JOC Article

Intermolecular Cycloaddition of *N*-Boranonitrone with Alkenes

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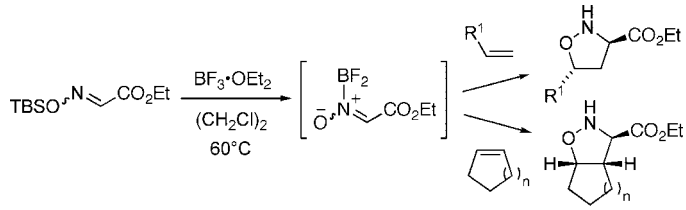
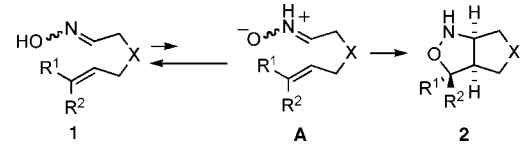


Ethyl glyoxylate *O*-*tert*-butyldimethylsilyloxime (**8**), on treatment with 2.2 equiv of $BF_3 \cdot OEt_2$, generated *N*-boranonitrone **E**, which underwent intermolecular cycloaddition with alkenes **18** to afford isoxazolidines **19** in moderate to high yields. The cycloaddition of *N*-boranonitrone **E** with most of the alkenes gave 3,5-*trans* isoxazolidines as the major isomers via a concerted mechanism. However, in the case of 1-methylated cyclic alkenes (**18j** and **18l**), the cycloaddition surprisingly furnished the 3,3a-*cis*-cycloadducts (**19j** and **19l**) as major isomers. A possible explanation is that the reaction of 1-methylated cyclic alkenes proceeds mainly via a stepwise mechanism. This reaction of terminal alkenes is very useful for synthesis of 1,3-*anti* aminoalcohol derivatives by reductive cleavage of an N−O bond.

Introduction

Nitrones are among the most useful and versatile nitrogen-containing substrates for organic reactions such as nucleophilic addition,[1] radical addition,[2] and cycloaddition.[3] Among them, intra- and intermolecular 1,3-dipolar cycloadditions of nitrones with alkenes are powerful tools for construction of the isoxazolidine ring system, which can be transformed into structurally complex and biologically active nitrogen-containing compounds through reductive cleavage of the nitrogen−oxygen bond. Compared with nitrone-olefin cycloaddition, intramolecular oxime-olefin cycloaddition, so-called IOOC,[4,5] seems to be a more attractive reaction, because an oxime functionality is more readily available and is more stable than is a nitrone function. IOOC is recognized to proceed via *NH*-nitrone intermediate **A** generated by proton transfer from oxygen to nitrogen in the oxime functionality, giving *N*-nonsubstituted cycloadduct **2** (Scheme 1).

SCHEME 1



[†] Showa Pharmaceutical University.
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(1) For reviews, see: (a) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759. (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. For leading references, see: (e) Chevrier, C.; Nouen, D. L.; Defoin, A.; Tarnus, C. *Eur. J. Org. Chem.* **2006**, 2384. (f) Merino, P.; Mannucci, V.; Tejero, T. *Tetrahedron* **2005**, *61*, 3335. (g) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817. (h) Merino, P.; Tejero, T. *Tetrahedron* **2001**, *57*, 8125. (i) Merino, P.; Franco, S.; Gascon, J. M.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1867.

(2) (a) Villamena, F. A.; Merle, J. K.; Hadad, C. M.; Zweier, J. L. *J. Phys. Chem. A* **2007**, *111*, 9995. (b) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. *J. Org. Chem.* **2005**, *70*, 6653. (c) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. *Chem. Commun.* **2003**, 426.

(3) For reviews, see: (a) Runa, P.; Subhash, G.; Koushik, C.; Amit, B. *Synlett* **2007**, 2321. (b) Cardona, F.; Goti, A., *Angew. Chem., Int. Ed.* **2005**, *44*, 7832. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (e) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075. (f) Kanemasa, S. *Synlett* **2002**, 1371. (g) Pedro, D. M.; Marta, F.; Josep, F. *Heterocycles* **1999**, *50*, 1213. (h) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. For leading references, see: (i) Partidge, K. M.; Anzovino, M. E.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 2920. (j) Shirahase, M.; Kanemasa, S.; Hasegawa, M. *Tetrahedron Lett.* **2004**, *45*, 4061. (k) White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950. (l) Ishikawa, T.; Kudo, T.; Shigemori, K.; Saito, S. *J. Am. Chem. Soc.* **2000**, *122*, 7633.

(4) For pioneering works, see: (a) Wildman, W. C.; Slabaugh, M. R. *J. Org. Chem.* **1971**, *36*, 3202. (b) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, *11*, 1117.

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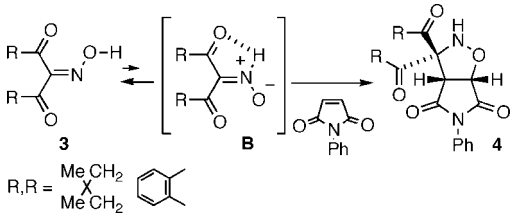
SCHEME 2



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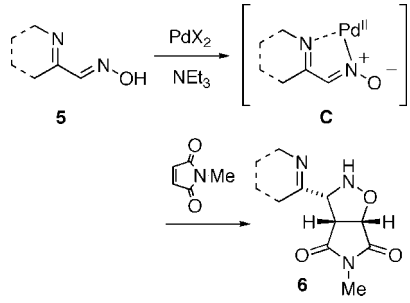
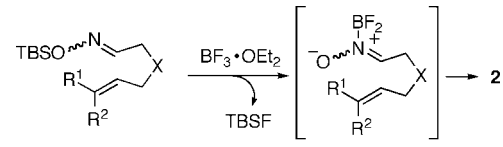


However, high temperature conditions are often required for effective IOOCs because of thermodynamically unfavorable tautomerization from oxime **1** to *NH*-nitrone **A** (Scheme 1).[6] Accordingly, one of the important factors influencing the efficiency of IOOC would be the tendency to form *NH*-nitrone **A** from oxime **1**. In fact, in the case of the intermolecular reaction, some groups have reported that an intramolecular hydrogen bond or metallo-nitrogen bond in the oxime moiety makes the cycloaddition of oximes more effective. For example, it was reported that *NH*-nitrone **B** generated from oxime **3** having an intramolecular hydrogen bond reacted with *N*-phenylmaleimides to afford the corresponding product **4** (Scheme 2).[7]

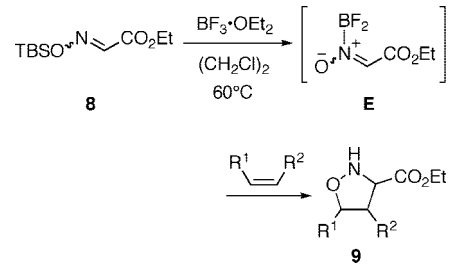
On the other hand, palladium(II) salt has been used as a catalyst to promote intermolecular oxime-olefin cycloaddition (Scheme 3).[8] Thus, treatment of oxime **5** with Pd(II) catalyst generates *N*-metallonitrone **C** as an active intermediate, which undergoes intermolecular cycloaddition with *N*-methylmaleimide, furnishing the corresponding isoxazolidine derivatives **6** in good to high yield.

Unfortunately, both reactions are applicable only to a limited range of activated olefins, such as *N*-methyl- or *N*-phenylmaleimide.

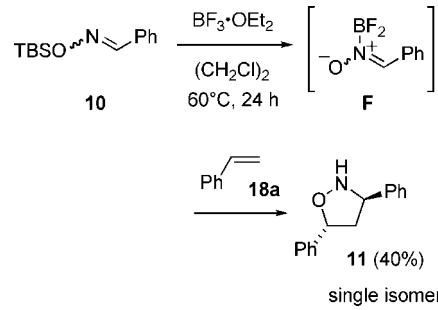
SCHEME 4



SCHEME 5



SCHEME 6



Recently, we reported a highly efficient BF_3-mediated cycloaddition of *O-tert*-butyldimethylsilyloximes bearing an olefin moiety, to provide *N*-nonsubstituted isoxazolidines **2** in good to high yield (Scheme 4).[9] Treatment of *O-tert*-butyldimethylsilyloximes **7** with $BF_3 \cdot OEt_2$ at room temperature smoothly gave the corresponding isoxazolidines **2** via *N*-boranonitrones **D** as active intermediates. This procedure effectively generates the nitrone intermediate **D** by utilizing the strong N−B[10] and Si−F affinities.

More recently, the methodology has been extended to the intermolecular cycloaddition of *O-tert*-butyldimethylsilyloximes **8** (*O*-TBS oxime) with various alkenes via *N*-boranonitrone **E**, furnishing *N*-nonsubstituted isoxazolidines **9** in good yields (Scheme 5).[11] In this paper, we present a full account of this work, including stereochemical investigation, mechanistic considerations, and further transformation of cycloadducts to 1,3-*anti*-aminoalcohols.

Results and Discussion

1. Simple Extension of Cycloaddition of *N*-Boranonitrone F to Intermolecular Variant. We initiated our study by

(5) For recent examples, see: (a) Singh, S.; Ishar, M. P. S.; Singh, G.; Singh, R. *Can. J. Chem.* **2005**, *83*, 260. (b) Noguchi, M.; Okada, H.; Tanaka, M.; Matsumoto, S.; Kakehi, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 917. (c) Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452. (d) Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem.* **1999**, *64*, 498. (e) Dransfield, P. J.; Moutel, S.; Shipman, M.; Sik, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3349. (f) Sharma, G. V. M.; Srinivas Reddy, I.; Goverdhan Reddy, V.; Rama Rao, A. V. *Tetrahedron: Asymmetry* **1999**, *10*, 229. (g) Baskaran, S.; Aurich, H. G. *Synlett* **1998**, 277. (h) Abiko, A.; Liu, J.-F.; Wang, G.; Masamune, S. *Tetrahedron Lett.* **1997**, *38*, 3261. (i) Hassner, A.; Maurya, R.; Friedman, O.; Gottlib, H. E.; Padwa, A.; Austin, D. *J. Org. Chem.* **1993**, *58*, 4539. (j) Hassner, A.; Singh, S.; Sharma, R.; Maurya, R. *Tetrahedron* **1993**, *49*, 2317. (k) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W. H. *J. Org. Chem.* **1991**, *56*, 2775.

(6) Formaldehyde oxime [HO−N=CH_2] was estimated to be 11.1 kcal/mol more stable than the corresponding nitrone [$^-$O−N$^+$(H)=CH_2] by theoretical analysis. See: Long, J. A.; Harris, N. J.; Lammertsma, K. *J. Org. Chem.* **2001**, *66*, 6762.

(7) (a) Shirai, M.; Kuwabara, H.; Matsumoto, S.; Yamamoto, H.; Kakehi, A.; Noguchi, M. *Tetrahedron* **2003**, *59*, 4113. (b) Grigg, R.; Thianpantagul, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 653.

(8) Frederickson, M.; Grigg, R.; Thornton-Pett, M.; Redpath, J. *Tetrahedron Lett.* **1997**, *38*, 7777.

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(11) Tamura, O.; Morita, N.; Takano, Y.; Fukui, K.; Okamoto, I.; Haung, X.; Tsutsumi, Y.; Ishibashi, H. *Synlett* **2007**, 658. Quite recently, *N*-nonsubstituted isoxazolidines were also obtained by cycloaddition of *N*-nosyl nitrones with alkenes followed by deprotection with a thiol. See ref 3i.

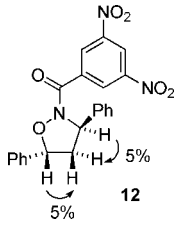
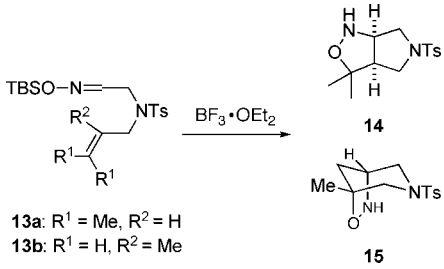


FIGURE 1. Selected NOEs of **12**.

SCHEME 7



examining the cycloaddition of benzaldehyde *O*-TBS oxime **10**[12] with styrene (**18a**) as a simple extension to an intermolecular variant. Oxime **10**, on treatment with styrene (**18a**) (10 equiv) in the presence of 2.2 equiv of $BF_3 \cdot OEt_2$ in 1,2-dichloroethane at 60 °C for 24 h,[13] underwent intermolecular cycloaddition via *N*-boranonitrone **F** to give the *trans*-cycloadduct **11** as a single isomer in 40% yield (Scheme 6).

The stereochemical assignment of the product **11** was carried out on the basis of NOE measurements of the acylated derivative **12** (Figure 1). We next attempted to improve the chemical yield but found that reproducibility of the reaction was poor, and the product **11** was unstable. Typically, we obtained low yield (~10%) with no stereoselectivity (1:1 mixture of diastereomers of the product **11**).

2. Design of *N*-Borano-*C*-ethoxycarbonyl Nitrone and Preparation of Its Precusor. During our study on the intramolecular cycloaddition of *N*-boranonitrone, we observed that electron-rich carbon in the olefin tends to attack the nitrone-carbon. For example, the reaction of oxime **13a** with $BF_3 \cdot OEt_2$ afforded the cycloadduct **14** having a bicyclo[3.3.0] system, whereas a similar reaction of oxime **13b** afforded the cycloadduct **15** having a bicyclo[3.2.1] system (Scheme 7).

These results show that *N*-boranonitrone is electrophilic in nature. Therefore, we anticipated that replacement of the phenyl group in *N*-boranonitrone **F** with an ester group would allow the generation of a more electrophilic intermediary *N*-boranonitrone, which may be activated and more readily undergo the cycloaddition (Figure 2).

To estimate the difference in electrophilic nature of the intermediary *N*-boranonitrones **E′** and **F**, preliminary calculations (AM1) were conducted for the *E*-form of *N*-boranonitrone (Figure 3). Comparison of calculated LUMOs indicates that *N*-boranonitrone having the ester group (**E′**) is more electrophilic than is *N*-boranonitrone bearing the phenyl group (**F**).

As shown in Scheme 8, the requisite *O*-TBS oxime **8** was prepared from commercially available chloral hydrate (**16**). Thus, hydrate **16** was converted into glyoxylate oxime **17**[14] by treatment with hydroxyammonium sulfate in the presence of

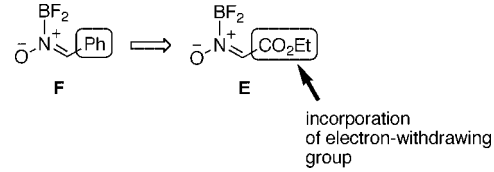


FIGURE 2. Electronic effect of *N*-boranonitrone.

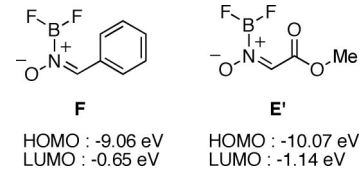
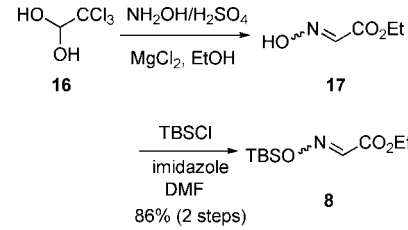


FIGURE 3. Frontier orbitals of **F** and **E′**.

SCHEME 8



$MgCl_2$ in ethanol. Silylation of ethyl glyoxylate oxime (**17**) under usual conditions afforded ethyl glyoxylate *O*-TBS oxime (**8**) in 86% yield (2 steps).

3. Reaction of *N*-Borano-*C*-ethoxycarbonyl Nitrone with Acyclic Alkenes. Treatment of *O*-TBS oxime **8** with various alkenes **18a**−**h** in the presence of 2.2 equiv of $BF_3 \cdot OEt_2$ in 1,2-dichloroethane at 60 °C under argon afforded the corresponding products **19a**−**h** in moderate to good yields (Table 1). In contrast to benzaldehyde *O*-TBS oxime **10**, reaction of *O*-TBS oxime **8** with styrene (**18a**) smoothly proceeded to give the cycloadduct **19a** in 71% yield as a 5:1 mixture of diastereomers (entry 1). This result shows that the *N*-boranonitrone bearing the ester group (**E**) is more electrophilic and reactive than is the *N*-boranonitrone having the phenyl group (**F**), as expected. In addition, reaction of *O*-TBS oximes **8** showed good reproducibility, differing from that of benzaldehyde *O*-TBS oxime **10** with styrene (**18a**). In the case of aliphatic terminal alkenes **18b** and **18c**, *trans*-cycloadducts **19b** and **19c** were obtained in 78% (77:1 diastereoselectivity) and 61% (7:1 diastereoselectivity) yields, respectively, although these reactions required prolonged reaction times (entries 2 and 3). 1,1-Disubstituted alkene **18d** reacted with *N*-boranonitrone **E**, giving rise to 5,5-disubstituted isoxazolidine **19d** in rather low yield, probably due to polymerization of the alkene **18d** during the reaction (entry 4). When *O*-TBS oxime **8** was treated with ethyl methacrylate (**18e**) in the presence of $BF_3 \cdot OEt_2$ for 15 h, cycloadduct **19e** was obtained in 53% yield as a 6:1 mixture of diastereomers (entry 5). This reaction would be applicable for syntheses of naturally occurring 4-hydroxy-4-substituted glutamic acids.[15] Next, reactions of 1,2-disubstituted alkenes were examined by using *trans*- and *cis*-3-hexene (**18f** and **18g**) (entries 6 and 7). Thus, *trans*-3-hexene (**18f**) furnished the corresponding product **19f** as a single isomer in 27% yield, whereas *cis*-3-hexene (**18g**) gave **19f** and **19g** in 33% yield as

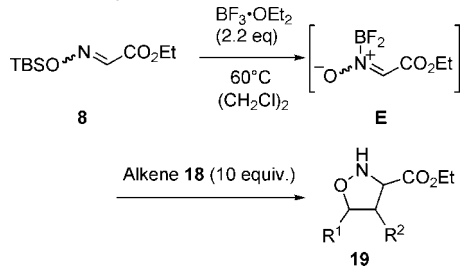
(12) Hoffmann, R. V.; Buntain, G. A. *Synthesis* **1987**, 831.

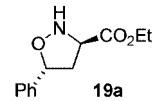
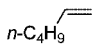
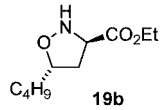
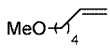
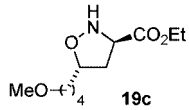
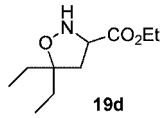
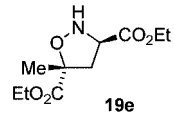
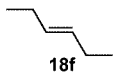
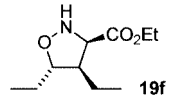
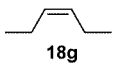
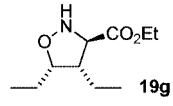
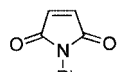
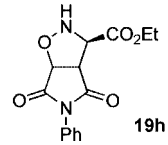
(13) For completion of the cycloaddition, 2 equiv of $BF_3 \cdot OEt_2$ are essential. See ref 9.

(14) Adachi, I.; Yamamori, T.; Hiramatsu, Y. JP 1977-50939.

(15) (a) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569. (b) Baldwin, S. W.; Long, A. *Org. Lett.* **2004**, *6*, 1653.

TABLE 1. Cycloaddition of *O*-TBS Oxime 8 with Alkenes 18a−h in the Presence of $BF_3 \cdot OEt_2$



Entry	Alkene	Time	Product (major)	% Yield [a]
1	**18a**	2 h	 **19a**	71 (5 : 1)
2	 **18b**	18 h	 **19b**	78 (77 : 1)
3	 **18c**	22 h	 **19c**	61 (7 : 1)
4	 **18d**	3 h	 **19d**	33
5	 **18e**	15 h	 **19e**	53 (6 : 1)
6	 **18f**	3 h	 **19f**	27 (single isomer)
7	 **18g**	3 h	 **19g**	33 (**19f**:**19g** = 1:2)
8	 **18h**	6 h	 **19h**	7 (single isomer)

[a] Isolated yields.

a 1:2 mixture of diastereomers. Low yields of the products in both cases may be ascribed to steric interaction and/or instability of olefins during the reactions. The reaction of *O*-TBS oxime **8** with *N*-phenylmaleimide (**18h**) as an electron-poor olefin afforded the corresponding product **19h** as a single isomer in miserable yield (entry 8).

We attempted to elucidate the stereochemistry of cycloadducts **19a−g** by means of NOE measurement. However, the ^{1}H NMR spectra of products **19** often showed broadened signals inappropriate for NOE measurements, probably due to partial coupling with NH of the isoxazolidines. Therefore, determination of the stereochemistry of cycloadducts **19** was carried out after acylation with 3,5-dinitrobenzoyl chloride under usual conditions (Figure 4). The NOE difference spectra revealed that major products **20a−e** have 3,5-*trans* stereochemistry of their isoxazolidine skeleton. The stereochemistry of the product **20f** derived from *trans*-3-hexene (**18f**) has 3,4-*cis* and 4,5-*trans* relationships, whereas the product **20g** derived from *cis*-3-hexene (**18g**) has 3,4-*trans* and 4,5-*cis* relationships of isoxazolidine.

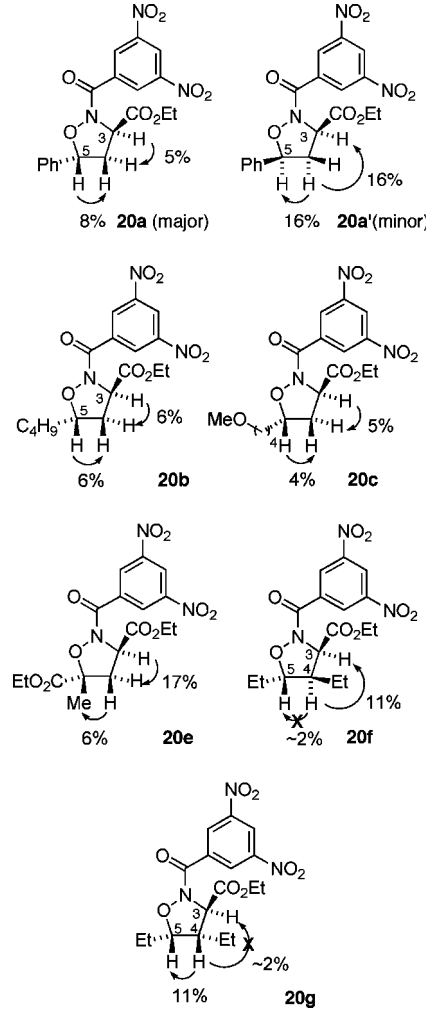
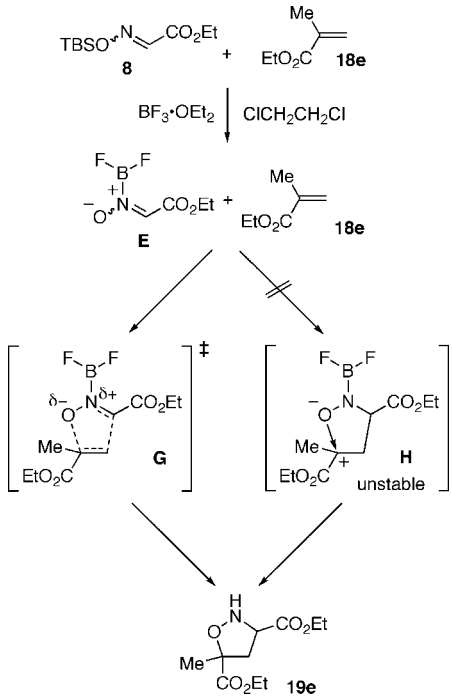


FIGURE 4. Selected NOEs of cycloadducts **20** derived from acyclic alkenes.

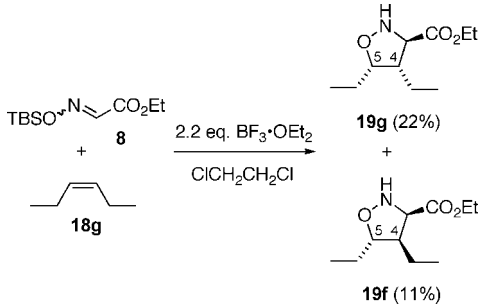
4. Mechanistic Considerations. Reaction of electron-rich styrene (**18a**) gave a good yield of cycloadduct, whereas electron-poor maleimide **18h** was inactive in the reaction (Table 1, entries 1 vs 8). These results strongly suggest that the intermediary *N*-boranonitrone **E** should be electrophilic. Since reaction of **18e** afforded the cycloadduct **19e**, the cycloaddition of *N*-boranonitrone **E** with olefins **18** would proceed through a concerted mechanism. If the reaction proceeds though a typical stepwise mechanism, it would involve the unstable intermediate **H** having a cation adjacent to the ester group (Scheme 9). Accordingly, the reaction should proceed predominantly via the concerted mechanism.

On the other hand, the reaction of *cis*-3-hexene (**18g**) with *N*-boranonitrone **E** gave the 4,5-*cis* cycloadduct **19g** (22%) along with the 4,5-*trans* cycloadduct **19f** (11%) (Scheme 10, Table 1, entry 7). This result indicates that the cycloaddition of **18g** involves both the concerted mechanism and in part the stepwise mechanism.

SCHEME 9



SCHEME 10



For a better understanding of the cycloaddition, calculations on the intermediary *N*-boranonitrone were next conducted. Four types of geometries **E′1**−**E′4** for nitrone **E′** were computed using the RHF/6-31G* basis set (Figure 5). The calculations indicated that (*E*)-nitrone **E′3** and **E′4** are much more stable than (*Z*)-nitrone **E′1** and **E′2**. Optimization of the geometries of **E′3** and **E′4** having the five-membered boracycles revealed that **E′4** is the most stable isomer among the four nitrones **E′1**−**E′4**.

Taking the geometry of **E′4** into account, the energy levels of the transition state (TS) models endo TS **I** and exo TS **J** (using propene as an alkene) were calculated, using the RHF/3-21G(*) basis set (Figure 6). Exo TS **J** was estimated to be 1.2 kcal/mol more stable than endo TS **I**, which may have steric interaction between the methyl group of alkene and the fluorine atom of the nitrone. Accordingly, the cycloaddition of *N*-boranonitrone **E** with terminal alkenes **18a**−**c** should proceed via exo TS **J**, affording the 3,5-*trans* cycloadducts **19a**−**c** (Table 1, entries 1−3). During the cycloaddition, a second equivalent of BF_3 might coordinate to the oxygen anion of *N*-boranonitrone **E**.[16]

5. Reaction of *N*-Borano-*C*-ethoxycarbonyl Nitrone with Cyclic Alkenes. The efficient cycloaddition of *N*-boranonitrone

(16) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725.

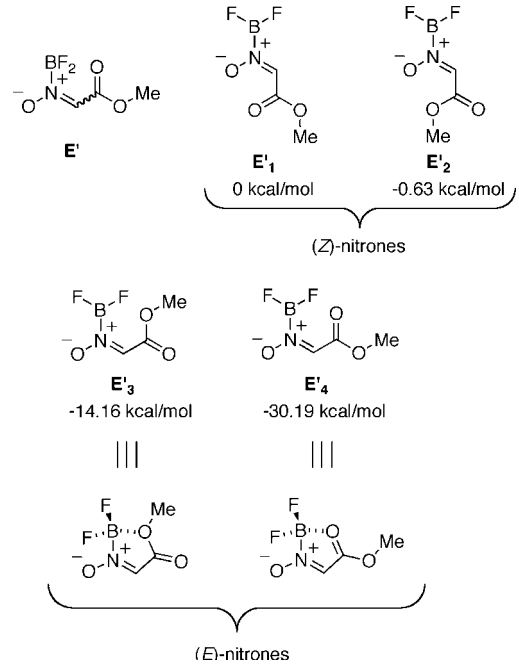


FIGURE 5. Calculation of *N*-boranonitrone **E′** by RHF/6-31G*.

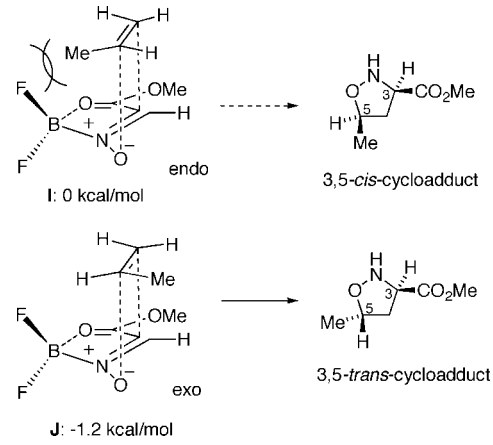


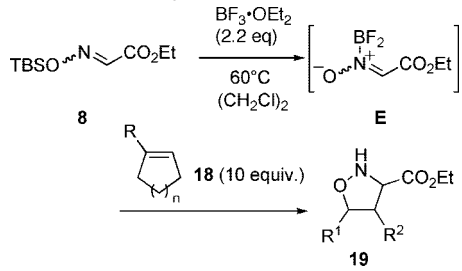
FIGURE 6. Calculation, using RHF/3-21G(*), of transition states for cycloaddition of *N*-boranonitrone with a terminal alkene.

E with acyclic olefins **18a**−**g** prompted us to examine the reaction with cyclic olefins, such as cyclopentenes and cyclohexenes (Table 2). Reactions of *O*-TBS oxime **8** with cyclopentenes **18i** and **18j** in the presence of BF_3•OEt_2 afforded bicyclic products **19i** (8:1 diastereomeric ratio) and **19j** (3:1 diastereomeric ratio) in 65% and 79% yields, respectively (entries 1 and 2). In contrast, it was found that the corresponding cyclohexenes were less reactive. Thus, cycloaddition of cyclohexenes **18k** and **18l** gave the corresponding products in 33% yield (**19k**) as a 8:1 mixture of diastereomers and in 32% yield (**19l**) as a 3:1 mixture of diastereomers (entries 3 and 4).

After acylation, as described above for **19a**−**g** (Figure 4), the stereochemistry of the bicyclic products **19i**−**l** was also determined by analysis of NOE difference spectra of **20i′**, **20j**, **20k′**, and **20l** (Figure 7). Surprisingly, the reaction of cyclopentene (**18i**) and cyclohexene (**18k**) provided 3,3a-*trans* adducts **19i** and **19k**, whereas 1-methylcyclopentene (**18j**) and 1-methylcyclohexene (**18l**) afforded 3,3a-*cis* adducts **19j** and **19l**, respectively.

To understand the difference in stereoselectivity of the reactions between nonsubstituted cyclic alkene (**18i** and **18k**)

TABLE 2. Cycloaddition of *O*-TBS Oxime 8 with Cyclic Alkenes 18i−l in the Presence of $BF_3 \cdot OEt_2$



Entry	Alkene	Time	Product (major)	% Yield [a]
1	**18i**	2 h	**19i**	65 (8 : 1)
2	**18j**	2 h	**19j**	79 (3 : 1)
3	**18k**	6 h	**19k**	33 (8 : 1)
4	**18l**	6 h	**19l**	32 (3 : 1)

and methylated cyclic alkenes (**18j** and **18l**), the energy levels of the transition states TS **K** and **L** for the reactions of cyclopentene and TS **M** and **N** for the reactions of 1-methylcyclopentene were calculated using the RHF/3-21G(*) basis set (Figure 8 and 9). The results indicated that TS **L** is more stable than TS **K** by 4.4 kcal/mol. This conclusion seems reasonable in view of the likely steric interaction between methylenes of cyclopentene and the boracycle of the nitrone and is consistent with the experimental results of cycloaddition of cyclopentene with *N*-boranonitrone, leading to cycloadduct **19i** (Figure 8, Table 2, entry 1). On the other hand, calculations of TSs **M** and **N** for cycloaddition of 1-methylcyclopentene with *N*-boranonitrone indicated that TS **N** leading to **19j′** (minor isomer) was more stable than TS **M** by 4.2 kcal/mol. However, this calculation is inconsistent with the fact that reaction of 1-methylcyclopentene with *N*-boranonitrone gave the 3,3a-*cis* adduct **19j** as the major isomer. This inconsistency may indicate that a stepwise mechanism operates in the reaction of 1-methylcyclopentene. Since even the reaction of *N*-boranonitrone **E** with *cis*-3-hexene (**18g**) proceeds via both a concerted mechanism and a stepwise mechanism, it seems reasonable to consider a stepwise mechanism for the reaction of 1-methylcyclopentene with *N*-boranonitrone, which may generate a stable *tert*-carbocation intermediate. TSs **O** and **P** are candidate transition states of the stepwise mechanism (Figure 10). Since TS **O** has severe steric interaction between the cyclopentene ring and fluorine atom of *N*-boranonitrone, the reaction may proceed via TS **P**. Thus, *N*-boranonitrone reacts with 1-methylcyclopentene (**18j**) via TS **P**, giving the zwitterionic intermediate **Q**, which undergoes C−O bond formation between the oxygen anion and *tert*-carbocation after rotation of the cyclopentane ring about the generated C−C single bond, affording the 3,3a-*cis*-adduct **19j**. Similarly, the reaction of cyclohexene (**18k**) would proceed via a concerted mechanism to give the 3,3a-*trans*-cycloadduct **19k**, whereas the reaction of 1-methylcyclohexene (**18l**) afforded the 3,3a-*cis* adduct **19l**, probably via a stepwise mechanism.

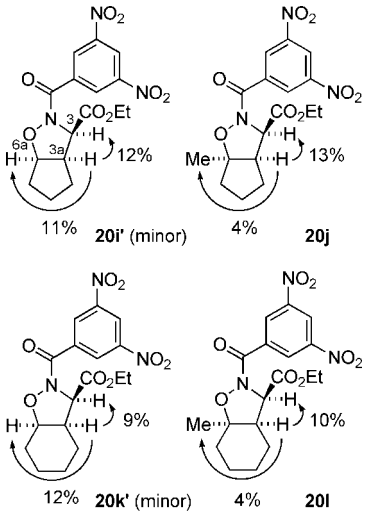


FIGURE 7. Selected NOEs of cycloadducts derived from cyclic alkenes.

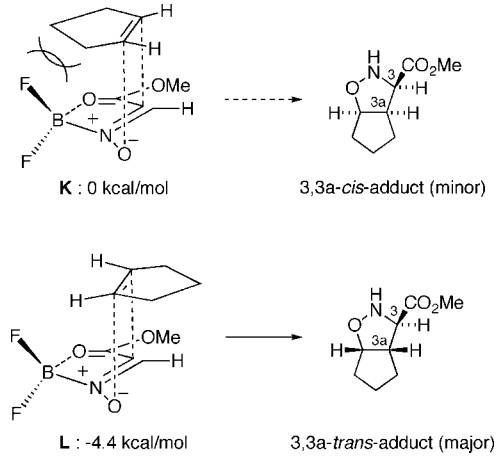


FIGURE 8. Calculated transition states, using RHF/3-21G(*), for cycloaddition of *N*-boranonitrone with cyclopentene (**18i**).

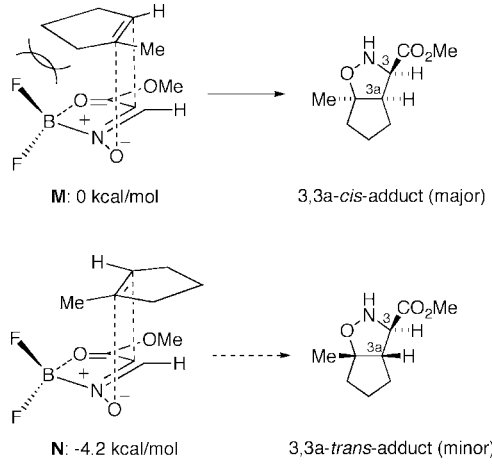


FIGURE 9. Calculated transition states, using RHF/3-21G(*), for cycloaddition of *N*-boranonitrone with 1-methylcyclopentene (**18j**).

6. Application to Synthesis of 1,3-*anti* Aminoalcohols. To validate the applicability of our methodology in organic

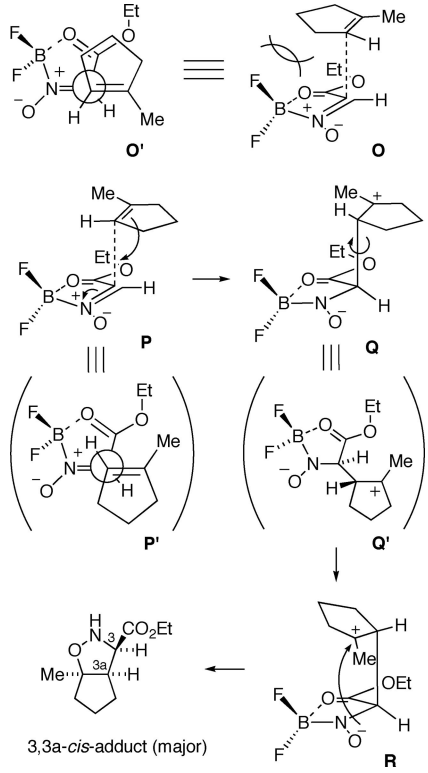
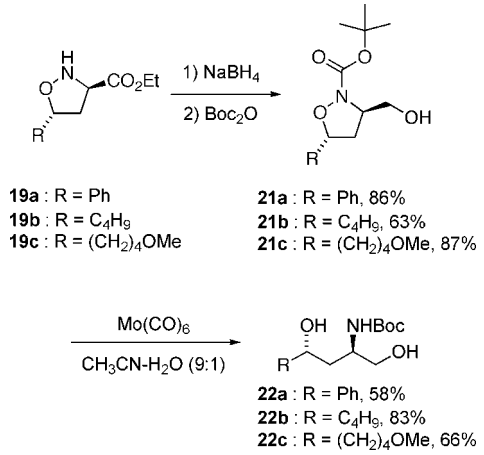


FIGURE 10. Proposed reaction mechanism for reaction of *N*-boranonitrone with 1-methylcyclopentene (**18j**).

SCHEME 11



synthesis, we tried the synthesis of 1,3-*anti* aminoalcohol (Scheme 11). Treatment of isoxazolidines **19a**−**c** with $NaBH_4$ in THF followed by protection with Boc_2O afforded the alcohol derivatives **21a**−**c** in 63−87% yields in two steps. The cleavage of the N−O bond with molybdenum hexacarbonyl in boiling CH_3CN−H_2O gave 1,3-aminoalcohols **22a**−**c** in 58−83% yield. This synthetic sequence demonstrates the potential utility of the present cycloaddition for the synthesis of natural products and related compounds of biological importance.[17]

7. Conclusions. We have explored a highly efficient intermolecular cycloaddition of *N*-boranonitrone **E** with various alkenes to give the corresponding isoxazolidine derivatives in moderate to high yields. *N*-Boranonitrone **E**, generated from *O*-TBS oxime **8** by utilizing the strong N−B and Si−F affinities, is a highly electrophilic and active intermediate. To our knowledge, this is the first example of intermolecular cycloaddition of oxime derivatives with various alkenes. Further extension of the procedure is currently under investigation in our laboratories.

Experimental Section

Ethyl Glyoxylate-*O*-*tert*-butyldimethylsilyloxime (8). To a solution of ethyl 2-hydroxyiminoacetate (**17**)[14] (0.91 g, 7.8 mmol) in DMF (12 mL) were added *tert*-butylchlorodimethylsilane (1.8 g, 12 mmol) and imidazole (1.6 g, 24 mmol) at 0 °C under argon. The mixture was stirred for 46 h, poured into water, and extracted with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography on silica gel with hexane−Et_2O (20:1) to afford **8** (1.8 g, 98%) as a colorless oil. IR (KBr) 1749, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s), 4.30 (2H, q, J = 7.1 Hz), 1.33 (3H, t, J = 7.1 Hz), 0.95 (9H, s), 0.23 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 146.1, 61.3, 25.7, 18.0, 14.0, −5.4; HRMS (EI) m/z calcd for $C_{10}H_{21}NO_3Si$ 231.1291, found 231.1270.

General Procedure for Cycloaddition of *O*-TBS Oxime 8 with Alkenes 18. To a solution of **8** in $(CH_2Cl)_2$ were added alkene **18** and $BF_3\cdot OEt_2$ at room temperature, and then the reaction mixture was stirred at 60 °C for 2−22 h under argon. After complete consumption of **8**, a saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture at 0 °C, and the whole was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane−AcOEt as eluent to afford the product **19**.

General Procedure for the Acylation of the Cycloadducts 19. To a solution of cycloadduct **19** in THF was added Et_3N and 3,5-dinitrobenzoyl chloride at 0 °C under argon. The mixture was stirred for 1−24 h at room temperature, poured into water, and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by evaporation, and the crude product was purified by column chromatography on silica gel with hexane−AcOEt to afford the product **20**.

(3*R,5*R**)-3,5-Diphenylisoxazolidine (11).** A mixture of **10** (200 mg, 0.85 mmol), **18a** (0.97 mL, 8.5 mmol) and $BF_3\cdot OEt_2$ (0.24 mL, 1.9 mmol) in $(CH_2Cl)_2$ (5 mL) furnished **11** (77 mg, 40%) as a colorless oil. [reaction time: 24 h/hexane−AcOEt = 10:1] ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.25 (10H, m), 5.21 (1H, dd, J = 8.1, 6.9 Hz), 4.72−4.65 (1H, br d, J = 7.5 Hz), 2.81−2.63 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 135.3, 129.1, 128.8, 128.1, 127.3, 126.1, 124.8, 83.3, 61.0, 41.5; HRMS (EI) m/z calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1148.

(3*R,5*R**)-3,5-Diphenyl-2-(3,5-dinitrobenzoyl)isoxazolidine (12).** A mixture of cycloadduct **11** (17 mg, 0.075 mmol), Et_3N (12 μL, 0.083 mmol) and 3,5-dinitrobenzoyl chloride (19 mg, 0.083 mmol) in THF (3 mL) furnished **12** (24 mg, 75%) as a colorless oil. [reaction time: 12 h/hexane−AcOEt = 5:1] IR (neat) 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.02 (1H, br t, J = 2.1 Hz), 8.66 (2H, d, J = 2.4 Hz), 7.53−7.13 (10H, m), 5.94 (1H, dd, J = 8.7, 5.7 Hz; spin saturation at δ = 3.21/5% NOE), 5.53 (1H, dd, J = 7.2, 4.2 Hz; spin saturation at δ = 2.84/5% NOE), 3.21 (1H, ddd, J = 12.9, 8.7, 3.9 Hz), 2.84 (1H, ddd, J = 12.9, 7.2, 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 148.1, 140.2, 136.4, 134.8, 129.7, 129.4, 129.1, 128.9, 128.1, 126.7, 126.2, 121.0, 85.3, 62.0, 45.6; HRMS (EI) m/z calcd for $C_{22}H_{17}N_3O_6$ 419.1117, found 419.1115.

(3*R,5*R**)-5-Phenylisoxazolidine-3-carboxylic Acid Ethyl Ester (19a) and (3*R**,5*S**)-5-Phenylisoxazolidine-3-carboxylic Acid Ethyl Ester (19a′).** A mixture of **8** (210 mg, 0.91 mmol), **18a** (1.5 mL, 13 mmol) and $BF_3\cdot OEt_2$ (0.25 mL, 1.9 mmol) in $(CH_2Cl)_2$ (5 mL)

(17) (a) Stauffer, C. S.; Bhaket, P.; Fothergill, A. W.; Rinaldi, M. G.; Datta, A. *J. Org. Chem.* **2007**, *72*, 9991. (b) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647. (c) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396.

afforded **19a** (120 mg, 59%) and **19a′** (25 mg, 12%), each as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 2:1] **19a**: IR (KBr) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (5H, m), 6.09 (1H, br s), 5.03 (1H, br s), 4.22 (2H, q, J = 7.2 Hz), 4.22−4.16 (1H, m), 3.02−2.93 (1H, m), 2.53−2.44 (1H, m), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 134.4, 128.6, 128.2, 126.4, 83.0, 61.8, 61.6, 42.7, 14.1; HRMS (EI) m/z calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1054. **19a′**: IR (KBr) 1734 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (5H, m), 7.10 (1H, br s), 5.03 (1H, br s), 4.23 (2H, q, J = 7.2 Hz), 4.20 (1H, m), 2.98 (1H, ddd, J = 12.6, 8.7, 7.5 Hz), 2.49 (1H, m), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 139.0, 128.6, 128.2, 126.4, 85.0, 62.0, 61.7, 41.6, 14.1; HRMS (FAB) m/z calcd for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1130, found 222.1128.

(3*R,5*R**)-2-(3,5-Dinitrobenzoyl)-5-phenylisoxazolidine-3-carboxylic Acid Ethyl Ester (20a).** A mixture of cycloadduct **19a** (43 mg, 0.19 mmol), Et_3N (32 μL, 0.23 mmol) and 3,5-dinitrobenzoyl chloride (58 mg, 0.25 mmol) in THF (5 mL) furnished **20a** (74 mg, 91%) as a colorless oil. [reaction time: 5 h/hexane−AcOEt = 2:1] IR (KBr) 1743, 1661 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.01 (1H, br t, J = 2.1 Hz), 8.74 (2H, d, J = 2.1 Hz), 7.51−7.29 (5H, m), 5.62 (1H, br t, J = 6.0 Hz), 5.33 (1H, dd, J = 9.0, 4.5 Hz), 4.29 (2H, q, J = 7.2 Hz), 3.13 (1H, ddd, J = 12.9, 9.0, 6.0 Hz; spin saturation at δ = 5.33/5% NOE), 3.00 (1H, ddd, J = 12.9, 6.0, 4.5 Hz; spin saturation at δ = 5.62/8% NOE), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 163.6, 147.9, 136.0, 135.0, 129.6, 129.3, 128.9, 127.0, 120.7, 82.9, 62.5, 59.0, 37.3, 14.2; HRMS (EI) m/z calcd for $C_{19}H_{17}N_3O_8$ 415.1016, found 415.1005.

(3*R,5*S**)-2-(3,5-Dinitrobenzoyl)-5-phenylisoxazolidine-3-carboxylic Acid Ethyl Ester (20a′).** A mixture of cycloadduct **19a′** (20 mg, 0.090 mmol), Et_3N (15 μL, 0.11 mmol) and 3,5-dinitrobenzoyl chloride (31 mg, 0.13 mmol) in THF (5 mL) furnished **20a′** (26 mg, 71%) as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 2:1] IR (KBr) 1745, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16−9.12 (3H, m), 7.42−7.35 (5H, m), 5.29 (1H, dd, J = 9.3, 7.5 Hz), 5.05 (1H, dd, J = 10.2, 6.0 Hz), 4.32 (2H, q, J = 7.2 Hz), 3.16 (1H, ddd, J = 12.6, 9.3, 6.0 Hz; spin saturation at δ = 5.29/16% NOE; δ = 5.05/16% NOE), 2.63 (1H, ddd, J = 12.6, 10.2, 7.5 Hz), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 163.6, 148.1, 135.7, 134.4, 129.7, 129.6, 129.0, 126.7, 121.2, 84.6, 62.4, 59.0, 39.7, 14.1; HRMS (EI) m/z calcd for $C_{19}H_{17}N_3O_8$ 415.1016, found 415.1007.

(3*R,5*S**)-5-Butylisoxazolidine-3-carboxylic Acid Ethyl Ester (19b) and (3*R**,5*R**)-5-Butylisoxazolidine-3-carboxylic Acid Ethyl Ester (19b′).** A mixture of **8** (300 mg, 1.3 mmol), **18b** (1.60 mL, 13 mmol) and $BF_3\cdot OEt_2$ (0.35 mL, 2.9 mmol) in $(CH_2Cl)_2$ (10 mL) afforded **19b** (200 mg, 77%) and **19b′** (3 mg, 1%), each as a colorless oil. [reaction time: 18 h/hexane−AcOEt = 2:1] **19b**: IR (KBr) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, br s), 4.22 (2H, q, J = 7.2 Hz), 4.00 (1H, br q, J = 4.5 Hz), 3.87−3.83 (1H, m), 2.35−2.25 (1H, m), 2.17−2.07 (1H, m), 1.70−1.62 (1H, m), 1.61−1.50 (1H, m), 1.48−1.30 (4H, m), 1.29 (3H, t, J = 7.2 Hz), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 81.8, 61.6, 61.1, 40.4, 32.7, 28.4, 22.6, 14.0, 13.9; HRMS (EI) m/z calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1382. **19b′**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (2H, q, J = 7.2 Hz), 4.03−3.90 (2H, m), 2.63 (1H, ddd, J = 12.3, 9.0, 7.2 Hz), 2.00−1.95 (1H, m), 1.70−1.20 (6H, m), 1.30 (3H, t, J = 6.9 Hz), 0.90 (3H, t, J = 6.9 Hz); HRMS (EI) m/z calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1362.

(3*R,5*S**)-5-Butyl-2-(3,5-dinitrobenzoyl)isoxazolidine-3-carboxylic Acid Ethyl Ester (20b).** A mixture of cycloadduct **19b** (7.0 mg, 0.035 mmol), Et_3N (40 μL, 0.29 mmol) and 3,5-dinitrobenzoyl chloride (41 mg, 0.18 mmol) in THF (5 mL) furnished **20b** (11 mg, 83%) as a colorless oil. [reaction time: 3 h/hexane−AcOEt = 4:1] IR (KBr) 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17−9.15 (3H, m), 5.01 (1H, dd, J = 9.6, 3.3 Hz; spin saturation at δ = 2.40/6% NOE), 4.57−4.48 (1H, m; spin saturation at δ = 2.60/6% NOE), 4.30 (2H, br q, J = 7.2 Hz), 2.60 (1H, ddd, J = 12.6, 5.4, 3.3 Hz), 2.40 (1H, ddd, J = 12.6, 9.3, 7.8 Hz), 1.65−1.55 (2H, m), 1.32 (3H, t, J = 7.2 Hz), 1.31−1.28 (4H, m), 0.86 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 161.0, 148.1, 136.0, 129.7, 121.0, 82.0, 62.3, 58.7, 37.2, 32.0, 28.1, 22.3, 14.1, 13.8; HRMS (EI) m/z calcd for $C_{17}H_{21}N_3O_8$ 395.1329, found 395.1327.

(3*R,5*S**)-5-(4-Methoxybutyl)isoxazolidine-3-carboxylic Acid Ethyl Ester (19c) and (3*R**,5*R**)-5-(4-Methoxybutyl)isoxazolidine-3-carboxylic Acid Ethyl Ester (19c′).** A mixture of **8** (290 mg, 1.30 mmol), **18c** (1.4 mL, 12 mmol) and $BF_3\cdot OEt_2$ (0.36 mL, 2.8 mmol) in $(CH_2Cl)_2$ (5 mL) afforded **19c** (150 mg, 53%) and **19c′** (24 mg, 8%), each as a colorless oil. [reaction time: 22 h/hexane−AcOEt = 1:1] **19c**: IR (KBr) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, br s), 4.22 (2H, q, J = 7.2 Hz), 4.02−3.97 (1H, m), 3.86 (1H, br s), 3.36 (2H, t, J = 6.3 Hz), 3.31 (3H, s), 2.35−2.28 (1H, m), 2.18−2.07 (1H, m), 1.75−1.43 (6H, m), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 81.6, 72.4, 61.6, 61.2, 58.5, 40.3, 32.8, 29.5, 22.9, 14.0; HRMS (EI) m/z calcd for $C_{11}H_{21}NO_4$ 231.1471, found 231.1447. **19c′**: IR (KBr) 1724 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, br s), 4.23 (2H, q, J = 7.2 Hz), 4.25−4.18 (1H, m), 4.01 (1H, dd, J = 9.3, 6.0 Hz), 3.38 (2H, t, J = 6.3 Hz), 3.33 (3H, s), 2.69−2.59 (1H, m), 2.05−1.95 (1H, m), 1.73−1.43 (6H, m), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 80.8, 72.5, 61.6, 61.4, 58.6, 43.3, 29.7, 29.5, 22.9, 14.1; HRMS (EI) m/z calcd for $C_{11}H_{21}NO_4$ 231.1471, found 231.1424.

(3*R,5*S**)-2-(3,5-Dinitrobenzoyl)-5-(4-methoxybutyl)isoxazolidine-3-carboxylic Acid Ethyl Ester (20c).** A mixture of cycloadduct **19c** (38 mg, 0.17 mmol), Et_3N (28 μL, 0.20 mmol) and 3,5-dinitrobenzoyl chloride (47 mg, 0.20 mmol) in THF (5 mL) furnished **20c** (37 mg, 52%) as a colorless oil. [reaction time: 24 h/hexane−AcOEt = 5:3] IR (KBr) 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.18−9.13 (3H, m), 5.02 (1H, dd, J = 9.6, 3.3 Hz; spin saturation at δ = 2.41/5% NOE), 4.56−4.47 (1H, m; spin saturation at δ = 2.61/4% NOE), 4.30 (2H, q, J = 6.9 Hz), 3.30 (2H, t, J = 6.0 Hz), 3.27 (3H, s), 2.61 (1H, ddd, J = 12.6, 9.3, 5.7 Hz), 2.41 (1H, ddd, J = 12.6, 9.3, 7.8 Hz), 1.64−1.36 (6H, m), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 161.3, 148.1, 135.9, 129.7, 121.0, 82.0, 72.1, 62.3, 58.6, 58.5, 37.2, 32.2, 29.3, 22.9, 14.1; HRMS (EI) m/z calcd for $C_{18}H_{23}N_3O_9$ 425.1434, found 425.1437.

5,5-Diethylisoxazolidine-3-carbozylic Acid Ethyl Ester (19d). A mixture of **8** (300 mg, 1.3 mmol), **18d** (1.5 mL, 12 mmol) and $BF_3\cdot OEt_2$ (0.36 mL, 2.8 mmol) in $(CH_2Cl)_2$ (5 mL) afforded **19d** (86 mg, 33%) as a colorless oil. [reaction time: 3 h/hexane−AcOEt = 3:1] IR (KBr) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (1H, br s), 4.23 (2H, q, J = 7.2 Hz), 3.99 (1H, dd, J = 9.0, 7.5 Hz), 2.32 (1H, dd, J = 12.5, 9.2 Hz), 2.03 (1H, m), 1.59 (4H, m), 1.30 (3H, t, J = 7.1 Hz), 0.92 (3H, t, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 88.6, 62.1, 61.4, 43.2, 28.6, 28.4, 14.1, 8.5, 8.3; HRMS (EI) m/z calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1361.

(3*R,5*R**)-5-Methylisoxazolidine-3,5-dicarboxylic Acid Diethyl Ester (19e) and (3*R**,5*S**)-5-Methylisoxazolidine-3,5-dicarboxylic Acid Diethyl Ester (19e′).** A mixture of **8** (210 mg, 0.92 mmol), **18e** (1.4 mL, 12 mmol) and $BF_3\cdot OEt_2$ (0.25 mL, 1.9 mmol) in $(CH_2Cl)_2$ (5 mL) afforded **19e** (99 mg, 46%) and **19e′** (15 mg, 7%), each as a colorless oil. [reaction time: 15 h/hexane−AcOEt = 4:1] **19e**: IR (KBr) 1739, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (1H, br d, J = 11.4 Hz), 4.16 (2H, dq, J = 7.2, 1.5 Hz), 4.15 (2H, q, J = 7.2 Hz), 4.07−3.97 (1H, m), 2.62 (1H, dd, J = 12.9, 6.3 Hz), 2.40 (1H, dd, J = 12.9, 9.9 Hz), 1.48 (3H, s), 1.24 (3H, t, J = 7.2 Hz), 1.22 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 170.6, 85.0, 61.7, 61.6, 61.4, 45.0, 21.7, 14.0, 14.0; HRMS (EI) m/z calcd for $C_{10}H_{17}NO_5$ 231.1107, found 231.1093. **19e′**: IR (KBr) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (1H, br s), 4.17 (2H, q, J = 7.2 Hz), 4.16 (2H, q, J = 7.2 Hz), 4.04 (1H, dd, J = 8.7, 4.2 Hz), 2.78−2.74 (1H, m), 2.45−2.40 (1H, m), 1.50 (3H, s), 1.23 (3H, t, J = 7.2 Hz), 1.22 (3H, t, J = 7.2 Hz); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 173.5, 171.5, 85.0, 61.9, 61.7, 61.6, 43.5, 21.3, 14.1, 14.0; HRMS (EI) *m/z* calcd for $C_{10}H_{17}NO_5$ 231.1107, found 231.1117.

(3*R,5*R**)-2-(3,5-Dinitrobenzoyl)-5-methylisoxazolidine-3,5-dicarboxylic Acid Diethyl Ester (20e).** A mixture of cycloadduct **19e** (40 mg, 0.17 mmol), Et_3N (30 μL, 0.20 mmol) and 3,5-dinitrobenzoyl chloride (44 mg, 0.19 mmol) in THF (4 mL) furnished **20e** (65 mg, 90%) as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 2:1] IR (KBr) 1747, 1649 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 9.34 (2H, d, J = 1.8 Hz), 9.20−9.15 (1H, br t, J = 2.1 Hz), 4.92 (1H, dd, J = 10.8, 2.7 Hz), 4.35 (2H, q, J = 7.2 Hz), 4.25 (2H, q, J = 7.2 Hz), 3.17 (1H, dd, J = 13.2, 2.7 Hz; spin saturation at δ = 1.60/6% NOE), 2.60 (1H, dd, J = 13.2, 10.5 Hz; spin saturation at δ = 4.92/17% NOE), 1.60 (3H, s), 1.34 (3H, t, J = 7.2 Hz), 1.31 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 168.0, 160.7, 148.2, 135.8, 129.9, 121.1, 85.9, 62.7, 62.3, 58.4, 40.8, 21.6, 14.0, 14.0; HRMS (EI) *m/z* calcd for $C_{17}H_{19}N_3O_{10}$ 425.1070, found 425.1076.

(3*R,4*R**,5*S**)-4,5-Diethylisoxazolidine-3-carboxylic Acid Ethyl Ether (19f).** A mixture of **8** (500 mg, 2.2 mmol), **18f** (2.6 mL, 28 mmol) and $BF_3\cdot OEt_2$ (0.57 mL, 4.5 mmol) in $(CH_2Cl)_2$ (8 mL) afforded cycloadduct **19f** (120 mg, 27%) as a colorless oil. [reaction time: 3 h/hexane−AcOEt = 2:1] IR (KBr) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, br s), 4.23 (2H, dq, J = 7.2, 3.0 Hz), 4.08 (1H, br d, J = 9.0 Hz), 3.57−3.49 (1H, m), 2.31−2.21 (1H, m), 1.75−1.65 (1H, m), 1.62−1.50 (1H, m), 1.48−1.33 (2H, m), 1.31 (3H, t, J = 7.2 Hz), 1.01 (3H, t, J = 7.2 Hz), 0.95 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 88.2, 65.6, 61.2, 52.4, 26.5, 21.6, 14.1, 12.4, 10.4; HRMS (EI) *m/z* calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1370.

(3*R,4*R**,5*S**)-2-(3,5-Dinitrobenzoyl)-4,5-diethylisoxazolidine-3-carboxylic Acid Ethyl Ester (20f).** The mixture of cycloadduct **19f** (60 mg, 0.30 mmol), NEt_3 (50 μL, 0.36 mmol) and 3,5-dinitrobenzoyl chloride (75 mg, 0.33 mmol) in THF (4 mL) furnished **20f** (87 mg, 74%) as a colorless oil. [reaction time: 1.5 h/hexane−AcOEt = 2:1] IR (KBr) 1747, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17−9.14 (3H, m), 5.03 (1H, d, J = 8.7 Hz), 4.31 (2H, dq, J = 7.2, 2.1 Hz), 4.19 (1H, dt, J = 8.7, 3.3 Hz), 2.49 (1H, ddt, J = 14.4, 8.7, 5.7 Hz; spin saturation at δ = 5.03/11% NOE), 1.83−1.71 (1H, m), 1.61−1.36 (3H, m), 1.35 (3H, t, J = 7.2 Hz), 1.12 (3H, t, J = 7.2 Hz), 1.01 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 160.1, 148.1, 135.9, 129.7, 120.9, 86.3, 62.9, 61.9, 50.3, 24.7, 19.9, 14.2, 12.5, 10.2; HRMS (EI) *m/z* calcd for $C_{17}H_{21}N_3O_8$ 395.1329, found 395.1325.

(3*R,4*S**,5*S**)-4,5-Diethylisoxazolidine-3-carboxylic Acid Ethyl Ether (19g).** A mixture of **8** (370 mg, 1.6 mmol), **18g** (2.0 mL, 16 mmol) and $BF_3\cdot OEt_2$ (0.5 mL, 3.6 mmol) in $(CH_2Cl)_2$ (5 mL) afforded **19g** (72 mg, 22%) and **19f** (36 mg, 11%), each as a colorless oil. [reaction time: 3 h/hexane−AcOEt = 5:1] **19g**: IR (KBr) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, br s), 4.24 (2H, dq, J = 7.2, 2.7 Hz), 3.72−3.65 (2H, m), 2.38−2.30 (1H, m), 1.65−1.45 (3H, m), 1.44−1.35 (1H, m), 1.30 (3H, t, J = 7.2 Hz), 1.00 (6H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 86.0, 66.4, 61.5, 52.9, 21.4, 21.1, 14.0, 11.9, 11.1; HRMS (EI) *m/z* calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1353.

(3*R,4*S**,5*S**)-2-(3,5-Dinitrobenzoyl)-4,5-diethylisoxazolidine-3-carboxylic Acid Ethyl Ester (20g).** A mixture of cycloadduct **19g** (10 mg, 0.050 mmol), Et_3N (15 μL, 0.11 mmol) and 3,5-dinitrobenzoyl chloride (12 mg, 0.050 mmol) in THF (2 mL) furnished **20g** (15 mg, 74%) as a colorless oil. [reaction time: 3 h/hexane−AcOEt = 4:1] IR (KBr) 1755, 1739, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (3H, s), 4.65 (1H, d, J = 5.1 Hz), 4.46−4.40 (1H, m), 4.31 (2H, q, J = 7.2 Hz), 2.70−2.62 (1H, m; spin saturation at δ = 4.46−4.40/11% NOE), 1.62−1.44 (4H, m), 1.34 (3H, t, J = 7.2 Hz), 1.08 (3H, t, J = 7.2 Hz), 0.88 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 160.8, 148.1, 135.9, 129.7, 121.0, 85.8, 63.2, 62.2, 50.2, 20.3, 20.3, 14.1, 12.0, 10.6; HRMS (EI) *m/z* calcd for $C_{17}H_{21}N_3O_8$ 395.1329, found 395.1327.

4,6-Dioxo-5-phenylhexahydropyrrolo[3,4-*d*]isoxazole-3-carboxylic Acid Ethyl Ester (19h). A mixture of **8** (410 mg, 1.8 mmol), **18h** (3.0 g, 13 mmol) and $BF_3\cdot OEt_2$ (0.50 mL, 3.9 mmol) in $(CH_2Cl)_2$ (3 mL) afforded cycloadduct **19h** (36 mg, 7%) as a colorless oil. [reaction time: 6 h/hexane−AcOEt = 2:1] IR (KBr) 1726, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.40 (3H, m), 7.29−7.27 (2H, m), 5.95 (1H, d, J = 13.5 Hz), 5.21 (1H, d, J = 7.5 Hz), 4.36 (1H, d, J = 9.0 Hz), 4.35−4.26 (2H, m), 4.02 (1H, dd, J = 9.0, 7.5 Hz), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.9, 167.5, 130.8, 129.4, 129.3, 126.3, 80.9, 65.3, 62.9, 52.5, 14.0; HRMS (EI) *m/z* calcd for $C_{14}H_{14}N_2O_5$ 290.0903, found 290.0895.

(3*R,3a*S**,6a*S**)-Octahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Ethyl Ester (19i) and (3*R**,3a*R**,6a*R**)-Octahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Ethyl Ester (19i′).** A mixture of **8** (100 mg, 0.43 mmol), **18i** (0.38 mL, 4.3 mmol) and $BF_3\cdot OEt_2$ (0.12 mL, 0.95 mmol) in $(CH_2Cl)_2$ (3 mL) afforded **19i** (46 mg, 58%) and **19i′** (6 mg, 7%) as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 4:1] **19i**: IR (KBr) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (1H, br s), 4.53 (1H, dd, J = 6.9, 5.4 Hz), 4.24 (2H, dq, J = 7.2, 1.8 Hz), 3.51 (1H, br d, J = 6.6 Hz), 2.94 (1H, br d, J = 6.0 Hz), 1.95−1.90 (1H, m), 1.80−1.65 (4H, m), 1.54−1.45 (1H, m), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 89.1, 69.3, 61.3, 54.1, 32.2, 31.2, 23.2, 14.0; HRMS (EI) *m/z* calcd for $C_9H_{15}NO_3$ 185.1052, found 185.1035. **19i′**: IR (KBr) 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, br s), 4.70 (1H, br s), 4.24 (2H, q, J = 7.2 Hz), 4.07 (1H, d, J = 7.8 Hz), 3.27−3.17 (1H, m), 1.92−1.80 (1H, m), 1.78−1.45 (5H, m), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 87.9, 66.1, 61.2, 50.7, 33.2, 27.8, 26.1, 14.2; HRMS (EI) *m/z* calcd for $C_9H_{15}NO_3$ 185.1052, found 185.1045.

(3*R,3a*R**,6a*R**)-2-(3,5-Dinitrobenzoyl)hexahydrocyclopenta[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (20i′).** A mixture of cycloadduct **19i′** (12 mg, 0.063 mmol), Et_3N (10 μL, 0.069 mmol) and 3,5-dinitrobenzoyl chloride (16 mg, 0.069 mmol) in THF (2 mL) furnished **20i′** (24 mg, quant.) as a colorless oil. [reaction time: 1 h/hexane−AcOEt = 3:1] IR (KBr) 1741, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (1H, br t, J = 2.1 Hz), 9.09 (2H, d, J = 2.1 Hz), 5.25 (1H, d, J = 9.6 Hz), 4.70−4.67 (1H, m), 4.31 (2H, q, J = 7.2 Hz), 3.47−3.37 (1H, m; spin saturation at δ = 5.25/12% NOE; δ = 4.70−4.67/11% NOE), 2.05−1.68 (6H, m), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 162.3, 148.1, 136.0, 129.7, 121.0, 89.8, 62.5, 61.9, 48.8, 29.9, 27.7, 25.2, 14.2; HRMS (EI) *m/z* calcd for $C_{16}H_{17}N_3O_8$ 379.1016, found 379.1029.

(3*R,3a*R**,6a*R**)-6a-Methyloctahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Ethyl Ester (19j) and (3*R**,3a*S**,6a*S**)-6a-Methyloctahydrocyclopenta[*c*]pyrrole-1-carboxylic Acid Ethyl Ester (19j′).** A mixture of **8** (300 mg, 1.3 mmol), **18j** (1.4 mL, 13.0 mmol) and $BF_3\cdot OEt_2$ (0.31 mL, 2.9 mmol) in $(CH_2Cl)_2$ (10 mL) afforded **19j** (160 mg, 61%) and **19j′** (47 mg, 18%), each as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 3:1] **19j**: IR (KBr) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (1H, br s), 4.22 (2H, q, J = 7.2 Hz), 4.12 (1H, d, J = 7.5 Hz), 2.73 (1H, dd, J = 14.4, 7.5 Hz), 1.82−1.72 (4H, m), 1.58−1.40 (2H, m), 1.40 (3H, s), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 95.5, 66.0, 61.1, 55.7, 39.5, 28.2, 26.4, 24.8, 14.2; HRMS (EI) *m/z* calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1187. **19j′**: IR (KBr) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (1H, br s), 4.24 (2H, dq, J = 7.2, 2.1 Hz), 3.56 (1H, d, J = 6.6 Hz), 2.49 (1H, br s), 1.98−1.90 (1H, m), 1.85−1.40 (5H, m), 1.37 (3H, s), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 96.1, 70.2, 61.4, 59.2, 38.5, 32.2, 24.4, 23.5, 14.1; HRMS (EI) *m/z* calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1201.

(3*R,3a*R**,6a*R**)-2-(3,5-Dinitrobenzoyl)-6a-methylhexahydrocyclopenta[*d*]-isoxazole-3-carboxylic Acid Ethyl Ester (20j).** A mixture of cycloadduct **19j** (72 mg, 0.36 mmol), Et_3N (56 μL, 0.40 mmol) and 3,5-dinitrobenzoyl chloride (92 mg, 0.40 mmol) in THF (3 mL) furnished **20j** (120 mg, 87%) as a colorless oil. [reaction time: 12

h/hexane−AcOEt = 3:1] IR (KBr) 1735, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.15 (1H, br t, J = 2.1 Hz), 9.09 (2H, d, J = 2.1 Hz), 5.24 (1H, d, J = 9.3 Hz), 4.31 (2H, q, J = 7.2 Hz), 3.07−2.99 (1H, m; spin saturation at δ = 5.24/13% NOE; δ = 1.36/4% NOE), 2.13−2.05 (1H, m), 2.01−1.62 (5H, m), 1.36 (3H, s), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 162.4, 148.1, 136.0, 129.7, 120.9, 98.0, 62.8, 61.8, 53.2, 36.2, 28.7, 25.4, 22.1, 14.2; HRMS (EI) *m*/*z* calcd for $C_{17}H_{19}N_3O_8$ 393.1172, found 393.1165.

(3*R,3a*S**,7a*S**)-Octahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (19k) and (3*R**,3a*R**,7a*R**)-Octahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (19k′).** A mixture of **8** (200 mg, 0.86 mmol), **18k** (0.88 mL, 8.6 mmol) and $BF_3\cdot OEt_2$ (0.24 mL, 1.9 mmol) in $(CH_2Cl)_2$ (5 mL) afforded an inseparable mixture of **19k** and **19k′** (57 mg, 33%, dr = 8:1 by ^1H NMR analysis) as a colorless oil. [reaction time: 6 h/hexane−AcOEt = 3:1] **19k** and **19k′**: IR (KBr) 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.33−4.28/3.85−3.82* (1H, m), 4.23* (2H, q, J = 7.2 Hz), 4.23/3.70* (1H, br d, J = 2.4 Hz), 2.56−2.52/2.51−2.43* (1H, m), 2.10−1.45 (8H, m), 1.30*/1.27 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8*, 77.7*, 66.9*, 65.1, 61.6*, 61.3, 61.2, 47.2*, 43.9, 27.9*, 25.9, 25.4*, 23.7*, 23.5, 21.7, 20.0*, 19.9, 14.0*, 13.9; HRMS (EI) *m*/*z* calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1212.

(3*R,3a*S**,7a*S**)-2-(3,5-Dinitrobenzoyl)octahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (20k) and (3*R**,3a*R**,7a*R**)-2-(3,5-Dinitrobenzoyl)octahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (20k′).** A mixture of cycloadduct **19k** and **19k′** (70 mg, 0.35 mmol), Et_3N (59 μL, 0.42 mmol) and 3,5-dinitrobenzoyl chloride (97 mg, 0.42 mmol) in THF (3 mL) furnished **20k** (71 mg, 51%) and **20k′** (7 mg, 5%), each as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 3:1] **20k**: IR (KBr) 1742, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.15−9.12 (3H, m), 4.67 (1H, br d, J = 3.3 Hz), 4.59 (1H, dd, J = 8.7, 4.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 2.73−2.71 (1H, m), 1.95−1.42 (8H, m), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.0, 148.1, 136.1, 129.6, 120.9, 79.3, 64.3, 62.2, 44.0, 26.3, 25.4, 22.6, 20.3, 14.1; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{20}N_3O_8$ $[M + H]^+$ 394.1250, found 394.1260. **20k′**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.18−9.13 (3H, m), 5.02 (1H, d, J = 6.9 Hz), 4.30 (2H, q, J = 7.2 Hz), 4.20−4.17 (1H, m), 2.92−2.83 (1H, m; spin saturation at δ = 5.02/9% NOE; δ = 4.20−4.17/12% NOE), 2.10−1.50 (8H, m), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 163.4, 148.1, 136.0, 129.9, 121.1, 81.1, 64.5, 61.9, 42.0, 25.4, 23.5, 22.7, 19.7, 14.3; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{20}N_3O_8$ $[M + H]^+$ 394.1250, found 364.1242.

(3*R,3a*R**,7a*R**)-7a-Methyloctahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (19l) and (3*R**,3a*S**,7a*S**)-7a-Methyloctahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (19l′).** A mixture of **8** (200 mg, 0.86 mmol), **18l** (1.0 mL, 8.6 mmol) and $BF_3\cdot OEt_2$ (0.24 mL, 1.9 mmol) in $(CH_2Cl)_2$ (5 mL) afforded an inseparable mixture of **19l** and **19l′** (59 mg, 32%, dr = 3:1 by ^1H NMR analysis) as a colorless oil. [reaction time: 6 h/hexane−AcOEt = 3:1] **19l** and **19l′**: ^1H NMR (300 MHz, CD_3OD) δ 4.31*/3.89 (1H, br d, J = 7.2 Hz), 4.21 (2H, q, J = 7.2 Hz), 2.46−2.38*/2.30−2.26 (1H, m), 1.87−1.80 (1H, m), 1.75−1.63 (1H, m), 1.60−1.40 (6H, m), 1.28*/1.27 (3H, t, J = 7.2 Hz), 1.26/1.24* (3H, s).

(3*R,3a*R**,7a*R**)-2-(3,5-Dinitrobenzoyl)-7a-methyloctahydrobenzo[*d*]isoxazole-3-carboxylic Acid Ethyl Ester (20l) and (3*R**,3a*S**,7a*S**)-2-(3,5-Dinitrobenzoyl)-7a-methyloctahydrobenzo[*d*]-isoxazole-3-carboxylic Acid Ethyl Ester (20l′).** A mixture of cycloadduct **19l** and **19l′** (40 mg, 0.18 mmol), Et_3N (28 μL, 0.20 mmol) and 3,5-dinitrobenzoyl chloride (47 mg, 0.20 mmol) in THF (10 mL) furnished **20l** (54 mg, 72%) and **20l′** (21 mg, 28%), each as a colorless oil. [reaction time: 2 h/hexane−AcOEt = 3:1] **20l**: IR (KBr) 1755, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21−9.12 (3H, m), 5.08 (1H, d, J = 7.2 Hz), 4.30 (2H, q, J = 7.2 Hz), 2.66−2.57 (1H, m; spin saturation at δ = 5.08/10% NOE; spin saturation at δ = 1.14/4% NOE), 2.08−2.03 (1H, m), 1.79−1.75 (1H, m), 1.66−1.30 (6H, m), 1.34 (3H, t, J = 7.2 Hz), 1.14 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 148.1, 136.1, 129.9, 129.9, 121.0, 85.7, 64.2, 61.9, 46.2, 32.5, 24.6, 24.0, 23.3, 21.0, 14.2; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{22}N_3O_8$ $[M + H]^+$ 408.1407, found 408.1396. **20l′**: IR (KBr) 1728, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16−9.14 (1H, m), 9.11 (2H, br d, J = 2.4 Hz), 4.78 (1H, d, J = 9.9 Hz), 4.30 (2H, dq, J = 7.5, 1.2 Hz), 2.57−2.54 (1H, m), 2.13−2.09 (1H, m), 1.79−1.50 (7H, m), 1.44 (3H, s), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 148.1, 136.1, 129.9, 129.8, 120.9, 86.5, 62.1, 61.7, 50.0, 31.4, 23.6, 22.8, 21.3, 19.9, 14.2; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{22}N_3O_8$ $[M + H]^+$ 408.1407, found 408.1415.

General Procedure for the Synthesis of 1,3-Anti Aminoalcohols 22. Reduction: To a solution of **19** in MeOH was added slowly $NaBH_4$ at 0 °C under argon. After complete consumption of **19** (the reaction was monitored by thin layer chromatograghy), the solvent was removed by evaporation. Ethyl acetate and water were added to the residue, and the whole was extracted with AcOEt. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude 3-hydroxymethylisoxazolidine derivative. This material was used for next reaction without further purification. Protection: To a solution of the above 3-hydroxymethylisoxazolidine derivative in CH_3CN was added slowly Boc_2O at 0 °C under argon, and the mixture was stirred at room temperature (for **21b**) or 60 °C (for **21a** and **21c**). After evaporation, the residue was purified by column chromatography on silica gel with hexane−AcOEt to afford the product **21** as a colorless oil. Cleavage of the N−O bond in isoxazolizine derivatives: To a solution of **21** in CH_3CN-H_2O (9:1) was added $Mo(CO)_6$ at room temperature. The reaction mixture was stirred at reflux and concentrated. The residue was purified by column chromatography on silica gel with hexane−AcOEt to afford **22** as a colorless oil.

(3*R,5*R**)-3-Hydroxymethyl-5-phenylisoxazolidine-2-carboxylic Acid *tert*-Butyl Ester (21a).** Reduction: A mixture of **19a** (50 mg, 0.23 mmol) and $NaBH_4$ (86 mg, 2.3 mmol) in MeOH (2 mL) afforded crude (3*R**,5*R**)-3-hydroxymethyl-5-phenylisoxazolidine [reaction time: 1 h]. Protection: A mixture of the above compound (41 mg, 0.23 mmol) and Boc_2O (82 mg, 0.34 mmol) furnished **21a** (54 mg, 86%). [reaction time: 1 h/hexane−AcOEt = 2:1] IR (KBr) 3450, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.31 (5H, m), 5.28 (1H, dd, J = 7.0, 5.0 Hz), 4.30 (1H, ddt, J = 8.5, 6.0, 3.6 Hz), 3.80 (1H, ddd, J = 11.0, 6.6, 3.6 Hz), 3.71 (1H, ddd, J = 11.0, 6.5, 5.0 Hz), 3.05 (1H, dd, J = 6.6, 5.0 Hz), 2.63 (1H, ddd, J = 12.5, 8.5, 5.0 Hz), 2.48 (1H, ddd, J = 12.5, 7.0, 6.0 Hz), 1.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 138.3, 128.4, 128.3, 126.6, 82.2, 81.1, 64.9, 60.8, 36.8, 28.0; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{22}NO_4$ $[M + H]^+$ 280.1549, found 280.1546.

(2*R,4*R**)-2-(*N*-*tert*-Butoxycarbonyl)amino-4-phenyl-1,4-butanediol (22a).** A mixture of **21a** (27 mg, 0.10 mmol) and $Mo(CO)_6$ (26 mg, 0.10 mmol) in CH_3CN-H_2O (9:1, 2 mL) afforded **22a** (16 mg, 58%). [reaction time: 1 h/hexane−AcOEt = 2:1] IR (KBr) 3400, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (5H, m), 5.16 (1H, br d, J = 8.1 Hz), 4.75 (1H, br d, J = 8.7 Hz), 4.03 (1H, br s), 4.02−3.95 (1H, m), 3.80−3.70 (1H, m), 3.68−3.60 (1H, m), 2.40 (1H, br s), 1.90−1.78 (2H, m), 1.47 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 144.1, 128.4, 127.3, 125.5, 80.2, 70.4, 65.5, 49.7, 42.3, 28.3; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{24}NO_4$ $[M + H]^+$ 282.1705, found 282.1694.

(3*R,5*S**)-5-Butyl-3-hydroxymethylisoxazolidine-2-carboxylic Acid *tert*-Butyl Ester (21b).** Reduction: A mixture of **19b** (47 mg, 0.23 mmol) and $NaBH_4$ (88 mg, 2.3 mmol) in MeOH (2 mL) afforded crude (3*R**,5*R**)-5-butyl-3-hydroxymethylisoxazolidine [reaction time: 2 h]. Protection: A mixture of the above compound (26 mg, 0.16 mmol) and Boc_2O (35 mg, 0.16 mmol) in CH_3CN (1 mL) furnished **21b** (26 mg, 63%). [reaction time: 3 h/hexane−AcOEt = 1:2] IR (KBr) 3455, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29−4.15 (2H, m), 3.73−3.66 (1H, m), 3.62−3.55 (1H, m), 2.76 (1H, br t, J = 4.9 Hz), 2.18−2.01 (2H, m), 1.58−1.47 (2H, m),

1.51 (9H, s), 1.40−1.28 (4H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 82.2, 80.8, 65.1, 60.5, 36.2, 33.2, 28.3, 28.2, 22.5, 14.0. HRMS (FAB) m/z calcd for $C_{13}H_{26}NO_4$ [M + H]$^+$ 260.1862, found 260.1867.

(2*R,4*S**)-2-(*N*-*tert*-Butoxycarbonyl)amino-1,4-octanediol (22b).** A mixture of **21b** (13 mg, 0.051 mmol) and $Mo(CO)_6$ (67 mg, 0.26 mmol) in CH_3CN-H_2O (9:1, 2 mL) afforded **22b** (11 mg, 83%). [reaction time: 2 h/hexane−AcOEt = 2:3] IR (KBr) 3385, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (1H, br d, J = 8.4 Hz), 3.94−3.86 (1H, m), 3.76−3.73 (1H, m), 3.65−3.59 (2H, m), 3.58 (1H, br s), 2.12 (1H, br s), 1.66−1.57 (2H, m), 1.54−1.46 (2H, m), 1.45 (9H, m), 1.42−1.26 (4H, m), 0.90 (3H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 80.0, 67.9, 65.7, 49.4, 40.1, 36.9, 28.3, 28.1, 22.6, 14.1. HRMS (FAB) m/z calcd for $C_{13}H_{28}NO_4$ [M + H]$^+$ 262.2018, found 262.2006.

(3*R,5*S**)-3-Hydroxymethyl-5-(4-methoxybutyl)isoxazolidine-2-carboxylic Acid *tert*-Butyl Ester (21c).** Reduction: A mixture of **19c** (88 mg, 0.39 mmol) and $NaBH_4$ (146 mg, 3.9 mmol) in MeOH (3 mL) afforded crude (3*R**,5*S**)-3-hydroxymethyl-5-(4-methoxybutyl)isoxazolidine [reaction time: 1.5 h]. Protection: A mixture of the above compound (73 mg, 0.39 mmol) and Boc_2O (93 mg, 0.42 mmol) furnished **21c** (97 mg, 87%). [reaction time: 2 h/hexane−AcOEt = 1:2] IR (KBr) 3455, 1701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29−4.16 (2H, m), 3.70 (1H, ddd, J = 11.5, 6.9, 3.6 Hz), 3.58 (1H, ddd, J = 11.5, 6.9, 5.0 Hz), 3.38 (2H, br t, J = 6.0 Hz), 3.33 (3H, s), 2.75 (1H, br t, J = 6.0 Hz), 2.15 (1H, ddd, J = 12.5, 6.9, 6.0 Hz), 2.06 (1H, ddd, J = 12.5, 8.7, 4.5 Hz), 1.62−1.56 (4H, m), 1.51 (9H, s), 1.46−1.37 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 82.3, 80.6, 72.5, 65.1, 60.5, 58.6, 36.1, 33.3, 29.4, 28.2, 22.8; HRMS (FAB) m/z calcd for $C_{14}H_{28}NO_5$ [M + H]$^+$ 290.1967, found 290.1960.

(2*R,4*S**)-8-Methoxy-2-(*N*-*tert*-butoxycarbonyl)amino-1,4-octanediol (22c).** A mixture of **21c** (40 mg, 0.14 mmol) and $Mo(CO)_6$ (73 mg, 0.28 mmol) in CH_3CN-H_2O (9:1, 3 mL) afforded **22c** (27 mg, 66%). [reaction time: 12 h/hexane−AcOEt = 1:3] IR (KBr) 3390, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (2H, br d, J = 8.4 Hz), 3.90−3.82 (2H, m), 3.75−3.68 (1H, m), 3.65−3.58 (1H, m), 3.38 (2H, br t, J = 6.0 Hz), 3.33 (3H, s), 2.55 (1H, br s), 1.66−1.40 (8H, m), 1.45 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 80.0, 72.7, 67.7, 65.5, 58.5, 49.4, 40.1, 36.9, 29.5, 28.3, 22.5; HRMS (FAB) m/z calcd for $C_{14}H_{30}NO_5$ [M + H]$^+$ 292.2124, found 292.2139.

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Supporting Information Available: Preparation of compounds; ^{1}H and ^{13}C NMR spectra for compounds; AM1 calculation of **E′** and **F**; RHF/6-31G* calculation of $\mathbf{E'_1}$, $\mathbf{E'_2}$, $\mathbf{E'_3}$, $\mathbf{E'_4}$; RHF/3-21G$^{(*)}$ calculation of TS **I**, TS **J**, TS **K**, TS **L**, TS **M**, and TS **N**. This material is available free of charge via the Internet at http://pubs.acs.org.

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