Tetrahedron Letters,Vol.25,No.46,pp 5331-5334,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

DIASTEREOFACIAL SELECTIVITY IN THE LEWIS ACID MEDIATED REACTIONS OF ALLYLSILANE WITH CHIRAL β-ALKOXY ACETAL

Syun-ichi Kiyooka,* Hiroko Sasaoka, and Ryoji Fujiyama

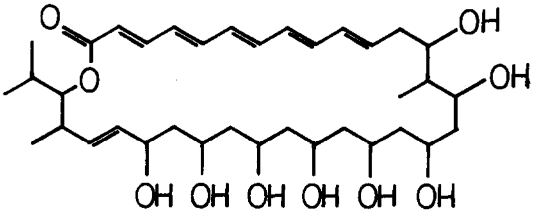
Department of Chemistry, Kochi University
Akebono-cho 2-5-1, Kochi 780, Japan

Clayton H. Heathcock*

Department of Chemistry, University of California
Berkeley, California 94720, U. S. A.

Abstract: 1,3-Syn diastereofacial selectivity (2.8 : 1) has been found in the titanium tetrachloride – titanium tetraisopropoxide mediated reaction of allylsilane with β-alkoxy acetal 2.

Flavofungin 1[1)] has continuous "1,3-diol" units which are assumed to be syn (erythro) like the 1,3-diol units in Amphotericin-B[2)] from the biosynthesis of polyene macrolide. In order to confirm the stereochemistry of the polyol function in 1, the stereoselective synthesis of continuous syn-1,3 units is important. A simple solution to this problem would be a repetitive



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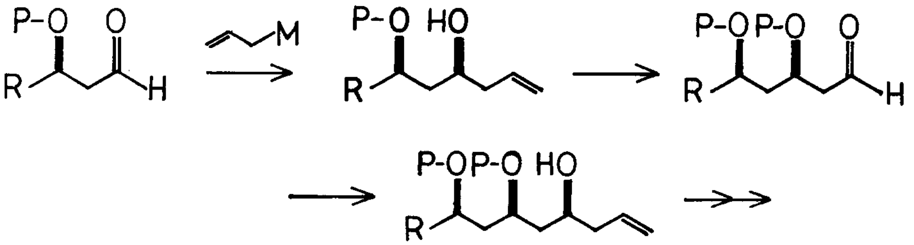


(1)

syn-selective reaction of allylsilane with chiral β-alkoxy aldehydes (Eq. 1). However, such reactions always show anti-selectivity.[3)]

It is well known that Lewis acids[4)] or trimethylsilyl trifluoromethanesulfonate (TMSOTf)[5)] mediated reactions of allylsilane with acetals afford homoallyl ethers. In a preliminary investigation[6)] of the reaction of allyltrimethylsilane with 2-phenylpropanal dimethylacetal, we found that the reaction shows the stereochemistry predicable by Cram's rule for asymmetric induction.[7)]

In this communication, we report that syn-selectivity is seen in the Lewis acid mediated reactions of allyltrimethylsilane with β-alkoxy acetals (Eq. 2).[8)] Data are presented in Table I. The selectivity (2.8 : 1, in entry 8) is not high, but a striking difference in the sence of the selectivity in comparison with that of β-alkoxy aldehydes.[3)]

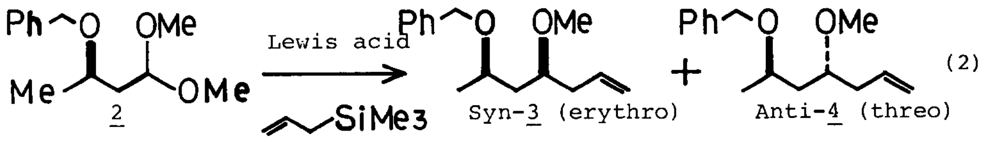
Table I. Lewis Acid Mediated Reaction of Allyltrimethylsilane with 3-Benzyloxybutanal Dimethylacetal (Eq. 2)

Entry	Lewis Acid[a] (mol.eq. to Acetal)	ratio Syn(3) : Anti(4)	yield
1	$TiCl_4$(1.5)	1.23 : 1	86%
2	$TiCl_4$(0.1)	1.28 : 1	81%
3	$TiCl_4$(0.05)	1.55 : 1	72%
4	$SnCl_4$(1.5)	1.12 : 1	53%
5	$BF_3 \cdot OEt_2$(1.5)	1.24 : 1	67%
6	$TiCl_4$–$Ti(O\text{-}{<})_4$(1.5)[b] [0°C]	1.33 : 1	24%
7	$TiCl_4$–$Ti(O\text{-}{<})_4$(1.5)[b]	1.84 : 1	92%
8	$TiCl_4$–$Ti(O\text{-}{<})_4$(1.5)[c]	2.80 : 1	94%
9	TMSOTf(1.0)	1.10 : 1	82%
10	TMSOTf(0.1) [6h]	1.00 : 1	78%
11	$ZnCl_2$(1.5) [0°C]	1.00 : 1	62%
12	$SnCl_2$(1.5) [0°C]	1.00 : 1	58%

a. Unless otherwise noted, the reactions listed were carried out with 2 mol. eq. of allyltrimethylsilane at -78°C for 2h.

b. Before addition of the acetal, $TiCl_4$ and $Ti(O\text{-}{<})_4$ were mixed in CH_2Cl_2.

c. The reaction procedure is described in the text.



2 Syn-3 (erythro) Anti-4 (threo) (2)

The reaction procedure of entry 8: A solution of 447 µL (426 mg, 1.5 mmol) of titanium tetraisopropoxide in 4 mL of dry methylene chloride was cooled to -78°C. To the solution was added dropwise a solution of 448 mg (2 mmol) of 3-benzyloxybutanal dimethylacetal using a syringe. The solution was stirred for 5 min and 165 µL (285 mg, 1.5 mmol) of titanium tetrachloride was added. After 3 min, 636 µL (457 mg, 4 mmol) of allyltrimethylsilane was added in one portion. After stirring at -78°C for 2 h, the reaction mixture was quenched with 5 mL of water. The resulting mixture was allowed to warm to room temperature and extracted with ether. The ethereal layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (10 g silica gel; 3% ethyl acetate in hexanes) to afford a clear liquid in 94% yield. Though the syn- and anti-isomers can be separated by chromatography, the isomer ratio was determined from integration of the methoxy signals in the ^{1}H-NMR spectra without separation of the isomers.

The following trends are notable with respect to stereochemistry;

1) TMSOTf, $ZnCl_2$, and $SnCl_2$ show no selectivity.
2) $TiCl_4$, $SnCl_4$, and $BF_3\cdot OEt_2$ show low syn selectivity.
3) Syn selectivity was slightly improved by decreasing the quantity of $TiCl_4$.
4) $TiCl_4$–$Ti(O{-}{<})_4$ shows considerable syn selectivity; moreover, the selectivity is enhanced by changing the order of addition of the reagents.

The reason for the observed 1,3-syn selectivity is not yet clear. The transition states for reaction of acetals with Lewis acid are complex,9) and the situation is further complicated by the β-alkoxy group. Experiments under the conditions (entry 8) are being continued to synthesize some polyols in order to confirm the stereochemistry of polyene macrolides. Further mechanistic studies are also in progress with improvement of the selectivity being the major goal.

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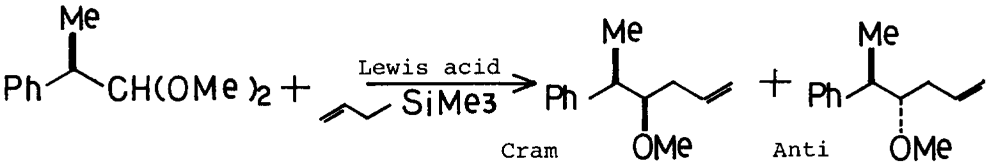

Table II. Lewis Acid Mediated Reaction of Allyltrimethylsilane with 2-Phenylpropanal Dimethylacetal

Entry	Lewis Acid (mol. eq. to Acetal)	temp.	ratio[a] Cram : Anti-Cram	yield
1	$BF_3 \cdot OEt_2$ (1.5)	-78°C(1h)	1.7 : 1	39%
2	$TiCl_4$ (1.5)	-78°C(1h)	2.8 : 1	63%
3	$SnCl_4$ (1.5)	-78°C(1h)	3.5 : 1	76%
4	$TiCl_4{-}Ti(O{-}{<})_4$ (1.5)	-78°C(1h)	1.7 : 1	82%
5	$ZnCl_2$ (1.5)	rt(1h)	1.8 : 1	92%
6	TMSOTf (0.1)	-78°C(6h)	2.0 : 1	32%

[a] The stereochemistry of products is determined by correlation with materials derived from the reaction of allylsilane with 2-phenylpropanal, followed by methylation.

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(Received in Japan 6 August 1984)