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Stereoselective Synthesis of an Optically Active Axially Chiral Lactam and Its Reaction with Some Electrophiles

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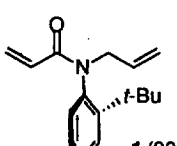
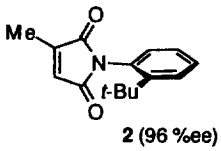
Abstract: An optically active form (≥ 98 %ee) of *N*-(*ortho-tert*-butylphenyl)-5-methoxymethyl-2-pyrrolidinone **3** having axial chirality was prepared from *ortho-tert*-butylaniline and (*S*)-5-(methoxymethyl)butylolactone in short steps and a completely stereoselective manner. The reactions of Li-enolate from lactam **3** with various electrophiles proceeded with 3,5-*cis*-selectivity.

Keywords: axial chirality, lactam, enolate, diastereoselective reaction

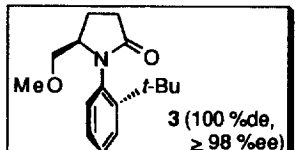
Highly stereoselective reactions (atroposelective reactions) with axially chiral amide compounds such as *ortho-tert*-butyl anilide derivatives and axially twisted imides such as *N-ortho-tert*-butylphenyl maleimides have been recently reported by Curran and several other groups.[1] However, anilides and imides used in these reactions are racemic forms and achiral compounds, respectively; thus, these compounds could not be applied to asymmetric reactions. We have succeeded in the first synthesis of non-biaryl axially chiral compounds with high optical purity and definite absolute configuration such as the following anilide **1** and imide **2**.[2,3] In addition, it was also found that iodine- and Lewis acid-mediated Diels-Alder reactions using **1** and **2** proceeded with high diastereoselectivity.[2] In the course of our work in relation to optically active non-biaryl axially chiral compounds, we attempted to prepare an optically active form of an axially chiral lactam. In this paper, we report the result of stereoselective synthesis of optically active *N*-(*ortho-tert*-butylphenyl)-5-methoxymethyl-2-pyrrolidinone **3** having axial chirality. Furthermore, the interesting character of lactam **3** and the result of stereoselective α-functionalization of the Li-enolate from **3** are also described.



1 (96 %ee)



2 (96 %ee)



3 (100 %de, ≥ 98 %ee)

In contrast to anilide **1** which can be stored without racemization more than one month at rt, in the case of 5-membered lactam, a free rotation of the N-Ar bond was assumed to easily occur at rt. That is, a diastereomeric mixture, on the basis of the α-chiral center and axial chirality, of racemic *N*-(*ortho-tert*-butylphenyl)-3-benzyl-2-pyrrolidinone **4** and **4'** could not be separated in diastereomerically pure form because of the relatively rapid epimerization, possibly due to the rotation of the N-Ar bond from the methylene side at the 5-position (Scheme 1). Accordingly, to prevent the free rotation, the preparation of axially chiral 5-membered lactam having a substituent at the 5-position was investigated (Scheme 2).

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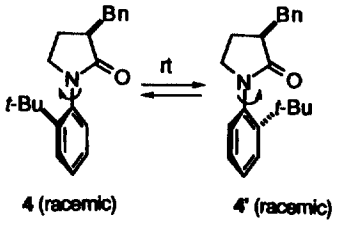
The aminocyclization reaction of mesylate **5**, which was prepared in two steps and in good yield from *ortho-tert*-butylaniline and (*S*)-5-(methoxymethyl)butylolactone, smoothly proceeded in the presence of *tert*-BuOK (2 eq) to give 5-methoxymethyl-2-pyrrolidinone **3** in good yield (87 %). When the cyclization reaction was performed by treating **5** with NaH, LDA or *n*-BuLi, formation of an *O*-cyclized product was also observed. In lactam **3** obtained in this reaction, the existence of a diastereomer on the basis of a chiral carbon and an axial chirality such as **3'** could not be detected.[4] In addition, optical purity of **3** was estimated to be ≥ 98 %ee by HPLC analysis using chiral column.[5] Thus, the aminocyclization, giving rise to **3**, should proceed with an almost complete chirality transfer both to a chiral carbon at the 5-position in an inversion manner and to an axially chiral moiety from a chiral carbon of **5**.

3' corresponding to the diastereomer of lactam **3** was found to be brought through the formation of enolate **6** from **3**. When Li-enolate **6** prepared from **3** and LDA in THF was gradually warmed up from -78 °C to rt and then protonated by HCl, a mixture of lactam **3** and **3'** was obtained in a ratio of 2.7 : 1.[6] **3'** could not be separated in diastereomerically pure form because of the relatively rapid isomerization to **3** at rt. The mixture of **3** and **3'** in a ratio of 1 : 2.6 obtained by MPLC separation was completely converted to **3** after 4 days at rt (tentative $t_{1/2}$ = 14 h at ca 25 °C). This result may suggest that **3'** having a *cis*-relationship between the *ortho-tert*-Bu and methoxymethyl groups easily isomerizes to more stable **3** having a *trans*-relationship. Indeed, the X-ray crystal structure of **3** indicates that the *ortho-tert*-Bu and methoxymethyl groups are in *trans*-relationship and the plane of the aryl group is almost perpendicular to the plane of the 5-membered ring (Fig. 1).

Scheme 1



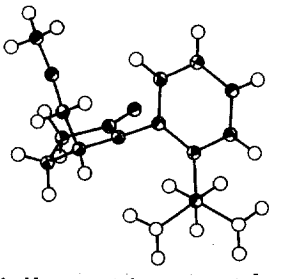
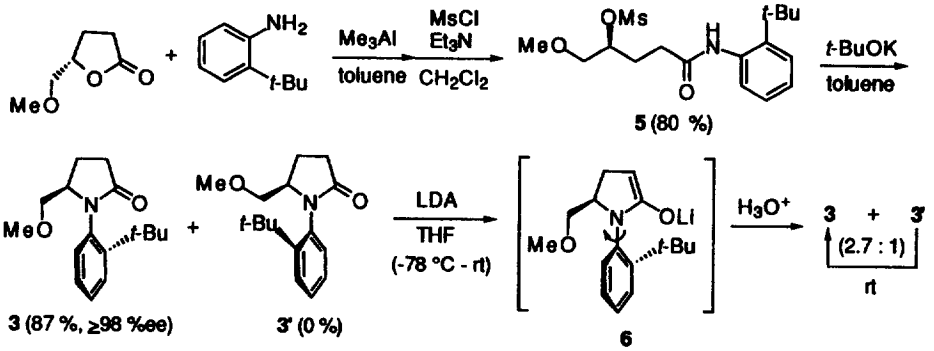


Fig. 1 X-ray crystal structure of **3**

Scheme 2

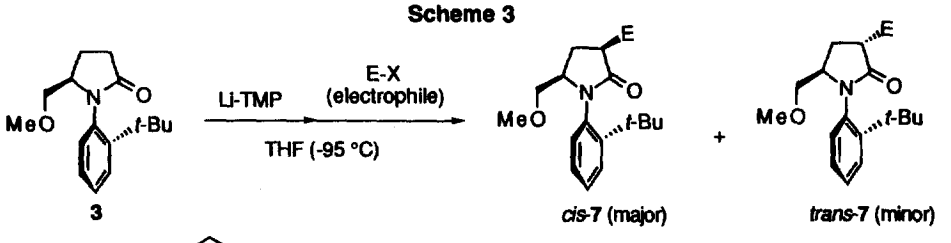


The isomerization of **3** was observed even on treating with LDA for 20 min at -78 °C. In this case, **3** and **3'** were obtained in a ratio of 40 : 1 after protonation by HCl, while isomerization via enolate formation was not observed within 20 min at -95 °C. On the basis of this result, we examined the stereoselectivity in the reaction of enolate **6** with electrophiles. The reactions of various electrophiles with the enolates from 5-substituted-2-pyrrolidinone which can be easily prepared from (*S*)-pyroglutamic acid, have been investigated by many groups.[7] Most of these reactions gave 3,5-*trans*-2-pyrrolidinone with moderate to high diastereoselectivity, because the attack of lactam enolates to electrophiles preferentially occurs from the

opposite side of the substituent at the 5-position. On the other hand, it was expected that a 3,5-*cis*-selective reaction which has been so far uncommon, may be achieved through the reaction with enolate **6**, because electrophiles may attack from the opposite side of the *ortho-tert*-Bu group close to the reaction site.

Indeed, the reaction of enolate **6** with various electrophiles proceeded in good yields to give products **7** with moderate to high 3,5-*cis*-selectivity (Scheme 3).[8] In particular, the hydroxylation reaction with Davis-reagent gave product **7c** in a ratio of *cis* : *trans* = 15 : 1 (Scheme 3). Since the reaction of *N*-phenyl-5-methoxymethyl-2-pyrrolidinone **8** with Davis-reagent under the same conditions gave product **9** in a ratio of *cis* : *trans* = 1 : 1.7, the contribution of axial chirality in these *cis*-selective reactions should be obvious (Scheme 4). All reactions shown in Scheme 3 were performed within 20 min at -95 °C to prevent rotation around the N-Ar bond.[9,10] Lithium tetramethylpiperidide (Li-TMP) was the most effective as a base, and the use of other bases such as LDA, *n*-BuLi or $(Me_3Si)_2NNa$ resulted in a considerable decrease in the yields of products **7**. In the benzylation reaction of the enolate from benzyl ether **10**, the decrease in 3,5-*cis*-selectivity (*cis*-**11** : *trans*-**11** = 3 : 1) was observed (Scheme 5); thus, the use of a substrate with a sterically less hindered ether part such as methyl ether should be required to achieve high *cis*-selectivity.

Scheme 3

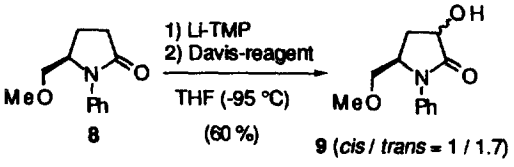


Li-TMP =

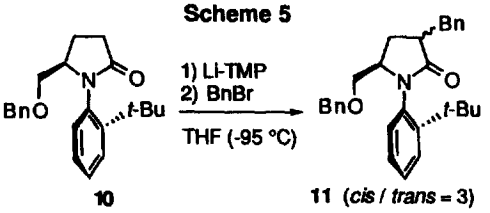
Davis-reagent =

E-X	7	E	Yield (%)	Ratio (*cis*/*trans*)
CH_2=CH-CH_2Br	**7a**	CH_2=CH-CH_2-	95	4
$PhCH_2$Br	**7b**	$PhCH_2$-	98	10
Davis-reagent	**7c**	HO-	65	15

Scheme 4

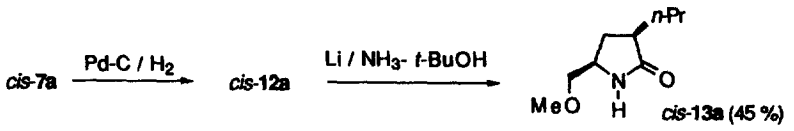


Scheme 5



For the removal of the *tert*-butylphenyl group from products **7**, although several methods such as RuO_4-oxidation, ozonolysis and Birch reduction were attempted, none has yet been completely successful. The best result at present is Birch reduction of *N*-(*ortho-tert*-butylphenyl)-3-*n*-propyl-5-methoxymethyl-2-pyrrolidinone *cis*-**12a** derived from *cis*-**7a**. In this case, N-H lactam *cis*-**13a** was obtained in a moderate yield (45 %, Scheme 6).[11] The formation of *trans*-**13a** was not observed under this basic reductive condition; that is, the reaction proceeded without isomerization at the α-chiral carbon.

Scheme 6



In conclusion, we have suceeded in the stereoselective synthesis of the optically active form (≥ 98 %ee) of *N*-(*ortho-tert*-butylphenyl)-5-methoxymethyl-2-pyrrolidinone **3** having axial chirality.[12] Futhermore, it was also found that the reactions of Li-enolate from lactam **3** with various electrophiles proceeded with moderate to high 3,5-*cis*-selectivity.

References and Notes

1. (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131-3132. (b) Kishikawa, K.; Tsuru, I.; Kohomoto, S.; Yamamoto, M.; Yamada, K. *Chem Lett.* **1994**, 1605-1606. (c) Hughes, A. D.; Price, D. A.; Shishkin, O.; Shimpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607-7610. (d) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955-3975.
2. (a) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447-4450. (b) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634-2640.
3. Quite recently, Shimpkins *et al.* also reported the synthesis of optically active *N*-(*ortho-tert*-butylphenyl)propanamide (93 %ee) in accordance with our optical resolution method (ref. 2). Hughes, A. D.; Shimpkins, N. S. *Synlett.* **1998**, 967-968.
4. Lactam **3**: white solid; mp 93-94.5 °C; $[\alpha]_D$ = +9.0 ($CHCl_3$, c = 1.0); ^{1}H-NMR ($CDCl_3$) δ: 7.53 (1H, dd, *J* = 2.0, 7.6 Hz), 7.20-7.32 (2H, m), 7.01 (1H, dd, *J* = 2.0, 7.6 Hz), 3.89 (1H, m), 3.44 (1H, dd, *J* = 3.5, 9.9 Hz), 3.35 (3H, s), 3.31 (1H, dd, *J* = 2.3, 9.9 Hz), 2.68 (1H, m), 2.25-2.45 (2H, m), 2.16 (1H, m), 1.38 (9H, s); ^{13}C-NMR ($CDCl_3$) δ: 176.5, 148.1, 134.8, 132.0, 128.3, 128.1, 126.6, 72.2, 61.7, 58.6, 35.4, 31.5, 30.2, 22.4.
5. The ee of **3** was determined by HPLC analysis using a CHIRALPAK AD column [25 cm x 0.46 cm i. d.; 10 % *i*-PrOH in hexane; flow rate, 1.0 ml/min; (+)-**3**; t_R = 13.0 min, (-)-**3**; t_R = 15.0 min].
6. From the molecular model study, it was assumed that the free rotation of the N-Ar bond in enolate **6** may occur more easily in comparison with lactam **3** having an sp^2 nitrogen atom bacause of the sp^3 character of the nitrogen atom in **6**.
7. (a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140-3143. (b) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329-323. (c) Baldwin, J. E.; Miranda, T.; Moloney, M. G.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459-7468. (d) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379-1380. (e) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749-5752. (f) Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1995**, *43*, 1081-1088.
8. The stereochemistries of products **7** were determined on the basis of NOE experiments.
9. Typical procedure in the reaction of enolate **6** with electrophiles: To lactam **3** (130.5 mg, 0.5 mmol) in THF (5 ml) was added 0.3 M THF solution of lithium 2,2,6,6-tetramethylpiperidide (1.8 ml, 0.54 mmol) under argon atmosphere at -95 °C (hexane - liq.N_2). After the mixture was stirred for 5 min, benzyl bromide (0.06 ml, 0.5 mmol) was added, and then the reaction mixture was stirred for 5 min at -95 °C. The mixture was poured into 10 % HCl and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane / AcOEt = 3) and subsequent MPLC (hexane / AcOEt = 3) gave *cis*-**7a** (156 mg, 89 %, less polar) and *trans*-**7a** (15 mg, 9 %, more polar).
10. The reaction of enolate **6** with a relatively unreactive electrophile such as EtI did not proceed at -95 °C, resulting in the recovery of lactam **3**.
11. The Birch reduction of 3-allyl-2-pyrrolidinone derivative *cis*-**7a** gave a complex mixture due to the reduction of the olefinic moeity of allyl group.
12. We also examined the preparation of racemic *N*-(*ortho-tert*-butylphenyl)-6-hydroxymethyl-2-piperidinone. Quite contrary to 5-membered lactam **3**, in the case of 6-membered lactam, piperidinone having *cis*-relationship between the substituent at the 6-position and the *ortho-tert*-Bu group was obtained as a single stereoisomer.