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Remarkable Endo Selectivity on Hydroxylation of Bicyclic Lactam Enolates with MoOPD and MoOPH

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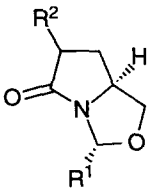
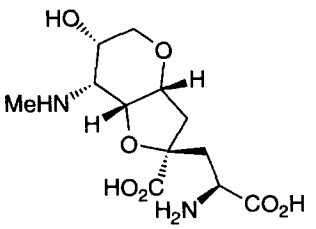
Abstract: Remarkable endo selectivity was observed during the hydroxylation of the enolates derived from the bicyclic lactam **1a** and its relatives with molybdenum oxidizing reagents, MoOPD and MoOPH, showing that the molybdenum reagents approach the enolate from the sterically hindered concave face of the lactam in spite of their bulkiness.

Keywords: hydroxylation;MoOPD;MoOPH; bicyclic lactam; endo selectivity

The bicyclic lactam **1a**,[1] derived from pyroglutamic acid, has been used as a chiral synthon for the syntheses of biologically active compounds.[2,3] In the course of our efforts directed towards the total synthesis of dysiherbaine **2**,[4] a selective agonist of non-NMDA type glutamate receptors, we needed the 7-hydroxylated bicyclic lactam **3** for construction of the hydroxylated quaternary carbon center and encountered the unusually endo selective hydroxylation of the bicyclic lactam **1a** and its relatives. Meyers and coworkers have recently reported the detailed studies of the diastereoselectivies for alkylation of the bicyclic lactam **1b** and the closely related lactams including a series of ab initio molecular orbital calculations.[5] Increasing interests concerning the bicyclic lactams have prompted us to disclose our investigation of the remarkable hydroxylation reaction to the bicyclic lactam enolates with endo selectivity using MoOPD (MoO_5• Py• DMPU) and MoOPH (MoO_5• Py• HMPA).[6-8]



1a: R^1 = Ph, R^2 = H
b: R^1 = *i*-Pr, R^2 = H



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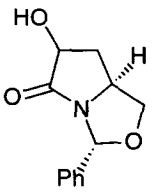

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The bicyclic lactam **1a** was prepared from commercially available (*S*)-pyroglutamic acid according to Thottathil's procedure.[1] Initial studies of the hydroxylation using Davis oxaziridine[9] failed to afford the desired product. However, replacement of the oxidant by MoOPD known as a hydroxylating reagent for the enolates

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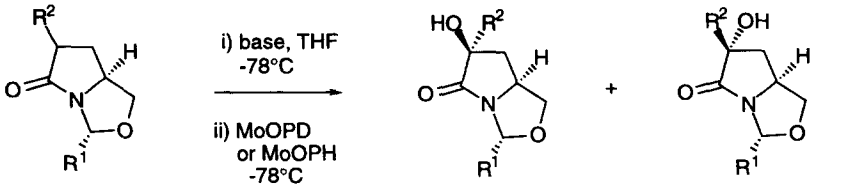
resulted in the following unexpected hydroxylation. The generation of the lithium enolate of the lactam **1a** by the treatment of LDA (1.5 eq) at -78℃ followed by the addition of MoOPD gave a 90:10 mixture of α-hydroxylated lactams **4a** and **5a** favoring the endo product in 78% yield (92 % conversion yield).[10] The stereochemistry of the major isomer of the α-hydroxylated lactam was determined by the NOE difference studies after protection of the alcohol function with the *t*-butyldimethylsilyl group.[11] This result is incomparably superior to the reported one of the hydroxylation reaction of the analogous lactam **1e** (R^1 = *p*-MeOPh, R^2 = H) with the Davis oxaziridine.[3e] We subsequently expected this endo hydroxylation to be extended to the bicyclic lactams **1b-d**. The lactam **1b** with a 2-isopropyl substituent also underwent the endo selective hydroxylation. The reaction of the allyl substituted lactam **1c** surprisingly proceeded in complete stereoselection to give the endo product **4c** as the sole diastereomer in 61 % yield. Several different bases for this reaction were tested and LDA was found to afford the best result based on the yield. Similarly, the cyclohexylmethyl substituted lactam **1d**, a model compound for the synthesis of dysiherbaine, furnished the hydroxylated product **4d** with endo selectivity of 92:8 under similar conditions. The stereochemistry of these compounds was unambiguously assigned by the difference NOE experiments. These results clearly indicate that the oxidant approaches the enolate from the sterically hindered concave face to afford the endo product (Fig. **A**). The oxidation with MoOPH was observed to give the comparable yields and diastereoselections to those of MoOPD (run 3 and 6). Nozoe[12] has recently reported that hydroxylation of the enolate from the *N*-Boc-pyroglutamic acid derivatives proceeds under chelation control between the lithium enolate and the Boc function to stereoselectively produce the trans-hydroxylated product. In order to examine the possibility of the similar chelation effect between the lithium enolate and MoOPD (Fig. **B**), we carried out the experiment in the presence of HMPA under typical conditions. No effect was observed in the facial selectivity (run 4).

In the case of the previous studies for the electrophilic addition reaction to the lithium enolate of **1a**, it has been reported that the electrophiles except small ones like iodomethane and a proton[3c] have generally approached from the less hindered convex face to mainly afford the exo products in moderate to high stereoselection.[1,3a,3b] The theoretical studies of the electrophilic addition to the bicyclic lactam enolate for obtaining the rational explanation have been reported by several groups.[5,13] Among them, Meyers and coworkers have recently demonstrated based on the ab initio molecular orbital calculation studies that the facial selectivity on the electrophilic addition reaction to the lithium enolate of **1b** depends on the stereoelectronic factor, the HOMO of the enolate from the bicyclic lactam **1b**, and the steric hindrance, the interaction with the hydrogen at the 4-position on the concave face.[5] In the case of the MoOPD, one possible explanation for the observed high endo selectivity is that MoOPD might serve as a small electrophile because the reaction takes place at the surface of the oxidant molecule (Fig. **C**[14]) and not at the center of the one, therefore, the reaction might proceed under the stereoelectronic effect of the bicyclic lactam enolate.

In summary, we demonstrated the highly endo selective hydroxylation of the bicyclic lactams **1a-d** using MoOPD and MoOPH for the first time. Although the reason for the high diastereoselectivity of the hydroxylation reaction remains to be clarified, this procedure provides new access to the stereoselective construction of the hydroxylated quaternary carbon center and the functionalized pyrrolidines. Further investigations directed towards the total synthesis of dysiherbaine and application of this hydroxylation to the synthesis of biologically active natural products are in progress in our laboratories.

Table. Hydroxylation of the bicyclic lactam enolates using MoOPD and MoOPH

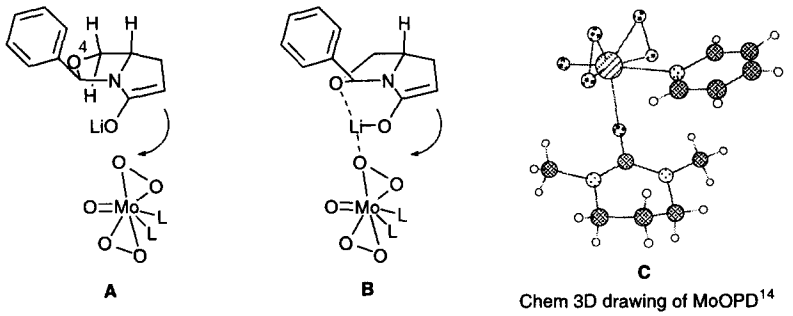


1a: R^1 = Ph, R^2 = H
b: R^1 = *i*-Pr, R^2 = H
c : R^1 = Ph, R^2 = allyl
d : R^1 = Ph, R^2 = cyclohexylmethyl

4 (endo) **5** (exo)

entry	compounds	base	oxidizing reagents	yield[a]	endo:exo **4:5**
1	**1a**	KHMDS (1.5 eq)	Davis (1.5 eq)[b]	-[c]	-
2	**1a**	LDA (1.5 eq)	MoOPD (1.5 eq)	78 % (92 %)	90:10
3	**1a**	LDA (1.5 eq)	MoOPH (1.5 eq)	66 % (79 %)	92:8
4[d]	**1a**	LDA (1.4 eq)	MoOPD (1.5 eq)	14 % (45%)[e]	96:4
5	**1b**	LDA (2 eq)	MoOPD (1.5 eq)	41 % (63 %)	86:14
6	**1b**	LDA (1.5 eq)	MoOPH(1.5 eq)	45 % (57 %)	92:8
7	**1c**	LDA (2 eq)	MoOPD (2 eq)	61 % (74 %)	100:0
8	**1c**	KHMDS (1.4 eq)	MoOPD (2 eq)	31 % (48 %)	100:0
9	**1c**	LHMDS (1.4 eq)	MoOPD (2 eq)	18 % (27 %)	100:0
10	**1d**	LDA (1.4 eq)	MoOPD (2 eq)	43 % (93 %)	92:8

a) Values in parentheses are yields based on consumed starting material. b) Davis reagent instead of molybdenum reagent was used. c) The starting material was recovered in 83 % yield. d) The reaction was carried out in the presence of HMPA. e) The starting material was recovered in 69 % yield.



Figure

Acknowledgment

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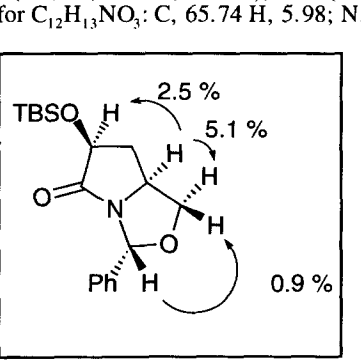
10. Typical procedure for the hydroxylation reaction: LDA was prepared by mixing diisopropylamine (0.98 ml, 7.03mmol) with *n*-BuLi (1.59 M in hexane, 4.4 ml, 7.03 mmol) in THF (10 ml) at 0 ℃ for 60 min. The bicyclic lactam **1a** (1.02g, 5.02 mmol) in THF (15 ml) was added to the precooled LDA solution at –78 ℃ and the mixture was stirred at –78 ℃ for 30 min. After addition of MoOPD (2.88 g, 7.53 mmol) at –78 ℃, the mixture was allowed to warm to –30 ℃ over 2 h and quenched with aqueous saturated Na_2SO_3 (20 ml). The entire mixture was extracted three times with ethyl acetate, washed with 5 % hydrochloric acid and brine, and dried over Na_2SO_4. Concentration in vacuo followed by column chromatography (silica gel, hexane-ethyl acetate = 3:1) gave the products **4a** and **5a** (863 mg, 78%) along with recovery of the starting material (153mg, 15%). After recrystallization from hexane/EtOAc, the major isomer **4a** was obtained as the sole product. Major product **4a**: mp 104 ℃; $[\alpha]_D^{24}$ +177.7 (c=1, $CHCl_3$); IRν_{max}^{KBr} 3350, 1690 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 (1H, br s), 1.86 (1H, ddd, 10.4 Hz, 8.1 Hz, 12.6 Hz), 2.86 (1H, ddd, 6.3 Hz, 8.2 Hz, 12.5 Hz), 3.63 (1H, dd, 7.6 Hz, 8.2 Hz), 4.03 (1H, m), 4.30 (1H, dd, 6.7 Hz, 8.4 Hz), 4.71 (1H, dd, 8.2 Hz, 10.3 Hz), 6.34 (1H, s), 7.34~7.45 (5H, m). Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74 H, 5.98; N, 6.39. Found: C, 65.47; H, 5.90; N, 6.34.
11. The NOE enhancement was observed as shown below.



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14. The 3D structure of MoOPD based on X-ray analysis was provided by courtesy of Cambridge Crystallographic Data Center.