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Diastereoselective [2+2]-Cycloaddition Reactions of Unsymmetrical Cyclic Ketenes with Imines: Synthesis of Modified Prolines and Theoretical Study of the Reaction Mechanism

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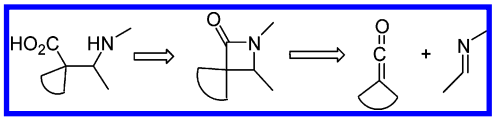
The synthesis of enantiomerically pure modified proline derivatives was achieved by using spiro β-lactams as starting material that were prepared in turn by the [2+2]-cycloaddition of unsymmetrical cyclic ketenes with optically active imines. A theoretical study of the [2+2]-cycloaddition reaction, using density-functional methods, gave insights on the origin of the observed stereoselectivity of the Staudinger reaction. The spiro β-lactams were transformed in the *N*-Boc derivatives and subjected to nucleophilic ring opening, affording the corresponding enantiomerically pure modified proline derivatives, isolated as orthogonally protected compounds.

Introduction

The development of new methodology directed to the preparation of modified α-[1] and β-amino acids[2] is a very active field in organic synthesis. The synthesis of conformationally constrained amino acids, which could present interesting biological properties, e.g., peptides derived from these modified amino acids could be more resistant to the degradative action of proteases, is of special interest. An interesting approach to conformationally constrained systems is the use of cyclic structures.[3] L-Proline constitutes a good example of how the presence of a ring can influence the secondary structure of peptides and proteins, and thus, methodology for the synthesis of several types of modified proline derivatives has been developed.[4] On the other hand, Seebach and Gellman and co-workers have shown that β-peptides formed by cyclic β-amino acids are able to form stable secondary structures in solution.[5a−c]

One of the most successful routes to access β-amino acids involves the use of β-lactams as synthetic intermediates.[6] These β-lactams, usually prepared through the ketene−imine cycloaddition route (Staudinger reaction),[7] will undergo a ring-opening reaction leading to β-amino acids. The use of β-lactams as starting material following the aforementioned protocol would lead to the stereoselective synthesis of α,α-geminally disubstituted β-amino acids (Scheme 1).[8]

SCHEME 1



Herein we report the results obtained following the synthetic route outlined in Scheme 1 that allowed us to achieve the synthesis of optically active proline derivatives **1**, which can also be considered as α,α-geminally disubstituted β-amino acids (Figure 1). Proline derivatives **1** were obtained by the nucleophile-promoted ring opening of spiro β-lactams prepared through an asymmetric Staudinger reaction of imines with unsymmetrical cyclic ketenes.

In addition, the results of a theoretical study aimed at understanding the factors controlling the stereochemical outcome of the Staudinger reaction are presented.

Results and Discussion

Synthesis of Enantiomerically Pure Spiro β-Lactams. According to previous results of our group,[8b] the

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(1) For a recent review see: Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342−351.

(2) *Enantioselective Synthesis of β-Aminoacids;* Juaristi, E., Ed.: Wiley-VCH: New York, 1997.

(3) The synthetic methodology for the synthesis of cyclic amino acid derivatives has been extensively reviewed: Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629−8659.

(4) See, for example: (a) Blanco, M. J.; Paleo, M. R.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786. (b) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438. (c) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.

(5) (a) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Apella, D. H.; Christianson, L. A.; Karle, I.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071.

(6) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Aminoacids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 279−389.

(7) For a review of the synthetic utility of the ketene−imine cycloaddition, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.;, VCH Publishers: New York, 1993; pp 295−368.

(8) (a) Alonso, E.; Pozo, C. del; González, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 571. (b) Alonso, E.; López-Ortiz, F.; Pozo, C. del; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333.

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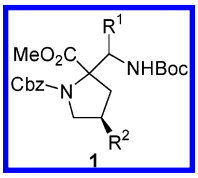


FIGURE 1. Proline derivatives obtained from the ring opening of spiro *β*-lactams.

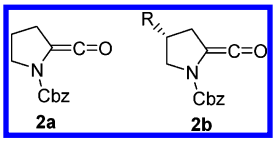
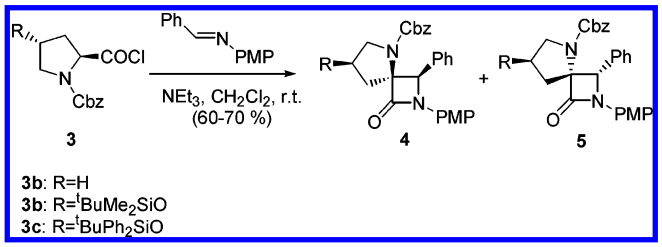


FIGURE 2. Unsymmetrical cyclic ketenes.

SCHEME 2



[2+2]-cycloaddition of the unsymmetrical ketene **2a** (see Figure 2), derived from the dehydrohalogenation of *N*-benzyloxycarbonyl L-proline acid chloride (see Scheme 2, **3a**, R = H) with triethylamine, takes place with complete stereoselectivity, giving the spiro *β*-lactam with a cis relative disposition of the substituent at the iminic carbon atom and the proline nitrogen.

To achieve asymmetric induction in the Staudinger reaction[7] we tried three different approaches: (i) the reaction of a ketene bearing a protected amino acid attached to the nitrogen of the L-proline, (ii) the use of an optically active ketene derived from *trans*-4-hydroxy-L-proline, **2b** (Figure 2), and (iii) the reaction of optically active imines derived from D-gliceraldehyde acetonide[9] and Garner's aldehyde.[10]

While the reaction of the acid chloride of the dipeptide *N*-phthaloyl-L-alanilproline with different imines failed to give the expected *β*-lactam (probably due to the steric hindrance of the intermediate ketene), the expected spiro *β*-lactams were obtained in the reactions, either of imines with ketene **2b** or of optically active imines with ketene **2a**. However, the stereochemical result of these two Staudinger reactions was quite different.

The reaction of the *O*-silyl-protected *N*-benzyloxycarbonyl *trans*-4-hydroxy-L-proline acid chloride **3b** or **3c** (Scheme 2)[11] with *N*-*p*-methoxyphenylbenzaldimine[12] in the presence of triethylamine, at room temperature, gave the corresponding spiro *β*-lactams as a 1:1 mixture of diastereoisomers **4** and **5** that were separated by column chromatography.[13]

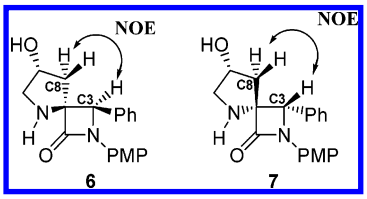


FIGURE 3. Determination of the relative configuration of spiro *β*-lactams.

As expected, the Staudinger reaction proceed with total cis stereoselectivity, giving the *β*-lactams **4** and **5**, with a cis relative disposition of the pyrrolidine nitrogen and the phenyl group, but no asymmetric induction was observed. A comparable stereochemical result was obtained when the reaction was carried out at −78 °C.

The relative configuration of the stereogenic centers of *β*-lactams **4** and **5** was deduced from the corresponding NOESY spectra of the deprotected (the Cbz and silyl protecting groups were removed to simplify the ^{1}H NMR spectra, avoiding the presence of rotamers) compounds **6** and **7** (see Figure 3 and Supporting Information). The methine proton of the *β*-lactam ring (at C3) showed a correlation with one proton (at C8) of the methylene group linked to the spiranic carbon atom. Taking into account the rigid geometry of the spiranic system, this correlation indicates a syn relationship between the imine hydrogen at C3 and the methylene group in the pyrrolidine ring. According to this result we can conclude that in the cycloaddition reactions between cyclic ketenes **3** and imines only the cis stereoisomer is formed.

The absolute configuration of *β*-lactam **4** was determined after its conversion in *β*-aminoester **1a** (see the next section on the synthesis of *β*-aminoester derivatives **1** and Supporting Information for details).

In sharp contrast with the precedent results, very good levels of asymmetric induction were achieved in the Staudinger reaction of ketene **2a** (Figure 2) with optically active imines **8**[9]and **9** [10] (Scheme 3). Thus, the reaction of *N*-benzyloxycarbonyl-L-proline acid chloride with the imine **8** gave the diastereomeric spiro *β*-lactams **10** and **11** which were separated by column chromatography. The diastereomeric ratio was determined to be 95:5 respectively by ^{1}H and ^{13}C NMR.

The cis relative configuration of *β*-lactam **10** was determined by analysis of the NOESY spectra of compound **10a**, in which the Cbz group was removed (as in the case of **4**; see Supporting Information).

On the other hand, the Staudinger reaction of imine **9** gave the *β*-lactam **12**, isolated as one diastereoisomer. The diastereomeric excess was determined by ^{1}H and ^{13}C NMR analysis of the reaction mixture, after hydrogenolysis to remove the Cbz protecting group (compound **12a**, see Supporting Information)

Having determined the cis relative stereochemistry of *β*-lactams **10** and **12**, we studied the sense of the asymmetric induction in the corresponding [2+2]-cy-

(9) (a) Bose, A. K.; Hedge, V. R.; Wagle, D. R.; Bari, S. S.; Manhas, M. G. *J. Chem. Soc., Chem. Commun.* **1986**, 161. (b) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K *J. Org. Chem.* **1988**, *53*, 4227. (c) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603.

(10) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Palomo, C.; Cossío, F. P.; Cuevas, C. *Tetrahedron Lett.* **1991**, *32*, 3109.

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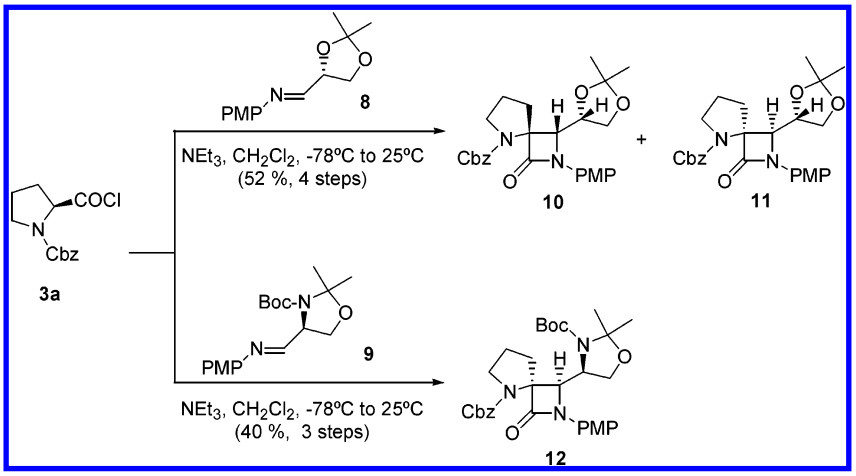
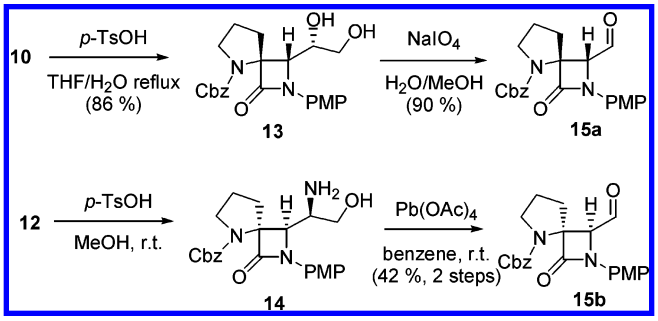
(12) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.

(13) *N*-*p*-Methoxyphenylbenzaldimine was used, as it allows easy oxidative removal of the *p*-methoxyphenyl group, with ammonium cerium (IV) nitrate, to give the *N*-unsubstituted *β*-lactam, as shown in: Kronenthal, D. R.; Han, C. Y.; Taylor M. K. *J. Org. Chem.* **1982**, *47*, 2765.

SCHEME 3



SCHEME 4



cloaddition reactions. Taking into account the absolute configuration of imines **8** and **9** and the results of the theoretical study on the reaction mechanism described later, it could be expected that the two chiral fragments exert an opposite effect. To verify this assertion, the *β*-lactams **10** and **12** were transformed in the 4-formyl derivatives **15** by a sequence of reactions involving the hydrolysis of the acetonide group in **10** and the simultaneous deprotection/hydrolysis in **12**, followed by oxidation of the intermediates **13** and **14** (see Scheme 4).[14,10b] Compounds **15a** and **15b** are enantiomers, and their optical rotations should be opposed, as it happens,[15] thus confirming the effect of the two chiral groups present in imines **8** and **9**.[16]

The enantiomeric purity of compounds **15a** and **15b** was determined by ^{1}H NMR, using europium shift reagents, and comparing with the data for the racemic 4-formyl derivative, *rac*-**15**-*cis* (see Supporting Information for details).[17]

The absolute configuration of **10** (and therefore of **12**) was determined after its conversion in the *β*-aminoester derivative **1d** (see the next section on the synthesis of *β*-aminoester derivatives **1**).

Theoretical Study of the [2+2]-Cycloaddition of Cyclic Ketenes with Imines. As reported above, the [2+2]-cycloaddition of unsymmetrical ketenes such as **2a** or **2b** (see Figure 2) took place with complete stereoselectivity, giving the spiro *β*-lactams with a cis relative disposition of the substituent at the iminic carbon atom and the nitrogen of the pyrrolidine ring. In addition, excellent asymmetric induction was achieved when optically active imines were employed (Scheme 3).

To get a deeper insight on the origins of the observed stereoselectivity, density-functional calculations[18] on the model reaction of cyclic ketene **I** with imine **II** (Figure 4) were carried out.

Previous theoretical studies, carried out at different levels of theory, on the mechanism of the [2+2]-ketene−imine cycloaddition showed that this reaction is a two-step process, involving the initial formation of a zwitterionic intermediate, which undergo a conrotatory ring closure to give the *β*-lactam.[19] Also, the stereoselectivity of the Staudinger reaction of unsymmetrical cyclic ketenes derived from 2- or 3-tetrahydrofuroyl chlorides has been studied with ab initio methods.[8a]

The stationary points located for the reaction of ketene, **I**, with *N*-methylacetaldimine, **II**, were fully optimized at the Becke3LYP/6-31+G* level of theory.[20] Two different reaction pathways were identified: the anti, in which the initial nucleophilic addition of the imine to the ketene

(14) (a) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. (b) Wagle, D. R.; Garai, C.; Monteleone, M. G. *Tetrahedron Lett.* **1988**, *29*, 1649.

(15) The values of the optical rotation $[\alpha]^{20}_D$ of **15a** and **15b**, measured in $CHCl_3$ (*c* 0.7), are +134.0 and −134.0, respectively.

(16) The relative stereochemistry of **15a** (and therefore **15b**) was studied by NMR (NOESY spectra), and was confirmed to be cis, thus excluding a possible epimerization of the carbon atom C3 (see Suporting Information).

(17) The racemic 4-formyl *β*-lactam, *rac*-**15**-*cis* was prepared according to a procedure previously described: (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. *J. Org. Chem.* **1992**, *57*, 5921.

(18) For a description of the theoretical methodology, see: Jensen, F.; *Introduction to Computational Chemistry*; Wiley: New York, 1999; pp 177−194.

(19) (a) Venturini, A.; González, J. *J. Org. Chem.* **2002**, *67*, 9089. (b) Sordo, J. A.; González, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249.

(20) The program Gaussian 98 was used: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11.3; Gaussian, Inc.: Pittsburgh, PA, 2002.

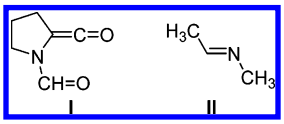


FIGURE 4. Model ketene and imine used in the density-functional study.

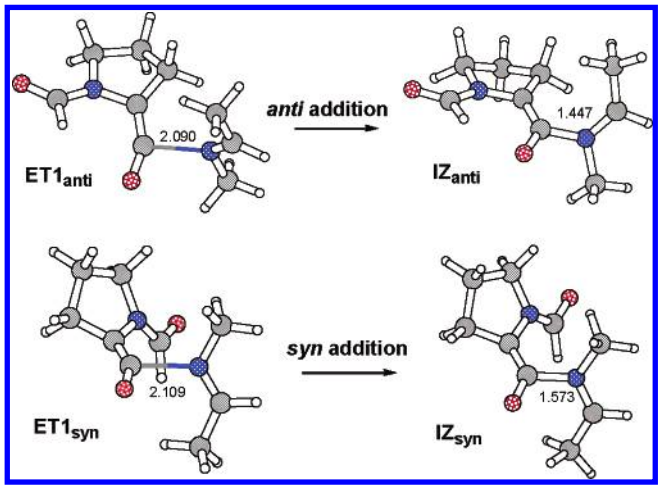


FIGURE 5. Anti and syn transition structures and zwitterionic intermediates in the addition of **II** to **I**.

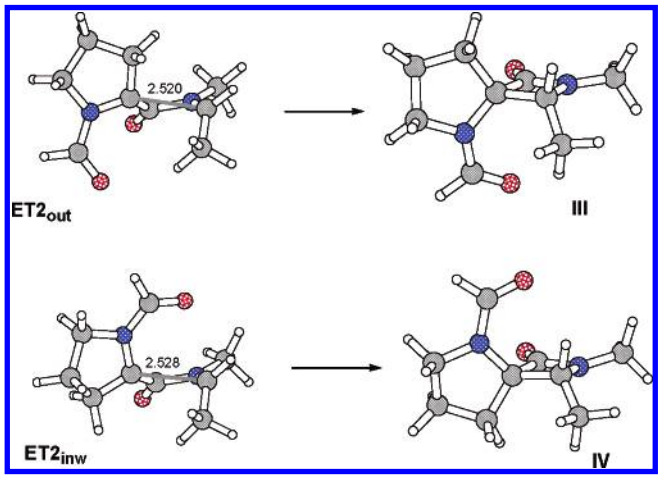


FIGURE 6. Outward and inward conrotatory ring closure transition structures.

takes place by the opposite side of the nitrogen atom of the pyrrolidine ring, and the syn, corresponding to the addition by the same side of the nitrogen.

For each reaction pathway, a transition structure for the nucleophilic attack, **ET1$_{anti}$** and **ET1$_{syn}$** (see Figure 5), in which a bond is being formed between the imine nitrogen and the central carbon atom of the ketene, was located. Following the first transition structure, a zwitterionic intermediate, having a fully formed carbon−nitrogen bond (**IZ$_{anti}$** and **IZ$_{syn}$**, Figure 5), was found.

The conrotatory ring closure of the zwitterionic intermediates results in the *β*-lactam derivatives: **IZ$_{anti}$** provides the cis *β*-lactam **III**, via the transition structure **ET2$_{out}$**, where the nitrogen is placed in the outward position, while **IZ$_{syn}$**, through transition structure **ET2$_{inw}$**, leads to the *trans* *β*-lactam **IV** (see Figure 6).

As can be seen in Figure 6, the carbon−carbon forming bond length in the two transition structures is almost

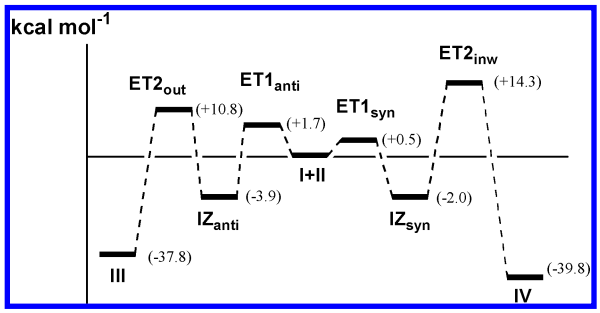


FIGURE 7. Becke3LYP/6-31+G* reaction profile corresponding to the formation of *β*-lactams **III** and **IV**.

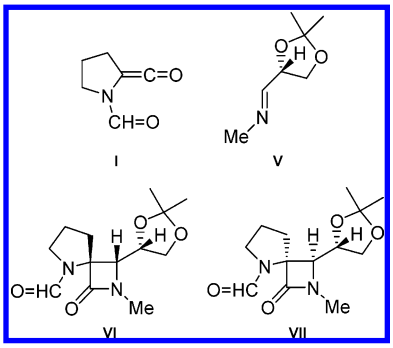


FIGURE 8. Model asymmetric Staudinger reaction.

the same, but in **ET2$_{out}$**, the nitrogen atom rotates outward, while in **ET2$_{inw}$**, the nitrogen is placed inward. According to previous work, there is a strong stereoelectronic preference (torquoelectronic effect)[21] in these types of transition structures for the ring closure in which the heteroatom rotates outward.[8a,22]

The relative energies of the anti and syn reaction pathways are shown in Figure 7, and according to these data, though the syn approach is favored, the rate-determining step corresponds to the *outward* transition structure, **ET2$_{out}$**, which is 3.5 kcal mol^{-1} more stable than **ET2$_{inw}$**. Thus, the cis *β*-lactam **III** is predicted to be the favored stereoisomer, in good agreement with the experimental evidence.

This result indicates that the cis stereoselectivity of the reaction is dictated by the stereoelectronic preference in the second transition structure for the outward position of the nitrogen atom of the pyrrolidine ring.

In addition to the electronic preference for the *outward* transition structure, steric effects should govern the high diastereoselectivity found in the reaction of the optically active imines **8** and **9** (Scheme 3).

The asymmetric Staudinger reaction was studied by using **V** as a model of the optically active imine (see Figure 8). The calculations were carried out at the Becke3LYP/6-31G* level of theory, and the transition structures corresponding to the two possible cyclization modes leading to the diastereomeric *β*-lactams **VI** and **VII** were located.

According to the reaction profile shown in Figure 6, the favored reaction pathway involves the outward

(21) For a description of the torquoelectronic effect, see: (a) Rondan, G. N.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

(22) López, R.; Sordo, T. L.; Sordo, J. A.; González, J. *J. Org. Chem.* **1993**, *58*, 7036.

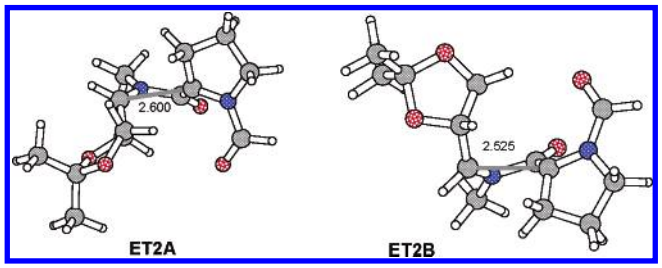
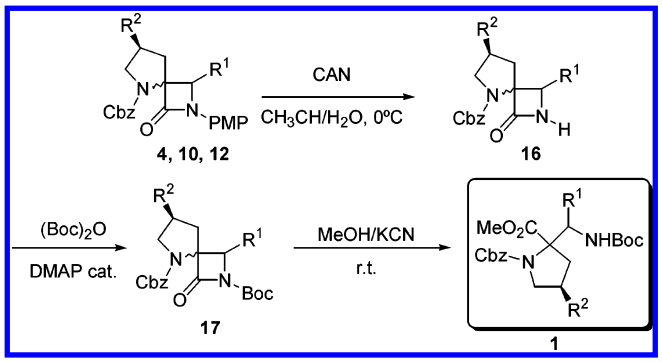


FIGURE 9. Two diastereomeric transition structures for the outward ring closure in the reaction of **I** with **V**.

SCHEME 5



transition structure $\mathbf{ET2}_{\mathbf{out}}$; in the case of the imine **V**, two diastereomeric outward transition structures, **ET2A** and **ET2B** (Figure 9), are possible, depending upon the sense of the relative rotation of the ketene and imine moieties.

The transition structure **ET2A** is 3.9 kcal mol^{-1} more stable than **ET2B**, and leads to the formation of the *β*-lactam **VI**, which presents the same absolute configuration as **10**, the major diastereoisomer observed in the reaction of the optically active imine **8** (see Scheme 3). The examination of **ET2A** shows that it is a less sterically crowded transition structure than **ET2B**, in which the dioxolane ring of the imine is pointing to the formyl substituent of the ketene. This result is also in good agreement with the fact that in the reaction of the optically active ketenes **3b** and **3c** (Scheme 2), having the stereogenic center far from the carbon−carbon bond forming, no stereoselectivity was found.

Synthesis of Optically Active α-(1-aminoalkyl)-proline Methyl Esters 1. According to the proposed synthetic plan, as shown in Scheme 1, the ring opening of the spiro *β*-lactams **4**, **10**, and **12** would provide the modified prolines in an enantiomerically pure form. The *β*-lactam ring can be hydrolyzed under strong acid or basic conditions to give directly the *β*-amino acids, but these reaction conditions could affect the integrity of the spiranic system. It seemed more convenient to follow a route involving the synthesis of the *N*-Boc *β*-lactam derivatives **17** (Scheme 5).[23] This procedure, while requiring more steps, allows for the *β*-lactam ring-opening reaction to be carried out in very mild conditions, due to the electron-withdrawing effect of the Boc group.[24] In addition, the *β*-aminoester derivatives **1** are isolated as orthogonally protected compounds simplifying any ulterior manipulation.

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(24) Herzig, J.; Antebi, A. *J. Org. Chem.* **1986**, *51*, 730.

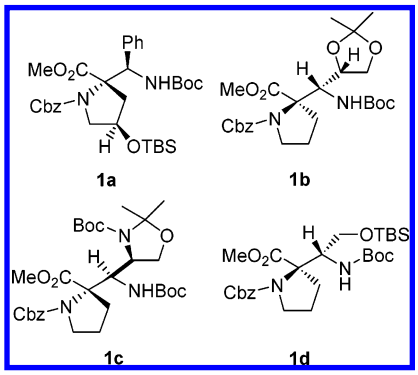

FIGURE 10. Optically active α-(1-aminoalkyl)proline methyl esters **1**.

The *β*-lactams **4**, **10**, and **12** were treated with ammonium cerium(IV) nitrate to remove the *p*-methoxyphenyl group;[13] the reaction of the *N*-unsubstituted derivatives **16** with $(Boc)_2O$ in the presence of catalytic amounts of DMAP furnished the *N*-Boc-protected *β*-lactams **17**, which, in the presence of methanol and potassium cyanide,[24] underwent ring opening to give the enantiomerically pure *β*-aminoester derivatives **1** (see Scheme 5 and Figure 10).

In addition, this synthetic sequence allows for the preparation of side-chain functionalized *β*-aminoesters, as **1d**. The reduction of 4-formyl *β*-lactam **15a** and *O*-silylation of the hydroxy group, followed by the oxidative cleavage of PMP, gave the *N*-unsubstituted *β*-lactam **18**; then, the cyanide-promoted ring opening of the *N*-Boc derivative **19** afforded the *O*-silyl-protected α-(1-aminoalkyl)proline **1d**, in 30% yield (5 steps).

The absolute configuration of the *β*-aminoester derivatives **1** was determined by the Mosher method,[25] and this allowed us to establish the configuration of the precursor spiro *β*-lactams (see Supporting Information).

Conclusions

The stereoselective synthesis of proline derivatives was achieved by the sequential [2+2]-cycloaddition reaction of an unsymmetrical cyclic ketene with optically active imines, and nucleophilic ring opening of the *β*-lactam formed. The reaction of the imines derived from D-gliceraldehyde acetonide and Garner's aldehyde took place with a high stereoselectivity. According to the density-functional calculations carried out on model reactions, the origin of this stereoselectivity appears to be related to steric and electronic factors operating in the transition structure during the cyclization of the zwitterionic intermediate formed in the nucleophilic attack of the imine to the ketene.

The methodology described here allows the preparation of the optically active α-(1-aminoalkyl)prolines as orthogonally protected compounds. Further developments and applications of these compounds on the synthesis of conformationally restricted peptides are currently underway.

Experimental Section

General Procedure for the Preparation of Spiro *β*-Lactams (4 and 5). To a stirred solution of *N*-*p*-methoxyphenylbenzaldimine (2 mmol) and dry triethylamine (0.41 mL, 3

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mmol) in dry dichloromethane (10 mL) was added dropwise the acid chloride **3b**, or **3c** (2 mmol) dissolved in dry dichloromethane (5 mL). The mixture was stirred for 16 h at room temperature, and was then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was washed twice with CH_2Cl_2 (15 mL), and the combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by column chromatography over SiO_2 with the appropriate mixture of ethyl acetate/hexane, affording the spiro *β*-lactams **4** and **5** as a 1:1 mixture of diastereoisomers. The diastereomers **4b**, **5b** and **4c**, **5c** were separated by flash chromatography (20% EtOAc/hexane).

(−)-(3*R*,4*S*,7*R*)-5-Benzyloxycarbonyl-7-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (4b). R_f 0.60 (33% EtOAc/hexane), 0.40 g of **4b**, 35% yield. White solid, $[\alpha]_D$ −45.1 (*c* 0.5, $CHCl_3$), mp 175−178 °C. ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) *δ* 0.09, 0.11, 0.12, 0.13 (s, 6H), 0.89, 0.91 (s, 9H), 2.50−2.65 (m, 2H), 3.19, 3.31 (AB syst, J = 10.2, 8.0 Hz; AB syst, J = 10.5, 8.0 Hz, 1H), 3.45, 3.60 (AB syst, J = 10.2, 7.4 Hz; AB syst, J = 10.5, 7.4 Hz, 1H), 3.76, 3.77 (s, 3H), 4.43−4.78 (m, 2H), 4.91−5.05 (m, 2H), 6.75−6.89 (m, 3H), 7.01 (m, 1H), 7.14−7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* −5.0, −4.9, 17.8, 25.5, 42.7, 44.0, 53.7, 54.4, 55.2, 66.5, 67.5, 67.6, 68.3, 69.6, 70.3, 76.0, 76.8, 114.0, 118.3, 118.4, 126.7, 127.3, 127.5, 127.6, 127.8, 127.9, 128.1, 130.8, 131.1, 133.1, 133.3, 135.2, 136.3, 153.2, 153.4, 155.9, 164.0, 164.2; IR (KBr) 1715, 1756 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 595 [(M + Na), 10], 573 [(M + H), 100]. Anal. Calcd for $C_{33}H_{40}N_2O_5Si$: C, 69.20; H, 7.04; N, 4.89. Found: C, 69.47; H, 7.02; N, 4.87.

(+)-(3*S*,4*R*,7*R*)-5-Benzyloxycarbonyl-7-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (5b). R_f 0.27 (33% EtOAc/hexane), 0.395 g of **5b**, 35% yield. Colorless oil, $[\alpha]_D$ +22.8 (*c* 0.3, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in a 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) *δ* 0.06, 0.08 (s, 3H), 0.19, 0.22 (s, 3H), 0.87, 0.99 (s, 9H), 2.30−2.70 (m, 2H), 3.25−3.90 (m, 5H), 4.30−4.75 (m, 2H), 4.90−5.25 (m, 2H), 6.78−7.50 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* −5.0, −4.9, 17.9, 18.3, 25.6, 25.8, 43.7, 45.1, 55.4, 57.4, 58.1, 66.6, 67.4, 68.7, 69.5, 70.4, 75.8, 113.9, 114.1, 118.5, 118.6, 127.4, 127.5, 127.9, 128.2, 128.5, 131.1, 131.5, 134.0, 135.0, 136.4, 153.4, 156.1, 165.5; IR (neat) 1702, 1765 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 573 [(M + H), 70]. Anal. Calcd for $C_{33}H_{40}N_2O_5Si$: C, 69.20; H, 7.04; N, 4.89. Found: C, 68.85; H, 7.01; N, 4.92.

(−)-(3*R*,4*S*,7*R*)-5-Benzyloxycarbonyl-7-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxyphenyl)-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (4c). R_f 0.55 (33% EtOAc/hexane), 0.42 g of **4c**, 30% yield. White foam, $[\alpha]_D$ −34.0 (*c* 0.5, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in a 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.08, 1.09 (s, 9H), 2.24−2.40 (m, 1H), 2.59−2.74 (m, 1H), 3.30−3.45 (m, 2H), 3.74, 3.76 (s, 3H), 4.40−4.78 (m, 3H), 5.00 (m, 1H), 6.50−7.90 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.9, 26.6, 42.2, 43.4, 53.2, 53.8, 55.3, 66.6, 67.6, 68.4, 69.1, 69.5, 70.2, 75.8, 114.1, 114.3, 118.3, 118.4, 126.6, 127.1, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 130.0, 135.5, 130.8, 131.1, 132.9, 133.0, 133.1, 135.3, 136.3, 153.2, 153.4, 156.0, 156.1, 163.9; IR (KBr) 1712, 1760 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 697 [(M + H), 35]. Anal. Calcd for $C_{43}H_{44}N_2O_5Si$: C, 74.11; H, 6.36; N, 4.02. Found: C, 73.85; H, 6.34; N, 4.04.

(+)-(3*S*,4*R*,7*R*)-5-Benzyloxycarbonyl-7-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxyphenyl)-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (5c). R_f 0.45 (33% EtOAc/hexane), 0.42 g of **5c**, 30% yield. White foam, $[\alpha]_D$ +25.6 (*c* 0.12, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in a 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.20, 1.21 (s, 9H), 2.32−2.58 (m, 2H), 3.43−3.78 (m, 2H), 3.79, 3.80 (s, 3H), 4.28−4.73 (m, 2H), 4.97 (m, 1H), 5.32 (m, 1H), 6.60−7.75 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 19.1, 26.8, 27.1, 43.4, 44.8, 55.4, 57.1, 57.9, 66.7, 67.6, 68.7, 69.4, 70.4, 71.4, 75.9, 114.2, 114.7, 118.5, 118.7, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.6, 129.9, 130.0, 130.1, 130.2, 135.4, 135.5, 131.3, 131.5, 132.7, 132.8, 132.9, 133.9, 134.1, 135.7, 136.4, 153.4, 156.0, 165.0, 165.5; IR (KBr) 1697, 1760 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 697 [(M + H), 35]. Anal. Calcd for $C_{43}H_{44}N_2O_5Si$: C, 74.11; H, 6.36; N, 4.02. Found: C, 73.81; H, 6.37; N, 3.99.

Synthesis of Spiro *β*-Lactams (10 and 12). To a stirred solution of the imine **8** or **9** (2 mmol) and dry triethylamine (0.41 mL, 3 mmol) in dry dichloromethane (10 mL) at −78 °C was added dropwise the *N*-benzyloxycarbonyl L-proline acid chloride **3a** (2 mmol) dissolved in dry dichloromethane (5 mL). The mixture was allowed to warm to room temperature overnight and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 (15 mL), and the combined organic layers were washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by column chromatography over SiO_2 with the appropriated mixture of ethyl acetate/hexane.

(3*RS*,4*RS*)-*cis*-5-Benzyloxycarbonyl-2-(4-methoxyphenyl)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-diazaspiro-[3.4]octan-1-one (10 and 11). Prepared from imine **8** (2 mmol), according to the general procedure described above, to afford a 95:5 mixture of the diastereoisomers **10**, **11** (52% overall yield, 4 steps), which were separated by flash chromatography (50% EtOAc/hexane).

(−)-(3*R*,4*R*)-5-Benzyloxycarbonyl-2-(4-methoxyphenyl)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-diazaspiro[3.4]-octan-1-one (10). Major isomer: R_f 0.37 (50% EtOAc/hexane), 0.456 g of **10**, 49% yield (4 steps). White solid, $[\alpha]_D$ −9.6 (*c* 0.4, $CHCl_3$), mp 125−130 °C. ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 2:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.13, 1.24 (s, 3H); 1.44, 1.48 (s, 3H), 1.78−2.27 (m, 3H), 2.40 (m, 1H), 3.40−3.65 (m, 3H), 3.69−3.87 (m, 1H), 3.79, 3.81 (s, 3H), 3.93, 3.99 (d, J = 8.3, 1H), 4.29, 4.63 (m, 1H), 5.04 (m, 1H), 5.25 (m, 1H), 6.85 (m, 2H), 7.10−7.74 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 22.3, 23.0, 24.9, 26.6, 34.8, 36.1, 48.0, 48.7, 55.4, 66.3, 67.5, 68.1, 71.5, 72.0, 73.6, 73.9, 75.2, 109.3, 113.8, 119.5, 128.1, 128.2, 128.3, 128.4, 131.1, 131.5, 135.0, 136.1, 153.8, 154.2, 156.1, 156.2, 165.4; IR (KBr) 1710, 1752 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 505 [(M + K), 100], 489 [(M + Na), 20], 467 [(M + H), 7]. Anal. Calcd for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.11; H, 6.50; N, 6.03.

(+)-(3*R*,4*S*)-5-Benzyloxycarbonyl-3-[(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2-(4-methoxyphenyl)-2,5-diazaspiro[3.4]octan-1-one (12). Prepared from imine **9** (2 mmol) according to the general procedure described above to afford **12** as a single diastereomer. R_f 0.37 (50% EtOAc/hexane), 0.450 g of **12**, 40% yield (3 steps). White foam, $[\alpha]_D$ +2.5 (*c* 0.5, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers. ^1H NMR (300 MHz, $CDCl_3$) *δ* 0.89, 1.03, 1.17, 1.43, 1.49, 1.67, 1.69, 1.79 (s, 15H), 1.90−2.45 (m, 4H), 3.44−3.71 (m, 4H), 3.75 (s, 3H), 4.07 (m, 1H), 4.56 (m, 1H), 4.95−5.34 (m, 2H), 6.75−6.89 (m, 2H), 7.27−7.60 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 22.0, 22.9, 22.7, 24.0, 27.0, 27.3, 27.7, 34.7, 36.0, 34.8, 36.0, 48.1, 48.9, 55.3, 57.1, 65.0, 65.5, 67.2, 69.1, 74.0, 80.0, 94.1, 94.5, 113.6, 113.7, 114.0, 117.7, 119.5, 127.9, 128.0, 128.2, 132.5, 136.3, 152.3, 154.2, 155.8, 165.9; IR (KBr) 1694, 1746, 1762 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 604 [(M + K), 100], 588 [(M + Na), 40]. Anal. Calcd for $C_{31}H_{39}N_3O_7$: C, 65.82; H, 6.95; N, 7.43. Found: C, 65.59; H, 6.93; N, 7.40.

Preparation of (−)-(3*R*,4*R*)-5-Benzyloxycarbonyl-3-(1,2-dihydroxyethyl)-2-(4-methoxyphenyl)-2,5-diazaspiro-[3.4]octan-1-one (13). To a solution of the *β*-lactam **10** (1 mmol) in THF/H_2O (1/1, 10 mL) was added solid *p*-TsOH·H_2O (1.1 mmol), and the resulting solution was refluxed overnight. The reaction mixture was allowed to cool to room temperature, the THF was removed under vacuum, and the aqueous residue was neutralized with saturated aqueous $NaHCO_3$. The aque-

ous layer was extracted twice with CH_2Cl_2 (15 mL) and the organic layer dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by flash chromatography (66% EtOAc/hexane) to afford 367 mg of **13**, 86% yield. White foam, $[\alpha]_D$ −17.6 (*c* 0.8, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers. ^1H NMR (300 MHz, $CDCl_3$) δ 1.75−2.46 (m, 4H), 3.52−3.70 (m, 4H), 3.77 (s, 3H), 3.88 (br s, 1H), 4.00−4.10 (m, 2H), 5.17 (m, 2H), 6.76−6.89 (m, 2H), 7.27−7.48 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 35.2, 48.4, 55.4, 65.1, 67.7, 68.0, 69.7, 74.8, 114.0, 120.4, 128.0, 128.2, 128.5, 131.1, 135.7, 155.7, 156.5, 165.8; IR (KBr) 1682, 1734, 3282, 3500 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 875 [(2M + Na), 25], 449 [(M + Na), 10], 427 [(M + H), 100]. Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57. Found: C, 64.94; H, 6.13; N, 6.55.

Preparation of (+)-(3*R*,4*R*)-*cis*-5-Benzyloxycarbonyl-3-formyl-2-(4-methoxyphenyl)-2,5-diazaspiro[3.4]octan-1-one (15a). To a solution of the β-lactam **13** (0.8 mmol) in MeOH/H_2O (1/1, 10 mL) was added $NaIO_4$ (1.6 mmol) and the mixture was maintained below 20 °C and stirred vigorously until total disappearance of the starting material (3 h, monitored by TLC). The MeOH was removed under vacuo and the resulting solution was diluted with water. The aqueous layer was extracted twice with CH_2Cl_2 (15 mL) and the organic layer dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by flash chromatography (33% EtOAc/hexane) to afford 284 mg of **15a**, 90% yield. White foam, $[\alpha]_D$ +134 (*c* 0.7, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in *ca*. 4:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 1.95−2.10 (m, 2H), 2.29 (m, 1H), 2.46 (m, 1H), 3.40−3.69 (m, 2H), 3.80, 3.81 (s, 3H), 4.17, 4.30 (d, J = 2.2, 1H), 5.02−5.16 (m, 2H), 6.80−6.92 (m, 2H), 7.10−7.38 (m, 7H), 9.34, 9.83 (d, J = 2.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.9, 34.4, 35.9, 47.6, 48.3, 55.2, 67.3, 68.2, 70.6, 70.9, 76.8, 77.2, 114.2, 114.4, 117.5, 117.6, 127.5, 127.9, 128.3, 130.4, 130.7, 135.5, 153.8, 156.3, 165.2, 196.7, 197.1; IR (KBr) 1693, 1722, 1765 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 426 [(M + MeOH), 40]. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.11; H, 5.59; N, 7.12.

(−)-(3*S*,4*S*)-*cis*-5-Benzyloxycarbonyl-3-formyl-2-(4-methoxyphenyl)-2,5-diazaspiro[3.4]octan-1-one (15b). To a solution of the β-lactam **12** (0.5 mmol) in MeOH (10 mL) was added solid *p*-TsOH·H_2O (0.55 mmol), and the resulting solution was stirred overnight. The MeOH was removed under vacuo, and the aqueous residue was neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with EtOAc (15 mL) and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give β-lactam **14** as a colorless oil, which was used without further purification. $Pb(OAc)_4$ (0.45 mmol) was added to a benzene solution (5 mL) of **14**, and the mixture was stirred at room temperature until total disappearance of the starting material (3 h, monitored by TLC). The solvent was removed in vacuo and an aqueous solution of saturated $NaHCO_3$ (15 mL) was added. The aqueous layer was extracted twice with CH_2Cl_2 (15 mL) and the organic layer dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by flash chromatography (33% EtOAc/hexane) to afford 83 mg of **15b**, 42% (overall yield). $[\alpha]_D$ −134 (*c* 0.7, $CHCl_3$).

Synthesis of *N*-Unsubstituted *β*-Lactams. The *N*-unsubstituted β-lactams **(16a−c**, **18)** were prepared according to the published procedure.[13] A solution of the *N*-PMP-β-lactam (1 mmol) in acetonitrile (10 mL) was cooled to 0 °C and treated with a solution of CAN (3 mmol) in water (15 mL) over 5 min. The reaction was stirred at 0 °C for 45 min and diluted with 50 mL of water. The mixture was extracted with EtOAc (2 × 25 mL). The organic extracts were washed with 5% sodium bicarbonate (25 mL) and the aqueous extracts back-washed with EtOAc (25 mL). The combined organic solutions were washed with 10% sodium sulfite (3 × 25 mL), 5% sodium bicarbonate (25 mL), and brine. The resulting solution was swirled over charcoal for 30 min, anhydrous Na_2SO_4 was added, and the mixture was filtered through Celite. The solution was then concentrated and purified by column chromatography over SiO_2 with the appropriate mixture of ethyl acetate/hexane. Compound **16a**, prepared from **4b**, was used in the next step without further purification.

(−)-(3*R*,4*R*)-5-Benzyloxycarbonyl-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-diazaspiro[3.4]octan-1-one (16b). Prepared from **10**, and purified through flash chromatography (50% EtOAc/hexane), to afford 234 mg of **16b**, in 65% yield. Pale yellow oil, $[\alpha]_D$ −2.4 (*c* 0.7, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 3:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12, 1.26, 1.35, 1.39 (s, 6H), 1.71−2.42 (m, 4H), 3.35−3.54 (m, 4H), 3.72−3.88 (m, 1H), 4.18, 4.53 (m, 1H), 4.97−5.37 (m, 2H), 6.33, 6.50 (br s, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 23.1, 24.8, 26.6, 34.8, 36.1, 48.0, 48.6, 66.0, 66.7, 67.3, 67.4, 67.9, 75.0, 75.4, 109.3, 128.0, 128.1, 128.2, 128.4, 135.5, 136.1, 153.9, 154.3, 168.4; IR (KBr) 1706, 1781, 3290 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 743 [(2M + Na), 100], 399 [(M + K), 29], 383 [(M + Na), 64], 361 [(M + H), 42]. Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.09; H, 6.73; N, 7.80.

(+)-(3*R*,4*S*)-5-Benzyloxycarbonyl-3-[(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2,5-diazaspiro-[3.4]octan-1-one (16c). Prepared from **12**, and purified through flash chromatography (50% EtOAc/hexane), to afford 285 mg of **16c**, in 62% yield. White solid, $[\alpha]_D$ +0.8 (*c* 0.65, $CHCl_3$), mp 182−184 °C. ^1H and ^{13}C NMR show the presence of rotamers. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25−1.60 (m, 15H), 1.79−2.42 (m, 4H), 3.37−4.50 (m, 6H), 4.97−5.50 (m, 2H), 6.67, 6.86 (br s, 1H), 7.26−7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 23.0, 27.1, 28.3, 34.8, 36.2, 48.2, 48.9, 57.9, 58.1, 64.6, 64.7, 67.4, 67.5, 67.8, 68.0, 75.8, 76.1, 80.7, 93.6, 94.1, 128.0, 128.1, 128.4, 129.2, 135.6, 136.2, 153.1, 153.8, 154.1, 168.4, 168.6; IR (KBr) 1694, 1770, 3215 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 482 [(M + Na), 100]. Anal. Calcd for $C_{24}H_{33}N_3O_6$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.54; H, 7.27; N, 9.11.

(+)-(3*R*,4*R*)-5-Benzyloxycarbonyl-3-(*tert*-butyldimethylsilyloxymethyl)-2,5-diazaspiro[3.4]octan-1-one (18). To a solution of **15a** (1 mmol) in MeOH (5 mL) cooled to 0 °C was added sodium borohydride (2.5 mmol). The mixture was stirred for 2 h and then quenched with saturated aqueous $NaHCO_3$. The MeOH was removed in vacuo, and the aqueous layer extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated to afford the corresponding alcohol, which was employed without further purification. This alcohol (0.9 mmol) was silylated by using *tert*-butyldimethylsilyl chloride (1.08 mmol) and imidazole (1.17 mmol) in DMF according to the general procedure[11a] to afford the protected *O*-silylated β-lactam, which was employed without further purification. The deprotection of the PMP group according to the general procedure[13]afford after flash chromatography (50% EtOAc/hexane) 182 mg of **18**, in 45% yield (3 steps). White foam, $[\alpha]_D$ +22.2 (*c* 0.1, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 3:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ −0.12, −0.04, −0.01 (s, 6H), 0.79, 0.84 (s, 9H), 1.75−2.33 (m, 4H), 3.38−3.87 (m, 5H), 4.99−5.28 (m, 2H), 6.30, 6.47 (br s, 1H), 7.25−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8, 18.0, 22.0, 22.7, 25.6, 34.4, 35.8, 47.8, 48.5, 61.7, 61.8, 64.2, 64.4, 67.1, 67.5, 75.5, 76.0, 127.9, 128.3, 135.7, 136.2, 154.1, 154.5, 169.2, 169.3; IR (KBr) 1704, 1777, 3314 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 831 [(2M + Na), 30], 809 [(2M + H), 45], 405 [(M + H), 100]. Anal. Calcd for $C_{21}H_{32}N_2O_4Si$: C, 62.34; H, 7.97; N, 6.92. Found: C, 62.17; H, 7.96; N, 6.89.

Synthesis of *N*-Boc-*β*-lactams (17 and 19). To a stirred solution of the *N*-unsubstituted β-lactam (**16**, **18**) (0.6 mmol) in acetonitrile (10 mL), cooled to 0 °C, were added di-*tert*-butyl dicarbonate (1.2 mmol) and a catalytic amount of DMAP, and the mixture was stirred at room temperature overnight. Then, methylene chloride (25 mL) was added, and the mixture was washed with 1 M $KHSO_4$ (15 mL) and brine. The organic layer

was dried over Na_2SO_4, and the solvent removed in vacuo. Products were purified by column chromatography over SiO_2 with the appropriate mixture of ethyl acetate/hexane. Compound **19**, prepared from **18**, was used in the next step without further purification.

(−)-(3*R*,4*S*,7*R*)-5-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-7-(*tert*-butyldimethylsilyloxy)-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (17a). Prepared from **16a** (1 mmol) according to the general procedure described above to afford, after flash chromatography (33% EtOAc/hexane), 329 mg of **17a**, in 58% yield (2 steps). Pale yellow solid, $[\alpha]_D$ −84.9 (*c* 0.4, $CHCl_3$), mp 110−112 °C. ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 0.08, 0.11, 0.12, 0.13 (s, 6H), 0.89, 0.90 (s, 9H), 1.41, 1.50 (s, 9H), 2.42−2.58 (m, 2H), 3.17, 3.30 (dd, J = 10.2, 7.7 Hz; dd, J = 10.5, 7.7 Hz, 1H), 3.46, 3.60 (dd, J = 10.2, 7.4 Hz; dd, J = 10.5, 7.4 Hz, 1H), 4.45, 4.71 (d, J = 12.0 Hz; d, J = 12.5 Hz, 1H), 4.50−4.66 (m, 1H), 4.85−5.01 (m, 2H), 6.69 (m, 1H), 6.98 (m, 1H), 7.12−7.45 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.9, 17.9, 25.6, 27.8, 27.9, 43.1, 44.4, 53.7, 54.4, 66.9, 67.9, 67.7, 68.4, 69.0, 69.3, 75.6, 76.1, 83.5, 83.6, 126.0, 126.5, 127.6, 127.8, 128.0, 128.3, 128.4, 133.0, 133.3, 135.0, 136.1, 147.9, 148.3, 152.8, 153.4, 164.8, 165.5; IR (KBr) 1713, 1814 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 1155 [(2M + Na), 100], 589 [(M + Na), 25]. Anal. Calcd for $C_{31}H_{42}N_2O_6Si$: C, 65.69; H, 7.47; N, 4.94. Found: C, 65.82; H, 7.50; N, 4.93.

(−)-(3*R*,4*R*)-5-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-diazaspiro-[3.4]octan-1-one (17b). Prepared from **16b** (0.6 mmol) according to the general procedure described above to afford, after flash chromatography (50% EtOAc/hexane), 260 mg of **17b**, in 94% yield. White solid, $[\alpha]_D$ −0.4 (*c* 3, $CHCl_3$), mp =113−117 °C. ^1H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 2.5:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05−1.50 (m, 15H), 1.60−2.41 (m, 4H), 3.30−3.94 (m, 5H), 4.07, 4.53 (m, 1H), 4.89−5.32 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 23.1, 24.9, 25.0, 26.3, 26.4, 27.7, 27.8, 35.3, 36.6, 47.8, 48.5, 65.9, 67.6, 68.1, 70.1, 70.6, 73.9, 74.1, 74.8, 74.9, 83.0, 109.0, 128.0, 128.2, 128.3, 128.4, 128.5, 134.8, 135.8, 147.4, 147.6, 153.3, 154.0, 166.2, 166.6; IR (KBr) 1704, 1738, 1796 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 483 [(M + Na), 100]. Anal. Calcd for $C_{24}H_{32}N_2O_7$: C, 62.59; H, 7.00; N, 6.08. Found: C, 62.38; H, 7.01; N, 6.06.

(−)-(3*R*,4*S*)-5-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-3-[(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2,5-diazaspiro[3.4]octan-1-one (17c). Prepared from **16c** (0.6 mmol) according to the general procedure described above to afford, after flash chromatography (33% EtOAc/hexane), 238 mg of **17c**, in 71% yield. Colorless oil, $[\alpha]_D$ −4.6 (*c* 0.9, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35−1.65 (m, 24H), 1.70−2.42 (m, 4H), 3.36−3.82 (m, 4H), 3.88−4.09 (m, 1H), 4.42−4.63 (m, 1H), 4.95−5.30 (m, 2H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.9, 23.2, 24.5, 26.9, 27.5, 28.1, 28.3, 28.4, 35.7, 37.2, 48.3, 49.0, 56.5, 56.8, 64.8, 65.1, 67.5, 67.7, 68.4, 74.4, 74.6, 79.7, 79.9, 80.6, 82.7, 83.6, 93.8, 94.4, 128.1, 128.3, 129.4, 136.0, 136.3, 148.3, 148.7, 152.2, 152.3, 152.7, 153.9 154.3, 165.6, 166.4; IR (KBr) 1698, 1732, 1821 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 598 [(M + K), 10], 582 [(M + Na), 100]. Anal. Calcd for $C_{29}H_{41}N_3O_8$: C, 62.24; H, 7.38; N, 7.51. Found: C, 62.36; H, 7.35; N, 7.54.

Synthesis of α-(1-Aminoalkyl)proline Methyl Esters (1). To a stirred solution of the *N*-Boc-*β*-lactam (**17** and **18**) (0.5 mmol) in MeOH (10 mL) was added potassium cyanide (0.5 mmol) and the mixture was stirred overnight. The MeOH was removed in vacuo and saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added. The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography afforded the desired *N*-Boc-protected proline derivatives.

Methyl (−)-(2*S*,3*R*)-2-[(*R*)-1-Benzyloxycarbonyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]-3-(*N*-*tert*-butoxycarbonylamino)propanoate (1a). Prepared from **17a**, and purified through flash chromatography (20% EtOAc/hexane), to afford 270 mg of **1a**, in 93% yield. Colorless oil, $[\alpha]_D$ −26.1 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ −0.10 (s, 3H), −0.09 (s, 3H), 0.80 (s, 9H), 1.37 (s, 9H), 2.17−2.38 (m, 2H), 3.12 (dd, J = 11.1, 5.4 Hz, 1H), 3.35−3.50 (m, 2H), 3.77 (s, 3H), 5.16−5.40 (m, 3H), 7.12−7.45 (m, 10H), 8.02 (d, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 17.7, 25.5, 28.3, 45.7, 52.4, 57.1, 59.6, 67.1, 67.2, 72.9, 78.8, 127.4, 127.6, 127.9, 128.1, 128.4, 128.8, 136.5, 138.0, 155.2, 156.5, 170.9; IR (neat) 1711, 1757, 3356 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 637 [(M + K), 100], 621 [(M + Na), 85]; HRMS calcd for ($C_{32}H_{46}N_2O_7Si$-^{t}BuO) 525.2415, found 525.2414. Anal. Calcd for $C_{32}H_{46}N_2O_7Si$: C, 64.19; H, 7.74; N, 4.68. Found: C, 64.38; H, 7.71; N, 4.70.

Methyl (+)-(2*R*,3*R*)-2-[1-Benzyloxycarbonylpyrrolidin-2-yl]-3-(*N*-*tert*-butoxycarbonylamino)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (1b). Prepared from **17b**, and purified through flash chromatography (25% EtOAc/hexane), to afford 172 mg of **1b**, in 70% yield. White foam, $[\alpha]_D$ +36.9 (*c* 0.3, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers in ca. 2:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20−1.45 (m, 15H), 1.62−2.43 (m, 4H), 3.28−3.89 (m, 6H), 4.03−4.18 (m, 1H), 4.30−4.61 (m, 2H), 4.85−5.45 (m, 2H), 6.19 (d, J = 9.4, 1H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 25.7, 26.0, 28.3, 34.3, 35.4, 48.7, 48.9, 51.9, 52.3, 53.4, 66.9, 67.1, 67.5, 67.8, 71.0, 74.0, 74.7, 79.0, 79.5, 109.2, 109.5, 127.7, 127.8, 128.2, 128.3, 128.5, 136.5, 136.7, 153.6, 155.1, 155.7, 155.9, 172.9, 173.5; IR (neat) 1707, 1739, 3368 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 493 [(M + H), 38], 393 [(M − Boc + 2H), 58]; HRMS calcd for $C_{25}H_{36}N_2O_3$ 492.2472, found 492.2496. Anal. Calcd for $C_{25}H_{36}N_2O_8$: C, 60.96; H, 7.37; N, 5.69. Found: C, 60.79; H, 7.39; N, 5.71.

Methyl (−)-(2*S*,3*R*)-2-[1-Benzyloxycarbonylpyrrolidin-2-yl]-3-(*N*-*tert*-butoxycarbonylamino)-3-[(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]propanoate (1c). Prepared from **17c**, and purified through flash chromatography (33% EtOAc/hexane), to afford 250 mg of **1c**, in 85% yield. White foam, $[\alpha]_D$ −42.8 (*c* 0.5, $CHCl_3$). ^1H and ^{13}C NMR show the presence of rotamers in ca. 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30−1.55 (m, 24H), 1.70−2.46 (m, 4H), 3.42−3.96 (m, 8H), 4.64, 4.75 (dd, J = 10.1, 4.4 Hz; dd, J = 9.7, 4.8 Hz, 1H), 5.09 (m, 2H), 6.05, 6.26 (d, J = 10.5 Hz; d, J = 10.2 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.3, 24.2, 26.1, 26.8, 28.2, 28.4, 28.6, 36.0, 36.6, 48.5, 48.6, 51.8, 52.1, 56.7, 57.2, 57.4, 67.1, 67.2, 67.6, 67.7, 70.7, 70.9, 78.6, 79.3, 80.0, 80.5, 93.0, 93.6, 127.7, 128.0, 128.3, 128.4, 129.2, 136.3, 136.5, 152.4, 153.7, 154.9, 155.3, 156.2, 156.5, 171.5, 171.9; IR (KBr) 1697, 1701, 1747, 3447 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 630 [(M + K), 100], 614 [(M + Na), 80]; HRMS calcd for $C_{30}H_{45}N_3O_9$ 591.3156, found 591.3178. Anal. Calcd for $C_{30}H_{45}N_3O_9$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.99; H, 7.70; N, 7.13.

Methyl (+)-(2*R*,3*R*)-2-[1-Benzyloxycarbonylpyrrolidin-2-yl]-3-(*N*-*tert*-butoxycarbonylamino)-4-(*tert*-butyldimethylsilyloxy)butanoate (1d). Prepared from **19** (0.5 mmol), and purified through flash chromatography (33% EtOAc/hexane), to afford 166 mg of **1d**, in 62% yield (2 steps). Colorless oil, $[\alpha]_D$ +3.1 (*c* 0.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.42 (s, 9H), 1.65−1.96 (m, 2H), 2.32 (m, 1H), 2.58 (m, 1H), 3.38−3.84 (m, 7H), 4.34 (m, 1H), 5.10−5.24 (m, 2H), 6.47 (d, J = 10.0, 1H), 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, 18.0, 22.1, 25.7, 28.3, 36.8, 49.0, 52.3, 54.6, 63.2, 67.1, 72.7, 78.7, 127.5, 127.9, 128.3, 128.4, 136.5, 155.5, 155.9, 172.1; MS (ESI^+) *m*/*z* (rel intensity) 575 [(M + K), 42], 559 [(M + Na), 18]. Anal. Calcd. for $C_{27}H_{44}N_2O_7Si$: C, 60.42; H, 8.26; N, 5.22. Found: C, 60.23; H, 8.24; N, 5.25.

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Supporting Information Available: General experimental methods, synthesis, and data for compounds **6**, **7**, **10a**, **12a**, *rac*-**15**-*cis*,**15a**, and **15b**, and determination of the optical purity of **15a** and **15b**; assignation of absolute configuration of proline derivatives **1** by the Mosher method; NOESY spectra of **6**, **7**, **10a**, and *rac*-**15**-*cis*; ^{1}H and ^{13}C NMR spectra of all new compounds; energies and Cartesian coordinates of the Becke3LYP/6-31G* optimized stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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