

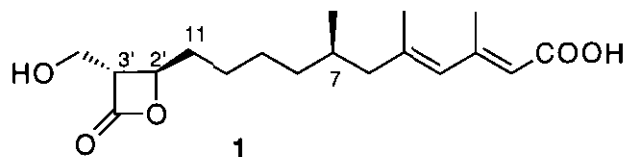
**A NEW SYNTHETIC APPROACH TO A FUNGAL
 β -LACTONE BASED ON THE ASYMMETRIC
 [2,3]-WITTIG REARRANGEMENT [§]**

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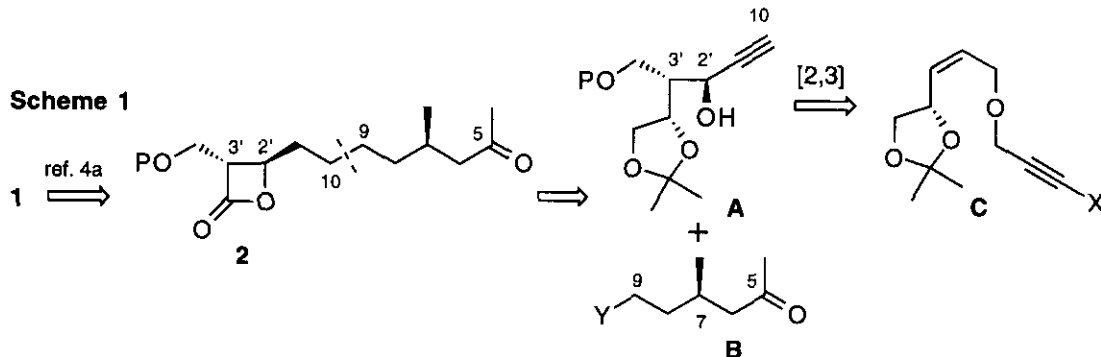
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Abstract — An asymmetric synthesis of the chiral β -lactone precursor of the HMG-CoA synthase, inhibitor L-659,699, is described, which involves as the key step an asymmetric [2,3]-Wittig rearrangement to control the stereogenic centers at the ring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

A fungal β -lactone L-659,699¹ (**1**) (also known as 1233A² or F-244³) 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'.

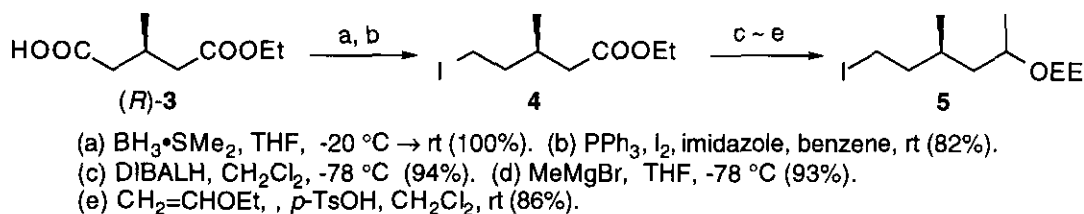


[§]This paper is dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.



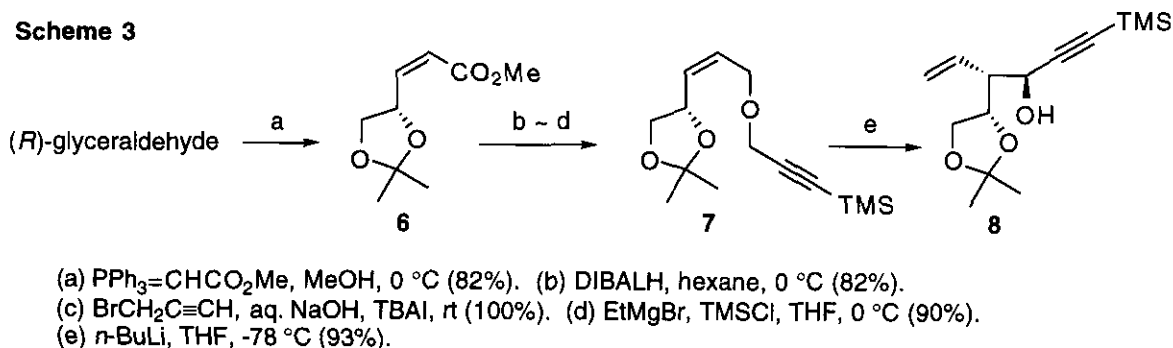
The C5-C9 fragment (**5**) (\equiv **B**) was readily prepared from commercially available (*R*)-ethyl hydrogen 3-methylglutarate (**3**) (>98% ee) in five steps (Scheme 2). The chemoselective reduction of **3**⁷ followed by the iodination gave ester (**4**). The reduction of **4** with DIBALH gave the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

Scheme 2



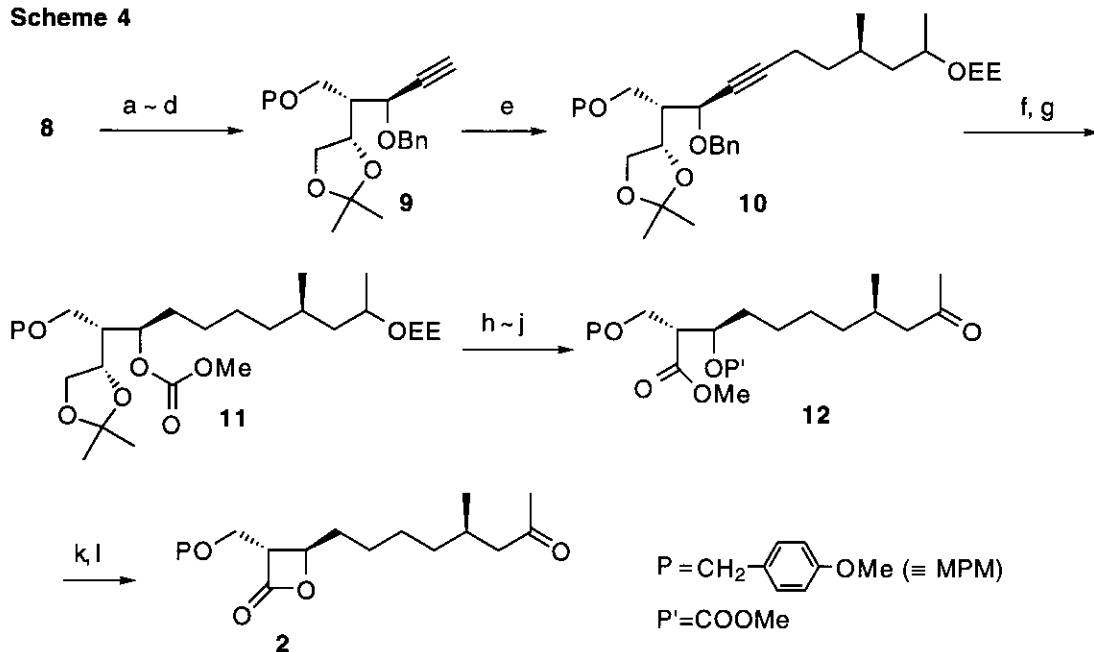
The requisite ether (**7**) (\equiv **C**) for the rearrangement was prepared from (*R*)-glyceraldehyde (>98% ee) (Scheme 3). The Wittig olefination of glyceraldehyde gave ester (**6**) as an 8:1 *Z/E* mixture. The geometrical pure isomer ((*Z*)-**6**), obtained *via* the column chromatography purification, was reduced with DIBALH to give (*Z*)-allylic alcohol which was then converted 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



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**) (\equiv **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) O₃, MeOH, -78 °C; NaBH₄, rt (84%). (d) MPMCl, aq. NaOH, TBAI, rt (88%). (e) *n*-BuLi, THF, 0 °C; **5**, HMPA, 0 °C (75%). (f) H₂, Raney-Ni (W-4), EtOH, rt (82%). (g) MeOCOC(OMe), pyridine, CH₂Cl₂ (100%). (h) 1N HCl, MeOH, rt (93%). (i) NaIO₄, acetone-H₂O, 0 °C; Jones reagent. (j) TMSCHN₂, benzene-MeOH, 0 °C (three steps 67%). (k) aq. NaOH (l) PhSO₂Cl, pyridine, 0 °C (two steps 42%).

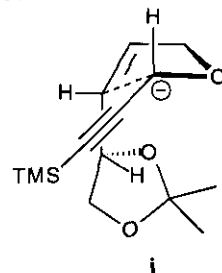
In summary, the β -lactone precursor (**2**) has been synthesized from commercially available (*R*)-ethyl hydrogen 3-methylglutarate and (*R*)-glyceraldehyde in a highly stereocontrolled manner. Since **2** ($P=\text{TBDPS}$) has been converted to the L-659,699 (**1**),^{4a} the present approach constitutes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

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8. All the compounds were characterized by ^1H , ^{13}C NMR, and IR. Data for selected products are as follows. **8**: ^1H 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**: ^1H 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**: ^1H 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**: ^1H 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.



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