Tetrahedron Letters, Vol. 33, No. 42, pp. 6315-6318, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Prins Cyclization to Tetrahydrofuran Units of Polyether Antibiotics: Remarkable Siloxy Effect for Stereocontrolled Cyclization

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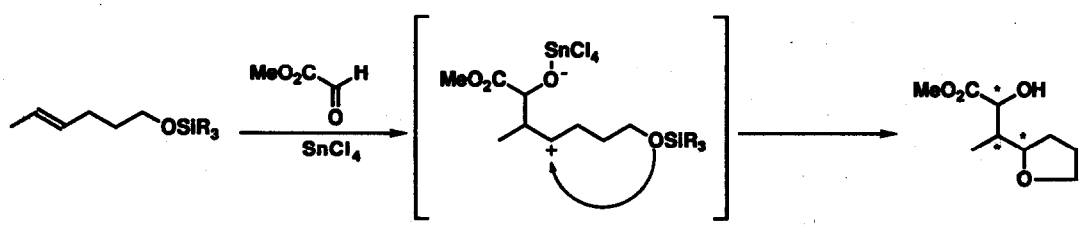
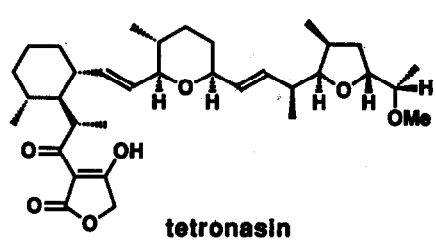
Abstract: A novel route to substituted tetrahydrofurans is described, which is based on the Lewis acid-promoted Prins cyclization with side chain formation of C-C bond. Bishomoallylic silyl ethers, rather than the (chloro)benzyl ethers and esters, provide selectively tetrahydrofurans, indicating the siloxy effect for facilitating the cyclization.

A substituted oxygen heterocycle possessing side chain chirality is a characteristic feature of polyether antibiotics (Figure 1), and methods for assembling these structural units in stereocontrolled fashion have been developed in recent years.[1] During the course of our research project to develop the carbonyl-ene reaction[2] as an efficient method for acyclic stereocontrol, we made unanticipated observations: a substituted tetrahydrofuran was obtained in the attempted glyoxylate-ene reaction of bishomoallylic silyl ether, presumably via the Prins reaction[3] to form C-C bond[4] followed by internal attack of the siloxy group into the cationic intermediate[5] (Scheme 1). Herein reported is the Lewis acid-promoted Prins cyclization as a stereocontrolled route to tetrahydrofuran units of polyether antibiotics.



Scheme 1



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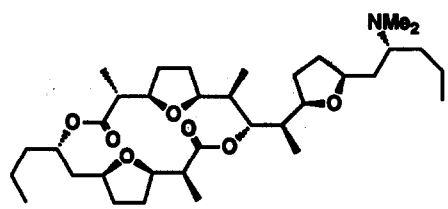
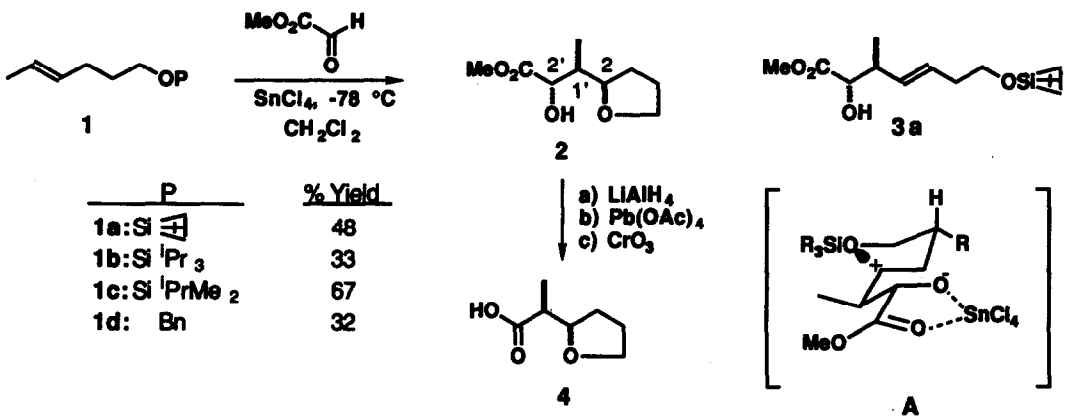


pamamycin-607

Figure 1

First, the reaction of dimethylthexylsilyl (*E*)-4-hexen-1-yl ether (**1a**) with methyl glyoxylate was found to give stereoselectively (>91%) the substituted tetrahydrofuran (**2**)[6] in 48% isolated

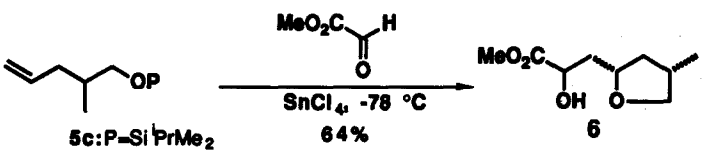
yield along with the glyoxylate-ene product **3a** (48% yield) in the presence of $SnCl_4$ (1 equivalent) at -78 °C in CH_2Cl_2 (Scheme 2). After screening the alcohol-protecting groups, the less bulky but relatively stable dimethyl-*iso*-propylsilyl group was found to be the best choice. The 1',2'-*anti*-configuration of **2** was deduced by the similarity in the ^1H NMR coupling constant of hydroxy methine proton (J = 3.9 Hz) to that of the corresponding *anti*-ene product **3a** (J = 3.6 Hz).[7] 2,1'-*syn*-Selectivity was then determined through further transformation to the known *syn*-compound (**4**).[8] Thus, the internal siloxy group attacks an intermediate (**A**: R = H) in an *anti*-fashion. A similar reaction with dichloromethyl methyl ether, which underwent vinylsilane-substitution reactions,[9] gave only a trace amount of the cyclized aldehyde.



P	% Yield
1a: Si	48
1b: Si ^{i}Pr$_3$	33
1c: Si ^{i}PrMe$_2$	67
1d: Bn	32

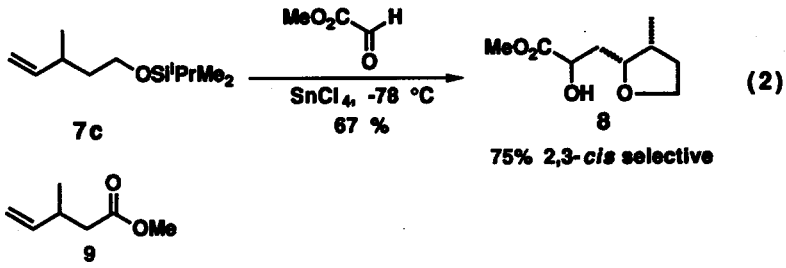
Scheme 2

Next, the reaction of silyl ether **5c** with glyoxylate was examined, wherein the problem of the 1,3-remote asymmetric induction arose (eq 1). 2,4-*cis*-Product **6** was obtained as determined by ^{13}C NMR spectral analysis.[10] 2,4-*cis*-Stereochemistry of **6** could be reasonably explained again by the figure **A** with the methyl group (R = Me) at the equatorial position. Interestingly, a similar reaction with 2,6-dichlorobenzyl ether **5e**, which provided tetrahydrofuran in the iodocyclization reaction,[11] gave the ene product along with the lactone cyclized thereof, rather than the Prins cyclization product.



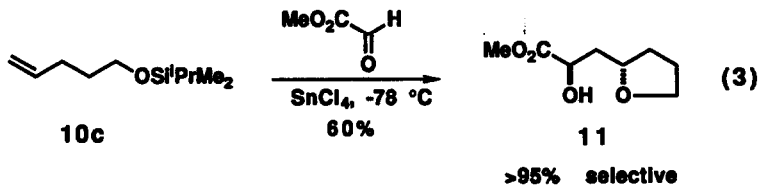
(1)

Furthermore, the 1,2-asymmetric induction was examined using silyl ether **7c** (eq 2). 2,3-*cis*-Stereochemistry of the cyclized product **8** was ascertained by ^{13}C NMR spectral analysis.[10] By contrast, a similar reaction with ester **9**, which was successfully employed in the iodolactonization reaction,[12] gave the ene product predominantly. Thus, these results clearly indicate the remarkable siloxy effect[13] for facilitating the Prins cyclization.



(2)

Finally, we found the high level (>95%) of 1,3-remote internal asymmetric induction[14] in the reaction with simple silyl ether **10c** to give **11** in 60% isolated yield[15] (eq 3). 2,2'-*anti*-Stereoselectivity could be deduced on the basis of the high 2,1'-*syn*- and 1',2'-*anti*-selectivities which were found with (4*E*)-hexenyl ether (**1c**) (Scheme 2).



(3)

Acknowledgement: The authors are grateful to Professor Takeshi Nakai for his continuous encouragement and useful discussions and to Shu-ichi Sakuda for his experimental help. We are also grateful to Professor Barry B. Snider for his comments and useful discussions during his stay as a visiting scholar in our university. This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education Japan, the Asahi-Kasei Award in Synthetic Organic Chemistry Japan, and Iwaki Scholarship Foundation.

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(6) ^{1}H NMR ($CDCl_3$) 0.96 (d, J=7.1 Hz, 3H), 3.68 (s, 3H), 4.09 (d, J=3.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) 174.5, 79.8, 74.7, 68.2, 51.9, 39.7, 28.7, 25.5, 11.3 ppm.

(7) *anti*-Methyl 2-hydroxy-3-methyl-4-pentenoate: J = 3.6 Hz, *syn*-diastereomer: J = 5.0 Hz: B. B. Snider, J. W. van Straten, *J. Org. Chem.* **1979**, *44*, 3567.

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(14) GLC and ^{13}C NMR spectral analysis ascertained the high level of stereoselectivity.

(15) ^{1}H NMR ($CDCl_3$) 1.41-1.53 (m, 1H), 1.77-2.04 (m, 5H), 3.67-4.22 (m, 4H), 3.72 (s, 3H), 4.36 (dd, J=7.7, 3.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) 175.1, 75.9, 69.1, 67.8, 52.2, 39.1, 31.6, 25.4 ppm.

(Received in Japan 21 April 1992)