Stereoselective Synthesis of (+)-Methyl 8-*epi*-nonactate†

Eun Lee,* Lee Taek Sung, and Sung Kil Hong

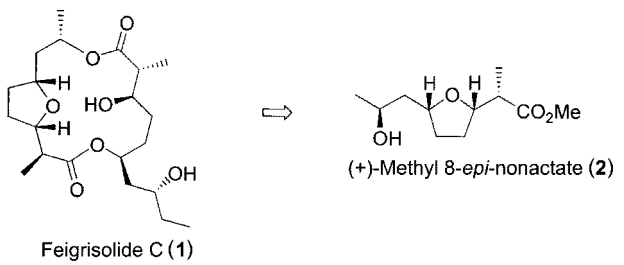
School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, Korea
Received February 6, 2002

Key Words : 8-*epi*-Nonactate, β-Alkoxymethacrylates, Radical cyclization

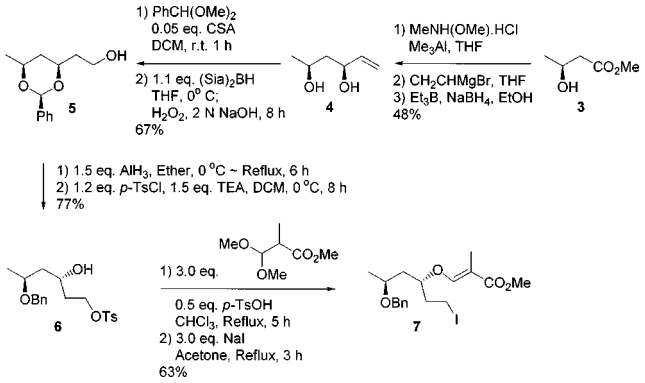
It is now well established that *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are obtained stereoselectively via radical cyclization of β-alkoxyacrylates.[1] Use of β-alkoxymethacrylates leads to products possessing an extra stereogenic center outside the ring, and stereocontrol therein is possible by hydrogen transfer under low temperature conditions: stereoselective synthesis of (+)-methyl nonactate was achieved in this fashion.[2] More recently, a total synthesis of pamamycin-607 was accomplished,[3] in which a key β-alkoxymethacrylate substrate was employed in a radical cyclization step. Feigrisolide C (**1**)[4] is a newly discovered antibiotic macrodiolide featuring (+)-8-*epi*-nonactic acid moiety (Scheme 1), and we wish to report here a stereoselective synthesis of (+)-methyl 8-*epi*-nonactate (**2**).[5]

The known diol **4**[6] was obtained from methyl (*R*)-3-hydroxybutyrate (**3**) *via* Weinreb amide formation, vinyl Grignard addition, and stereoselective reduction[7] using sodium borohydride and triethylborane (Scheme 2). Hydroboration-oxidation of the benzylidene acetal of **4** produced the primary alcohol **5**. Regioselective alane reduction[8] of alcohol **5** and the subsequent tosylation provided the secondary alcohol **6**. The pivotal β-alkoxymethacrylate intermediate **7** was prepared by the reaction of alcohol **6** with excess methyl 3,3-dimethoxy-2-methylpropanoate[9] in the presence of an acid catalyst.

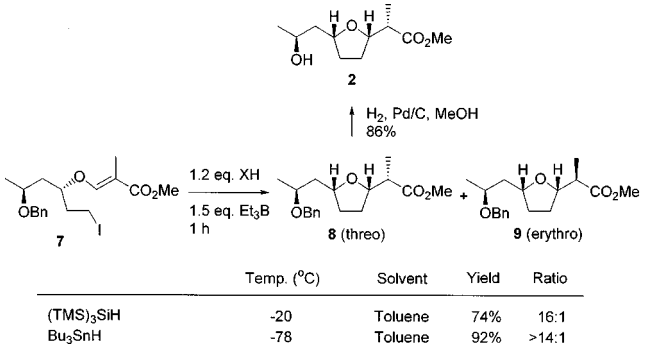
When the β-alkoxymethacrylate **7** was allowed to react with tris(trimethylsilyl)silane in the presence of triethylborane at -20 °C, the desired threo isomer **8** was stereoselectively (16 : 1) obtained in 74% yield (Scheme 3). Using tributylstannane as the hydrogen-transferring agent at -78 °C, an improved yield (92%) of the threo isomer **8** was obtained with similar stereoselectivity (>14 : 1). (+)-Methyl 8-*epi*-nonactate (**2**) was finally prepared *via* hydrogenolysis of benzyl ether **8**.



Scheme 1



Scheme 2



	Temp. (°C)	Solvent	Yield	Ratio
$(TMS)_3SiH$	-20	Toluene	74%	16:1
Bu_3SnH	-78	Toluene	92%	>14:1

Scheme 3

In this synthesis, the threo selectivity was maintained in the β-alkoxymethacrylate radical cyclization providing a further example of stereocontrol in radical reactions.

Acknowledgment. The authors thank the Ministry of Science and Technology, Republic of Korea, and Korea Institute of Science and Technology Evaluation and Planning for a National Research Laboratory grant (1999). A Brain Korea 21 graduate fellowship grant to L. T. Sung is gratefully acknowledged.

References

1. For selected examples of β-alkoxyacrylaye radical cyclizations, see: (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.*

†Dedicated to Prof. Sang Chul Shim, a scholar, teacher, and statesman in chemistry.

1993, *34*, 4831-4834. (b) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017-8018. (c) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757-7758. (d) Lee, E.; Yoo, S.-K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998**, *39*, 317-318. (e) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 176-178. (f) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384-385. (g) For further references, see: Lee, E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 303-333.

2. Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127-1128.
3. Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131-10132.
4. Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S. *J. Antibiot.* **2000**, *53*, 934-943.
5. Preparation of (–)-methyl 8-*epi*-nonactate was reported in conjunction with the synthesis of nonactin; (a) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304-5311. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557-2560. (c) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996**, *52*, 571-588.
6. (a) Mohr, P.; Tamm, C. *Tetrahedron Lett*. **1987**, *28*, 395-396. (b) Mohr, P. *Tetrahedron Lett*. **1992**, *33*, 2455-2458.
7. Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923-1926.
8. Alane reduction of **5** proceeded with high regioselectivity; Lipták, A.; Jodál, I.; Nánási, P. *Carbohydr. Res.* **1975**, *44*, 1-11.
9. Walkup, R. D.; Obeyesekere, N. U. *Synthesis* **1987**, 607-611.