HETEROCYCLES, Vol. 53, No. 5, 2000, pp. 1011 - 1016, Received, 2nd February, 2000

A NEW APPROACH FOR CONSTRUCTION OF QUARTERNARY CHIRAL CENTERS: PREPARATION OF α-BRANCHED SERINE DERIVATIVES

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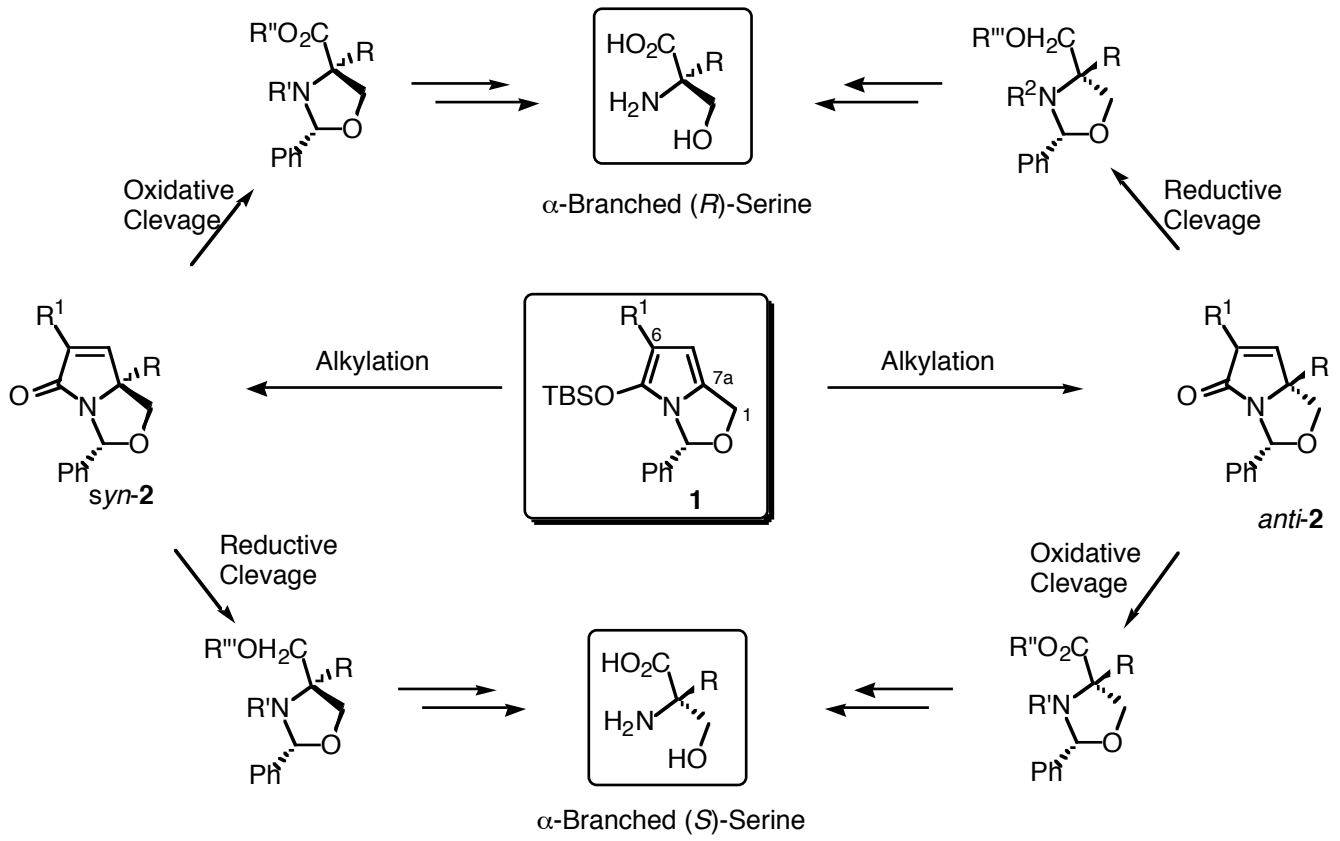
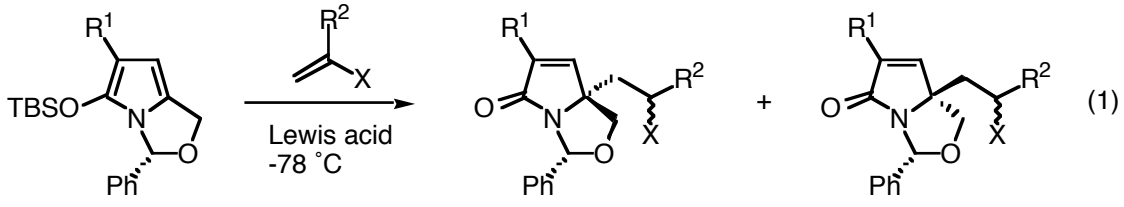
Abstract—In the presence of a Lewis acid, the Michael-type reaction of (3*R*)-5-*tert*-butyldimethylsiloxy-3-phenyl-*1H*-pyrrolo[1,2-*c*]oxazole (**1**) with nitro olefins smoothly occurred to give 7a-alkylated pyrrolo[1,2-*c*]oxazol-5-ones (**2**) in good yields. The products (**2**) were successfully transformed to a α-branched serine derivatives *via* reductive denitration followed by lactam-ring cleavage.

In the synthesis of amino acids, use of the nucleophilic reaction at a nitrogen-bearing carbon is very important, and many successful examples[1] have been reported for this purpose. Methods[1] utilizing diastereoselective reactions of chiral auxiliaries or building blocks represented by Evans' oxazolones, Schöllkopf's bislactims, Williams' piperadinones, and Seebach's oxazolones deserve attention due to their wide applicability and high reliability. In some cases, however, construction of quarternary chiral centers by these methods still encounter low selectivity and/or poor yields mainly due to reversible nature of such reactions. Great attention has been paid for the Mukaiyama-type aldol reactions[2] to overcome this problem. We have reported the selective construction of chiral quartenary centers based on the Lewis acid-promoted reactions of chiral siloxypyrroles (**1** and *ent*-**1**) derived from (L)- and (D)-glutamic acid leading to lactacystin and its analogues.[3] This method can be utilized for the construction of the quarternary center of α-branched serine derivatives,[4] if the lactam ring is cleaved. In this communication we would like to describe the novel synthesis of these abnormal amino acids *via* this route.



Scheme 1. Synthetic Strategy to the α-Branched Serines

Our strategy to the synthesis of serine derivatives is shown in Scheme 1. If we achieve the alkylation at the 7a position of the siloxypyrrole (**1**) stereoselectively, we can get both *S* and *R* α-branched serine derivatives *via* the oxidative and reductive cleavage of the γ-lactam ring of **2**. First, we attempted to alkylate the siloxypyrrole (**1**) under the similar conditions employed for the alkylation of 1-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsilyl-oxypyrrole.[5] In spite of all our efforts, however, no reaction or complete decomposition was observed and no alkylated product such as **2** was obtained. Next, we examined the Michael-type reaction of **1** with various Michael acceptors such as α,β-unsaturated carbonyl compounds, and the reaction took place at the 7a position of **1** (Eq 1 and Table 1).



1a: R^1 = Me
1b: R^1 = H

syn-**2**

anti-**2**

Table 1. The Reaction of Siloxypyrrole (**1**) with Michael Acceptors

Entry	Siloxy-	Michael Acceptor			Lewis Acid	Solvent	Products	Yield	Ratio
	pyrrole	R^2	X	equiv	(equiv)			(%[a])	*syn*/*anti*[b]
1	**1a**	H	COMe	1.0	$TiCl_4$ (1.2)	ether	**2aa**	62[c]	1/12
2	**1a**	H	COMe	1.0	$SnCl_4$ (1.2)	ether	**2aa**	36	1/4
3	**1a**	H	COMe	1.0	$SnCl_4$ (1.2)	CH_2Cl_2	**2aa**	66	1/3
4	**1a**	H	COMe	1.0	$BF_3{\cdot}OEt_2$ (1.2)	ether	**2aa**	49[c]	1/11
5	**1a**	Me	CHO	1.0	$BF_3{\cdot}OEt_2$ (1.2)	ether	**2ab**[d]	35[c]	-/1[e]
6	**1a**	H	NO_2	1.5	$SnCl_4$ (1.0)	ether	**2ac**	30	2/1
7	**1a**	H	NO_2	1.5	$SnCl_4$ (1.0)	CH_2Cl_2	**2ac**	62	7/1
8	**1a**	H	NO_2	1.5	$BF_3{\cdot}OEt_2$ (1.2)	ether	**2ac**	21	2/1
9	**1a**	H	NO_2	1.5	$SnCl_4$ (0.5)	CH_2Cl_2	**2ac**	73	6/1
10	**1a**	H	NO_2	1.5	$SnCl_4$ (1.0)	CH_2Cl_2	**2ac**	62	7/1
11	**1a**	H	NO_2	2.0	$SnCl_4$ (0.1)	CH_2Cl_2	**2ac**	66[c]	19/1
12	**1b**	H	NO_2	2.0	$SnCl_4$ (1.0)	CH_2Cl_2	**2bc**	54[f]	1/2
13	**1a**	Me	NO_2	1.0	$SnCl_4$ (0.1)	CH_2Cl_2	**2ad**[g]	60	1/2
14	**1a**	Et	NO_2	2.0	$SnCl_4$ (0.1)	CH_2Cl_2	**2ae**[g]	37	1/3

[a] Combined yield of the chromatographed material. [b] The ratio was calculated by the NMR analysis of the reaction mixture. [c] Isolated yield of the major isomer(s). [d] This product was obtained as a TBS enol ether. [e] The ratio could not be estimated due to complexity of the reaction mixture. [f] The product reacted at the 6 position was obtained in 13% yield. [g] The product was obtained as a mixture of four diastereomers, additional chiral center of which could not be assigned.

In the presense of $TiCl_4$, the siloxypyrrole (**1a**) reacted with methyl vinyl ketone only at the 7a position to give *anti*-**2aa** in 62% yield (*syn*-**2aa** : *anti*-**2aa** = *ca.* 1 : 12, Entry 1). The face selectivity was not affected by the choice of Lewis acid and solvent (Entries 2, 3, and 4), although lower yields were realised in ether. The reactions with 1,1-unsubstituted 2-nitroalkenes occurred smoothly to give nitro compounds in moderate to good yields (Entries 6-14), while β-nitrostyrene, ethyl acrylate, acrylonitrile, and ethyl propiolate did not react. In the cases of 2-nitropropene, 2-nitrobutene, and 3-methyl-2-nitrobutene, *syn*- and *anti*-isomers were determined by the NOE experiments, although the additional stereogenic center at the nitro-substituted carbon could not be assigned. In the reaction of **1b**, the Michael-type reaction with nitroethylene occurred at both 7a and 6 positions, although the major product was **2bc** (Entry 12).

We turned our attention to the face selectivity in the Michael-type addition of siloxypyrroles (**1**). All reactions except for the reaction of **1a** with nitroethylene took place at the 7a position from the opposit face against the 3-phenyl group. This approach of the Michael acceptors seems to be reasonable (Figure 1, **T1**), if we consider the steric requirement only around the 7a carbon in the synclinal transition states; the 3-phenyl group would interfere the approach of the Michael acceptors from the same site (Figure 1, **T2**).[6] In our previous papers, we have discussed about the importance of the Diels-Alder-type transition states in the reactions of 2-siloxypyrroles.[3,7] In the case of highly reactive Michael acceptors such as nitroalkenes, the orbital interaction of the starting materials should be important and the Diels-Alder-like transition states could become very important, if the steric requirement allows the transitiion states (Figure 1, **T3** and **T4**). The TBS group of **1a** (not **1b**) is thought to be fixed in the opposite site to the 3-phenyl group due to the steric interaction with 3-phenyl and 6-methyl groups. In fact, the diastereotopic methyl groups of the TBS of **1a** were observed in similar fields (0.02 and 0.09 ppm), while the methyl groups of **1b** were observed in well-separated places (-0.04 and 0.17 ppm) probably due to the anisotropic effect of the 3-phenyl group. Thus, in the case of **1a**, nitroethylene would preferably approach from the same face to the 3-phenyl group (**T4**) to give the *syn* product. In other nitroalkenes, the alkyl groups (R^2) would interact with the 3-phenyl group, so the synclinal transition state (**T1**) would be favored to give the *anti* products.

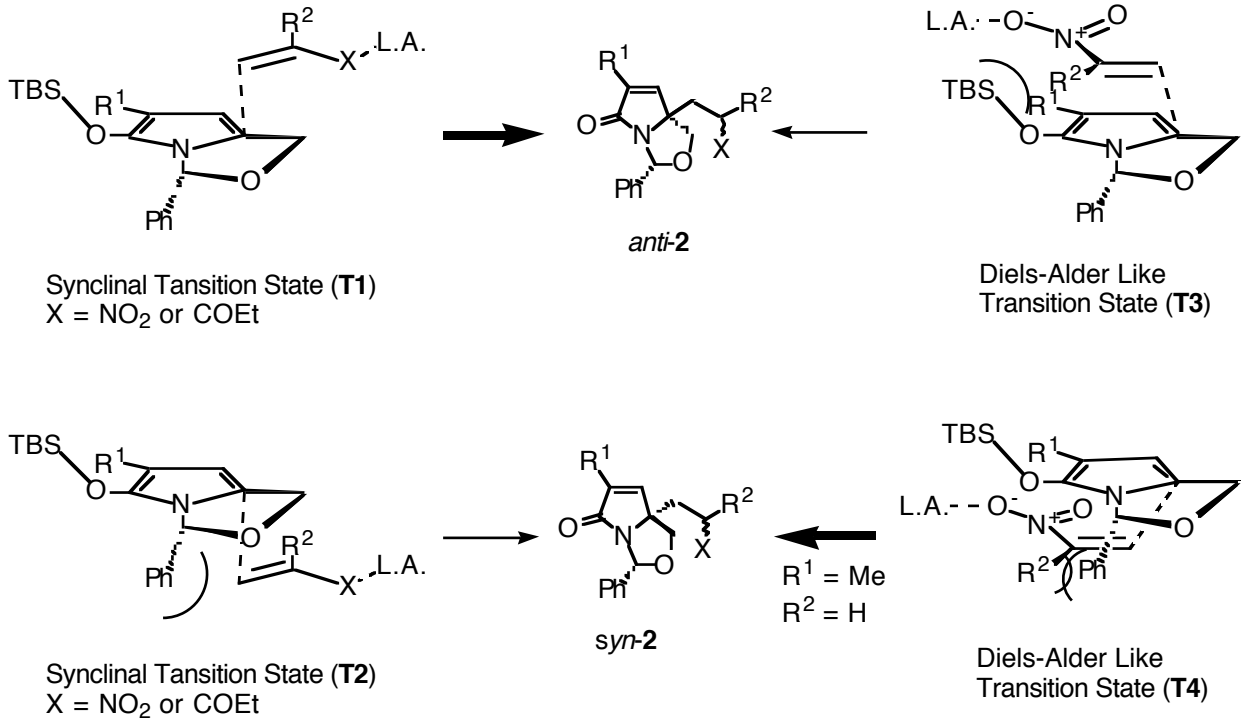
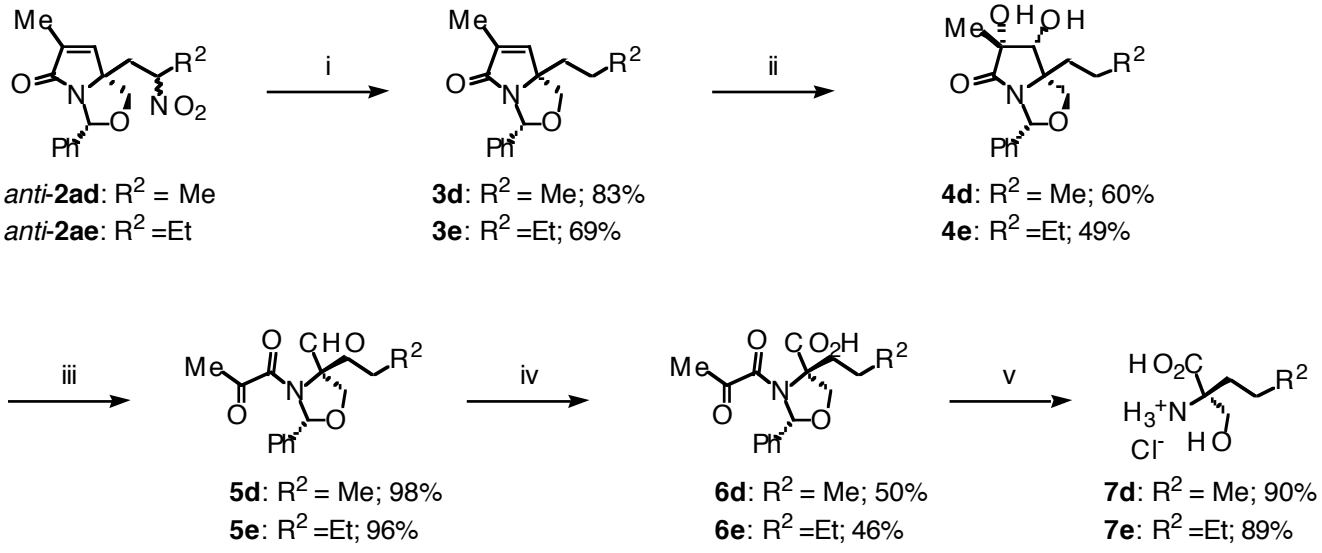


Figure 1. Proposed Transition States

Next, cleavage of the γ-lactam ring in the major adducts (**2**) was examined (Scheme 2). However, dihydroxylation of **2ac** and **2ae** by OsO_4 did not occur, and no reaction or decompositon was observed. Since both types of the ring system was dihydroxylated in the synthesis of lactacystin and its analogues,[3] the nitro group would interfere the osmylation.[8] Therefore, the adducts were refluxed with *n*-Bu_3SnH in the presence of AIBN in toluene to remove the nitro group.[9] The secondary nitro group of **2ad** and **2ae** was easily removed to give the corresponding compounds (**3d** and **3e**) in good yields, while no product was obtained from the reaction of the primary nitro compound **2ac**. These products (**3d** and **3e**) were succesfully dihydroxylated under the usual osmylation conditions to give diols (**4d** and **4e**), which were transformed to the aimed α-branched serine derivatives (**7d** and **7e**) by cleavage[10] with $Pb(OAc)_4$ followed by oxidation[11] with $NaClO_2$ and deprotection with 6 N HCl. The specific rotation of **7d** and **7e** was $[\alpha]_D^{23}$ = +10° (*c* 0.160, 1 N HCl) and +27° (*c* 0.253, 1 N HCl) , respectively.



anti-**2ad**: R^2 = Me
anti-**2ae**: R^2 =Et

3d: R^2 = Me; 83%
3e: R^2 =Et; 69%

4d: R^2 = Me; 60%
4e: R^2 =Et; 49%

5d: R^2 = Me; 98%
5e: R^2 =Et; 96%

6d: R^2 = Me; 50%
6e: R^2 =Et; 46%

7d: R^2 = Me; 90%
7e: R^2 =Et; 89%

Scheme 2. *Reagents and Conditions:* i) *n*-Bu_3SnH, AIBN, toluene, reflux; ii) OsO_4, NMO, *t*-BuOH, rt; iii) $Pb(OAc)_4$, K_2CO_3, benzene, rt; iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt; v) 6 N HCl, reflux.

In conclusion, the Michael-type reaction of (3*R*)-5-*tert*-butyldimethylsiloxy-6-methyl-3-phenyl-*1H*-pyrrolo[1,2-*c*]oxazole (**1**) with 1,1-unsubstituted 2-nitroalkenes occurred at the 7a position preferentially from the opposite face to the 3-phenyl group. The adducts were successfully converted to the α-branched serine derivatives.

ACKNOWLEDGEMENT

Financial support from Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture is greatly acknowledged.

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