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Enantiomerically Pure Polyheterocyclic Spiro-β-lactams from *trans*-4-Hydroxy-L-proline

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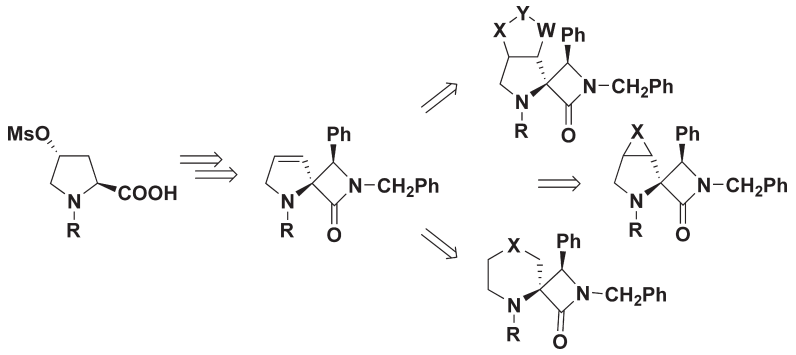
Received January 18, 2010



The "Staudinger ketene−imine reaction" between ketenes generated from natural *O*,*N*-protected *trans*-4-hydroxy-L-prolines and the *N*-benzyl-*N*-benzylideneamine led to mixtures of diastereoisomeric, enantiomerically pure pyrrolidine-derived spiro-β-lactams with a relative *cis* configuration. These were transformed into the corresponding pyrroline-spiro-β-lactams by means of treatment with a base and the new C=C double bond was submitted to a number of different reactions in order to evaluate its reactivity and obtain new polyheterocyclic enantiomerically pure spiro-β-lactams.

Introduction

β-Lactam rings are key structures in the most widely used antibiotics and of great interest to medicinal chemistry.[1] Their use as synthetic intermediates in organic chemistry (the β-lactam synthon method)[2] and recent discoveries of their different biological activities[3−8] have led to increasing interest in them and their asymmetric synthesis, particularly by means of a Staudinger ketene−imine reaction,[9] which makes it possible to obtain mono, di-, tri-, and even spirocyclic β-lactams.

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Published on Web 02/26/2010 DOI: 10.1021/jo100061s
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Structures with a spiro-β-lactam skeleton have attracted the attention of medicinal chemists because of their antiviral[10a] and antibacterial properties,[10b] and because they inhibit cholesterol absorption.[10c] In peptidomimetic chemistry, spiro-β-lactams are used as β-turn mimetics[11] and synthetic precursors of cyclic α,α-disubstituted β-amino acids and peptidomimetics,[12] which is why their synthesis has aroused particular interest.[13]

We have previously described our studies of the synthesis[14] and reactivity[15] of heterocyclic spiro-β-lactams. In particular, we were interested in producing various substituted 4-spiro-β-lactams by means of a Staudinger reaction between imines and nonsymmetrical cyclic ketenes generated from cyclic *N*-acyl α-amino acids. At the same time, we also realized the stereoselective synthesis of 4-spiro-β-lactams using ketenes obtained from chiral, enantiomerically pure *N*-acyl α-amino acids.[15c,16]

Achieving enantiopure β-lactams always arouses considerable interest because of their various important biological activities. With this in mind, and recalling our previous work on the use of natural *trans*-4-hydroxy-L-proline as a cyclic *N*-substituted α-amino acid,[16a] we decided to use this substrate (conveniently *N*,*O*-protected) as a chiral synthon for the stereoselective synthesis of spiro-β-lactams susceptible to further transformation. We have already used this amino acid as a profitable precursor for the stereoselective synthesis of heterocyclic compounds, such as pyrrolidine-derived spiro-β-lactams and condensed bicyclic imidazoles.[16a] More recently, Thiruvazhi et al. have described the use of *trans*-4-hydroxy-L-proline derivatives as precursors of the chiral cyclic ketenes used in a Staudinger synthesis of enantiopure pyrrolidine-derived spiro-β-lactams.[17] In addition to allowing asymmetric induction, we considered that the presence of the conveniently protected hydroxyl group on the pyrrolidine ring could allow further modifications of the pyrrolidine ring. In fact, carrying out a base-promoted elimination reaction converting pyrrolidine-derived spiro-β-lactams into pyrroline-derived spiro-β-lactams[17] makes it possible to introduce a versatile double bond that we have conceived to test toward a series of olefin reactions, such as cycloaddition reactions and oxidation and cyclopropanation reactions, thus leading to chemical diversity from the same precursor. These transformations could afford new polyheterocyclic spiro-β-lactams, interesting compounds as such. Additionally, these spiro-β-lactams derivatives could be used as potential scaffolds to construct β-turn mimetics. In fact, proline-derived spirocyclic β-lactams have already been shown to exhibit valuable conformational properties useful for their utilization as efficient β-turn nucleators.[11] The modification of proline ring and in particular the introduction of a fused ring, could establish a further restriction of the conformational freedom of the peptide chain, providing structural stabilization when incorporated into a peptide.

Although many practical and theoretical studies have been carried out since the Staudinger reaction was first described more than 100 years ago,[18] its rationalization (and, consequently, its stereochemical course) is still debated.[19] In general, the stereochemistry of the products depends on the nature of the substrates (stereoelectronic aspects) and the experimental conditions. The use of different protecting groups on the pyrrolidine nitrogen, besides influencing the course of the Staudinger reaction, could also be opportune in case the subsequent transformations may be unsuited to one of them. As a consequence, we have designed a method to use *N*-carbobenzyloxy- or *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline derivatives as starting materials in the Staudinger reaction.

Results and Discussion

Synthesis of Pyrroline-Spiro-β-lactams. First, we synthesized (2*S*,4*R*)-4-methanesulfonyloxypyrrolidine-1,2-dicarboxylic acid 1-benzyl or 1-*tert*-butyl esters **1a** and **1b** as convenient ketene precursors following known procedures (Scheme 1). Compound **1a**[17] was quantitatively obtained starting from commercially available *N*-Cbz-(4*R*)-hydroxy-L-proline. Compound **1b** was synthesized starting from *trans*-4-hydroxy-L-proline, which was transformed into the (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxy-2-pyrrolidinecarboxylic acid[20] and then *O*-protected using Schäfer method[21] with 34% total yield.

The geometry and electronic properties of imines also play a key role in the Staudinger reaction. We have previously and extensively used electron-rich (*E*)-*N*-benzylidene-1-phenylmethanamine **2**[15b,16b] as a convenient imine partner for the Staudinger reaction, not least because of the gain in β-lactam stability due to the *N*-benzyl substitution, and so imine **2** was allowed to react with 4-hydroxy-L-proline derivatives **1a**,**b**.

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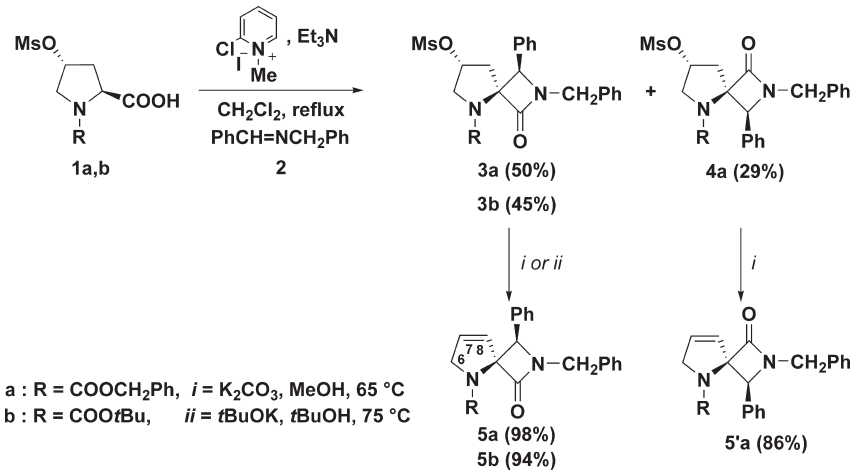
SCHEME 1



We applied our usual method to activate the proline carboxylic group and generate in situ the intermediate ketene[15c] by heating a mixture of amino acids **1a**,**b**, imine **2**, and 2-chloro-1-methylpyridinium iodide, Mukaiyama's reagent, in the presence of TEA in refluxing dichloromethane for 24 h. In the case of **1a**, the reaction with imine **2** afforded a diastereoisomeric mixture of the two spiro-β-lactams (**3*R*,4*S*,7*R*-3a** and (**3*S*,4*R*,7*R*-4a** in a ratio of 1.7:1, both of which have been shown to have a relative *cis* configuration between *N*-Cbz and phenyl groups.[17] In this case, the stereochemical results and obtained ratio were almost the same when the activator reagent of the amino acid was changed (acyl chloride[17] versus ester with Mukaiyama's reagent). A different course was observed when the *N*-Boc-protected precursor **1b** was used because only the corresponding *N*-Boc-protected spiro-β-lactam **3b** was obtained, as shown by the ^{1}H NMR spectra of the crude reaction mixture. Compound **3b** was obtained in 45% yield, along with about 30% of unreacted **1b** and a mixture of unidentified products. This different result could be ascribed to a minor reactivity of the ketene and/or zwitterionic intermediates owing to a larger steric encumbrance generated by the contiguous *N*-Boc group. The ^{1}H NMR spectra of **3b** (recorded at $T = 55$ °C to avoid the complication due to the existence of rotamers about the carbamate bond) showed a close relation with **3a**, thus suggesting the analogous structure (**3*R*,4*S*,7*R*-3b** (Scheme 1). This assignment was successively confirmed by means of chemical transformation of **3b** into a known compound (vide infra).

Having exhausted the role of the hydroxylated stereocenter in the amino acid ring as a chiral auxiliary, subsequent removal of methansulfonic acid makes it possible to introduce the desired double bond in order to obtain the corresponding pyrroline derivatives. The elimination reaction on compounds **3a**, **4a**, and **3b** was performed by means of basic treatment, but once again, the behavior of the products was different. Treatment of *N*-Cbz-protected **3a** and **4a** with K_2CO_3 (in methanol at $T = 65$ °C for 8 h) led to the enantiomeric pyrroline-spiro-β-lactams (**3*R*,4*S*-5a** and (**3*S*,4*R*-5′a** in high yields,[17] but the same conditions were unsuccessful in the case of the *N*-Boc derivative **3b** as the reaction remained incomplete even after prolonging the time, adding more K_2CO_3, or using different bases. Finally, we found that treatment with excess *t*-BuOK in *tert*-butyl alcohol at $T = 75$ °C for 3 h provided the desired enantiopure pyrroline spiro-β-lactam (**3*R*,4*S*-5b** in excellent yield (Scheme 1).

Like those of **5a** (5.83 and 6.07 ppm), the alkene protons of **5b** resonate at 5.90 and 6.09 ppm: these values and the absence of any signals at about 7.0 ppm suggest that the double bond is between C-7 and C-8 for both compounds, thus denying the possibility of a C-6/C-7 double bond in the isolated products.[22] Furthermore, the chemical shift values for protons H-6 (at 4.2−4.4 ppm for **5a** and at 3.82−4.17 ppm for **5b**) confirmed their α-position in relation to the pyrroline nitrogen atom.[23]

Compound **5b** was used to confirm the (3*R*,4*S*) absolute configurations of **3b**: hydrogenation of the double bond followed by elimination of the *N*-Boc group allowed to obtain a compound having the same optical rotation than the known compound (3*R*,4*S*)-2-benzyl-3-phenyl-2,5-diazaspiro[3.4]octan-1-one.[17]

At this point, taking into account the lower yields of intermediates **1b** and **3b** and the useful availability of both the enantiomeric pyrroline derivatives **5a**,**5′a**, we decided to use these latter as the reference substrates in the following series of olefin reactions.

Cycloaddition Reactions of Pyrroline-Spiro-β-lactams. The regio- and stereochemical behavior of the double bond of compound **5a** was evaluated in relation to the [4 + 2] and [3 + 2] cycloaddition reactions, with the aim of obtaining new functionalized tricyclic β-lactams. It was first submitted to the Diels−Alder reaction using various electron-rich dienes such as Danishefsky's diene or reactive cyclic dienes such as in situ depolymerized cyclopentadiene, cyclohexadiene, and furan. Different reaction conditions, varying solvents (toluene, CH_2Cl_2, DMF), reaction temperature (from 50 to 170 °C), or pressure (from 1 to 5 atm), using irradiation with microwaves or ultrasound and even adding Lewis acids as catalysts ($Yb(OTf)_3$ or $EtAlCl_2$), showed a complete lack of reactivity of alkene **5a**. Indeed, it was always recovered unchanged from the reaction mixtures. We also tested an electron-poor cyclic diene (methyl coumalate),[24] but once

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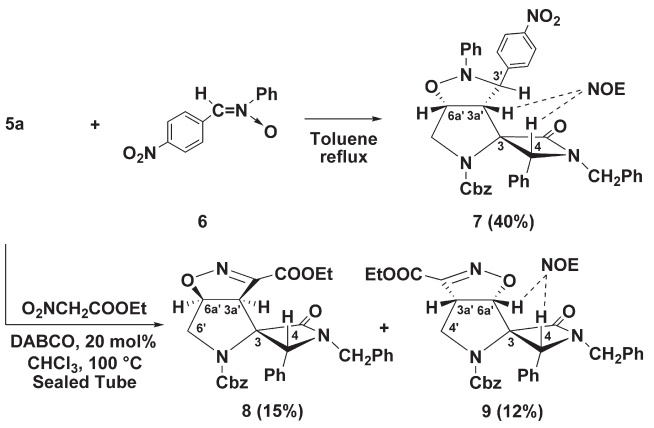
SCHEME 2



again the alkene did not react. This complete lack of reactivity to Diels−Alder cycloadditions is probably partially attributable to the electronic condition of the starting alkene, which seems to be neither electron poor nor electron rich, but mainly to the steric encumbrance generated by the β-lactam ring perpendicular to the pyrroline ring,[16a,25] as examples of Diels−Alder reactions of sterically less hindered pyrroline derivative have been reported.[26]

On the basis of our previous experience in the field of the 1,3-dipolar cycloadditions,[27] we treated **5a** with different 1,3-dipoles, such as nitrones, nitriloxides, münchnones, and diazomethane, but the double bond showed very little reactivity because only the reaction with the *C*-*p*-nitrophenyl-*N*-phenylnitrone **6** and the ethyl nitroacetate, in the presence of catalytic amounts of DABCO, afforded new heteropolycyclic-derived spiro-β-lactams. Heating a solution of **5a** and an equimolar amount of *C*-phenyl-*N*-methylnitrone in refluxing toluene for 95 h did not afford any product; the reagents were recovered unchanged. On the contrary, the reaction of **5a** with the more activated and stable *C*-*p*-nitrophenyl-*N*-phenylnitrone **6** conducted in refluxing toluene for 100 h led, in 40% yield, only to the diastereoisomer (**3*S*,3′*R*,3a′*R*,4*R*,6a′*R*)-7** as shown by the ^{1}H NMR spectra of the crude reaction mixture (Scheme 2), and unreacted **5a** was recovered in 50% yield. This result was achieved using a 20% molar excess of nitrone **6**, but no improvement of the yield was observed increasing the excess of the nitrone until 2-fold.

The exact stereochemistry of compound **7** was assigned by comparison with the ^{1}H NMR data of a known similar compound[28] whose absolute stereochemistry had been established by X-ray analysis and was confirmed by COSY and NOESY experiments. In particular, the positive NOE effect between H-3a′/H-4 and H-3a′/H-6a′observed in **7** made it possible to assign the shown configurations to the carbons C-4, C-3a′, and C-6a′. Moreover, the absence of NOE effect between H-3′ and H-3a′ and comparison of the measured value of the H-3′/H-3a′ coupling constant (J = 5.1 Hz) with

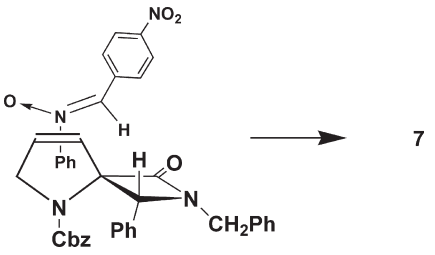


FIGURE 1

the corresponding value reported for the known compound (J_{cis} = 9.5 Hz)[28] allowed us to assign the hydrogens a *trans* relationship. Despite the poor yield, the stereochemical outcome of the reaction was excellent because, taking into account a concerted mechanism, two possible regioisomers with three new stereocenters (i.e., a total of eight stereoisomers) could theoretically be generated. As depicted in Figure 1, the complete regio- and stereoselectivity observed was explained by the *endo* approach of the *E*-nitrone to the double bond from the less hindered side of the pyrroline ring. The β-lactam ring is perpendicular to the pyrroline ring as highlighted by X-ray analysis of very similar compounds.[16] Its presence, and in particular the steric hindrance of the C-phenyl group, could direct the nitrone attack from the less hindered side that is opposite to the C-phenyl group.

Alkene **5a** was fully recovered when reacted with ethoxycarbonylnitrile oxide in situ generated from the corresponding ethyl chlorooximinoacetate and Et_3N,[29] but the desired isoxazolines were obtained using a recently proposed method.[30] Heating a solution of **5a** and ethyl nitroacetate in $CHCl_3$ in a sealed vessel at T = 100 °C, in the presence of catalytic amounts of DABCO, led to rather low yields of the regioisomeric adducts **8** and **9** (Scheme 2). They were separated by means of column chromatography, and their structures were determined by means of suitable high-temperature ^{1}H NMR spectra and COSY and NOESY experiments (DMSO-d_6 at T = 120 °C). First, the ^{1}H NMR spectra allowed us to assign the regiochemistry: in adduct **9**, the proton at the lower chemical shift value of 5.75 δ (i.e., the proton near to the oxygen)[31] showed only one coupling (with H-3a′), whereas the proton at 5.42 δ in adduct **8** also showed a double doublet coupling with one H-6′. This was confirmed by COSY experiments, which made it possible to assign the chemical shifts to proton H-3a′ in both compounds. The adducts' stereochemistry was established by means of NOESY data: the presence of a positive NOE effect between H-3a′ and H-6a′ in both **8** and **9** confirmed the *cis* junction between the condensed pyrrolidine, and isoxazoline rings suggested by their respective coupling constant values of 9.1 and 8.9 Hz. Finally, the positive NOE effect observed between H-4 and H-6a′ in **9** was not present between H-4 and H-3a′ in **8**, thus allowing us to assign the configurations (**3*S*,3a′*R*,4*R*,6a′*S*)-8** and (**3*R*,3a′*R*,4*R*,6a′*S*)-9**.

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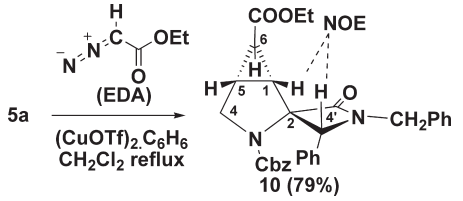
SCHEME 3



Analogously to the approach reported in Figure 1, the formation of the isomer **8** could be ascribe to the concerted attack of the proposed intermediate[30b] from the more hindered side of the alkene with the same regiochemistry as that observed in **7**. On the contrary, **9** may derive from an attack on the less hindered side of the alkene, with the opposite regiochemistry. The above cycloaddition reactions were also conducted using the enantiomer alkene **5′a**, which lead to the enantiomeric cycloadducts **7′**, **8′**, and **9′**.

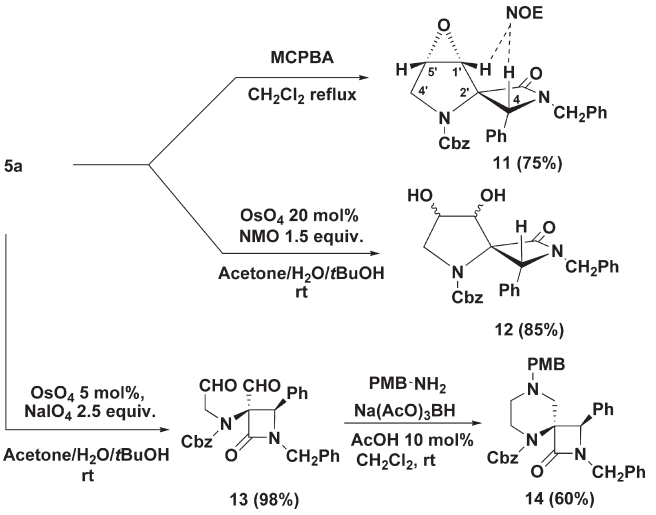
Cyclopropanation Reaction of Pyrroline-Spiro-*β*-lactams. We then approached the reaction of alkene **5a** with the carbene generated by the metal-catalyzed decomposition of ethyl diazoacetate (EDA).[32] This reaction should lead to the formation of particularly interesting tricyclic spiro-*β*-lactams because of their similarity to previously reported pharmacologically active compounds such as glutamate agonists.[33] Various experimental conditions were tested, and the best results were obtained using a $(CuOTf)_2$–benzene complex as catalyst and a large excess of EDA. This reaction led to the formation of the enantiopure adduct (**1*R*,2*S*,4′*R*,5*S*,6*R*)-10** in good yield (Scheme 3).

As three new stereocenters were generated, the reaction once again proceeded with total diastereoselectivity. The stereochemistry was attributed by means of ^{1}H NMR spectra and NOESY experiments at high temperature (120 °C, DMSO-d_6) considering the molecular models of all four possible diastereoisomers. A positive NOE effect was observed between the singlet at 4.89 δ (H-4′) and the proton at 2.50 δ. The latter also showed a positive NOE effect with the proton at δ 2.16, but neither had a positive effect with the third cyclopropane proton at δ 1.82. Furthermore, the proton at δ 2.16 showed a positive NOE effect with one of the two H-4 protons. On the basis of all this spectroscopic evidence, we were able to assign the signals at δ 2.50, 2.16, and 1.82 to H-1, H-5, and H-6 protons and the absolute configurations shown in Scheme 3 to the corresponding carbons. Also in this case the high degree of stereoselectivity could be explained as a consequence of the selective attack of the carbenoid species on the less hindered face of the pyrroline ring, opposite the C-4′ of the lactam ring.

Oxidation Reactions of Pyrroline-Spiro-*β*-lactams. The reactivity of the double bond to oxidation was also considered. These reactions would produce polyfunctionalized *β*-lactams by preserving (epoxidation, *syn*-dihydroxylation) or opening the five-membered ring (double-bond oxidative cleavage).

Epoxidation. We first considered the epoxidation reaction of **5a**, which was easily converted under classical conditions

SCHEME 4



to the tricyclic derivative (**1′*R*,2′*R*,4*R*,5′*S*)-11** (Scheme 4).[34] Once again, the ^{1}H NMR spectra of the crude reaction mixture confirmed the formation of only one diastereoisomer in good yield, whose stereochemical features were attributed by means of NOESY and ^{1}H NMR experiments at high temperature (120 °C, DMSO-d_6). As in the case of the assignment mentioned above, the presence of a positive NOE effect between H-4 (4.91 δ) and the doublet at 4.22 δ (H-1′) suggested the attributed configurations.

***syn*-Dihydroxylation.** We then subjected alkene **5a** to *syn*-dihydroxylation: various reagents were tried, but the best results were obtained using catalytic amounts of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant.[35] Unfortunately, the reaction led to an inseparable mixture of two diastereoisomeric diols **12** in 85% yield and a ratio of 83:17, as detected by ^{1}H NMR analysis (Scheme 4).

Double-Bond Oxidative Cleavage. In order to further oxidize these diols to the corresponding dialdehyde, the mixture was treated with a number of oxidizing reagents,[36,37] but without any positive result. We therefore decided to perform the direct oxidative cleavage of the enantiomeric alkenes **5a** and **5′a** and did so using catalytic OsO_4 in the presence of an excess of $NaIO_4$ either as a co-oxidant and as a reagent for the following oxidation.[38] The desired dialdehydes, (**3*R*,4*R*)-13** and its enantiomer (**3*S*,4*S*)-13′**, were obtained in very good yields (Scheme 4).

At this point, we considered the possible transformations of these versatile products and were particularly attracted by the possibility of generating spiranic hetereocycles to give access to new categories of spiro-*β*-lactams. A preliminary experiment using hydrazine to obtain the corresponding triazepine derivative completely failed, but reductive amination of the dialdehyde led to good results as the treatment of both enantiomers **13** and **13′** with $Na(AcO)_3BH$ in the presence of *p*-methoxybenzylamine (PMB-NH_2) furnished

(32) For a recent review on cyclopropanation reactions, see: Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.
(33) Marinozzi, M.; Natalini, B.; Ni, M. H.; Costantino, G.; Pellicciari, N. *Il Farm.* **1995**, *50*, 327.
(34) (a) Chapman, T. M.; Courtney, S.; Hay, P. *Chem.—Eur. J.* **2003**, *9*, 3397. (b) Garcia, A. L. L.; Correia, C. R. D. *Tetrahedron Lett.* **2003**, *44*, 1553.
(35) Murruzzu, C.; Riera, A. *Tetrahedron: Asymmetry* **2007**, *18*, 149.
(36) Giersch, W.; Ohloff, G. *Angew. Chem., Int. Ed.* **1973**, *12*, 401.
(37) Quenau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043.
(38) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

the corresponding piperazine-derived spiro-β-lactams (**3*R*,4*S*)-14** and (**3*S*,4*R*)-14′**, respectively (Scheme 4).[39]

Conclusions

Our studies of the reactivity of the pyrroline-derived spiro-β-lactams **5a** and **5′a** allowed us to synthesize several new enantiomerically pure polyfunctionalized β-lactams, some of which were also susceptible to subsequent transformations, thus leading to greater chemical diversity. Alkenes **5a** and **5′a** were generally little reactive against cycloaddition reactions, but all of the other reactions led to good yields. The stereochemical outcomes were largely excellent as only one diastereoisomer was generally obtained. These results can be attributed to the presence of the β-lactam ring which, by promoting the attack of the reactant from the less hindered side of the alkene, increases diastereoselectivity. To the best of our knowledge, the reported compounds are the first examples of new polyheterocyclic spiro-condensed β-lactams.

Experimental Section

General Procedure for the Reactions of 1a,b with 2 and Mukaiyama's Reagent. A mixture of **1a** or **1b** (1.1 mmol), imine **2** (1.0 mmol), 2-chloro-*N*-methylpyridium iodide (1.2 mmol), and Et_3N (3.0 mmol) in dry CH_2Cl_2 (15 mL) was heated at reflux temperature for 16−24 h under a nitrogen atmosphere. After cooling, the solution was washed with 5% aq HCl, 5% aq $NaHCO_3$, and then with H_2O. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (SiO_2, *n*-exane/AcOEt = 50:50). Spectroscopic data of compounds **3a** and **4a** were identical to those previously reported.[17]

(3*R*,4*S*,7*R*)-2-Benzyl-7-methanesulfonyloxy-1-oxo-3-phenyl-2,5-diazaspiro[3.4]octane-5-carboxylic Acid *tert*-Butyl Ester (3b). Colorless solid. Yield: 45%. Mp: 139−141 °C (*i*-PrOH/*i*-Pr_2O). $[\alpha]^{20}_D = -66.4$ ($c = 0.53$ in $CHCl_3$). ^{1}H NMR ($T = 50$ °C): $\delta = 1.33$ (s, 9H, $(CH_3)_3C$); 2.59 (dd, $J = 13.2, 6.5$, 1H, H-8); 2.77 (dd, $J = 13.2, 8.5$, 1H, H-8); 3.08 (s, 3H, SO_2CH_3); 3.47 (dd, $J = 12.2, 7.2$, 1H, H-6); 3.68 (m, 1H, H-6); 4.14 (d, $J = 14.7$, 1H, CH_2Ph); 4.34 (s, 1H, H-3); 5.10 (d, $J = 14.7$, 1H, CH_2Ph); 5.23 (quintet, 1H, H-7); 7.22−7.35 (m, 10H, Ph). ^{13}C NMR shows the presence of two rotamers: δ = 27.8, 28.0 ($(CH_3)_3C$); 38.7 (CH_3SO_2); 39.4, 40.6 (C-8); 45.1, 45.4 (CH_2Ph); 51.4, 51.6 (C-6); 68.9, 69.2 (C-3); 73.5, 73.8 (C-7); 80.7 ($(CH_3)_3C$); 82.2 (C-4); 126.8−129.0 (Ph); 133.9, 135.4 (Ph), 153.2 (*C*OO-*t*-Bu); 166.8 (C-1). IR (Nujol): 1703 (ν_{CO}, NCOO-*t*-Bu), 1751 (ν_{CO}, N-CO). MS-FAB$^+$ (*m*/*z*): 487 $[MH]^+$. Anal. Calcd for $C_{25}H_{30}N_2O_6S$: C, 61.71; H, 6.21; N, 5.76. Found: C, 61.62; H 6.15; N, 5.71.

(3*R*,4*S*)-2-Benzyl-1-oxo-3-phenyl-2,5-diazaspiro[3.4]oct-7-ene-5-carboxylic Acid *tert*-Butyl Ester (5b). *t*-BuOK (0.47 g, 4.2 mmol) was added to a solution of **3b** (0.34 g, 0.7 mmol) in *t*-BuOH (15 mL). The mixture was heated at 75 °C for 3 h. The solvent was removed under reduced pressure, and the residue was taken up with water (20 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was recrystallized from *i*-Pr_2O to afford a colorless solid (0.256 g, 94%). Mp: 78−80 °C. $[\alpha]^{20}_D = -196.9$ (c 0.55, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 1.19 (s, 9H, $(CH_3)_3C$); 3.82 (dt, $J = 16.2, 2.0$, 1H, H-6); 4.17 (d, $J = 16.2$, 1H, H-6); 4.37 (d, $J = 15.1$, 1H, CH_2Ph); 4.53 (s, 1H, H-3); 4.83 (d, $J = 15.1$, 1H, CH_2Ph); 5.90 (dt, $J = 6.2, 2.1$, 1H, H-7); 6.09 (d, $J = 6.2$, 1H, H-8); 7.11−7.33 (m, 10H, Ph). ^{13}C NMR shows the presence of two rotamers: δ 27.7, 28.0 ($(CH_3)_3C$); 45.3, 45.8 (CH_2Ph); 54.7, 54.9 (C-6); 66.9, 67.5 (C-3); 79.9, 81.3 ($(CH_3)_3C$); 84.3, 84.9 (C-4); 126.3−128.9 (Ph); 134.7−138.1 (Ph, C-7, C-8); 152.4, 153.0 (*C*OO-*t*-Bu); 168.1, 168.3 (C-1). IR (Nujol): 1692 (ν_{CO}, NCOO-*t*-Bu), 1763 (ν_{CO}, N-CO). MS-FAB$^+$ (*m*/*z*): 391 $[MH]^+$. Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.79; H 6.72; N, 7.09.

(3*S*,3′*R*,3a′*R*,4*R*,6a′*R*)-1-Benzyl-3′-(4-nitrophenyl)-2-oxo-2′,4-diphenyltetrahydrospiro[azetidine-3,4′-pyrrolo[3,4-*d*]isoxazole]-5′(2′*H*)-carboxylic Acid Benzyl Ester (7). (*E*)-*C*-*p*-Nitrophenyl-*N*-phenylnitrone **6** (0.21 g, 0.86 mmol) was added to a solution of **5a** (0.30 g, 0.72 mmol) in toluene (10 mL). The mixture was heated at reflux temperature for 100 h. The solvent was evaporated under reduced pressure. The residue was treated with hot MeOH (10 mL) and filtered to afford a colorless crystalline solid (0.19 g, 40%). Mp: 220−21 °C. $[\alpha]^{20}_D = +54.2$ (c 0.63, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 3.03 (dd, $J = 12.8, 6.0$, 1H, H-6′); 3.61 (dd, $J = 12.8, 1.5$, 1H, H-6′); 3.89 (dd, $J = 7.1, 5.1$, 1H, H-3a′); 4.04 (d, $J = 15.2$, 1H, CH_2Ph); 4.68 (s, 1H, H-4); 4.76 (d, $J = 15.2$, 1H, CH_2Ph); 4.78 (d, $J = 12.7$, 1H, CH_2Ph-(Cbz)); 4.89 (d, $J = 12.7$, 1H, CH_2Ph(Cbz)); 5.27 (dd, $J = 5.9, 1.5$, 1H, H-6a′); 5.46 (d, $J = 5.1$, 1H, H-3′); 6.89−7.37 (m, 20H, Ph); 7.70 (d, $J = 8.7$, 2H, 4-NO_2Ph); 8.20 (d, $J = 8.7$, 2H, 4-NO_2Ph). ^{13}C NMR shows the presence of two rotamers: δ 44.8, 45.0 (C-6′); 51.3, 51.7 (CH_2Ph); 65.6, 67.0 (C-3a′); 67.5, 68.4 (CH_2Ph(Cbz)); 68.9, 69.9 (C-4); 70.6 (C-3′); 79.5, 79.7 (C-6a′); 118.5−147.9 (Ph); 153.8, 154.1 ($COOCH_2Ph$); 165.2, 164.5 (C-2). IR (Nujol): 1710 (ν_{CO}, $NCOOCH_2Ph$), 1759 (ν_{CO}, N-CO). MS-FAB$^+$ (*m*/*z*): 667 $[M + H]^+$. Anal. Calcd for $C_{40}H_{34}N_4O_6$: C, 72.06; H, 5.14; N, 8.40. Found: C, 72.00; H 5.02; N, 8.29.

(3*R*,3′*S*,3a′*S*,4*S*,6a′*S*)-1-Benzyl-3′-(4-nitrophenyl)-2-oxo-2′,4-diphenyltetrahydrospiro[azetidine-3,4′-pyrrolo[3,4-*d*]isoxazole]-5′(2′*H*)-carboxylic Acid Benzyl Ester (7′). From **5′a** and (*E*)-*C*-*p*-nitrophenyl-*N*-phenylnitrone **6** (45%). $[\alpha]^{20}_D = -50.1$ (c 0.54, CH_2Cl_2).

Reaction of 5a with Ethyl α-Nitroacetate. A solution of **5a** (0.29 g, 0.68 mmol), ethyl α-nitroacetate (0.15 mL, 1.37 mmol), and DABCO (20 mol %, 15 mg, 0.14 mmol) in $CHCl_3$ (10 mL) was heated in a sealed tube at 100 °C for 65 h. The solvent was removed under reduced pressure. The products were purified by means of column chromatography (SiO_2, toluene/AcOEt = 98:2).

(3*S*,3a′*R*,4*R*,6a′*S*)-1-Benzyl-2-oxo-4-phenyl-6′,6a′-dihydrospiro[azetidine-3,4′-pyrrolo[3,4-*d*]isoxazole]-3′,5′(3a′*H*)-dicarboxylic Acid 5′-Benzyl 3′-Ethyl Ester (8). Colorless solid (15%). Mp: 155−6 °C (*i*-PrOH). $[\alpha]^{20}_D = -195.9$ (c 0.90, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 1.34 (t, $J = 7.1$, 3H, $COOCH_2CH_3$); 3.11 (dd, $J = 13.2, 4.5$, 1H, H-6′); 3.89 (d, $J = 13.2$, 1H, H-6′); 4.27 (d, $J = 14.8$, 1H, CH_2Ph); 4.28 (q, $J = 7.2$, 1H, $COOCH_2CH_3$); 4.37 (q, $J = 7.1$, 1H, $COOCH_2CH_3$); 4.67 (d, $J = 14.8$, 1H, CH_2Ph); 4.81 (d, $J = 9.1$,1H, H-3a′); 4.83 (d, $J = 12.5$, 1H, CH_2Ph(Cbz)); 4.93 (d, $J = 12.5$, 1H, CH_2Ph-(Cbz)); 5.42 (dd, $J = 9.1, 4.5$, 1H, H-6a′); 5.65 (s, 1H, H-4); 7.22−7.38 (m, 15H, Ph). ^{13}C NMR shows the presence of two rotamers: δ 14.1 ($COOCH_2CH_3$); 45.0 (C-6′); 53.4, 53.9 (CH_2Ph); 58.0, 59.2 (C-3a′); 62.4 ($COOCH_2CH_3$); 67.3, 68.1 (CH_2Ph(Cbz)); 70.0 (C-4); 81.2, (C-3); 84.8, 85.4 (C-6a′); 126.4−134.4 (Ph); 150.3, 153.1 ($COOCH_2Ph$, $COOCH_2CH_3$); 160.8 (C-2). IR (Nujol): 1639 (ν_{CO}, $COOCH_2CH_3$); 1712 (ν_{CO}, $NCOOCH_2Ph$), 1766 (ν_{CO}, N-CO). MS-FAB$^+$ (*m*/*z*): 540 $[M + H]^+$. Anal. Calcd for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 68.92; H 5.37; N, 7.65.

(3*R*,3a′*R*,4*R*,6a′*S*)-1-Benzyl-2-oxo-4-phenyl-3a′,6a′-dihydrospiro[azetidine-3,6′-pyrrolo[3,4-*d*]isoxazole]-3′,5′(4′*H*)-dicarboxylic Acid 5′-Benzyl 3′-Ethyl Ester (9). Amorphous solid (12%). $[\alpha]^{20}_D = +42.7$ (c 0.15, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 1.29 (t, $J = 7.0$, 3H, $COOCH_2CH_3$); 3.01 (dd, $J = 11.9, 8.5$, 1H, H-4′); 3.71 (dd, $J = 11.9, 2.5$, 1H, H-4′); 4.24

(39) Gelmi, M. L.; Cattaneo, C.; Pellegrino, S.; Clerici, F.; Montali, M.; Martini, C. *J. Org. Chem.* **2007**, *72*, 9811.

(d, J = 15.2, 1H, CH_2Ph); 4.29 (q, J = 7.0, 2H, COOCH_2CH$_3$); 4.31 (m, 1H, H-3a′); 4.77 (d, J = 15.2, 1H, CH_2Ph); 4.81 (s, 1H, H-4); 4.81 (d, J = 12.6, 1H, CH_2Ph(Cbz)); 4.91 (d, J = 12.6, 1H, CH_2Ph(Cbz)); 5.75 (d, J = 8.9, 1H, H-6a′); 7.22−7.38 (m, 15H, Ph). ^{13}C NMR (DMSO-d_6) shows the presence of two rotamers: δ 13.8 (COOCH$_2$CH$_3$); 44.5 (CH$_2$Ph); 47.8, 48.8 (C-3a′); 49.5, 50.2 (CH$_2$Ph); 61.7 (COOCH$_2$CH$_3$); 65.9, 66.1 (C-4); 66.8 (CH$_2$Ph(Cbz)); 82.1 (C-3); 91.9, 93.2 (C-6a′); 126.1−135.7 (Ph); 152.5, 152.9 (COOCH$_2$Ph, COOCH$_2$CH$_3$); 159.4 (C-2). IR (Nujol): 1654 (ν_{CO}, COOCH$_2$CH$_3$); 1714 (ν_{CO}, NCOOCH$_2$Ph), 1764 (ν_{CO}, NCO). MS-FAB$^+$ (m/z): 540 [M + H]$^+$. Anal. Calcd for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 68.90; H 5.39; N, 7.68.

(3*R*,3a′*S*,4*S*,6a′*R*)-1-Benzyl-2-oxo-4-phenyl-6′,6a′-dihydrospiro[azetidine-3,4′-pyrrolo[3,4-*d*]isoxazole]-3′,5′(3a′*H*)-dicarboxylic Acid 5′-Benzyl 3′-Ethyl Ester (8′). From **5′a** and ethyl α-nitroacetate (17%). $[\alpha]^{20}_D$ = +187.3 (*c* 0.65, CH_2Cl_2).

(3*S*,3a′*S*,4*S*,6a′*R*)-1-Benzyl-2-oxo-4-phenyl-3a′,6a′-dihydrospiro[azetidine-3,6′-pyrrolo[3,4-*d*]isoxazole]-3′,5′(4′*H*)-dicarboxylic Acid 5′-Benzyl 3′-Ethyl Ester (9′). From **5′a** and ethyl α-nitroacetate (12%). $[\alpha]^{20}_D$ = −38.1 (*c* 0.74, CH_2Cl_2).

(1*R*,2*S*,4′*R*,5*S*,6*R*)-1′-Benzyl-2′-oxo-4′-phenyl-3*H*-spiro[3-azabicyclo[3.1.0]hexane]-2,3′-azetidine]-3,6-dicarboxylic Acid 3-Benzyl 6-Ethyl Ester (10). $(CuOTf)_2C_6H_6$ (5.8 mg, 0.011 mmol) was added to a solution of **5a** (0.10 g, 0.23 mmol) in dry CH_2Cl_2 (1.5 mL) under nitrogen atmosphere. The mixture was heated at 40 °C, and then ethyl diazoacetate (EDA) (0.11 mL, 0.92 mmol) was dropped in during 7 h. After 24 h, other $(CuOTf)_2C_6H_6$ (5.8 mg, 0.011 mmol) was added, and a second amount of ethyl diazoacetate (EDA) (0.11 mL, 0.92 mmol) was dropped in during 3 h. The mixture was heated at reflux for a total of 48 h. The solvent was then removed under reduced pressure, and the crude product was purified by means of column chromatography (SiO_2, toluene/AcOEt = 90/10). The product was recrystallized from *i*-Pr$_2$O/*n*-hexane to afford a colorless solid (0.09 g, 79%): mp 126−9 °C; $[\alpha]^{20}_D$ = −84.5 (*c* 1.025, $CHCl_3$). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 1.22 (t, J = 7.0, 3H, COOCH$_2$CH_3); 1.82 (t, J = 3.1, 1H, H-6); 2.16 (m, 1H, H-5); 2.50 (dd, J = 7.1, 3.0, 1H, H-1); 3.20 (dd, J = 11.1, 4.0, 1H, H-4); 3.63 (d, J = 11.1, 1H, H-4); 4.15 (q, J = 7.0, 2H, COOCH_2CH$_3$); 4.32 (d, J = 15.1, 1H, CH_2Ph); 4.70 (d, J = 15.1, 1H, CH_2Ph); 4.72 (d, J = 12.6, 1H, CH_2Ph(Cbz)); 4.87 (d, J = 12.6, 1H, CH_2Ph(Cbz)); 4.89 (s, 1H, H-4′); 7.16−7.37 (m, 15H, Ph). ^{13}C NMR shows the presence of two rotamers: δ 14.0 (C-6); 22.0, 22.7 (COOCH$_2$CH$_3$); 30.9, 32.2 (C-5); 45.1 (CH$_2$Ph); 48.9, 49.4 (C-4); 60.5 (COOCH$_2$CH$_3$); 65.7,66.5 (CH$_2$Ph(Cbz)); 68.1, 68.4 (C-4′); 78.2, 78.9 (C-2); 126.5−135.9 (Ph); 151.7, 152.8 (COOCH$_2$Ph, COOCH$_2$CH$_3$); 170.9 (C-2′). IR (Nujol): 1717 (ν_{CO}, NCOOCH$_2$Ph), 1766 (ν_{CO}, NCO). MS-FAB$^+$ (m/z): 533 [M + Na]$^+$, 511 [M + H]$^+$. Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49. Found: C, 72.76; H 5.92; N, 5.39.

(1′*R*,2′*R*,4*R*,5′*S*)-1-Benzyl-2-oxo-4-phenyl-3′*H*-spiro[azetidine-3,2′-[6]oxa[3]azabicyclo[3.1.0]hexane]-3′-carboxylic Acid Benzyl Ester (11). A solution of *m*-chloroperbenzoic acid (*m*-CPBA) (0.14 g, 1.06 mmol, purity ≤77%) in dry CH_2Cl_2 (4 mL) was dropped into a solution of **5a** (0.15 g, 0.35 mmol) in dry CH_2Cl_2 (1.5 mL) heated at 40 °C during 4 h under nitrogen atmosphere for 24 h. The mixture was cooled and washed with 5% aq $NaHCO_3$. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, toluene/AcOEt = 90:10) to afford a colorless oil (0.12 g, 75%). $[\alpha]^{20}_D$ = −166.7 (*c* 0.72, $CHCl_3$). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 3.50 (d, J = 12.7, 1H, H-4′); 3.72 (dd, J = 12.7, 2.4, 1H, H-4′); 4.09 (m, 1H, H-5′); 4.22 (d, J = 3.1, 1H, H-1′); 4.41 (d, J = 15.1, 1H, CH_2Ph); 4.84 (d, J = 15.1, 1H, CH_2Ph); 4.84 (d, J = 12.8, 1H, CH_2Ph-(Cbz)); 4.85 (d, J = 12.8, 1H, CH_2Ph(Cbz)); 4.91 (s, 1H, H-4); 7.10−7.37 (m, 15H, Ph). ^{13}C NMR shows the presence of two rotamers: δ 45.0, 45.7 (C-4′); 49.6, 50.1 (CH$_2$Ph); 57.0, 57.4 (C-4); 60.4, 61.3 (C-5′); 63.3, 63.6 (C-1′); 66.8, 67.7 (CH$_2$Ph(Cbz)); 77.8, 78.5 (C-3); 126.5−136.0 (Ph); 153.8 (COOCH$_2$Ph), 168.4 (C-2). IR (neat): 1716 (ν_{CO}, NCOOCH$_2$Ph), 1763 (ν_{CO}, NCO). MS-FAB$^+$ (m/z) 463 [M + Na]$^+$, 441 [M + H]$^+$. Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36. Found: C, 73.51; H 5.60; N, 6.39.

(3*R*,4*R*)-2-Benzyl-7,8-dihydroxy-1-oxo-3-phenyl-2,5-diazaspiro[3.4]octane-5-carboxylic Acid Benzyl Ester (12). 4-Methylmorpholine *N*-oxide (NMO) (0.11 g, 0.94 mmol) and OsO_4 (2.5% w/w solution in *t*-BuOH, 20 mol %, 1.58 mL, 0.13 mmol) were added to a solution of **5a** (0.27 g, 0.68 mmol) in an acetone/water 10:1 mixture (20 mL). The mixture was stirred at room temperature for 40 h. The solvent was removed under reduced pressure, and the residue was taken up with AcOEt (10 mL) and washed with 5% aq HCl and saturated $Na_2S_2O_3$ solution. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude products were purified by column chromatography (SiO_2, *n*-hexane/AcOEt = 25:75) to afford a colorless oil (0.26 g, 85%, inseparable mixture of two diastereoisomers with a ratio = 83:17 determined by NMR). ^{1}H NMR (DMSO-d_6, T = 120 °C): major diastereoisomer δ 3.22 (dd, J = 10.3, 6.9, 1H, H-6); 3.32 (dd, J = 10.3, 7.2, 1H, H-6); 4.20 (d, J = 15.4, 1H, CH_2Ph); 4.22 (m, 1H, H-7); 4.35 (t, J = 4.2, 1H, H-8); 4.46 (m, 2H, OH); 4.55 (s, 1H, H-3); 4.75 (d, J = 15.4, 1H, CH_2Ph); 4.77 (d, J = 12.4, 1H, CH_2Ph(Cbz)); 4.92 (d, J = 12.4, 1H, CH_2Ph(Cbz)); 7.16−7.34 (m, 15H, Ph); minor diastereoisomer δ 5.07 (s, 1H, H-3).^{13}C NMR shows the presence of two rotamers: major diastereoisomer δ 45.5, 45.6 (C-6); 51.6, 52.2 (CH$_2$Ph); 66.4, 66.9 (C-3); 67.3, 68.3 (CH$_2$Ph(Cbz)); 69.5, 70.1 (C-7); 76.9, 78.1 (C-8); 81.0 (C-4); 127.2−136.8 (Ph); 154.8 (COOCH$_2$Ph); 167.4 (C-1); minor diastereoisomer δ 45.8 (C-6); 52.9, 53.2 (CH$_2$Ph); 62.5, 63.8 (C-3); 67.1, 68.1 (CH$_2$Ph(Cbz)); 69.0, 69.9 (C-7); 73.6, 74.6 (C-8); 80.4 (C-4); 127.2−136.8 (Ph). IR (Nujol): 1707 (ν_{CO}, NCOOCH$_2$Ph), 1750 (ν_{CO}, NCO). MS-ESI (m/z): 481 [M + Na]$^+$. Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.60; H 5.66; N, 6.25.

(3*R*,4*R*)-1-Benzyl-3-formyl-2-oxo-4-phenylazetidin-3-yl(2-oxoethyl)carbamic Acid Benzyl Ester (13). $NaIO_4$ (0.16 g, 0.77 mmol) and OsO_4 (2.5% w/w solution in *t*-BuOH, 5 mol %, 188 μL, 0.015 mmol) were added to a solution of **5a** (0.13 g, 0.31 mmol) in an acetone/water 5:1 mixture (6 mL). The mixture was stirred at room temperature for 46 h. The solvent was removed under reduced pressure, and the residue was taken up with CH_2Cl_2 (10 mL). The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a colorless amorphous solid (0.14 g, 98%). $[\alpha]^{20}_D$ = +35.1 (*c* 1.41, $CHCl_3$). ^{1}H NMR (C_6D_6) shows the presence of two rotamers: δ major rotamer 3.57 (d, J = 15.0, 1H, CH_2CHO); 3.91 (d, J = 18.6, 1H, CH_2Ph); 4.32 (d, J = 18.6, 1H, CH_2Ph); 4.44 (d, J = 12.2, 1H, CH_2Ph(Cbz)); 4.56 (d, J = 15.0, 1H, CH_2CHO); 4.68 (d, J = 12.2, 1H, CH_2Ph(Cbz)); 5.29 (s, 1H, H-4); 6.60−7.05 (m, 15H, Ph); 8.96 (s, 1H, CHO); 9.90 (s, 1H, CHO); minor rotamer 3.47 (d, J = 15.0, 1H, CH_2CHO); 3.83 (d, J = 18.2, 1H, CH_2Ph); 4.40 (d, J = 18.2, 1H, CH_2Ph); 4.50 (d, J = 12.1, 1H, CH_2Ph(Cbz)); 4.58 (d, J = 15.0, 1H, CH_2CHO); 4.60 (d, J = 12.1, 1H, CH_2Ph(Cbz)); 4.96 (s, 1H, H-4); 6.60−7.05 (m, 15H, Ph); 9.41 (s, 1H, CHO); 9.93 (s, 1H, CHO). ^{13}C NMR shows the presence of two rotamers: δ 44.9, 45.2 (CH$_2$Ph); 56.5, 56.8 (CH$_2$CHO); 62.2, 62.7 (C-4); 68.2, 68.7 (CH$_2$Ph(Cbz)); 84.5 (C-3); 127.8−129.3, (Ph); 155.0 (COOCH$_2$Ph); 161.4 (C-2); 193.5, 194.6 (CHO); 195.9, 196.1 (CHO). IR (nujol): 1726 (ν_{CO}, NCOOCH$_2$Ph), 1769 (ν_{CO}, NCO). MS-EI$^+$ (m/z): 456 (M$^+$). Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.10; H 5.22; N, 6.24.

(3*S*,4*S*)-1-Benzyl-3-formyl-2-oxo-4-phenylazetidin-3-yl(2-oxoethyl)carbamic Acid Benzyl Ester (13′). From **5′a** and $NaIO_4$–OsO_4 (98%): $[\alpha]^{20}_D = -44.6$ (*c* 0.87, $CHCl_3$).

(3*R*,4*S*)-2-Benzyl-8-(4-methoxybenzyl)-1-oxo-3-phenyl-2,5,8-triazaspiro[3.5]nonane-5-carboxylic Acid Benzyl Ester (14). *p*-Methoxybenzylamine (41 μL, 0.32 mmol), sodium triacetoxyboronhydride (0.16 g, 0.73 mmol, 95% purity), and acetic acid (10 mol %, 22 mg, 0.003 mmol) were added to a solution of **13** (0.13 g, 0.29 mmol) in dry CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 4 h. The reaction was treated with 5% $NaHCO_3$ aq solution. The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, toluene/AcOEt = 80:20) to afford a colorless oil (98 mg, 60%). $[\alpha]^{20}_D = -82.4$ (*c* 0.98, $CHCl_3$). ^{1}H NMR (DMSO-d_6, T = 120 °C): δ 2.10 (dt, J = 11.8, 3.6, 1H, H-6/7); 2.44 (dt, J = 11.8, 3.6, 1H, H-6/7); 2.77 (m, 1H, H-6/7); 2.83 (d, J = 11.5, 1H, H-9); 2.84 (d, J = 11.5, 1H, H-9); 3.40 (d, J = 13.0, 1H, CH_2PMP); 3.54 (m, 1H, H-6/7); 3.62 (d, J = 13.0, 1H, CH_2PMP); 3.83 (s, 3H, OCH_3); 3.98 (d, J = 15.0, 1H, CH_2Ph); 4.44 (s, 1H, H-3); 4.61 (d, J = 15.0, 1H, CH_2Ph); 4.97 (s, 2H, CH_2Ph(Cbz)); 6.88–7.38 (m, 19H, Ph). ^{13}C NMR: δ 42.1 (C-6/7); 44.3 (*C*H$_2$Ph); 52.1 (C-6/7); 55.2 (O*C*H$_3$); 57.7 (C-9); 61.8 (*C*H$_2$PMP); 61.9 (*C*H$_2$Ph(Cbz)); 67.3 (C-3); 82.5 (C-3); 113.8–133.7 (Ph); 158.9 (*C*OOCH$_2$Ph); 167.4 (C-1). IR (Nujol): 1706 (ν_{CO}, NCOOCH$_2$Ph), 1761 (ν_{CO}, NCO). MS-EI$^+$ (m/z): 561 [M]$^+$. Anal. Calcd for $C_{35}H_{35}N_3O_4$: C, 74.84; H, 6.28; N, 7.48. Found: C, 74.75; H 6.32; N, 7.41.

(3*S*,4*R*)-2-Benzyl-8-(4-methoxybenzyl)-1-oxo-3-phenyl-2,5,8-triazaspiro[3.5]nonane-5-carboxylic Acid Benzyl Ester (14′). From **13′** and *p*-methoxybenzylamine, sodium triacetoxyboronhydride, and acetic acid (58%). $[\alpha]^{20}_D = +92.5$ (*c* 2.35, $CHCl_3$).

Supporting Information Available: Compounds ^{1}H and ^{13}C NMR spectra and NOESY experiments. This material is available free of charge via the Internet at http://pubs.acs.org.