STEREOCHEMICAL CHANGE IN THE LEWIS ACID-PROMOTED REACTION OF 2-SILOXYPYRROLE DERIVED FROM (L)-GLUTAMIC ACID. SYNTHESIS OF A LACTACYSTIN ANALOGUE

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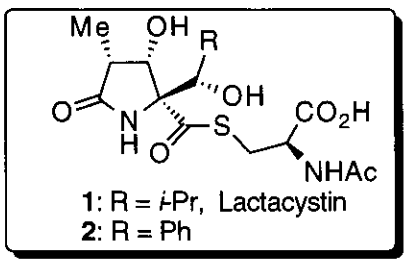
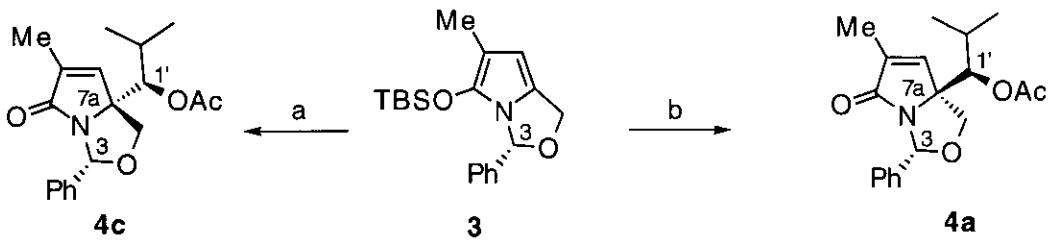
Abstract—In the presence of $BF_3 \cdot OEt_2$, the reaction of (3R)-5-*t*-butyldimethylsiloxy-6-methyl-3-phenyl-*1H*-pyrrolo[1,2-*c*]oxazole (**3**) with aliphatic aldehydes in ether occurred stereoselectively to give the corresponding *(3R,7aR,1'R)*-isomers (**4a** and **6a**) as the major products, while the similar reaction with aromatic aldehydes afforded the *(3R,7aR,1'S)*-isomers (**7b**, **8b**, and **9b**) predominantly. The product (**7b**) from the reaction with benzaldehyde was successfully transformed to a lactacystin analogue.

Considerable attention has been paid for the synthetic applications of the Lewis acid-promoted reactions of 2-siloxy-substituted five-membered heterocycles such as 2-siloxy-furans, thiophenes, and pyrroles due to the facile transformation of the products into compounds with the aimed functionalities.[1] In these reactions, high regioselectivity of the other α-position is usually realized. On the other hand, stereochemistries of newly created stereogenic centers largely depend upon the reaction conditions including the choice of Lewis acids and solvents, as these phenomena are often encountered in the Mukaiyama-type aldol reactions.[2] One of authors has also reported the alteration of diastereofacial selectivity in the $BF_3 \cdot OEt_2$- and $SnCl_4$-assisted reactions of chiral siloxypyrrole (**3**) derived from (S)-glutamic acid with isobutyraldehyde[3] (Scheme 1) and application for the total synthesis of lactacystin[4] which inhibits cell cycle progression and induces neurite

outgrowth in a murine Neuro-2A cell line by inhibition of proteasome activities.[5] During studies on the reactions of the siloxypyrrole (**3**) with various aldehydes directed toward synthesis of lactacystin analogs, we have found the remarkable stereochemical behavior in the reaction of **3** with aromatic aldehydes. In this communication, we describe the studies on the stereochemical course of the reaction as well as preparation of lactacystin analogue (**2**).





Scheme 1. *Reagents, conditions, and yields:* (a) isobutyraldehyde, $SnCl_4$, ether; pyridine, Ac_2O; 63%; (b) isobutyraldehyde, $BF_3{\cdot}OEt_2$, ether; pyridine, Ac_2O; 64%.

In the presence of $BF_3{\cdot}OEt_2$, the reaction of (**3**) with isobutyraldehyde in ether occurred from the opposite face to the 3-phenyl group to give (**4a**, 7a,1'-*erythro*) as a main product after acetylation. However, the similar reaction in the presence of $SnCl_4$ took place from the other face mainly to afford (**4c**, 7a,1'-*threo*), relative stereochemistry of which was required for the lactacystin synthesis.[3] Concerning with the side chain center, the same *re*-face of isobutyraldehyde was preferred in both cases. The similar results were obtained in the cases of cyclohexanecarbaldehyde and propionaldehyde (Eq 1 and Table 1). The stereochemistry of the products was determined by the NOE experiments as well as their acid rearrangement to *spiro* acetals (**10**) and (**11**) (Figure 1). Contrary to this, the *si*-face of benzaldehyde was favored in the case of $BF_3{\cdot}OEt_2$ (Entry 5), while low diastereoselectivity was observed in the case of $SnCl_4$ (Entry 6). Other aromatic aldehydes such as *p*-anisaldehyde and *p*-cyanobenzaldehyde also showed the similar selectivity (Entries 7 and 8).

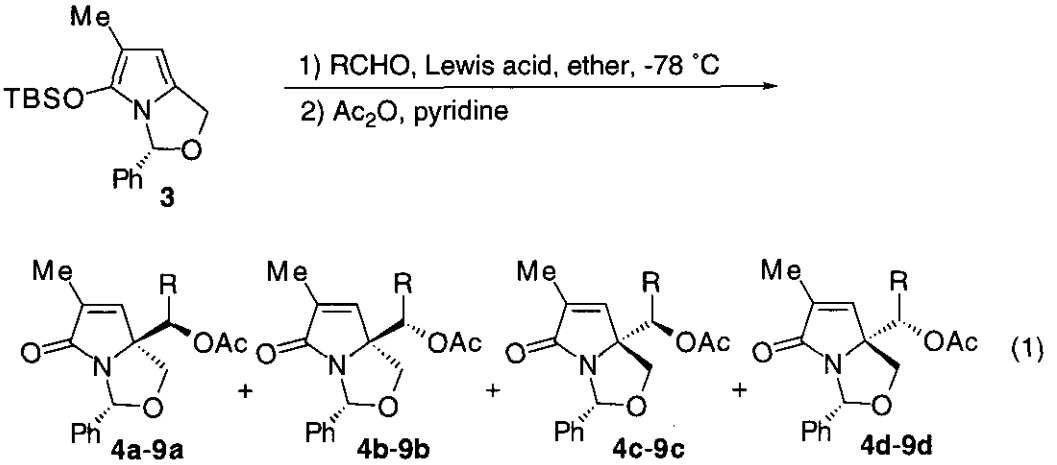


Table 1. Lewis acid-mediated reaction of **3** with various aldehydes

Entry	Product	Lewis acid	Yield[a] /%	Diastereomer ratio[b] a	b	c	d
1	**4** (R = *i*-Pr)	BF_3·OEt_2	89	**72**	6	16	6
2	**4** (R = *i*-Pr)	$SnCl_4$	65[c]	-	-	> 90	< 10
3	**5** (R = *c*-C_6H_{11})	$SnCl_4$	50[c]	-	-	> 90	< 10
4	**6** (R = Et)	BF_3·OEt_2	65	**65**	18	17[d]	
5	**7** (R = Ph)	BF_3·OEt_2	65	18	**73**	9[d]	
6	**7** (R = Ph)	$SnCl_4$	50	24	**41**	20+5[e]	
7	**8** (R= C_6H_4-*p*-OMe)	BF_3·OEt_2	56	14	**76**	10[d]	
8	**9** (R = C_6H_4-*p*-CN)	BF_3·OEt_2	89	25	**65**	6+4[e]	

[a] The combined yield of diastereomers after chromatography. [b] The ratio was determined by ^{1}H NMR analysis of the reaction mixture. [c] The reaction mixture was directly chromatographed without acetylation. [d] One of the diastereomers (**c**) or (**d**) was obtained and the determination was not carried out. [e] Determination of the isomers could not be done.

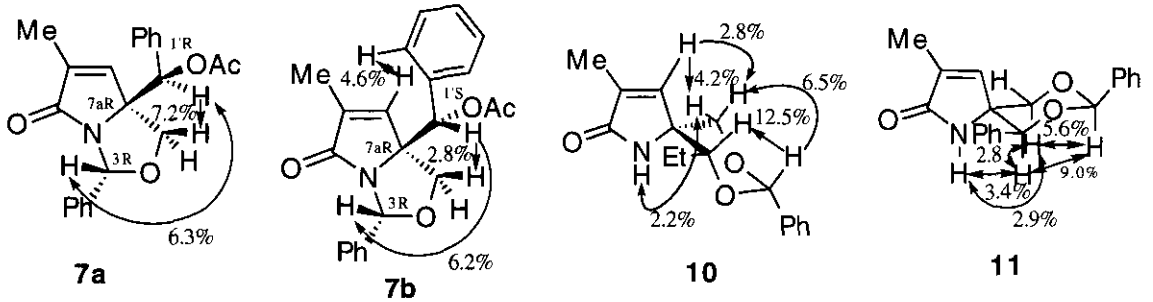
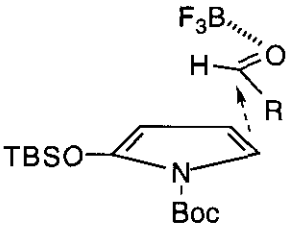
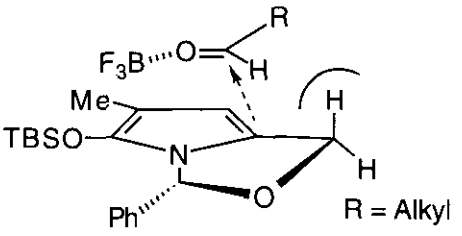


Figure 1. Key NOE values for **7a**, **7b**, **10**, and **11**. The compounds (**10**) and (**11**) were obtained by the acid rearrangement of the corresponding alcohols of **6a** and **7b**, respectively.

Transition states leading to *threo* and *erythro* products in the Lewis acid-mediated reactions of 2-siloxy heterocycles have been discussed in terms of steric, orbital, and charge interactions, and the preferental *threo* selectivity observed in most cases is well rationalized by the Diels-Alder like arrangement between the heterocycles and aldehydes.[1a] The stereochemical change between aliphatic and aromatic aldehydes observed in our experiments may be possibly rationalized as follows (Figure 2). In the case of BF_3-promoted reaction of *N*-Boc-2-(*t*-butyldimethylsiloxy)pyrrole (TBSOP), the predominant *erythro* selectivity was explained by the synclinal transition state (**T1**) in terms of the charge interaction.[1b] In our BF_3-assisted reactions of the siloxypyrrole (**3**) with aliphatic aldehydes, we thought the *erythro* selectivity would be due to the Diels-Alder like transition state (**T2**), because the steric influence of the oxazolidine ring would disfavor the model (**T1**).[3] In the case of aromatic aldehydes, the π-π interaction between the pyrrole moiety and the aromatic ring would become a major controlling factor and the other synclinal transition state (**T3**) giving the *threo* isomers would be favored.

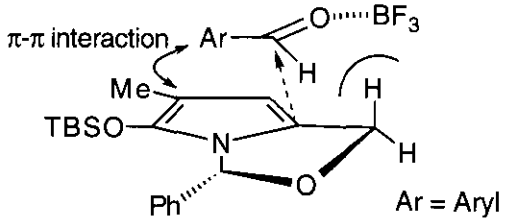


T1: Synclinal Transition State for TBSOP



T2: Favored Diels-Alder like Transition State for **3**

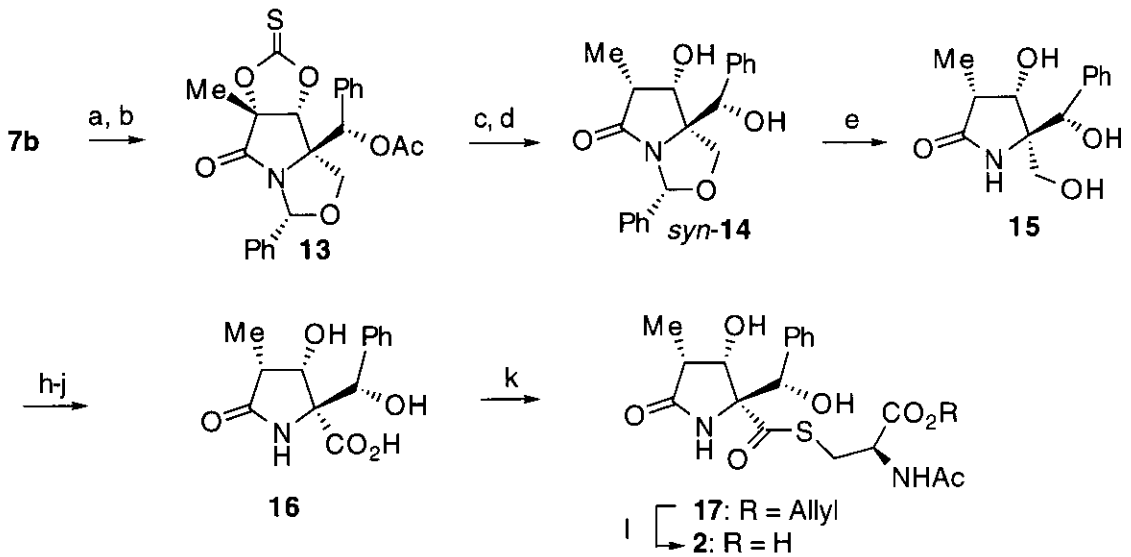
⇒ **4a-9a**



T3: Favored Synclinal Transition State for **3**

⇒ **4b-9b**

Figure 2. Proposed transition states



Scheme 2. *Reagents and conditions:* (a) OsO_4, NMO, *t*-BuOH; (b) TCDI, THF; (c) *n*-Bu_3SnH, AIBN, toluene, reflux; (d) 0.5 N MeOH-H_2O, 3 d; (e) conc. HCl, MeOH; (f) Et_3SiCl, pyridine; (g) Ac_2O, pyridine; (h) 50% HF, MeCN; (i) Jones' reagent; (j) 0.2 N NaOH; (k) *N*-acetylcysteine allyl ester, BOPCl; (l) $Pd(Ph_3P)_4$, $HCO_2H{\cdot}NEt_3$.

Next, we carried out the synthesis of the lactacystin analogue (**2**) along our route (Scheme 2).[4] The compund (**7b**) was converted to cyclic thiocarbonate (**13**) by osmylation followed by thiocarbonylation (80%). Fortunately, recrystalization of the thiocarbonate gave fine crystals for X-Ray and this compound (**13**) was unambiguously confirmed to have the required absolute stereochemistry as estimated by the NOE and acid rearrangement experiments. Reduction of the cyclic thiocarbonate (**13**) with *n*-Bu_3SnH resulted in formation of a diastereomeric β-hydroxy lactam in a *syn*:*anti* ratio of 1:2.8 (93%). Treatment of the lactam with an aqueous alkaline solution at 0~4 °C for 3 days caused epimerization of the methyl group as well as saponification to give desired *syn*-**14** in a ratio of 7.7:1, from which the pure *syn* isomer was isolated by recrystallization (71%).[6] The benzylidene group of *syn*-**14** was removed in acidic MeOH to give triol (**15**) (88%), primary and secondary hydroxyl groups of which were protected by Et_3Si and acetyl groups, respectively (69%). Regeneration of the primary hydroxyl group followed by Jones' oxidation and hydrolysis gave pyroglutamic acid derivative (**16**) (46%). The final conversion to **2** {white amorphous solid, $[\alpha]_D^{24}$ +32° (*c* 0.077, MeOH)} was accomplished by using Corey's protocol.[7] The bioactivity of **2** is now fully investigated and the results will be published elsewhere.

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