Tetrahedron: Asymmetry Vol. 3, No. 7, pp. 853-856, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Stereocontrolled Route to the δ-Benzylidenemethyl-β-hydroxy-δ-lactone System Utilizing a New Chiral Epoxyacetylene Building Block

Seiichi Takano,* Takashi Kamikubo, Takumichi Sugihara, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(*Received* 5 *June* 1992)

Abstract: Stereocontrolled route to the δ-benzylidenemethyl-β-hydroxy-δ-lactone system has been developed utilizing a new epoxyacetylene building block prepared from optically active epichlorohydrin. The present synthesis allowed efficient construction of goniothalamin in natural and unnatural forms and its 3-hydroxy derivative having the essential *anti*-β/δ-stereochemistry for HMG Co-A reductase inhibition.

We have recently demonstrated that the chiral hydroxyacetylene (**1**) has versatile utility as a powerful building block for the construction of a wide variety of optically active natural products.[1] We report here the preparation and a utilization of a new acetylene building block, 4,5-epoxy-1-trimethylsilyl-1-butyne (**2**), relating to **1**. Although this compound may be taken merely as a synthetic equivalent of **1**, it has much higher potentiality owing to its high electrophilicity by the terminal epoxide and nucleophilicity by the masked terminal acetylene besides the chirality at the secondary carbon center. We demonstrate an enantiospecific synthesis of both natural and unnatural products having benzylidenemethyl group at δ-position of the δ-lactone moiety and stereocontrolled introduction of hydroxy group at β-position by exploiting electrophilic and nucleophilic characters of this new chiral building block (**2**). Since some δ-arylidenemethyl-β-hydroxy-δ-lactone derivatives (e.g., **3**), possessing the same lactone stereochemistry as compactin (**4**) and mevinolin (**5**), were reported to be highly potent inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG Co-A) reductase,[2] the present synthesis utilizing **2** is promising as a general entry to a variety of their structural analogues[3] (**Figure 1**).

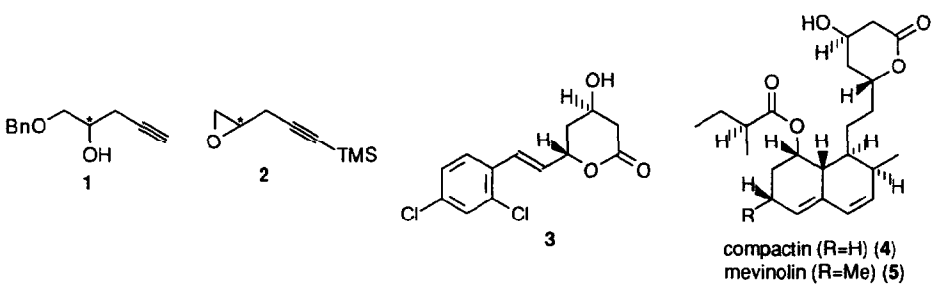
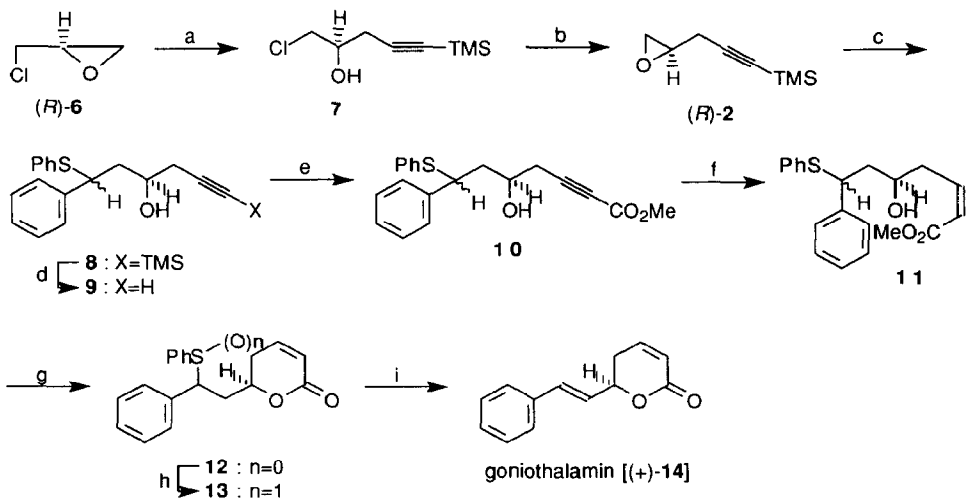


Figure 1

Reaction of (*R*)-epichlorohydrin[4] [(*R*)-**6**] with lithium trimethylsilylacetylide, generated from trimethylsilylacetylene in the same flask, in the presence of boron trifluoride etherate[5] afforded the (*R*)-

chlorohydrin[6] [(*R*)-**7**], $[\alpha]_D^{29}$ –12.8 (*c* 1.0, $CHCl_3$), in 93% yield. This compound was then exposed to potassium hydroxide in THF to furnish the key epoxyacetylene [(*R*)-**2**], $[\alpha]_D^{30}$ –30.0 (*c* 1.0, $CHCl_3$), in quantitative yield. Reaction of (*R*)-**2** with the carbanion, generated from benzyl phenyl sulfide in the same flask, afforded the hydroxy sulfide (**8**) in 80% yield as an inseparable epimeric mixture at the benzylic center. After removal of the trimethylsilyl group by treating **8** with potassium carbonate in methanol,[7] the resulting terminal acetylene (**9**), obtained in 80% yield, was exposed to carbon monoxide under atmospheric pressure in methanol in the presence of palladium(II) chloride, copper(II) chloride, and sodium acetate[8,9] to give rise to the methyl propiolate (**10**) in 71% yield. Hydrogenation of **10** using Lindlar catalyst followed by stirring the resulting *Z*-ester (**11**) in methanol containing a catalytic amount of hydrochloric acid at room temperature allowed facile cyclization to give the δ-lactone (**12**) in 93% overall yield.

Having constructed the unsaturated δ-lactone moiety, **13** was next treated with *m*-chloroperbenzoic acid at low temperature (–78 - –40 °C) in dichloromethane in the presence of sodium hydrogen carbonate to give the sulfoxide (**14**) in 95% yield. Thermolysis of **13** was carried out in refluxing toluene in the presence of calcium carbonate[10] to yield natural (+)-goniothalamin[11] [(+)-**14**], mp 82-85 °C, $[\alpha]_D^{28}$ +171.3 (*c* 0.49, $CHCl_3$) [natural[11c,12]: mp 81-82 °C, $[\alpha]_D$ +178.5 (*c* 2.0, $CHCl_3$)], quantitatively, as a single isomer having *E*-benzylidenemethyl configuration (**Scheme 1**).

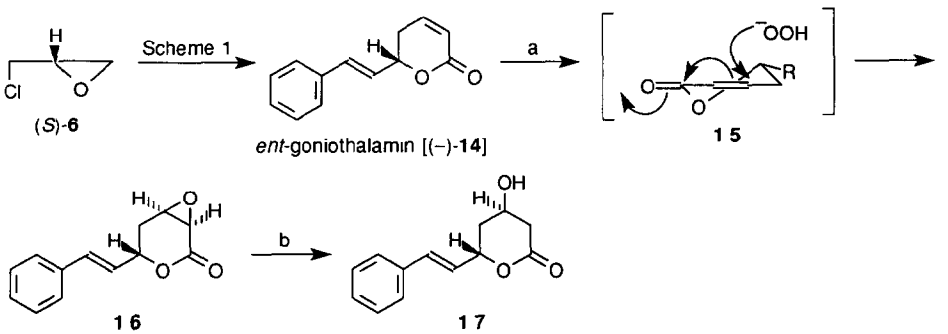


Scheme 1

Reagents and conditions: a) trimethylsilylacetylene, *n*-BuLi, then BF_3·OEt_2, then (*R*)-**6**, THF, –78 °C (25 min), –30 °C (18 h); b) KOH, THF, 0 °C, 4 h; c) benzyl phenyl sulfide, *n*-BuLi, then (*R*)-**2**, THF, –78 °C (1.5 h), –20 °C (10 h); d) K_2CO_3, MeOH, room temperature, 9 h; e) $PdCl_2$ (cat.), $CuCl_2$, NaOAc, CO, MeOH, room temperature, 5 h; f) H_2, Lindlar catalyst, MeOH, room temperature, 11 h; g) conc. HCl (cat.), MeOH, room temperature, 4 h; h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, –40 °C, 2 h; i) $CaCO_3$, toluene, reflux, 1 h.

To fabricate the *anti* β,δ-β-hydroxy-δ-lactone having the requisite absolute configuration for HMG Co-A reductase inhibiting activity, unnatural *ent*-goniothalamin [(–)-**14**], mp 83-85 °C, $[\alpha]_D^{28}$ –178.1 (*c* 0.6, $CHCl_3$), was first prepared in a comparable overall yield starting from (*S*)-epichlorohydrin [(*S*)-**6**] *via* the enantiomeric (*S*)-chlorohydrin [(*S*)-**7**], $[\alpha]_D^{28}$ +12.6 (*c* 1.01, $CHCl_3$), and (*S*)-epoxyacetylene [(*S*)-**2**], $[\alpha]_D^{24}$

+29.4 (*c* 1.02, $CHCl_3$). When *ent*-goniothalamin [(–)-**14**] thus obtained was treated with alkaline hydrogen peroxide at 0 °C, the reaction took place stereoselectively to afford the epoxide (**16**), mp 104-105 °C, $[\alpha]_D^{29}$ +52.9 (*c* 1.11, $CHCl_3$), in 82% yield as a single isomer. Apparently, the hydroperoxide ion was introduced from the stereoelectronically more favored β-face of the unsaturated δ-lactone molecule in the transition state[1h, i] (**15**) as well-recognized in the cyclohexenone analogues.[13] Treatment of **16** with phenylselenolate complex, generated in the same flask from diphenyl diselenide and sodium borohydride in THF,[1h,9,14] furnished the β-hydroxylactone (**17**), mp 109-111 °C, $[\alpha]_D^{27}$ +9.86 (*c* 0.80, $CHCl_3$), having *anti* β,δ-stereochemistry with the requisite absolute configuration in 83% yield as a single product by regioselective cleavage (**Scheme 2**).



Scheme 2

Reagents and conditions: a) 30% H_2O_2, 4N-NaOH, MeOH, 0 °C, 1 h; b) diphenyl diselenide, NaBH, AcOH (cat.), THF, then 16, 0 °C, 20 min.

In conclusion, stereocontrolled route to optically active δ-lactones having δ-benzylidenemethyl and β-hydroxy functionalities has been established utilizing the new epoxy acetylene building block (**2**) accessible from optically active epichlorohydrin (**6**). Further exploitation of this building block (**2**) is currently in progress in our laboratory.

References and Notes

1. a) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139. b) Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1555. c) Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett.* **1989**, *30*, 4001. d) Takano, S.; Sekiguchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 445. e) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Chem. Lett.* **1988**, 2041. f) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1527. g) *idem. ibid.* **1989**, 1371. h) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539. i) Takano, S.; Shimazaki, Y.; Moriya, M.; Ogasawara, K. *Chem. Lett.* **1990**, 1177. j) Takano, S.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3225. k) Takano, S.; Shimazaki, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 2101. l) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619. m) Takano, S.; Sekiguchi, Y.; Ogasawara, K.

Heterocycles **1992**, *33*, 59. n) Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *ibid.* **1992**, *33*, 713.

2. Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J. Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
3. Reddy, G. B.; Minami, T.; Hanamoto, T.; Hiyama, T. *J. Org. Chem.* **1991**, *56*, 5752 and references cited therein.
4. Optical purity ≥98% ee was used. We thank DAISO Co. Ltd., Osaka, Japan, for donation of a large quantity of (*R*)- and (*S*)-enantiomers of epichlorohydrin.
5. cf. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391; Nicolaou, K. C.; Skokotas, G.; Maligres, P.; Zuccarello, Z.; Schweiger, E. J.; Toshima, K.; Wendeborn, S. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1272.
6. All new compounds described have satisfactory analytical (combustion and/or high resolution mass) and spectral (ir, ^{1}H nmr, mass) data.
7. cf. Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369; Suffert, J. *Tetrahedron Lett.* **1990**, *31*, 7437.
8. Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849.
9. Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 533.
10. Trost, B. M.; Salzman, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.
11. Former chiral syntheses, see: a) Meyer, H. H. *Ann. Chem.* **1979**, 484. b) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201. c) Bennett, F.; Knight, D. W. *ibid.* **1988**, *29*, 4625. d) Honda, T.; Kametani, T.; Kanai, K.; Tsuzaki, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1733.
12. Sam, T. W.; -Yeu, C. S.; Matsjeh, S.; Gan, E. K.; Razak, D.; Mohamed, A. L. *Tetrahedron Lett.* **1987**, *28*, 2541. The absolute structure of natural (+)-goniothalamin in this paper is depicted in the antipodal (6*S*)-stereochemistry which should be revised.
13. cf. Deslongchamps, P. 'Stereoelectronic Effects in Organic Chemistry,' Pergamon, Oxford, 1983, p. 209.
14. Miyashita, M.; Suzuki, T.; Yoshikoshi, A. Tetrahedron Lett. 1987, 28, 4293; Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. Chem. Lett. 1988, 507. The original procedure employed an alcoholic solvent which induced alcolysis to give rise to a seco-ester as a by-product (sometimes a major product).
15. Optical purities of natural and unnatural forms of goniothalamin were determined to be ≥96% ee by hplc using a chiral column (CHIRALCEL OJ, *i*-PrOH-hexane, 1:9 v/v).