Tandem Transesterification and Intramolecular Cycloaddition of α-Methoxycarbonylnitrones with Chiral Acyclic Allyl Alcohols: Systematic Studies on the Factors Affecting Diastereofacial Selectivity of the Cycloaddition

Osamu Tamura,*,† Naka Mita,‡ Toshiyuki Okabe,‡ Tatsuya Yamaguchi,‡ Chieko Fukushima,‡ Masayuki Yamashita,# Yasuhiro Morita,‡ Nobuyoshi Morita,‡ Hiroyuki Ishibashi,† and Masanori Sakamoto*,‡

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan, Meiji Pharmaceutical University, Noshio, Kiyose, Tokyo 204-8588 Japan, and Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8414, Japan

tamura@dbs.p.kanazawa-u.ac.jp

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Factors affecting the stereochemical course of the intramolecular cycloaddition of intermediary α-allyloxycarbonylnitrone resulting from transesterification of α-methoxycarbonylnitrones **1a**−**d** with chiral allyl alcohols **5** or **6** were investigated systematically. It was found that the factors of diastereofacial selection are highly dependent on the geometries of the allyl alcohols. In the cases where primary or secondary chiral (*Z*)-allyl alcohols are used, A(1,3)-strain arising from the chiralities in the (*Z*)-nitrone transition states of the intramolecular cycloaddtion is the most important factor. In contrast, in the case of the reaction using chiral nitrones **1c,d** and (*E*)-allyl alcohols, steric interaction between the chiral *N*-substituent and the *trans* substituent of the olefin moiety in the intermediate is dominant. These aspects were applied to geometry-differentiated cycloaddition using a mixture of (*E*)-**5** and (*Z*)-**5**. As a typical example, treatment of bulky **1b** with a 1:1 mixture of (*E*)-**5** and (*Z*)-**5** in the presence of a catalytic amount of $TiCl_4$ and MS 4A gave **7b** as the predominant product among four possible products.

Introduction

1,3-Dipolar cycloaddition of nitrones with olefins leads to spontaneous formation of carbon−carbon bonds and carbon−oxygen bonds to give isoxazolidines, in which the geometries of the olefins are reflected in the stereochemistries of the products.[1] Since reductive cleavage of nitrogen−oxygen bonds of the resulting isoxazolidines is quite facile, nitrone cycloaddition is a useful method for the syntheses of γ-amino alcohols.[1,2] Intermolecular cycloaddition of a nitrone, however, gives principally four isomers: endo and exo-isomers as well as two sets of regioisomers.[1] In the case of intramolecular cycloadditions of nitrones connected with olefin moieties by tethers of appropriate lengths, the regiochemical problem can be neglected and diastereoselectivity (endo- and exo-selectivity) can also be dramatically improved.[3] This methodology has been successfully applied to the syntheses of natural products such as alkaloids, β-lactam antibiotics, and amino sugars.[4] In these syntheses, high regio- and stereoselectivties were achieved. For the intramolecular cycloadditions, however, long and multistep synthetic routes have been required to set up two reaction sites, nitrone groups and olefin moieties, at appropriate positions in the molecules. As a solution for this drawback, we recently explored "tandem transesterification and intramolecular 1,3-dipolar cycloaddition methodology".[5,6] In this methodology, transesterification of equilibrating mixtures of (*E*)- and (*Z*)-α-methoxycarbonylnitrones (**1**) with allyl alcohols **2** provides α-allyloxycarbonylnitrones **3** as the intermediates, which, in turn, undergo intramolecular cycloaddition via (*Z*)-nitrone transition states **A**[7] to give relative stereochemistry-controlled cycloadducts **4** in one step (eq 1). It should be noted that the tandem process acquires operational simplicity of intermolecular cycloaddition as well as excellent regio-

* To whom correspondence should be sent.
† Kanazawa University.
‡ Meiji Pharmaceutical University.
# Kyoto Pharmaceutical University.

(1) For reviews of cycloadditions of nitrones, see: (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. (b) Deshong, P.; Lander, S. W., Jr.; Leginus, J. M.; Dicken, C. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1988; Vol. 1, p 87. (c) Little, R. D. Thermal cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 5, p 239. (d) Padwa, A. Intermolecular 1,3-dipolar cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069.

(2) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(3) For reviews see: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253. (b) Padwa, A.; Schoffstall, A. M. Intramolecular 1,3-Dipolar Cycloaddition Chemistry. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1990; Vol. 2, p 1. (c) Wade, P. A. Intramolecular 1,3-dipolar cycloaddition. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1113.

(4) For a review, see: Frederickson, M. *Tetrahedron*, **1997**, *53*, 403. For representative examples, see: (a) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956; Wovkulich, P. M.; Uskokovic, *Tetrahedron* **1985**, *41*, 3455. (b) Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 9. (c) Smith, A. L.; Williams, S. F.; Holms, A. B.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696. (d) Jung, M. K.; Vu, B. T. *J. Org. Chem.* **1996**, *61*, 4427. (e) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046 and references sited therein. (f) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 686. (g) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holms, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900.

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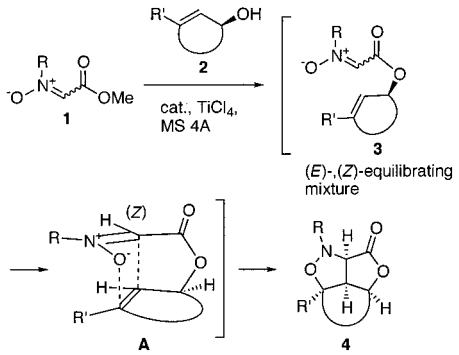
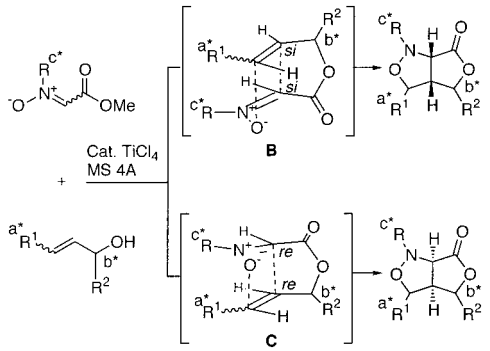
Scheme 1



Scheme 2



and stereoselectivity of intramolecular cycloaddition.[7] In that work,[5b] we also found that the reactivities of (*Z*)-allyl alcohols are much higher than those of (*E*)-allyl alcohols, and that this phenomenon could be extended to "geometry-differentiated cycloaddition" in which the reaction of **1** with a mixture of (*E*)- and (*Z*)-allyl alcohols predominantly gives intramolecular cycloadducts from (*Z*)-allyl alcohols.

In this type of reaction, the use of chiral cyclic secondary allyl alcohols enables the control of the absolute stereochemistries of three newly formed stereogenic centers (Scheme 1),[5] whereas the use of chiral acyclic allyl alcohols, as shown in Scheme 2, generates two possibilities of the diastereofacial selections (*si*−*si* attack **B** or *re*−*re* attack **C**) due to their flexibilities. To control the absolute stereochemistries by using an acyclic allyl alcohol, a chirality (or chiralities a*−c*) should be introduced in the intramolecular system.[8] To investigate efficient factor to affect the diastereofacial selection, we devoted our efforts to examine systematically diastereofacial selectivities in light of the position of chirality (a*−c*) and geometry of olefin moiety by employing nitrones **1a**−**d**, primary allyl alcohols (*Z*)- and (*E*)-**5**, and secondary allyl alcohols **6** (Figure 1). We have now found that the factors of diastereofacial selection depend on the geometry of the allyl alcohol. Thus, in the case where chiral (*Z*)-**5** or (*Z*)-**6** is used, A(1,3)-strain arising from chirality a* or b* is the important factor in the control of the diastereofacial selectivity, while in the case where (*E*)-**6** is used, chirality c* controls the diastereofacial selection, and the combined use of chiralities b* and c* causes double asymmetric induction to exhibit high selectivity.[9]

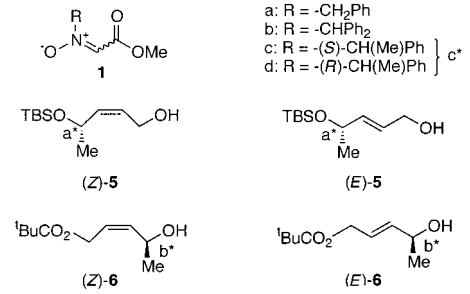


Figure 1. Nitrones and allyl alcohols employed.

Results and Discussion

1. The Effect of Chirality a* in Cases Where Primary Allyl Alcohols are Used. First, we examined the reactions of nitrones **1a,b** with primary allyl alcohol (*Z*)-**5** and (*E*)-**5** to gain insights into the effects of tether-outer chirality (chirality a*) in the intramolecular cycloaddition. As shown in Scheme 3, treatment of nitrones **1a,b** with primary allyl alcohol (*Z*)-**5** in the presence of catalytic amounts of titanium tetrachloride and molecular sieves 4A (MS4A) induced smooth transesterification and intramolecular cycloaddition to afford the cycloadducts **7a,b** as the major isomers along with small amounts of **8a,b** independent of substituents (R) of the nitrones **1a,b**. The stereochemistry of the cycloadduct **7a**

(5) (a) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009. (b) Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 107. (c) Tamura, O.; Okabe, T.; Yamaguchi, T.; Kotani, J.; Gotanda, K.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 119. For closely related tandem acylation and intramolecular cycloaddition, see: (d) Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073. For tandem hemiacetalization and intramolecular nitrone cycloaddition, see: (e) Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87. (f) Kanemasa, S.; Tsuruoka, T.; Yamamoto, H. *Tetrahedron Lett.* **1995**, *36*, 5019.

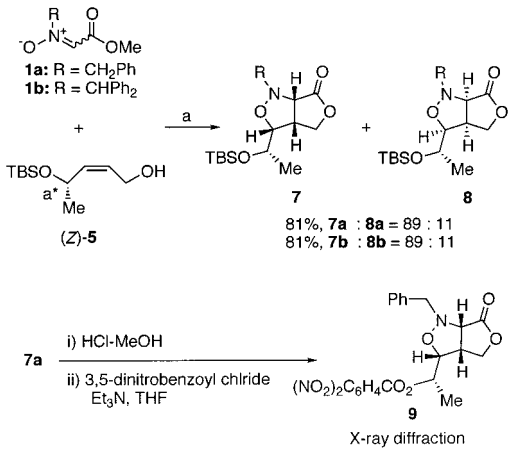
(6) For a reviews on tandem reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. See also: (b) Frederickson, M.; Grigg, R.; Markandu, J.; Thornton-Pett, M.; Redpath, J. *Tetrahedron* **1997**, *53*, 15051 and references therein. (c) Denmark S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875 and references sited therein.

(7) Owing to its operational simplicity, Schreiber and co-workers successfully applied the tandem nitrone cycloaddition concept to construction of a large chemical library. See ref 5d. They proposed an (*E*)-nitrone transition state instead of (*Z*)-nitrone transition state in Scheme 1. However, preliminary calculations for transition state **A** (R = Bn, R′ = H) derived from 1a and cyclohex-2-en-1-ol and the corresponding (*E*)-nitrone transition state showed that the (*Z*)-nitrone tansition state is more stable by 9.6 kcal/mol than is the (*E*)-nitrone transition state. Therefore, the stereochemical aspects in this work are discussed by employing the (*Z*)-nitrone transition state model. See Supporting Information.

(8) For reviews of diastereofacial selectivity of intramolecular cycloaddition of nitrones, see: (a) Chiacchio, U.; Rescifina, A.; Romeo, G. *Targets Heterocycl. Syst.* **1997**, *1*, 225. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. See also the following recent examples: (c) Aurich, H. G.; Biesemeier, F.; Harms, K. *Liebigs Ann./Recl.* **1997**, 469. (d) Aurich, H.; Soeberdt, M.; Harms, K. *Tetrahedron* **1999**, *55*, 1249. (e) Marcus, J.; Brussee, J.; Van del Gen, A. *Eur. J. Org. Chem.* **1998**, 2513. (f) Uddin, M. J.; Kikuchi, M.; Takedatsu, K.; Arai, K.; Fujimoto, T.; Motoyoshiya, J.; Kakehi, A.; Iriye, R.; Shirai, H.; Yamamoto, I. *Synthesis* **2000**, 365. (g) Broggini, G.; Folcio, F.; Sardone, N.; Sordone, N.; Sonzogni, M.; Zecchi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 797. (h) Arnold, W.; Mohr, P. *Synlett* **1996**, 1215. (i) Annunziata, R.; Benaglia, M.; Clinquini, M.; Cozzi, F.; Raimondi, L. *Eur. J. Org. Chem.* **1998**, 1823. (j) Hems, W. P.; Tan, C.-H.; Stork, T.; Feeder, N.; Holms, A. B. *Tetrahedron Lett.* **1999**, *40*, 1393. (k) Tan. C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1397. (l) Aurich, H. G.; Geiger, M.; Gentes, C.; Harms, K.; Köster, H. *Tetrahedron* **1998**, *54*, 3181. (m) Shing, T. K. M.; Zhong, Y.-L.; Mak, T. C. W.; Wang R.-J.; Xue, F. *J. Org. Chem.* **1998**, *63*, 414. (n) Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1997**, *38*, 8581. (o) Bar, N. C.; Roy, A.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1997**, *62*, 8948.

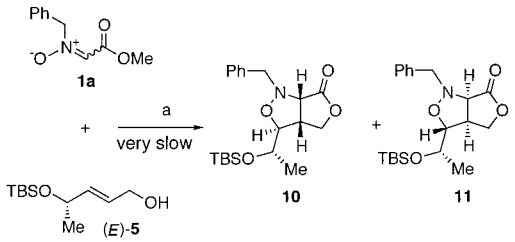
(9) Preliminary communication for a part of this work: Tamura, O.; Yamaguchi, T.; Okabe, T.; Sakamoto, M. *Synlett* **1994**, 620.

Scheme 3[a]



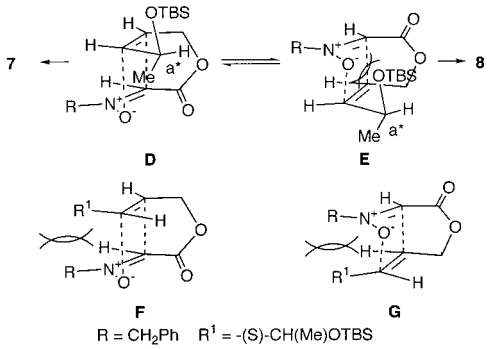
[a] (a) 0.1 equiv $TiCl_4$, MS4A, $ClCH_2CH_2Cl$, rt.

Scheme 4[a]



[a] (a) 0.1 equiv $TiCl_4$, MS4A, $ClCH_2CH_2Cl$, 80 °C.

Scheme 5



was definitely established by transformation of **7a** into 3,5-dinitrobenzoate **9** and its X-ray diffraction. On the other hand, intramolecular cycloaddition products **10** and **11** could not be isolated from **1a** and (*E*)-**5** under similar conditions since the cycloaddition was very slow despite the smooth transesterification (Scheme 4).[10]

As depicted in Scheme 5, the observed diastereofacial selection shown in Scheme 3 can be rationalized by considering transition models **D** and **E** with minimum A(1,3)-strains[11] resulting from chirality a*. Since model **E** has severe steric interaction between the nitrone moiety and the bulky *tert*-butyldimethylsilyloxy group, the reaction would proceed mainly by way of model **D** to afford the major isomer **7** predominantly.[12] The very slow reaction of nitrone **1a** with allyl alcohol (*E*)-**5** may be explained by taking into acount the steric hindrances in both models **F** and **G** (Scheme 5).

2. The Effect of Chiralities b* and c* in the Case Where Secondary Allyl Alcohol (*Z*)-6 is Used. Next, we investigated the tandem reaction of nitrones **1a**−**d** with allyl alcohol (*Z*)-**6** to determine whether tether-inner chirality b* affects the diastereofacial selectivity of the cycloaddition. We also chose (*Z*)-**6** to clarify the effects of chiralities c* of **1c,d** on the diastereofacial selectivities. Since the diastereofacial selectivities should be reflected directly in the relative stereochemistries between 5- and 6-positions of the rigid products **12** and **13**, the methyl group of (*Z*)-**6** would be an excellent stereochemical indicator for diastereofacial intramolecular cycloaddition (Table 1). Treatment of nitrone **1a** with alcohol (*Z*)-**6** in the presence of a catalytic amount of titanium tetrachloride and MS4A led to smooth transesterification and intramolecular cycloaddition even at room temperature to afford **12a** accompanied by a small amount of **13a** (entry 1). The more bulky nitrone **1b** also reacted with (*Z*)-**6** under the same conditions, giving **12b** and **13b** in an excellent combined yield with high diastereofacial selectivity (entry 2). It was also found that reactions of chiral nitrones **1c,d** with (*Z*)-**6** proceeded smoothly to give **12c,d** as the major cycloadducts in excellent yields with high diastereofacial selectivities which were independent of the chiralities of nitrones **1c,d** (entries 3,4).

Since the relative stereochemistries of cycloadducts **12** must be opposite to those of **13** with respect to their methyl groups, the stereochemical assignments of **12** and **13** were readily made based on the coupling constants (J_{ab}) in their ^{1}H NMR spectra, as shown in Figure 2. For example, the smaller J_{ab} (3.3 Hz) of **12a** clearly shows that H_a and H_b have a *trans*-relationship, while the larger coupling constant (J_{ab} = 6.6 Hz) of **13a** indicates that H_a and H_b bear a *cis* relationship. The stereochemistries of **12b**−**d** and **13b**−**d** were also assigned in the same manner, and the stereochemistries of **12a** and **12d** were further confirmed by the NOE difference spectra.

The observed selectivities may be rationalized by considering transition state models **H** and **I** in the intramolecular cycloaddition step, as shown in Scheme 6. In the case where (*Z*)-**6** is used, the transition state model **H** appears to be more favorable than model **I**, since **I** has a severe A(1,3)-strain between the methyl group and the bulky pivaloyloxymethyl group (R^1). Moreover, the R group lies too far to interact with the R^1 group. Accordingly, the reactions of the chiral nitrones **1c,d** with (*Z*)-**6** gave **12c,d** predominantly, independent of chirality c* on the R group by way of **H**. This tendency indicates that the chirality b* of (*Z*)-**6** makes the olefin moiety react from the *si* face by A(1,3)-strain.

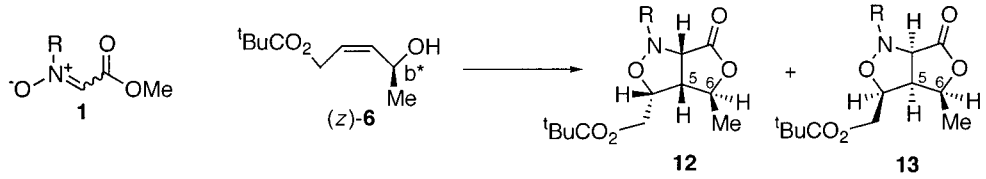
3. The Effect of Chiralities b* and c* in the Case Where the Secondary Allyl Alcohol (*E*)-6 is Used. Next, we examined the reactions of nitrones **1a**−**d** with (*E*)-**6** to determine the factors affecting the diastereofacial selectivity in the cases where (*E*)-allyl alcohols are used (Table 2). In contrast to the reactions employing (*Z*)-**6**, reactivities and diastereofacial selectivities in the reactions using (*E*)-**6** were highly dependent on the substit-

(10) When the cycloaddition is not completed, the cycloadducts can not be isolated by chromatography since the polarities of the cycloadducts are between those of the (*E*)- and (*Z*)-isomers of the starting nitrone.

(11) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1984; Vol 3, p 1. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(12) The diastereofacial selection may be also explained in terms of dipole−dipole interaction between the silyloxy group and the oxygen atom of the nitrone group. See ref 8i.

Table 1. Tandem Transesterificaton and Intramolecular Cycloaddition of A-Methoxycarbonylnitrones 1a−d with Allyl Alkohol (*Z*)-6[a]



Entry	Nitrone	Conditions	Product	Yield (%)[b]	Ratio[c] 12 : 13
1	**1a**: R=CH_2Ph	0.1 eq. $TiCl_4$, rt, 2 days	**12a** and **13a**	quant.	95 : 5
2	**1b**: R=$CHPh_2$	0.1 eq. $TiCl_4$, rt, 2 days	**12b** and **13b**	quant.	95 : 5
3	**1c**: R = Ph, Me (*S*)	0.1 eq. $TiCl_4$, rt, 2 days	**12c** and **13c**	91	92 : 8
4	**1d**: R = Ph, Me (*R*)	0.1 eq. $TiCl_4$, rt, 4 h	**12d** and **13d**	quant.	93 : 7

[a] All reactions were carried out with MS4A in 1,2-dichloroethane at room temperature. [b] The yields were obtained after purification by column chromatography on silica gel. [c] The ratios were estimated on the basis of the ^1H NMR spectra of the diastereomeric mixtures.

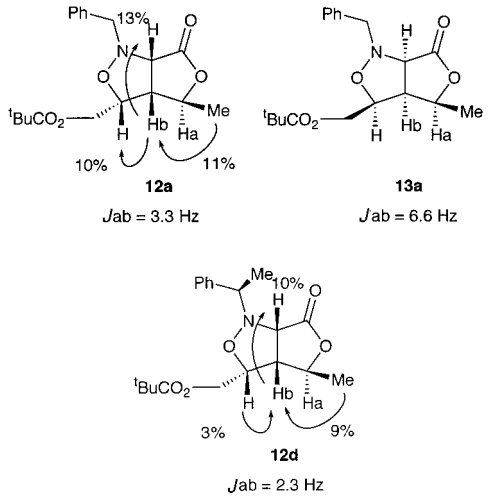
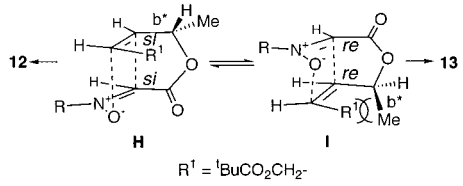


Figure 2. Selected coupling constants of **12a**, **13a**, and **12d** and NOEs of **12a** and **12d**.

Scheme 6



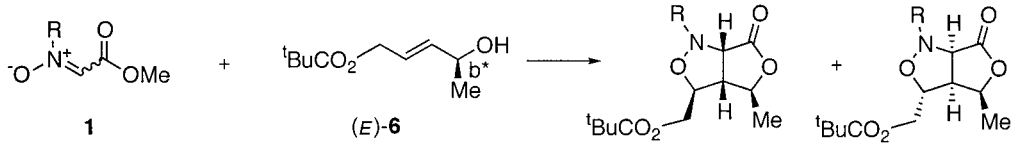
uents (R) of nitrones **1a**−**d**. Thus, the reaction of *N*-benzyl nitrone **1a** with (*E*)-**6** gave cycloadducts **14a** and **15a** in a ratio of 40:60 (entry 1). Although transesterification of *N*-benzhydryl nitrone **1b** with (*E*)-**6** proceeded, intramolecular cycloaddition was quite slow even at a higher temperature for a longer reaction time (entry 2).[10] Chiralities c* of R groups in *N*-1-phenylethyl nitrones **1c,d** strongly affected diastereofacial selectivities in the reactions employing (*E*)-**6** (entries 3 and 4). Cycloaddition of nitrone **1c** having an (*S*)-1-phenylethyl group with (*E*)-**6** took place in a highly stereoselective manner to afford **15c** in high yield (entry 3). In contrast, reaction of nitrone **1d** bearing an (*R*)-1-phenylethyl group with (*E*)-**6** exhibited a reversal of selectivity, giving rise to **14d** predominantly with moderate selectivity (entry 4).

The methyl groups of the cycloadducts **14a,c,d** and **15a,c,d** were again good indicators for the stereochemical assignments (Figure 3). For example, the smaller J_{ab} (4.0 Hz) in the ^1H NMR spectrum of **14a** clearly shows a *trans* relationship of H_a and H_b, while the ^1H NMR spectrum of **15a** having a *cis* relationship of H_a and H_b shows a larger coupling constant (J_{ab} = 6.6 Hz). The stereochemistries of the other cycloadducts **14c,d** and **15c,d** were also assigned on the basis of their *J* values (J_{ab}), and were confirmed by NOEs.

The diastereofacial selectivities of the reactions of nitrones **1a**−**d** with allyl alcohol (*E*)-**6** were rather complicated compared to those of the reactions using (*Z*)-**6**. These selectivities may be interpreted by taking into account (*Z*)-nitrone transition state models **J** and **K** (Scheme 7). In **J** and **K**, A(1,3)-strains were released more than they were in **H** and **I**, the models for the reactions of **1** with (*Z*)-**6** (see Scheme 6). As a result, the reaction of *N*-benzyl nitrone **1a** having no chirality gave poor diastereofacial selectivity. Since the R group of the nitrones occupies a position very close to the R^1 group in **J** and **K**, bulky nitrone **1b** (R = $CHPh_2$) showed a very low reactivity due to the steric interaction between the R and R^1 groups. Due to the closeness between R^1 and R, chiral environment is conveyed from c* to R^1 group; therefore, the combined uses of chiralities of the nitrones **1c,d** and chirality b* of (*E*)-**6** cause double asymmetric induction.[13] Thus, high diastereofacial selectivity was achieved by employing *N*-(*S*)-1-phenylethyl nitrone **1c** and (*E*)-**6** to afford **15c** by way of **K** due to making a matched pair.[13b] On the other hand, *N*-(*R*)-1-phenylethyl nitrone **1d** forms a mismatched pair[13b] with (*E*)-**6**, and the effect of the chirality c* of **1d** overcomes that of the chirality b* of (*E*)-**6**, affording the cycloadduct **14d** in moderate selectivity by way of **J**. These results clearly showed that chirality c* of **1** strongly affects the diaste-

(13) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1984; Vol.3, p 111. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

Table 2. Tandem Transesterificaton and Intramolecular Cycloaddition of A-Methoxycarbonylnitrones 1a−d with Allyl Alkohol (*E*)-6[a]



Entry	Nitrone	Conditions	Yield (%)[b]	Products	Ratio[c] 14 : 15
1	**1a**: R=CH_2Ph	0.15 eq. $TiCl_4$, 75 °C, 28 h	71	**14a** and **15a**	40 : 60
2	**1b**: R=$CHPh_2$	0.3 eq. $TiCl_4$, 75 °C, 2 days	-------[d]	-------[d]	-------[d]
3	**1c**: R= Ph, Me (*S*) c*	0.3 eq. $TiCl_4$, rt, 3 days	quant.	**14c** and **15c**	8 : 92
4	**1d**: R= Ph, Me (*R*) c*	0.3 eq. $TiCl_4$, rt, 3 days	91	**14d** and **15d**	63 : 37

[a] All the reactions were carried out with MS4A in 1,2-dichloroethane. [b] The yields were obtained after purification by column chromatography on silica gel. [c] The ratios were estimated on the basis of the ^1H NMR spectra of the diastereomeric mixtures. [d] Not determined.[10]

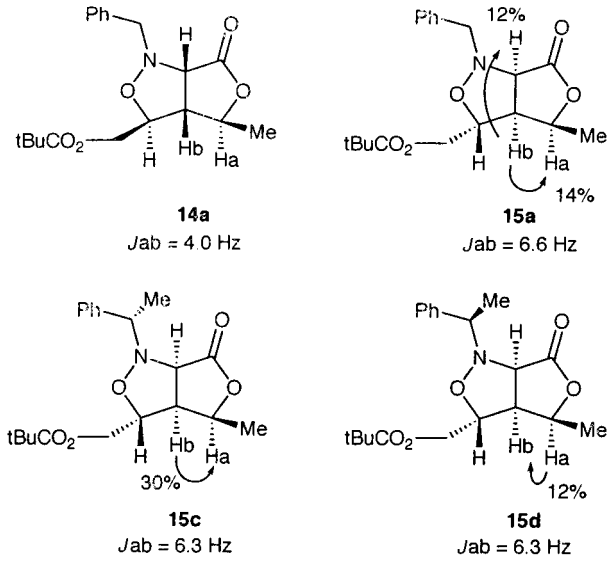
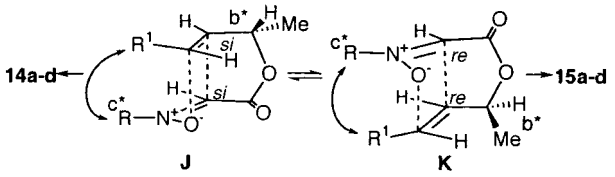


Figure 3. Selected coupling constants of **14a**, **15b**, **15c**, and **15d** and NOEs of **15a**, **15c** and **15d**.

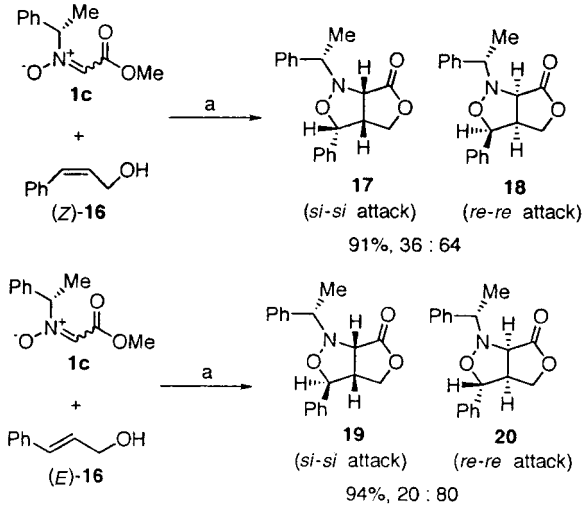
Scheme 7



reofacial selectivities of the reaction with (*E*)-allyl alcohol, in contrast to the small effects of chirality c* of **1** in the reaction with (*Z*)-allyl alcohol (*Z*)-**6**. In the reactions of **1c** and **1d**, the (*S*)-1-phenylethyl group favors *re* face attack of the nitrone, and the (*R*)-1-phenylethyl group has a tendency of *si* face attack.[14]

The difference between the effects of chirality c* with the use of a (*Z*)-allyl alcohol and the use of its (*E*)-isomer could also be observed in reactions with achiral allyl alcohols. As shown in Scheme 8, the reaction of **1c** with (*Z*)-cinnamyl alcohol (*Z*)-**16** gave a ca. 1:1.8 mixture of *si*−*si* attack product **17** and *re*−*re* attack product **18**. In contrast, use of the (*E*)-cinnamyl alcohol (*E*)-**16** showed a much higher diastereofacial selectivity. Thus, a similar reaction of **1c** with (*E*)-**16** gave a 1:4 mixture of *si*−*si* attack product **19** and *re*−*re* attack product **20**.

Scheme 8[a]



[a] (a) 0.1 equiv $TiCl_4$, MS4A, $ClCH_2CH_2Cl$.

As shown in Figure 4, the information on the effects of chiralities b* and c* can be summarized by using a (*Z*)-nitrone transition state model. In cases where (*Z*)-allyl alcohols are used, chirality b* is the most important factor in terms of A(1,3)-strain between R^1 and R^2. In cases where (*E*)-allyl alcohols are used, the chirality c* becomes the most important factor due to the closeness between R and R^1.

4. Geometry-Differentiated Intramolecular Cycloaddition. In our recent work, we developed a method for preparing cycloadducts of (*Z*)-allyl alcohols from geometrical mixtures of allyl alcohols, namely, geometry-

(14) (a) Baldwin, S. W.; McFadyen, R. B.; Aubé, J.; Wilson, J. D. *Tetrahedron Lett.* **1991**, *32*, 4431. (b) Aurich, H. G.; Quintero, J.-L. R. *Tetrahedron* **1994**, *50*, 3929. See also refs 4a and 8g.

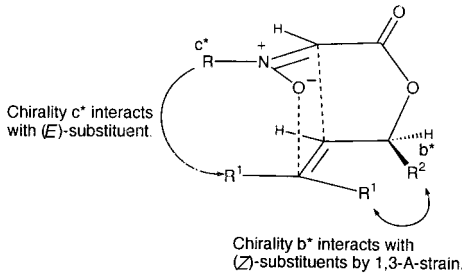
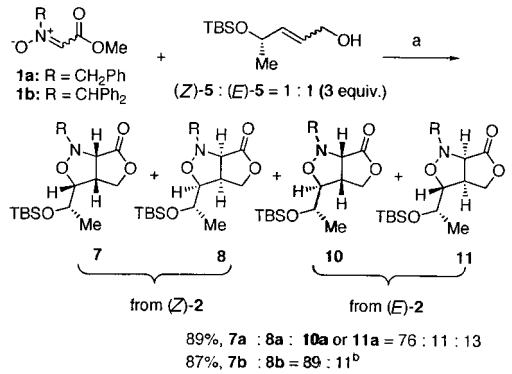


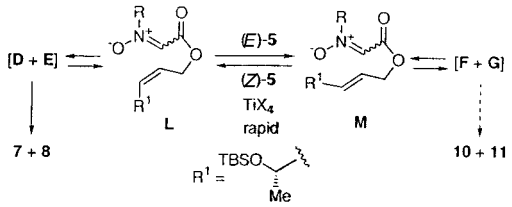
Figure 4. Major factors affecting diastereofacial selectivities in the intramolecular cycloaddition.

Scheme 9[a]



[a] (a) 0.1 equiv $TiCl_4$, MS4A, $ClCH_2CH_2Cl$, rt, 92 h. (b) The mixture after completion of the reaction contained a 35:65 ratio of (*Z*)-**5** and (*E*)-**5** (GLC analysis, OV-1, 0.2 mm × 25 m).

Scheme 10



differentiated cycloaddition.[5b] We applied this method to diastereofacial selective cycloaddition by employing mixtures of primary allyl alcohol (*Z*)- and (*E*)-**5**. As shown in Scheme 9, treatment of *N*-benzyl nitrone **1a** with an excess amount of a 1:1 mixture of (*Z*)-**5** and (*E*)-**5** under conditions similar to those in Scheme 3 afforded mainly the cycloadduct **7a** along with two diastereomers. In the case where a bulkier *N*-benzhydryl nitrone **1b** was used, the reaction proceeded more (*Z*)-selectively to afford only **7b** and **8b** with high diastereofacial selectivity (**7b**/**8b**), which was the same as that obtained in Scheme 3. After completion of the reaction, GLC analysis revealed that (*Z*)-**5** selectively reacted with **1b**.

Since geometrical isomerization of the allyl alcohols does not take place under the reaction conditions (Schemes 3, 4 and 8; Tables 1 and 2), transesterification may play a key role of the (*Z*)-selectivities observed (Scheme 10). Transesterification of **1** with (*Z*)- and (*E*)-**5** takes place to give intermediates **L** and **M**. Interconversion between **L** and **M** may be sufficiently rapid due to facile transesterification of esters **L** and **M** with (*E*)-**5** and (*Z*)-**5**, respectively. Moreover, cycloaddition of **M** should be unfavorable due to their steric interactions in the transition states **F** and **G**, as shown in Scheme 5. As a result, the intramolecular cycloaddition mainly proceeds from **L** via the equilibrium, giving mainly **7** and **8** by way of transition states **D** and **E** (Scheme 5). Furthermore, in the case of using **1b** having a bulky R group, **7b** was obtained in high selectivity among the four possible isomers by a combination of good (*Z*)-selection and high diastereofacial selection, as depicted in Scheme 5.

Conclusion

We have investigated diastereofacial selectivity of intramolecular cycloaddition of chiral α-allyloxycarbonyl nitrones by employing the tandem process. Although both the (*E*)-nitrone transition state and the (*Z*)-nitrone transition state can be considered, each stereochemical outcome obtained in this work is well explained by taking into account the (*Z*)-nitrone transition state (typically, Figure 4). Further applications of the present tandem cycloaddition are now currently under investigation.[15]

Experimental Section

Melting points are uncorrected. ^1H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were measured in $CDCl_3$. Mass spectra were determined at an ionizing voltage of 70 eV. Unless oterwise stated, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator. The nitrones, methyl [(phenylmethyl)imino] acetate *N*-oxide (**1a**),[5b] methyl [(diphenylmethyl)imino]acetate *N*-oxide (**2b**),[5b] methyl [(*S*)−(1-phenylethyl)imino]acetate *N*-oxide (**2c**),[16] and methyl [(*R*)−(1-phenylethyl)-imino]acetate *N*-oxide (**2d**)[16] were prepared by reported methods.

General Procedure for the Tandem Transesterification and Intramolecular Cycloaddition of the Nitrones 1 with Allyl Alcohols (5 or 6). To a stirred suspension of an allyl alcohol **5** (or **6**) and MS4A in 1,2-dichloroethane was added successively titanium tetrachloride (0.1 M solution in 1,2-dichloroethane) and a solution of nitrone **1** in 1,2-dichloroethane at room temperature. After stirring under the conditions indicated in Schemes 3, 4, 8, and 9 and Tables 1 and 2, a small amount of water was added to the mixture and the mixture was stirred for 1 h. The mixture was filtered through a pad of Celite, and then the filtrate was diluted with water, extracted with CH_2Cl_2, and dried over $MgSO_4$. After filtration, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to give cyclized products.

(1*R*,4*R*,5*R*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-phenylmethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (7a) and Its (1*S*,4*S*,5*S*)-Isomer (8a). Following general procedure, a diastereomeric mixture of **7a** and **8a** (345 mg, 81%, **7a**/**8a** = 89:11) was obtained from **1a** (217 mg, 1.1 mmol), (*Z*)-**5** (356 mg, 1.6 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 1.70 mL, 0.17 mmol), and MS4A (780 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 30:1). Further purification by column chromatography on silica gel (Et_2O−hexane, 1:2) gave pure **7a** and **8a**. **7a**: mp 98−99 °C (hexane−AcOEt); $[\alpha]^{25}_D$ +41.2 (*c* 1.53, $CHCl_3$); IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR δ 0.09 (3 H, s), 0.10 (3 H, s), 0.87 (9 H, s), 1.26 (3 H, d, J = 5.9 Hz), 3.54 (1 H, tdd, J = 8.1, 7.1, and 3.6 Hz), 3.99 (1 H, dq, J = 7.1 and 5.9 Hz), 4.00 (1 H, d, J = 13.5 Hz), 4.01 (1 H, d, J = 8.1 Hz), 4.08 (1 H, br t, J = 7.1 Hz), 4.26 (1 H, d, J = 13.5 Hz), 4.28 (1 H, dd, J = 9.9 and 8.1 Hz), 4.71 (1 H, dd, J = 9.9 and 3.6 Hz), 7.16−7.33 (5 H, m); ^{13}C NMR δ −4.7, −3.7, 17.8, 21.9, 25.6, 44.1, 66.6, 66.8, 82.9, 127.7, 128.4, 129.1, 136.0, 174.0; HRMS calcd for $C_{20}H_{31}NO_4Si$ 377.2022, found 377.2026. Anal. Calcd

(15) For example, see: (a) Tamura, O.; Mita, N.; Kusaka, N.; Suzuki, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 429. (b) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553.

(16) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212.

for $C_{20}H_{31}NO_4Si$: C, 63.63; H, 8.28; N, 3.71. Found: C, 63.49; H, 8.36; N, 3.64. **8a**: mp 102−103.5 °C (hexane−Et_2O); $[\alpha]^{25}_D$ −38.4 (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 1781 cm^{-1}; ^1H NMR δ −0.07 (3 H, s), 0.02 (3 H, s), 0.83 (9 H, s), 1.16 (3 H, d, J = 6.3 Hz), 3.47 (1 H, tdd, J = 8.3, 5.9, and 4.9 Hz), 3.89−4.03 (1 H, m), 3.98 (1 H, d, J = 8.3 Hz), 4.03 (1 H, d, J = 12.8 Hz), 4.20 (1 H, dd, J = 7.9 and 5.9 Hz), 4.27 (1 H, d, J = 12.8 Hz), 4.29 (1 H, dd, J = 9.6 and 8.3 Hz), 4.46 (1 H, dd, J = 9.6 and 4.9 Hz), 7.28−7.43 (5 H, m); HRMS calcd for $C_{20}H_{31}NO_4Si$ 377.2022, found 378.2127. Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.63; H, 8.28; N, 3.71. Found: C, 63.33; H, 8.31; N, 3.68.

(1*R*,4*R*,5*R*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-diphenylmethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (7b) and Its (1*S*,4*S*,5*S*)-Isomer (8b). Following general procedure, a diastereomeric mixture of **7b** and **8b** (359 mg, 81%, **7b**/**8b** = 89:11) was obtained from **1b** (269 mg, 1.0 mmol), (*Z*)-**5** (324 mg, 1.5 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 1.0 mL, 0.1 mmol), and MS4A (600 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 30:1). Further purification by column chromatography on silica gel (Et_2O−hexane, 1:2) gave pure **7b** and **8b**. **7b**: mp 180−182 °C (hexane−AcOEt); $[\alpha]^{25}_D$ +9.4 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 1782 cm^{-1}; ^1H NMR δ 0.05 (3 H, s), 0.06 (3 H, s), 0.86 (9 H, s), 1.06 (3 H, d, J = 5.9 Hz), 3.50 (1 H, dtd, J = 8.6, 7.9, and 3.3 Hz), 3.89 (1 H, dq, J = 7.9 and 5.9 Hz), 4.10 (1 H, d, J = 13.5 Hz), 4.11 (1 H, d, J = 8.6 Hz), 4.21 (1 H, dd, J = 9.9 and 7.9 Hz), 4.66 (1 H, dd, J = 9.9 and 3.3 Hz), 5.05 (1 H, br s), 7.15−7.58 (10 H, m); ^{13}C NMR δ −4.9, −3.4, 17.8, 21.9, 25.7, 43. 4, 65.9, 66.3, 66.7, 72.4, 82.8, 127.2, 127.6, 127.8, 127.9, 128.2, 128.8, 140.5, 140.9, 174.0; HRMS calcd for $C_{26}H_{35}NO_4Si$ 453.2336, found 453.2343. Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.76; H, 7.81; N, 3.08. **8b**: mp 228−130 °C (hexane−AcOEt); $[\alpha]^{25}_D$ −32.9 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 1782 cm^{-1}; ^1H NMR δ −0.40 (3 H, s), −0.13 (3 H, s), 0.63 (9 H, S), 1.07 (3 H, d, J = 6.3 Hz), 3.33 (1 H, tdd, J = 8.6, 5.9, and 4.3 Hz), 8.82 (1 H, dq, J = 7.9 and 6.3 Hz), 3.98 (1 H, d, J = 8.6 Hz), 4.12 (1 H, dd, J = 9.9 and 8.6 Hz), 4.18 (1 H, dd, J = 7.9 and 5.9 Hz), 4.32 (1 H, dd, J = 9.9 and 4.3 Hz), 5.09 (1 H, s), 7.06−7.50 (10 H, m); ^{13}C NMR δ −5.1, −4.8, 18.2, 21.2, 25.9, 44.4, 66.0, 67.0, 73.0, 84.0, 127.5, 127.9, 128.1, 128.3, 128.7, 129.1, 141.0, 141.7, 174.4; HRMS calcd for $C_{26}H_{35}NO_4Si$ 453.2336, found 453.2343. Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.63; H, 7.80; N, 3.09.

(1*R*,4*R*,5*R*)-4-[(*S*)-1-(3,5-Dinitrobenzoyl)oxyethyl]-2-phenylmethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (9). To a stirred solution of **7a** (200 mg, 0.53 mmol) in MeOH (10 mL) was added dropwise acetyl chloride (3 mL) at 0 °C. After stirring for 30 min under the same conditions, the mixture was concentrated in vacuo. The residue was diluted with a saturated solution of $NaHCO_3$, and the mixture was extracted with AcOEt. The organic phase was washed with a saturated solution of NaCl and dried over $MgSO_4$. After filtration, the filtrate was concentrated in vacuo to give crude (1*R*,4*R*,5*R*)-4-[(*S*)-1-hydroxyethyl]-2-phenylmethyl-3,7-dioxa-2-azabicyclo-[3.3.0] octan-8-one (131 mg). The crude product was dissolved in THF (10 mL) and then Et_3N (0.40 mL, 2.75 mmol) and 3,5-dinitrobenzoyl chloride (605 mg, 2.62 mmol) was added to the solution at room temperature. After stirring for 30 min, a saturated solution of $NaHCO_3$ (1 mL) was added to the mixture, and the mixture was vigorously stirred for 30 min. The mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with a saturated solution of NaCl and dried over $MgSO_4$. After filtration, the filtrate was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel (AcOEt−hexane) to afford **9** (172 mg, 71%): mp 154 °C (hexane−AcOEt). $[\alpha]^{25}_D$ +55.9 (*c* 0.501, $CHCl_3$); IR ($CHCl_3$) 1792, 1736 cm^{-1}; ^1H NMR δ 1.45 (3 H, d, J = 6.6 Hz), 3.60 (1 H, qd, J = 6.6 and 3.0 Hz), 4.00 (1 H, d, J = 13.0 Hz), 4.05 (1 H, d, J = 6.9 Hz), 4.21 (1 H, d, J = 13.0 Hz), 4.29 (1 H, dd, J = 10.0 and 6.9 Hz), 4.44 (1 H, t, J = 6.9 Hz), 4.49 (1 H, dd, J = 10.0 and 3.0 Hz), 5.40 (1 H, quin, J = 6.9 Hz), 7.15−7.45 (5 H, m), 9.06 (2 H, br d, J = 2.0 Hz), 9.17 (1 H, br t, J = 2.0 Hz); HRMS calcd for $C_{21}H_{19}N_3O_9$: 457.1122, found 457.1124. Anal. Calcd for $C_{21}H_{19}N_3O_9$: C, 55.45; H, 4.19; N, 9.19. Found: C, 54.98; H, 4.23; N, 9.11.

Crystal Data of 9. Colorless and column single crystals of **9** were grown in hexane−AcOEt and a single crystal (0.20 mm × 0.20 mm × 0.20 mm) was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R difractometer with filtered Cu Kα radiation (λ = 1.54178 Å) and a rotating anode generater at 296 K. The structure was solved by direct method with SHELEXS-86 and refined by the full-matrix least-squares method. All the non-hydrogen atoms were refined anisotropically, and all hydrogen refinements were located by calculation. The final cycles of the least-squares were based on 1431 observed reflections (I > 3.00s I/I) and 299 variable parameters. Formula $C_{21}H_{19}N_3O_9$, formula weight = 457.40, monoclinic, space group $P2_1$ (#4), a = 5.877(1) Å, b = 10.147(1) Å, c = 17.4531(7) Å, b = 96.234(8)°, V = 1034.6(2) Å, Z = 2, D_{calc} = 1.468 g/cm^3, R = 0.029 (R_w = 0.042), GOF = 1.18.

(1*S*,4*R*,5R,6*S*)-6-Methyl-2-(phenylmethyl)-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (12a) and Its (1*R*,4*S*,5*R*,6*S*)-Isomer (13a) (Table 1, Entry 1). Following general procedure, a diastereomeric mixture of **12a** and **13a** (40.8 mg, 100%, **12a**/**13a** = 95:5) was obtained from **1a** (22.7 mg, 0.12 mmol), (*Z*)-**6** (32.6 mg, 0.18 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 120 μL, 12 μmol), and MS4A (220 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 20:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:3) gave pure **12a** (38.8 mg) and **13a** (2.0 mg). **12a**: mp 131−132 °C (AcOEt−hexane); $[\alpha]^{25}_D$ +4.0 (*c*, 1.14, $CHCl_3$); IR ($CHCl_3$) 1784, 1732 cm^{-1}; ^1H NMR δ 1.20 (9 H, s), 1.42 (3 H, d, J = 6.4 Hz, spin saturation at δ = 3.18 → 4% NOE; at δ = 4.73 → 7% NOE), 3.18 (1 H, td, J = 7.8 and 3.3 Hz, spin saturation at δ = 1.42 → 11% NOE; at δ = 4.11 → 4% NOE; δ = 4.51 → 12% NOE), 4.04 (1 H, d, J = 13.2 Hz), 4.11 (1 H, d, J = 7.8 Hz, spin saturation at δ = 3.18 → 13% NOE), 4.23 (1 H, d, J = 13.2 Hz), 4.26 (1 H, dd, J = 11.7 and 6.3 Hz), 4.31 (1 H, dd, J = 11.7 and 5.9 Hz), 4.51 (1 H, br q, J = 6.4 Hz, spin saturation at δ = 3.18 → 10% NOE), 4.73 (1 H, qd, J = 6.4 and 3.3 Hz, spin saturation at δ = 1.42 → 15% NOE), 7.26−7.43 (5 H, m); ^{13}C NMR δ: 23.2, 27.5, 39.2, 52.1, 61.5, 67.8, 74.8, 76.6, 128.2, 128.9, 129.5, 136.2, 173.3, 178.5; HRMS calcd for $C_{19}H_{25}NO_5$ 347.1733, found 347.1736. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.74; H, 7.30; N, 3.96. **13a**: mp 130−130.5 °C (AcOEt−hexane); $[\alpha]^{25}_D$ +10.1 (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1784, 1726 cm^{-1}; ^1H NMR δ 1.19 (9 H, s), 1.59 (3 H, d, J = 6.6 Hz), 3.47 (1 H, td, J = 7.6 and 6.6 Hz), 4.05 (1 H, d, J = 13.2 Hz), 4.13 (1 H, d, J = 7.6 Hz), 4.22 (1 H, d, J = 13.2 Hz), 4.22−4.62 (3 H, m), 4.72 (1 H, quin, J = 6.6 Hz), 7.22−7.47 (5 H, m); ^{13}C NMR δ 17.1, 27.0, 38.7, 48.7, 61.6, 69.3, 75.7, 77.2, 127.8, 128.4, 129.2 135.6, 173.0, 178.1; HRMS calcd for $C_{19}H_{25}NO_5$ 347.1733, found 347.1738. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.45; H, 7.37; N, 3.95.

(1*S*,4*R*,5*R*,6*S*)-6-Methyl-2-(diphenylmethyl)-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (12b) and Its (1*R*,4*S*,5*S*,6*S*)-Isomer (13b) (Table 1, Entry 2). Following general procedure, a diastereomeric mixture of **12b** and **13b** (47.3 mg, 100%, **12b**/**13b** = 95:5) was obtained from **1b** (30.1 mg, 0.17 mmol), (*Z*)-**6** (31.7 mg, 0.17 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 110 μL, 11 μmol), and MS4A (200 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 20:1). Further purification by preparative TLC on silica gel (Et_2O−hexane, 1:1) gave pure **12b** (44.9 mg) and **13b** (2.4 mg). **12b**: mp 225−227 °C (AcOEt−hexane); $[\alpha]^{25}_D$ −11.1 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 1784, 1732 cm^{-1}; ^1H NMR δ 1.10 (9 H, s), 1.35 (3 H, d, J = 6.6 Hz), 3.17 (1 H, td, J = 8.1 and 2.3 Hz), 4.19 (1 H, dd, J = 11.7 and 6.6 Hz), 4.24 (1 H, d, J = 8.1 Hz), 4.26 (1 H, dd, J = 11.7 and 5.6 Hz), 4.54 (1 H, br q, J = 6.4 Hz), 4.68 (1 H, qd, J = 6.6 and 2.3 Hz), 5.01 (1 H, br s), 7.17−7.56 (10 H, m); ^{13}C NMR δ 22.9, 26.9, 38.7, 50.7, 61.1, 66.3, 72.5, 73.8, 76.0, 127.4, 127.5, 127.7, 127.9, 128.4, 128.9, 140.4, 140.6, 173.1, 177.9; HRMS calcd for $C_{25}H_{29}NO_5$ 423.2046, found 423.2045. Anal. Calcd for $C_{25}H_{29}NO_3$: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.02; H, 6.99; N, 3.24. **13b**: mp 188−189 °C

($CHCl_3$−hexane); $[\alpha]^{25}_D$ +12.6 (*c* 0.870, $CHCl_3$); IR ($CHCl_3$): 1790, 1725 cm^{-1}; ^1H NMR δ 1.05 (9 H, s), 1.56 (3 H, d, *J* = 5.6 Hz), 3.46 (1 H, td, *J* = 7.6 and 5.6 Hz), 4.17 (1 H, dd, *J* = 11.6 and 7.6 Hz), 4.27 (1 H, d, *J* = 7.6 Hz), 4.51 (1 H, td, *J* = 7.6 and 3.6 Hz), 4.60 (1 H, dd, *J* = 11.6 and 3.6, Hz), 4.63 (1 H, quin, *J* = 5.6 Hz), 5.01 (1 H, br s), 7.17−7.55 (10 H, m); ^{13}C NMR δ 17.2, 26.9, 38.6, 48.3, 61.7, 68.6, 72.4, 35.4, 77.3, 127.4, 127.7, 127.8, 127.9, 128.4, 128.9, 140.5, 140.5, 173.1, 178.1; HRMS calcd for $C_{25}H_{29}NO_5$ 423.2046, found: 423.2044.

(1*S*,4*R*,5*R*,6*S*)-6-Methyl-2-[(*S*)-1-phenylethyl]-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (12c) and Its (1*R*,4*S*,5*S*,6*S*)-Isomer (13c) (Table 1, Entry 3). Following general procedure, a diastereomeric mixture of **12c** and **13c** (41.6 mg, 100%, **12c**/**13c** = 92:8) was obtained from **1c** (23.8 mg, 0.16 mmol), (*Z*)-**6** (32.0 mg, 0.17 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 115 μL, 11.5 μmol), and MS4A (220 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 30:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:4) gave pure **12c** (38.3 mg) and **13c** (3.3 mg). **12c**: mp 153−153.5 °C (AcOEt−hexane); $[\alpha]^{25}_D$ −41.1 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 1782, 1732 cm^{-1}; ^1H NMR δ 1.14 (9 H, s), 1.39 (3 H, d, *J* = 6.6 Hz), 1.50 (3 H, d, *J* = 6.6 Hz), 3.06 (1 H, ddd, *J* = 9.9, 8.3, and 4.0 Hz), 4.12 (1 H, d, *J* = 8.3 Hz), 4.15−4.31 (4 H, m), 4.68 (1 H, qd, *J* = 6.6 and 4.0 Hz), 7.28−7.42 (5 H, m); ^{13}C NMR δ 22.0, 22.9, 27.5, 39.2, 53.2, 61.6, 74.7, 76.5, 128.1, 128.2, 128.8, 142.0, 173.8, 188.2; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1885. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.30; H, 7.66; N, 3.79. **13c**: mp 159−159.5 °C (AcOEt−hexane); $[\alpha]^{20}_D$ −39.7 (*c* 0.920, $CHCl_3$); IR ($CHCl_3$) 1790, 1727 cm^{-1}; ^1H NMR δ 1.22 (9 H, s), 1.50 (3 H, d, *J* = 6.6 Hz), 1.57 (3 H, d, *J* = 6.9 Hz), 3.38 (1 H, br td, *J* = 7.6 and 5.6 Hz), 3.86 (1 H, br q, *J* = 6.6 Hz), 4.14 (1 H, d, *J* = 7.9 Hz), 4.25 (1 H, dd, *J* = 11.6 and 7.6 Hz), 4.51 (1 H, td, *J* = 7.6 and 3.3 Hz), 4.60 (1 H, quin, *J* = 6.9 Hz), 4.67 (1 H, dd, *J* = 11.6 and 3.3 Hz), 7.30−7.44 (5 H, m); ^{13}C NMR δ 17.5, 21.9, 27.5, 39.2, 48.2, 53.2, 62.3, 64.2, 69.6, 75.8, 128.1, 128.6, 129.4, 141.9, 173.8, 178.6; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1893. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.07; H, 7.63; N, 3.78.

(1*S*,4*R*,5*R*,6*S*)-6-Methyl-2-[(*R*)-1-phenylethyl]-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (12d) and Its (1*R*,4*S*,5*S*,6*S*)-Isomer (13d) (Table 1, Entry 4). Following general procedure, a diastereomeric mixture of **12d** and **13d** (35.6 mg, 100%, **12d**/**13d** = 93:7) was obtained from **1d** (20.4 mg, 98 μmol), (*Z*)-**6** (32.0 mg, 0.17 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 100 μL, 10 μmol), and MS4A (210 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 20:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:4) gave pure **12d** (33.1 mg) and **13d** (2.5 mg). **12d**: mp 119−119.5 °C (AcOEt−hexane); $[\alpha]^{25}_D$ +47.1 (*c* 0.850, $CHCl_3$); IR ($CHCl_3$) 1790, 1732 cm^{-1}; ^1H NMR δ 1.22 (9 H, s), 1.34 (3 H, d, *J* = 6.6 Hz), 1.49 (3 H, d, *J* = 6.3 Hz), 3.09 (1 H, td, *J* = 7.8 and 2.3 Hz, spin saturation at δ = 1.34 → 9% NOE; at δ = 4.51 → 3% NOE), 3.90 (1 H, q, *J* = 6.3 Hz), 4.10 (1 H, d, *J* = 7.8, Hz, spin saturation at δ = 3.09 → 10% NOE), 4.30 (1 H, dd, *J* = 11.7 and 6.3 Hz), 4.35 (1 H, dd, *J* = 11.7 and 5.6 Hz), 4.51 (1 H, br q, *J* = 6.4 Hz), 4.68 (1 H, qd, *J* = 6.6 and 2.3 Hz, spin saturation at δ = 1.34 → 14% NOE), 7.26−7.45 (5 H, m, Ar−H); ^{13}C NMR δ 21.7, 22.9, 27.0, 38.8, 50.2, 61.2, 64.0, 66.3, 73.8, 75.9, 127.6, 128.1 128.9, 141.5, 173.3, 177.9; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1882. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.29; H, 7.64; N, 3.83. **13d**: mp 148−149 °C (AcOEt−hexane); $[\alpha]^{25}_D$ +50.6 (*c* 1.24, $CHCl_3$); IR ($CHCl_3$): 1782, 1728 cm^{-1}; ^1H NMR δ 1.13 (9 H, s), 1.52 (3 H, d, *J* = 6.6 Hz), 1.55 (3 H, d, *J* = 6.6 Hz), 3.36 (1 H, dt, *J* = 7.6 and 6.6 Hz), 4.11 (1 H, d, *J* = 7.6 Hz), 4.11−4.35 (3 H, m), 4.48 (1 H, dd, *J* = 11.2 and 3.3 Hz), 4.69 (1 H, quin, *J* = 6.6 Hz), 7.25−7.45 (5 H, m); ^{13}C NMR δ 17.4, 21.7, 26.9, 38.6, 49.9, 61.8, 67.2, 75.6, 77.3, 77.8, 127.5, 127.7, 128.3, 141.5, 173.3, 178.1; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1893. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.40; H, 7.62; N, 3.81.

(1*S*,4*S*,5*R*,6*S*)-6-Methyl-2-(phenylmethyl)-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (14a) and Its (1*R*,4*R*,5*S*,6*S*)-Isomer (15a) (Table 2, Entry 1). Following general procedure, a diastereomeric mixture of **14a** and **15a** (75.0 mg, 71%, **14a**/**15a** = 40:60) was obtained from **1a** (59.1 mg, 0.31 mmol), (*E*)-**6** (85.5 mg, 0.46 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 300 μL, 30 μmol), and MS4A (410 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 30:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:3) gave pure **14a** (30.0 mg) and **15a** (45.0 mg). **14a**: mp 99−99.5 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −25.1 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 1774, 1730 cm^{-1}; ^1H NMR δ 1.19 (9 H, s), 1.43 (3 H, d, *J* = 6.6 Hz), 2.90 (1 H, dt, *J* = 8.2 and 4.0 Hz), 3.88 (1 H, d, *J* = 8.2 Hz), 4.07−4.26 (3 H, m), 4.17 (1 H, d, *J* = 14.2 Hz), 4.30 (1 H, d, *J* = 14.2 Hz), 4.69 (1 H, qd, *J* = 6.6 and 4.0 Hz,), 7.25−7.41 (5 H, m); ^{13}C NMR δ 22.0, 27.1, 38.7, 54.5, 63.6, 79.9, 81.0, 127.5, 128.2, 129.0, 136.1, 172.0, 178.0; HRMS calcd for $C_{19}H_{25}NO_5$ 347.1732, found 347.1733. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.45; H, 7.20; N, 4.02. **15a**: mp 80−81 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −56.3 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 1772, 1726 cm^{-1}; ^1H NMR δ 1.19 (9 H, s), 1.49 (3 H, d, *J* = 6.6 Hz, spin saturation at δ = 4.74 → 8% NOE), 3.18 (1 H, ddd, *J* = 7.9, 6.6, and 5.3 Hz), 4.08 (1 H, d, *J* = 7.9 Hz, spin saturation at δ = 3.18 → 12% NOE), 4.12 (1 H, dd, *J* = 11.6 and 5.3 Hz), 4.22 (1 H, d, *J* = 13.9 Hz), 4.25 (1 H, dd, *J* = 11.6 and 6.6 Hz), 4.32 (1 H, d, *J* = 13.9 Hz), 4.44 (1 H, br q, *J* = 5.3 Hz), 4.74 (1 H, quin, *J* = 6.6 Hz, spin saturation at δ = 3.18 → 14% NOE), 7.27−7.43 (5 H, m); ^{13}C NMR d: 17.1, 27.1, 38.7, 49.7, 64.3, 74.8, 76.5, 127.5, 128.3, 128.9 136.3, 172.6 178.2; HRMS calcd for $C_{19}H_{25}NO_5$ 347.1733, found 347.1729. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.80; H, 7.31; N, 4.00.

(1*S*,4*S*,5*R*,6*S*)-6-Methyl-2-[(*S*)-1-phenylethyl]-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (14c) and Its (1*R*,4*R*,5*S*,6*S*)-Isomer (15c) (Table 2, Entry 3). Following general procedure, a diastereomeric mixture of **14c** and **15c** (90.7 mg, 100%, **14c**/**15c** = 8:92) was obtained from **1c** (51.9 mg, 0.25 mmol), (*E*)-**6** (70.0 mg, 0.38 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 750 μL, 75 μmol), and MS4A (440 mg) after purification by column chromatography on silica gel (CH_2Cl_2−Et_2O, 30:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:6) gave pure **14c** (7.3 mg) and **15c** (83.4 mg). **14c**: mp 90−92 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −30.8 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 1771, 1728 cm^{-1}; ^1H NMR δ 1.18 (9 H, s), 1.34 (3 H, d, *J* = 6.3 Hz), 1.52 (3 H, d, *J* = 6.6 Hz), 2.70 (1 H, ddd, *J* = 7.9, 4.0, and 3.3 Hz), 3.77 (1 H, d, *J* = 7.9 Hz), 4.04 (1 H, dd, *J* = 10.9 and 4.0 Hz), 4.19 (1 H, dt, *J* = 5.9 and 4.0 Hz), 4.27 (1 H, dd, *J* = 10.9 and 5.9 Hz), 4.36 (1 H, br), 4.63 (1 H, qd, *J* = 6.6 and 3.3 Hz), 7.24−7.46 (5 H, m); ^{13}C NMR δ 21.5, 22.1, 27.1, 38.7, 53.8, 63.5, 79.8, 80.3, 127.6 128.2, 128.4, 140.5, 172.4, 178.0; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1890. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.26; H, 7.55; N, 3.79. **15c**: mp 101−101.5 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −75.0 (*c* 0.800, $CHCl_3$); IR ($CHCl_3$) 1782, 1728 cm^{-1}; ^1H NMR δ 1.18 (9 H, s), 1.47 (3 H, d, *J* = 6.3 Hz), 1.51 (3 H, d, *J* = 6.3 Hz, spin saturation at δ = 4.69 → 8% NOE), 3.15 (1 H, dt, *J* = 6.3 and 5.6 Hz, spin saturation at δ = 4.69 → 12% NOE), 4.10−4.31 (3 H, m), 4.13 (1 H, br dd, *J* = 10.9 and 5.6 Hz), 4.42 (1 H, br q, *J* = 5.6 Hz), 4.69 (1 H, quin, *J* = 6.3 Hz, spin saturation at δ = 1.51 → 5% NOE; at δ = 3.15 → 30% NOE), 7.22−7.39 (5 H, m); ^{13}C NMR δ: 16.8, 21.7, 27.1, 38.7, 49.3, 64.9, 74.2, 126.9, 127.5, 128.6, 142.8, 172.8, 178.1; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1890. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.34; H, 7.47; N, 3.84.

(1*S*,4*S*,5*R*,6*S*)-6-Methyl-2-[(*R*)-1-phenylethyl]-4-pivaloyloxymethyl-3,7-dioxa-2-azabicyclo[3.3.0]octan-8-one (14d) and Its (1*R*,4*R*,5*S*,6*S*)-Isomer (15d) (Table 2, Entry 4). Following general procedure, a diastereomeric mixture of **14d** and **15d** (81.9 mg, 91%, **14d**/**15d** = 63:37) was obtained from **1d** (51.9 mg, 0.25 mmol), (*E*)-**6** (70.0 mg, 0.38 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 750 μL, 75 μmol), and MS4A (450 mg) after purification by column

chromatography on silica gel ($CH_2Cl_2-Et_2O$, 30:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:2) gave pure **14d** (51.6 mg) and **15d** (30.3 mg). **14d**: mp 80−81 °C (Et_2O−hexane); $[\alpha]^{25}_D$ +56.6 (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 1771, 1728 cm^{-1}; ^1H NMR δ 0.93 (9 H, s), 1.32 (3 H, d, J = 6.6 Hz), 1.44 (3 H, d, J = 6.6 Hz), 2.81 (1 H, ddd, J = 5.6, 4.4, and 1.7 Hz), 4.03−4.22 (5 H, m), 4.54 (1 H, qd, J = 6.6 and 1.7 Hz), 7.15−7.32 (5 H, m); ^{13}C NMR δ 21.0, 22.4, 27.0, 38.7, 52.3, 63.7, 64.2, 78.9, 81.9, 127.1, 127.5, 128.5, 142.4, 172.6, 177.8; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1898. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.43; H, 7.62; N, 3.83. **15d**: mp 101 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −33.9 (*c* 1.29, $CHCl_3$); IR ($CHCl_3$) 1772, 1726 cm^{-1}; ^1H NMR δ 1.21 (9 H, s), 1.46 (3 H, d, J = 6.6 Hz), 1.47 (3 H, d, J = 6.3 Hz, spin saturation at δ = 4.61 → 6% NOE), 2.94 (1 H, ddd, J = 7.9, 6.3, and 4.8 Hz, spin saturation at δ = 4.61 → 7% NOE), 4.05 (1 H, dd, J = 11.1 and 4.8 Hz), 4.2−4.6 (3 H, m), 4.61 (1 H, quin, J = 6.3 Hz, spin saturation at δ = 1.43 → 16% NOE; at δ = 2.94 → 13% NOE), 7.26−7.49 (5 H, m); ^{13}C NMR δ 16.8, 21.8, 27.1, 38.7, 50.0, 64.0, 64.1, 64.8, 74.27, 74.34, 127.6, 128.1, 128.3, 141.8, 172.8, 178.5; HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1884. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.80; H, 7.65; N, 3.86.

(1*S*,4*R*,5*S*)-4-Phenyl-2-[(*S*)-1-phenylethyl]-3,7-dioxa-2-aza-bicyclo[3.3.0]octan-8-one (17) and Its (1*R*,4*S*,5*R*)-Isomer (18). Following general procedure, a diastereomeric mixture of **17** and **18** (28.1 mg, 91%, **17**/**18** = 36:64) was obtained from **1c** (20.7 mg, 0.10 mmol), (*Z*)-**16** (20.1 mg, 0.15 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 100 μL, 10 μmol), and MS4A (300 mg) after purification by column chromatography on silica gel ($CH_2Cl_2-Et_2O$, 40:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:3) gave pure **17** (10.1 mg) and **18** (18.0 mg). **17**: mp 234−236 °C (AcOEt−hexane); $[\alpha]^{25}_D$ −155.7 (*c* 0.730, $CHCl_3$); IR ($CHCl_3$) 1790 cm^{-1}; ^1H NMR δ 1.47 (3 H, d, J = 6.3 Hz), 3.51 (1 H, br qd, J = 7.9 and 1.3 Hz), 3.60 (1 H, dd, J = 10.2 and 1.3 Hz), 3.90 (1 H, dd, J = 10.2 and 7.9 Hz), 4.00 (1 H, q, J = 6.3 Hz), 4.07 (1 H, d, J = 7.9 Hz), 5.46 (1 H, d, J = 7.9 Hz), 7.17−7.41 (10 H, m); ^{13}C NMR δ 21.8, 45.4, 63.7, 66.5, 66.6, 81.3, 126.8, 127.5, 128.0, 128.6, 128.8, 128.9, 134.7, 141.8, 174.4; HRMS calcd for $C_{19}H_{19}NO_3$: 309.1365, found 309.1366. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.54; H, 6.22; N, 4.46. **18**: mp 203−205 °C (AcOEt−hexane); $[\alpha]^{25}_D$ +75.0 (*c* 0.640, $CHCl_3$); IR ($CHCl_3$) 1779 cm^{-1}; ^1H NMR δ 1.48 (3 H, d, J = 6.3 Hz), 3.47 (1 H, qd, J = 7.3 and 2.6 Hz), 3.66 (1 H, dd, J = 10.2 and 2.6 Hz), 3.94 (1 H, dd, J = 10.2 and 7.3 Hz), 4.15 (1 H, d, J = 7.3 Hz), 4.25 (1 H, br), 5.21 (1 H, d, J = 7.3 Hz), 7.11−7.44 (10 H, m); ^{13}C NMR δ 22.1, 47.2, 65.3, 66.8, 81.5, 126.6, 127.6, 127.8, 128.4, 128.5, 128.7, 135.1, 141.8, 174.0; HRMS calcd for $C_{19}H_{19}NO_3$: 309.1365, found 309.1362. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.47; H, 6.24; N, 4.49.

(1*S*,4*S*,5*S*)-4-Phenyl-2-[(*S*)-1-phenylethyl]-3,7-dioxa-2-aza-bicyclo[3.3.0]octan-8-one (19) and Its (1*R*,4*S*,5*R*)-Isomer (20). Following general procedure, a diastereomeric mixture of **19** and **20** (70.3 mg, 94%, **19**/**20** = 20:80) was obtained from **1c** (50.0 mg, 0.24 mmol), (*E*)-**16** (48.6 mg, 0.36 mmol), titanium tetrachloride (0.1 M solution in 1,2-dichloroethane, 240 μL, 24 μmol), and MS4A (400 mg) after purification by column chromatography on silica gel ($CH_2Cl_2-Et_2O$, 40:1). Further purification by column chromatography on silica gel (AcOEt−hexane, 1:3) gave pure **19** (14.1 mg) and **20** (56.2 mg). **19**: mp 128−130 °C (AcOEt−hexane); IR ($CHCl_3$) 1779 cm^{-1}; ^1H NMR δ 1.56 (3 H, d, J = 6.9 Hz), 3.06 (1 H, dtd, J = 9.2, 6.9, and 3.3 Hz), 3.81 (1 H, d, J = 9.2 Hz), 4.21−4.33 (3 H, m), 4.75 (1 H, d, J = 6.9 Hz), 7.17−7.42 (10 H, m); ^{13}C NMR δ 21.1, 51.8, 64.4, 69.2, 84.8, 126.5, 127.7, 128.1, 128.5, 128.7, 129.0, 140.0, 173.8; HRMS calcd for $C_{19}H_{19}NO_3$ 309.1365, found: 309.1365. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.59; H, 6.27; N, 4.43. **20**: mp 92−94 °C (Et_2O−hexane); IR ($CHCl_3$) 1786 cm^{-1}; ^1H NMR δ 1.71 (3 H, d, J = 6.6 Hz), 3.36 (1 H, br m), 4.27 (1 H, d, J = 8.5 Hz), 4.36 (1 H, q, J = 6.6 Hz), 4.45 (1 H, dd, J = 10.5 and 2.6 Hz), 4.49 (1 H, dd, J = 10.5 and 5.5 Hz), 4.97 (1 H, d, J = 6.9 Hz), 7.37−7.57 (10 H, m); ^{13}C NMR δ 19.8, 50.2, 64.7, 68.5, 84.7, 126.4, 127.7, 128.0, 128.4, 128.5, 128.7, 141.5, 173.8; HRMS calcd for $C_{19}H_{19}NO_3$ 309.1365, found: 309.1362. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 6.25; N, 4.45.

The Tandem Transesterification and Intramolecular Cycloaddition of the Nitrone 1a with a Geometrical Mixture of Allyl Alcohols (*Z*)-5 and (*E*)-5. Following the general procedure, a 76:11:13 mixture of three diastereomers **7a**, **8a**, **10a**, or **11a** (52.4 mg, 89%) was obtained from **1a** (30.0 mg, 0.16 mmol), **5** [50.4 mg, 0.23 mmol for each (*Z*)-**5** and (*E*)-**5**], 0.1 M titanium tetrachloride in 1,2-dichloroethane (155 μL, 15 μmol), and MS4A (300 mg) after column chromatography on silica gel with $CH_2Cl_2-Et_2O$ (30:1). The daistereomeric distribution of the products were determined by comparing doublets due to methyl groups in the ^1H NMR spectrum with those of **7a** and **8a** (see Supporting Information). ^1H NMR ($CDCl_3$, 270 MHz) δ −0.07 (3 H × 76/100, s), 0.02 (3 H × 11/100 + 13/100, s), 0.05 (3 H × 13/100, s), 0.09 (3 H × 76/100, s), 0.10 (3 H × 76/100, s), 1.11 (3 H × 13/100, d, J = 5.9 Hz), 1.16 (3 H × 11/100, d, J = 6.3 Hz), 1.26 (3 H × 13/100, d, J = 5.9 Hz), 3.36 (1 H × 13/100), 3.47 (1 H × 11/100, tdd, J = 8.3, 5.9, and 4.9 Hz), 3.54 (1 H × 76/100, tdd, J = 8.1, 7.1, and 3.6 Hz), 3.91−4.12 (3 H, m), 4.16−4.37 (2 H, m), 4.45 (1 H × 13/100, dd, J = 9.6 and 7.9 Hz), 4.46 (1 H × 11/100, dd, J = 9.6 and 4.9 Hz), 4.71 (1 H × 76/100, dd, J = 9.9 and 3.6 Hz), 7.24−7.46 (5 H, m).

The Tandem Transesterification and Intramolecular Cycloaddition of the Nitrone 1b With a Geometrical Mixture of Allyl Alcohols (*Z*)-5 and (*E*)-5. Following the general procedure, an 89:11 mixture of two diastereomers **7b** and **8b** (45.0 mg, 87%) was obtained from **1b** (30.0 mg, 0.11 mmol), **5** [36.0 mg, 0.17 mmol for each (*Z*)-**5** and (*E*)-**5**], 0.1 M titanium tetrachloride in 1,2-dichloroethane (111 μL, 10 μmol), and MS4A (300 mg) after column chromatography on silica gel with $CH_2Cl_2-Et_2O$ (40:1). The daistereomeric distribution of the products were determined by comparing doublets due to methyl groups in the ^1H NMR spectrum with those of **7b** and **8b** (see, Supporting Information). ^1H NMR ($CDCl_3$, 270 MHz) δ −0.40 (3 H × 11/100, s), −0.13 (3 H × 11/100, s), 0.05 (3 H × 89/100, s), 0.06 (3 H × 89/100, s), 0.63 (9 H × 11/100, s), 0.86 (9 H × 89/100, s), 1.06 (3 H × 89/100, d, J = 5.9 Hz), 1.07 (3 H, d × 11/100, J = 6.3 Hz), 3.33 (1 H, tdd × 11/100, J = 8.6, 5.9, and 4.3 Hz), 3.50 (1 H × 89/100, dtd, J = 8.6, 7.9, and 3.3 Hz), 3.89 (1 H × 89/100, dq, J = 7.9, 5.9 Hz), 4.10 (1 H × 89/100, d, J = 13.5 Hz), 4.11 (1 H × 89/100, d, J = 8.6 Hz), 4.21 (1 H × 89/100, dd, J = 9.9 and 7.9 Hz), 3.80−4.20 (3 H × 11/100, m), 4.32 (1 H × 11/100, dd, J = 9.9 and 4.3 Hz), 4.66 (1 H × 89/100, dd, J = 9.9 and 3.3 Hz), 5.05 (1 H × 89/100, br s), 5.09 (1 H × 11/100, s), 7.06−7.58 (10 H, m).

Supporting Information Available: Further discussion for (*Z*)-nitrone transition state vs (*E*)-nitrone transition state containing computational results (Cartesian coodinates and total energies) of (*Z*)- and (*E*)-nitrone transition states of cycloaddtion of **3** (R = Bn, R′ = H) derived from **1a** and cyclohex-2-en-1-ol; crystallographic data of compound **9** (CIF); experimental procedure for (*Z*)-**5**, (*E*)-**5**, (*Z*)-**6**, and (*E*)-**6**; ^1H NMR of **13b**, a mixture of **7a**, **8a**, **10a,** or **11a** obtained by reaction of **1a** with a 1:1 mixture of (*Z*)-**5** and (*E*)-**5**, a mixture of **7b** and **8b** obtained by reaction of **1b** with a 1:1 mixture of (*Z*)-**5** and (*E*)-**5**, (*Z*)-**5**, (4*S*,*Z*)-4-*tert*-butyldimethylsilyloxy-1-pivaloyloxy-2-pentene, (*Z*)-**6**, (*E*)-**5**, (4*S*,*E*)-4-*tert*-butyldimethylsilyloxy-1-pivaloyloxy-2-pentene, and (*E*)-**6**. This material is available free of charge via Internet at http://pubs.acs.org.

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