

Original Article

A Convenient Synthesis of (4*S*, 6*Z*)- and (4*S*, 6*E*)-6-Dodecen-4-olide, Known to Significantly Contribute to Milk Flavor

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Abstract - A new synthesis route of (4*S*, 6*Z*)-6-dodecen-4-olide 1 and (4*S*, 6*E*)-6-dodecen-4-olide 2, which are known to flavor milk, is described. The condensation of (*R*)-epichlorohydrin and 1-heptyne using vinylmagnesium chloride gave (*R*)-chlorohydrin 3. 3 was reacted with dimethyl malonate, followed by hydrolysis and decarboxylation to give the (*R*)-lactone 4. 4 was hydrogenated with the Lindlar catalyst to give 1 in a total 49% yield. The *cis-trans*-isomerization of 1 using *p*-toluenesulfonic acid gave 2 in 64% yield.

Keywords - (4*S*, 6*Z*)-6-dodecen-4-olide, (4*S*, 6*E*)-6-dodecen-4-olide, (*R*)-epichlorohydrin, 1-heptyne, *Cis-trans*-isomerization.

1. Introduction

Optically active *cis*-6-dodecen-4-olide 1, which has been identified in butter [1,2], the male tarsal scent of black-tailed deer [3-5], the cultured broth of the microorganism *Sporobolomyces odorus* [6], in the lamb flavor from animals fed a lipid-protected dietary supplement [19], and in the pedal gland exudate of the bontebok [8]. The synthesis of the racemic and optically-active forms of 1 has been reported by various methods [9-16]. On the other hand, *trans*-6-dodecen-4-olide 2 has not been found in nature, and little has been reported about the synthesis of 2 except for obtaining a by-product [4]. The discriminant function for the difference

between 1 and 2 did not show a significant difference. However, the author postulates that *trans*-lactone 2 is considered a significant value as the milk-smelling compound. Furthermore, the previously reported synthetic methods of 1 are considered unsuitable for economic and large-scale production because the total yields are low and expensive reagents and available starting materials are used. To develop the practical syntheses of 1 and 2, the author has studied a new procedure and now reports the synthetic route of 1 and 2, which is an efficient, safe, and cost-effective process.

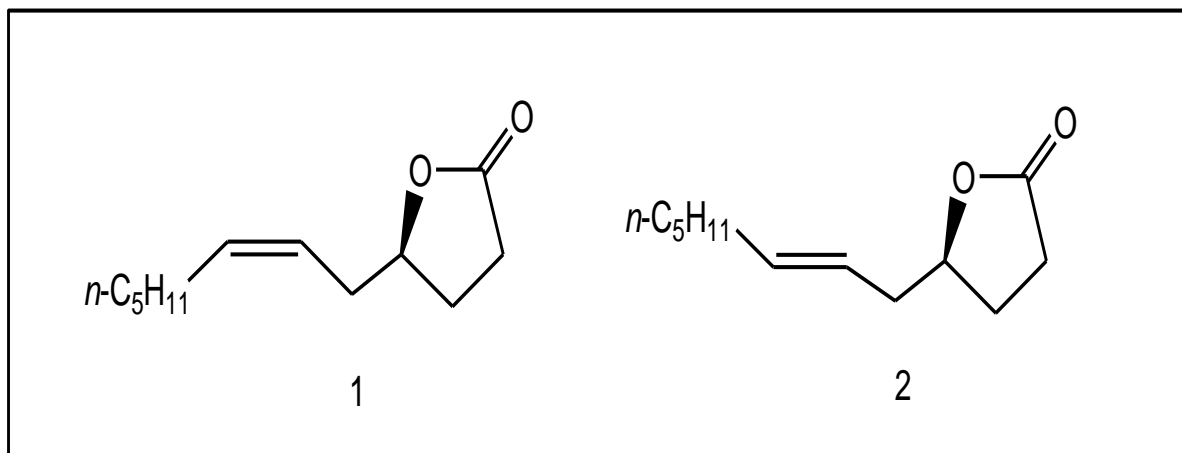
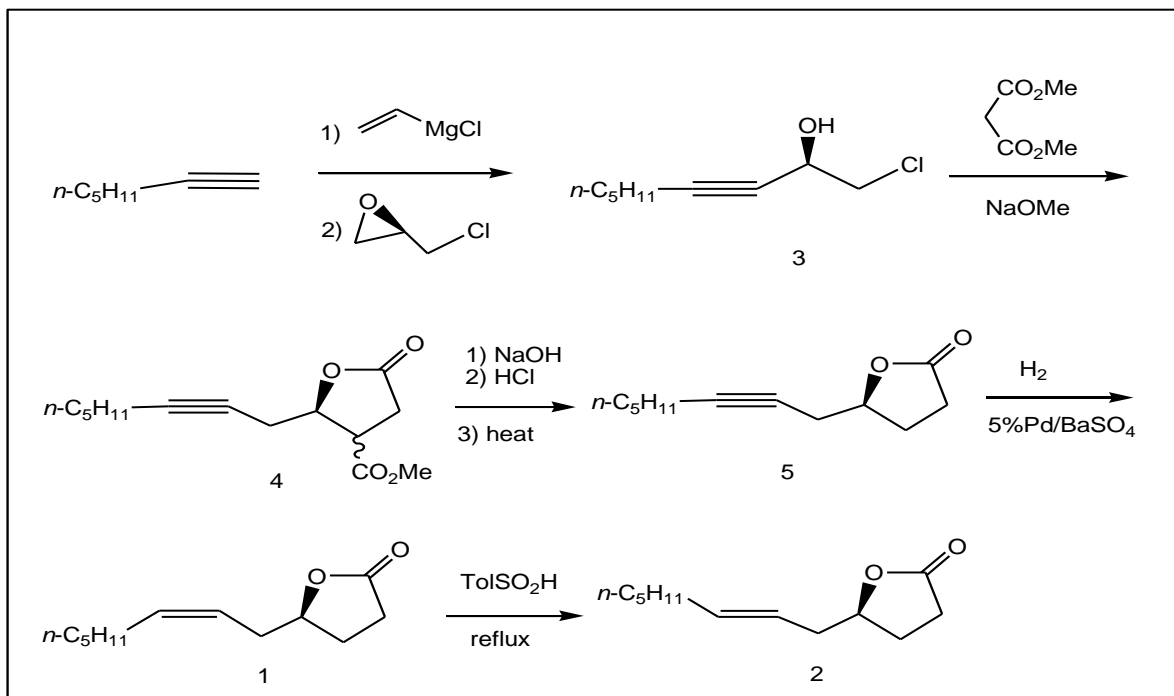


Fig. 1 The structures of (4*S*, 6*Z*)-6-dodecen-4-olide 1 and (4*S*, 6*E*)-6-dodecen-4-olide 2



2. Results and Discussion

(4*S*, 6*Z*)-6-Dodecen-4-olide **1** was synthesized by the route shown in Scheme. 1-Heptyne and (*R*)-epichlorohydrin were of commercial grades.



Scheme The synthetic routes of **1** and **2**

First, to the 1-heptyne magnesium complex in a THF solution from the preparation of 1-heptyne and vinyl magnesium chloride, (*R*)-epichlorohydrin was added at 30 °C to give chlorohydrin **3** in 80% yield. The distillate chlorohydrin **3** was 97% ee by GC using a chiral column (CHIRALDEX G-TA) without racemization. The condensation of **3** with excess dimethyl malonate gave the α -carbomethoxy- γ -heptyn- γ -lactone **4**, which was a spontaneously processed condensation and lactonization, in 90% yield. **4** was a mixture of the α - β -configuration with the ratio of 73/27 by GC. **4** was used in the next step without purification. **4** was then hydrolyzed by a NaOH solution and followed by a 10% HCl solution to give the α -carboxy- γ -heptyn- γ -lactone, then heated at 110 °C in toluene to form the (*S*)-decarboxylactone **5** in 89% yield from **4**. It is well known that the triple bond is reduced to the *cis*-type double bond by the Lindlar catalyst [16]. Thus, **5** was hydrogenated with Lindlar catalyst to yield **1** in 90%. The enantiomeric excess of **1** was 97% ee by GC using a chiral column. The *cis*-*trans*-isomerization of olefins by *p*-toluenesulfonic acid (PTSA), which does not rearrange double bonds, is known [17,18]. According to this information, **1** was reacted with PTSA at reflux for 6h, and the unchanged **1** was removed by silica gel column chromatography to give **2** in 60% yield.

Among the geometric isomers, the *cis*-isomer **1** was more floral and fluty, while the *trans*-isomer had a heavier and fatty character. The titer of the *trans*-form **2** is stronger than that of the *cis*-form. Therefore, *trans*-lactone **2** is considered to be significant as a milk flavor.

3. Materials and Methods

1-Heptyne and (*R*)-epichlorohydrin were purchased from Aldrich and Daiso (Osaka, Japan), respectively. All reagents and solvents were obtained commercially and used without further purification. Boiling points: uncorrected values. NMR: Bruker DRX-500. ¹H and ¹³C NMR were measured at 500 MHz and 125 MHz, respectively. The NMR spectra were recorded in CDCl₃ with TMS as the internal standard. The chemical shifts were given in δ (ppm). IR: Nicolet Avatar 360 FT-IR. MS: Hitachi M-80A mass spectrometer at 70 eV. GC was done using a Shimadzu GC-14A with an FID detector. Column 1; Neutrabond-1 produced by GL Sciences, Inc., Japan, $d_f = 0.25 \mu\text{m}$, 0.25 mm ID \times 30 m; carrier gas N₂, 0.1 MPa, oven temperature, 70 – 230 °C programmed at 5 °C /min; injection temperature, 230 °C, detector temperature, 250 °C. Column 2; CHIRALDEX G-TA produced by Advanced Separation Technologies, Inc., USA, $d_f = 0.25 \mu\text{m}$, 0.25 mm ID \times 30 m carrier gas N₂, 0.1 MPa, oven temperature, 80 °C isothermal, injection temperature, 230 °C, detector temperature, 230 °C.

3.1. Synthetic Procedures

3.1.1. (2R)-1-Chloro-4-decyn-2-ol (3)

A 1.94 M/L vinyl-magnesium chloride in THF (430 g, 835 mM, 1.3 equiv.) solution was dropwise added to 1-heptyne (61.8 g, 643 mM) at 35°C for 1h. The solution was stirred at 35 °C for 20 h. The solution was dropwise added (*R*)-epichlorohydrin (85.0 g, 918.6 mM, 97.8%ee) at 5 °C and stirred at 35°C for 7h. The reaction mixture was cooled to 5°C, then a 10% HCl solution (570 g) was added. The organic layer was washed with water (300 ml). The solvent was recovered, and the residue was distilled under reduced pressure to give 3 (97.0 g, 80%). Bp. 90 – 94°C/1 torr. $[\alpha]_D^{21} = -12.31^\circ$ (c = 2.8, CHCl₃), ¹H NMR: 0.90 (3H, t, J = 7Hz, CH₃), 1.29 – 1.37 (4H, m, CH₂), 1.46 – 1.51 (2H, m, CH₂), 2.14 – 2.18 (2H, m, CH₂), 2.43 – 2.56 (3H, m, CH₂), 3.62 (1H, dd, J = 6.2, 11.2 Hz), 3.71 (1H, dd, J = 4.6, 11.1 Hz), 3.94 (1H, m, OH); ¹³C NMR: 9.81 (CH₃), 13.91 (CH₃), 18.62(CH₂), 22.13 (CH₂), 24.67 (CH₂), 28.52 (CH₂), 31.03 (CH₂), 48.27 (CH₂), 69.98(CH), 74.32 (C), 83.89 (C); IR (neat): 3394, 2957, 2932, 2860, 1458, 1432, 1084, 1050 cm⁻¹; EI-MS (m/e, relative intensity): 173 (M⁺-15, 3), 155(3), 153 (2), 145 (6), 135 (17), 132(13), 121 (10), 109 (50), 95 (57), 83 (50), 81 (87), 68 (57), 67 (80), 54 (100), 43 (47), 41 (33).

3.1.2. (4R)-6-Dodecyn-2*-methoxycarbonyl-4-olide (4)

Dimethyl malonate (520.9 g, 3.94 M) and NaOMe (228.2 g, 1.18 M) were stirred at 60°C under N₂ gas. After 1h, 3 (75.0 g, 399 mM) was dropwise added to the solution at the same temperature and reacted for 1h. After cooling, AcOH (94.7 g, 1.58 M) and water (600 g) were added to the reaction mixture. The organic layer was separated, and the residue was distilled under reduced pressure to give 4 (90.5 g, 90%). Bp. 145 – 150 °C/0.3 torr., $[\alpha]_D^{22} = +4.30^\circ$ (c = 1.37, MeOH), ¹H NMR: 0.92 (3H, t, J = 7.2Hz, CH₃), 1.28 – 1.39 (4H, m, CH₂), 1.48 – 1.53 (2H, m, CH₂), 2.12 – 2.18 (2H, m, CH₂), 2.37 – 2.44 (1/2H, m, CH₂), 2.51 – 2.64 (2H, m, CH₂), 2.71 – 2.75 (1/2H, m, CH₂), 2.75 – 2.85 (1/2H, m, CH₂), 3.65 – 3.72 (1/2H, m, CH), 3.75 – 3.79 (1/2H, m, CH), 3.83 (3H, s, CH₃), 4.52 – 4.59 (1/2H, m, CH), 4.74 – 4.79 (1/2H, m, CH); ¹³C NMR: 13.88 (CH₃), 18.55 (CH₂), 22.09 (CH₂), 25.18 (CH₂), 25.41 (CH₂), 28.34 (CH₂), 28.39 (CH₂), 30.39 (CH₂), 30.39 (CH₂), 46.49 (CH), 46.94 (CH), 53.00 (CH₃), 53.07 (CH₃), 72.95 (C), 73.04 (C), 83.86 (C), 84.11 (C), 167.96 (CO), 168.23 (CO), 171.15 (CO), 171.46 (CO); IR (neat): 2956, 2933, 2860, 1785, 1741, 1640, 1437, 1354, 1163, 1032 cm⁻¹; EI-MS (m/e, relative intensity): 251 (M⁺-1, 3), 238(2), 220 (3), 192 (3), 164 (6), 143(100), 134 (10), 115 (17), 111 (90), 91 (7), 83 (7), 67 (7), 55 (17), 41 (7).

3.1.3. (4S)-6-Dodecyn-4-olide (5)

4 (80.0 g, 317 mM) and 10% NaOH (250 g) were stirred at 70 °C for 2h. After cooling, 10% HCl (250 g) and toluene (300 mL) were added to the reaction mixture. The toluene layer was washed with brine; then, the toluene was recovered by giving a viscous oil (67.8 g, 89%). The product was

heated and stirred at 90 – 160 °C until the CO₂ evolution stopped. After cooling, the product was distilled under reduced pressure to give 5 (47.0 g, 85%). The optical purity was 98%ee by GC (Column-2). Bp. 120 – 123 °C/0.3 torr. {lit.,[8] 79-81°C/0.05 mmHg, lit.,[11] 150-160C/0.5 torr.}, $[\alpha]_D^{22} = +7.63^\circ$ (c = 1.44, MeOH), ¹H NMR: 0.89 (6H, t, J = 7.3Hz, CH₃), 1.30 – 1.35 (4H, m, CH₂), 1.46 – 1.51 (2H, m, CH₂), 2.09 – 2.16 (3H, m, CH₂), 2.34 – 2.42 (1H, m, CH₂), 2.49 – 2.62 (4H, m, CH₂), 4.58 – 4.63 (1H, m); ¹³C NMR: 13.75 (CH₃), 18.41 (CH₂), 21.96 (CH₂), 25.30 (CH₂), 26.27 (CH₂), 28.27 (CH₂), 30.81 (CH₂), 73.43 (C), 77.96(CH), 83.29 (C), 176.71 (CO); IR (neat): 2932, 2860, 1779, 1460, 1422, 1179, 1034 cm⁻¹; EI-MS (m/e, relative intensity): 195(M⁺-1, 3), 179 (3), 165 (6), 151 (6), 147 (10), 134 (10), 111 (10), 109 (13), 107 (13), 86 (67), 85 (100), 79 (10), 57 (20), 55 (10), 29 (37).

3.1.4. (4S, 6Z)-6-Dodecen-4-olide (1)

5 (40 g, 206 mM) in EtOAc (200 mL) was charged into a 500-mL autoclave and 5%Pd-BaSO₄ (0.1 g) and thiophene (0.2 g) were added under N₂ gas. After the H₂ gas (5MPa) was replaced, it was reacted at 20 °C for 2h. The catalyst was then filtered off. The solvent was recovered, and the residue was distilled under reduced pressure to give 1 (36.3 g, 90%). The optical purity was 97.5%ee by GC (Column-2). Bp. 114 – 116 °C/0.2 torr. {lit., [11] 150 – 160°C/0.5 mm}, $[\alpha]_D^{21} = +18.15^\circ$ (c = 2.9, MeOH) {lit., [12] $[\alpha]_D^{20} = +15.0^\circ$ (c = 0.1, MeOH), lit., [13] $[\alpha]_D^{25} = +16.5^\circ$ (c = 2.6, MeOH); lit., [15] $[\alpha]_D^{23} = +17.7^\circ$ (c = 3.7, MeOH)}, ¹H NMR: 0.90 (3H, t, J = 6.8Hz, CH₃), 1.27 – 1.39 (6H, m, CH₂), 1.87 – 1.95 (1H, m, CH₂), 2.01 – 2.08 (2H, m, CH₂), 2.29 – 2.34 (1H, m, CH₂), 2.38 – 2.45 (1H, m, CH₂), 2.50 – 2.54 (3H, m, CH₂), 4.50 – 4.56 (1H, m), 5.33 – 5.39 (1H, m), 5.56 – 5.61 (1H, m); ¹³C NMR: 13.96 (CH₃), 22.46 (CH₂), 27.09 (CH₂), 27.37(CH₂), 28.69 (CH₂), 29.07 (CH₂), 31.41 (CH₂), 32.84 (CH₂), 80.23 (CH), 122.12 (=CH), 134.16 (=CH), 177.07 (CO); IR (neat): 3011, 2857, 1779, 1460, 1422, 1350, 1179, 1028 cm⁻¹; EI-MS (m/e, relative intensity): 196 (M⁺, 6), 178 (3), 160 (2), 136 (2), 121 (3), 100 (3), 85 (100), 69 (6), 55 (6).

3.1.5. (4S, 6E)-6-Dodecen-4-olide (2)

To 1 (33.35 g, 170 mM) in dioxane (135 mL), PTSA (2.60 g, 17 mM) was added and allowed to react at 110 °C for 3h. The solvent was then recovered. Heptane (150 mL) and 1N NaOH (50 mL) were added to the residue, and the organic layer was washed with 1N NaOH and brine. The heptane was recovered, and the residue was distilled under reduced pressure to give the crude 2. The purification of the crude 2 by silica gel column chromatography (EtOAc: hexane = from 1:20 to 1:5) afforded the pure 2. (21.56 g, 64%). The optical purity was 98 %ee by GC. Bp. 106 – 109 °C/0.1 torr., $[\alpha]_D^{21} = +22.19^\circ$ (c = 2.9, MeOH), ¹H NMR: 0.88 (3H, t, J = 6.8Hz, CH₃), 1.24 – 1.39 (6H, m, CH₂), 1.88 – 1.96 (1H, m, CH₂), 2.00 – 2.08 (2H, m, CH₂), 2.25 – 2.37 (2H, m, CH₂), 2.41 – 2.49 (1H, m, CH₂), 2.50 – 2.57 (2H, m,

CH₂), 4.49 – 4.55 (1H, m), 5.34 – 5.40 (1H, m), 5.55 – 5.61 (1H, m); ¹³C NMR: 13.97 (CH₃), 22.42(CH₂), 26.87 (CH₂), 28.88 (CH₂), 31.28 (CH₂), 32.51 (CH₂), 38.25 (CH₂), 80.27 (CH), 122.92 (=CH), 135.36 (=CH), 177.18 (CO); IR (neat): 2927, 2856, 1778, 1461, 1423, 1353, 1179, 1025 cm⁻¹; EI-MS (m/e, relative intensity): 196 (M⁺, 3), 180 (3), 162 (3), 141 (3), 128 (11), 114(6), 100 (6), 85 (100), 83(9), 69 (11), 55 (9).

4. Conclusion

The author has studied the new synthetic route of lactones 1 and 2 from the condensation of the optically-

active (*R*)-epichlorohydrin and 1-heptyne, and now report the practical and effective synthesis of 1 and 2, and with the result to provide high purity odorous compounds as the milk flavor.

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