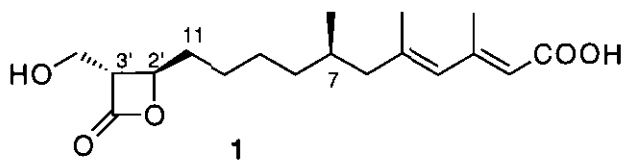
A NEW SYNTHETIC APPROACH TO A FUNGAL β-LACTONE BASED ON THE ASYMMETRIC [2,3]-WITTIG REARRANGEMENT §

Katsuhiko Tomooka, Takahiro Takeda, Au Wing Kuen, and Takeshi Nakai*

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

Abstract —— An asymmetric synthesis of the chiral β-lactone precursor of the HMG-CoA synthase, inhibitor L-659,699, is described, which involves as the key step an asymmetric [2,3]-Wittig rearrangement to control the stereogenic centers at the ring carbons (C2' and C3').

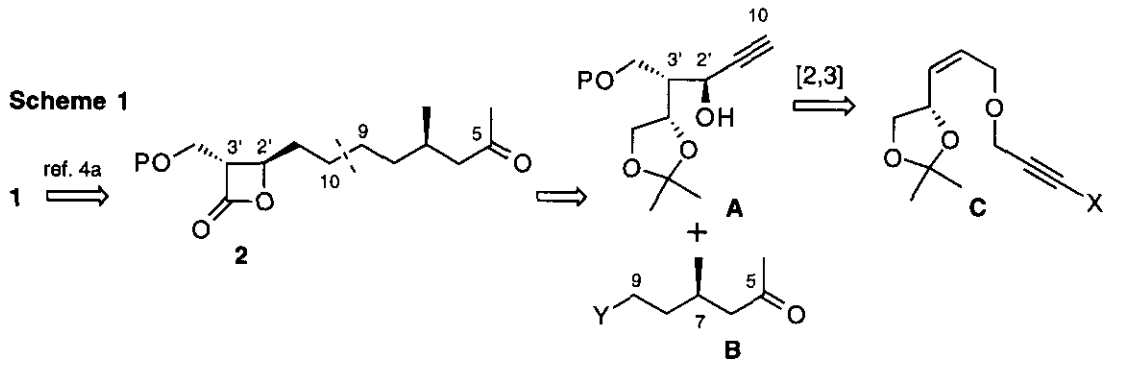
A fungal β-lactone L-659,699[1] (**1**) (also known as 1233A[2] or F-244[3]) is a potent, specific inhibitor of the HMG-CoA synthase and cholesterol biosynthesis in cell culture. Thus, L-659,699 has been the target molecule of recent synthetic efforts.[4] The Merck group has accomplished the first total synthesis of **1**, using the chiral β-lactone (**2**) as the key precursor.[4a] As part of our studies on synthetic application of the asymmetric [2,3]-Wittig rearrangement, we planned the retrosynthetic route to **2** (Scheme 1) which involves as the key step an asymmetric induction *via* [2,3]-Wittig process (**C**→**A**) [5,6] to control the stereogenic centers C2' and C3'.



1

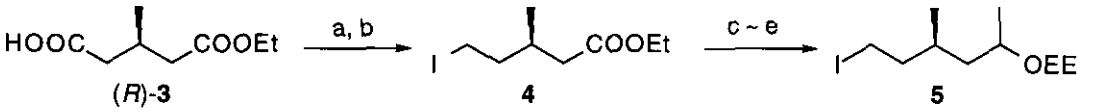
§This paper is dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Scheme 1



The C5-C9 fragment (**5**) (≡ **B**) was readily prepared from commercially available (*R*)-ethyl hydrogen 3-methylglutarate (**3**) (>98% ee) in five steps (Scheme 2). The chemoselective reduction of **3**[7] followed by the iodination gave ester (**4**). The reduction of **4** with DIBALH gave the aldehyde which was then successively treated with MeMgBr followed by the protection of the hydroxyl group to afford iodide (**5**).

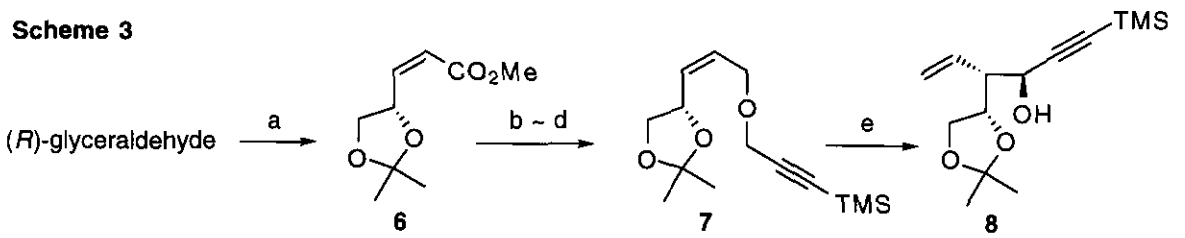
Scheme 2



(a) BH_3•SMe_2, THF, -20 °C → rt (100%). (b) PPh_3, I_2, imidazole, benzene, rt (82%).
(c) DIBALH, CH_2Cl_2, -78 °C (94%). (d) MeMgBr, THF, -78 °C (93%).
(e) CH_2=CHOEt, , *p*-TsOH, CH_2Cl_2, rt (86%).

The requisite ether (**7**) (≡ **C**) for the rearrangement was prepared from (*R*)-glyceraldehyde (>98% ee) (Scheme 3). The Wittig olefination of glyceraldehyde gave ester (**6**) as an 8:1 *Z* / *E* mixture. The geometrical pure isomer ((*Z*)-**6**), obtained *via* the column chromatography purification, was reduced with DIBALH to give (*Z*)-allylic alcohol which was then convered to propargyl ether (**7**) by the standard sequence. The [2,3]-Wittig rearrangement of **7** was carried out with *n*-BuLi in THF to afford alcohol (**8**)[8] as a single diastereomer in 93% isolated yield.[9]

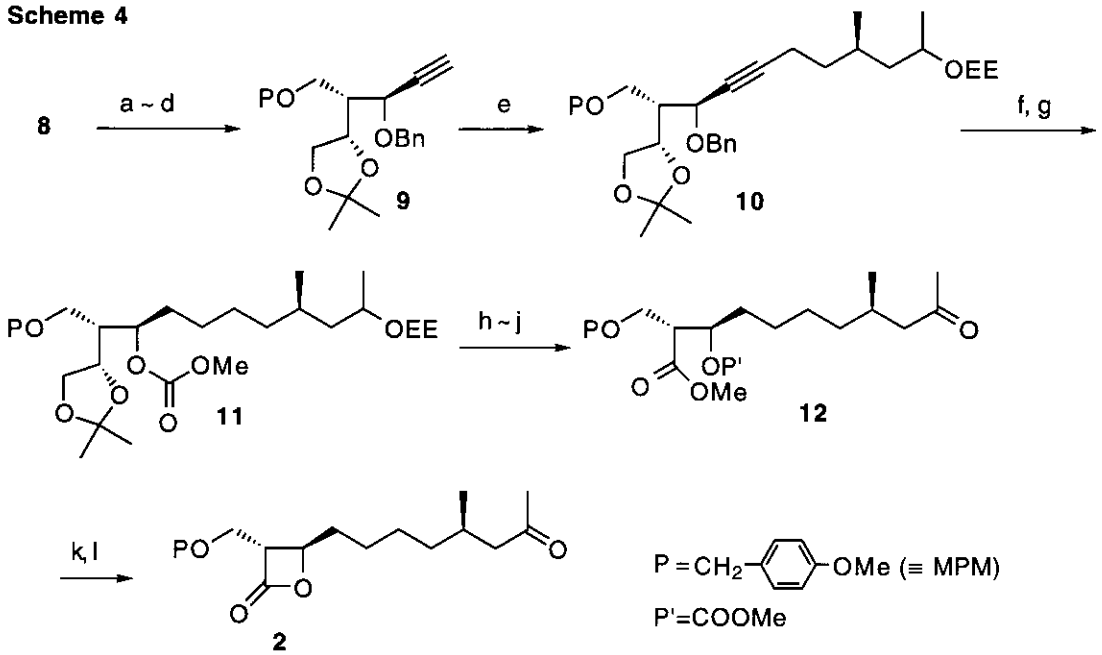
Scheme 3



(a) PPh_3=$CHCO_2Me$, MeOH, 0 °C (82%). (b) DIBALH, hexane, 0 °C (82%).
(c) $BrCH_2C$≡CH, aq. NaOH, TBAI, rt (100%). (d) EtMgBr, TMSCl, THF, 0 °C (90%).
(e) *n*-BuLi, THF, -78 °C (93%).

The transformation of the [2,3]-Wittig product (**8**) to the desired β-lactone precursor (**2**) is depicted in Scheme 4. Thus, alcohol (**8**) was converted to the fragment (**9**) (≡ **A**) by the standard sequence: desilylation, protection of the hydroxy group, ozonolysis of the double bond, and protection of the hydroxy group. Treatment of **9** with *n*-BuLi followed by reaction with iodide (**5**) afforded the coupling product (**10**)[8] in 75% yield. Further elaboration of **10**, including hydrogenation, protection of the hydroxy group with the carbonate,[10] oxidation of the triol formed *via* deprotection, and lactonization, furnished the β-lactone (**2**).[8]

Scheme 4



(a) TBAF, THF, rt (98%). (b) BnBr, aq. NaOH, TBAI, rt (92%). (c) O_3, MeOH, -78 °C; $NaBH_4$, rt (84%). (d) MPMCl, aq. NaOH, TBAI, rt (88%). (e) *n*-BuLi, THF, 0 °C; **5**, HMPA, 0 °C (75%). (f) H_2, Raney-Ni (W-4), EtOH, rt (82%). (g) MeOCOCl, pyridine, CH_2Cl_2 (100%). (h) 1N HCl, MeOH, rt (93%). (i) $NaIO_4$, acetone-H_2O, 0 °C; Jones reagent. (j) $TMSCHN_2$, benzene-MeOH, 0 °C (three steps 67%). (k) aq. NaOH (l) $PhSO_2Cl$, pyridine, 0 °C (two steps 42%).

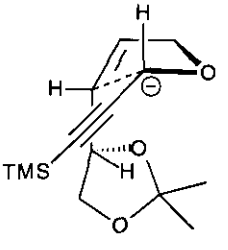
In summary, the β-lactone precursor (**2**) has been synthesized from commercially available (*R*)-ethyl hydrogen 3-methylglutarate and (*R*)-glyceraldehyde in a highly stereocontrolled manner. Since **2** (P=TBDPS) has been converted to the L-659,699 (**1**),[4a] the present approach constitutes a formal total synthesis of **1**.

REFERENCES AND NOTES

1. Isolation: M. D. Greenspan, J. B. Yudkovitz, C.-Y. L. Lo, J. S. Chen, A. W. Alberts, V. M. Hunt, M. N. Chang, S. S. Yang, K. L. Thompson, Y.-C. P. Chiang, J. C. Chabala, R. L. Monaghan, and R. E. Schwartz, *Proc. Natl. Acad. Sci. U.S.A.* 1987, **84**, 7488. Determination of the absolute configuration: Y.-C. P. Chiang, M. N. Chang, S. S. Yang, J. C. Chabala, and J. V. Heck, *J. Org. Chem.*, 1988, **53**,

4599.

2. D. C. Aldridge, D. Gile, and W. B. Turner, *J. Chem. Soc. C*, 1971, 3888.
3. S. Omura, H. Toma, H. Kumagai, M. D. Greenspan, J. B. Yudkovitz, J. S. Chen, A. W. Alberts, I. Martin, S. Mochales, R. L. Monaghan, J. C. Chabala, R. E. Schwartz, and A. A. Patchett, *J. Antibiot.*, 1987, **40**, 1356.
4. Total synthesis of **1**: a) Y.-C. P. Chiang, S. S. Yang, J. V. Heck, J. C. Chabala, and M. N. Chang, *J. Org. Chem.*, 1989, **54**, 5708. b) S. Wattanasin, H. D. Do, N. Bhongle, and F. G. Kathawala, *J. Org. Chem.*, 1993, **58**, 1610. c) P. M. Wovkulich, K. Shankaran, J. Kiegiel, and M. R. Uskoković, *J. Org. Chem.*, 1993, **58**, 832.
5. Reviews : J. A. Marshall, 'Comprehensive Organic Synthesis,' Vol. 3, ed. by B. M. Trost, and I. Fleming, Pergamon, New York, 1991, p. 975; T. Nakai and K. Mikami, *Organic Reactions*, 1994, **46**, 105.
6. a) E. Nakai and T. Nakai, *Tetrahedron Lett.*, 1988, **29**, 4587. b) R. Brückner and H. Priepke, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 278.
7. A. S. Kende and P. Fludzinski, *Org. Synth., Coll. Vol.*, 1990, **VII**, 221.
8. All the compounds were characterized by ^{1}H, ^{13}C NMR, and IR. Data for selected products are as follows. **8**: ^{1}H NMR ($CDCl_3$) δ 5.92 (dt, J=19.4, 9.6 Hz, 1H), 5.35-5.15 (m, 2H), 4.55 (q, J=7.0 Hz, 1H), 4.40 (dd, J=8.0, 5.2 Hz, 1H), 4.06 (dd, J=7.6, 7.0 Hz, 1H), 3.72 (t, J=7.6 Hz, 1H), 2.75 (d, J=8.0 Hz, 1H), 2.45-2.35 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 133.6, 119.5, 108.9, 105.5, 90.7, 74.9, 67.3, 63.9, 56.2, 25.3, −0.3. **10**: ^{1}H NMR ($CDCl_3$) δ 7.35-7.20 (m, 7H), 6.85-6.80 (m, 2H), 4.77 (d, J=11.7 Hz, 1H), 4.75-4.65 (m, 1H), 4.40-4.35 (m, 4H), 4.25-4.20 (m, 1H), 4.12 (dd, J=8.3, 5.9 Hz, 1H), 3.86 (t, J=8.1 Hz, 2H), 3.80-3.45 (m, 7H), 2.30-2.20 (m, 2H), 2.10-2.00 (m, 1H), 1.70-1.50 (m, 5H), 1.35 (s, 3H), 1.34 (s, 3H), 1.30-1.10 (m, 9H), 0.95-0.90 (m, 3H); IR (neat, cm^{-1}) 3416, 2934, 1613, 1516, 1456, 1371, 1249, 1160, 1058, 737, 700. **12**: ^{1}H NMR ($CDCl_3$) δ 7.30-7.20 (m, 2H), 6.90-6.80 (m, 2H), 5.05 (q, J=6.1 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.75-3.70 (m, 1H), 3.60 (dd, J=9.3, 5.5 Hz, 1H), 2.96 (q, J=5.8 Hz, 1H), 2.38 (dd, J=15.8, 5.8 Hz, 1H), 2.21 (dd, J=15.8, 8.0 Hz, 1H), 2.12 (s, 3H), 2.00-1.10 (m, 9H), 0.87 (d, J=6.6 Hz, 3H); $[\alpha]_D^{28}$ +2.0 ($CHCl_3$, c 0.56). **2**: ^{1}H NMR ($CDCl_3$) δ 7.30-7.20 (m, 2H), 6.90-6.80 (m, 2H), 4.50 (d, J=3.3 Hz, 2H), 4.25-4.20 (m, 1H), 3.81 (s, 3H), 3.75-3.65 (m, 2H), 3.45-3.35 (m, 1H), 2.40-2.20 (m, 2H), 2.13 (s, 3H), 2.10-1.00 (m, 9H), 0.89 (d, J=6.0 Hz, 3H); IR (neat, cm^{-1}) 2926, 1827, 1717, 1516, 1464, 1251, 1123.
9. The stereochemical outcome observed in the present [2,3]-Wittig variant is explicable in terms of the rearrangement proceeding exclusively *via* the transition state (**i**) (*cf.* ref. 6a).
10. It should be noted that the use of an acetoxy protecting group instead of the carbonate group led to considerable acetyl migration when the acetonide moiety was deprotected.



i

Received, 3rd July, 1997