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Novel Synthetic Strategy to Chiral Alkylated Lactams Employing Cyclic Imides with C_2-Symmetry

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Abstract: *Reductive deoxygenation of quarternary α-hydroxy lactams, readily prepared from alkylation of C_2-symmetrical imides, with Et3SiH in the presence of Lewis acid displayed an extremely high stereoselectivity to provide the corresponding lactams. Stereochemistry of the new stereogenic center generated has been confirmed unambiguously to be S, resulting from an unprecedented trans-selective reaction, by the transformation into the known lactam.*

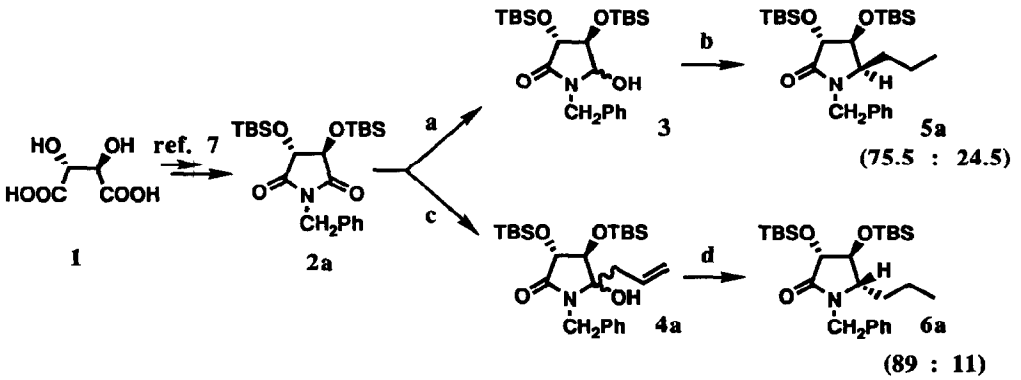
Owing to their useful structural features in the sythesis of chiral substances possessing a wide range of biological activity, asymmetric reactions employing reagents with a C_2-axis of symmetry are of great interest.[1] Over the last two decades they have led to a rapid growing speciality in the general field of synthetic organic chemistry. Therefore, a number of efficient techniques and synthetic strategies have appeared for the construction of those compounds in optically pure form[2] and further exploitation of much more convenient methods is subject to continual refinement.

On the other hand, the synthetic utility of *N*-acyliminium ions obtained from the partial reduction of cyclic imides has been demonstrated in the preparation of nitrogen-containing natural products such as alkaloids.[3] In addition, very recently moderate *cis*-selective intermolecular alkylation of an α-alkoxy *N*-acyliminium ion was first reported[4] as part of a radical cyclization methodology.[5] In spite of the impressive behavior of such intermediates, little, if any, effort has been made for the utilization of the quarternary carbon center present in the α-hydroxy lactams (**4**).[6]

As part of our recent continuing investigations designed to extend the employment of C_2-symmetrical imide (**2**), a diastereomer differentiated reaction[7] and the application to the total synthesis of natural cerulenin, antibiotic[8] have been developed from this laboratory. The central purpose of the present communication is to detail the unprecedented results that *trans*-selective (with respect to the C–4 substituent) deoxygenation of the quartenary α-hydroxy lactams (**4**)[9] could be accomplished exclusively.

In order to introduce an alkyl group stereoselectively, homochiral imide (**2a**) prepared in one pot from L-

tartaric acid was first reduced with $NaBH_4$ to give a mixture of two stereoisomeric hydroxy lactams (**3**).[10] As shown in Scheme 1, acid-induced alkylation of **3** proceeding via an *N*-acyliminium intermediate[4,5] upon treatment with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ resulted in the moderate *cis*-selective formation of **5a**[11] at 0 °C (**5a** : **6a** = 75.5 : 24.5 determined by HPLC[12]). Next, we investigated the utilization of the alkylated quarternary α-hydroxy lactam (**4a**) prepared by the Grignard addition to **2a** according to our method.[7] When **4a** was treated with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ at 0 °C, it reversely afforded deoxygenated lactam **6a** cleanly and *trans*-selectively in the ratio of 89 : 11.[11]



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, -15 °C; 91%; (b) 1, allyltrimethylsilane, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; 96%; 2, H_2, Pd/C, EtOH; 100%; (c) allylmagnesium bromide, THF, -78 - 0°C; 74%; (d) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; 87%.

With the above unusual stereoselective results in hand, we further examined the reactions with several types of **4** under similar conditions but at low temperature (-78 °C) in order to enhance the selectivity. The details are summarized in Table 1. The reaction proceeded in high yield in each case. Increasing the steric bulkiness of the silyl-protecting groups as well as lowering the reaction temperature led to an increase of the diastereoselectivity in the reaction (Entries 3:4 and 5:7), however, the products were still obtained with high selectivity even with TBS groups (Entries 1,2). A change from the benzyl substituent on the nitrogen atom to a smaller methyl group enhanced the selectivity a little (Entries 3:5 and 4:7). In the case of the reactions with a benzyl side chain, complete diastereodifferentiation was observed (Entries 6,9, and 10).

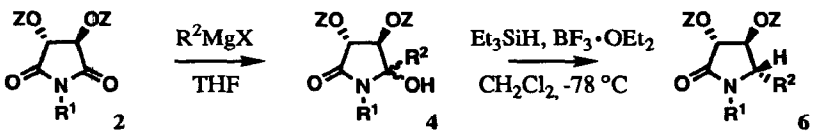
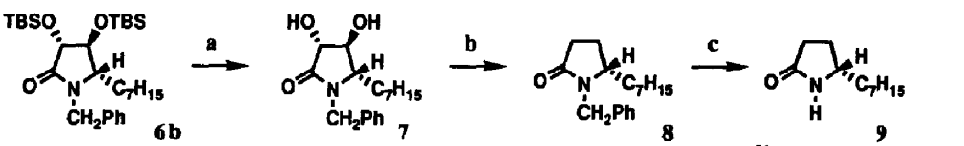


Table 1 Reductive Deoygenation of quarternary α-hydroxy lactams (4)[a]

Entry	R^1	Z	R^2	Yield[b] of 4 (%)	Yield[b] of 6 (%)		Ratio[c] of 6 (5S) : (5R)
1	$PhCH_2$	TBS	n-C_3H_7	98	78	(6a)	95.1 : 4.9
2	$PhCH_2$	TBS	n-C_7H_{15}	95	91	(6b)	94.7 : 5.3
3	$PhCH_2$	TBS	n-C_8H_{17}	99	76	(6c)	95.5 : 4.5
4	$PhCH_2$	TIPS	n-C_8H_{17}	100	98	(6d)	97.2 : 2.8
5	CH_3	TBS	n-C_8H_{17}	97	96	(6e)	97.2 : 2.8
6	CH_3	TBS	$PhCH_2$	91	83	(6f)	> 99 : 1
7	CH_3	TIPS	n-C_8H_{17}	98	95	(6g)	98.5 : 1.5
8	CH_3	TIPS	n-C_3H_7	95	85	(6h)	> 99 : 1
9	CH_3	TIPS	$PhCH_2$	91	70	(6i)	> 99 : 1
10	CH_3	TIPS	p-$MeOPhCH_2$	-	55 [d]	(6j)	> 99 : 1

a) 5-10 equiv. of Et_3SiH and $BF_3 \cdot OEt_2$ were used. b) Isolated yield. c) Determined by HPLC (Daicel Chiralpak AS) and ^{13}C NMR. d) Based on 2.

The stereochemistry of the newly created stereogenic center of **6** was proven by transformation into known lactam **9**, as shown in Scheme 2. Compound **6b** (Entry 2) was submitted to sequential desilylation and dehydration with triiodoimidazole in the presence of Zn[7a,13] followed by hydrogenation, leading to the saturated lactam (**8**). Finally, **8** was subjected to debenzylation to produce **9**, which could be assigned as *S* form in comparison of its specific rotation with that reported.[9b]



Scheme 2. Reagents and conditions: (a) concd. HCl, MeOH; 95%; (b) 1, triiodoimidazole, imidazole, Ph_3P, Zn, toluene, 70 °C; 2, Mg, MeOH; 49% (2 steps); (c) Na, NH_3, -78 °C; 97%.

Although the reason why such an unusual *trans*-selective deoxygenation reaction was observed is not clarified at present, an efficient and general method to construct chiral alkylated lactams has been established by using C_2-symmetrical imide as a template. This strategy provides a new synthetic opportunity for the synthesis of natural indolidizine alkaloids. The following paper describes our results concerning the total synthesis of biologically active lentiginosine.

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9. Recently two independent groups reported stereoselective deoxygenation of a quarternary α-hydroxy (or alkoxy) lactam elucidated via an *N*-acyliminium ion: (a) Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.*, **1990**, *31*, 7329; (b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656, in which (*R*)-**9** was shown to have $[\alpha]^{26}_{D}$+9.0 (c 2.0, CH_2Cl_2). The chiral center of (*S*)-**9** thus obtained seems to racemize during the dehydration process.
10. The ratio of the two stereoisomers was not determined.
11. ^{1}H NMR data ($CDCl_3$, 90 MHz) for **5** and **6a**. **5**: δ 0.00 (3H, s), 0.10 (3H, s), 0.17 (3H, s), 0.23 (3H, s), 0.76-1.56 (7H, m), 0.89 (9H, s). 0.95 (9H, s), 3.39 (1H, dt, $J_{4,5}$, $J_{5,6}$ = 6.2, 6.2 Hz), 3.81-4.25 (3H, m), 4.95 (1H, d, J = 15.2 Hz), 7.28 (5H, s). **6a**: d 0.01 (3H, s), 0.08 (3H, s), 0.19 (3H, s), 0.21 (3H, s), 0.73-1.61 (7H, m), 0.84 (9H, s), 0.93 (9H, s), 3.15 (1H, dt, $J_{4,5}$, $J_{5,6}$ = 2.0, 5.9 Hz), 3.85 (1H, dd, J = 2.0, 2.0 Hz), 3.90 (1H, d, J = 15.4 Hz), 4.02 (1H, d, J = 2.0 Hz), 5.09 (1H, d, J = 15.4 Hz), 7.24 (5H, s). Observed chemical sift and vicinal coupling constants ($J_{4,5}$ and $J_{5,6}$) of the other major isomers (**6b** - **6j**)[4,5] were almost identical with those of **6a**. And the absolute configuration of the generated stereogenic center of **6** was clearly determined as shown in Scheme 2.[9b]
12. HPLC conditions were as follows. Column: Daicel Chiralpak AS, 4.6 x 250mm. Eluent: hexane - 2-propanol (800 : 1), 0.7 ml/min. Detection: UV at 220 nm.
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