatrien-3-ol (8).** To a suspension of $LiAlH_4$ (209 mg, 5.5 mmol) in dry diethyl ether (15 ml) compound **7** (1.20 g, 5.5 mmol) in diethyl ether (10 ml) was added dropwise and the mixture was stirred at room temperature. After 2.5 h a mixture of sodium sulphate decahydrate and celite 545 (4:1, w:w) (2 g) was added and the slurry was stirred continuously until the color turned to white. After filtration and evaporation of the solvent, followed by column chromatography product **8** was obtained in a yield of 84% (1.02 g). $^1$H NMR δ 1.62 (3H, s, -$CH_3$), 1.73 (3H, s, -$CH_3$), 1.64-1.70 (2H, m, -$CH_2$-), 1 99-2.09 (2H, m, -$CH_2$-), 2.23 (4H, br, -$CH_2$-), 4.05 (1H, t, J = 6 Hz, -CHOH-), 4.83-5.29 (7H, m, -CH=, $CH_2$=), 6.38 (1H, dd, J = 17, 11 Hz, -CH=). $^{13}$C NMR δ 16.07 ($CH_3$), 17.67 ($CH_3$), 26.62 $CH_2$), 31.39 ($CH_2$), 33.23 ($CH_2$), 35.72 ($CH_2$), 75.70 (CHOH), 111.05 ($CH_2$), 113.14 ($CH_2$), 115.79 ($CH_2$), 124.53 (CH), 135.20 (CH), 138.98 (CH), 146.09 (C), 147.55 (C).

**(*E,E*)-2,6,10-Trimethyl-17-methylene-2,6,10,15-hexadecatetraen-3-one (9).** To a mixture of compound **8** (440 mg, 2 mmol) and acetal **4** (782 mg, 6 mmol) in toluene (3 ml) was added 2,4-dinitrophenol (368 mg, 2 mmol) and the reaction mixture was heated to 110 °C for 8 h and

then cooled to room temperature. The pure product was obtained by column chromatography in 90% yield (515 mg). $^1$H NMR δ 1.59 (3H, s, -$CH_3$), 1.60 (3H, s, -$CH_3$), 1.87 (3H, s, -$CH_3$), 1.95-2.31 (6H, m, -$CH_2$-), 2.77 (2H, t, J = 7 Hz, -$CH_2$-), 5.00-5.28 (6H, m, -CH=, $CH_2$=), 5.76 (1H, s, $CH_2$=), 5.95 (1H, s, $CH_2$=), 6.38 (1H, dd, J = 18, 11 Hz, -CH=). $^{13}$C NMR δ 16.07 ($CH_3$), 16.16 ($CH_3$), 17.72 ($CH_3$), 26.62 ($CH_2$), 26.65 ($CH_2$), 31.46 ($CH_2$), 34.41 ($CH_2$), 36.43 ($CH_2$), 39.60 ($CH_2$), 113.09 ($CH_2$), 115.75 ($CH_2$), 124.18 (CH), 124.34 ($CH_2$), 124.84 (CH), 133.92 (C), 135.29 (C), 139.03 (CH), 144.60 (C), 146.16 (C), 201.99 (CO).

**(*E*)-β-Springene (2).** Compound **9** (143 mg, 0.5 mmol) and *p*-toluenesulfonylhydrazide (93 mg, 0.5 mmol) were mixed in acetic acid (1 ml) and stirred for 40 min, $NaBH_3CN$ (63 mg, 1 mmol) was then added. After continuous stirring for 4 h, the reaction mixture was worked up as described for the preparation of compound **1**. The yield was 74% (101 mg). $^1$H NMR δ 1.60 (9H, s, -$CH_3$), 1.68 (3H, s, -$CH_3$), 2.00 (4H, m, -$CH_2$-), 2.08 (4H, m, -$CH_2$-), 2.22 (4H, m, -$CH_2$-), 5.00 (1H, s, =$CH_2$), 5.01 (1H, s, =$CH_2$), 5.05 (1H, d, J = 11 Hz, $CH_2$=), 5.10 (1H, t, J = 8 Hz, -CH=), 5.12 (1H, t, J = 8 Hz, -CH=), 5.17 (1H, t, J = 7 Hz, -CH=), 5.25 (1H, d, J = 17 Hz, $CH_2$=), 6.38 (1H, dd, J = 17, 11 Hz, -CH=). $^{13}$C NMR δ 16.00 ($CH_3$), 16.03 ($CH_3$), 17.67 ($CH_3$), 25.68 ($CH_3$), 26.61($CH_2$), 26.63 ($CH_2$), 26.77 ($CH_2$), 31.42 ($CH_2$), 39.69 ($CH_2$), 39.72 ($CH_2$), 113.03 ($CH_2$), 115.69 ($CH_2$), 124.03 (CH), 124.21 (CH), 124.39 (CH), 131.26 (CH), 134.95 (C), 135.40 (C), 139.00 (C), 146.15 (C).

**(*E*)-2,6-Dimethyl-10-(3′-furyl)-1,6-decadien-3-one (10).** To a mixture of 2-methyl-5-(3′-furyl)-1-penten-3-ol (**6**) (130 mg, 0.78 mmol) and acetal **4** (300 mg, 2.31 mmol) in toluene (1 ml) was added 2,4-dinitrophenol (145 mg, 0.79 mmol). The mixture was heated to 110 °C for 8 h, and then cooled to room temperature. Column chromatography of the entire reaction mixture gave product **10** in a yield of 88% (160 mg). $^1$H NMR δ 1.60 (3H, s, -$CH_3$), 1.87 (3H, s, -$CH_3$), 2.21-2.32 (4H, m, -$CH_2$-), 2.44 (2H, t, J = 8 Hz, -$CH_2$-), 2.77 (2H, t, J = 8 Hz, -$CH_2$-), 5.76 (1H, s, $CH_2$=), 5.95 (1H, s, $CH_2$=), 6.26 (1H, s, -CH=), 7.26 (1H, s, -OCH=), 7.33 (1H, s, -OCH=). $^{13}$C NMR δ 16.20 ($CH_3$), 17.70 ($CH_3$), 21.53 ($CH_2$), 24.95 ($CH_2$), 34.34 ($CH_2$), 36.28 ($CH_2$), 111.09 (CH), 124.31 (CH), 124.39 ($CH_2$), 124.88 (C), 134.75 (C),138.88 (CH), 142.62 (CH), 144.59 (C), 201.88 (CO).

**Dendrolasin (3).** Compound **10** (116 mg, 0.5 mmol) and *p*-toluenesulfonylhydrazide (93 mg, 0.5 mmol) were mixed in acetic acid (1 ml). After 40 min, $NaBH_3CN$ (63 mg, 1 mmol) was added and the mixture was stirred for 4 h. The reaction mixture was worked up as described for preparation of compound **1**. The yield was 79% (81 mg). $^1$H NMR δ 1.59 (3H, s, -$CH_3$), 1.60 (3H, s, -$CH_3$), 1.68 (3H, s, -$CH_3$), 1.99 (2H, m, -$CH_2$-), 2.06 (2H, m, -$CH_2$-), 2.26 (2H, m, -$CH_2$-), 2.45 (2H, t, J = 8 Hz, -$CH_2$-), 5.07 (1H, t, J = 7 Hz and small splits, -CH=), 5.17 (1H, t, J = 7 Hz and small splits, -CH=), 6.28 (1H, s, -CH=), 7.21 (1H, s, -OCH=), 7.34 (1H, s, -OCH=). $^{13}$C NMR δ 16.02 ($CH_3$), 17.67 ($CH_3$), 25.03 ($CH_2$), 25.68 ($CH_3$), 26.65 ($CH_2$), 28.44 ($CH_2$), 39.68 ($CH_2$), 111.09 (CH), 123.74 (CH), 124.30 (CH), 124.98 (CH), 131.35 (CH), 135.75 (C), 138.83 (C), 142.51(C).

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