Efficient Synthesis of (3S,4R)-(+)-3-Methyl-6-hepten-4-olide

Woosun Jun, Yunkyung Jeong, and Ho-Jung Kang

Department of Chemistry, Kyunghee University, Seoul 130-701, Korea. *E-mail: hjkang@khu.ac.kr

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γ-Butyrolactone functionality possesses great importance in natural product chemistry and constitutes an essential part of many molecules with pharmacological applications. The existence of γ-butyrolactone ring as a constitutional unit in many natural products attracted lots of interests on the synthesis and configurational assignments of variously substituted γ-butyrolactones. In our synthetic study of massarilactone A, trans β-methyl-γ-allyl-γ-butyrolactone (3-methyl-6-hepten-4-olide) was selected to be a suitable early material. Several routes for racemic synthesis of cis and trans β-methyl-γ-allyl-γ-butyrolactone were known. At first, synthesis of optically active 3-methyl-6-hepten-4-olide was envisaged to be similar to that of eldanolide. But some preliminary work led us to realize that more efficient synthetic pathway should be devised for a large quantity of material. Here we wish to report a short and efficient synthesis of (3S,4R)-(+)-3-methyl-6-hepten-4-olide (1).

In Scheme 1, commercially available (S)-(+)3-hydroxy-2-methylpropionate (2) was silylated with TBDMSCl and its ester function was reduced to aldehyde using DIBAH. Following addition of allylmagnesium bromide to the aldehyde produced a diastereomeric mixture of alcohols 3 and 4 which was easily separated by MPLC (3 : 4 = 1 : 4). Alcohol 3 had a right configuration for our purpose and alcohol 4 needs to be inverted at its hydroxyl site. Alcohol 3 was converted to cyanooxolol 5 through a series of reactions including desilylation, selective tosylation and displacement to cyanide. Sequential desilylation, bismesylation and selective displacement of alcohol 4 with NaCN generated cyanomethylene intermediate which was then smoothly inverted to its acetate 6 using CsOAc.

Finally, both cyanooxolol 5 and acetate 6 were successfully transformed into the target material (3S,4R)-(+)-3-methyl-6-hepten-4-olide (1) under hydrolytic condition with c-HCl.

In conclusion, (3S,4R)-(+)-3-methyl-6-hepten-4-olide (1) was efficiently synthesized from (S)-(+)3-hydroxy-2-methylpropionaae (2) as a staring material by 7 steps in overall yield of 37%. This protocol can also be applied effectively to the synthesis of optically active eldanolide and related compounds.

Experimental Section

1-(tert-Butyldimethylsilyloxy)-2-methylhex-5-en-3-ol (3 and 4). A mixture of ester 1 (15.1 g, 128 mmol), imidazole (26.1 g, 384 mmol), and TBDMSCl (23.2 g, 154 mmol) in CHCl₃ (130 mL) was stirred for 1 h. before it was quenched with H₂O. The resulting mixture was washed with H₂O (50 mL × 3) and the aqueous layers were extracted with CHCl₃ (50 mL × 3). The combined organic layers were dried over MgSO₄, concentrated, and the residue was purified by silica gel chromatography (elution with hexane containing 7.7% EtOAc) to give a desired silylated ester (29.7 g, 100%).

To a toluene solution (150 mL) of the above silylated ester (11.6 g, 50.0 mmol) at −95 ℃ was added DIBAH (150 mL, 150 mmol, 1 M in hexane) and the resulting mixture was stirred for 2 h before it was quenched with methanol (10 mL) and warmed to room temperature. An aqueous solution of citric acid (100 mL, 1 M) was added and the aqueous
layer was extracted with CH₂Cl₂ (100 mL × 3). Normal work-up gave crude aldehyde which was dissolved in THF (60 mL). Allylmagnesium bromide (40 mL, 40 mmol, 1 M in Et₂O) was added slowly to the solution at 0°C and stirring continued for 1 h. The resulting solution was quenched with aqueous NaHCO₃ (50 mL, saturated) and extracted with CH₂Cl₂ (100 mL × 3). The combined organic layers were washed with H₂O (100 mL) and brine (100 mL), dried over MgSO₄, and concentrated to produce crude alcohols 3 and 4 which were purified by MPLC (elution with 7.7% EtOAc in hexane) to yield pure alcohol 3 (3.52 g, 29%) and alcohol 4 (5.65 g, 46%).

To a stirred solution of alcohol 3 of 48% HF/CH₃CN (20 mL) was added aqueous HF (30 mL, 5% v/v 0.07 (s, 6H).

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\begin{align*}
\text{δ} & = 7.4, 10.0 \text{ Hz, 1H), 2.36 (dd, } J = 7.4, 14.2 \text{ Hz, 1H), 2.21 (dt, } J = 14.2, 7.6 \text{ Hz, 1H), 1.79-1.69 (m, 1H), 0.90 \text{ (s, 9H), 0.87 (d, } J = 6.9, 3 \text{ Hz), 0.08 (s, 6H).}
\end{align*}
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The reaction mixture was quenched with saturated NaHCO₃ solution (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic phases were washed with H₂O, dried over MgSO₄, and concentrated to give crude bismesylate (3.89 g) which was used in the next step without further purification. A DMSO solution (30 mL) of crude bismesylate and NaCN (3.50 g, 71.5 mmol) was stirred for 4 h at 50°C before EtOAc (200 mL) was added to the reaction mixture. The resulting solution was washed with H₂O (100 mL × 3) and aqueous phases were extracted with EtOAc (50 mL × 3). The combined organic layers were dried over MgSO₄ and concentrated to produce crude cyanide (1.77 g) which was dissolved in benzene (20 mL). CsOAc (4.70 g, 24.5 mmol) and 18-Crown-6 (1.08 g, 4.08 mmol) were added to it and the resulting mixture was refluxed for 3 h. usual work-up with EtOAc gave a crude oil which was purified by silica gel chromatography (elution with 25% EtOAc in hexane) to produce cyanide 6 (1.23 g, 47% overall for 4 steps). [δₒ = +58.5° (c 2.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.76-5.65 (m, 1H), 5.13-5.08 (m, 2H), 4.83 (dt, J = 5.1, 6.8 Hz, 1H), 2.68 (dd, J = 4.9, 16.8 Hz, 1H), 2.47-2.30 (m, 2H), 2.25 (dd, J = 8.1, 16.8 Hz, 1H), 2.17-2.08 (m, 1H), 2.06 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H).

(3S,4R)-(+)-3-Methyl-6-hepten-4-olide (1). A solution of cyanide 6 (1.23 g, 6.79 mmol) in concentrated HCl (15 mL) was stirred at room temperature for 4 hr before it was quenched with saturated NaHCO₃ at 0°C. When the solution became neutral, CH₂Cl₂ (100 mL) was added to it. The aqueous phase was separated and extracted with CH₂Cl₂ (50 mL × 3). The combined organic layers were washed with H₂O (100 mL), dried over MgSO₄ and concentrated to produce a crude oil which was purified by silica gel chromatography (elution with 20% EtOAc in hexane) to produce lactone 1 (0.79 g, 83%).

Cyanide 5 was also subjected to the same hydrolysis procedure and lactone 1 was produced in the same yield. [δₒ = +58.5° (c 2.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.82 (dd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.19-5.13 (m, 1H), 4.08 (dd, J = 5.1, 6.8 Hz, 1H), 2.67 (dd, J = 7.9, 17.0 Hz, 1H), 2.51-2.35 (m, 2H), 2.34-2.23 (m, 1H), 2.18 (dd, J = 9.3, 17.0 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H).

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References


11. Stereochemistry of 3 and 4 was determined as follows.