JOC Article

Efficient Entry to Highly Functionalized β-Lactams by Regio- and Stereoselective 1,3-Dipolar Cycloaddition Reaction of 2-Azetidinone-Tethered Nitrones. Synthetic Applications

Benito Alcaide,*[,†] Pedro Almendros,[†] Jose M. Alonso,[†] Moustafa F. Aly,[†,§] Carmen Pardo,[†] Elena Sáez,[†] and M. Rosario Torres[‡,||]

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain, and Laboratorio de Difracción de Rayos X, Facultad de Química, Universidad Complutense 28040-Madrid, Spain

alcaideb@quim.ucm.es

Received May 10, 2002

Racemic as well as optically pure 2-azetidinone-tethered nitrones, both cyclic and acyclic, were smoothly prepared from 4-oxoazetidine-2-carbaldehydes. The regio- and diastereoselectivities of the intermolecular 1,3-dipolar cycloaddition reactions of 2-azetidinone-tethered nitrones with substituted alkenes and alkynes were investigated. 2-Azetidinone-tethered nitrones on reacting with various dipolarophiles yielded isoxazolinyl-, isoxazolidinyl-, or fused polycyclic-β-lactams, exhibiting good regio- and facial stereoselectivity in the most of the cases. In addition, some interesting transformations of these cycloadducts were performed, yielding aziridinyl β-lactams or functionalized β-alkoxycarbonyl γ-lactams (derivatives of the aza analogue of paraconic acid).

Introduction

The presence of the 2-azetidinone ring in several widely used families of antibiotics has stimulated considerable activity directed at the stereocontrolled synthesis of β-lactams (the most widely employed class of antimicrobial agents to date).[1] In recent years several natural monocyclic β-lactams were shown to exhibit high antibacterial activity, suggesting that a suitably substituted monocyclic 2-azetidinone ring might perhaps be the minimum requirement for biological activity.[2] Antielastase activity of 1,3,4-trisubstituted and 3,4-disubstituted 2-azetidinones has been determined against enzymes, for example, human leucocyte elastase.[3] The recent discoveries of some 1,3,4-trisubstituted-β-lactams as new potent cholesterol absorption inhibitors,[4] human cytomegalovirus protease inhibitors,[5] and thrombin inhibitors[6] justify a renewed interest in these compounds.[7] Furthermore, isoxazoline and isoxazolidine heterocycles are commonly found in polycyclic compounds with biological activity, and there are also numerous examples of these *N*,*O*-heterocycles being used as key building blocks in the total synthesis of natural and unnatural compounds. The 1,3-dipolar cycloaddition reaction of nitrones with alkenes in particular has received considerable attention in asymmetric synthesis.[8] Mechanistically, the nitrone cycloaddition is a [4π + 2π]-type concerted process similar to the Diels−Alder reaction. One of the reasons for the success of the synthetic application of nitrones is that, contrary to the majority of other 1,3-dipoles, most nitrones are stable compounds that do not require in situ formation. In the 1,3-dipolar

* To whom correspondence should be addressed. Fax: +34-91-3944103.

† Departamento de Química Orgánica I.

‡ Laboratorio de Difracción de Rayos X.

§ Permanent adress: Department of Chemistry, Faculty of Science at Qena, South Valley University, Qena, Egypt.

|| To whom correspondence regarding the X-ray crystal structure should be adressed.

(1) For reviews on this subject, see: (a) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (b) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (c) *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (d) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992. (e) Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer: Vienna, 1985; Vol. 47, p 1.

(2) Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144.

(3) For reviews, see: (a) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata, E. G.; Roveri, O. A. *Curr. Med. Chem.* **1995**, *1*, 441. (b) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127.

(4) (a) Vaccaro, W. D.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313. (b) Vaccaro, W. D.; Sher, R.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 35. (c) Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339.

(5) (a) Borthwick, A. D.; Weingarte, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365. (b) Ogilvie, W.; Bailey, M.; Poupart, M.-A.; Abraham, A.; Bhavsar, P.; Bonneau, P.; Bordeleau, J.; Bousquet, Y.; Chabot, C.; Duceppe, J.-S.; Fazal, G.; Goulet, S.; Grand-Maitre, C.; Guse, I.; Halmos, T.; Lavallee, P.; Leach, M.; Malefant, E.; O'Meara, J.; Plante, R.; Plouffe, C.; Poirier, M.; Soucy, F.; Yoakim, C.; Deziel, R. *J. Med. Chem.* **1997**, *40*, 4113.

(6) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123.

(7) Miller, M. J., Ed.; Recent Aspects of the Chemistry of β-Lactams-II. *Tetrahedron* **2000**, *56*, 5553−5742.

(8) For selected reviews, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (d) Padwa, A. Intermolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 9, pp 1069−1109. (e) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 9, pp 83−168.

10.1021/jo025924e CCC: $22.00
Published on Web 09/07/2002

cycloaddition reaction of nitrones with alkenes, up to three new contiguous chiral centers can be formed in the adduct.[9] Generally, facial selectivity of the cycloaddition can be influenced by a chiral building block in which one face of the nitrone or dipolarophile is blocked preferentially. Although many investigations have been made in this field into various types of systems,[10] there is no information available regarding the regio- and stereochemistry of reactions involving 2-azetidinone-tethered nitrones, either cyclic or acyclic, as chiral building blocks on the intermolecular 1,3-dipolar cycloaddition reaction. During the course of our ongoing project directed toward developing efficient routes to prepare chiral functionalized 2-azetidinones and their synthetic applications,[11] we have used the intramolecular nitrone-alkene(alkyne) cycloaddition of 2-azetidinone-tethered alkenyl(alkynyl)-nitrones for the preparation of nonclassical polycyclic β-lactams, as well as indolizidine and quinolizidine derivatives.[11g−i] In connection with this work, we wish to report here the intermolecular 1,3-dipolar cycloaddition reaction of both cyclic and acyclic 2-azetidinone-tethered nitrones with electron-deficient alkenes or alkynes, as well as some interesting transformations of the resulting cycloadducts.

Results and Discussion

Starting substrates, 4-oxoazetidine-2-carbaldehydes **1a**−**g**, were prepared both in the racemic form and in optically pure form using standard methodology. Racemic compounds **1c**−**g** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N*,*N*-di(*p*-methoxyphenyl)glyoxal diimine.[12] Enantiopure 2-azetidinones **2a,b** were obtained as single *cis*-enantiomers from the corresponding imine of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N.[13] Standard acetonide hydrolysis of compounds **2** followed by oxidative cleavage of the resulting diols smoothly provided 4-oxoazetidine-2-carbaldehydes **1a** and **1b** (Figure 1).[11] Having obtained the aldehydes, the next stage was set to carry out the key nitrone formation and the subsequent dipolar cycloaddition reactions.

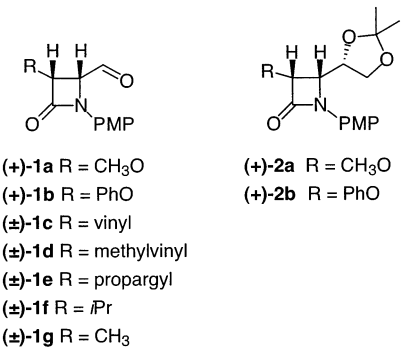
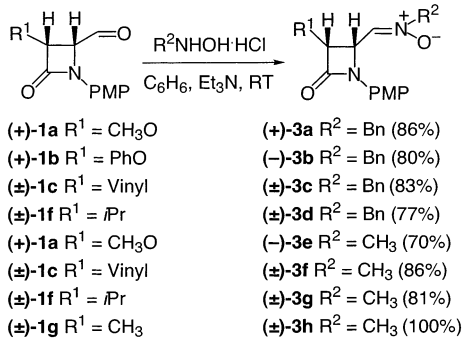


FIGURE 1.

SCHEME 1



The target molecules in the present study were derived from 1,3-dipolar cycloaddition of the corresponding β-lactam nitrone with the appropriate alkene or alkyne. This strategy allowed us to employ a large arsenal of commercially available alkenes and alkynes for the cycloaddition process. Cycloadduct precursors, 2-azetidinone-tethered nitrones **3**, were smoothly prepared by the condensation of 4-oxoazetidine-2-carbaldehydes **1** with *N*-alkylhydroxylamines such as *N*-benzylhydroxylamine and *N*-methylhydroxylamine in benzene at room temperature in the presence of triethylamine (Scheme 1). Nitrones **3** were obtained in almost quantitative yields and were used for the next step without further purification. Importantly, the β-lactam ring stereochemistry was unaffected by this process. The configuration of nitrones **3** was unambiguously established by NOE experiments, indicating a *Z* geometry.[14] Alternatively, the synthesis of nitrones **3** can be promoted by sodium carbonate, on reacting aldehydes **1** with *N*-alkylhydroxylamines in methanol. However, the ^{1}H NMR spectrum of the crude reaction mixtures showed in some cases partial epimerization of the starting *cis*-β-lactams.[15]

(9) Torssell, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinheim, 1998.

(10) For recent selected references, see: (a) Merino, P.; Mates, J. A.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Romeo, G.; Iannazzo, D.; Romeo, R. *Tetrahedron: Asymmetry* **2002**, *13*, 173. (b) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437. (c) Liu, Y.; Maden, A.; Murray, W. *Tetrahedron* **2002**, *58*, 3159. (d) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413. (e) Tranmer, G. K.; Keech, P.; Tam, W. *Chem. Commun.* **2000**, 863. (f) Carda, M.; Portolés, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragozá, R. J.; Röper, H. *J. Org. Chem.* **2000**, *65*, 7000. (g) Becalli, E. M.; Broggini, G.; La Rosa, C.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **2000**, *65*, 8924.

(11) See, for instance: (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719. (d) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925. (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (f) Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* **2001**, *3*, 4205. (g) Alcaide, B.; Sáez, E. *Tetrahedron Lett.* **2000**, *41*, 1647. (h) Alcaide, B.; Alonso, J. M.; Aly, M. F.; Sáez, E.; Martínez-Alcázar, M. P.; Hernández-Cano, F. *Tetrahedron Lett.* **1999**, *40*, 5391. (i) Alcaide, B.; Pardo, C.; Sáez, E. *Synlett* **2002**, 85.

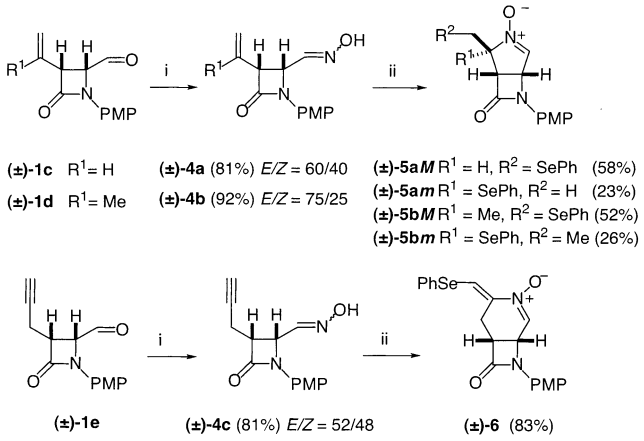
(12) (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.* **1991**, *32*, 803. (b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

(13) For recent reviews on the ketene−imine approach to β-lactams, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (b) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp 518−527. (c) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: Weinheim, New York, 1993; Chapter 3, p 295. (d) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (e) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 85.

(14) Irradiation of the benzyl (CH_2Ph) or methyl groups in nitrones **3** led to 6−7% NOE enhancements of the signals corresponding to the azomethine proton (C*H*=N$^+$).

(15) Alcaide, B.; Aly, M. F.; Rodríguez, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453.

SCHEME 2[a]

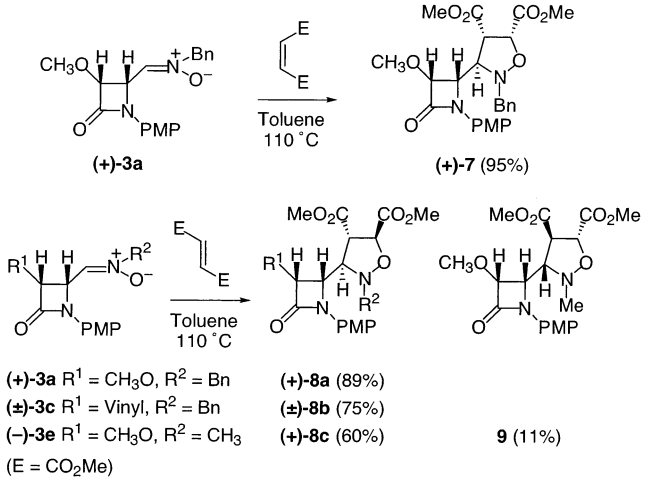


[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl/Et_3N/C_6H_6$/RT; (ii) $PhSeBr/CH_2Cl_2$/rt; (iii) Et_3N/RT.

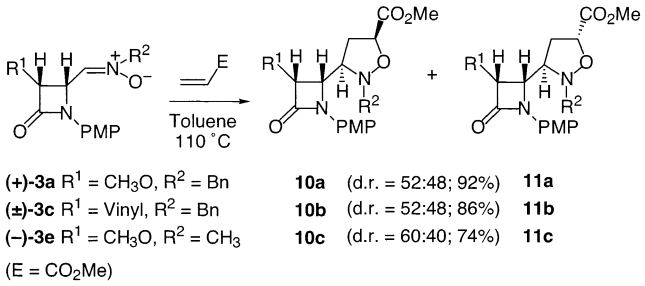
Next, we turned our attention to the synthesis of a different class of β-lactam nitrones, the hitherto unknown bicyclic nitrones of the 2-azetidinone *N*-oxide type, **5** and **6** (Scheme 2). Besides their utility as intermediates in 1,3-dipolar cycloaddition reactions, these compounds show potential antibacterial interest because they are novel fused bicyclic-2-azetidinones with nonclassical structure.[16] The formation of bicyclic nitrones **5** and **6** from aldehydes **1c**−**e** was achieved in a two-step route.[17] Condensation of aldehydes **1** with hydroxylamine hydrochloride in benzene at room temperature in the presence of triethylamine provided oximes **4a**−**c** as inseparable mixtures of *E*/*Z* isomers. Compounds **4** were obtained in good yields and were used for the next step without further purification. Oximes **4** were treated with phenylselenyl bromide in dichloromethane at room temperature, followed by addition of triethylamine as outlined in Scheme 2. Bicyclic nitrones **5a** and **5b** were obtained from oximes **4a** and **4b**, respectively, as diastereoisomeric mixtures of the same relative proportion (67/33) in both cases. Fortunately, compounds **5*M*** and **5*m*** were easily separable by flash chromatography. The reaction of oxime **4c** proceeded with total stereoselectivity to give bicyclic nitrone **6** as a single isomer. Detailed NMR studies have established the structure and stereochemistry of bicycles **5** and **6**.

The dipolar cycloaddition occurs with diversely substituted alkenes and alkynes partners, which should allow us to build a comprehensive profile of *N*,*O*-heterocycle-substituted β-lactams. On treatment of 2-azetidinone-tethered nitrones **3a** and **3c** with acyclic diactivated dipholarophiles such as dimethyl fumarate or dimethyl maleate under argon atmosphere in toluene at 110 °C, a smooth cycloaddition reaction took place to give isoxazolidines **7** and **8** in a total diastereoselective manner (Scheme 3). The stereoselectivities of the addition reactions were highly dependent on the bulkiness of *N*-substituents of nitrones **3**. Thus, when less hindered

SCHEME 3



SCHEME 4



N-methylhydroxylamine-derived nitrone **3e** rather than the *N*-benzyl nitrones **3a** and **3c** was used for cycloadduct formation in the reaction with dimethyl fumarate, a mixture (85:15) of diastereoisomers **8c** and **9** was formed. The major isomer **8c** could be isolated in an analytical pure form by column chromatography.

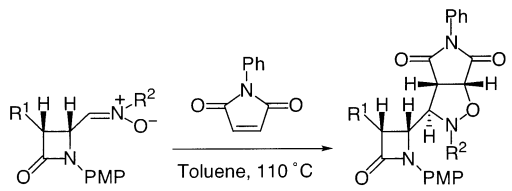
The cycloaddition concerning 2-azetidinone-tethered nitrones **3** with the monoactivated alkene methyl acrylate was totally regioselective, yielding exclusively 5-substituted isoxazolidinyl β-lactams, but very poor stereoinduction was observed (Scheme 4). The diastereoisomeric cycloadducts **10** and **11** prepared using methyl acrylate as the trapping agent could not be separated and were characterized as mixtures. NMR studies (HMQC $^{13}C-^{1}H$ and coupling constants) of the mixture of epimers **10** and **11** revealed their regio- and stereochemistries. The position of the carboxymethyl moiety in cycloadducts **10** and **11** was deduced from an examination of the methylene signals in the ^{13}C NMR spectra of the epimeric mixture. No new signals from oxygenated methylenes, expected for 4-substituted isoxazoline regioisomers were found. Instead, new methylene signals appeared in the range 35.9−35.4 ppm, which were only possible for 5-substituted regioisomers. The observed regiochemistry is in agreement with a previous experimental and theoretical report for the 1,3-dipolar cycloaddition between hetaryl nitrones and methyl acrylate.[18]

We therefore sought to explore the reactivity of 2-azetidinone-tethered nitrones with cyclic dipolarophiles. Intermolecular 1,3-dipolar cycloaddition of nitrones **3** with *N*-phenylmaleimide gave products **12** in good stereoselectivity and in reasonable to excellent yields (40−95%). In some cases, small amounts of isomeric cycload-

(16) For a review on the synthesis and biological properties of bicyclic-β-lactams with nonclassical structure, see: Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.

(17) (a) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem Commun.* **1992**, 1389. (b) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem Commun.* **1993**, 1341.

TABLE 1. Intermolecular 1,3-Dipolar Cycloaddition Reaction of 2-Azetidinone-Tethered Nitrones 3 with *N*-Phenylmaleimide. Synthesis of Isoxazolidinyl *β*-Lactams 12[a]



3 12

entry	R^1	R^2	nitrone	adduct	dr[b]	yield (%)[c]
1	CH_3O	Bn	(+)-**3a**	(+)-**12a**	100:0	95
2	vinyl	Bn	(±)-**3c**	(±)-**12b**	100:0	94
3	*i*Pr	Bn	(±)-**3d**	(±)-**12c**	100:0	40
4	CH_3O	CH_3	(−)-**3e**	(+)-**12d**	73:9:9:9	80
5	vinyl	CH_3	(±)-**3f**	(±)-**12e**	80:13:6:1	85
6	*i*Pr	CH_3	(±)-**3g**	(±)-**12f**	69:21:10	73
7	CH_3	CH_3	(±)-**3h**	(±)-**12g**	76:9:8:7	95

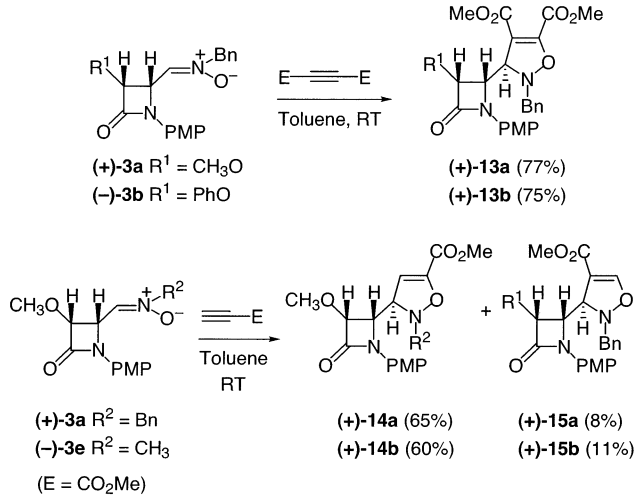
[a] PMP = 4-$MeOC_6H_4$. [b] Determined by integration of well resolved signals in the ^1H NMR spectra of crude reaction mixtures prior to purification. [c] The listed yields are for the pure combined mixture of diastereoisomers. The major isomeric products could be isolated by column chromatography and were characterized with correct analytical and spectral data.

ducts were formed as byproducts (Table 1; only major isomers for adducts **12** are represented). The steric properties of the *N*-substituent of the nitrone appear to influence the stereoselectivity of the cycloaddition. Clearly, the greater the size of the group attached to the nitrogen atom, the greater the diastereoisomeric ratio. In fact, one single isomer was obtained by using nitrones derived from *N*-benzylhydroxylamine, whereas *N*-methyl nitrones afforded enriched mixtures (see Table 1).

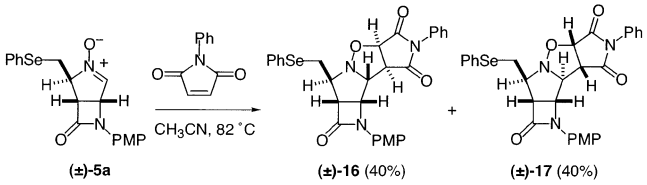
Having decided to extend this study to electron-deficient alkynes, we tested the ability of acetylenedicarboxylate and methyl propiolate to give regio- and diastereoselectivity in their reactions with nitrones **3**. The reaction of nitrones **3a** and **3b** with acetylenedicarboxylate proceeds well in toluene at room temperature and resulted in a total stereoselective fashion to isoxazolines **13a** and **13b**. We found that the reaction with methyl propiolate proceeded as well with full diastereocontrol but gave an approximately 85:15 mixture of regioisomeric 5-substituted and 4-substituted isoxazoline derivatives **14** and **15** (Scheme 5). Fortunately, the regioisomeric cycloadducts **14** and **15** could be easily separated by flash chromatography, as the major isomeric products were the less polar compounds. Regio- and stereochemistries on adducts **14** and **15** were readily deduced from their ^1H NMR spectra. The relative positions of the olefinic hydrogens of the regioisomeric products **14** and **15** are well separated in their ^1H NMR spectra with about 1 ppm chemical shift value.

To illustrate the use of this chemistry in fused polycyclic *β*-lactam synthesis, cyclic nitrone **5a** was reacted

SCHEME 5



SCHEME 6



with *N*-phenylmaleimide. Unfortunately, the reaction was not stereoselective and yielded two stereoisomers in a 1:1 ratio (Scheme 6). However, there is not lack of synthetic utility for the process because compounds **16** and **17** were easily separated by gravity flow chromatography.

The above overall results suggest that the 1,3-dipolar cycloaddition reaction of 2-azetidinone-tethered nitrones with electron-poor alkenes and alkynes would proceed with the selective attack on the *re* face of chiral nitrone. The *π*-facial selectivity of these cycloaddition reactions may be controlled by the aryl moiety in the substituted *β*-lactam ring at the dipole in which one face of the nitrone is blocked and thus the dipolarophile approaches preferentially to the less hindered face in the transition state. In addition, when the substituent in the nitrones **3** is a benzyl group, MM2 calculations point out that the *si* face of the nitrone in its more stable conformation is blocked by the phenyl moiety of the benzyl group. The sense of the stereochemistry in the [3 + 2] cycloaddition step by using dimethyl maleate or *N*-phenylmaleimide may be explained involving an *endo*-cycloaddition, as depicted in Figure 2 for cycloadducts **12**. In Figure 2 it seems that the *re* face in the *endo*-approach is blocked by the R^1 group from the *β*-lactam even more than the Ar group at the ring nitrogen. However, it should be noted that is a two-dimensional picture and the R^1 group intended to be down, being actually placed far from the incoming dienophile.

For dimethyl fumarate, the are two possible orientations on approaching to the nitrone, **I** and **II** (Figure 3). In our 2-azetidinone-tethered nitrones, the only observed adduct was derived from approach **I**, which is consistent with a previous report.[19]

(18) This study showed by molecular orbital calculations that the energy differences between the HOMO of hetaryl nitrones and the LUMO of methyl acrylate were smaller than that of the opposite combination (LUMO of nitrone and HOMO of dipholarophile). As a consequence, isoxazolidine-5-carboxylate regioisomers were obtained preferentially. See: (a) Merino, P.; Anoro, S.; Merchán, F.; Tejero, T. *Heterocycles* **2000**, *53*, 861. (b) Tejero, T.; Dondoni, A.; Rojo, I.; Merchán, F. L.; Merino, P. *Tetrahedron* **1997**, *53*, 3301.

(19) Greé, R.; Carrie, R. *Bull. Soc. Chim. Fr.* **1975**, 1319.

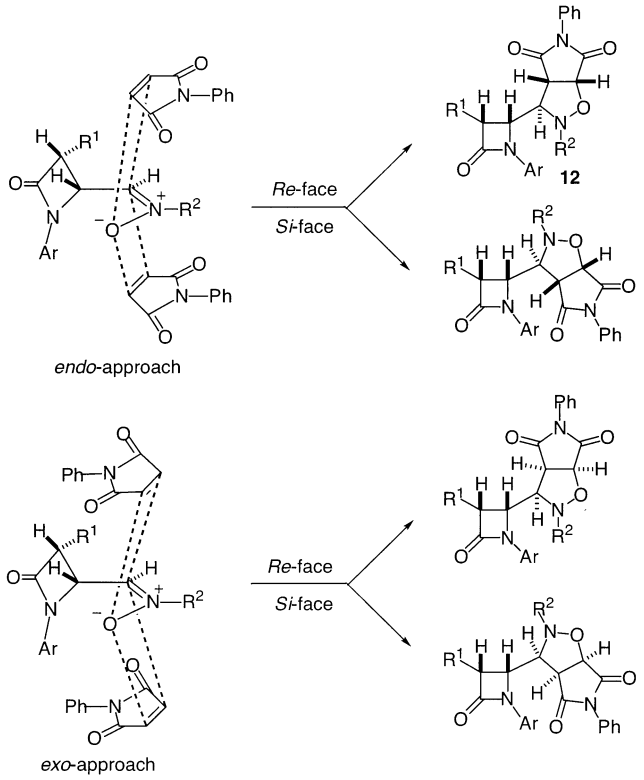


FIGURE 2.

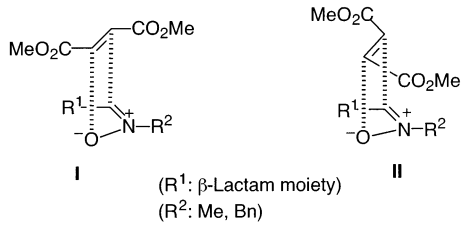


FIGURE 3.

The cyclic nitrone **5a** reacted with *N*-phenylmaleimide to afford the corresponding cycloadducts **16** and **17** via the least sterically demanding *exo*-mode on both faces of the nitrone. Cycloadduct **16** could be formed through an *exo*-approach on the *re* face (opposite to the phenylselenyl group) of nitrone, whereas cycloadduct **17** could be formed through an *exo*-approach on the *si* face (opposite to the β-lactam moiety) of nitrone **5a** (Figure 4).

Configurational Assignment. The structure and stereochemistry of compounds **7**−**17** have been assigned by NMR techniques and by X-ray diffraction. The *cis*-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during the further synthetic steps. The relative stereochemistries at the isoxazolidine rings were deduced from a detailed study of the coupling constants values in the ^{1}H NMR spectra. Thus, the H5−H9 (according to the X-ray numbering) coupling constant values at the isoxazolidine ring are always in the range 0−3.3 Hz, in agreement with an *anti*-disposition for these protons. It should be noted that the vicinal coupling constants of the two protons (H4 in the β-lactamic ring and H5, hydrogen α to the nitrogen in the five-membered ring) located at the single bond connecting the two rings

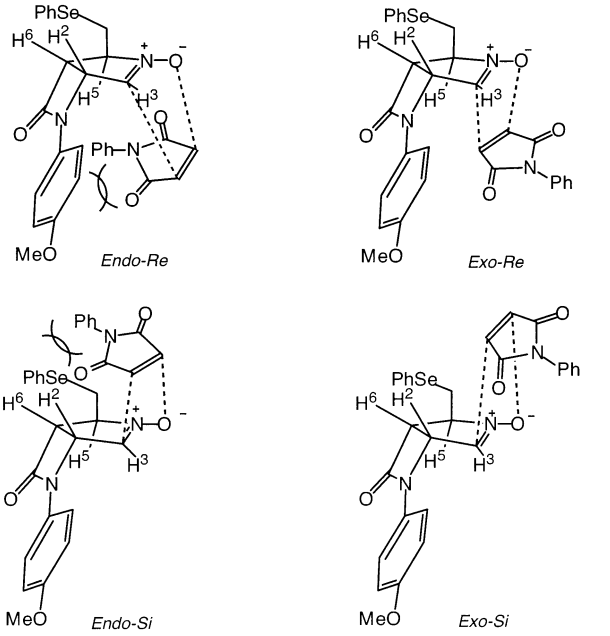
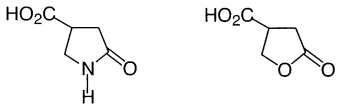


FIGURE 4.

were diagnostic for the stereochemistry at the isoxazolidine-C5 stereocenter. These vicinal coupling constants for all cycloadducts **7**, **8**, and **11**−**15** are in the range 5.9−9.9 Hz, suggesting a relative *anti*-stereochemistry for this connection, whereas this vicinal coupling constant for the minor isomer **9** is 2.7 Hz, suggesting a relative *syn*-stereochemistry. This configurational assignment was confirmed via an X-ray diffraction analysis of the cycloadduct **7** (see Supporting Information).[20] Qualitative homonuclear difference spectra performed on fused polycyclic products **5**, **6**, **16**, and **17** are in agreement with the proposed stereochemistries.

Synthetic Transformations of Cycloadducts. To test the reactivity of these polyfunctionalized substrates, cycloadducts **14a** and **14b** were submitted to thermal treatment. Interestingly, as we previously communicated for a related fused tricyclic isoxazoline-β-lactam,[11g] by heating compounds **14a** and **14b** in toluene at 110 °C the aziridinyl β-lactams **18** were obtained as single isomers (Scheme 7).[21,22] This process can be rationalized through a thermally induced sigmatropic rearrangement according to Baldwin et al.[23] The relative stereochemistry between the hydrogens at the three-membered ring in compounds **18** was assigned by NOE experiments as well as by the coupling constant values for methine protons in their ^{1}H NMR spectra.[24] We think that on the thermal isomerization of **14** to **18** the stereochemical outcome is

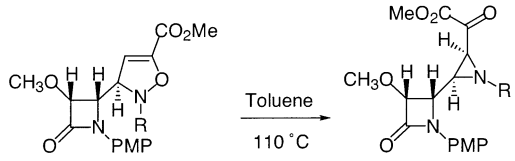
(20) **X-ray data of 7**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{25}H_{28}N_2O_8$ (M_r = 484.49); monoclinic; space group = *P*2(1); *a* = 12.4382 (14) Å, *b* = 5.8976 (7) Å; *c* = 16.8160 (19) Å; β = 94.767(3)°; *V* = 1229.3(2) Å^3; *Z* = 2; d_c = 1.309 mg m^{-3}; μ = 0.098 mm^{-1}; F(000) = 512. A transparent crystal of 0.14 × 0.20 × 0.28 mm^3 was used; 3990 independent reflections were collected on a Bruker Smart CCD difractometer. The structure was solved by direct methods and Fourier synthesis. The refinement was done by full matrix least-squares procedures on F^2 (SHELXTL version 5.1). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined the coordinates only. Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. on quoting the depository number CCDC 184077.



19 **20**

FIGURE 5.

SCHEME 7



(+)-14a R = Bn
(+)-14b R = Me

(+)-18a (50%)
(+)-18b (40%)

controlled by steric reasons, the new stereocenter being placed anti to the bulky β-lactam substituent at the ring.

A number of compounds containing the γ-lactam moiety exhibit interesting biological and pharmacological activities.[25] They are also key intermediates in the synthesis of other biologically important compounds. Despite their intrinsic potential for biological activity, both the racemic and enantiomerically pure derivatives of the γ-lactam bearing a carboxylic group at the β-position **19** (aza analogue of the natural product paraconic acid **20**)[26] have received little attention (Figure 5).[27] We identified cycloadducts **7**−**11** as precursors of enantiomerically pure and highly functionalized β-alkoxycarbonyl γ-lactams. To successfully achieve our aim, we needed to find an expedient transformation of the cycloadducts into γ-lactam systems. First, molybdenum hexacarbonyl[28] was tested as reagent for the reductive ring opening of isoxazolidine derivatives **7** and **8a**. However, no reaction was observed. Then, we decided to move to a different strategy. Selective 2-azetidinone ring opening on adducts **7** and **8a** to give isoxazolidinyl-β-aminoesters **21a** and **21b** was achieved when the reaction was conducted in methanol at reflux temperature under 37% aqueous hydrochloric acid catalysis. Reductive ring opening/lactamization in compounds **21** by the use of molybdenum hexacarbonyl afforded as the only isomers highly substituted γ-lactams **22a** and **22b** (Scheme 8). The formation of γ-lactams **22** involves a N−O bond cleavage at the five-membered ring, followed by a selective rearrangement under the reaction conditions.

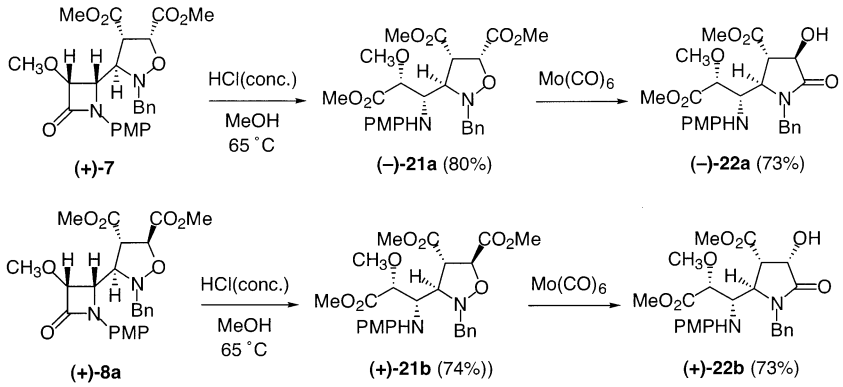
The reaction of the epimeric mixture of *N*-methyl isoxazolidinyl-β-lactams **10c** and **11c** with molybdenum hexacarbonyl produced the ring opening of the isoxazolidine nucleus followed by cyclization to yield γ-lactam **23** as a mixture (60:40) of epimers. These results revealed that the $Mo(CO)_6$-promoted reaction is highly dependent on the steric hindrance. Treatment of compound **23** under standard mesylate formation conditions followed by reaction with DBU gave the chloroderivative **24** (Scheme 9).

In conclusion, the present study provides the first insight into the manner in which different types of racemic and optically pure 2-azetidinone-tethered nitrones, both cyclic and acyclic, undergo intermolecular 1,3-dipolar cycloaddition reaction with a variety of alkenes or alkynes. In addition, in most of the cases the reaction has been shown to be regio- and stereoselective, providing a synthetically feasible entry into various types of racemic and homochiral 1,3,4-trisubstituted- or fused polycyclic-β-lactams in a controlled manner. In addition, some interesting transformations of these cycloadducts were performed, yielding aziridinyl β-lactams or highly substituted β-alkoxycarbonyl γ-lactams (aza derivatives of the natural product paraconic acid).

Experimental Section

General. General experimental data and procedures have been previously reported.[11c] NMR spectra were recorded in $CDCl_3$ solutions, except as otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). All commercially available compounds were used

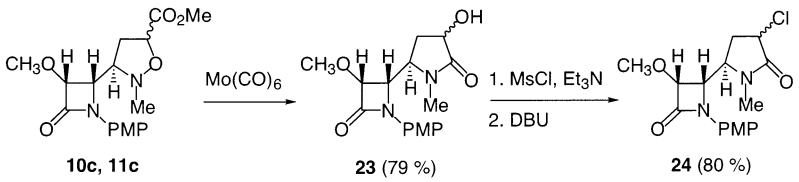
SCHEME 8



(+)-7 **(−)-21a** (80%) **(−)-22a** (73%)

(+)-8a **(+)-21b** (74%)) **(+)-22b** (73%)

SCHEME 9



10c, 11c **23** (79 %) **24** (80 %)

without further purification. Compounds **1a**−**g** and **2a,b** were prepared according to our previously reported methods.[11,12]

General Procedure for the Synthesis of 2-Azetidinone-Tethered Nitrones 3. The appropriate *N*-alkylhydroxylamine hydrochloride (2.00 mmol) and triethylamine (2.00 mmol) were sequentially added at room temperature to a well stirred solution of the corresponding 4-oxoazetidine-2-carbaldehyde **1** (1.00 mmol) in benzene (10 mL). After the resulting suspension was stirred at room temperature for 16 h, the solvent was removed under reduced pressure. Then, the mixture was diluted with chloroform and washed with saturated aqueous $NaHCO_3$ and water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **3**. Spectroscopic and analytical data for some representative pure forms of **3** follow.[29]

Nitrone (+)-3a. From 1.00 g (4.25 mmol) of aldehyde (+)-**1a**, 1.20 g (86%) of compound (+)-**3a** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/30). Mp: 192−193 °C (hexanes/ethyl acetate). $[\alpha]_D = +40.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.40 (s, 3H), 3.78 (s, 3H), 4.80 (d, 1H, J = 4.7 Hz), 4.96 (AB system, 2H, J = 13.7 Hz), 5.39 (dd, 1H, J = 7.3, 4.7 Hz), 6.82 (d, 2H, J = 9.0 Hz), 6.96 (d, 1H, J = 7.3 Hz), 7.32 (d, 2H, J = 9.0 Hz), 7.40 (s, 5H). ^{13}C NMR: δ 162.8, 156.7, 133.0, 132.3, 130.1, 129.3, 129.2, 128.9, 118.3, 114.5, 84.8, 70.4, 59.7, 55.5, 53.6. IR (KBr, cm^{-1}): ν 1747, 1512. MS (CI) *m*/*z*: 341 (M^+ + 1, 100), 340 (M^+, 16). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.97; H, 5.95; N, 8.19.

Nitrone (−)-3b. From 156 mg (0.52 mmol) of aldehyde (+)-**1b**, 168 mg (80%) of compound (−)-**3b** was obtained as a brown solid after purification by flash chromatography (hexanes/ethyl acetate 1/25). Mp: 166−168 °C (hexanes/ethyl acetate). $[\alpha]_D = -19.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.80 (s, 3H), 4.82 (AB system, 2H, J = 13.7 Hz), 5.47 (d, 1H, J = 4.6 Hz), 5.73 (dd, 1H, J = 8.0, 4.6 Hz), 6.89 (m, 4H), 7.05 (m, 2H), 7.35 (m, 9H). ^{13}C NMR: δ 161.0, 156.8, 132.0, 131.7, 129.8, 129.7, 128.9, 122.7, 118.3, 114.6, 80.6, 70.2, 55.5, 52.8. IR (KBr, cm^{-1}): ν 1745, 1511. MS (EI) *m*/*z*: 402 (M^+ + 1, 10), 401 (M^+, 100). Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.61; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.55; N, 7.00.

Nitrone (−)-3e. From 1.00 g (4.25 mmol) of aldehyde (+)-**1a**, 784 mg (70%) of compound (−)-**3e** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/30). Mp: 147−148 °C (hexanes/ethyl acetate). $[\alpha]_D = -6.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.40 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.84 (d, 1H, J = 4.9 Hz), 5.42 (dd, 1H, J = 7.6, 4.9 Hz), 6.87 (d, 2H, J = 9.0 Hz), 6.90 (d, 1H, J = 7.6 Hz), 7.38 (d, 2H, J = 9.0 Hz). ^{13}C NMR: δ 163.0, 156.8, 133.9, 130.1, 118.3, 114.6, 84.7, 59.8, 55.5, 53.4. IR (KBr, cm^{-1}): ν 1748, 1514. MS (CI) *m*/*z*: 265 (M^+ + 1, 100), 264 (M^+, 8). Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.16; H, 6.15; N, 10.56.

Nitrone (±)-3f. From 115 mg (0.50 mmol) of aldehyde (±)-**1c**, 115 mg (86%) of compound (±)-**3f** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/25). Mp: 149−150 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 3.70 (s, 3H), 3.72 (s, 3H), 4.35 (m, 1H), 5.35 (m, 2H), 5.53 (dt, 1H, J = 17.3, 1.5 Hz), 5.82 (ddd, 1H, J = 17.3, 10.2, 6.7 Hz), 6.85 (dd, 1H, J = 7.3, 0.9 Hz), 6.87 (d, 2H, J = 9.3 Hz), 7.32 (d, 2H, J = 9.3 Hz). ^{13}C NMR: δ 163.9, 156.5, 134.8, 130.6, 127.9, 121.6, 118.0, 114.8, 56.5, 55.5, 53.2, 51.0. IR (KBr, cm^{-1}): ν 1749, 1516. MS (CI) *m*/*z*: 261 (M^+ + 1, 100), 260 (M^+, 14). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.70; H, 6.15; N, 10.72.

General Procedure for the Synthesis of 2-Azetidinone-Tethered Oximes 4. Hydroxylamine hydrochloride (2.00 mmol) and triethylamine (2.00 mmol) were sequentially added at room temperature to a well stirred solution of the corresponding 4-oxoazetidine-2-carbaldehyde **1** (1.00 mmol) in benzene (10 mL). After the resulting suspension was stirred at room temperature overnight, the solvent was removed under reduced pressure. Then, the mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$ and water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate gave analytically pure compounds **4**. Spectroscopic and analytical data for some representative pure forms of **4** follow.

Oxime (±)-4b. From 494 mg (2.00 mmol) of aldehyde (±)-**1d**, 480 mg (92%) of compound (±)-**4b**, as a *E*/*Z* mixture (75:25) of isomers, was obtained as a colorless solid after purification by flash chromatography (ethyl acetate). ^{1}H NMR: δ 1.66 (s, 2.25H), 1.68 (s, 0.75H), 3.68 (s, 2.25H), 3.69 (s, 0.75H), 4.04 (d, 0.75H, J = 5.9 Hz), 4.09 (d, 0.25H, J = 5.9 Hz), 4.62 (dd, 0.75H, J = 8.5, 5.9 Hz), 5.05 (s, 0.25H), 5.07 (m, 1H), 5.15 (m, 0.25H), 5.20 (m, 0.75H), 6.87 (m, 2.25H), 7.40 (m, 2.75H), 8.40 (brs, 0.75H), 9.30 (brs, 0.25H). ^{13}C NMR: δ 165.4 (*M*+*m*), 154.2 (*M*+*m*), 148.7 (*M*+*m*), 136.0 (*M*+*m*), 132.0 (*M*+*m*), 118.3 (*M*+*m*), 116.4 (*M*+*m*), 114.5 (*M*+*m*), 59.3 (*M*+*m*), 55.6 (*M*+*m*), 53.8 (*M*+*m*), 31.1 (*M*+*m*), 22.5 (*M*+*m*). IR (KBr, cm^{-1}): ν 3307, 1720. MS (EI) *m*/*z*: 261 (M^+ + 1, 11), 260 (M^+, 100).

General Procedure for the Synthesis of Bicyclic Nitrones 5 and 6. Phenylselenyl bromide was added at room temperature to a well stirred solution of the corresponding oxime **4** (1.00 mmol) in dichloromethane (20 mL). After the resulting suspension was stirred at room temperature for 3 h, triethylamine (1.00 mmol) was added and the mixture was stirred for an additional 1 h. The solvent was removed under reduced pressure. Then, the mixture was diluted with dichloromethane and washed with brine and water. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **5** and **6**. Spectroscopic and analytical data for some representative pure forms of **5** and **6** follow.

Treatment of Oxime (±)-4a with Phenylselenyl Bromide and Triethylamine. From 123 mg (0.50 mmol) of oxime (±)-**4a**, and after flash chromatography eluting with ethyl acetate, 115 mg (58%) of the less polar compound (±)-**5a*M*** and 45 mg (23%) of the more polar compound (±)-**5a*m*** were obtained.

Bicyclic Nitrone (±)-5a*M*. Colorless solid. Mp: 129−130 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 3.41 (d, 2H, J = 4.8 Hz), 3.71 (s, 3H), 3.85 (dd, 1H, J = 5.0, 2.6 Hz), 4.51 (m, 1H),

(21) Compounds **18a** and **18b** can also be obtained in one-pot from nitrones **3a** and **3e**, although in lower yields, by reaction of the appropriate nitrone with methyl propiolate in refluxing toluene.

(22) Aziridines are useful building blocks in organic synthesis. For reviews, see: (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (b) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A, p 1. (c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (d) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p 469.

(23) Baldwin, J. E.; Pudussery, E. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325.

(24) Vicinal coupling constants values of 6−7 Hz are typical for *cis*-2,3-disubstituted aziridines. See, for example: Batterham, T. J. In *NMR Spectra of Simple Heterocycles*; Taylor, E. C., Weissberger, A., Eds.; Wiley: New York, 1973; p 139.

(25) For use as psychotropic agents, see: (a) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 7277. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. For use as antihypertensive agents, see: (c) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492. For use as inhibitors of proteolytic catalysis, see: (d) Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1. For use as antimuscarinic agents, see: (e) Nilsson, B. M.; Ringdhal, B.; Hacksell, U. A. *J. Med. Chem.* **1990**, *33*, 580.

(26) Crawforth, J. M.; Rawlings, B. J. *Tetrahedron Lett.* **1995**, *36*, 6345.

(27) Felluga, F.; Pitacco, G.; Prodan, M.; Pricl, S.; Visintin, M.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 3241.

(28) (a) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633. (b) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; de Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(29) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in Supporting Information.

4.95 (dt, 1H, J = 5.0, 1.5 Hz), 6.80 (d, 2H, J = 9.2 Hz), 7.21 (m, 6H), 7.53 (m, 2H). ^{13}C NMR: δ 162.3, 156.8, 133.6, 130.7, 130.3, 129.6, 128.1, 127.9, 117.6, 114.7, 71.2, 55.5, 55.4, 51.8, 29.9. IR (KBr, cm^{-1}): ν 1745, 1629. MS (EI) m/z: 401 (M$^+$, 7), 179 (100). Anal. Calcd for $C_{19}H_{18}N_2O_3Se$: C, 56.86; H, 4.52; N, 6.98. Found: C, 56.97; H, 4.48; N, 6.94.

Bicyclic Nitrone (±)-5a*m*. Colorless solid. Mp: 164−166 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 3.10 (dd, 1H, J = 12.5, 10.6 Hz), 3.80 (s, 3H), 3.90 (dd, 1H, J = 12.5, 3.7 Hz), 4.32 (m, 1H), 4.36 (d, 1H, J = 4.8 Hz), 4.90 (dt, 1H, J = 4.8 Hz, 1.5 Hz), 6.90 (d, 2H, J = 8.9 Hz), 7.40 (m, 6H), 7.62 (m, 2H). ^{13}C NMR: δ_160.9, 156.8, 132.9, 130.3, 129.9, 129.4, 129.0, 127.6, 117.6, 114.7, 71.3, 55.6, 53.9, 51.2, 26.1. IR (KBr, cm^{-1}): ν 1728, 1514. MS (EI) m/z: 401 (M$^+$, 8), 179 (100). Anal. Calcd for $C_{19}H_{18}N_2O_3Se$: C, 56.86; H, 4.52; N, 6.98. Found: C, 56.99; H, 4.56; N, 6.89.

Bicyclic Nitrone (±)-6. From 82 mg (0.30 mmol) of nitrone (±)-**4c**, 108 mg (83%) of compound (±)-**6** was obtained as a pale orange solid after purification by flash chromatography (ethyl acetate). Mp: 119−121 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 2.90 (m, 2H), 3.64 (s, 3H), 3.95 (m, 1H), 4.48 (dd, 1H, J = 7.9, 5.7 Hz), 6.75 (s, 1H), 6.83 (d, 2H, J = 8.9 Hz), 7.32 (m, 5 h), 7.49 (m, 3H). ^{13}C NMR: δ 164.8, 156.1, 147.6, 132.5, 131.4, 129.5, 128.3, 127.9, 118.0, 117.5, 114.2, 111.2, 55.3, 53.3, 51.4, 30.6. IR (KBr, cm^{-1}): ν 1722, 1512. MS (EI) m/z: 413 (M$^+$, 16), 179 (100). Anal. Calcd for $C_{20}H_{18}N_2O_3Se$: C, 58.12; H, 4.39; N, 6.78. Found: C, 58.20; H, 4.37; N, 6.75.

Reaction between Nitrones 3 and Acyclic Alkenes. General Procedure for the Synthesis of Isoxazolidinyl *β*-Lactams 7−11. To a solution of the corresponding nitrone **3** (0.50 mmol) in anhydrous toluene (30 mL) was added the appropriate dipolarophile (0.60 mmol) under argon atmosphere. The reaction was stirred at reflux temperature until complete disappearance of the nitrone (TLC), and the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **7**−**11**.

Cycloadduct (+)-7. From 100 mg (0.33 mmol) of nitrone (+)-**3a**, 135 mg (95%) of compound (+)-**7** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/1). Mp: 141−143 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +84.3 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 3.60 (s, 3H), 3.63 (s, 3H), 3.74 (dd, 1H, J = 9.2, 3.3 Hz), 3.75 (s, 3H,), 3.79 (s, 3H), 3.96 (d, 1H, J = 13.1 Hz), 4.03 (dd, 1H, J = 8.4, 3.3 Hz), 4.15 (dd, 1H, J = 8.4, 4.9 Hz), 4.36 (d, 1H, J = 13.1 Hz), 4.53 (d, 1H, J = 4.9 Hz), 4.91(d, 1H, J = 9.2 Hz), 6.82 (d, 2H, J = 9.0 Hz), 7.10 (m, 2H), 7.18 (m, 2H), 7.36 (d, 2H, J = 9.0 Hz). ^{13}C NMR: δ 170.9, 169.6, 164.7, 156.5, 136.4, 130.4, 129.7, 128.0, 127.3, 119.7, 113.8, 82.6, 79.0, 69.3, 61.9, 59.7, 58.4, 55.4, 54.5, 52.4. IR (KBr, cm^{-1}): ν 1742, 1735. MS (CI) m/z: 486 (M$^+$ + 1, 100), 485 (M$^+$, 32). (Anal. Calcd for $C_{25}H_{28}N_2O_8$: C, 61.98; H, 5.83; N, 5.78. Found: C, 61.93; H, 5.80; N, 5.75).

Cycloadduct (+)-8a. From 100 mg (0.33 mmol) of nitrone (+)-**3a**, 127 mg (89%) of compound (+)-**8a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D$ = +102.5 (c 2.0, $CHCl_3$). ^{1}H NMR: δ 3.52 (dd, 1H, J = 7.1, 3.2 Hz), 3.57(s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.87 (d, 1H, J = 12.9 Hz), 3.98 (dd, 1H, J = 9.5, 3.2 Hz), 4.11 (d, 1H, J = 12.9 Hz), 4.43 (dd, 1H, J = 9.5, 5.4), 4.55 (d, 1H, J = 5.4 Hz), 4.97 (d, 1H, J = 7.1 Hz), 6.83 (d, 2H, J = 9.3 Hz), 6.95 (m, 2H), 7.13 (m, 2H), 7.46 (d, 2H, J = 9.3 Hz). ^{13}C NMR: δ 171.8, 169.3, 164.8, 156.4, 135.5, 130.4, 129.0, 128.0, 127.3, 120.2 113.6, 82.0 78.6, 70.0, 60.0, 59.2, 58.6, 55.5, 55.3, 52.7, 52.6. IR ($CHCl_3$, cm^{-1}): ν 1743, 1710. MS (EI) m/z: 486 (M$^+$ + 1, 12), 485 (M$^+$, 100). Anal. Calcd for $C_{25}H_{28}N_2O_8$: C, 61.98; H, 5.83; N, 5.78. Found: C, 62.07; H, 5.81; N, 5.83.

Cycloadducts 10a and 11a. From 100 mg (0.33 mmol) of nitrone (+)-**3a**, 115 mg (92%) of compound **10a**, containing ca. 48% of its epimer **11a**, was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D$ = +114.2 (c 1.3, $CHCl_3$). ^{1}H NMR: δ 2.28 (ddd, 0.5H, J = 13.4, 6.0, 2.4 Hz), 2.50 (ddd, 0.5H, J = 13.4, 9.0, 1.7 Hz), 2.90 (m, 1H), 3.61 (s, 1.5H), 3.63 (s, 1.5H), 3.64 (d, 0.5H, J = 12.0 Hz), 3.77 (d, 0.5H, J = 12.0 Hz), 3.79 (s, 1.5H), 3.80 (s, 1.5H), 3.81 (s, 1.5H), 3.81 (s, 1.5H), 3.91 and 4.12 (d, each 0.5H, J = 12.0 Hz), 4.22 (dd, 1H, J = 9.7, 5.4 Hz), 4.53 (d, 0.5H, J = 5.4 Hz), 4.54 (d, 0.5H, J = 5.7 Hz), 4.65 (t, 0.5H, J = 8.4 Hz), 4.76 (dd, 0.5H, J = 9.6, 6.0 Hz), 6.85 (m, 2H), 6.94 (m, 2H), 7.14 (m, 3H), 7.56 (m, 2H). ^{13}C NMR: δ 172.8, 171.4, 165.3, 165.1, 156.4, 156.3, 136.7, 136.1, 130.9, 128.7, 128.6, 128.1, 127.9, 127.3, 127.1, 120.3, 120.1, 113.6, 113.5, 82.0, 81.9, 76.6, 74.4, 66.6, 66.5, 62.0, 60.8, 59.4, 59.3, 58.9, 58.2, 55.5, 55.5, 52.6, 52.5, 35.5, 34.7. IR ($CHCl_3$, cm^{-1}): ν 1743, 1720. MS (CI) m/z: 427 (M$^+$ + 1, 100), 426 (M$^+$, 12).

Reaction between Nitrones 3 and *N*-Phenylmaleimide. General Procedure for the Synthesis of Isoxazolidinyl *β*-Lactams 12. A solution of the corresponding nitrone **3** (0.50 mmol) and *N*-phenylmaleimide (0.60 mmol) in anhydrous toluene (30 mL) was stirred at reflux temperature under argon atmosphere. After complete disappearance of the nitrone (TLC), the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **12**.

Cycloadduct (+)-12a. From 50 mg (0.15 mmol) of nitrone (+)-**3a**, 71 mg (95%) of compound (+)-**12a** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 6/4). Mp: 123−125 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +60.3 (c 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6): δ 3.65 and 3.82 (s, each 3H), 3.96 and 4.12 (d, each 1H, J = 13.2 Hz), 4.18 (dd, 1H, J = 7.8, 1.1 Hz), 4.24 (dd, 1H, J = 9.1, 1.1 Hz), 4.56 (dd, 1H, J = 9.1, 5.4 Hz), 4.81 (d, 1H J = 5.4 Hz), 5.21 (d, 1H, J = 7.8 Hz), 6.76 (m, 4H), 7.01 (m, 3H), 7.34 (m, 7H). ^{13}C NMR (acetone-d_6): δ 175.3, 174.9, 165.7 157.3, 137.2, 134.2, 132.2, 129.9, 129.8, 129.4, 128.8, 128.1, 127.1, 120.8, 114.3, 83.6, 79.5, 69.4, 63.6, 59.9, 59.2, 55.7, 53.8. IR (KBr, cm^{-1}): ν 1741, 1718. MS (EI) m/z: 513 (M$^+$ + 1, 7), 512 (M$^+$, 100). Anal. Calcd for $C_{29}H_{27}N_3O_6$: C, 67.83; H, 5.30; N, 8.18. Found: C, 67.89; H, 5.34; N, 8.13.

Cycloadduct (±)-12b. From 336 mg (1.00 mmol) of nitrone (±)-**3c**, 480 mg (94%) of compound (±)-**12b** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/1). Mp: 136−138 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 3.67 (d, 1H, J = 12.1 Hz), 3.76 (dd, 1H, J = 8.1, 0.7 Hz), 3.83 (s, 3H), 4.09 (m, 3H), 4.31 (dd, 1H, J = 9.9, 5.9 Hz), 5.05 (d, 1H, J = 8.1 Hz), 5.49 (m, 2H), 6.11 (m, 1H), 6.72 (m, 2H), 6.87 (d, 2H, J = 8.7 Hz), 7.11 (m, 2H), 7.19 (m, 1H), 7.34 (m, 2H), 7.40 (d, 2H, J = 8.7 Hz), 7.53 (m, 3H). ^{13}C NMR: δ 173.9, 173.5, 164.8, 156.6, 134.5, 131.2, 130.5, 129.5, 129.2, 129.1, 128.4, 128.1, 128.0, 125.5, 123.2, 120.9, 113.6, 78.0, 69.5, 63.1, 55.8, 55.5, 54.9, 52.5. IR (KBr, cm^{-1}): ν 1744, 1730. MS (EI) m/z: 510 (M$^+$ + 1, 3), 509 (M$^+$, 5), 91 (100). Anal. Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.62; H, 5.30; N, 8.30.

Cycloadduct (+)-12d. From 75 mg (0.28 mmol) of nitrone (−)-**3e**, 81 mg (66%) of compound (+)-**12d** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 6/4). Mp: 198−200 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +64.7 (c 1.2, $CHCl_3$). ^{1}H NMR: δ 2.76 (s, 3H), 3.73 (s, 3H), 3.79 (s, 3H), 3.95 and4.09 (dd, each 1H, J = 7.8, 1.5 Hz), 4.33 (dd, 1H, J = 7.8, 5.4 Hz), 4.70 (d, 1H, J = 5.4 Hz), 4.94 (d, 1H, J = 7.8 Hz), 6.87 (d, 2H, J = 9.0 Hz), 7.25 (m, 2H), 7.52 (m, 5H). ^{13}C NMR: δ 174.0, 173.4, 164.9, 156.7, 131.3, 130.4, 129.3, 128.9, 125.7, 119.9, 114.0, 82.4, 71.0, 59.8, 58.6, 55.4, 52.7, 46.7. IR (KBr, cm^{-1}): ν 1749, 1720. MS (CI) m/z: 438 (M$^+$ + 1, 100), 437 (M$^+$, 15). Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.61. Found: C, 63.22; H, 5.33; N, 9.55.

Reaction between Nitrones 3 and Alkynes. General Procedure for the Synthesis of Isoxazolinyl *β*-Lactams 13−15. To a solution of the corresponding nitrone **3** (0.50 mmol) in anhydrous toluene (30 mL) was added the appropriate dipolarophile (0.60 mmol) under argon atmosphere. The reaction was stirred at room temperature until complete

disappearance of the nitrone (TLC), and the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **13**−**15**.

Cycloadduct (+)-13a. From 100 mg (0.33 mmol) of nitrone (+)-**3a**, 109 mg (77%) of compound (+)-**13a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D$ = +166.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.59 (s, 3H), 3.61 (s, 3H), 3.71 (s, 3H), 3.76 (s, 3H), 4.11 (AB, 2H, *J* = 13.7 Hz), 4.57 (d, 1H, *J* = 5.1 Hz), 4.55 (d, 1H, *J* = 2.2 Hz), 4.63 (dd, 1H, *J* = 5.1, 2.2 Hz), 6.73 and 7.26 (d, each 2H, *J* = 9.0 Hz), 7.31 (m, 5H). ^{13}C NMR: δ 165.2, 162.6, 158.4, 156.5, 152.7, 136.5, 130.2, 129.1, 128.3, 127.7, 120.2, 113.9, 105.7, 82.3, 68.3, 62.9, 59.2, 58.0, 55.5, 52.7, 52.1. IR ($CHCl_3$, cm^{-1}): ν 1749, 1703, 1656. MS (EI) *m*/*z*: 483 (M^+ + 1, 15), 482 (M^+, 100). Anal. Calcd for $C_{25}H_{26}N_2O_8$: C, 62.23; H, 5.43; N, 5.81. Found: C, 62.14; H, 5.40; N, 5.86.

Treatment of Nitrone (+)-3a with Methyl Propiolate. From 100 mg (0.33 mmol) of nitrone (+)-**3a**, and after flash chromatography eluting with hexanes/ethyl acetate (1:1), 80 mg (65%) of the less polar compound (+)-**14a** and 10 mg (8%) of the more polar compound (+)-**15a** were obtained.

Cycloadduct (+)-14a. Colorless oil. $[\alpha]_D$ = +175.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ 3.65 (s, 3H), 3.71 (d, 1H, *J* = 12.9 Hz), 3.82 (s, 3H), 3.86 (s, 3H), 4.12 (d, 1H, *J* = 12.9 Hz), 4.26 (dd, 1H, *J* = 8.7, 4.9 Hz), 4.31 (dd, 1H, *J* = 8.7, 3.0 Hz), 4.53 (d, 1H, *J* = 4.9 Hz), 5.93 (d, 1H, *J* = 3.0 Hz), 6.85 (d, 2H, *J* = 9.0 Hz), 6.98 (m, 2H), 7.17 (m, 2H), 7.61 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR: δ 164.9, 159.2, 156.6, 146.8, 134.7, 130.7, 129.4, 128.2, 127.6, 120.3, 113.7, 107, 81.9, 72.0, 62.6, 59.4, 59.3, 55.5, 52.5. IR ($CHCl_3$, cm^{-1}): ν 1735, 1700. MS (CI) *m*/*z*: 425 (M^+ + 1, 100), 424 (M^+, 22). Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.15; H, 5.74; N, 6.55.

Cycloadduct (+)-15a. Colorless oil. $[\alpha]_D$ = +339.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.64 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 4.00 (dd, 1H, *J* = 13.9, 0.5 Hz), 4.29 (dd, 1H, *J* = 13.9, 1.0 Hz), 4.57 (t, 1H, *J* = 1.1 Hz), 4.62 (d, 1H, *J* = 5.1 Hz), 4.75 (dd, 1H, *J* = 5.1, 1.1 Hz), 6.74 (d, 2H, *J* = 9.0 Hz), 6.86 (m, 1H), 7.22 (d, 2H, *J* = 9.0 Hz), 7.37 (m, 5H). ^{13}C NMR: δ 165.6, 164.1, 156.4, 154.5, 136.5, 130.4, 128.7, 128.4, 127.6, 120.3, 113.7, 105.4, 82.4, 66.2, 63.1, 59.2, 57.8, 55.4, 51.5. IR ($CHCl_3$, cm^{-1}): ν 1751, 1705. MS (CI) *m*/*z*: 425 (M^+ + 1, 100), 424 (M^+, 16). Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.00; H, 5.74; N, 6.67.

Treatment of Cyclic Nitrone (±)-5a*M* with *N*-phenylmaleimide. From 200 mg (0.50 mmol) of nitrone (±)-**5a*M*** and after flash chromatography eluting with hexanes/ethyl acetate (1:1), 41 mg (40%) of the less polar compound (±)-**16** and 41 mg (40%) of the more polar compound (±)-**17** were obtained.

Cycloadduct (±)-16. Colorless solid. Mp: 148−150 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 2.72 (dd, 1H, *J* = 12.9, 8.1 Hz), 3.10 (dd, 1H, *J* = 12.9, 5.9 Hz), 3.74 (s, 3H), 3.82 (d, 1H, *J* = 7.7 Hz), 3.97 (d, 1H, *J* = 4.4 Hz), 4.18 (d, 1H, *J* = 4.4 Hz), 4.38 (dd, 1H, *J* = 8.1, 5.9 Hz), 4.50 (d, 1H, *J* = 7.7 Hz), 4.90 (t, 1H, *J* = 4.4 Hz), 6.87 (d, 2H, *J* = 8.9 Hz), 7.50 (m, 12H). ^{13}C NMR: δ 173.9, 173.0, 164.8, 156.6, 133.2, 131.1, 130.1, 129.4, 129.2, 129.1, 128.8, 127.8, 126.3, 118.4, 115.0, 75.0, 67.7, 65.2, 61.0, 59.4, 55.5, 50.1, 29.9. IR (KBr, cm^{-1}): ν 1751, 1720. MS (CI) *m*/*z*: 575 (M^+ + 1, 100), 574 (M^+, 15). Anal. Calcd for $C_{29}H_{25}N_3O_5Se$: C, 60.63; H, 4.39; N, 7.31. Found: C, 60.71; H, 4.37; N, 7.34.

Cycloadduct (±)-17. Colorless solid. Mp: 148−150 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 3.15 (dd, 1H, *J* = 12.1, 8.8 Hz), 3.39 (dd, 1H, *J* = 12.1, 5.9 Hz), 3.78 (s, 3H), 3.98 (m, 2H), 4.09 (d, 1H, *J* = 3.7 Hz), 4.40 (d, 1H, *J* = 7.4 Hz), 4.81 (t, 1H, *J* = 4.4 Hz), 5.18 (d, 1H, *J* = 7.4 Hz), 6.85 (d, 2H, *J* = 8.9 Hz), 7.45 (m, 12H). ^{13}C NMR: δ 172.9, 163.0, 156.5, 133.9, 131.0, 130.6, 129.2, 129.1, 128.9, 127.6, 126.2, 117.3, 114.9, 75.5, 71.8, 66.9, 65.0, 62.6, 55.5, 52.9, 27.8. IR (KBr, cm^{-1}): ν 1751, 1724. MS (EI) *m*/*z*: 575 (M^+ + 1, 9), 574 (M^+, 7), 59 (100). Anal. Calcd for $C_{29}H_{25}N_3O_5Se$: C, 60.63; H, 4.39; N, 7.31. Found: C, 60.55; H, 4.37; N, 7.28.

Thermal Treatment of Isoxazolinyl *β*-Lactams 14a and 14b. Synthesis of Aziridinyl *β*-Lactams 18. A solution of the appropriate cycloadduct **14** (0.20 mmol) in anhydrous toluene (15 mL) was stirred at reflux temperature under argon atmosphere for 2 h. The reaction mixture was concentrated under reduced pressure, and then chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **18**.

Compound (+)-18a. From 75 mg (0.177 mmol) of adduct (+)-**14a**, 37 mg (50%) of compound (+)-**18a** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate 2/1). $[\alpha]_D$ = +73.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 2.39 (t, 1H, *J* = 6.6 Hz), 3.47 (s, 3H), 3.49 (d, 1H, *J* = 6.6 Hz), 3.52 and 3.69 (d, each 1H, *J* = 13.2 Hz), 3.73 (s, 3H), 3.87 (s, 3H), 4.21 (dd, 1H, *J* = 6.6, 5.4 Hz,), 4.33 (d, 1H, *J* = 5.4 Hz), 6.67 (d, 2H, *J* = 8.7 Hz), 7.30 (m, 5H), 7.32 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR: δ 188.6, 163.8, 160.2, 156.4, 136.7, 130.4, 128.7, 128.6, 127.9, 118.5, 114.5, 81.8, 63.7, 58.9, 56.8, 55.5, 53.2, 47.7, 44.1. IR ($CHCl_3$, cm^{-1}): ν 1747, 1728. MS (CI) *m*/*z*: 425 (M^+ + 1, 100), 424 (M^+, 11). Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.16; H, 5.75; N, 6.56.

General Procedure for the Synthesis of Isoxazolidinyl *β*-Amino Esters 21. To a solution of the appropriate cycloadduct **7** or **8** (1 mmol) in methanol (10 mL) was added a catalytic amount (a few drops) of 37% aqueous hydrochloric acid. The resulting solution was heated under reflux for 8 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The mixture was diluted with ethyl acetate (15 mL), washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. After chromatography of the residue eluting with ethyl acetate/hexanes (1:1) gave analytically pure compounds **21**.

Isoxazolidinyl *β*-Amino Ester (−)-21a. From 111 mg (0.22 mmol) of cycloadduct (+)-**7**, 95 mg (80%) of compound (−)-**21a** was obtained as a yellow oil. $[\alpha]_D$ = −18.9 (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 3.47 (s, 3H), 3.56 (s, 3H), 3.62 (s, 3H), 3.72 (m, 4H), 3.75 (s, 3H), 3.91 (t, 1H, *J* = 4.6 Hz), 4.04 (dd, 2H, *J* = 8.8, 4.6 Hz), 4.15 and 4.42 (d, each 1H, *J* = 12.9 Hz), 4.26 (d, 1H, *J* = 2.4 Hz), 4.79 (d, 1H, *J* = 8.8 Hz), 6.38 and 6.68 (d, each 2H, *J* = 9.0 Hz), 7.35 (m, 3H), 7.47 (m, 2H). ^{13}C NMR: δ 171.4, 171.2, 169.9, 152.4, 140.3, 137.1, 129.6, 128.3, 127.4, 115.1, 114.7, 79.0, 68.4, 62.3, 58.6, 58.2, 55.6, 53.7, 52.4, 52.3, 51.9. IR ($CHCl_3$, cm^{-1}): ν 3392, 1747. MS (CI) *m*/*z*: 517 (M^+ + 1, 100), 516 (M^+, 35). Anal. Calcd for $C_{26}H_{32}N_2O_9$: C, 60.46; H, 6.24; N, 5.42. Found: C, 60.56; H, 6.18; N, 5.49.

General Procedure for the Hexacarbonylmolybdenum-Promoted Reductive Ring Opening/Ring Closure of Isoxazolidinyl *β*-Amino Esters 21. Preparation of Functionalized *β*-Alkoxycarbonyl *γ*-Lactams. A mixture of the corresponding isoxazolidine derivative **21** (1 mmol) and $Mo(CO)_6$ (0.7 mmol) in acetonitrile (15 mL) was heated under reflux for 4 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. After chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **22**.

***β*-Alkoxycarbonyl *γ*-Lactam (−)-22a.** From 24 mg (0.046 mmol) of compound (−)-**21a**, 16 mg (73%) of compound (−)-**22a** was obtained as a yellow oil after purification by flash chromatography (hexanes/ethyl acetate 1/2). $[\alpha]_D$ = −35.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 3.47 (dd, 1H, *J* = 6.9, 6.6 Hz), 3.48 (s, 3H), 3.59 (s, 3H), 3.65 (s, 3H), 3.69 (s, 3H) 3.87 (dd, 1H, *J* = 6.6, 5.1 Hz), 3.97 (s, 1H), 4.09 and 4.12 (d, each 1H, *J* = 15.1 Hz), 4.64 (d, 1H, *J* = 6.8 Hz), 5.34 (d, 1H, *J* = 15.1 Hz), 6.07 and 6.54 (d, each 2H, *J* = 9.0 Hz), 7.25 (m, 1H), 7.40 (m, 4H). ^{13}C NMR: δ 173.8, 172.3, 171.3, 152.4, 139.4, 134.4, 129.5, 128.3, 114.7, 114.6, 77.3, 73.0, 58.6, 56.3, 55.6, 55.5, 52.6, 52.4, 47.0, 45.3. IR ($CHCl_3$, cm^{-1}): ν 3412, 1740, 1728. MS (CI) *m*/*z*: 487 (M^+ + 1, 100), 486 (M^+, 31). Anal. Calcd for $C_{25}H_{30}N_2O_8$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.83; H, 6.26; N, 5.71.

Acknowledgment. Support for this work by the DGI-MCYT (project BQU2000-0645) is gratefully acknowledged. We thank the UCM and the DGES (MEC, Spain) for predoctoral grants to J.M.A. and E.S.

Supporting Information Available: Spectroscopic and analytical data for compounds (±)-**3c**, (±)-**3d**, (±)-**3g**, (±)-**3h**, (±)-**4a**, (±)-**4c**, (±)-**5b*M***, (±)-**5b*m***, (±)-**8b**, (+)-**8c**, **9**, **10b**, **10c**, **11b**, **11c**, (±)-**12c**, (±)-**12e**−**g**, (+)-**13b**, (+)-**14b**, (+)-**15b**, (+)-**18b**, (+)-**21b**, (+)-**22b**, **23**, and **24**; general experimental procedures for compounds **23** and **24**; and X-ray data for compound (+)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025924E