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Stereoselective synthesis of diastereomeric atropisomeric lactam with various ring sizes and their structural characterization

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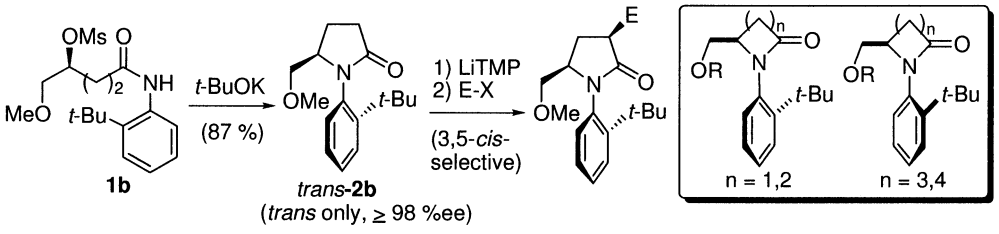
Abstract

Diastereomeric atropisomeric *N-ortho-tert*-butylphenyl lactams with ring sizes from four to seven were prepared with high diastereoselectivity through an aminocyclization reaction. In the case of four- and five-membered ring formation, thermodynamically stable atropisomeric lactams having a *trans*-relationship between the *ortho-tert*-butyl group and the C-4 or C-5 substituent were obtained, while in the six- and seven-membered ring-forming reaction, *cis*-atropisomeric lactams, kinetic controlled products, were exclusively isolated.

Keywords: atropisomerism; lactam; isomerization; diastereoselection.

In the course of our work in relation to optically active atropisomeric anilide chemistry,[1–3] we recently reported a diastereoselective reaction using the lithium enolate of optically pure atropisomeric 5-methoxymethyl-*N-ortho-tert*-butylphenyl-2-pyrrolidinone *trans*-**2b** (Scheme 1).[2c,2e,4] In the reactions of the lactam enolate with electrophiles, stereocontrol on the basis of



Scheme 1.

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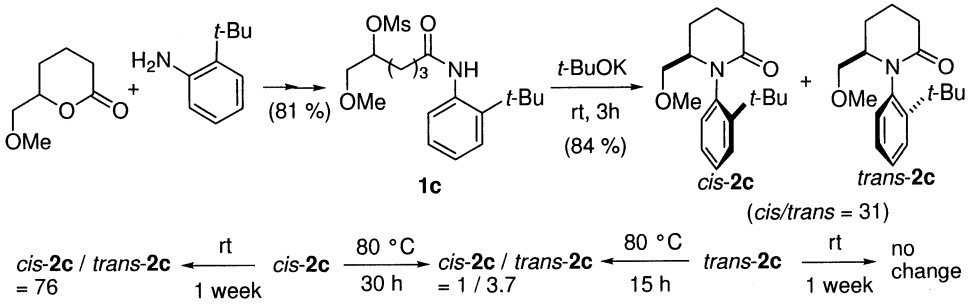
C–N atropisomerism overcame the usual influence of a chiral carbon (C-5) to preferentially give 3,5-*cis*-disubstituted-2-pyrrolidinone, which is difficult to obtain through known methodology.[5] The optically pure atropisomeric anilide *trans*-**2b** having a *trans*-relationship between the *ortho*-*tert*-butyl group and the C-5 substituent was prepared with a complete stereoselectivity through an aminocyclization reaction of the mesylate **1b** prepared from (*S*)-5-(methoxymethyl)butyrolactone and *ortho*-*tert*-butylaniline, while the origin of the *trans*-selectivity was not clear. In contrast to the complete *trans*-selectivity in the preparation of the five-membered lactam, it was found that the six-membered lactam-forming reaction with the mesylate **1c** proceeds with high *cis*-selectivity (*cis*/*trans* = 31) (Scheme 2). These contrasting results prompted us to study the synthesis of diastereomeric atropisomeric lactams with various ring sizes and their stereochemistries. In this paper, we report a stereoselective synthesis of diastereomeric atropisomeric *N*-*ortho*-*tert*-butylphenyl lactams with ring sizes from four to seven and their structural characterization.



Scheme 2.

As mentioned above, the aminocyclization reaction of the mesylate **1c** gave *cis*-6-methoxymethyl-*N*-*ortho*-*tert*-butylphenyl-2-piperidinone *cis*-**2c** with high diastereoselectivity (*cis*/*trans* = 31) (Scheme 2).[6] The stereochemistry of lactam *cis*-**2c** having a *cis*-relationship between the *ortho*-*tert*-butyl group and the C-6 substituent was determined by X-ray analysis after conversion to hydroxymethyl derivative *cis*-**3c** (Fig. 1). The aminocyclization, which preferentially formed the *cis*-**2c** at rt, should be based on kinetic control, because isomerization between *cis*- and *trans*-**2c** via the free rotation around the C–N bond could hardly be observed after standing for a week at rt (Scheme 2).

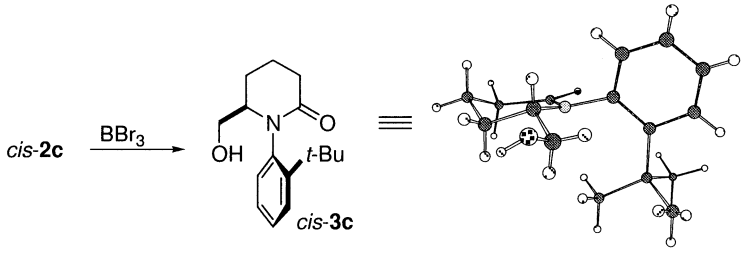
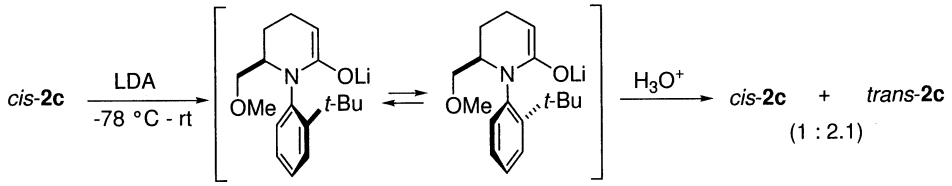


Figure 1. X-ray crystal structure of *cis*-**3c**

The isomerization was found to easily occur at 80°C. For example, on heating both diastereomerically pure *cis*-**2c** (30 h) and *trans*-**2c** (15 h) at 80°C, each isomer reached the thermodynamic ratio (*cis*/*trans* = 1/3.7) (Scheme 2). This result is in contrast to that of a

five-membered lactam which easily and completely isomerizes to *trans*-**2b** from *cis*-**2b** at rt ($t_{1/2}$ = ca. 14 h). The higher rotational barrier of **2c** (*cis*-**2c**: $t_{1/2}$ = 602 days at 27°C, rotational barrier = 28.3 kcal/mol)[7] than that of **2b** could possibly be explained on the basis of the comparison of the C–N–C angle obtained by X-ray analysis of *trans*-2b[2c,2e] and *cis*-**3c**. That is, the larger C(2)–N–C(6) angle (124.1°) of the six-membered lactam *cis*-**3c** in comparison with the C(2)–N–C(5) angle (112.7°) of the five-membered lactam *trans*-**2b** should result in a higher barrier of free rotation around the C(Ar)–N bond. It is noteworthy that isomerization to *trans*-**2c** from *cis*-**2c** through the formation of a lactam enolate easily occurs even below rt (Scheme 3).[8] Isomerization of the lactam enolate having sp^3-nitrogen may occur more easily than that of lactam *cis*-**2c** having sp^2-nitrogen, because the tetrahedral structure of nitrogen may reduce steric repulsion between the *tert*-butyl group and carbonyl oxygen or the C-6 substituent during rotation around the C–N bond.



Scheme 3.

High *cis*-selectivity observed in the aminocyclization of **1c** may be rationalized on the basis of the transition-state model shown in Fig. 2. In the six-membered ring chair-type transition-state model $A^{\neq}$ and $B^{\neq}$ having a perpendicular Ar group to the (*Z*)-potassium iminoalcoholate plane, a counterclockwise rotation of the iminoalcoholate and Ar moieties may simultaneously occur with the cyclization. Since the *ortho*-*tert*-butyl group is located outside of the six-membered ring, the counterclockwise rotation should lead to the formation of a lactam having a β-*tert*-butyl group and not an α-one. Thus, the reaction through transition-state model $A^{\neq}$ and $B^{\neq}$ gives *cis*-**2c** and *trans*-**2c**, respectively. From the viewpoint of 1,3-diaxial repulsion, the reaction via $A^{\neq}$ having an equatorial methoxymethyl group at the C-6 position should be preferred more than that via $B^{\neq}$ having an axial one.

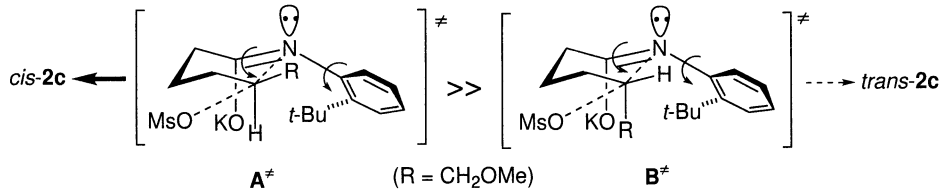
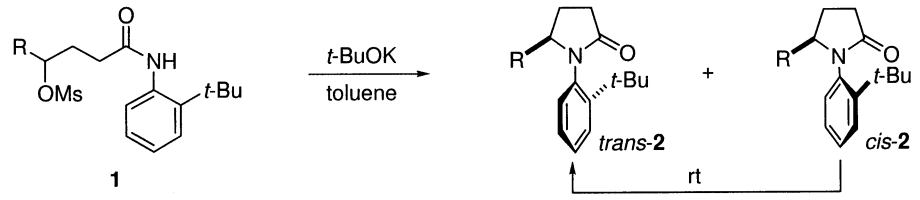


Figure 2. Possible transition state model of aminocyclization of **1c**

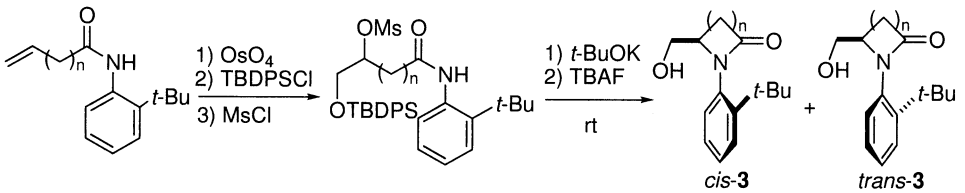
Although we previously reported that the five-membered lactam-forming reaction (rt, 3 h) with mesylate **1b** exclusively gives *trans*-**2b** after extractive work-up and purification by column chromatography,[2c,2e] the result of the six-membered lactam-forming reaction prompted us to reinvestigate the reaction of **1b** (Scheme 4). When ^{1}H NMR of the reaction mixture was quickly measured after aminocyclization of **1b** for 30 min at 0°C and subsequent extractive work-up, but without further purification, *cis*-**2b** was found to be formed as a major product (*cis*-**2b**/*trans*-**2b** = 2.1/1). Under these conditions, starting material **1b** was not completely consumed. Further-

more, isomerization of *cis*-**2b** to thermodynamically stable *trans*-**2b** was observed at rt. This result indicates that the exclusive formation of *trans*-**2b** reported previously should involve the isomerization of initially formed *cis*-**2b**.[9] The preferential formation of a *trans*-five-membered lactam through isomerization of *cis*-lactam was also observed in the reaction of mesylate **1e**; that is, a mixture of *trans*- and *cis*-**2e** (*trans*/*cis* = 1.5), which was obtained by aminocyclization of **1e** for 3 h at rt reached the thermodynamic ratio (*trans*/*cis* = 20) after standing for several weeks at rt.[10]



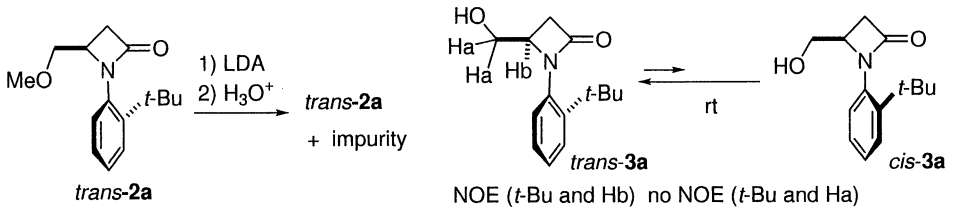
Scheme 4.

On the basis of these results, it was assumed that aminocyclization leading to the lactam having a large rotational barrier around the C–N bond (large C–N–C angle) may give a *cis*-lactam as a major stereoisomer through kinetic control. On the other hand, for the lactam having a small rotational barrier (small C–N–C angle), a *trans*-lactam may be preferentially formed through the isomerization of an unstable *cis*-lactam. To confirm this assumption, diastereomeric atropisomeric *N-ortho-tert*-butylphenyl lactams with ring sizes from four to seven were prepared in accordance with the reaction pathway shown in Scheme 5, and their stereochemistries were investigated. Four-membered lactam-forming reaction through aminocyclization of mesylates **4a** and subsequent desilylation gave *trans*-4-hydroxymethylazetidinone *trans*-**3a** in good yield (71%). Although existence of the *cis*-isomer could not be detected even through the enolate formation of 4-methoxymethylazetidinone *trans*-**2a**,[8] the *trans*-conformer in **3a** could be confirmed by NOE experiment (Scheme 6). In the four-membered lactam, free rotation around the C–N bond may easily occur at rt because of the smaller C–N–C angle than that of the five-membered lactam. Contrarily, the seven-membered lactam-forming reaction with



Scheme 5.

mesylate **4d** gave *cis*-lactam *cis*-**3d** with complete stereoselectivity at rt, while the chemical yield is extremely low (Scheme 5). The stereochemistry of lactam *cis*-**3d** was determined by X-ray analysis. Since no isomerization of *cis*-**3d** having a large C–N–C angle (124.2°) similar to that of six-membered lactam **3c** was observed at rt, exclusive formation of *cis*-**3d** in aminocyclization of **4d** should be due to kinetic control. Similarly to the preparation of 5- and 6-methoxymethyl lactams **2b** and **2c**, five- and six-membered lactam-forming reaction with mesylates **4b** and **4c** gave *trans*-**3b** and *cis*-**3c** with high diastereoselectivity, respectively.



Scheme 6.

In conclusion, we have found that diastereomeric atropisomeric *N-ortho-tert*-butylphenyllactams with various ring sizes can be prepared with high diastereoselectivity. The results described here should provide useful information on atropisomeric anilide chemistry.

Acknowledgements

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5. For review: Najera, C; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
6. The aminocyclization reaction was performed in accordance with our reported procedure (see Refs. 2c and 2e). *cis*-**2c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ: 7.53 (1H, dd, $J=1.9$, 7.9 Hz), 7.24 (2H, m), 7.00 (1H, dd, $J=1.9$, 7.9 Hz), 3.90 (1H, m), 3.33 (1H, dd, $J=8.2$, 9.0 Hz), 3.18 (3H, s), 3.16 (1H, dd, $J=3.5$, 9.0 Hz), 2.39–2.62 (2H, m), 2.20 (1H, m), 2.05 (1H, m), 1.80–1.94 (2H, m), 1.36 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 172.7, 147.3, 138.3, 130.1, 128.0, 127.3, 127.0, 73.2, 60.8, 58.7, 36.5, 33.6, 32.0, 27.1, 19.6. *trans*-**2c**: colorless oil; ^{1}H NMR ($CDCl_3$) δ: 7.54 (1H, dd, $J=1.7$, 8.0 Hz), 7.24 (2H, m), 6.95 (1H, dd, $J=1.6$, 8.0 Hz), 3.69 (1H, m), 3.42 (1H, dd, $J=6.5$, 9.4 Hz), 3.37 (1H, dd, $J=3.3$, 9.4 Hz), 3.29 (3H, s), 2.59 (1H, m), 2.45 (1H, m), 2.05–2.20 (3H, m), 1.6 (1H, m), 1.36 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.7, 146.3, 138.4, 132.6, 129.3, 127.7, 126.2, 72.0, 58.9, 58.6, 35.7, 32.8, 31.7, 25.2, 17.8.
7. Rotational barrier and half-life of *cis*-**2c** were calculated from the Eyring equation.
8. The isomerization through the enolate formation has been also observed in five-membered lactam *trans*-**2b** (see Refs. 2c and 2e). Isomerization to thermodynamically unfavorable *cis*-**2b** from stable *trans*-**2b** partially occurred through the formation of the lithium enolate and subsequent protonation to give a mixture of *cis*- and *trans*-**2b** in a ratio of 1: 2.6.
9. Isomerization to a stable diastereomer through the rotation of the atropisomeric axis has also been found in diastereomeric atropisomeric naphthamide derivative. Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556–2558.
10. The decrease in the chemical yield in the reaction of **1e** is due to the formation of *O*-cyclized products as a side product.