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A Practical and Convenient Synthesis of Hotrienol, an Excellent Fruity Smelling Compound

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The practical and convenient synthesis of hotrienol, which is an excellent fruity smelling compound, has been performed by the ene-type chlorination of linalyl acetate and then dehydrochlorinated by lithium bromide and lithium carbonate in DMF, followed by hydrolysis in three steps with an overall yield of 55%.

KEYWORDS: Hotrienol; linalool; linalyl acetate; 6-chloro-3,7-dimethyl-1,7-octadien-3-yl acetate; 3,7-dimethyl-1,5(*E*),7-octatrien-3-yl acetate; ene-type chlorination; dehydrochlorination; hydrolysis;

INTRODUCTION

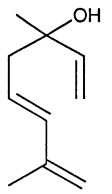
Hotrienol, 3,7-dimethyl-1,5(*E*),7-octatrien-3-ol (**1**) (**Figure 1**), occurs as the 3*S*-(+)-enantiomorph in Ho leaf oil (*1*), while the *R*-enantiomorph has been isolated from tea, both black (*2*) and green (*3*). Before it had been reported as a natural product, Matsuura et al. had prepared it from one of the photooxidation products of 3*R*-(−)-linalool (*4*). On the other hand, Nakatani et al. also started from *R*-linalyl acetate (**2a**), followed by the treatment of *N*-bromosuccimide, dehydrobromination by diethylaniline, and then hydrolysis to give (3*R*)-**1** (*2*), however, the experimental workup was not reported in detail. Other synthetic methods for the preparation of **1** have been reported by many groups up to now (*5*−*11*). Recently, **1** was reported to contribute to the grape-like smelling compound (*12, 13*).

The previously reported methods are considered unsuitable for economic and large scale production, because the total yields are low and expensive reagents and/or available starting materials are used. To develop the practical synthesis of **1**, we have studied a new procedure, and we now report a practical synthetic route of **1**, which is an efficient, safe, and cost-effective process. Thus, **1** was obtained in three steps with a good yield by the ene-type chlorination of linalyl acylate (**2**) to give γ-chloro-α-linalyl acylate (**3**) and then dehydrochlorination with lithium bromide and lithium carbonate in DMF, followed by hydrolysis of dehydro-α-linalyl acylate (**4**).

MATERIAL AND METHODS

Chemicals. All reagents and solvents were obtained from Sigma-Aldrich Japan, Inc. (Tokyo, Japan), Wako Pure Chemical Industries, Ltd. (Tokyo, Japan), and Nacalai Tesque (Kyoto, Japan) and used without further purification.

Instruments. Boiling points are given as uncorrected values. The NMR spectra were obtained with a Bruker DRX-500. The ^{1}H and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively, in $CDCl_3$, with TMS as the internal standard. The chemical shifts are given in δ (ppm). The IR spectra were obtained using a Nicolet Avatar 360 FT-IR. The mass spectra (electronic impact) were obtained with a Hitachi M-80A mass spectrometer. The GC analysis used a Shimadzu GC-17A with an FID detector (column, Neutrabond-1, df = 0.15 μm, 0.25 mm ID × 30m; carrier gas N_2, 0.1MPa, oven temperature, 100−200 °C programmed at 10°/min; injection temperature, 230 °C, detector temperature, 230 °C).



(1)

Figure 1. The structure of hotrienol.

General Procedure of Linalyl Acylate (2). To a 300-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, a thermometer and a pressure-equalizing dropping funnel, was added linalool (270 mmol) in THF (100 mL). To the mixture, stirred at −20 °C, was added, dropwise, a 1.6 M solution of *n*-BuLi in hexane (170 mL) over 30 min. The reaction mixture was stirred at room temperature for 1.5 h cooled to −20 °C, and then acyl chloride (270 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. To the residue, EtOAc (150 mL) and water (150 mL) were added, and the organic layer was separated and washed twice with 10% NaCl solutions. The solvent was removed under vacuum, and the product was distilled under reduced pressure to give (**2**).

Linalyl Propionate (2b). The product was recovered as an oil (44.8 g, 79%). The purity was 98% by GC. Bp. 61−62 °C/0.3 Torr; IR-(neat) 3090, 2975, 1736, 1644, 1458 cm^{-1}; ^{1}H NMR 1.11 (t, J = 7.6 Hz, 3H), 1.54, 1.58, and 1.67 (each s, 3H), 1.73−1.79 (m, 1H), 1.84−1.90 (m, 1H), 1.94−1.99 (m, 2H), 2.28 (q, J = 7.6, 15.2 Hz, 2H), 5.08−5.17 (m, 3H), 5.97(dd, J = 7.6, 17.6 Hz, 1H); ^{13}C NMR 9.14 (CH_3), 17.46 (CH_3), 22.28 (CH_2), 25.57 (CH_3), 28.52 (CH_2), 39.68 (CH_2), 82.50 (C), 112.90 (CH_2), 123.80 (CH), 131.64 (C), 141.91 (CH), 173.19 (C=O); MS *m*/*z* 210 (2) (M^+), 195 (1), 183 (1), 165 (11), 154 (3), 136 (8), 121 (30), 107 (9), 93 (100), 80 (29), 69 (22), 57 (31), 41 (19), 29 (10).

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Linalyl Isobutyrate (2c). The product was recovered as an oil (46 g, 76%). The purity was 99% by GC. Bp. 68−69 °C/0.3 Torr; IR-(neat) 3087, 2973, 2932, 1733, 1644, 1468 cm^{-1}; ^1H NMR 1.15 (t, J = 7 Hz, 3H), 1.53, 1.59, and 1.67 (each s, 3H), 1.72−1.78 (m, 1H), 1.85−1.95 (m, 1H), 1.96−2.00 (m, 2H), 2.46−2.52 (m, 1H), 5.08−5.17 (m, 3H), 5.95 (dd, J = 11, 17.5 Hz, 1H); ^{13}C NMR 17.48 (CH_3), 18.99 ($CH_3 \times 2$), 22.27 (CH_2), 23.63 (CH_3), 25.60 (CH_3), 34.81 (CH), 39.79 (CH_2) 82.27 (C), 112.85 (CH_2), 123.83 (CH), 131.69 (C), 141.98 (CH), 175.82 (C═O); MS m/z 224 (2) (M^+), 209 (1), 197(1), 181 (1), 154 (2), 136 (8), 121 (7), 107 (7), 93 (100), 80 (27), 69 (26), 57 (8), 43 (24), 41 (20), 27 (3).

Linalyl Benzoate (2d). The product was recovered as an oil (43.2 g, 62%). The purity was 95% by GC. Bp. 110−112 °C/0.3 Torr; IR-(neat) 3085, 2970, 2727, 1718, 1643, 1601, 1451 cm^{-1}; ^1H NMR 1.59, 1.65, and 1.69 (each s, 3H), 1.89−1.94 (m, 1H), 1.97−2.11 (m, 3H), 5.12−5.28 (m, 3H), 6.09 (dd, J = 11, 17.5 Hz, 1H), 7.39−7.50 (m, 2H), 7.51−7.54 (m, 1H), 8.01−8.02 (m, 2H); ^{13}C NMR 17.52 (CH_3), 22.42 (CH_2), 23.71 (CH_3), 25.57 (CH_3), 40.01 (CH_2), 83.46 (C), 113.22 (CH_2), 123.78 (CH), 128.18 (CH), 129.40 (CH × 2), 131.59 (C), 131.69 (C), 132.50 (CH × 2), 141.81 (CH), 165.16 (C═O); MS m/z 258 (2) (M^+), 243 (1), 229 (1), 215 (1), 207 (1), 189 (2), 175 (2), 153 (2), 136 (9), 121 (21), 105 (100), 93 (97), 77 (29), 69 (15), 51 (9), 41 (16), 27 (3).

General Procedure for the Preparation of 6-Chloro-3,7-dimethyl-1,7-octadien-3-yl Acylate (3) by Ene-Type Chlorination. To a 200-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, a thermometer and a pressure-equalizing dropping funnel were added linalyl acylate (50 mmol) in CH_2Cl_2 (50 mL), 60% calcium hypochlorite (5.8 g, 25 mmol), and boric acid (6.2 g, 100 mmol). To the mixture, stirred at 5 °C, water (10 mL) was added dropwise over 3.5 h. The reaction mixture was stirred at the same temperature for 1 h, and then sodium sulfide (2.5 g, 19.9 mol) was added. The inorganic salt was filtered off, and the organic layer was separated and washed twice with 10% NaCl solutions. The solvent was removed under vacuum, and the product was distilled under reduced pressure to give **3**.

6-Chloro-3,7-dimethyl-1,7-octadien-3-yl Acetate (3a). The product was recovered as an oil (10.1 g, 88%) from linalyl acetate **2a** (9.8 g, 50 mmol). The purity was 94% by GC. From 1500 g of **2a**, 1545 g (88%) of **3a** was obtained, by a scale-up proceduce. The purity was 92% by GC. Bp. 69−72 °C/0.3 Torr; IR(neat) 3084, 2977, 1738, 1646, 1450, 1371 cm^{-1}; ^1H NMR (diastereomer mixture) 1.53 and 1.55 (each s, 3H), 1.63−1.70 (m, 1H), 1.77−1.87 (m, 2H), 1.78 (s, 3H), 1.90−1.97 (m, 1H), 1.99 (s, 3H), 4.31 (t, J = 7.4 Hz, 1H), 4.88 and 4.99 (each brs, 1H), 5.10−5.16 (m, 2H), 5.91 (dt, J = 11.3, 17.5 Hz, 1H); ^{13}C NMR (diastereomer mixture) 16.75 (CH_3), 16.77 (CH_3), 20.04 (CH_3), 22.04 (CH_3), 23.62 (CH_3), 23.74 (CH_3), 30.69 (CH_2), 30.72 (CH_2), 37.00 (CH_2), 37.02 (CH_2), 66.47 (CH), 66.54 (CH), 82.15 (C), 82.27 (C), 113.47 (CH_2), 113.52 (CH_2), 114.41 (CH_2), 114.46 (CH_2), 141.16 (CH), 141.30 (CH), 143.88 (C), 143.92 (C), 169.73 (C═O); MS m/z 230 (1) (M^+), 195 (10), 171 (2), 153 (14), 135 (22), 121 (31), 107 (29), 93 (100), 80 (61), 67 (49), 55 (24), 43 (84).

6-Chloro-3,7-dimethyl-1,7-octadien-3-yl Propionate (3b). The product was recovered as an oil (10.6 g, 87%) from linalyl propionate **2b** (10 g, 50 mmol). The purity was 94% by GC. Bp. 85−87 °C/1 Torr; IR(neat) 3085, 2979, 2943, 1738, 1645, 1460 cm^{-1}; ^1H NMR (diastereomer mixture) 1.11 (t, J = 7.5 Hz, 3H), 1.65 and 1.66 (each s, 3H), 1.68−2.00 (m, 4H), 1.79 (s, 3H), 2.29 (q, J = 8.5, 15.1 Hz, 2H), 4.32−4.35 (m, 1H), 4.91 and 5.01 (each brs, 1H), 5.12−5.19 (m, 2H), 5.89−5.97 (m, 1H); ^{13}C NMR (diastereomer mixture) 9.15 (CH_3), 16.79 (CH_3), 16.80 (CH_3), 23.72 (CH_3), 23.85 (CH_3), 28.49 (CH_2), 28.51 (CH_2), 30.73 (CH_2), 30.76 (CH_2), 37.06 (CH_2), 37.07 (CH_2), 66.53 (CH), 66.60 (CH), 81.90 (C), 82.03 (C), 113.44 (CH_2), 113.49 (CH_2), 114.45 (CH_2), 114.50 (CH_2), 141.32 (CH), 141.48 (CH), 143.92 (C), 143.97 (C), 173.18 (C═O); MS m/z 215(1) ($M^+ - 29$), 209(6), 170 (2), 155 (4), 141 (6), 135 (42), 127 (21), 119 (13), 107 (30), 93 (32), 81 (47), 68 (43), 57 (100), 41 (17), 29 (17).

6-Chloro-3,7-dimethyl-1,7-octadien-3-yl 2-Methylpropionate (3c). The product was recovered as an oil (11 g, 85%) from linalyl isobutyrate **2c** (11.2 g, 50 mmol). The purity was 95% by GC. Bp. 93−96 °C/0.6 Torr; IR(neat) 3083, 2975, 2938, 1733, 1640, 1468 cm^{-1}; ^1H NMR (diastereomer mixture) 1.15 (d, J = 7 Hz, 3H), 1.54 and 1.79 (each s, 3H), 1.67−2.02 (m, 4H), 1.79 (s, 3H), 2.47−2.53 (m, 1H), 4.32−4.35 (m, 1H), 4.91 and 5.01 (each brs, 1H), 5.12−5.19 (m, 2H), 5.87−5.95 (m, 1H); ^{13}C NMR (diastereomer mixture) 16.77 (CH_3), 16.78 (CH_3), 18.96 ($CH_3 \times 2$), 23.75 (CH_3), 23.90 (CH_3), 30.69 (CH_2), 30.72 (CH_2), 34.72 (CH), 34.75 (CH), 36.98 (CH_2), 66.48 (CH), 66.55 (CH), 81.62 (C), 81.75 (C), 113.32 (CH_2), 113.37 (CH_2), 114.39 (CH_2), 114.45 (CH_2), 141.37 (CH), 141.52 (CH), 143.91 (C), 143.96 (C), 175.73 (C═O), 175.74(C═O); MS m/z 258 (1), (M^+), 223 (11), 215 (1), 207 (2), 197 (1), 188 (2), 179 (2), 171 (2), 155 (4), 143 (15), 135 (71), 127 (3), 119 (14), 107 (43), 93 (46), 81 (58), 71 (100), 55 (28), 43 (69), 27 (8).

6-Chloro-3,7-dimethyl-1,7-octadien-3-yl Benzoate (3d). The product was recovered as an oil (8.7 g, 80%) from linalyl benzoate **2d** (9.5 g, 37 mmol). The purity was 92% by GC. Bp. 135−138 °C/0.6 Torr; IR(neat) 3087, 2975, 1717, 1646 1601, 1584, 1451 cm^{-1}; ^1H NMR (diastereomer mixture); 1.69, 1.70, and 1.79 (each s, 3H), 1.81−2.16 (m, 4H), 4.36−4.40 (m, 1H), 4.91, and 5.03 (each brs, 1H), 5.19−5.23 (m, 1H), 5.25−5.31 (m, 1H), 6.01−6.10 (m, 1H), 7.09−7.46 (m, 2H), 7.52−7.56 (m, 1H), 7.99−8.01 (m, 2H); ^{13}C NMR (diastereomer mixture) 16.85 (CH_3), 23.87 (CH_3), 23.94 (CH_3), 30.79 (CH_2), 30.81 (CH_2), 37.20 (CH_2), 37.23 (CH_2), 66.48 (CH), 66.56 (CH), 82.84 (C), 82.97 (C), 113.73 (CH_2), 113.77 (CH_2), 114.48 (CH_2), 114.53 (CH_2), 128.21 (CH × 2), 128.26 (CH × 2), 129.38 (CH × 2), 129.51 (CH × 2), 132.70 (CH), 141.24 (CH), 141.33 (CH), 143.86 (C), 143.92 (C), 165.09 (C═O); MS m/z 257 (13), (M^+-35), 207 (2), 188 (2), 170 (2), 155 (2), 135 (37), 119 (9), 105 (100), 93 (20), 77 (45), 68 (20), 53 (13), 41 (11).

General Procedure for the Preparation of 3,7-Dimethyl-1,5(*E*),7-octatrien-3-yl Acylate (4) by Dehydrochlorination. To a 200-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser and a thermometer were added **3** (8.6 g, 35 mmol) in DMF (70 mL), lithium carbonate (6.46 g, 87.5 mmol), and lithium bromide (11.7 g, 52.5 mmol). The reaction mixture was stirred at 130 °C for 2 h. The conversion and selectivity were 98% and 78%, respectively. The vessel was cooled to 70 °C and then DMF was recovered under vacuum. Toluene (100 mL) and water (100 mL) were added to the residue. The organic layer was washed with water (100 mL) and then 10% NaCl solution (100 mL). The solvent was recovered under vacuum, and the product was distilled under reduced pressure to give **4**.

3,7-Dimethyl-1,5(*E*),7-octatrien-3-yl Acetate (4a). The product was recovered as an oil (4.9 g, 73%) from **3a** (8.1 g). The purity was 94% by GC. 725 g (73%) of **4a** was obtained from 1200 g of **3a** by a scale-up proceduce. The purity were 93% by GC. Bp. 48 °C/0.4 Torr. IR (neat) 3084, 2977, 2940, 1738, 1645, 1609, 1437 cm^{-1}; ^1H NMR 1.44 and 1.76 (each s, 3H) 1.92 (s, 3H), 2.51−2.60 (m, 2H), 4.89 (brs, 2H), 5.06 (d, J = 11 Hz, 1H), 5.09 (d, J = 16.2 Hz, 1H), 5.49 (dt, J = 7.4, 15.6 Hz, 1H), 5.94 (dd, J = 11, 17.5 Hz, 1H), 6.09 (d, J = 15.6 Hz, 1H); ^{13}C NMR 18.54 (CH_3), 22.04 (CH_3), 23.55 (CH_3), 42.72 (CH_2), 82.42 (C), 113.43 (CH_2), 115.26 (CH_2), 124.19 (CH), 136.43 (CH), 141.47 (CH), 141.73 (C), 169.83 (C═O); MS m/z 194 (1) (M^+), 151 (1), 134 (51), 119 (76), 113 (7), 105 (17), 91 (45), 71 (100), 55 (94), 43 (94).

3,7-Dimethyl-1,5(*E*),7-octatrien-3-yl Propionate (4b). The product was recovered as an oil (4.8 g, 71%) from **3b** (8.0 g, 32.7 mmol). The purity was 94% by GC. Bp. 52−54 °C/0.3 Torr. IR (neat) 3084, 2979, 2941, 1737, 1645, 1609, 1460 cm^{-1}; ^1H NMR 1.09 (t, J = 7.6 Hz, 3H), 1.52 and 1.82 (each s, 3H), 2.26 (q, J = 7.6, 15.6 Hz, 2H), 2.59−2.68 (m, 2H), 4.89 (brs, 2H), 5.14 (dd, J = 1.1, 10 Hz, 1H), 5.17 (dd, J = 1.1, 20.4 Hz, 1H), 5.57 (dt, J = 7.6, 15.6 Hz, 1H), 6.01 (dd, J = 10.9, 17.5 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H); ^{13}C NMR 9.15 (CH_3), 18.54 (CH_3), 23.67 (CH_3), 28.55 (CH_2), 42.68 (CH_2), 82.10 (C), 113.34 (CH_2), 115.22 (CH_2), 124.25 (CH), 136.40 (CH), 141.63 (CH), 141.74 (C), 173.21 (C═O). MS m/z 208 (1), (M^+), 179 (1), 165 (1), 151 (1), 140 (6), 134 (53), 127 (15), 119 (74), 105 (17), 91 (32), 79 (23), 71 (17), 57 (100), 41 (4), 29 (13).

3,7-Dimethyl-1,5(*E*),7-octatrien-3-yl 2-Methylpropionate (4c). The product was recovered as an oil (5.4 g, 69%) from **3c** (9.0 g). The purity was 93% by GC. Bp. 63−65 °C/0.2 Torr. IR (neat) 3084, 2974, 2937, 1735, 1646, 1610, 1469 cm^{-1}; ^1H NMR 1.12 (d, J = 7.4 Hz, 3H), 1.52 and 1.82 (each s, 3H), 2.44−2.50 (m, 1H), 2.65 (d, J = 7.4

Hz, 2H), 4.89 (brs, 2H), 5.14 (dd, J = 19 Hz, 1H), 5.17 (d, J = 24.9 Hz, 1H), 5.57 (dt, J = 7.4, 15.6 Hz, 1H), 5.99 (dd, J = 11, 17.5 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H); ^{13}C NMR 18.55 (CH_3), 18.95 (CH_3 × 2), 23.82 (CH_3), 34.77 (CH), 42.57 (CH_2), 81.82 (C), 113.24 (CH_2), 115.22 (CH_2), 124.28 (CH), 136.42 (CH), 141.74 (CH), 141.75 (C), 175.80 (C═O). MS *m*/*z* 222 (1), (M^+), 179 (1), 154 (4), 141 (8), 134 (44), 119 (64), 107 (15), 91 (26), 79 (21), 71 (100), 55 (21), 43 (66).

3,7-Dimethyl-1,5(*E*),7-octatrien-3-yl Benzoate (4d). The product was recovered as an oil (3.8 g, 65%) from **3d** (6.8 g, 23.2 mmol). The purity was 93% by GC. Bp. 102−105 °C/0.1 Torr. IR (neat) 3085, 2974, 2938, 1718, 1646, 1603, 1451 cm^{-1}; ^{1}H NMR 1.68 and 1.79 (each s, 3H), 2.71−2.85 (m, 2H), 4.89 (s, 2H), 5.22 (d, J = 25.3 Hz, 1H), 5.25 (d, J = 31.9 Hz, 1H), 5.66 (dt, J = 7.5, 15.6 Hz, 1H), 6.14 (dd, J = 10.9, 17.5 Hz, 1H), 6.24 (d, J = 15.6 Hz, 1H), 7.40−7.43 (m, 2H), 7.51−7.54 (m, 1H), 7.99−8.01 (m, 2H); ^{13}C NMR 18.57 (CH_3), 23.53 (CH_3), 43.41 (CH_2), 83.03 (C), 113.72 (CH_2), 115.33 (CH_2), 124.24 (CH), 128.24 (CH × 2), 129.38 (CH × 2), 131.49 (C), 132.56 (CH), 136.69 (CH), 141.42 (CH), 141.73 (C), 165.20 (C), 175.80 (C═O). MS *m*/*z* 188 (1), 175 (2), 134 (15), 119 (19), 105 (100), 91 (7), 77 (28), 65 (3), 51 (6), 41 (5).

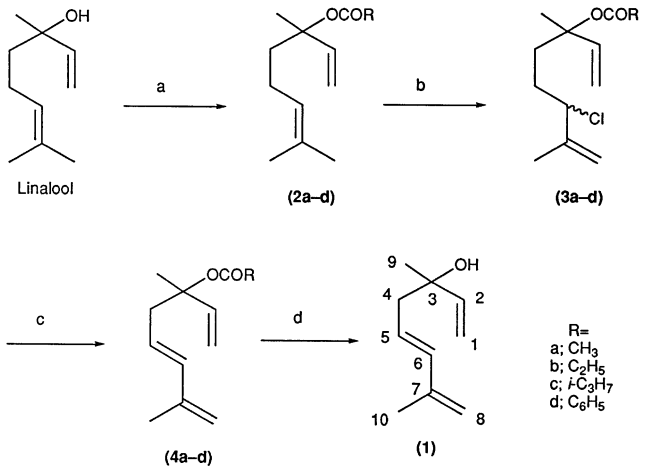
Scale-Up Procedure for the Preparation of 3,7-Dimethyl-1,5(*E*),7-octatrien-3-ol (1). To a 3-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, a thermometer and a pressure-equalizing dropping funnel was added **4a** (490 g, 2.3 mol). To the flask, stirred at 20−30 °C, was added dropwise 10% NaOH in 50% MeOH aqueous solution (1012 g) over 1 h and stirred for 5 h. The conversion and selectivity were 100 and 95%, respectively. The vessel was cooled to room temperature and acetic acid (20.72 g, 0.35 mol) was added and concentrated under vaccum. To the residue, EtOAc (500 mL) and water (500 mL) were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (500 mL × 2). The combined organic layer was washed with 5% $NaHCO_3$ (200 mL) and 5% NaCl solution (200 mL), and then concentrated under vacuum to give crude **1** (396 g). Compound **1** was purified by using a five theoretical plate column distillation with helipac No. 3, to give 306.3 g (85%) with 98% purity by GC. Bp. 45−46 °C/0.6 Torr. (Lit. 80−84 °C/15 Torr; (*4*), 85−90 °C/5−7 Torr; (*7*)). IR (neat) 3417, 2974, 2927, 1609, 1645, 1454, 1372 cm^{-1}; ^{1}H NMR 1.28 (s, 3H, 9 − CH_3), 1.65 (s, 1H, OH), 1.83 (s, 3H, 10 − CH_3), 2.31 (dd, J = 7, 13.7 Hz, 1H, 4 − CH_2), 2.37 (dd, J = 7, 13.7 Hz, 1H, 4 − CH_2), 4.91 (brs, 2H, 8 − CH_2), 5.06 (dd, J = 1.3, 10.7 Hz, 1H, 1 − CH_2), 5.21 (dd, J = 1.3, 17.3 Hz, 1H, 1 − CH_2), 5.62 (dt, J = 8, 15.6 Hz, 1H, 5 − CH), 5.94 (dd, J = 10.7, 17.3 Hz, 1H, 2 − CH), 6.21 (d, J = 15.6 Hz, 1H, 6 − CH); ^{13}C NMR 18.59 (CH_3, C − 10), 27.40 (CH_3, C − 9), 45.73 (CH_2, C − 4), 72.76 (C, C − 3), 111.92 (CH_2, C − 1), 115.49 (CH_2, C − 8), 124.89 (CH, C − 5), 136.90 (CH, C − 6), 141.70 (C, C − 7), 144.73 (CH, C − 2). MS *m*/*z* 152 (1), (M^+), 137 (2), 119 (4), 107 (2), 91 (2), 82 (75), 71(100), 67 (32), 55 (32), 53 (10), 43 (42), 41 (43), 39 (11), 27 (8).

RESULTS AND DISCUSSION

Hotrienol (**1**) was synthesized via the route shown in **Scheme 1**. The linalyl acetate (**2a**) was of a commercial grade. The other linalyl acylates, propionate (**2b**), isobutyrate (**2c**), and benzoate (**2d**) were prepared by the acylation of linalool, using *n*-BuLi and the corresponding acyl chloride. Thus, to the THF solution of linalool was added 1.6 mole *n*-BuLi solution in hexane at −20 °C, and then acyl chloride was added to give **2b**, **2c,** and **2d**, in 79, 76, and 62% yield, respectively.

The ene-type chlorination of terpenes is well-known (*14*, *15*), and that for linalyl acetate (**2a**) has already been reported (*16*−*18*). We tried this ene-type chlorination of **2a** using $Ca(OCl)_2$ and some additive acids and the best yield was obtained in a case of using H_3BO_3 as the acid (shown in **Table 1**). Thus, the ene-type chlorination of **2a** was carried out in CH_2Cl_2−H_2O solution at 5 °C for 5 h, to give γ-chloro-α-linalyl acetate (**3a**) in 88% isolated yield with 94% purity by distillation (**Table 1**). The distillate **3a** was found to be a diastereomixture by GC and ^{13}C NMR. The yield of (**3b**−**d**) in this chlorination are shown in **Table 2**.

Scheme 1. The synthesis of hotrienol from linalyl acylate



Reagents: (a) *n*-BuLi, RCOCl, THF, −20 °C ∼room temperature. 4.5 h, 62–79%. (b) 60% $Ca(ClO)_2$, H_3BO_3, CH_2Cl_2–H_2O, 5 °C, 4.5 h, 80–88%. (c) Li_2CO_3, LiBr, DMF, 130 °C, 2 h, 65–73%. (d) 10% NaOH-MeOH/H_2O, 20–30 °C, 6 h, 84–88%.

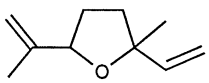
Table 1. The Ene-Type Chlorination of **2a**, Using $Ca(OCl)_2$ and a Variety of Acids

acid	conversion[b] (%)	yield of **3a** (%)
H_3BO_3 [a]	100	88
AcOH[a]	99	85
CO_2(dry ice)	98	81

[a] 7.8 Mol equiv for **2a** was used. [b] The conversion was measured by GC.

Table 2. The Ene-Type Chlorination Results of **3**, Using $Ca(OCl)_2$ and H_3BO_3

3	R	yield (%)
a	CH_3	88
b	C_2H_5	87
c	*i*-C_3H_7	85
d	C_6H_5	80



(5)

Figure 2. The structure of the by-product in dehydrochlorination.

In this ene-reaction using linalool, 2-methyl-2-vinyl-5-isopropenyl tetrahydrofuran (**5**) was primarily produced as the major byproduct on the basis of GC-MS. Compound **5** is a well-known compound (**Figure 2**) (*19*).

Next, we investigated the dehydrochlorination of **3a,** according to the conventional method (*20* and refs therein). Various bases were examined, and the best yield of (**4a**) was obtained when using LiF and Li_2CO_3 in DMF (**Table 3**). Furthermore, the different lithium halides were examined (**Table 4**), and the best result was obtained in the case using LiBr. For the treatment of (**3b**−**d**) under similar conditions, the yields of (**4b**−**d**) are shown in **Table 5**.

The hydrolysis of **4** by NaOH afforded Hotrienol **1** in good yield (**Table 6**). The scale-up production was carried out using **2a** as the starting material (see Materials and Methods), because **2a** is a commercially available and more cost-effective material.

Table 3. The Dehydrochlorination of **3a**, Using a Variety of Bases[a]

base	solvent	yield of **4a** (%)
NaOH	MeOH	0
NaH	EtOH-toluene	0
DBU	toluene	20
LiF/Li_2CO_3	DMF	65
LiF/Li_2CO_3	DMSO	21

[a] Reaction conditions were carried out according to the literature (*20*).

Table 4. The Dehydrochlorination of **3a**, Using Some Lithium Halides[a]

LiX	solvent	time (h)	yield of **4a** (%)
LiF	DMF	8	65
LiCl	DMF	8	56
LiBr	DMF	2	73

[a] Reaction conditions: 1.5 equivalent moles of LiX and 2.5 equivalent moles of Li_2CO_3 for **3a**. reaction temperature: 130 °C.

Table 5. The Dehydrochlorination Results of **4**, Using LiBr/Li_2CO_3

4	R	yield (%)
a	CH_3	73
b	C_2H_5	71
c	*i*-C_3H_7	69
d	C_6H_5	65

Table 6. The Yields of **1** by the Hydrolysis of **4**

4	R	yield of **1** (%)
a	CH_3	85
b	C_2H_5	86
c	*i*-C_3H_7	84
d	C_6H_5	88

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