Design, Synthesis, and 1,3-Dipolar Cycloaddition of (5*R*)- [and (5*S*)]-5,6-Dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-Oxides as Chiral (*E*)-Geometry-Fixed α-Alkoxycarbonylnitrones

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Optically pure (5*R*)- [and (5*S*)]-5,6-dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-oxides [(5*R*)- and (5*S*)-**2**] were designed as chiral (*E*)-geometry-fixed α-alkoxycarbonylnitrones **1**. The nitrones (5*R*)- and (5*S*)-**2** were synthesized by three-step oxidation of (*R*)- and (*S*)-phenylglycinols [(*R*)- and (*S*)-**3**], condensation of the resulting (*R*)- and (*S*)-2-hydroxylamino-2-phenylethanols [(*R*)- and (*S*)-**5**] with glyoxylic acid, and cyclization of the intermediary nitrones (*R*)- and (*S*)-**6b**. The nitrone (5*R*)-**2** reacted with olefins **7**−**14** under mild conditions to afford the corresponding cycloadducts **15**−**22** as the main products via the least sterically demanding exo modes. Cycloadduct **30** obtained from (5*S*)-**2** and cyclopentadiene was effectively elaborated to (1*S*,4*S*,5*R*)-4-benzyloxycarbonylamino-2-oxabicyclo[3.3.0]oct-7-en-3-one (**28**), the key synthetic intermediate of carbocyclic polyoxin C.

Introduction

Cycloadditions of nitrones with alkenes form carbon−carbon bonds and carbon−oxygen bonds in one step to give cycloadducts having isoxazolidine ring systems.[1] Reductive cleavage of the nitrogen−oxygen bonds of the cycloadducts provides 3-amino alcohols.[2] Thus, nitrone cycloaddition is quite a useful method for construction of nitrogen-containing carbon frameworks. Mechanistically, the nitrone cycloaddition is a $[4\pi + 2\pi]$-type concerted process similar to the Diels−Alder reaction.[3] One of the problems in nitrone cycloaddition compared to the Diels−Alder reaction is the possibility of geometrical isomerization of the nitrone moiety during the cycloaddition reaction. In particular, nitrones **1** having electron-withdrawing groups (e.g., esters) are known to exist as equilibrating mixtures of (*E*)-**1** and (*Z*)-**1** in solution even at room temperature (eq 1).[4] As a result, cycloadditions of nitrones **1** with alkenes often give mixtures of diastereomers, although they have been utilized for the syntheses of natural products and compounds of biological interest.[5,6] Moreover, the isomerization makes it difficult to predict the stereochemistry of the main cycloadduct and makes analysis of the transition states complicated because a couple of transition states give the same stereoisomer. For example, as shown in eq 2, both the (*E*)-nitrone-endo and the (*Z*)-nitrone-exo transition states afford the same stereochemical outcome.[5c] To eliminate these ambiguities, we recently reported the design, synthesis, and reactions of 5,6-dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-oxide (**2**) as a chiral (*E*)-geometry-fixed α-alkoxycarbonylnitrone (eq 3).[7,8] We present here a full account of this work and an application of the cycloaddition of **2** to the key synthetic intermediate of carbocyclic polyoxin C.

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(1) For reviews of cycloadditions of nitrones, see: (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173. (b) Deshong, P.; Lander, S. W., Jr.; Leginus, J. M.; Dicken, C. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 87−128. (c) Carruthers, W. *Cycloaddition Reaction in Organic Synthesis*; Pergamon Press: Oxford, 1990. (d) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 239−270. (e) 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, Chapter 9, pp 1069−1109. (f) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

(2) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425.

(3) Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, U.K., 1986; pp 256−262.

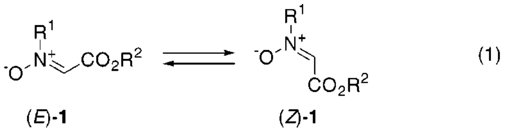
(4) (a) Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407−1410. (b) Inouye, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 244−247. (c) Inouye, Y.; Takaya, K.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3541−3542. (d) Aurich, H. G.; Franzke, M.; Kesselheim, H. P. *Tetrahedron* **1992**, *48*, 663−668. In general, for the case of a nitrone having no electron-withdrawing group at the nitrone−carbon atom, the (*Z*) form is sterically more stable than the corresponding (*E*) isomer. For example, N-alkylation of an (*E*)-*O*-trimethylsilylated oxime initially gives (*E*)-nitrone as a major isomer, which in turn isomerizes to pure (*Z*) isomer during purification. See: (e) LeBel, N. A.; Balasubramaiain, N. *Tetrahedron Lett.* **1985**, *26*, 4331−4334.

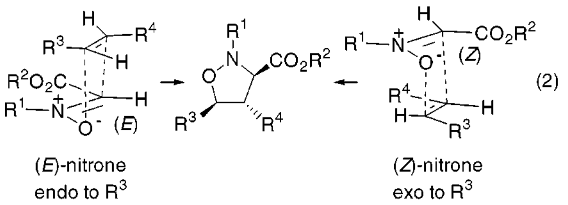
(5) For recent examples, see: (a) Baumgartner, H.; O'Sullivan, A. C.; Schneider, J. *Heterocycles* **1997**, *45*, 1537−1549. (b) Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28−36. (c) Ondrus, V.; Orsag, M.; Fisera, L.; Pronayova, N. *Tetrahedron* **1999**, *55*, 10425−10436.

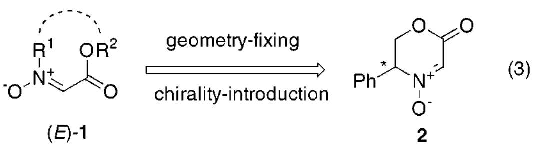
(6) For efforts to control the geometry of the nitrone **1**, see: (a) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49−50. (b) Tokunaga, Y.; Ihara, M.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37*, 6157−6160. (c) Tamura, O.; Mita, N.; Gotanda, K.; Yamada, K.; Nakano, T.; Katagiri, R.; Sakamoto, M. *Heterocycles* **1997**, *46*, 95−99. Quite recently, asymmetric reaction of nitrone **1** with vinyl ethers was reported. Although high enantiomeric excesses were obtained in the reactions, diastereoselectivites were not high enough. See: (d) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353−2360.

(7) For preliminary communication, see: Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861−1862.

10.1021/jo000903a CCC: $19.00



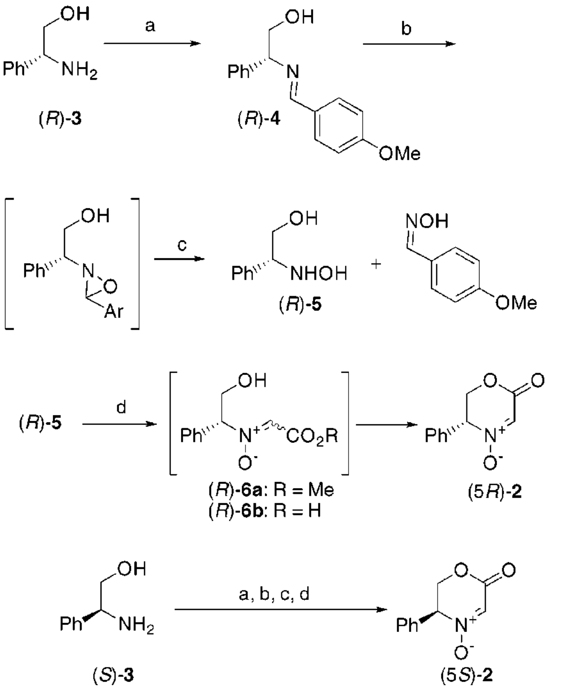




Results and Discussion

1. Synthesis of (5*R*)- [and (5*S*)]-5,6-Dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-Oxides [(5*R*)- and (5*S*)-2]. Our synthesis of the chiral (*E*)-geometry-fixed nitrone (5*R*)-**2** began with three-step oxidation of (*R*)-phenylglycinol [(*R*)-**3**] to the corresponding hydroxylamine [(*R*)-**5**], as shown in Scheme 1.[9−11] Thus, imine formation of (*R*)-**3** with *p*-methoxybenzaldehyde and oxidation of the resulting imine (*R*)-**4** with *m*-chloroperbenzoic acid gave the corresponding oxaziridine,[9] which was treated with hydroxylamine hydrochloride in methanol to furnish the chiral hydroxylamine (*R*)-**5** in an excellent overall yield. Conversion of the hydroxylamine (*R*)-**5** to the cyclic nitrone (5*R*)-**2** was next examined. Heating hydroxylamine (*R*)-**5** with methyl glyoxylate in boiling benzene followed by treatment of the resulting nitrone (*R*)-**6a** with 1,3-bis(isothiocyanate)tetrabutyldistannoxane[12] for intramolecular transesterification gave the desired nitrone (5*R*)-**2** as a crystalline material in 45% yield (Table 1, entry 1). The yield was improved to 64% by the use of anhydrous *p*-toluenesulfonic acid (TsOH) for the cyclization of (*R*)-**6a** instead of the tin catalyst (entry 2). The best result was obtained by employing glyoxylic acid. Thus, treatment of the hydroxylamine (*R*)-**5** with a 40% aqueous solution of glyoxylic acid in dichloromethane followed by azeotropic removal of water afforded nitrone carboxylic acid (*R*)-**6b** in dichloromethane, which, without isolation, was cyclized with TsOH, giving rise to (5*R*)-**2** in 85% yield (entry 3). In the same manner, the antipodal (5*S*)-**2** could be readily prepared from (*S*)-phenylglycinol [(*S*)-**3**]. The structures of the nitrones (5*R*)- and (5*S*)-**2** were unambiguously confirmed by an X-ray diffraction of (5*S*)-**2** (see the Supporting Information). To our knowledge, this is the first case of syntheses of both enantiomers of optically pure six-membered-ring nitrone.[13−15] Nitrones (5*R*)- and (5*S*)-**2** can be handled under ambient air and can be stored for several months in a refrigerator.

Scheme 1[a]



[a] Key: (a) *p*-methoxybenzaldehyde, toluene, reflux; (b) *m*-CPBA, CH_2Cl_2; (c) $NH_2OH\cdot HCl$, MeOH, 93% from (*R*)-**3**; (d) see Table 1.

Table 1. Preparation of (5*R*)-2 from (*R*)-5

entry	conditions	yield (%)
1	$OHC-CO_2Me$, C_6H_6, reflux, then $[(SCN)^nBu_2Sn]_2O$, MS4A	45
2	$OHC-CO_2Me$, C_6H_6, reflux, then 1 equiv of TsOH, 70 °C	64
3	40% $OHC-CO_2H$(aq), CH_2Cl_2, rt, then 1 equiv of TsOH, reflux	85

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(8) For closely related five-membered-ring nitrones, see: (a) Katagiri, N.; Sato, H.; Kurimoto, A.; Okada, M.; Yamada, A.; Kaneko, C. *J. Org. Chem.* **1994**, *59*, 8101−8106. (b) Katagiri, N.; Okada, M.; Kaneko, C. *Tetrahedron Lett.* **1996**, *37*, 1801−1804. (c) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Chem. Commun.* **1996**, 2137−2138. (d) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725−5746.

(9) For the three-step oxidation of primary amine into hydroxylamine, see: Połónski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453−2456. Because oxidation of secondary amines leading to nitrones is known, direct oxidation of (5*R*)-perhydro-5-phenyloxazin-2-one to the nitrone (5*R*)-**2** was also attempted. However, the oxidation with $Na_2WO_4-H_2O_2$[10a] or $SeO_2-H_2O_2$[10b] gave only a low yield of (5*R*)-**2** (<10%) probably because of its instability under the oxidation conditions. After our communication,[6] it was reported that (5*R*)-perhydro-5-phenyloxazin-2-one can be oxidized with dimethyl dioxirane to afford (5*R*)-**2** as an orange oil.[11]

(10) (a) Murahashi, S.; Shiota, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265−271. (b) Murahashi, S.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2382−2385. See also: (c) Joseph, R.; Sudalai, A.; Ravindranathan, T. *Synlett* **1995**, 1177−1178.

(11) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819−6822.

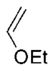
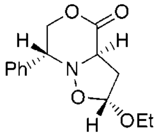
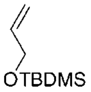
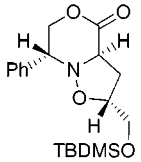
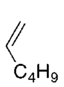
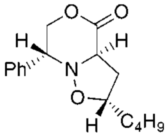
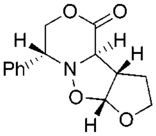
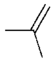
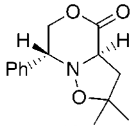
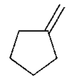
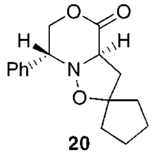
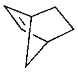
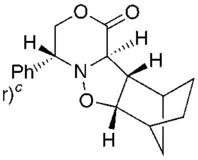
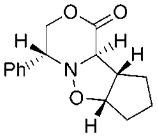
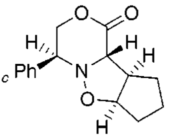
(12) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311.

(13) Although several types of chiral five-membered-ring nitrones are known,[14] optically pure six-membered-ring nitrone is quite rare. See: Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554−560.

(14) For examples of optically pure five-membered-ring nitrones, see: (a) Bernet, B.; Krawczyk, E.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 2299−2311. (b) Bérranger, T.; André-Barrès, C.; Kobayakawa, M.; Langlois, Y. *Tetrahedron Lett.* **1993**, *34*, 5079−5082. (c) Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523−5526. (d) Langlois, Y. *Curr. Org. Chem.* **1998**, *2*, 1−18 and references therein. (f) McCaig, A. E.; Wightman, R. G. *Tetrahedron Lett.* **1993**, *34*, 3939−3942. (g) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274−5275. (h) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949−952. (i) Brandi, A.; Cicchi, S.; Goti, A.; Koprowski, M.; Pietrusiewicz, K. M. *J. Org. Chem.* **1994**, *59*, 1315−1318. (j) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806−6812. (k) Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Synlett* **1997**, 25−26. (l) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863−1864. (m) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123−125. See also refs 8b−d.

2. Intermolecular Cycloaddition of the Cyclic Nitrones (5*R*)- and (5*S*)-2 with Alkenes 7−14. With both enantiomers of the cyclic nitrones in hand, we next examined their reactivity and stereoselectivity in cycloadditions, using nitrone (5*R*)-**2**. As shown in Table 2, the nitrone (5*R*)-**2** reacted with various alkenes **7**−**14** under mild conditions from the less hindered side in an exo mode to give cycloadducts **15**−**22** as the main products. Typically, treatment of nitrone (5*R*)-**2** with ethyl vinyl ether (**7**) in benzene at room temperature gave cycloadduct **15** along with small amounts of other stereoisomers (entry 1). Reactions of nitrone (5*R*)-**2** with other terminal alkenes **8**, **9**, and 2,3-dihydrofuran (**10**) also gave products **16**−**18** bearing the same stereochemical sense as that of **15** accompanied by stereoisomers (entries 2−4). In contrast, cycloaddition with 1,1-disubstituted alkenes **11** and **12** and with cyclic alkenes **13** and **14** was much cleaner and gave cycloadducts **19**−**21** and (9*R*)-**22** as single stereoisomers, respectively (entries 5−8). Reaction of the antipodal nitrone (5*S*)-**2** with cyclopentene **14**, of course, gave the enantiomeric cycloadduct (9*S*)-**22**. In sharp contrast to the above reactions, the nitrone (5*R*)-**2** did not react with *N*-methylmaleimide at all. This fact clearly shows that the cycloaddition of the nitrone seems to be a LUMO−nitrone-controlled cycloaddition.[1f] The cycloadducts of the nitrone (5*R*)-**2** are conformationally rigidified by the six-membered rings, and their stereostructures could therefore be readily assigned on the basis of the NOE difference spectra of **15**, **16**, **19**, **20**, and **22** or the NOESY spectrum of **21**, as depicted in Figure 1.

Table 2. Cycloaddition of (5*R*)-2 with Alkenes[a]

Entry	Alkene	Conditions	Yield (%) (ratio)	Main Product
1	 **7**	rt,16 h	87 (83:8:9)[b]	 **15**
2	 **8**	60 °C, 12 h	89 (75:5:11:9)[b]	 **16**
3	 **9**	60 °C, 8 h	86 (85:7:8)[b]	 **17**
4	 **10**	rt to 50°C 19 h	83 (87:13)[b]	 **18**
5	 **11**	60 °C, 25 h	95 (single isomer)[c]	 **19**
6	 **12**	rt to 50°C 32 h	87 (single isomer)[c]	 **20**
7	 **13**	rt, 9 h	92 (single isomer)[c]	 **21**
8	 **14**	rt, 30 h	90 (single isomer)[c]	 (9*R*)-**22**
9[d]	 **14**	rt, 30 h	88 (single isomer)[c]	 (9*S*)-**22**

[a] The nitrone (5*R*)-**2** was treated with 10 equiv of a dipolarophile except for **12** (3 equiv). [b] The ratio was obtained from HPLC analysis. [c] No other isomer was detected by 270 MHz ^{1}H NMR. [d] The antipode (5*S*)-**2** was used.

The stereochemical course of the reactions of (5*R*)-**2** may be rationalized by taking into account four possible transition-state models **A**−**D**, as illustrated in Scheme 2. Thus, the transition states **A** and **B** reacting from the α face would be apparently unfavorable because of the nonbonded interactions between a dipolarophile and the phenyl group of the nitrone. Because the *β*-endo transition state **C** would also bear steric interaction between the R group of the dipolarophile and the ring of the nitrone, the cycloaddition of (5*R*)-**2** mainly proceeds via the model **D**, having the least steric interaction to afford cycloadducts **15**−**21** and (9*R*)-**22**.

It was recently reported that the related five-membered-ring nitrones undergo cycloaddition with electron-rich alkenes to give cycloadducts.[8] However, the reactivities of these nitrones are much lower than those of the six-membered-ring nitrone (5*R*)-**2**. For example, cycloaddition of the nitrone (5*R*)-**2** with ethyl vinyl ether (**7**) smoothly proceeds at room temperature in a benzene solution (Table 2, entry 1), whereas cycloaddition of the five-membered-ring nitrone **23** requires high-pressure conditions (8000 bar) even though ethyl vinyl ether (**7**) is used as the solvent.[8a,d] This remarkable difference in reactivity appears to be rationalized by two factors (Figure 2). One is, of course, the number of substituents. Each of the *π* faces of **23** would be shielded by the methylene group of the cyclohexane ring, whereas the phenyl group of nitrone (5*R*)-**2** blocks only the α face. Consequently, reaction of **23** with dipolarophile **7** may suffer from severe steric interaction. The other factor might arise from a difference in ring sizes. The distance of Cα−Cα′ of the five-membered-ring nitrone **23** may be

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(15) For other structurally related 1,3-dipoles, see: (a) Harwood, L. M.; Lilley, I. A. *Tetrahedron Lett.* **1993**, *34*, 537−540. (b) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527−6532. (c) Roussi, F.; Bonin, M.; Chiaroni, A.; Micoin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 3727−3730 and references therein.

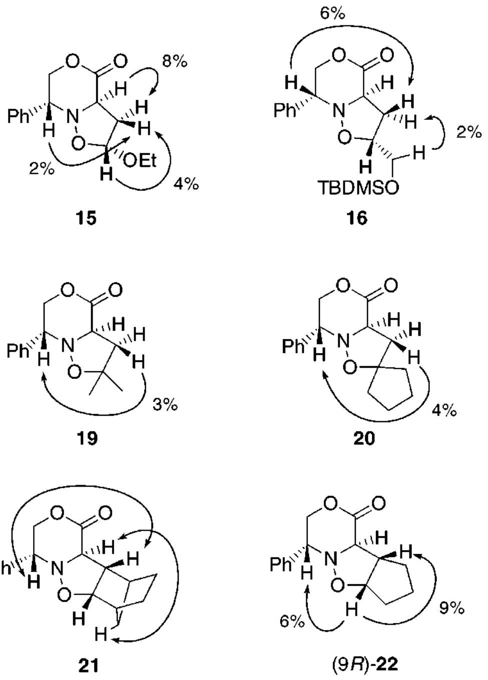
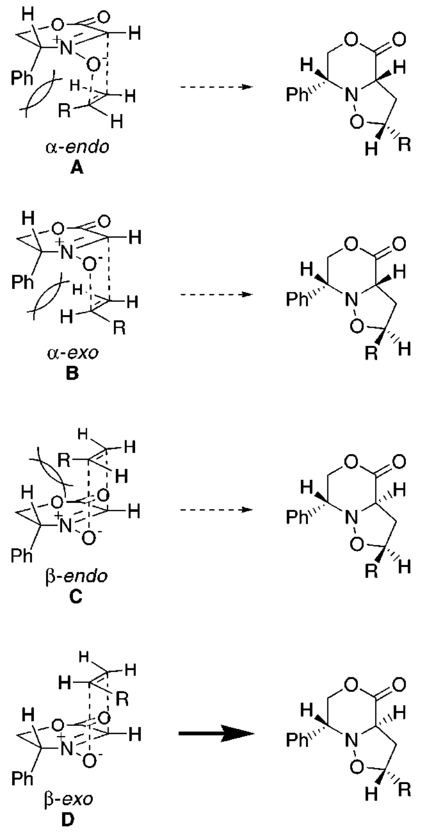


Figure 1. Selected NOEs of the cycloadducts.

Scheme 2



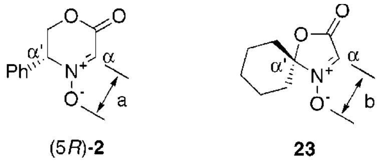
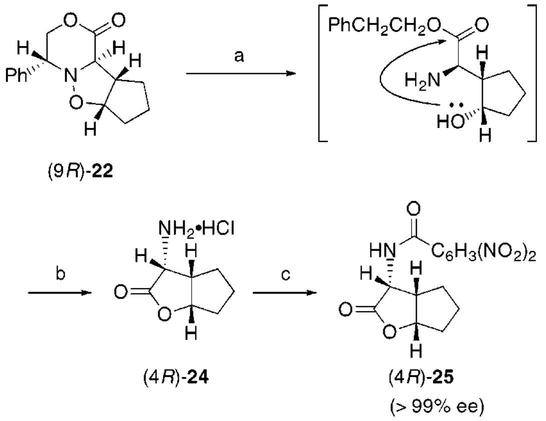


Figure 2. Distances between α and α′ and between reaction sites of the nitrones (5*R*)-**2** and **23**: α−α′ of (5*R*)-**2** > α−α′ of **23**; *a* < *b*.

Scheme 3[a]



[a] Key: (a) 20% Pd(OH)$_2$−C, H$_2$ (6 atm), AcOH, rt; (b) HCl−EtOH, 90% from (9*R*)-**22**; (c) 3,5-dinitrobenzoyl chloride, Et$_3$N, THF, 90%.

shortened compared to that of the six-membered-ring nitrone (5*R*)-**2**. This might enhance the steric repulsion between the methene groups and dipolarophile **7**. Moreover, the distance between the Cα and the oxygen atom of the nitrone **23** seems to be more expanded by the five-membered ring than by the six-membered ring of nitrone (5*R*)-**2** (length *a* < length *b*). Consequently, the LUMO orbitals of (5*R*)-**2** may overlap more effectively with the HOMO orbitals of the vinyl ether **7** than do those of **23** (for further discussion, see the Supporting Information).[16,17]

3. Transformations of the Cycloadducts: Synthesis of the Intermediate of Carbocyclic Polyoxin C. To determine both the facility of "deprotection" of the cycloadduct and the optical purity of the products, chemical transformations of enantiomeric cycloadducts (9*R*)-**22** and (9*S*)-**22** were next examined. Hydrogenolysis of (9*R*)-**22** in the presence of 20% palladium hydroxide on charcoal in acetic acid caused simultaneous reductive cleavage of both N−O and N−CHPh bonds and lactonization to give hydrochloride (4*R*)-**24** after treatment with ethanolic hydrogen chloride. The hydrochloride (4*R*)-**24** was acylated with 3,5-dinitrobenzoyl chloride under the usual conditions to afford benzamide (4*R*)-**25**. The antipode (4*S*)-**25** was produced in the same manner. Chiral HPLC analyses of benzamides (4*R*)-**25** and (4*S*)-**25** revealed that both enantiomers had at least 99% ee and that no racemization of **2** took place during both the preparation of **2** and the cycloaddition steps (Scheme 3).

Carbocyclic polyoxin C (**26**) is an analogue of uracil polyoxin C, which is known as the C-terminal amino acid of an antibiotic nikkomycin Bz (Scheme 4). Interest has

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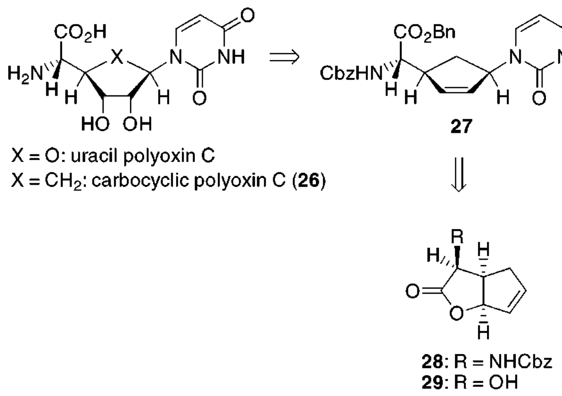
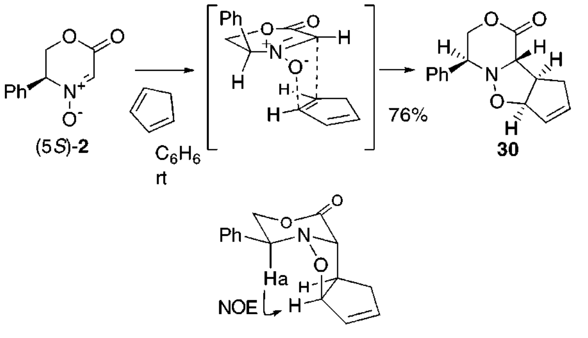
(16) In cycloaddition chemistry, the distance of the reaction site often plays an important role. It is known that reactivity of cyclopentadiene with tetracyanoethene is 2600-fold higher than that of cyclohexa-1,3-diene.[17a] Ali et al. reported that the reaction of tetrahydropyridine 1-oxide (six-membered-ring nitrone) with ethyl vinyl ether is 27 times faster than that of 1-pyrroline-1-oxide.[17b] Kotera et al. reported that cycloaddition of six-membered-ring carbonyl ylide with ethyl vinyl ether gives a higher yield of cycloadduct than does that of seven-membered-ring carbonyl ylide.[17c]

(17) (a) Sustmann, R.; Böhm, M.; Sauer, J. *Chem. Ber.* **1979**, *112*, 883−889. See also: (a) Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* **1980**, *113*, 1663−1690. (b) Ali, Sk. A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1789−1792. (c) Kotera, M.; Ishii, K.; Tamura, O.; Sakamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 313−318.

Scheme 4



Scheme 5

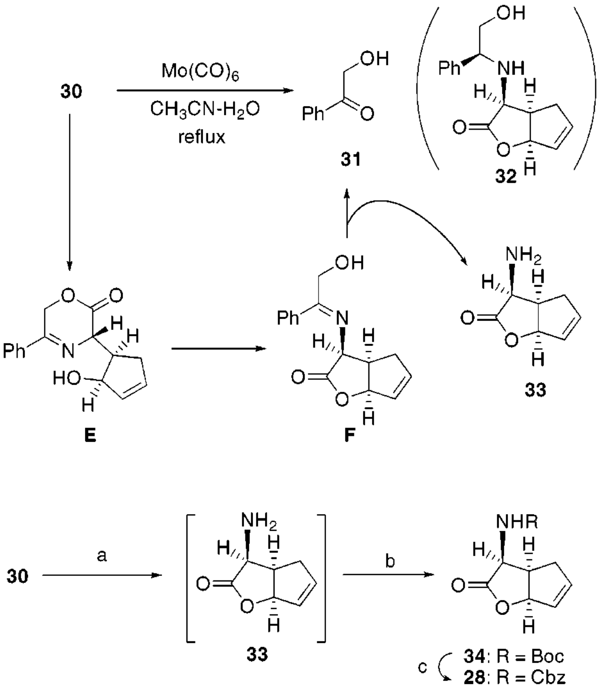


Ha: δ 4.12 (dd, J = 10.5, 3.7 Hz)

been shown in its structure−activity relationship, and it has been synthesized by several groups.[18] One of the most direct syntheses of **26** was demonstrated by Aggarwal's group.[18a,b] Palladium-catalyzed introduction of uracil to lactone **28** followed by benzylation of the generated carboxyl group gives cyclopentene **27**, which leads to **26** by dihydroxylation of the carbon−carbon double bond and deprotection. In the original synthesis of **26**, preparation of optically active **28** took four steps from hydroxyl congener **29**, which was synthesized by the Diels−Alder reaction of cyclopentadiene and glyoxylic acid, separation of the resulting diastereomeric mixture, and optical resolution.[19] Accordingly, direct access to the lactone **28** may be the key point in the efficient synthesis of carbocyclic polyoxin C (**26**). We envisioned a short-step entry to the key intermediate **28** from (5*S*)-**2**.

Our synthesis of the lactone **28** began with the cycloaddition of (5*S*)-**2** to cyclopentadiene, as shown in Scheme 5.[20] Treatment of nitrone (5*S*)-**2** with excess cyclopentadiene in benzene at room temperature gave an 80:16:4 mixture of diastereomers. The main product **30**, assigned by NOE, was readily isolated in 76% yield by crystallization and chromatography.

Scheme 6[a]



[a] Key: (a) Mo(CO)$_6$, CH$_3$CN−H$_2$O (10:1), reflux; (b) (Boc)$_2$O, 0 °C, 68%; (c) TsOH, CH$_2$Cl$_2$, 40 °C, then CbzCl, NaHCO$_3$(aq).

With cycloadduct **30** in hand and having all stereocenters, our attention turned to the reductive cleavage of the N−O bond of the cycloadduct **30** with the preserving of the carbon−carbon double bond. For this aim, molybdenum hexacarbonyl[21] was employed instead of hydrogenolysis conditions (Scheme 6). Heating the cycloadduct **30** with molybdenum hexacarbonyl in boiling acetonitrile−water (10:1) gave, to our surprise, α-hydroxyacetophenone (**31**) instead of an expected lactone **32**. This unexpected reaction is interpreted as follows. Nonreductive cleavage of the N−O bond of **30** gives cyclic imine **E**, which lactonizes to afford **F**. The imine moiety of **F** then undergoes hydrolysis under the reaction conditions to give α-hydroxyacetophenone (**31**) and deprotected lactone **33**. Although it is assumed that the lactone **33** should be produced under these conditions, it was not isolated probably because of the high polarity of **33**. We reasoned that effective protection of the primary amino group of **33** under the conditions employed might make possible a straightforward synthesis of lactone **28**. After some effort, we were delighted to find such reaction conditions. Thus, cycloadduct **30** was heated with molybdenum hexacarbonyl in acetonitrile−water followed by treatment with di-*tert*-butyl dicarbonate at low temperature to afford Boc-protected lactone **34** in 68% yield. Finally, treatment of lactone **34** with TsOH followed by acylation with benzyloxycarbonyl chloride afforded the key synthetic intermediate **28** of carbocyclic polyoxin C (**26**) in 86% yield.[22]

Although the exact mechanism for the formation of the lactone **33** from cycloadduct **30** remains unknown, one

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(18) For syntheses of optically active **26**, see: (a) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192−1193. (b) Aggarwal, V. K.; Monteiro, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2531−2537. (c) Kapeller, H.; Griengl, H. *Tetrahedron* **1997**, *43*, 14635−14644. For syntheses of racemic **26**, see: (d) Baumgartner, H.; Marschner, C.; Pucher, R.; Singer, M.; Griengl, H. *Tetrahedron Lett.* **1992**, *43*, 6443−6444. (e) Ward, S. E.; Holmes, A. B.; McCague, R. *Chem. Commun.* **1997**, 2085−2086.

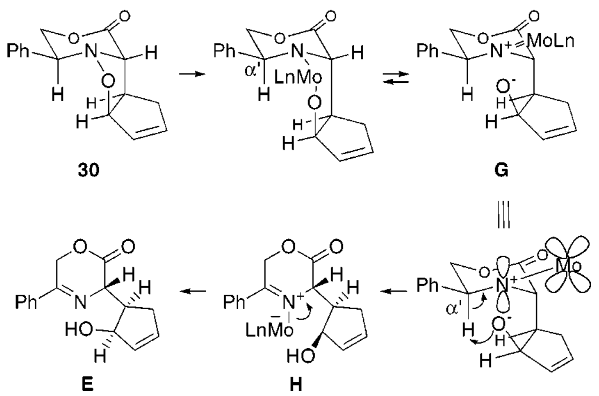
(19) For preparation of racemic **28**, see ref 18e.

(20) A carbocyclic nucleoside, carbovir, was also synthesized by employing cycloaddition of a chiral five-membered-ring nitrone with cyclopentadiene. See ref 14c. For general reviews on carbocyclic nucleosides, see: (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571−623. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611−10669.

(21) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.

(22) Direct protection of **33** with a benzyloxycarbonyl group instead of a Boc group was unsuccessful. Attempts to deprotect the Boc group by trifluoroacetic acid, ethanolic hydrogen chloride, or trimethylsilyl trifluoromethansulfonate particularly failed to lead only to low yields of **34** (<30%).

Scheme 7



possible explanation may be derived from consideration of both the rigid structure of **30** and the mechanism proposed[21] for reductive cleavage of the N−O bond by molybdenum hexacarbonyl, as shown in Scheme 7. Oxidative addition of molybdenum into the N−O bond of adduct **30** followed by elimination of an oxygen atom from the molybdenum may give molybdenum complex **G**.[23] The oxy anion of **G** might abstract the axial-oriented α′ proton, which could overlap with the p orbital of the nitrogen atom, giving rise to iminium complex **H**.[24] The complex **H** may then release molybdenum to afford cyclic imine **E** (for further discussion, see the Supporting Information).

Conclusion

We have designed and synthesized chiral and geometry-fixed α-alkoxycarbonylnitrones (5*R*)- and (5*S*)-**2**. The cycloadditions of the nitrones proceeded under mild conditions with good stereoselectivities. The stereochemistries of the major cycloadducts were readily predicted and were confirmed by NOE experiments because of the rigid structures. Moreover, the cycloaddition of nitrone (5*S*)-**2** could be applied to a short synthesis of the key intermediate of carbocyclic polyoxin C. Further applications of the cycloaddition of **2** are currently under investigation.[25]

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise stated, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure using a rotary evaporator. HPLC analyses were performed using a Finepack SIL-5 (column A) or a SUMICHIRAL OA 4600 (column B).

(*R*)-3-Hydroxyamino-2-phenylethanol [(*R*)-5]. A solution of (*R*)-phenylglycinol [(*R*)-**3**; 15.4 g, 0.11 mol] and *p*-methoxybenzaldehyde (10.6 g, 0.080 mol) in benzene (150 mL) was heated at reflux with a Dean−Stark trap for 2 h. After cooling, the mixture was concentrated in vacuo to give crude (*R*)-2-phenyl-*N*-(4-methoxybenzylidene)aminoethanol [(*R*)-**4**]. This was used for the next reaction without further purification. The crude imine (*R*)-**4** was dissolved in dichloromethane (100 mL), and to the solution was added dropwise a solution of *m*-chloroperbenzoic acid (75% purity, 27.3 g, 0.121 mol) in dichloromethane (200 mL) at 0 °C over 1.5 h. After further stirring for 30 min, precipitated *m*-chlorobenzoic acid was filtered off, and the filtrate was washed with a 10% aqueous solution of potassium carbonate and dried ($MgSO_4$). After filtration, the filtrate was concentrated in vacuo to give a residue which was dissolved in methanol (160 mL). To the solution was added hydroxylamine hydrochloride (12.0 g, 0.16 mol) in methanol at room temperature, and the mixture was further stirred for 18 h. Concentrated hydrochloric acid (15 mL) was added to the mixture, and the mixture was concentrated in vacuo to give a residue, which was partitioned between water (100 mL) and ether (200 mL). The aqueous phase was further washed with ether until no nonpolar materials were observed by TLC analysis. The aqueous phase was neutralized by adding sodium carbonate and then extracted with chloroform (50 mL × 8) with salting-out. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford (*R*)-**5** (10.8 g, 94%) as a crystalline solid. This material was pure enough for the next step. An analytical sample was obtained by recrystallization (ethyl acetate−hexane): mp 67−68 °C; $[\alpha]^{20}_D$ −38° (*c* 0.99, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 2.17 (1H, s), 3.21 (1H, br s), 3.93 (1H, s), 3.88 (2H, d, $J = 5.9$ Hz), 4.14 (1H, t, $J = 5.9$ Hz), 7.27−7.39 (5H, m). HRMS calcd for $C_8H_{11}NO_2$, 153.0790; found, 153.0786. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.68; H, 7.06; N, 9.06.

(5*R*)-5,6-Dihydro-5-phenyl-1,4-oxadin-2-one [(5*R*)-2]. To a suspension of a 40% aqueous solution of glyoxylic acid (10.0 g, 54 mmol) in dichloromethane (100 mL) was added dropwise a solution of (*R*)-**5** (7.50 g, 49 mmol) in dichloromethane (100 mL), and the mixture was stirred for 30 min. The water of the mixture was removed azeotropically by using a dropping funnel with an equalization arm. Anhydrous *p*-toluenesulfonic acid (10.1 g, 54 mmol) was added to the mixture, and the mixture was heated at reflux for 2 h. After cooling, the mixture was washed with water, and the aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/1) to afford (5*R*)-**2** (10.6 g, 85%) as a crystalline solid: mp 67−68 °C (hexane−ethyl acetate); $[\alpha]^{20}_D$ +80° (*c* 1.03, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 4.66 (1H, dd, $J = 12.5, 5.0$ Hz), 4.76 (1H, dd, $J = 12.5, 4.0$ Hz), 5.02 (1H, br t, $J = 4.6$ Hz), 7.28−7.40 (5H, m). HRMS *m*/*z* calcd for $C_{10}H_9NO_3$, 191.0582; found, 191.0579.

(*S*)-3-Hydroxyamino-2-phenylethanol [(*S*)-5]. This was obtained from (*S*)-phenylglycinol [(*S*)-**3**] by the same procedure as that described for (*R*)-**5**: mp 66−68 °C (hexene−ethyl acetate); $[\alpha]^{23}_D$ +38° (*c* 0.32, $CHCl_3$).

(5*S*)-5,6-Dihydro-5-phenyl-1,4-oxadin-2-one [(5*S*)-2]. This was obtained from (*S*)-**5** by the same procedure as that described for (5*R*)-**2**: mp 67−68 °C (hexene−ethyl acetate); $[\alpha]^{20}_D$ −80° (*c* 1.03, $CHCl_3$).

(1*R*,5*R*,8*R*)-6-Aza-8-ethoxy-3,7-dioxa-5-phenylbicyclo-[4.3.0]nonan-2-one (15). A solution of nitrone (5*R*)-**2** (20.0 mg, 0.1 mmol) and ethyl vinyl ether (**7**; 100 μL, 1.05 mmol) in benzene (1 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo to give the residue, which was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 3/2) to afford a diastereomeric mixture of cycloadducts (83:8:9, 24.0 mg, 87%). HPLC (column A, hexanes/ethyl acetate = 3/1, 1.0 mL/min), retention time (min) 14.92 (83%), 18.78 (8), 27.52 (9). An analytical sample of **15** was obtained by column chromatography on silica gel (hexane/ethyl acetate = 4/1); mp 72−73 °C (hexanes−ether); $[\alpha]^{25}_D$ −208° (*c* 1.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.19 (3H, t, $J = 6.9$ Hz), 2.68 (1H, ddd, $J = 13.2, 8.2, 1.0$ Hz, spin saturation at $\delta = 4.49 \rightarrow 8\%$ NOE), 2.79 (1H, ddd, $J = 13.2, 8.9, 5.0$ Hz, spin saturation at $\delta = 4.12 \rightarrow 2\%$ NOE, $\delta = 5.19 \rightarrow 4\%$ NOE), 3.42 (1H, dq, $J = 9.6, 6.9$ Hz, spin saturation at $\delta = 5.19 \rightarrow 5\%$ NOE), 3.72 (1H, dq, $J = 9.6, 6.9$ Hz, spin

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[23] Normally, a nitrenium complex undergoes hydrolysis under the conditions to afford a 3-amino alcohol. See ref 21.

[24] The same type of abstraction of a pseudoaxial proton was reported in oxidative ring opening of a bicyclic isoxazolidine. See: (a) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron Lett.* **1992**, *33*, 3219−3222. (b) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron Lett.* **1993**, *34*, 137−140. See also ref 14c.

[25] For example, see: Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett.* **1999**, *40*, 895−898.

saturation at $\delta = 5.19 \rightarrow 2\%$ NOE), 4.12 (1H, dd, $J = 9.9$, 3.6 Hz), 4.27 (1H, dd, $J = 11.9$, 9.9 Hz), 4.36 (1H, dd, $J = 11.9$, 3.6 Hz, spin saturation at $\delta = 4.12 \rightarrow 7\%$ NOE), 4.49 (1H, br t, $J = 8.2$ Hz), 5.19 (1H, br d, $J = 5.0$ Hz), 7.34−7.50 (5H, m). HRMS calcd for $C_{14}H_{17}NO_4$, 263.1158; found, 263.1161. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.63; H, 6.55; N, 5.33.

(1*R*,5*R*,8*R*)-6-Aza-8-(*tert*-butyldimethylsilyloxymethyl)-3,7-dioxa-5-phenylbicyclo[4.3.0]nonan-2-one (16). A solution of nitrone (5*R*)-**2** (60.0 mg, 0.31 mmol) and 3-(*tert*-butyldimethylsilyl)oxy-1-propene (**8**; 500 mg, 3.14 mmol) in benzene (6 mL) was stirred at 60 °C for 12 h. The mixture was concentrated in vacuo to give the residue, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 4/1) to afford a diastereomeric mixture of cycloadducts (75:5:11:9, 101.8 mg, 89%). HPLC (column A, hexane/ethyl acetate = 4/1, 1.0 mL/min), retention time (min) 6.32 (5%), 7.78 (75), 11.28 (11), 12.72 (9). An analytical sample of **16** was obtained by recrystallization: mp 53−55 °C (hexane); $[\alpha]^{23}_{D}$ −92° (*c* 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 2.69 (1H, ddd, $J = 12.8$, 8.9, 7.9 Hz, spin saturation at $\delta = 4.07 \rightarrow 6\%$ NOE), 2.73 (1H, ddd, $J = 12.8$, 8.9, 5.2 Hz), 3.57 (1H, dd, $J = 11.0$, 4.9 Hz, spin saturation at $\delta = 3.64 \rightarrow 11\%$ NOE), 3.64 (1H, dd, $J = 11.0$, 4.3 Hz, spin saturation at $\delta = 3.57 \rightarrow 13\%$ NOE), 4.07 (1H, dd, $J = 10.4$, 3.7 Hz), 4.20 (1H, dd, $J = 11.9$, 10.4 Hz), 4.25 (1H, br dd, $J = 8.2$, 4.6 Hz, spin saturation at $\delta = 3.57 \rightarrow 7\%$ NOE, $\delta = 3.64 \rightarrow 10\%$ NOE), 4.28 (1H, dd, $J = 11.9$, 3.7 Hz, spin saturation at $\delta = 4.07 \rightarrow 11\%$ NOE), 4.34 (1H, t, $J = 8.9$ Hz, spin saturation at $\delta = 3.57 \rightarrow 2\%$ NOE), 7.31−7.44 (5H, m). HRMS calcd for $C_{19}H_{29}NO_4Si$, 363.1866; found, 363.1866. Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.61; H, 8.06; N, 3.80.

(1*R*,5*R*,8*S*)-6-Aza-8-butyl-3,7-dioxa-5-phenylbicyclo[4.3.0]-nonan-2-one (17). A solution of nitrone (5*R*)-**2** (66.6 mg, 0.35 mmol) and 1-hexene (**9**; 436 μL, 3.48 mmol) in benzene (2 mL) was stirred at 60 °C for 8 h. The mixture was concentrated in vacuo to give the residue, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 1/1) to afford a diastereomeric mixture of cycloadducts (85:7:8, 82 mg, 86%). HPLC (column A, hexane/ethyl acetate = 3/1, 1.0 mL/min), retention time (min) 6.06 (85%), 7.78 (75), 12.51 (8). Further column chromatography on silica gel (hexane/ethyl acetate = 1/1) and recrystallization from hexanes−ether gave pure **17**: mp 80−81 °C (ether−hexane); $[\alpha]^{28}_{D}$ −118° (*c* 0.84, $CHCl_3$); ^1H NMR (500 MHz, CD_3CO_2D) δ 0.86 (3H, t, $J = 7.0$ Hz), 1.22−1.62 (6H, m), 2.44 (1H, ddd, $J = 12.5$, 9.5, 6.7 Hz), 2.84 (1H, dt, $J = 12.5$, 7.6 Hz), 4.25 (1H, dd, $J = 10.7$, 3.7 Hz), 4.25 (1H, m), 4.31 (1H, dd, $J = 11.6$, 3.7 Hz), 4.37 (1H, dd, $J = 11.6$, 10.7 Hz), 4.52 (1H, dd, $J = 9.5$, 7.6 Hz), 7.32−7.49 (5H, m). HRMS *m/z* calcd for $C_{16}H_{21}NO_3$, 275.1521; found, 275.1521. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.73; H, 7.70; N, 5.05.

(1*R*,2*S*,6*R*,9*R*)-8-Aza-5,7,11-trioxa-9-phenyltricyclo-[6.4.0.0^{2,6}]dodecan-12-one (18). A solution of nitrone (5*R*)-**2** (20.0 mg, 0.10 mmol) and 2,3-dihydrofuran (**10**; 79 μL, 1.0 mmol) in benzene (1 mL) was stirred at room temperature for 18 h. The mixture was concentrated in vacuo to give the residue, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford a diastereomeric mixture of cycloadducts (87:13, 22.7 mg, 83%). HPLC (column A, hexane/ethyl acetate = 3/1, 1.0 mL/min), retention time (min) 21.60 (87%), 24.48 (13). Recrystallization from hexanes−ethyl acetate gave pure **18**: mp 204−205 °C (ethyl acetate−hexane); $[\alpha]^{26}_{D}$ −100° (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (1H, br dd, $J = 13.0$, 5.5 Hz), 2.23 (1H, ddt, $J = 13.0$, 11.6, 8.5 Hz), 3.73 (1H, dddd, $J = 8.5$, 5.2, 3.7, 1.2 Hz), 3.87 (1H, d, $J = 3.7$ Hz), 4.06 (1H, td, $J = 8.5$, 1.5 Hz), 4.14 (1H, ddd, $J = 11.3$, 8.5, 5.5 Hz), 4.31 (1H, dd, $J = 8.2$, 4.0 Hz), 4.38 (1H, dd, $J = 11.9$, 8.2 Hz), 4.63 (1H, dd, $J = 11.9$, 4.0 Hz), 5.83 (1H, d, $J = 5.2$ Hz), 7.33−7.48 (5H, m). HRMS *m/z* calcd for $C_{14}H_{15}NO_4$, 261.1001; found, 261.0992. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; N, 5.36. Found: C, 64.09; H, 5.80; N, 5.31.

(1*R*,5*R*)-6-Aza-8,8-dimethyl-3,7-dioxa-5-phenylbicyclo-[4.3.0]nonan-2-one (19). Isobutene (**11**) was bubbled through a solution of nitrone (5*R*)-**2** (40.2 mg, 0.21 mmol) in benzene (1 mL) at 0 °C, and then the mixture was stirred at 60 °C in a sealed tube for 18 h. The mixture was concentrated in vacuo to give the residue, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 1/1) to afford **19** (49.2 mg, 95%): mp 47−48 °C (hexanes−ether); $[\alpha]^{28}_{D}$ −104° (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 0.55 (3H, s), 0.57 (3H, s), 1.54 (1H, dd, $J = 12.8$, 8.5 Hz, spin saturation at $\delta = 1.92 \rightarrow 11\%$ NOE), 1.92 (1 H, dd, $J = 12.8$, 7.3 Hz, spin saturation at $\delta = 1.54 \rightarrow 17\%$ NOE, $\delta = 3.41 \rightarrow 3\%$ NOE), 3.14 (1H, dd, $J = 11.6$, 10.4 Hz), 3.29 (1H, dd, $J = 8.5$, 7.3 Hz, spin saturation at $\delta = 1.54 \rightarrow 10\%$ NOE, $\delta = 1.92 \rightarrow 8\%$ NOE), 3.31 (1H, dd, $J = 11.6$, 3.7 Hz), 3.41 (1H, dd, $J = 10.4$, 3.7 Hz, spin saturation at $\delta = 1.92 \rightarrow 3\%$ NOE), 6.55−6.74 (5H, m). HRMS *m/z* calcd for $C_{14}H_{17}NO_3$, 247.1208: found, 247.1205. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.75; H, 6.92; N, 5.60.

(1*R*,5*R*)-6-Aza-3,7-dioxa-5-phenylspiro[bicyclo[4.3.0]-nonane-8,1′-cyclopentan]-2-one (20). A solution of nitrone (5*R*)-**2** (20.0 mg, 0.10 mmol) and methylencyclopentane (**12**; 33 μL, 0.31 mmol) in benzene (1 mL) was stirred at 50 °C for 32 h. The mixture was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to afford **20** (24.4 mg, 87%): mp 99−100 °C (hexanes−ethyl acetate); $[\alpha]^{26}_{D}$ −93° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 0.86−0.92 (1H, m), 0.93−1.01 (2H, m), 1.07−1.19 (3H, m), 1.37 (1H, m), 1.60 (1H, m), 1.87 (1H, dd, $J = 12.5$, 8.2 Hz, spin saturation at $\delta = 2.25 \rightarrow 17\%$ NOE, $\delta = 3.53 \rightarrow 9\%$ NOE), 2.25 (1H, dd, $J = 12.5$, 7.9 Hz, spin saturation at $\delta = 1.87 \rightarrow 21\%$ NOE), 3.35 (1H, dd, $J = 11.6$, 10.7 Hz, spin saturation at $\delta = 1.87 \rightarrow 12\%$ NOE, $\delta = 3.53 \rightarrow 4\%$ NOE), 3.50 (1H, dd, $J = 11.6$, 3.7 Hz), 3.53 (1H, br t, $J = 7.9$ Hz), 3.60 (1H, dd, $J = 10.7$, 3.7 Hz, spin saturation at $\delta = 2.25 \rightarrow 4\%$ NOE), 6.73−6.94 (5H, m, Ar−H). HRMS *m/z* calcd for $C_{16}H_{19}NO_3$, 273.1365; found, 273.1363. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.11; H, 7.01; N, 5.08.

(1*R*,2*S*,3*R*,7*R*,10*S*,11*R*)-8-Aza-5,9-dioxa-7-phenyl-tetracyclo[9.2.1^{2,6}.0^{3,8}]tetradecan-4-one (21). A solution of nitrone (5*R*)-**2** (60.0 mg, 0.31 mmol) and norbornylene (**13**; 295 mg, 3.14 mmol) in benzene (6 mL) was stirred at room temperature for 9 h. The mixture was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford **21** (82.4 mg, 92%): mp 149−150 °C (ethyl acetate−hexane); $[\alpha]^{28}_{D}$ −208° (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.97−1.01 (1H, m), 1.12 (1H, ddd, $J = 9.5$, 2.7, 1.5 Hz), 1.16 (1H, dt, $J = 11.6$, 2.4 Hz), 1.52−1.61 (2H, m), 1.67 (1H, d quin, $J = 9.5$, 1.5 Hz), 2.30 (1H, br d, $J = 4.3$ Hz), 2.54 (1H, br d, $J = 3.1$ Hz), 2.70 (1H, ddd, $J = 7.9$, 6.4, 1.2 Hz), 3.83 (1H, d, $J = 7.9$ Hz), 4.02 (1H, dd, $J = 10.4$, 4.0 Hz), 4.06 (1H, br d, $J = 6.4$ Hz), 4.20 (1H, dd, $J = 11.6$, 10.4 Hz), 4.25 (1H, dd, $J = 11.6$, 4.0 Hz), 7.34−7.45 (5H, m). HRMS *m/z* calcd for $C_{17}H_{19}NO_3$, 285.1365; found, 285.1366. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.49; H, 6.84; N, 4.89.

(1*R*,2*S*,6*S*,9*R*)-8-Aza-7,11-dioxa-9-phenyltricyclo[6.4.0.0^{2,6}]-dodecan-12-one [(9*R*)-22]. A solution of nitrone (5*R*)-**2** (200.0 mg, 1.05 mmol) and cyclopentene (**14**; 1.9 mL, 20.92 mmol) in benzene (10 mL) was stirred at room temperature for 30 h. The mixture was concentrated in vacuo to give the residue. HPLC (column A, ethyl acetate/hexane = 1/4, 1.0 mL/min), retention time (min) 11.62 (100%). An analytical sample of (9*R*)-**22** (247.8 mg, 91%) was obtained by recrystallization from ethyl acetate−hexane: mp 206−207 °C; $[\alpha]^{28}_{D}$ −186° (*c* 1.03, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.43−1.89 (5H, m), 2.02−2.07 (1H, m), 3.35 (1H, br q, $J = 6.9$ Hz, spin saturation at $\delta = 4.70 \rightarrow 9\%$ NOE), 3.85 (1H, d, $J = 8.6$ Hz), 4.10 (1H, dd, $J = 9.9$, 4.0 Hz, spin saturation at $\delta = 4.70 \rightarrow 6\%$ NOE), 4.20 (1H, dd, $J = 10.9$, 9.9 Hz), 4.27 (1H, dd, $J = 10.9$, 4.0 Hz), 4.70 (1H, br dd, $J = 6.9$, 5.3 Hz), 7.34−7.46 (5H, m). HRMS *m/z* calcd for $C_{15}H_{17}NO_3$, 259.1209; found, 259.1207. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.57; N, 5.36.

(1*S*,2*R*,6*R*,9*S*)-8-Aza-7,11-dioxa-9-phenyltricyclo[6.4.0.0^{2,6}]dodecan-12-one [(9*S*)-22]. This was obtained from (5*S*)-**2** and **14** by the same procedure as that described for (9*R*)-**22**: mp 206−207 °C (hexane−ethyl acetate); $[\alpha]^{28}_{D}$ +183° (*c* 0.99, $CHCl_3$).

(1*S*,4*R*,5*S*)-3-Oxo-2-oxabicyclo[3.3.0]octa-4-ylammonium Chloride [(4*R*)-24] and (1*S*,4*R*,5*S*)-4-(3,5-Dinitrobenzoyl)amino-2-oxabicyclo[3.3.0]octan-3-one [(4*R*)-25]. A mixture of (9*R*)-**22** (102 mg, 0.39 mmol) and 20% palladium hydroxide on charcoal (247 mg) in acetic acid (8 mL) was stirred at room temperature under hydrogen (6 kg/cm^2) for 6 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in ethanolic hydrogen chloride, and then the mixture was concentrated in vacuo. The residue was dissolved in a minimum amount of ethanol, and then slow addition of ether gave precipitates of (4*R*)-**24** (62.5 mg, 90%): mp 178−180 °C (ethanol−ether); $[\alpha]^{23}_{D}$ −64° (*c* 0.98, CH_3OH); ^1H NMR (270 MHz, CD_3OD) δ 1.49−2.02 (6H, m), 3.07 (1H, ddt, J = 5.6, 5.3, 8.9 Hz, spin saturation at $\delta = 4.48 \rightarrow 7\%$ NOE, $\delta = 5.02 \rightarrow 4\%$ NOE), 4.48 (1H, d, J = 8.9 Hz, spin saturation at $\delta = 3.07 \rightarrow 6\%$ NOE, $\delta = 5.02 \rightarrow 2\%$ NOE), 5.02 (1H, ddd, J = 5.3, 4.3, 1.7 Hz, spin saturation at $\delta = 3.07 \rightarrow 4\%$ NOE, $\delta = 4.48 \rightarrow 2\%$ NOE). This compound was used for the next step without further purification because of its hygroscopicity. To a stirred suspension of (4*R*)-**24** (2.8 mg, 20 μmol) in dry THF (0.5 mL) were successively added triethylamine (24 mL, 0.17 mmol) and 3,5-dinitrobenzoyl chloride (36.3 mg, 0.16 mmol) in dry THF (1 mL) at room temperature. After stirring for 1 h, an aqueous saturated solution of sodium bicarbonate (1 mL) was added to the mixture, and the mixture was vigorously stirred for 20 min. The mixture was diluted with water and extracted several times with dichloromethane. The organic phases were combined, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel to afford (4*R*)-**25** (4.7 mg, 90%): mp 231−232 °C (ethyl acetate−hexane); $[\alpha]^{25}_{D}$ −152° (*c* 1.10, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.76−2.14 (6H, m), 3.28−3.39 (1H, m), 5.05 (1H, dd, J = 8.6, 5.6 Hz), 5.10 (1H, dt, J = 1.3, 5.3 Hz), 7.54 (1H, br d, J = 4.9 Hz), 8.94 (2H, d, J = 2.0 Hz), 9.12 (1 H, br t, J = 2.0 Hz). HRMS *m/z* calcd for $C_{14}H_{13}N_3O_7$, 335.0754; found, 335.0757. Anal. Calcd for $C_{14}H_{13}N_3O_7$: C, 50.15; H, 3.91; N, 12.53. Found: C, 50.01; H, 3.95; N, 12.54. The HPLC analyses using this sample and (4*S*)-**25** obtained below indicated that optical purity of (4*R*)-**25** was at least 99% ee. HPLC (column B, hexane/1,2-dichloroethane/ethanol = 60/30/10, 1.0 mL/min); mixture of (4*R*)-**25** and (4*S*)-**25**, retention time (min) 5.52, 7.00; (4*R*)-**25**, retention time (min) 6.90 (100%).

(1*R*,4*S*,5*R*)-3-Oxo-2-oxabicyclo[3.3.0]octa-4-ylammonium Chloride [(4*S*)-24] and (1*R*,4*S*,5*R*)-4-(3,5-Dinitrobenzoyl)amino-2-oxabicyclo[3.3.0]octan-3-one [(4*S*)-25]. Compound (4*S*)-**24** was obtained from (9*S*)-**22** by the same procedure as that described for (4*R*)-**24**: mp 175−177 °C (ethanol−ether); $[\alpha]^{23}_{D}$ +68° (*c* 0.95, CH_3OH). Compound (4*S*)-**25** was obtained from (4*S*)-**24** by the same procedure as that described for (4*R*)-**25**: mp 231−233 °C (ethyl acetate−hexane); $[\alpha]^{25}_{D}$ −148° (*c* 1.10, $CHCl_3$). The HPLC analyses using this sample and (4*R*)-**25** obtained below indicated that optical purity of (4*S*)-**25** was at least 99% ee. HPLC (column B, hexane/1,2-dichloroethane/ethanol = 60/30/10, 1.0 mL/min); mixture of (4*R*)-**25** and (4*S*)-**25**, retention time (min) 5.52, 7.00; (4*S*)-**25**, retention time (min) 5.24 (100%).

(3a*R*,3b*S*,7*S*,8a*S*)-7-Phenyl-3,3a,3b,6,7,8a-hexahydro-5,8-dioxa-7a-azacyclopenta[*a*]inden-4-one (30). A mixture of (5*S*)-**2** (50.0 mg, 0.26 mmol) and cyclopentadiene (0.1 mL, 2.62 mmol) in benzene (10 mL) was stirred at room temperature for 4 h. The mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford a mixture of diastereomers. HPLC (column A, CH_2Cl_2/ethyl acetate = 10/1, 1.0 mL/min), retention time (min) 4.66 (80%), 6.38 (16), 7.76 (4). The following preparative experiment was carried out. A mixture of (5*S*)-**2** (2.65 g, 14 mmol) and cyclopentadiene (9 mL, 0.14 mol) in benzene (30 mL) was stirred at room temperature for 4 h. Crystals precipitated were collected by filtration to yield **30** (1.66 g). The filtrate was concentrated in vacuo to give a residue, which was purified by chromatography on silica gel (CH_2Cl_2/hexane = 5/1) to afford additional **30** (398 mg, total 78%): mp 219−220 °C (hexanes−ethyl acetate); $[\alpha]^{20}_{D}$ +185° (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.66−2.79 (2H, m), 3.54 (1H, dddd, J = 8.8, 7.8, 6.8, 2.4 Hz), 3.82 (1H, d, J = 8.8 Hz), 4.12 (1H, dd, J = 10.5, 3.7 Hz), 4.21 (1H, dd, J = 11.5, 10.5 Hz), 4.30 (1H, dd, J = 11.5, 3.7 Hz), 5.30 (1H, br d, J = 7.8 Hz, spin saturation at $\delta = 4.12 \rightarrow 4\%$ NOE), 5.70 (1H, dq, J = 5.6, 2.4 Hz), 5.91 (1H, dtd, J = 5.6, 2.2, 1.0 Hz), 7.34−7.46 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 49.5, 62.0, 70.3, 70.7, 88.1, 128.2, 129.3, 129.5, 130.0, 134.4, 135.8, 173.7. HRMS *m/z* calcd for $C_{15}H_{15}NO_3$, 257.1052: found, 257.1051. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.86; H, 5.88; N, 5.42.

(1*S*,4*S*,5*R*)-4-(*tert*-Butyloxycarbonyl)amino-2-oxabicyclo[3.3.0]oct-7-en-3-one (34). A mixture of **30** (200 mg, 0.77 mmol) and molybdenum hexacarbonyl (410 mg, 1.55 mmol) in acetonitrile−water (10:1, 25 mL) was heated at reflux for 2 h. After cooling to 0 °C, di-*tert*-butyl dicarbonate (1.7 mL, 7.8 mmol) was added to the mixture, and the mixture was stirred at room temperature for 10 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/ether = 20/1) to afford **34** (127 mg, 68%): mp 173−174 °C (ether−hexane); $[\alpha]^{20}_{D}$ +43° (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (9H, s), 2.33 (1H, br d, J = 17.3 Hz), 2.43 (1H, br dd, J = 17.3, 8.8 Hz), 3.36 (1H, br ddd, J = 8.8, 8.3, 6.4 Hz), 4.58 (1H, br dd, J = 8.3, 4.0 Hz), 5.08 (1H, br s), 5.31 (1H, br d, J = 6.4 Hz), 5.88 (1H, br dq, J = 4.6, 2.2 Hz), 6.16 (1H, br dt, J = 4.6, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 32.3, 41.0, 53.8, 80.5, 87.4, 128.5, 141.1, 156, 174. HRMS *m/z* calcd for $C_{12}H_{17}NO_4$, 239.1156; found, 239.1158. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.20; H, 7.15; N, 5.84.

(1*S*,4*S*,5*R*)-4-Benzyloxycarbonylamino-2-oxabicyclo[3.3.0]oct-7-en-3-one (28). To a stirred solution of **34** (100 mg, 0.42 mmol) in dry dichloromethane (3 mL) was added anhydrous *p*-toluenesulfonic acid (159 mg, 0.84 mmol) at room temperature, and then the mixture was stirred at 40 °C for 2 h. After cooling to 0 °C, to the mixture was successively added a saturated aqueous solution of sodium bicarbonate (1.5 mL) and benzyl chloroformate (123 μL, 0.84 mmol), and then the mixture was stirred for 2 h under these conditions. The mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give a reside, which was purified by column chromatography on silica gel (ether/hexane = 1/1) to afford **28** (98.0 mg, 86%): mp 146−147 °C (ethyl acetate−hexane); $[\alpha]^{20}_{D}$ +35° (*c* 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, −53 °C, two broad signals at room temperature) δ 2.39 (1H, ddt, J = 18.0, 6.4, 2.2 Hz), 2.54 (1H, ddt, J = 18.0, 9.1, 2.2 Hz), 3.49 (1H, tt, J = 9.1, 6.4 Hz), 4.80 (1H, dd, J = 9.1, 4.9 Hz), 5.13 (1H, d, J = 11.9 Hz), 5.18 (1H, d, J = 11.9 Hz), 5.46 (1H, dd, J = 6.4, 2.2 Hz), 5.51 (1H, d, J = 4.9 Hz), 6.01 (1H, dq, J = 5.5, 2.2 Hz), 6.30 (1H, dt, J = 5.5, 2.2 Hz), 7.40−7.45 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$, −53 °C) δ 31.9, 40.2, 53.5, 67.3, 87.1, 127.4, 128.2, 128.4, 128.5, 135.2, 141.1, 156.0, 174.4. HRMS *m/z* calcd for $C_{15}H_{15}NO_4$, 273.1001; found, 273.1006. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.75; H, 5.56; N, 5.10. These physical data are identical to those reported.[18b]

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Supporting Information Available: ORTEP diagram and CIF file of the X-ray structure of (5*S*)-**2**, supplementary discussions for Figure 2 and for Scheme 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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