Efficient Synthesis of (3*S*,4*R*)-(+)-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*

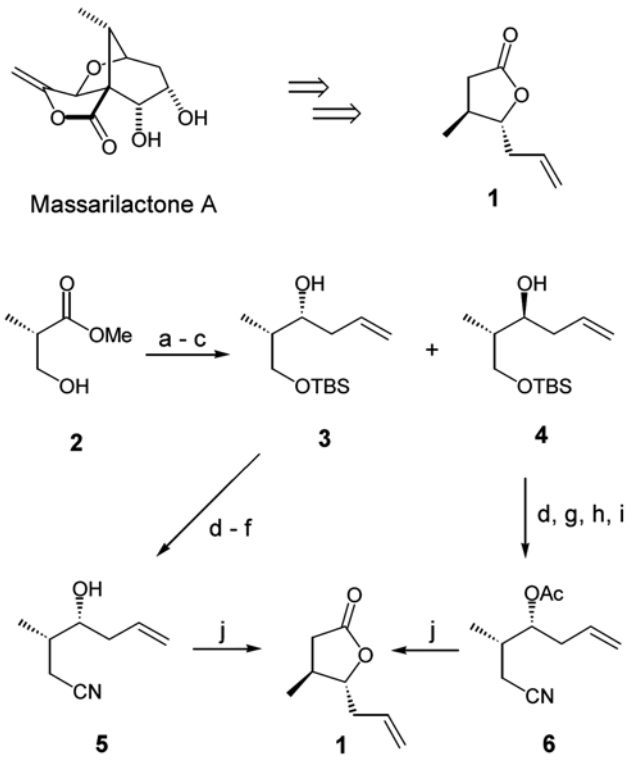
Received August 3, 2005

Key Words : Massarilactone A, γ-Butyrolactone, 3-Methyl-6-hepten-4-olide

γ-Butyrolactone functionality possesses great importance in natural product chemistry[1] and constitutes an essential part of many molecules with pharmacological applications.[2] 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.[3,4,5] In our synthetic study of massarilactone A,[6] 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.[7] At first, synthesis of optically active 3-methyl-6-hepten-4-olide was envisaged to be similar to that of eldanolide.[8] 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 (3*S*,4*R*)-(+)-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.[9] 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 : 1.4).[10,11] 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 cyanoalcohol **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 cyanomesylate intermediate which was then smoothly inverted to its acetate **6** using CsOAc.[12] Finally, both cyanoalcohol **5** and acetate **6** were successfully transformed into the target material (3*S*,4*R*)-(+)-3-methyl-6-hepten-4-olide (**1**) under hydrolytic condition with *c*-HCl.

In conclusion, (3*S*,4*R*)-(+)-3-methyl-6-hepten-4-olide (**1**) was efficiently synthesized from (*S*)-(+)-3-hydroxy-2-methylpropionate (**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.



Scheme 1. Synthesis of optically active lactone **1**. reagents and conditions: (a) TBDMSCl, Im, CH_2Cl_2, 100%; (b) DIBAH, Toluene, −95 °C; (c) CH_2=$CHCH_2MgBr$, THF, 75% (overall 2 steps); (d) HF, CH_3CN, 100%; (e) TsCl, DMAP, Et_3N, CH_2Cl_2, 81%; (f) NaCN, DMSO, 50 °C, 94%; (g) MsCl, Py, 95%; (h) NaCN, DMSO, 50 °C, 60%; (i) CsOAc, 18-Cr-6, PhH, reflux, 83%; (j) *c*-HCl, 83%.

Experimental Section

1-(*tert*-Butyldimethylsilanyloxy)-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 CH_2Cl_2 (130 mL) was stirred for 1 h. before it was quenched with H_2O. The resulting mixture was washed with H_2O (50 mL × 3) and the aqueous layers were extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried over $MgSO_4$, 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 °C 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 CH_2Cl_2 (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 Et_2O) was added slowly to the solution at 0 °C and stirring continued for 1 h. The resulting solution was quenched with aqueous $NaHCO_3$ (50 mL, saturated) and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, 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%).

3: $[\alpha]_D$ +16.8° (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.87 (m, 1H), 5.14-5.08 (m, 2H), 3.79 (dd, *J* = 4.2, 10.0 Hz, 1H), 3.72 (d, *J* = 2.9 Hz, 1H), 3.63-3.57 (m, 1H), 3.59 (dd, *J* = 7.4, 10.0 Hz, 1H), 2.36 (md, *J* = 14.2 Hz, 1H), 2.21 (dt, *J* = 14.2, 7.6 Hz, 1H), 1.79-1.69 (m, 1H), 0.90 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 6H).

4: $[\alpha]_D$ +6.2° (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H), 5.14-5.06 (m, 2H), 3.89-3.85 (m, 1H), 3.76 (dd, *J* = 4.0, 9.8 Hz, 1H), 3.66 (dd, *J* = 5.2, 9.8 Hz, 1H), 3.03 (br d, *J* = 2.0 Hz, 1H), 2.32-2.15 (m, 2H), 1.78-1.70 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

(3*S*,4*R*)-(+)-4-Hydroxy-3-methylhept-6-enenitrile (5). To a stirred solution of alcohol **3** (2.24 g, 9.17 mmol) in acetonitrile (20 mL) was added aqueous HF (30 mL, 5% v/v of 48% HF/CH_3CN) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C before being quenched with Na_2CO_3 powder (4 g). Filtration and concentration of the resulting mixture gave crude diol which was dissolved in CH_2Cl_2 (170 mL). Tosyl chloride (2.45 g, 12.8 mmol) was added to it and the whole mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (500 mL × 3). The combined organic phases were washed with H_2O, dried over $MgSO_4$, and concentrated to give crude tosylate which was purified by silica gel chromatography (elution with 25% EtOAc in hexane) to yield pure tosylate (2.11 g, 81% for overall 2 steps).

A solution of tosylate and NaCN (1.82 g, 37.1 mmol) in DMSO (20 mL) was stirred for 4 h at 50 °C before EtOAc (200 mL) was added to the reaction mixture. The resulting solution was washed with H_2O (100 mL × 3) and aqueous phases were extracted with EtOAc (50 mL × 3). The combined organic layers were dried over $MgSO_4$ and concentrated to produce a crude product which was purified by silica gel chromatography (elution with 25% EtOAc in hexane) to yield cyanide **5** (0.972 g, 94%). $[\alpha]_D$ −34.0° (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.76 (m, 1H), 5.23-5.17 (m, 2H), 3.49-3.45 (m, 1H), 2.56 (dd, *J* = 4.5, 16.7 Hz, 1H), 2.48 (dd, *J* = 7.4, 16.7 Hz, 1H), 2.43 (md, *J* = 14.0 Hz, 1H), 2.12 (dt, *J* = 14.0, 8.5 Hz, 1H), 1.92-1.84 (m, 2H), 1.12 (d, *J* = 5.2 Hz, 3H).

(3*S*,4*R*)-(+)-4-Acetoxy-3-methylhept-6-enenitrile (6). To a stirred solution of alcohol **4** (3.50 g, 14.3 mmol) in acetonitrile (20 mL) was added aqueous HF (40 mL, 5% v/v of 48% HF/CH_3CN) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C before being quenched with Na_2CO_3 powder (5 g). Filtration and concentration of the resulting mixture gave crude diol which was dissolved in pyridine (20 mL). Mesyl chloride (4.93 g, 43.0 mmol) was added to it and the whole mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic phases were washed with H_2O, dried over $MgSO_4$, 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 H_2O (100 mL × 3) and aqueous phases were extracted with EtOAc (50 mL × 3). The combined organic layers were dried over $MgSO_4$ 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). $[\alpha]_D$ +58.5° (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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).

(3*S*,4*R*)-(+)-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 $NaHCO_3$ at 0 °C. When the solution became neutral, CH_2Cl_2 (100 mL) was added to it. The aqueous phase was separated and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$ 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%).

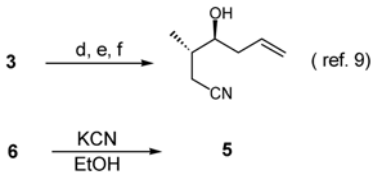
Cyanide **5** was also subjected to the same hydrolysis procedure and lactone **1** was produced in the same yield. $[\alpha]_D$ +58.5° (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.19-5.13 (m, 1H), 4.08 (dt, *J* = 5.1, 6.8 Hz, 1H), 2.67 (dd, *J* = 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).

Acknowledgement. The authors are grateful to Kyunghee University for its financial support (University Research Fund 2003) for this work.

References

1. Nakanishi, K.; Goto, T.; Ito, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha Ltd.: Tokyo, 1974.
2. Levine, F. A.; Ferrendelli, F. A.; Corey, P. F. *J. Med. Chem.* **1986**,

29, 1996.
3. For reviews on γ-butyrolactone syntheses, see (a) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661. (b) Boyd, G. V. In *The Chemistry of Acid Derivatives*, Suppl. B, Part 1; Patai, S., Ed.; John Wiley: New York, 1979; Chapter 8, p 491. (c) Grieco, P. A. *Synthesis* **1975**, 65. (d) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.
4. (a) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725. (b) Ortuño, R. M.; Ariza, J.; Font, J. *Tetrahedron Lett.* **1991**, 1979. (c) Naji, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241. (d) Vekemans, J. A. J. M.; Franken, G. A. M.; Chittenden, G. J. F.; Godefroi, E. F. *Tetrahedron Lett.* **1987**, 2299. (e) Wood, W. W.; Rashid, A. *Tetrahedron Lett.* **1987**, 1933. (f) Kang, S.-G.; Shin, D.-S.; Lee, J.-O.; Goh, H.-G. *Bull. Korean Chem. Soc.* **1986**, *7*, 144. (g) Kang, H.-Y.; Ji, Y.; Yu, Y.-K.; Yu, J.-Y.; Lee, Y.; Lee, S.-J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1819.
5. (a) Davies, S. G.; Polywka, R.; Warner, P. *Tetrahedron* **1990**, *46*, 4847. (b) Jaine, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946. (c) Hussain, S. M. A. T.; Ollis, W. D.; Smith, D.; Stoddart, J. F. *J. C. S. Perkin I* **1975**, 1480.
6. Oh, H.; Swenson, D. C.; Gloer, J. B.; Shearer, C. A. *Tetrahedron Lett.* **2001**, 975.
7. (a) Yadav, J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1824. (b) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. I* **1986**, 1351. (c) Janowitz, A.; Kunz, T.; Handke, G.; Reissig, H.-U. *Synlett* **1989**, 24. (d) Kunz, T.; Reissig, H.-U. *Angew. Chem.* **1988**, *100*, 297.
8. Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: New York, 1992; Vol 9, p 491.
9. Aissa, C.; Riveiros, R.; Ragot, J.; Furstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512.
10. (a) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181. (b) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.
11. Stereochemistry of **3** and **4** was determined as follows.



12. Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, 6145.