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

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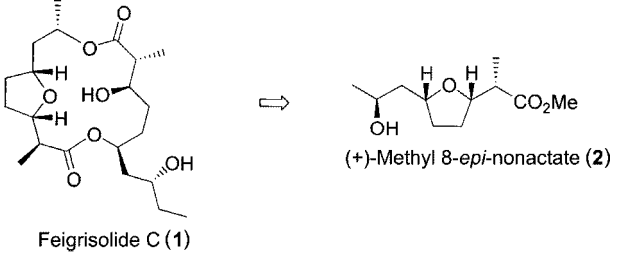
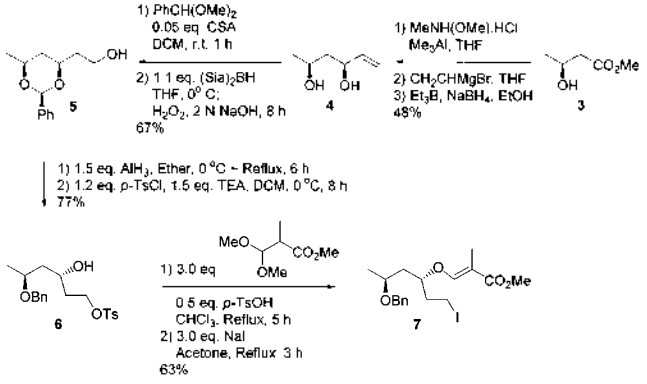
It is now well established that *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are obtained stereoselectively via radical cyclization of β-alkoxyacrylates.[1] Use of β-alkoxymethacrylates leads to products possessing an extra stereogenic center outside the ring, 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.

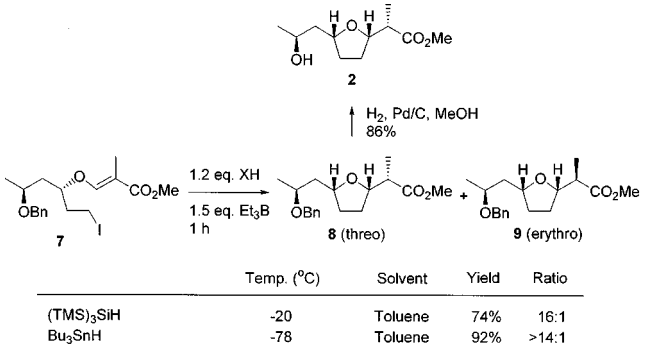
When the β-alkoxymethacrylate **7** was allowed to react with tris(trimethylsilyl)silane in the presence of triethylborane at -20 °C, the desired threo isomer **8** was stereoselectively (16 : 1) obtained in 74% yield (Scheme 3). Using tributylstannane as the hydrogen-transferring agent at -78 °C, an improved yield (92%) of the threo isomer **8** was



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

obtained with similar stereoselectivity (>14 : 1). (+)-Methyl 8-*epi*-nonactate (**2**) was finally prepared *via* hydrogenolysis of benzyl ether **8**.

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

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

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