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

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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'.

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

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 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)\textsuperscript{8} as a single diastereomer in 93% isolated yield.\textsuperscript{9}
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,\(^9\) oxidation of the triol formed via deprotection, and lactonization, furnished the β-lactone (2).\(^8\)

**Scheme 4**

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\begin{align*}
\text{8} & \xrightarrow{a-d} \text{PO} & \xrightarrow{\text{Bn}} & \text{PO} \\
& \xrightarrow{e} & \text{OBn} & \xrightarrow{f, g} \\
& \xrightarrow{\text{MeOH, } -78 \degree C; \text{NaBH}_4, \text{rt}} & \text{OBn} & \xrightarrow{\text{h, i}} \\
& \xrightarrow{\text{MeOCOCl, pyridine, } \text{CH}_2\text{Cl}_2, \text{rt}} & \text{P} = \text{CH}_2\text{-} & \text{12} \\
& \xrightarrow{\text{k, l}} & \text{P'} = \text{COO\text{Me}} &
\end{align*}
\]

(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 (88%). (g) MeOCOCl, pyridine, CH\(_2\)Cl\(_2\) (100%). (h) 1N HCl, MeOH, rt (93%). (i) NaIO\(_4\), acetone-H\(_2\)O, 0 °C; Jones reagent. (j) TMSCHN\(_2\), benzene-MeOH, 0 °C (three steps 67%). (k) aq. NaOH (l) PhSO\(_2\)Cl; 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 (I),\(^{4a}\) the present approach constitutes a formal total synthesis of 1.

**REFERENCES AND NOTES**

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

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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