

### Enantioselective Synthesis of (4*S*,*E*)-4-Methylhex-2-enoic Acid and (4*R*,*E*)-4-Methylhex-2-enoic Acid

Suk-Ku Kang\*, Jae-Hoon Jeon, and Young-Won Park

Department of Chemistry, Sung Kyun Kwan University,  
Natural Science Campus, Suwon 440-746

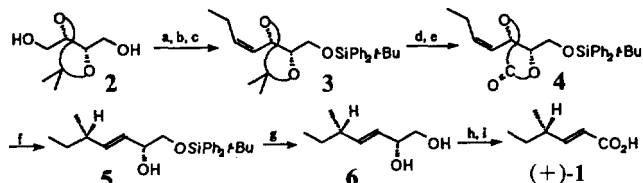
Received January 8, 1993

(+)-(4*S*,*E*)-4-Methylhex-2-enoic acid [(+)-1]<sup>1</sup> is the key constituent of the peptide antibiotics leucinostatins possessing antibiotic, antitumoral, antibacterial and phytotoxic activities. Three syntheses have been reported<sup>2</sup> for (+)-1. In connection with our research programs to utilize optically active carbonates and sulfites as activating groups,<sup>3</sup> we were interested in the synthesis of (+)-1. Here we report an enantioselective synthesis of (+)-1 and its enantiomer (-)-1 based on *S<sub>N</sub>2'* addition of organocuprates to chiral allylic cyclic carbonates.



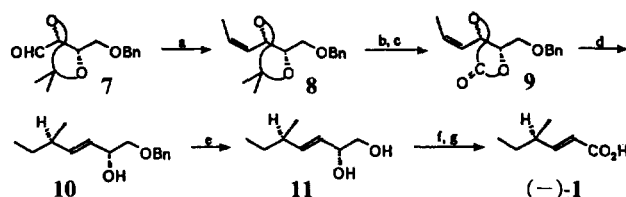
The acetonide 3<sup>4</sup> was prepared from (2*S*,3*S*)-2,3-*O*-isopropylidenedioxy-1,4-butanediol 2<sup>5</sup> in a three-step sequence *via* monosilylation, Swern oxidation<sup>6</sup> and Wittig olefination reaction. Deprotection of the acetonide followed by carbonylation with carbonyl diimidazole afforded the allylic cyclic carbonate 4. Highly diastereoselective (>99%) *S<sub>N</sub>2'* addition of 4 with MeMgBr, CuI (3 mol%), and BF<sub>3</sub>·Et<sub>2</sub>O afforded the allylated compound 5<sup>4</sup>, which constitute the key step for the introduction of chirality. The diastereoselection was determined by NMR spectroscopy with a chiral shift reagent [<sup>1</sup>H-NMR, 300 MHz, chiral Eu(tfc)<sub>3</sub>]. The exclusive (*E*)-stereochemistry was judged by <sup>1</sup>H-NMR (300 MHz) coupling constants of the two vinyl protons. Deprotection of the silyl group in 5 gave the diol 6<sup>4</sup>, which was transformed into the target compound, (+)-1<sup>5</sup>, [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +47.8 (*c* 0.12, CHCl<sub>3</sub>), (lit.<sup>1b</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +49.7) by oxidative cleavage with NaIO<sub>4</sub> followed by NaClO<sub>2</sub> oxidation (Scheme 1).

Alternatively, the enantiomer (-)-1 was also synthesized



a) NaH, *t*-BuPh<sub>2</sub>SiCl, DME, -20°C, 3 h (91%); b) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 1 h (91%); c) *n*-BuLi, Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>-CH<sub>2</sub>CH<sub>2</sub>Br<sup>-</sup>, THF, -78°C, 10 h (63%); d) 70% AcOH, 40°C, 5 h (89%); e) CO(Im)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> rt, 10 min (93%); f) MeMgBr (2 equiv), CuI (3 mol%), BF<sub>3</sub>·Et<sub>2</sub>O (1 equiv), THF, -78°C, 30 min (87%); g) (*n*-Bu)<sub>4</sub>NF, THF, rt, 2 h (96%); h) NaIO<sub>4</sub>, SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 1 h (89%); i) NaClO<sub>2</sub>, *t*-BuOH, NaH<sub>2</sub>PO<sub>4</sub>, rt, 8 h (68%).

Scheme 1.



a) *n*-BuLi, Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>CH<sub>2</sub>Br<sup>-</sup>, THF, -78°C, 10 h (75%); b) Dowex 50 W X 8 resin, MeOH, 45°C, 6 h (92%); c) CO(Im)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 min (84%); d) EtMgBr (2 equiv), CuI (3 mol%), BF<sub>3</sub>·Et<sub>2</sub>O (1 equiv), THF, -78°C, 30 min (75%); e) Na, NH<sub>3</sub> (1), THF, -78°C, 3 h (91%); f) NaIO<sub>4</sub>, SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 1 h (90%); g) NaClO<sub>2</sub>, *t*-BuOH, NaH<sub>2</sub>PO<sub>4</sub>, rt, 8 h (67%).

Scheme 2.

from 4-*O*-benzyl-2,3-isopropylidene-*L*-threose 7<sup>6b</sup> by the similar methodology, which is shown in Scheme 2.

**Acknowledgement.** Generous financial support by Korea Science and Engineering Foundation (KOSEF)-the Organic chemistry Research Center (OCRC) is gratefully acknowledged.

### References and Notes

- (a) T. Arai, Y. Mikami, K. Fukushima, and K. Yazawa, *J. Antibiotics*, **26**, 157 (1973); (b) Y. Mori, M. Tsuboi, M. Suzuki, K. Fukushima, and T. Arai, *J. Chem. Soc. Chem. Commun.*, **94** (1982); (c) J. G. Stroh, K. L. Rinehart, J. Carter Cook, T. Kihara, M. Suzuki, and T. Arai, *J. Am. Chem. Soc.*, **108**, 858 (1986).
- (a) V. Galamb, M. Gopal, and H. Alper, *Organometallics*, **2**, 801 (1983); (b) L. Crombie and P. A. Jenkins, *J. Chem. Soc. Chem. Commun.*, **870** (1967); (c) L. Crombie and P. A. Jenkins, *J. Chem. Soc. Perkin Trans. I*, 1090 (1975); (d) M. E. Hadrami, J-P. Lavergne, P. Viallefont, M. Y. Itto, and A. Hasnaoui, *Tetrahedron Lett.*, **32**, 3985 (1991).
- (a) S-K. Kang, D-H. Lee, Y-S. Kim, and S-C. Kang, *Synth. Commun.*, **22**, 1109 (1992); (b) S-K. Kang, Y-W. Park, S-G. Kim, and J-H. Jeon, *J. Chem. Soc. Perkin Trans. I*, 405 (1992); (c) S-K. Kang, Y-W. Park, D-H. Lee, H-S. Sim, and J-H. Jeon, *Tetrahedron: Asymmetry*, **3**, 705 (1992); (d) S-K. Kang, S-G. Kim, and J-S. Lee, *ibid.*, **3**, 1139 (1992); (e) S-K. Kang, S-G. Kim, and D-G. Cho, *ibid.*, **3**, 1509 (1992); (f) S-K. Kang, S-G. Kim, D-G. Cho, and J-H. Jeon, *Synth. Commun.*, **23**, 681 (1993); (g) S-K. Kang, D-H. Lee, H-S. Sim, and J-S. Lim, *Tetrahedron Lett.*, **34**, 91 (1993); (h) S-K. Kang, S-G. Kim, D-C. Park, J-S. Lee, and W-J. Yoo, *J. Chem. Soc. Perkin Trans. I*, **9** (1993).
- Satisfactory spectral and physical data were obtained for all new compound and are in accord with the assigned structure. Selected spectral data are as follows. (+)-1: <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 0.92 (t, 3H), 1.05 (d, 3H), 1.45 (m, 2H), 2.22 (m, 1H), 5.80 (d, 1H, *J* = 16 Hz), 6.89 (dd, 1H, *J* = 16.8 Hz), 12.25 (s, 1H). IR (neat) 3600-2400, 1685, 1640 cm<sup>-1</sup>. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +47.8 (*c* 0.12, CHCl<sub>3</sub>) (-)-1: [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -47.2 (*c* 0.14, CHCl<sub>3</sub>) 5: TLC; SiO<sub>2</sub>, EtOAc/hexane 1 : 3, *R<sub>f</sub>* = 0.71. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H, *J* = 7.5 Hz), 0.96 (d, 3H, *J* = 6.9 Hz), 1.08 (s, 9H), 1.26 (m, 2H), 2.05 (m, 1H), 3.56 (m, 1H), 3.65 (m, 1H), 4.20 (m, 1H), 5.35 (dd, 1H, *J* = 15.5, 6.5 Hz), 5.62 (dd, 1H, *J* = 15.5,

- 7.5 Hz), 7.38-7.46 (m, 6H), 7.67-7.70 (m, 4H). IR (neat) 3400, 3050, 2950  $\text{cm}^{-1}$ ,  $[\alpha]_D^{25} = +8.0$  (*c* 0.15,  $\text{CHCl}_3$ ). MS (*m/e*) 325 (M-*t*Bu), 269, 247, 199 (base peak), 181, 139, 135, 109, 57. **6**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 (t, 3H), 0.95 (d, 2H), 1.25-1.34 (m, 6H), 2.05 (m, 1H), 3.50 (m, 1H), 3.65 (m, 1H), 4.22 (m, 1H), 5.40 (dd, 1H), 5.65 (m, 1H). IR (neat) 3300, 2950  $\text{cm}^{-1}$ ,  $[\alpha]_D^{25} = +1.82$  (*c* 0.17,  $\text{CHCl}_3$ ).
- 10**: TLC;  $\text{SiO}_2$ , EtOAc/hexane 1 : 5,  $R_f = 0.33$ ,  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t, 3H,  $J = 7.5$  Hz), 0.97 (d, 3H,  $J = 6.9$  Hz), 1.27-1.37 (m, 1H), 3.57 (dd, 1H,  $J = 11.4, 7.8$  Hz), 3.69 (dd, 1H,  $J = 10, 3.6$  Hz), 4.22 (m, 1H), 4.58 (s, 2H), 5.38 (ddd, 1H,  $J = 15.5, 6.6, 1$  Hz), 5.65 (ddd, 1H,  $J = 15.5, 6.6, 1$  Hz), 7.35 (s, 5H). **11**:  $[\alpha]_D^{24} = -39.8$  (*c* 3.0,  $\text{CHCl}_3$ ).
5. (a) E. Hungerbühler, and D. Seebach, *Helv. Chim. Acta*, **64**, 696 (1981); (b) T. Mukaiyama, K. Suzuki, T. Yamada, and F. Tabusa, *Tetrahedron*, **46**, 265 (1990).
6. K. Omura and D. Swern, *Tetrahedron*, **34**, 1651 (1978).

### Synthesis of Steroidal Cyclophosphamide, 2-Bis(2-chloroethyl)amino-2-oxo-6-(5 $\alpha$ -cholestanyl)-1,3,2-oxazaphosphorinane

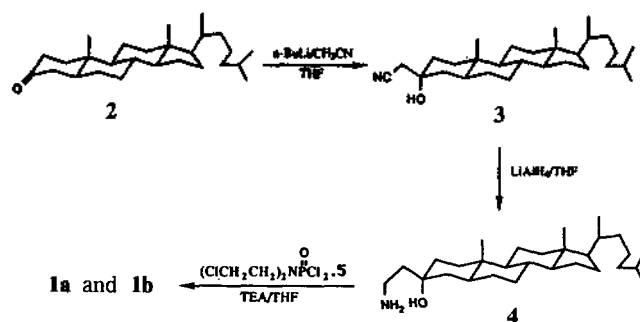
Jack C. Kim\*, Hyoung-Do Paek, Sung-Hwan Moon†, and Si-Hwan Kim‡

*Department of Chemistry, College of Natural Science, Pusan National University, Pusan 609-735, Korea*

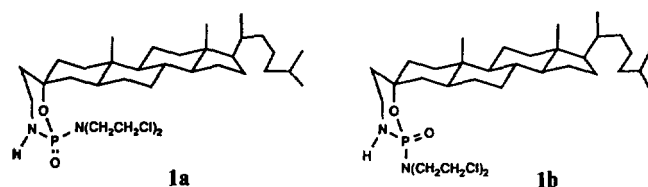
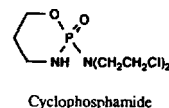
Received January 8, 1993

Cyclophosphamide and its analogues are important clinical agents in the treatment of cancer.<sup>1</sup> We have prepared steroidal cyclophosphamides (**1a** and **1b**). The approach used for the synthesis of **1a** and **1b** is outlined in Scheme 1. Treatment of cholestanone (**2**) with *n*-butyllithium and acetonitrile gave a 72.5% yield of  $\beta$ -hydroxynitrile derivative **3**<sup>2</sup>, which was subsequently reacted with  $\text{LiAlH}_4$  to give aminoethyl derivative **4**.<sup>3</sup> Cyclization of **4** with bis(2-chloroethyl)phosphoramidic dichloride (**5**) in the presence of 2 equiv. of  $\text{Et}_3\text{N}$  afforded crude mixtures of **1a** and **1b**, which were chromatographed on silica gel with EtOAc :  $\text{CH}_2\text{Cl}_2$  : hexane = 2 : 2 : 1 to give analytically pure crystals of the faster (mp. 192-194°C) and slower (mp. 178-180°C) eluting diastereomers of **1a** and **1b** in 58% yield. Assignment of cyclophosphamide structures to the faster and slower eluting diastereomeric cyclization products has been suggested by the IR,  $^1\text{H-NMR}$ ,  $^{31}\text{P-NMR}$ , and  $^{13}\text{C-NMR}$ .

Our measurements of **1a** and **1b** indicated the  $^1\text{H-NMR}$  chemical-shift difference between the NH resonances at 2.73 and 2.50 ppm for the faster and slower eluting diastereomers of **1a** and **1b**, respectively. The substantial deshielding (0.23 ppm) of N-H proton thus exhibited by the faster moving



Scheme 1.



compound **1a**, suggests more efficient intramolecular H-bonding to the adjacent P=O functionality. This difference in H-bonding was also founded in  $^{13}\text{C-NMR}$  by the deshielding of chemical shift [41.9 ppm (-NH- $\text{CH}_2$ -)] in the proposed **1a**, as opposed by the shielding of chemical shift [36.0 ppm (-NH- $\text{CH}_2$ -)] in the proposed **1b**. These compounds may have a greater impact as anticancer agents by their lipophilicity. Compounds **1a** and **1b** were found no activity against Hepatoma cells<sup>5</sup>.

### Experimental

**3-Cyanomethyl-5 $\alpha$ -cholestan-3-ol (3)**. To a stirred solution of 1.6 M *n*-butyllithium in 9.5 ml (15 mmol) hexane, at  $-80^\circ\text{C}$  under nitrogen, was rapidly added a solution of 0.82 ml (15 mmol) of acetonitrile in 30 ml of anhydrous THF. After stirring for 1 hr, the resulting white suspension was treated with a solution of 3.0 g (7.5 mmol) **2** in 10 ml of THF. The cold-ice bath was removed and stirred for additional 10 min before it was poured into ice-water hydrochloric acid. The aqueous layer was extracted with three 50 ml portions of  $\text{Et}_2\text{O}$ . The combined ether extracts were dried ( $\text{MgSO}_4$ ) and evaporated in vacuo, and the residual crude product was chromatographed on silica gel with  $\text{CH}_2\text{Cl}_2$  as an eluent, and obtained 2.4 g (73% yield) of white solids, mp. 158-159  $^\circ\text{C}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.6 (s, 2H,  $-\text{CH}_2\text{CN}$ ), 0.6-2.0 (m, H steroid); IR (KBr) 3480 (-OH), 2930, 2255 (-CN), 1460, 1370, 1080, 1050  $\text{cm}^{-1}$ .

**3 $\beta$ -Aminoethylene-5 $\alpha$ -cholestan-3-ol (4)**. To a stirred solution of 1.7 g (3.9 mmol) of **3** in 150 ml of anhydrous THF was added in small portions, 0.75 g (19.5 mmol) of lithium aluminum hydride. The mixture was refluxed with stirring for 17 hrs. After decomposing excess lithium aluminum hydride with 0.75 ml water and 2.3 ml of 20% NaOH, the mixture was filtered and filtrate was evaporated in vacuo to obtain yellow oily residues (45% yield). All attempts

\* Present address: Suntory Institute for Bioorganic Research, Shimamoto-cho, Osaka 618, Japan

‡ Research Institute of Industrial Science & Technology, Pohang 790-600, Korea