Synthesis of Optically Active 5-Substituted-2-pyrrolidinone Derivatives Having Atropisomeric Structure and 3,5-*Cis*-Selective Reaction of Their Enolates with Electrophiles

Masao Fujita, Osamu Kitagawa, Yoichiro Yamada, Hirotaka Izawa, Hiroshi Hasegawa, and Takeo Taguchi*

Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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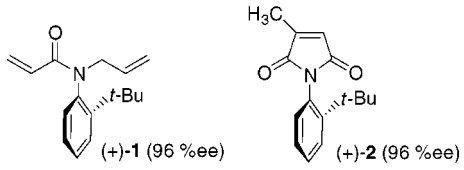
Optically pure forms (≥98% ee) of *N*-(*o*-*tert*-butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone having atropisomerism and *N*-(*o*-*tert*-butyldiphenylsiloxyphenyl)-5-(methoxymethyl)-2-pyrrolidinone having an atropisomerism-like structure were prepared from *ortho*-substituted aniline derivatives and (*S*)-5-(methoxymethyl)butyrolactone in a stereoselective manner. The reactions of Li-enolates from these lactams with various electrophiles and subsequent dearylation of the products gave 3,5-*cis*-disubstituted-2-pyrrolidinone derivatives.

Introduction

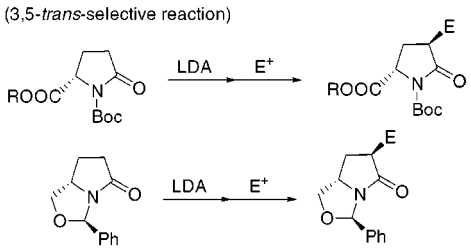
N-Substituted anilide derivatives bearing a large substituent such as a *tert*-Bu group at the *ortho*-position are known to resist racemization and have atropisomerism due to the high rotation barrier of the N−Ar bond.[1,2a] Although the application of such atropisomeric anilide derivatives to stereoselective reaction has been reported initially by Curran, followed by several other groups, these compounds could not be applied to asymmetric reaction because of the use of the racemic or achiral forms.[2] As an evolution of atropisomeric anilide chemistry, we have recently succeeded in the first synthesis of the amide (+)-**1** and the imide (+)-**2** with high optical purity and definite absolute configuration, and the development of an asymmetric Diels−Alder reaction using (+)-**1** and (+)-**2** (Scheme 1).[3,4] In relation to this work, we have investigated further utilization of such optically active atropisomeric amides.

The reactions of chiral 2-pyrrolidinone enolates with various electrophiles, in particular, the diastereoselective reactions with optically active 5-substituted-2-pyrrolidinone enolates which can be easily derived from pyroglutamic acid, have been widely used as a key step for the asymmetric synthesis of alkaloids and biologically active compounds.[5] In these reactions, *trans*-3,5-disubstituted-2-pyrolidinone derivatives are generally obtained as a major product, because the attack of an electrophile to lactam enolate preferentially occurs from the opposite site of a substituent at the C-5 position (Scheme 2).[6] On the other hand, 3,5-*cis*-selective reactions with 5-substituted-2-pyrrolidinone enolates have not been reported so far, aside from a few exceptional cases.[7]

Scheme 1



Scheme 2



* To whom correspondence should be addressed. Fax and tel: 81-426-76-3257. e-mail: kitagawa@ps.toyaku.ac.jp or taguchi@ps.toyaku.ac.jp.

(1) (a) Kashima, C.; Katoh, A.; *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599. (b) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076.

(2) (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.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *Chem Lett.* **1994**, 1605. (c) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607. (d) Clayden, J.; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.

(3) (a) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447. (b) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634.

(4) Recently, Simpkins et al. also reported the synthesis of optically active *N*-(*o*-*tert*-butylphenyl)propanamide (93% ee) in accordance with our optical resolution method (ref 2). (a) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967. (b) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295. On the other hand, the synthesis of optically pure forms of atropisomeric amides and imides through the optical resolution using chiral chromatography has been reported by two groups, while the absolute configuration of these atropisomeric compounds has not yet been determined. (c) 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. (d) Kondo, K.; Fujita, H.; Suzuki, T.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 5577.

(5) (a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. (b) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329. (c) Baldwin, J. E.; Miranda, T.; Moloney, M. G.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459. (d) Hon, Y.; Chang, Y.; Gong, M. *Heterocycles* **1990**, *31*, 191. (e) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379. (f) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749. (g) Langlois, N.; Rojas, A.; *Tetrahedron Lett.* **1993**, *34*, 2477. (h) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665. (i) Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1995**, *43*, 1081. (j) Charrier, J. D.; Duffy, J. E. S.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1998**, *39*, 2199. (k) Zhang, R.; Brownewell, F.; Madalengoitia, J. S. *Tetrahedron Lett.* **1999**, *40*, 2707. For review: (l) Nàjera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245. See also ref 6b.

(6) Papers in relation to the origin of 3,5-*trans*-selectivity: (a) Seebach, D.; Maetzke, T.; Petter, W.; Klotzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781. (b) Meyers, A. I.; Seefeld, M. A.; Bruce, A. L.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565. (c) Ando, K.; Green, N. S.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 5334.

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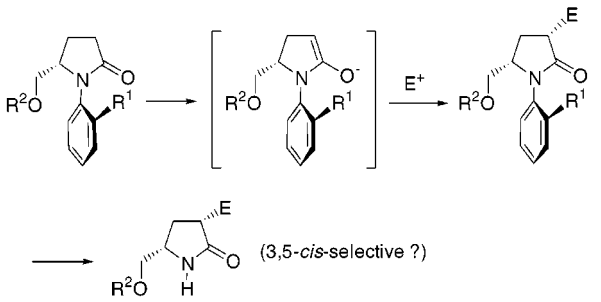
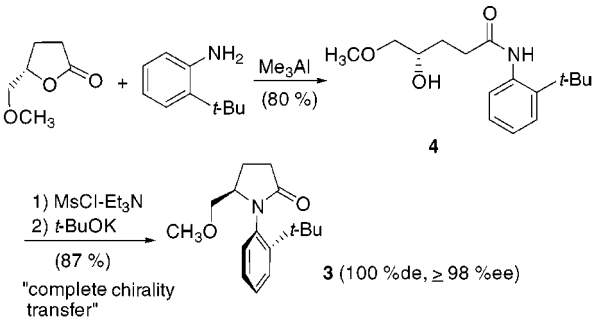
Scheme 3



Scheme 4

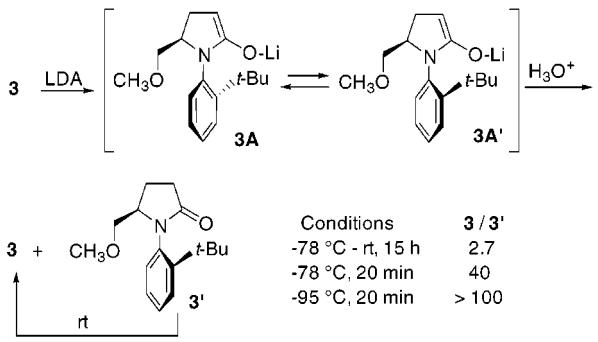


We expected that in the reaction of the enolate from the atropisomeric lactam having a *trans*-relationship between an *ortho*-substituent (R^1) and an alkoxymethyl group at the C-5 position, an electrophile may preferentially attack from the opposite site of the *ortho*-substituent close to the reaction center; thereby, *cis*-3,5-disubstituted-2-pyrrolidinone may be obtained as a major product after removal of the Ar group (Scheme 3). In this paper, we report stereoselective synthesis of 5-substituted-2-pyrrolidinone derivatives having atropisomerism or an atropisomerism-like structure, and 3,5-*cis*-selective reactions of Li-enolates from these lactams with various electrophiles.[8] Furthermore, interesting features of these atropisomeric lactams are also described.

Results and Discussion

Stereoselective Synthesis of *N*-(*o*-*tert*-butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone Having Atropisomerism and Its Reaction with Some Electrophiles. As an optically active 5-substituted-2-pyrroridinone derivative having atropisomerism, *N*-(*o*-*tert*-butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone **3** which can be easily derived from commercially available (*S*)-5-(hydroxymethyl)butyrolactone and *o*-*tert*-butylaniline, was chosen. The synthesis of lactam **3** is shown in Scheme 4; mesylation and subsquent aminocyclization reaction of γ-hydroxyamide **4** which was prepared in a good yield from (*S*)-5-(methoxymethyl)butyrolactone and *o*-*tert*-butylaniline, gave the desired lactam **3** in 87% yield. The lactam **3** obtained through the aminocyclization was a single isomer and the existence of a diastereomer on the basis of a chiral carbon and atropisomerism could not be detected by the NMR spectrum. Furthermore, since optical purity of **3** was estimated to be ≥98% ee by HPLC analysis using a chiral column, the aminocyclization, giving rise to **3**, should proceed with an almost complete chirality transfer both to the chiral carbon at the 5-position in an inversion manner and to an axially chiral moiety from the chiral carbon of **4**.

Scheme 5



The diastereomeric lactam **3′** was found to be formed through the protonation of the enolate prepared from lactam **3**. That is, when the Li-enolate **3A** prepared by treating **3** with LDA in THF was gradually warmed from −78 °C to room temperature and then protonated by HCl, a mixture of lactam **3** and **3′** was obtained in a ratio of 2.7:1 (Scheme 5). The isomerization due to the free rotation around the N−Ar bond was not observed on treating with LDA for 20 min at −95 °C, while the treatment for 20 min at −78 °C resulted in a mixture of **3** and **3′** in a ratio of 40:1 (Scheme 5). The isomerization to **3′** from **3** through the enolate formation may be due to the sp^3 character of the nitrogen atom in the enolate. The free rotation around the N−Ar bond in the enolate **3A** was assumed to easily occur even at low temperature because of the sp^3 character of the nitrogen atom.[9] In addition, a molecular model study of the enolate indicates that steric repulsion between the *tert*-butyl and methoxymethy groups in enolate **3A′** considerably diminishes in comparison with that in lactam **3′** having an sp^2 nitrogen atom. Thus, the decrease in the gap of the thermodynamic stability between enolates **3A** and **3A′** may result in the partial isomerization to **3A′** from **3A**.

Lactam **3′** could not be separated in diastereomerically pure form because of the relatively rapid isomerization

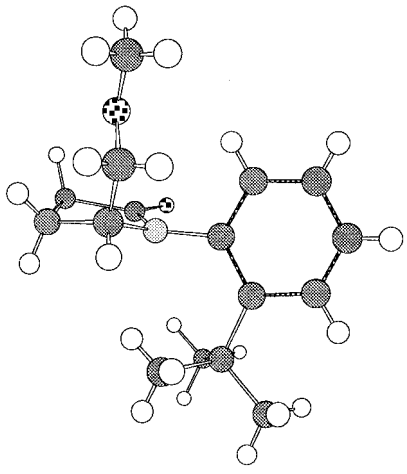
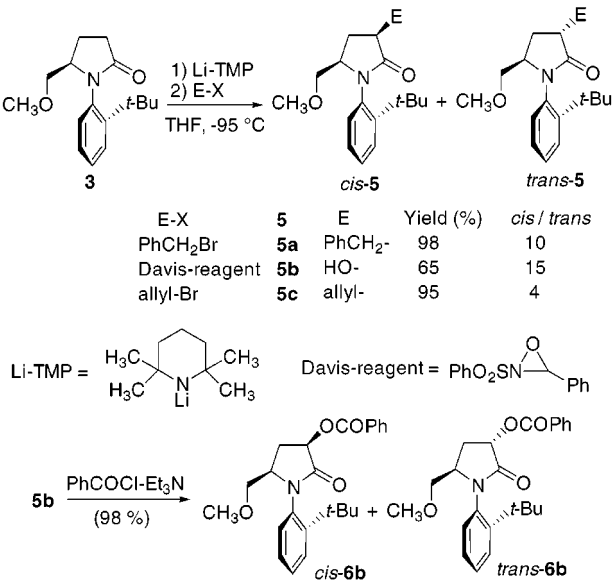


Figure 1. Chem 3D drawing of **3** obtained by X-ray analysis.

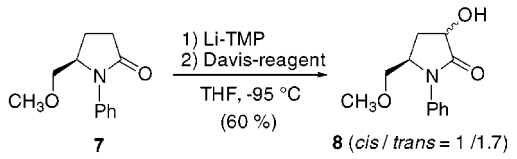
(7) Moderate 3.5-*cis*-selectivity (*cis*/*trans* = 5) has been observed in the reaction of bicyclic lactam enolate with a small electrophile such as MeI, while under the same conditions, the reaction with other electrophiles such as allyl bromide and benzyl bromide proceeded in a nonselective manner or with low 3,5-*trans*-selectivity. See refs 5f, 5j, and 5k.

(8) Preliminary communication of this work: Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 1949.

Scheme 6



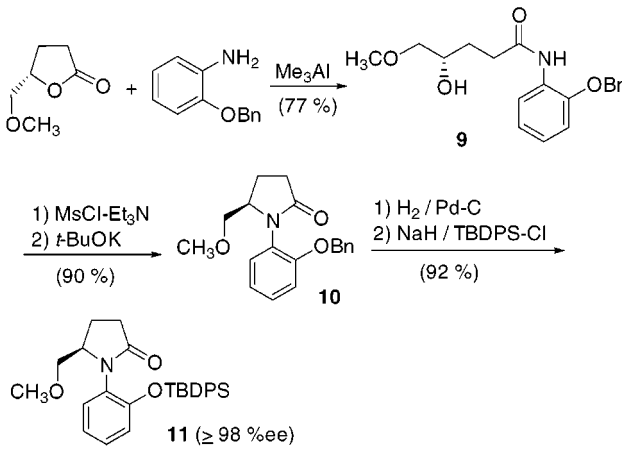
Scheme 7



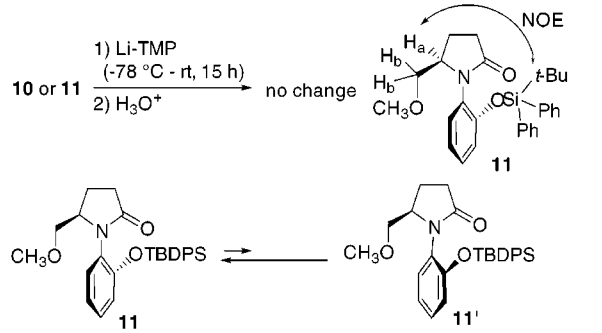
to **3** at room temperature. The mixture of **3** and **3′** in a ratio of 1:2.7 obtained by MPLC separation was completely converted to **3** after 4 days at room temperature (tentatively $t_{1/2}$ = 14 h at ca. 25 °C). This result should suggest that **3′** having a *cis*-relationship between the *o*-*tert*-butyl and methoxymethyl groups easily isomerizes to the more stable **3** having a *trans*-relationship. Indeed, the X-ray crystal structure of **3** indicates that the *o*-*tert*-butyl and methoxymethyl groups are in a *trans*-relationship with a large torsion angle (76.4°) between the amide and *tert*-butylphenyl groups (Figure 1).

The reactions of enolate **3A** from lactam **3** with some electrophiles were investigated (Scheme 6). All the reactions were performed within 20 min at −95 °C to prevent the rotation around the N−Ar bond. 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 chemical yields of products **5**. As expected, the reactions with benzyl bromide and Davis-reagent proceeded with high 3,5-*cis*-selectivity to give 3,5-disubstituted lactams **5a** (*cis*/*trans* = 10) and **5b** (*cis*/*trans* = 15), respectively.[10−12] Although a decrease in the selectivity was observed, the reaction with allyl bromide also gave 3,5-*cis*-lactam **5c** (*cis*/*trans* = 4) as a major product.[10,12] The contribution of an atropisomerism in these *cis*-selective reactions should be obvious, because the reaction of *N*-phenyl-5-(methoxymethyl)-2-pyrrolidinone **7** with Davis-reagent under the same conditions proceeded with low 3,5-*trans*-selectivity (*cis*/*trans* = 1/1.7, Scheme 7).[10]

Scheme 8



Scheme 9



For the removal of the *tert*-butylphenyl part from product **5a**, although several methods such as RuO_4-oxidation, ozonolysis, and Birch reduction were attempted, none has been successful. Accordingly, we further investigated the synthesis of an atropisomeric lactam having a removable aryl group and its 3,5-*cis*-selective reaction.

Stereoselective Synthesis of *N*-(*o*-*tert*-Butyldiphenylsiloxyphenyl)-5-(methoxymethyl)-2-pyrrolidinone Having an Atropisomerism-Like Structure and Its Reaction with Some Electrophiles. As an atropisomeric lactam possessing an aryl group may be easily removed by CAN-oxidation,[13] we devised *N*-(*o*-*tert*-butyldiphenylsiloxyphenyl)-5-(methoxymethyl)-2-pyrrolidinone **11**. Lactam **11** was prepared in a good yield in accordance with Scheme 8. Mesylation of γ-hydroxyamide **9** prepared from (*S*)-5-(methoxymethyl)butyrolactone and *o*-benzyloxyaniline, and subsequent aminocyclization of the mesylate gave lactam **10** in a good yield. **10** was converted to lactam **11** by hydrogenation followed by *tert*-butyldiphenylsilylation. The ee of lactam **11** was found to be ≥98% ee by HPLC analysis using a chiral column.

To confirm the existence of atropisomerism in the lactams **10** and **11**, similar to the case of *N*-(*o*-*tert*-butylphenyl)-lactam **3** (Scheme 5), the isomerization through the enolate formation was examined, but the generation of atropisomers of **10** and **11** could not be detected (Scheme 9). The X-ray crystral structure of the lactam **11** indicates *cis*-relationship between the meth-

(9) It has been reported that nitrogen of amide Li-enolates is completely tetrahedralized. (a) Laube, T.; Dunitz, J. D. Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764.

(10) The stereochemistries of the products were determined on the basis of NOE experiments.

(11) The stereochemistries of *cis*- and *trans*-**5b** were determined after conversion to benzoate **6b,** because *cis*- and *trans*-**6b** can be easily separated in comparison with *cis*- and *trans*-**5b** (Scheme 6).

(12) The diastereomer ratio was determined by 300 MHz ^{1}H NMR.

(13) Yamazaki, N.; Ito, T.; Kibayashi, C. *Synlett* **1999**, 37.

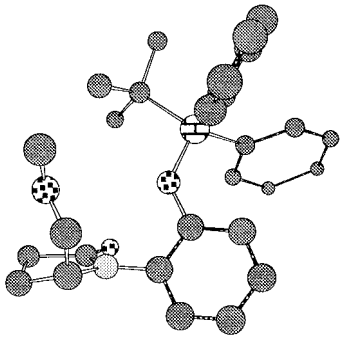
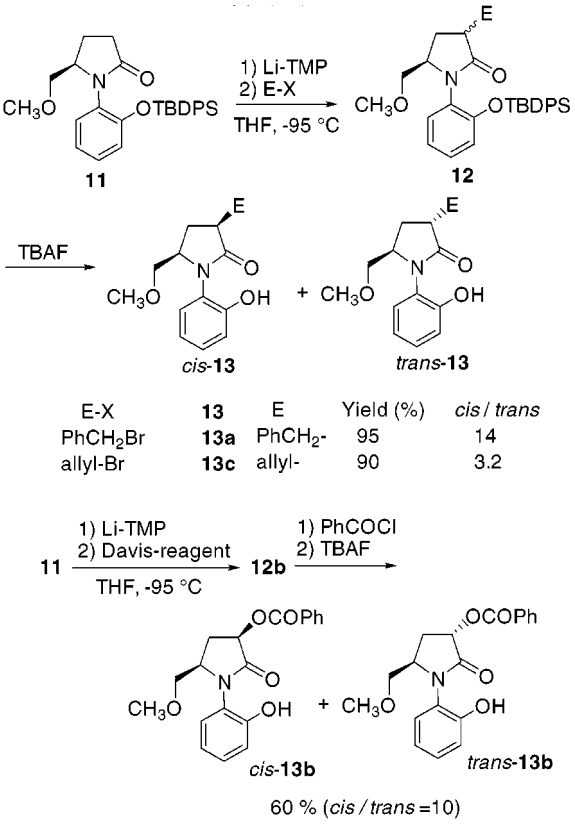


Figure 2. Chem 3D drawing of **11** obtained by X-ray analysis. Hydrogen atoms have been omitted for clarity.

Scheme 10

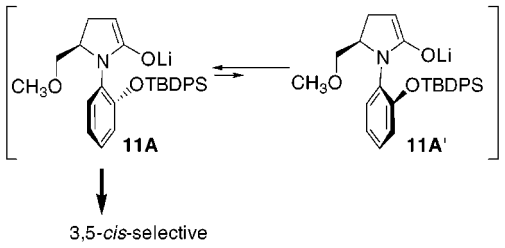


E-X		E	Yield (%)	*cis* / *trans*
$PhCH_2Br$	**13a**	$PhCH_2$-	95	14
allyl-Br	**13c**	allyl-	90	3.2

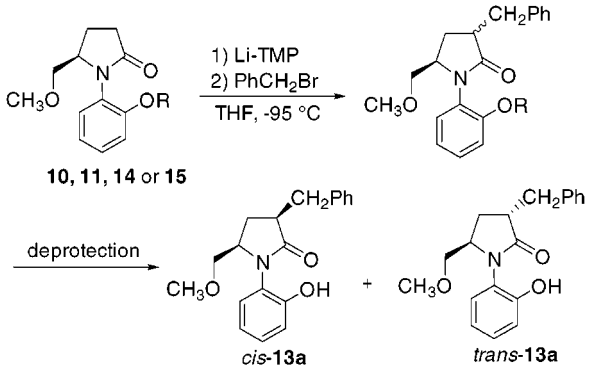
oxymethyl and *tert*-butyldiphenylsiloxy (TBDPSO) groups (Figure 2). In contrast, a conformer having a *trans*-relationship between the methoxymethyl and TBDPSO groups was found to preferentially occur in solution by NOE experiment (Scheme 9). That is, in $CDCl_3$, a strong NOE was observed between Ha at the 5-position and the *tert*-butyl hydrogen of the TBDPS group, while no NOE was observed between Hb of the methoxymethyl group and the *tert*-butyl hydrogen (Scheme 9). These results strongly suggest that the free rotation around N−Ar bond of lactam **11** easily occurs at room temperature. On the other hand, if the preference of the *trans*-confomer which was observed in solution of lactam **11** is also applicable to the case of Li-enolate **11A**, 3,5-*cis*-selective reaction with electrophiles may be possible.

Indeed, the reaction of Li-enolate **11A** prepared from Li-TMP and **11** with some electrophiles proceeded with moderate to high *cis*-selectivity to give 3,5-disubstituted lactam **12** in good yields (Scheme 10). In the reaction with benzyl bromide, in comparison with the case of enolate

Scheme 11

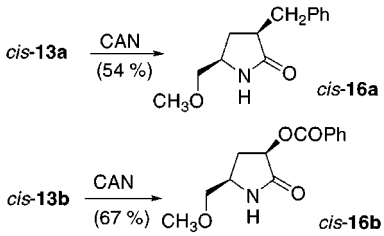


Scheme 12



R		Yield (%)	*cis* / *trans*
TBDPS	**11**	95	14
$PhCH_2$	**10**	81	1 / 1.5
Ph_3Si	**14**	95	2.7
Ph_3C	**15**	57	5

Scheme 13



3A, increase in the *cis*-selectivity was observed (*cis*/*trans* = 14), while in the reaction with Davis-reagent and allyl bromide, a slight decrease in the *cis*-selectivity was resulted (*cis*/*trans* = 10 and 3.2, respectively).[10] The diastereomer ratios in the reactions were determined after conversion to phenol derivatives **13**.[12,14] The result shown in Scheme 10 may indicate that a major conformer of Li-enolate from **11** is **11A** having a *trans*-relationship between the methoxymethyl and TBDPSO groups (and not **11A′**), and the electrophiles preferentially attack from the opposite side of the TBDPSO group in **11A** (Scheme 11). These results obtained here indicated that for the achievement of 3,5-*cis*-selectivity, the existence of stable atropisomerism such as lactam **3** is not always required.

The effect of the TBDPSO group as an *ortho*-substituent should be noteworthy, because the benzylation of the enolates from the lactams **10** and **14** possessing benzyloxy and triphenylsiloxy groups proceeded with low 3,5-*trans*- and 3,5-*cis*-selectivies (*cis*/*trans* = 1/1.5 and 2.7), respectively (Scheme 12). In the reaction of *o*-trityloxy derivative **15**, although moderate 3,5-*cis*-selectivity was observed (*cis*/*trans* = 5), a considerable decrease in the chemical yield was resulted (57%).

(14) Separation of the *cis*- and *trans*-**13** was easily carried out in comparison with that of *cis*- and *trans*-**12**.

The removal of the Ar group from the products *cis*-**13a** and *cis*-**13b** was effectively achieved by CAN oxidation (Scheme 13).[15] These dearylations proceeded without any epimerization to give NH lactams *cis*-**16a** and *cis*-**16b**, respectively.

In conclusion, we have succeeded in the development of the stereoselective synthesis of *N*-(*o*-*tert*-butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone having atropisomerism and *N*-(*o*-*tert*-butyldiphenylsiloxyphenyl)-5-(methoxymethyl)-2-pyrrolidinone having an atropisomerism-like structure, and the 3,5-*cis*-selective reaction of their Li-enolates with some electrophiles. The present reaction should be noted not only as a synthetic method for 3,5-*cis*-disubstituted-2-pyrrolidinone derivatives but also as a new concept for stereoselective reaction.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300-MHz spectrometer. In ^{1}H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. Column chromatography was performed on silica gel, Wakogel C-200 (75−150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

Starting Material. (*S*)-5-(Methoxymethyl)butyrolactone was prepared from commercially available (*S*)-5-(hydroxymethyl)butyrolactone in accordance with reported procedures.[16]

(4*S*)-*N*-(*o*-*tert*-Butylphenyl)-4-hydroxy-5-methoxypentanamide (4). To a solution of (*S*)-5-(methoxymethyl)butyrolactone (2.34 g, 18 mmol) in toluene (50 mL) was added 0.98 M hexane solution of Me_3Al (22 mL, 21.6 mmol) under an argon atmosphere at room temperature. After being stirred for 10 min at room temperature, *o*-*tert*-butylaniline (2.8 mL, 18 mmol) was added, and then the reaction mixture was refluxed for 1 h. The mixture was carefully treated with 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 = 1) gave **4** (4.02 g, 80%). **4:** white solid; mp 75−77 °C; $[\alpha]_D$ = −5.5 ($CHCl_3$, *c* = 1.0); IR (KBr) 3466, 3241, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.54 (1H, d, *J* = 7.8 Hz), 7.39 (1H, d, *J* = 7.8 Hz), 7.38 (1H, br s), 7.13−7.26 (2H, m), 3.91 (1H, m), 3.44 (1H, dd, *J* = 3.9, 9.6 Hz), 3.40 (3H, s), 3.32 (1H, dd, *J* = 7.0, 9.6 Hz), 2.94 (1H, d, *J* = 3.3 Hz), 2.61 (2H, t, *J* = 6.9 Hz), 1.99 (1H, m), 1.81 (1H, m) 1.41 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 172.0, 143.2, 134.9, 129.0, 126.5, 126.5, 126.4, 76.7, 69.5, 58.9, 34.5, 33.4, 30.6, 28.5. MS (*m*/*z*) 279 (M^+). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.89; H, 8.97; N, 5.11.

(5*R*)-1-(*o*-*tert*-Butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone (3). To a solution of amide **4** (2.79 g, 10 mmol) and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (50 mL) was added MsCl (0.9 mL, 12 mmol) under an argon atmosphere at 0 °C. After being stirred for 30 min at 0 °C, the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave the mesylate. To a solution of the mesylate in toluene (80 mL) was added *tert*-BuOK (2.24 g, 20 mmol) under an argon atmosphere at room temperature, and then the reaction mixture was stirred for 3 h at room temperature. The mixture was poured into saturated aqueous $KHSO_4$ solution and extracted with AcOEt. The AcOEt extracts were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 3) gave lactam **3** (2.28 g, 87%). The ee of **3** was determined by HPLC analysis using a CHIRALPAK AD column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 0.5 mL/min; (+)-**3**; t_R = 13.0 min, (−)-**3**; t_R = 15.0 min]. **3**: white solid; mp 93−94.5 °C; $[\alpha]_D$ = +9.0 ($CHCl_3$, *c* = 1.0); IR (KBr) 3448, 2961, 1685 cm^{-1}; ^{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. MS (*m*/*z*) 262 (M^+ + 1). Anal. Calcd for $C_{16}H_{22}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.84; N, 5.42.

(5*R*)-1-(*o*-*tert*-butylphenyl)-5-(methoxymethyl)-2-pyrrolidinone (3′). To a solution of lactam **3** (78 mg, 0.3 mmol) in THF (3 mL) was added 0.3 M THF solution of lithium diisopropylamide (1.1 mL, 0.33 mmol) under an argon atmosphere at −78 °C, and then the reaction mixture was stirred for 15 h at −78 °C to room temperature. 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 = 1) and subsequent MPLC (hexane/AcOEt = 2) gave a mixture (76 mg, 97%) of **3** and **3′** in a ratio of 1:2.6. **3′**: ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, dd, *J* = 1.8, 7.7 Hz), 7.17−7.30 (2H, m), 7.00 (1H, dd, *J* = 2.0, 7.7 Hz), 4.16 (1H, m), 3.38−3.48 (2H, m), 3.24 (3H, s), 2.30−2.58 (3H, m), 2.21 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 176.8, 148.1, 135.4, 129.9, 127.5, 127.4, 126.7, 73.0, 62.4, 58.6, 36.3, 32.0, 31.0, 23.2.

General Procedure for the Reaction of Enolate from 3 with Electrophiles. To a solution of 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, 0.55 mmol) under an 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*-**5a** (156 mg, 89%, less polar) and *trans*-**5a** (15 mg, 9%, more polar).

(3*R*,5*R*) and (3*S*,5*R*)-1-(*o*-*tert*-Butylphenyl)-5-(methoxymethyl)-3-phenylmethyl-2-pyrrolidinone (*cis*-5a and *trans*-5a). *cis*-**5a:** colorless oil; $[\alpha]_D$ = −9.0 ($CHCl_3$, *c* = 1.11); IR (KBr) 2958, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.54 (1H, dd, *J* = 1.7, 7.9 Hz), 7.20−7.38 (7H, m), 6.99 (1H, dd, *J* = 1.7, 7.9 Hz), 3.92 (1H, m), 3.33 (1H, d, *J* = 10.8 Hz), 3.27 (3H, s), 3.14 (1H, dd, *J* = 2.9, 9.8 Hz), 3.06 (1H, dd, *J* = 4.1, 9.8 Hz), 2.89 (1H, dd, *J* = 10.7, 10.8 Hz), 2.83 (1H, m), 2.29 (1H, ddd, *J* = 8.5, 9.7, 13.3 Hz), 1.91 (1H, ddd, *J* = 5.4, 6.7, 13.3 Hz), 1.36 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 176.8, 148.0, 140.0, 134.4, 132.4, 129.0, 128.8, 128.6, 128.2, 126.6, 126.0, 71.6, 59.6, 58.4, 42.8, 36.9, 35.6, 31.7, 27.1. MS (*m*/*z*) 351 (M^+); HRMS calcd for $C_{23}H_{29}NO_2$ 351.2198, found 351.2211. *trans*-**5a:** white solid; mp 108−109 °C; $[\alpha]_D$ = +41.0 ($CHCl_3$, *c* = 0.50); IR (KBr) 2953, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.52 (1H, dd, *J* = 1.9, 7.7 Hz) 7.20−7.34 (7H, m), 7.00 (1H, dd, *J* = 1.9, 7.7 Hz), 3.74 (1H, m), 3.41 (1H, dd, *J* = 3.5, 9.9 Hz), 3.38 (1H, dd, *J* = 3.0, 13.7 Hz), 3.31 (3H, s), 3.25 (1H, dd, *J* = 2.3, 9.9 Hz), 3.11 (1H, m), 2.62 (1H, dd, *J* = 10.4, 13.7 Hz), 2.01−2.22 (2H, m), 1.34 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 177.2, 148.1, 139.4, 135.2, 131.9, 128.9, 128.3, 128.1, 128.1, 126.6, 125.9, 72.0, 60.1, 58.5, 42.5, 37.3, 35.5, 31.6, 29.5. MS (*m*/*z*) 351 (M^+). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.56; H, 8.22; N, 4.04.

(3*R*,5*R*) and (3*S*,5*R*)-1-(*o*-*tert*-Butylphenyl)-3-(benzoyloxy)-5-(methoxymethyl)-2-pyrrolidinone (*cis*-6b and *trans*-6b). *cis*-**5b** and *trans*-**5b** were prepared through the reaction of Li-enolate from **3** (130.5 mg, 0.5 mmol) with Davis-reagent (144 mg, 0.55 mmol) in accordance with general

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procedure. Purification by column chromatography (hexane/AcOEt = 1) gave a mixture of *cis*-**5b** and *trans*-**5b** (90 mg, 65%) in a ratio of 15:1. To a solution of **5b** (90 mg, 0.32 mmol) and Et_3N (0.07 mL, 0.48 mmol) in CH_2Cl_2 (3 mL) was added benzoyl chloride (0.04 mL, 0.38 mmol) at room temperature, and then the reaction mixture was stirred for 1 h. 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*-**6b** (112 mg, 92%, less polar) and *trans*-**6b** (7 mg, 6%, more polar). *cis*-**6b**: white solid; mp 114−116 °C; $[\alpha]_D = -33.5$ ($CHCl_3$, $c = 1.02$); IR (KBr) 2960, 1730, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.12−8.20 (2H, m) 7.55−7.62 (2H, m), 7.43−7.49 (2H, m), 7.24−7.38 (2H, m), 7.19 (1H, dd, $J = 1.7$, 7.7 Hz), 5.57 (1H, dd, $J = 7.2$, 9.0 Hz), 4.07 (1H, m), 3.35 (1H, dd, $J = 3.9$, 10.1 Hz), 3.30 (1H, dd, $J = 3.2$, 10.1 Hz), 3.26 (3H, s), 2.89 (1H, ddd, $J = 7.5$, 9.1, 13.6 Hz), 2.31 (1H, ddd, $J = 6.1$, 7.2, 13.6 Hz), 1.38 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.0, 166.1, 148.0, 133.6, 133.2, 132.6, 130.0, 129.5, 128.9, 128.8, 128.3, 126.9, 71.0, 70.7, 58.7, 58.6, 35.8, 31.9, 29.5. MS (*m*/*z*) 381 (M^+). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.14; N, 3.67. Found: C, 72.48; H, 7.32; N, 3.73. *trans*-**6b**: white solid; mp 192−194 °C; $[\alpha]_D = -27.3$ ($CHCl_3$, $c = 0.33$); IR (KBr) 2971, 1718, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.08−8.12 (2H, m) 7.53−7.60 (2H, m), 7.40−7.47 (2H, m), 7.25−7.38 (2H, m), 7.02 (1H, dd, $J = 1.8$, 7.8 Hz), 5.81 (1H, t, $J = 8.4$ Hz), 3.94 (1H, m), 3.52 (1H, dd, $J = 2.4$, 10.1 Hz), 3.43 (3H, s), 3.31 (1H, dd, $J = 1.8$, 10.1 Hz), 2.85 (1H, ddd, $J = 1.1$, 8.4, 13.0 Hz), 2.34 (1H, ddd, $J = 8.6$, 8.8, 13.6 Hz), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.8, 166.1, 148.5, 134.6, 133.2, 131.6, 129.9, 129.7, 128.8, 128.7, 128.3, 127.1, 71.4, 71.2, 59.7, 58.9, 35.8, 31.9, 31.8. MS (*m*/*z*) 381 (M^+). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.14; N, 3.67. Found: C, 72.36; H, 7.12; N, 3.75.

(4*S*)-*N*-(*o*-(Benzyloxy)phenyl)-4-hydroxy-5-methoxypentanamide (9). Amide **9** was prepared from (*S*)-5-(methoxymethyl)butyrolactone (1.90 g, 14.6 mmol) and *o*-(benzyloxy)aniline (2.91 g, 14.6 mmol) in accordance with the procedure for the synthesis of hydroxyamide **4**. Purification by column chromatography (hexane/AcOEt = 2) gave **9** (3.70 g, 77%). **9**: white solid; mp 91−92 °C; $[\alpha]_D = +3.8$ ($CHCl_3$, $c = 1.19$); IR (KBr) 3449, 2941, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.37 (1H, dd, $J = 1.5$, 7.2 Hz), 8.03 (1H, br s), 7.45−7.35 (5H, m), 7.05−6.91 (3H, m), 5.11 (2H, s), 3.84 (1H, m), 3.38 (1H, dd, $J = 3.6$, 9.5 Hz), 3.37 (3H, s), 3.26 (1H, dd, $J = 7.4$, 9.5 Hz), 2.73 (1H, d, $J = 3.3$ Hz), 2.54 (2H, t, $J = 7.0$ Hz), 1.90 (1H, m), 1.74 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 171.1, 147.0, 136.2, 128.5, 128.1, 127.7, 127.4, 123.5, 121.2, 120.0, 111.5, 76.6, 70.6, 69.1, 58.8, 33.7, 28.4. MS (*m*/*z*) 329 (M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.35; H, 7.14; N, 4.34.

(5*R*)-1-(*o*-(Benzyloxy)phenyl)-5-(methoxymethyl)-2-pyrrolidinone (10). Lactam **10** was prepared from amide **9** (2.27 g, 6.9 mmol) in accordance with the procedure for the synthesis of lactam **3**. Purification by column chromatography (hexane/AcOEt = 2) gave **10** (1.94 g, 90%). **10**: white solid; mp 73−75 °C; $[\alpha]_D = +22.8$ ($CHCl_3$, $c = 1.28$); IR (KBr) 2929, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.20−7.40 (7H, m), 6.98−7.03 (2H, m), 5.08 (2H, s), 4.18 (1H, m), 3.27 (1H, dd, $J = 3.3$, 10.0 Hz), 3.25 (1H, dd, $J = 4.7$, 10.0 Hz), 3.24 (3H, s), 2.62 (1H, ddd, $J = 7.2$, 9.8, 16.9 Hz), 2.44 (1H, ddd, $J = 5.9$, 9.7, 16.9 Hz), 2.22 (1H, dddd, $J = 7.2$, 8.2, 9.7, 15.5 Hz), 2.06 (1H, dddd, $J = 4.7$, 5.9, 9.8, 15.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 175.5, 154.1, 136.5, 130.0, 128.7, 128.3, 127.7, 126.9, 126.0, 121.0, 113.3, 72.7, 70.2, 59.3, 58.7, 30.4, 22.1. MS (*m*/*z*) 311 (M^+). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.29; H, 6.65; N, 4.59.

(5*R*)-1-(*o*-*tert*-butyldiphenylsiloxyphenyl)-5-(methoxymethyl)-2-pyrrolidinone (11). To a solution of **10** (1.94 g, 6.2 mmol) in AcOEt (30 mL) was added 10% Pd−C, and then the reaction mixture was stirred under a hydrogen atmosphere for 5 h. After removal of Pd−C by filtration and evaporation of AcOEt, THF (30 mL) and NaH (60%, 298 mg, 7.4 mmol) were added to the residue. After being stirred for 20 min at room temperature, *tert*-butyldiphenylsilyl chloride (1.6 mL, 6.8 mmol) was added, and then the reaction mixture was stirred for 3 h at room temperature. The mixture was poured into saturated aqueous $KHSO_4$ solution 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 = 7) gave lactam **11** (2.62 g, 92%). The ee of **11** was determined by HPLC analysis using a CHIRALPAK AD column [25 cm × 0.46 cm i.d.; 5% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**11**; t_R = 9.0 min, (−)-**11**; t_R = 11.5 min]. **11**: white solid; mp 116−117 °C; $[\alpha]_D = +69.4$ ($CHCl_3$, $c = 1.02$); IR (KBr) 2933, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.74 (2H, dd, $J = 1.5$, 7.7 Hz), 7.72 (2H, dd, $J = 1.7$, 7.7 Hz), 7.31−7.47 (6H, m), 7.20 (1H, m), 6.80−6.92 (2H, m), 6.48 (1H, d, $J = 1.5$, 7.7 Hz), 4.30 (1H, m), 3.39 (2H, d, $J = 3.9$ Hz), 3.31 (3H, s), 2.70 (1H, ddd, $J = 7.3$, 10.1, 17.1 Hz), 2.54 (1H, ddd, $J = 5.5$, 9.9, 17.1 Hz), 2.36 (1H, m), 2.16 (1H, m), 1.06 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 175.3, 151.5, 135.4, 135.2, 132.3, 131.3, 130.2, 130.2, 130.0, 128.4, 127.8, 127.8, 127.4, 121.3, 120.0, 73.0, 59.6, 58.9, 30.5, 26.3, 22.2, 19.2. MS (*m*/*z*) 459 (M^+). Anal. Calcd for $C_{28}H_{33}NO_3Si$: C, 73.16; H, 7.24; N, 3.05. Found: C, 72.88; H, 7.31; N, 3.06.

(3*R*,5*R*) and (3*S*,5*R*)-1-(*o*-Hydroxyphenyl)-5-(methoxymethyl)-3-(phenylmethyl)-2-pyrrolidinone (*cis*-13a and *trans*-13a). *cis*-**12a** and *trans*-**12a** were prepared through the reaction of Li-enolate from **11** (230 mg, 0.5 mmol) with benzyl bromide (0.07 mL, 0.55 mmol) in accordance with general procedure. Purification by column chromatography (hexane/AcOEt = 3) gave a mixture of *cis*-**12a** and *trans*-**12a** in a ratio of 14:1 (262 mg, 95.%). 1 M THF solution of TBAF (1 mL, 1 mmol) was added to THF solution of **12a**, and the reaction mixture was stirred for 1 h at room temperature. The mixture was poured into water 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 = 1) and subsequent MPLC (hexane/AcOEt = 3) gave *cis*-**13a** (138 mg, 89%, more polar) and *trans*-**13a** (10 mg, 6%, less polar). *cis*-**13a**: white solid; mp 118−120 °C; $[\alpha]_D = +53.9$ ($CHCl_3$, $c = 1.09$); IR (KBr) 3200, 2989, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.57 (1H, s), 7.19−7.48 (6H, m), 7.02−7.08 (2H, m), 6.93 (1H, m), 4.17 (1H, m), 3.34 (1H, dd, $J = 3.8$, 13.5 Hz), 3.27 (1H, dd, $J = 2.5$, 10.1 Hz), 3.22 (3H, s), 3.18 (1H, dd, $J = 4.4$, 10.1 Hz), 3.02 (1H, ddt, $J = 3.9$, 9.0, 9.5 Hz), 2.86 (1H, dd, $J = 9.9$, 13.5 Hz), 2.32 (1H, ddd, $J = 7.9$, 9.5, 13.0 Hz), 1.98 (1H, ddd, $J = 7.4$, 9.0, 13.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 177.3, 152.6, 139.1, 128.9, 128.8, 128.3, 126.2, 126.0, 124.6, 120.3, 118.7, 71.1, 58.8, 58.2, 43.4, 37.0, 27.2. MS (*m*/*z*) 311 (M^+). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.26; H, 6.60; N, 4.63. *trans*-**13a**: colorless oil; $[\alpha]_D = +218.8$ ($CHCl_3$, $c = 1.00$); IR (KBr) 3239, 2924, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.54 (1H, s), 7.35−7.18 (6H, m), 7.06 (1H, dd, $J = 1.2$, 7.7 Hz), 6.90−6.93 (2H, m), 3.94 (1H, m), 3.25 (3H, s), 3.11−3.28 (4H, m), 2.85 (1H, dd, $J = 8.5$, 13.4 Hz), 2.25 (1H, ddd, $J = 3.5$, 9.0, 13.1 Hz), 2.13 (1H, ddd, $J = 8.2$, 8.5, 13.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 171.1, 152.5, 138.7, 129.1, 128.8, 128.4, 126.4, 125.4, 124.8, 120.6, 119.3, 72.0, 59.2, 59.1, 43.4, 37.3, 28.3. MS (*m*/*z*) 311 (M^+).

(3*R*,5*R*)-5-(Methoxymethyl)-3-(phenylmethyl)-2-pyrrolidinone (*cis*-16a). A solution of *cis*-**13a** (342 mg, 1.1 mmol) in acetonitile (12 mL) was cooled to 0 °C and treated with a solution of CAN (1.81 g, 3.3 mmol) in water (15 mL) over 3 min. The reaction mixture was stirred at room temperature for 5 h, and then the mixture was poured into water and extracted with AcOEt. The AcOEt extracts were successively washed with saturated aqueous $NaHCO_3$ solution, sodium sulfite solution, and brine, and dried over $MgSO_4$. The resulting solution was filtered through Celite and evaporated to dryness. Purification of the residue by flash column chromatography (hexane/AcOEt = 1) gave *cis*-**16a** (130 mg, 54%). *cis*-**16a**: white solid; mp 50−52 °C; $[\alpha]_D = -138.5$ ($CHCl_3$, $c = 0.22$); IR (KBr) 3267, 2924, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.15−7.33 (5H, m), 5.98 (1H, br s), 3.72 (1H, m), 3.32 (1H, dd, $J = 3.5$, 13.4 Hz), 3.31 (3H, s), 3.25 (1H, dd, $J = 3.6$, 13.4 Hz), 2.98 (1H, dd, $J = 9.0$, 9.9 Hz), 2.76 (1H, m), 2.65 (1H, dd, $J = 9.9$, 13.5 Hz), 2.16 (1H, ddd, $J = 7.1$, 8.7, 12.6 Hz), 1.36 (1H, ddd, $J = 8.5$, 9.4, 12.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 178.2, 139.4,

128.9, 128.5, 126.3, 76.7, 59.0, 51.8, 42.8, 36.8, 29.2; MS (*m*/*z*) 219 (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.03; H, 7.81; N, 6.30.

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Supporting Information Available: Characterization data and experimental procedures of *cis*-**5c,** *trans*-**5c, 7,** *cis*-**8,** *trans*-**8,** *cis*-**13b,** *trans*-**13b,** *cis*-**13c,** *trans*-**13c,** *cis*-**16b**, and X-ray crystal data of **3** and **11.** This material is available free of charge via the Internet at http://pubs.acs.org.

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