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Synthesis of Pipecolic Acid-Based Spiro Bicyclic Lactam Scaffolds as β-Turn Mimics

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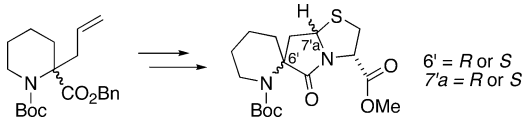

A series of 6.5.5 spiro bicyclic lactam scaffolds were synthesized from pipecolic acid in a sequence of reactions that was initiated with the α-allylation of *tert*-butoxycarbonyl pipecolic acid. Oxidative cleavage of the olefin to give an aldehyde followed by condensation with D-cysteine methyl ester gave a mixture of pipecolyl thiazolidines. Cyclization of the pipecolyl thiazolidines with Mukaiyama's reagent yielded the spiro bicyclic lactams **4a**−**d**. Epimerization of the 7′a bridgehead carbon under acidic conditions was observed for those spiro bicyclic lactam scaffolds with an *S* stereochemistry at this position. The 6.5.5 spiro bicyclic lactam scaffold with the 3′*S*,6′*R*,7′a*R* stereochemistry mimicked a type II β-turn, while the scaffold with the 3′*S*,6′*S*,7′a*R* stereochemistry mimicked a right-handed poly-D-proline II helix.

Introduction

Proteins and peptides play important roles in numerous fundamental physiological processes. Reverse turns constitute ubiquitous structural motifs of many peptides and proteins[1] and they are considered to play a major role in protein−protein and peptide−protein recognition events.[2] Type I and type II β-turns are among the most important reverse turns observed in peptides.[3] β-Turns are defined by the ϕ and ψ torsion angles of the $i+1$ and $i+2$ residues occupying the turn region (Figure 1). Hydrogen bonding between the carbonyl of residue i and the amide hydrogen of residue $i+3$ is often indicative of a β-turn, though it is not an essential feature.

Knowledge of the bioactive conformation of a peptide or protein for its receptor becomes important in understanding the recognition process and in developing compounds that potentially can affect such systems and be used as drugs. Several non-peptide based scaffolds have been developed in the process of elucidating biologically active conformations of peptides and they have been successfully used for the development of potent enzyme inhibitors and receptor modulators.[4] A common method to mimic the bioactive conformation of peptides is to synthesize conformationally constrained analogues via backbone−backbone or backbone−side chain cyclization.[5] Lactam or bicyclic lactam formation is a widely used

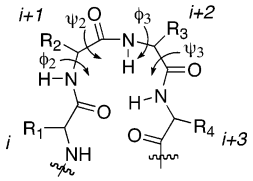

FIGURE 1. Schematic representation of a β-turn.

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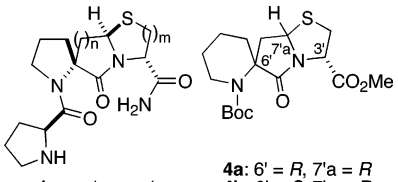
method for constraining the torsion angles for the synthesis of peptidomimetics.[6,7] Most lactam constraints that have been developed and incorporated into peptides, however, only restrict one or two torsion angles out of the four that define a β-turn conformation.

We developed a class of spiro bicyclic lactams that restrict three out of four torsion angles that define a β-turn.[8] Spiro bicyclic lactams such as **1**−**3** were synthesized to explore the bioactive conformation of L-prolyl-L-leucyl-glycinamide (PLG), an endogenous peptide known to exert important modulatory effects on dopaminergic neurotransmission in the central nervous system.[9,10] In our early studies, the ring size of the bicyclic portion of the scaffold was altered. Such changes were found to have an effect on the ψ_2 and ϕ_3 torsion angles, that in turn had an effect on the pharmacological activity of the PLG peptidomimetics.[10] In a continuation of these studies, we wanted to explore the effect of increasing the conformational freedom of the ϕ_2 torsion angle. We envisioned this could be achieved by changing the spiro pyrrolidine residue found in **1**−**3** to the six-membered piperidine moiety as illustrated in spiro bicyclic lactam scaffold **4**. The present report describes the synthesis and chemistry of the diastereomeric 6.5.5 spiro bicyclic lactam scaffolds **4a**−**d**.



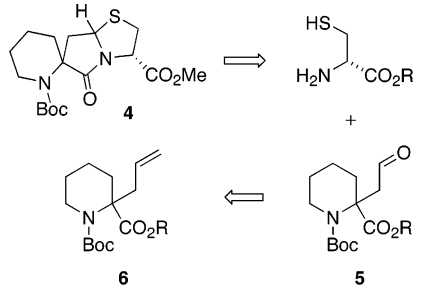
1: n = 1, m = 1
2: n = 1, m = 2
3: n = 2, m = 1

4a: 6' = *R*, 7'a = *R*
4b: 6' = *S*, 7'a = *R*
4c: 6' = *S*, 7'a = *S*
4d: 6' = *R*, 7'a = *S*

Results and Discussion

The retrosynthetic analysis for spiro bicyclic lactam scaffold **4** is depicted in Scheme 1. We envisioned that this scaffold could be obtained through the condensation of D-cysteine with pipecolyl aldehyde **5** in a manner analogous to that used in the synthesis of the prolyl-based spiro bicyclic lactam scaffolds.[8−10] Aldehyde **5** could be obtained from the α-allyl pipecolic acid derivative **6**. This route provided a potential means to control the stereochemistry of the spiro center provided **6** could be obtained in chiral form. Unfortunately, Seebach's method of self-reproduction of chirality, an excellent method for asymmetric alkylation of proline and the method used to control the spiro center stereochemistry in the prolyl-based spiro bicyclic lactam scaffolds, could not be extended to pipecolic acid, as this compound does not condense with pivalaldehyde under a variety of conditions.[11]

SCHEME 1. Retrosynthesis of Pipecolyl Spiro Bicyclic Lactam Scaffold 4



Although the pool of methods available for the asymmetric synthesis of 2-alkyl pipecolic acid derivatives is rather limited, we initially investigated several chiral auxiliary mediated alkylations in an effort to obtain **6** in chiral form. The method of Wanner and colleagues[12] provided α-allylpipecolic acid, but only in modest yield after 10 steps. The use of this method on a large-scale preparation of **6** was viewed as prohibitive, however, because of the costly (−)-camphanic acid required for the chiral auxiliary synthesis. When either William's oxazinone[13] or Husson's 2-cyano-6-phenyloxazolopiperidine[14] was used as the chiral auxiliary excellent stereoselectivity in the alkylation with allyl bromide was observed. However, cleavage of the chiral auxiliary without affecting the allyl group could not be achieved. Due to these limitations, we felt it would be more efficient and cost-effective to carry out the synthesis of the pipecolyl-based spiro bicyclic lactams starting with the cheap and widely available racemic pipecolic acid. Although this approach would yield a mixture of diastereoisomers, successful separation of the diastereoisomers would provide a family of pipecolyl-based spiro bicyclic lactams. Described below is the successful synthesis and isolation of the diastereomeric spiro bicyclic lactam scaffolds **4a**−**d**.

Our initial approach to the 6.5.5 spiro bicyclic lactam scaffold was to synthesize pipecolyl thiazolidine derivatives that could be cyclized under thermal conditions to give the 6.5.5 scaffold, since this was an approach that

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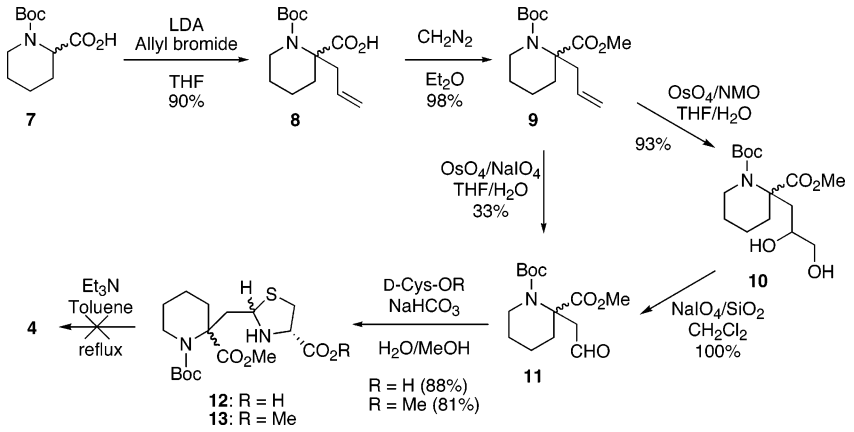
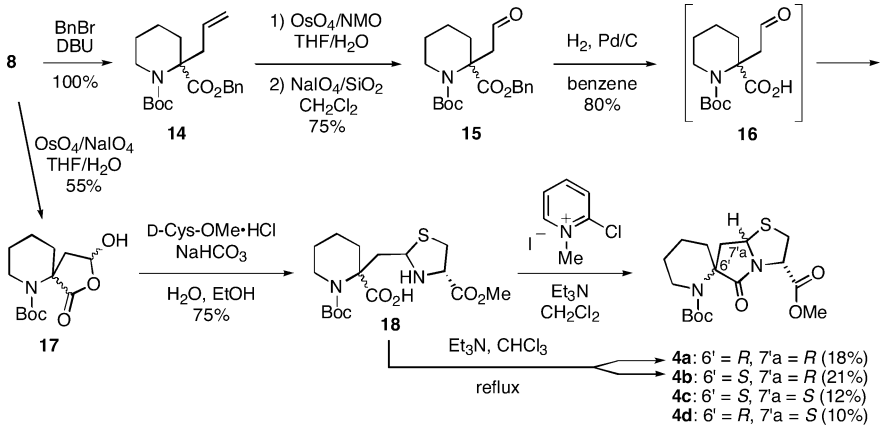
SCHEME 2



SCHEME 3



previously proved successful in the synthesis of the 5.5.5 and 5.5.6 spiro bicyclic lactam scaffolds.[8–10] This approach is depicted in Scheme 2. Racemic pipecolic acid was protected with the *tert*-butoxycarbonyl group in 95% yield, using the conditions of Khalil et al.[15] to give **7**. An LDA mediated allylation[16] of **7** afforded racemic 2-allyl pipecolic acid **8** in excellent yield (90%). This material was treated with diazomethane to give methyl ester **9** in 98% yield. Initially, oxidative cleavage of olefin **9** was carried out with OsO_4 and $NaIO_4$,[10] but this method only provided aldehyde **11** in a very modest 33% yield after column chromatography. A modified procedure involving first the dihydroxylation of **9** to give **10**, followed by the treatment of **10** with silica adsorbed with $NaIO_4$[17] gave a superior yield (>90% over two steps) of **11** without the need for column chromatography.

Aldehyde **11** was condensed with D-Cys-OH to give a mixture of thiazolidines (**12**), which was subsequently heated in toluene in the presence of Et_3N. The reaction mixture showed the formation of several nonpolar products along with unreacted starting material after prolonged heating. One of the nonpolar products was characterized to be the decarboxylation product of the spiro bicyclc lactam, but none of the desired cyclization products was detected. In another attempt, the diester pipecolyl thiazolidine **13** was synthesized in an 81% yield by condensing D-Cys-OMe with **11** in the presence of $NaHCO_3$. However, subjecting **13** to thermal cyclization conditions also failed to yield any of the desired cyclization products. These cyclization problems were similar to those observed previously when attempts were made to obtain the 5.6.5 spiro bicyclic lactam scaffold under thermal conditions.[10]

To overcome the cyclization problems encountered above, an alternate route to the spiro bicyclic lactams **4** was employed as outlined in Scheme 3. Compound **8** was treated with BnBr in the presence of DBU to afford the benzyl ester **14** in quantitative yield.[18] Oxidative cleavage of **14** with the OsO_4/NMO and $NaIO_4/SiO_2$ sequence gave aldehyde **15** in a 75% yield. Hydrogenolysis of **15** resulted in deprotection of the benzyl ester. However, the product that was isolated in 80% yield when benzene was used as the solvent was not carboxylic acid **16**, but rather hydroxy lactone **17**. When EtOH was used as the solvent in the hydrogenolysis reaction the formation of unwanted hemiacetal/acetal products resulted. If the hydrogenolysis of **15** was carried out in EtOH under pressure (60 psi), **17** was obtained in a 26% yield along with about 5% of the corresponding ethoxy lactone derivative and 53% of the ethyl hemiacetal of **15**. Hydroxy lactone **17** also could be obtained directly through the oxidative cleavage of **8**

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with OsO_4/$NaIO_4$. In this case a 55% yield of **17** was obtained after column chromatography.

The condensation of **17** with D-Cys-OMe gave the pipecolyl thiazolidine **18** as a mixture of diastereoisomers as indicated by ^{1}H NMR and mass spectral analyses. Interestingly, the presence of molecular ion peaks corresponding to the cyclization product in the mass spectrum of the condensation reaction mixture suggested that **18**, in contrast to the pipecolyl thiazolidines **12** and **13**, had a propensity to cyclize to the spiro bicyclic lactam system under mild reaction conditions. Thus, a $CHCl_3$ solution of **18** and Et_3N was heated at reflux. TLC analysis of the reaction mixture showed the formation of two products, which were isolated by column chromatography (~15% isolated yield for each) and subsequently shown to be the spiro bicyclic lactams **4a** and **4b**. The formation in this case of the two spiro-bicyclic lactam scaffolds having the 3′ and 7a′ hydrogens in an anti configuration was consistent with the results obtained previously by us in the thermal cyclization of the 5.5.5 and 5.5.6 spiro bicyclic lactam systems.[8,10]

When the cyclization of the diastereoisomeric mixture **18** was carried out with Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) under the conditions previously reported by Khalil et al.[10] for the synthesis of the 5.6.5 spiro bicyclic lactam scaffold, four cyclization products, **4a**−**d**, were obtained. On TLC (EtOAc/hexanes, 1:1) **4a**−**d** possessed R_f values of 0.75, 0.58, 0.51, and 0.48, respectively. The chromatographic isolation of **4a** from the mixture of isomers was straightforward and provided **4a** in an 18% yield. The separation of the other isomers from one another, on the other hand, proved more difficult because of their relatively close R_f values. However, **4b** could be isolated in pure form and in a 21% yield through the use of Ready Sep prepacked silica gel columns. Although **4c** and **4d** could be separated from one another in this system, these compounds were contaminated by the presence of the byproduct of Mukaiyama's reagent, 1-methyl-1*H*-pyridin-2-one. They were obtained in yields of 12% and 10%, respectively.

The assignment of the stereochemistry of the spiro carbon 6′ and the bridgehead carbon 7′a of **4a** and **4b** was delineated through X-ray crystallographic analysis. An X-ray crystal structure of compound **4a** unambiguously established the stereochemistry of both the bridgehead and spiral carbon atoms (Figure 2) to have the *R* configuration. Likewise, an X-ray crystal structure of a derivative of **4b**, compound **20b** (Figure 3), established the stereochemistry of the bridgehead and spiral carbon atoms for this isomer to be *R* and *S*, respectively. In the case of **4d**, 1D and 2D NOE studies (Figure 4) showed a significant NOE between the 3′ hydrogen and the bridgehead hydrogen. Also, a weak NOE was observed between the bridgehead hydrogen and the hydrogens of the piperidine ring. These results suggested that the spiral and bridgehead carbon atoms possessed the *R* and *S* configurations, respectively. By the process of elimination, **4c** was postulated to possess the *S* stereochemistry at both the bridgehead and spiro carbon atoms. Support for this assumption was an observed weak NOE between the 3′ and 7′a hydrogens of **4c**.

The spiro bicyclic lactam scaffolds **4a**−**d** were carried on in reactions that would give analogues of the dopamine receptor modulating peptide, L-prolyl-L-leucyl-glycinamide. The *tert*-butoxycarbonyl group was removed from each diastereoisomer with HCl in dioxane and the deprotected species then was coupled to Boc-Pro-OH. In the case of **4a**, a number of coupling conditions were investigated. Coupling of the Boc-deprotected **4a** to Boc-Pro-OH (2.5 equiv) with EDCI and HOBt (2.5 equiv of each in dry DMF for 3 days) yielded only 10% of **19a**. Increasing the amount of EDCI and Boc-Pro-OH 3-fold resulted in a 30% yield of **19a**. When DCC, HOBt, and Boc-Pro-OH (7.5 equiv of each) were reacted for 3 days the yield of **19a** was increased to 50%. However, the best results were obtained when the coupling was performed in DMF with Mukaiyama's reagent (2.5 equiv) in the presence of Hunig's base (Scheme 4). An overnight reaction gave the desired coupled product in a 70% yield after purification. The ^{1}H NMR spectrum of **19a** showed the presence of rotamers in the ratio of 7:3 at room temperature. Similar coupling of the Boc-deprotected

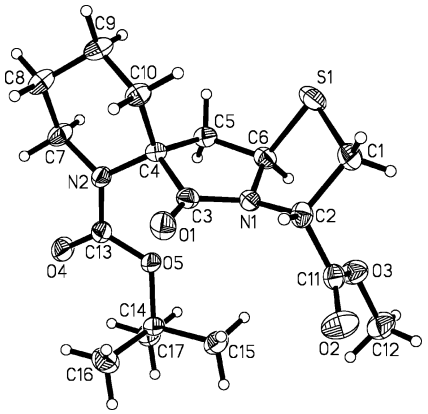


FIGURE 2. ORTEP representation of the X-ray structure of **4a** at the 50% probability level for non-hydrogen atoms with the crystallographic numbering system.

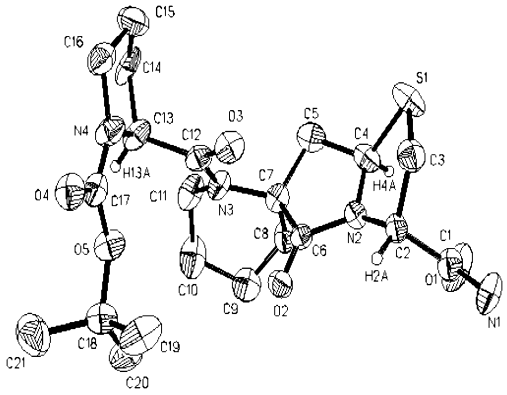


FIGURE 3. ORTEP representation of the X-ray structure of **20b** at the 50% probability level for non-hydrogen atoms with the crystallographic numbering system.

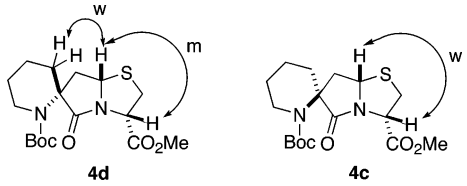
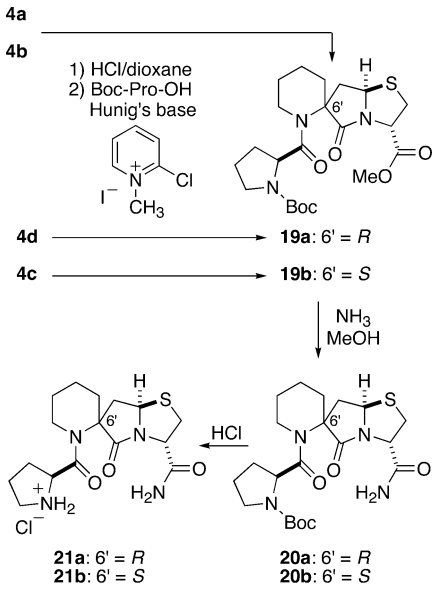
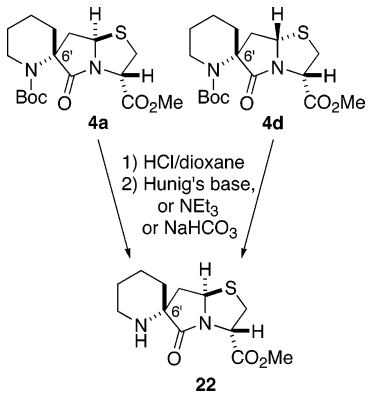


FIGURE 4. Observed NOEs for **4d** and **4c** (m = medium, w = weak).

SCHEME 4



SCHEME 5

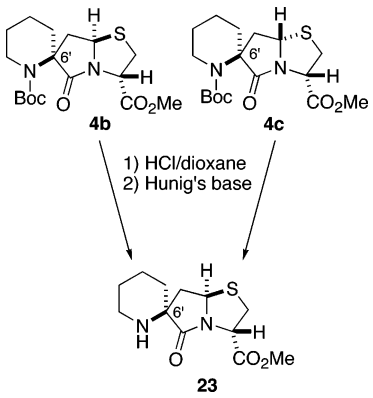


derivative of **4b** to Boc-Pro-OH gave **19b** in a 75% yield. The ^{1}H NMR spectrum of **19b** also showed the presence of rotamers about the carbamate bond in the ratio of 9:1. Transformation of **19a** and **19b** to the corresponding carboxamides **20a** and **20b** was smoothly achieved in 81% and 78% yields, respectively, with a saturated solution of NH_3 in MeOH. Deprotection of **20a** and **20b** gave the PLG peptidomimetics **21a** and **21b**, respectively.

When either **4c** or **4d** was Boc-deprotected with HCl/dioxane and the corresponding HCl salts then coupled to Boc-Pro-OH with Mukaiyama's reagent in the presence of Hunig's base, the expected peptidomimetics were not obtained. Rather, **4c** was found to yield **19b**, while **4d** gave **19a**. These results indicated that epimerization of the bridgehead carbon occurred during the deprotection and coupling sequence of the reactions.

To explore further the epimerization of the spiro bicyclic lactam scaffolds possessing an *S* stereochemistry at the bridgehead carbon, **4d** was treated with HCl/dioxane and the hydrochloride salt that was obtained was neutralized with different bases (Hunig's base, Et_3N, or $NaHCO_3$). This gave the free amine spiro bicyclic lactam scaffold **22** (Scheme 5). This same compound was obtained when **4a** was subjected to the same treatment as **4d**, suggesting that **4d** underwent epimerization during the acidic deprotection reaction. This was supported by

SCHEME 6



the fact that the ^{1}H NMR spectra of the HCl salts resulting from the deprotection of **4a** and **4d** were identical. These results suggest that the spiro bicyclic ring system of **4a** wherein the bridgehead hydrogen is in a α-orientation is more thermodynamically stable than the spiro bicyclic system of **4d**, wherein the bridgehead hydrogen is in a *β*-orientation. Ab initio calculations on **22** and the corresponding isomer with the bridgehead hydrogen in a *β*-orientation using the Gaussian 03[19] suite of programs at the Hartree−Fock level of theory showed that the isomer with the bridgehead hydrogen in a *β*-orientation is 3.81 kcal/mol higher in energy compared to **22** in which the bridgehead hydrogen is in a α-orientation.

The treatment of **4c** first with HCl/dioxane followed by Hunig's base gave compound **23**, which was identical with the compound obtained when **4b** was treated with HCl/dioxane followed by Hunig's base (Scheme 6). Like **4d**, **4c** underwent epimerization at the bridgehead position during the deprotection reaction. However, when **4c** was treated with HCl/dioxane followed by treatment with NH_3 overnight two compounds were formed. One compound corresponded to the epimerized bridgehead species, **23**. The second compound showed a molecular ion peak in the mass spectrum that was the same as that for **23**, but the NMR was different than that for either **22** or **23**. This suggested that the 3′ position also might have epimerized during the treatment with ammonia. A significant NOE between the bridgehead hydrogen and the 3′-hydrogen indicated a syn relationship. On the basis of these observations the structure of this product was tentatively assigned to be **24** (Scheme 7).

Conformational Analysis. A comparison of the torsion angles of the piperidine-based spiro bicyclic lactam scaffolds **4a**, **20a**, and **20b** described in this paper with

(19) Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision A.1; Gaussian, Inc.: Pittsburgh, PA, 2003.

SCHEME 7

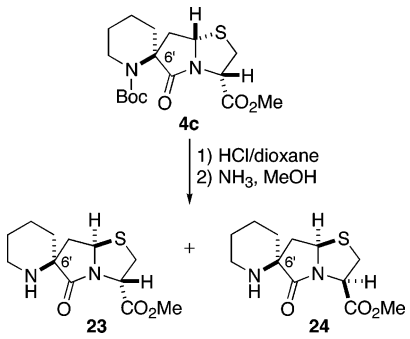


TABLE 1. Torsion Angle Comparisons of the Spiro Bicyclic Lactam Scaffolds

system	ϕ_2	ψ_2	ϕ_3	ψ_3
ideal type II β-turn	-60 ± 30	120 ± 30	80 ± 30	0 ± 30
5.5.5 (**1**)[a]	−40.3	108.1	77.7	−16.7
5.5.6 (**2**)[b]	−48.9	134.1	116.0	−29.8
5.6.5 (**3**)[b]	−56.0	133.7	97.3	−19.9
6.5.5 (**4a**)[c]	−47.4	131.2	115.6	−121.2
6.5.5 (**20a**)[c]	−41.8	117.0	102.5	−11.2
6.5.5 (**20b**)[c]	50.1	−146.9	121.3	−167.5

[a] Data for the 5.5.5 spiro bicyclic lactam scaffold are from ref 8. [b] Data for the 5.5.6 and 5.6.5 spiro bicyclic lactam scaffolds are from ref 10. [c] Data for this 6.5.5 spiro bicyclic lactam scaffold are derived from the X-ray structure.

the corresponding pyrrolidine-based spiro bicyclic lactam scaffolds described by us previously[8,10] is summarized in Table 1. The torsion angles for the 6.5.5 spiro bicyclic lactams **4a**, **20a**, and **20b** were obtained from their X-ray structures, which are shown in Figures 3, 5, and 4, respectively. In the case of **4a** and **20a**, which possess the 6.5.5 spiro bicyclic lactam scaffold with the 3′*S*,6′*R*,7′a*R* stereochemistry, the ϕ_2, ψ_2, and ϕ_3 torsion angles were found to be constrained close to the values found in an ideal type II β-turn. An overlay of the X-ray structure of **20a** with Pro-Leu-Gly-NH_2 (PLG) in its type II β-turn conformation (Figure 6) gave an RMS deviation of 0.37 Å, thereby illustrating the ability of the 6.5.5 spiro bicyclic lactam scaffold with the 3′*S*,6′*R*,7′a*R* stereochemistry to mimic a type II β-turn. Although both **4a** and **20a** contain the same spiro bicyclic lactam scaffold, differences of up to 14° were observed between the two compounds in the values of the constrained torsion angles indicating that there is some degree of flexibility in the 6.5.5 scaffold.

In the case of **20a** wherein the 3′-carboxyl moiety was in the form of a carboxamide, the N···O distance of 3.125 Å seen in the X-ray structure (Figure 5) indicated the presence of a hydrogen bond between the trans carboxamide hydrogen and the carbonyl of the N-terminal prolyl residue.[3a] The presence of such a hydrogen bond also was supported in H^1 NMR studies. The ^{1}H NMR spectrum of **20a** in the non-hydrogen bonding solvent $CDCl_3$ showed a high downfield shift for one of the carboxamide hydrogens (δ 7.7 ppm) suggesting its participation in an intramolecular hydrogen bond. The chemical shift for the suspected non-H-bonded hydrogen was 5.5 ppm. Also, the low value of the temperature coefficient for downfield hydrogen ($\Delta\delta/\Delta T$ = 0.28 ppb/K) suggested that this hydrogen was involved in a hydrogen-bonded conformation.[20] Furthermore, ^{1}H NMR titration studies with DMSO-d_6, which were carried out by the sequential addition of 50 μL of DMSO-d_6 each time to 10 mg of **20a** in 500 μL of $CDCl_3$ up to a total of 300 μL of DMSO-d_6, resulted in a gradual disruption of the intramolecular hydrogen bond, ultimately rendering the two carboxamide protons equivalent (δ 6.5 ppm).

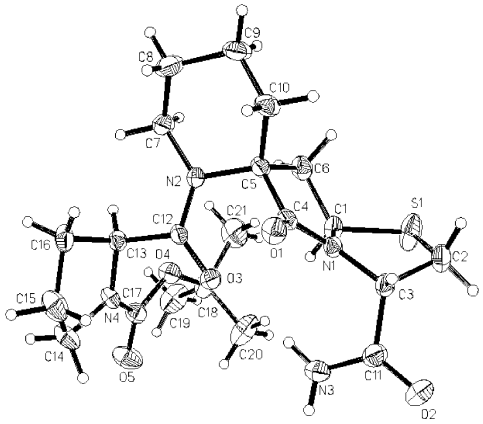


FIGURE 5. ORTEP representation of the X-ray structure of **20a** at the 50% probability level for non-hydrogen atoms with the crystallographic numbering system.

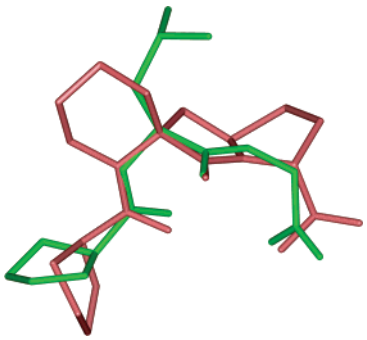


FIGURE 6. Overlay of the X-ray structure of peptidomimetic **20a** (maroon) and Pro-Leu-Gly-NH_2 (PLG) in an ideal type II β-turn (green). The superimposition was carried out with Insight II by calculating the best fit for the 10 backbone atoms (RMS = 0.37 Å). For clarity, the hydrogens of **20a** and PLG and the Boc group of **20a** have not been included.

Compound **20b** showed no hydrogen bonding between the 3′-carboxamide hydrogens and the prolyl carbonyl in the X-ray structure. The torsion angles observed for **20b** (Table 1) clearly show that it does not exist in a β-turn. Instead, the ϕ_2 and ψ_2 torsion angels for **20b** were found to be similar to the values that are observed for a right-handed poly-D-proline II helix (75° and −145° respectively for ϕ and ψ).[21] An overlay of seven backbone atoms from the X-ray crystal structure of **20b** with the corresponding atoms of an energy minimized structure of D-Pro-D-Pro-D-Pro-NH_2 in a poly-D-prolyl II helix (Figure 7) gave an RMS deviation of 0.24 Å.

Conclusion

In summary, this report describes the first synthesis and characterization of a series of pipecolic acid-based

(20) (a) Belvisi, L.; Gennari, A.; Mielgo, D.; Potenza, C.; Scolastico. C. *Eur. J. Org. Chem.* **1999**, 389−400. (b) Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem*. **2000**, 2563−2569.

(21) Adzhubei, A. A.; Sternberg, M. J. E. *J. Mol. Biol.* **1993**, *229*, 472−493.

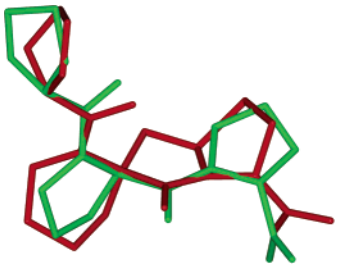


FIGURE 7. Overlay of the X-ray structure of peptidomimetic **20b** (maroon) and D-Pro-D-Pro-D-Pro-NH_2 in a right-handed poly-D-proline II type helix (green). The superimposition was carried out with Insight II by calculating the best fit for the seven backbone atoms (RMS = 0.24 Å). For clarity, the hydrogens of **20b** and D-Pro-D-Pro-D-Pro-NH_2 and the Boc group of **20b** have not been included.

spiro bicyclic lactam scaffolds as potential β-turn mimics. X-ray studies showed that the system possessing the 3′*S*,6′*R*,7′a*R* stereochemistry (**20a**) was capable of mimicking a type II β-turn, while the system possessing the 3′*S*,6′*S*,7′a*R* stereochemistry (**20b**) mimicked a right-handed poly-D-proline II helix. This work extends our efforts to determine the effect that alterations in ring size have on the torsion angles that are constrained by these novel and highly conformationally constrained scaffolds.

Experimental Section

Ab Initio Calculations. Ab initio calculations were carried out with the Gaussian 03[19] suite of programs at the Hartree−Fock level of theory. Initial optimizations were conducted at the level of HF/STO-3G and further optimized sequentially at the HF/3-21G** and HF/6-31G* levels. Characterization of stationary points as minima was done by harmonic vibrational frequency analysis of analytic second derivative at each level. Single-point energies were calculated at the 6-31G* level[22] by enforcing Tight convergence of the wave function for the more accurate energies.

N-(*tert*-Butoxycarbonyl)-DL-pipecolic Acid (7). DL-Pipecolic acid (5 g, 38.7 mmol) and tetramethylammonium hydroxide pentahydrate (TMAH, 7.02 g, 38.7 mmol) were suspended in CH_3CN. The mixture was stirred at room temperature until a solution was obtained. $(Boc)_2O$ (12.7 g, 58.0 mmol) was then added and the reaction was stirred for a day. On the second day, additional $(Boc)_2O$ (4.2 g, 19.4 mmol) was added and the mixture was stirred for another day. The CH_3CN was removed under reduced pressure and the white solid obtained was partitioned between H_2O (100 mL) and Et_2O (50 mL). The aqueous layer was reduced to one-third of its volume under reduced pressure and then was acidified with solid $NaHSO_4$ until the pH of the solution was between 3 and 4. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated to give **7** as a white solid in a 95% yield. Mp 128−130 °C (lit.[23] mp 130−131 °C). ^1H and ^{13}C NMR spectra matched the previously reported data.[23]

***N-tert*-Butoxycarbonyl-2-allyl-DL-pipecolic Acid (8).** To an ice-chilled solution of diisopropylamine (10.9 mL, 77.5 mmol) in dry THF (55 mL) was added slowly under N_2 *n*-butyllithium (38.5 mL of a 2.0 M solution in *n*-hexane, 77.5 mmol). After the mixture was stirred for 30 min, a solution of **7** (7.1 g, 31.0 mmol) in dry THF (30 mL) was added dropwise over a period of 20 min. The resulting yellowish solution was stirred for 40 min and then allyl bromide (5.36 mL, 62.0 mmol) was added dropwise. The reaction mixture was stirred for 24 h to give a colorless solution. The pH of the solution was adjusted to 2.5 with 3 N HCl. The organic layer was separated and extracted with saturated $NaHCO_3$ solution. The aqueous layer was acidified with 3 N HCl to pH 2, saturated with sodium chloride, and then extracted with EtOAc (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to give **8** as a light yellow oil in a 90% yield. This material was used directly for the next reaction without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 5.80−6.0 (m, 1H), 5.02−5.20 (m, 2H), 3.88 (dt, 1H, J = 12.9 Hz), 2.94−3.10 (m, 1H), 2.86 (dd, 1H, J = 7.2 and 13.8 Hz), 1.43 (s, 9H), 2.62 (dd, 1H, J = 7.2 and 13.8 Hz), 1.50−2.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 155.5, 134.1, 118.6, 81.2, 62.7, 41.2, 38.8, 32.1, 28.6, 23.1, 17.8; HRMS (ESI) *m/z* 292.1524, $C_{14}H_{23}NO_4 + Na^+$ $[M + Na]^+$ requires 292.1520.

***N-tert*-Butoxycarbonyl-2-allylpipecolic Acid Methyl Ester (9).** To a solution of **8** (2.0 g, 7.4 mmol) in dry Et_2O (40 mL) at 0 °C was added an Et_2O solution of diazomethane until the evolution of gas ceased. The reaction mixture then was stirred for an additional 1 h. The reaction was stripped of solvent and excess reagent under reduced pressure to give **9** as pale yellow oil in a 98% yield. An analytically pure sample for spectral analysis was obtained by purification through flash chromatography with EtOAc and hexanes (1:10). ^1H NMR (300 MHz, $CDCl_3$) δ 5.82−6.02 (m, 1H), 5.0−5.14 (m, 2H), 3.87 (br d, 1H, J = 12.9 Hz), 3.71(s, 3H), 2.99 (m, 1H), 2.82 (dd, 1H, J = 7.5 and 13.8 Hz), 2.61 (dd, 1H, J = 7.5 and 13.8 Hz), 1.46−1.92 (m, 6H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 155.5, 134.4, 118.3, 80.6, 62.8, 52.2, 41.3, 38.9, 32.1, 28.6, 23.3, 18.1; HRMS (ESI) *m/z* 306.1682, $C_{15}H_{25}NO_4 + Na^+$ $[M + Na]^+$ requires 306.1681.

***N-tert*-Butoxycarbonyl-2-(2-oxoethyl)pipecolic Acid Methyl Ester (11): Method A.** Methyl ester **9** (1.9 g, 6.7 mmol) was placed in a mixture of THF and water (4:1, 115 mL). To this solution was added a *tert*-butyl alcohol solution of OsO_4 (2.5 wt %, 3.46 mL, 0.34 mmol) dropwise. After the reaction was stirred for 5 min, $NaIO_4$ was added in several portions. The reaction mixture was stirred overnight. The solids that formed were removed by gravity filtration and the clear filtrate was concentrated to one-fourth of its volume after which time it was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over Na_2SO_4 and then were concentrated under vacuum to give a brown oil, which upon purification by silica gel chromatography gave 0.64 g of aldehyde **11** (33%) along with 0.60 g of intermediate diol **10** (31%).

Method B. In a modified procedure, **9** (0.5 g, 1.77 mmol) was placed in a mixture of THF and water (4:1, 20 mL) to which was added a *tert*-butyl alcohol solution of OsO_4 (2.5 wt %, 0.87 mL, 0.09 mmol) followed by the addition of *N*-methylmorpholine oxide (NMO, 50% aqueous solution, 0.72 g, 2.6 mmol). The reaction was stirred overnight, and then it was quenched with a saturated solution of Na_2SO_3 (15 mL). The reaction was concentrated to remove THF and the aqueous fraction was extracted with EtOAc (3 × 50 mL). The combined EtOAc fractions were washed with 10% citric acid and then dried over Na_2SO_4. Removal of the EtOAc gave a mixture of diastereomeric diols (**10**) as a pale brown thick syrup (0.52 g, 93%). MS (ESI) *m/z* 340.2 $[M + Na]^+$.

To a solution of **10** (0.52 g, 1.64 mmol) in dichloromethane (25 mL) was added $NaIO_4$ adsorbed onto silica gel (3.28 g, 2.0 g of reagent/mmol of diol). The reaction was stirred for 20 min and then it was filtered through a sintered glass funnel. The silica gel was washed with $CHCl_3$ (3 × 20 mL) and the combined organic layers were concentrated to give a quantitative yield of **11**. ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (t, 1H, J = 2.7 Hz), 3.85 (dt, 1H, J = 3.6 and 13.8 Hz), 3.75 (s, 3H), 3.04

(22) A detailed description of methods, basis sets, and standard computational methods can be found in: Forceman, J. B.; Frisch, A. E. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian Inc.: Pittsburgh, PA, 1996.

(23) Heller, B.; Sundermann, B.; Buschmann, H.-J.; Drexler, H.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414−4422.

(ddd, 1H, J = 3.6, 10.2, and 13.8 Hz), 2.80−2.94 (m, 2H), 1.46−1.98 (m, 6H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 174.2 and 171.7, 155.6, 81.4 and 81.6, 62.7 and 62.0, 52.7 and 53.2, 46.4, 41.5, 33.7 and 31.9, 28.5 and 28.2, 23.8, 18.5; MS (ESI) *m/z* 308.1 $[M + Na]^+$; HRMS (ESI) *m/z* 286.1644, $C_{14}H_{23}NO_5 + H^+$ $[M + H]^+$ requires 286.1649.

(2*RS*,4*S*)-2-[[2′-(*RS*)-*N*-(*tert*-Butoxycarbonyl)-2′-carbmethoxypiperidinyl]methyl]thiazolidine-4-carboxylic Acid (12). D-Cysteine·HCl (0.35 g, 2.0 mmol) was dissolved in H_2O (3 mL). NaOH (80 mg, 2.0 mmol) in H_2O (3 mL) was added to the solution followed by a solution of **11** (0.6 g, 2.11 mmol) in 95% EtOH (8.5 mL). The reaction mixture was stirred overnight at room temperature and then it was concentrated under reduced pressure. The white solid that was obtained was partitioned between H_2O and EtOAc. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to give **12** in the form of a white solid and as a mixture of diastereomers (0.7 g, 88%). Mp 77−79 °C; MS (ESI) *m/z* 411.2 $[M + Na]^+$; HRMS (ESI) *m/z* 389.1745, $C_{17}H_{28}N_2O_6S + H^+$ $[M + H]^+$ requires 389.1741.

(2*RS*,4*S*)-2-[[2′-(*RS*)-*N*-(*tert*-Butoxycarbonyl)-2′-carbmethoxypiperidinyl]methyl]thiazolidine-4-carboxylic Acid Methyl Ester (13). To the suspension **11** (0.45 g, 1.58 mmol) in H_2O (5.0 mL) at 0 °C was added solid $NaHCO_3$ (0.13 g, 1.58 mmol) and EtOH (5.0 mL) followed by the addition of D-cysteine methyl ester·HCl (0.27 g, 1.58 mmol) in one portion. The pH of the reaction mixture was adjusted to ca. 7 with 10% $NaHCO_3$ and the reaction was warmed to room temperature. The reaction was stirred for 16 h and the solvents then were removed under vacuum. The residue obtained was dissolved in H_2O (15.0 mL), which was extracted with EtOAc (2 × 35 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to a light yellow oil, which was passed through a small silica gel column with 40% EtOAc in hexanes to give 0.5 g (81.5%) of **13** as a mixture of diastereoisomers. HRMS (ESI) *m/z* 403.1892, $C_{18}H_{30}N_2O_6S + H^+$ $[M + H]^+$ requires 403.1903.

***N*-*tert*-Butoxycarbonyl-2-allylpipecolic Acid Benzyl Ester (14).** To a solution of **8** (3.5 g, 13.0 mmol) in benzene (50 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.94 mL, 13.0 mmol), followed by the dropwise addition of benzyl bromide (1.55 mL, 14.3 mmol). A white precipitate appeared after ca. 10 min. The mixture was refluxed for 3 h after which time the reaction mixture was cooled to room temperature where it was filtered to remove the precipitate. The residue was washed with benzene and EtOAc and the combined filtrates were washed with H_2O, 10% citric acid, 5% $NaHCO_3$, and finally again with H_2O. The organic layer was dried over Na_2SO_4 and it was concentrated to give **14** in a quantitative yield as a pale brown oil. An analytically pure sample for spectral analyses was prepared by purification through flash chromatography with EtOAc/hexanes (1:19) as the eluting solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.37 (m, 5H), 5.87−6.01 (m, 1H), 4.99−5.30 (m, 4H), 3.85 (m, 1H), 2.98−3.08 (m, 1H), 2.92 (dd, 1H, J = 6.8 and 13.2 Hz), 2.64 (dd, 1H, J = 7.2 and 13.2 Hz), 1.47−1.91 (m, 6H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 155.5, 134.4, 128.6, 128.3, 128.2, 127.8, 118.4, 80.6, 66.9, 62.9, 41.4, 39.3, 32.1, 28.7, 23.2, 18.0; HRMS (ESI) *m/z* 382.1993, $C_{21}H_{29}NO_4 + Na^+$ $[M + Na]^+$ requires 382.1989.

***N*-*tert*-Butoxycarbonyl-2-(2-oxoethyl)pipecolic Acid Benzyl Ester (15).** Benzyl ester **14** (4.7 g, 13.1 mmol) was placed in a mixture of THF and H_2O (4:1, 100 mL). To this solution was added a *tert*-butyl alcohol solution of OsO_4 (2.5 wt %, 6 mL, 0.3 mmol) followed by the addition of *N*-methylmorpholine oxide (50% aqueous solution, 5.3 g, 19.6 mmol). The reaction was stirred overnight and then it was quenched with a saturated solution of Na_2SO_3 (15 mL). The reaction mixture was concentrated to remove THF. The residue was extracted with EtOAc, which then was washed with 10% citric acid, followed by H_2O. The organic layer was dried over Na_2SO_4 and it was concentrated to give a mixture of diastereomeric diols as a pale brown thick syrup (5.09 g, 99%). HRMS (ESI) *m/z* 416.2043, $C_{21}H_{31}NO_6 + Na^+$ $[M + Na]^+$ requires 416.2044.

To a solution of the above diol (5.0 g, 12.9 mmol) in dichloromethane (150 mL) was added $NaIO_4$ adsorbed onto silica gel (25.9 g, 2 g of reagent/mmol of diol). The reaction was stirred for 20 min and then it was filtered through a sintered glass funnel. The silica gel was washed with $CHCl_3$ (3 × 30 mL). The combined organic layers were concentrated to give 4.8 g of the crude aldehyde, which was purified by column chromatography (EtOAc/hexanes, 1:2) to give **15** in a 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (t, 1H, J = 3.0 Hz), 7.28−7.45 (m, 5H), 5.18 (dd, 2H, J = 12.3 and 16.2 Hz), 3.84 (dt, 1H, J = 4.2 and 13.8 Hz), 3.0−3.15 (m, 1H), 2.93 (d, 2H, J = 3.0 Hz), 1.22−1.98 (m, 6H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 173.5, 159.1, 128.8, 128.5, 128.4, 100.4, 67.5, 62.8, 46.6, 41.7, 33.8, 28.5, 23.8, 18.5; HRMS (ESI) *m/z* 384.1775, $C_{20}H_{27}NO_5 + Na^+$ $[M + Na]^+$ requires 384.1782.

3-Hydroxy-1-oxo-2-oxa-6-(*N*-*tert*-butoxycarbonyl)-azaspiro[4.5]decane (17). To a flask containing **15** (2.0 g, 5.54 mmol) dissolved in benzene (40 mL) was added 10% Pd/C (0.40 g, 20 mol % by wt). The mixture was stirred vigorously under a hydrogen atmosphere overnight. The reaction mixture was filtered through a plug of Celite, which was then washed copiously with EtOAc. The combined filtrates were concentrated to give the corresponding debenzylated product **16**, which spontaneously cyclized to the corresponding hydroxy lactone **17**. Mp 147−150 °C; IR (film) 1694, 1775, 3380 (br) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.1 (OCHOH); HRMS (ESI) *m/z* 294.1306, $C_{13}H_{21}NO_5 + Na^+$ $[M + Na]^+$ requires 294.1312.

(2*RS*,4*S*)-2-[[2′-(*RS*)-*N*-(*tert*-Butoxycarbonyl)-2′-carboxypiperidinyl]methyl]thiazolidine-4-carboxylic Acid Methyl Ester (18). To the suspension of **17** (5.7 g, 21.0 mmol) in H_2O (57.0 mL) at 0 °C was added solid $NaHCO_3$ (1.76 g, 31.0 mmol) and ethanol (57 mL) followed by the addition of D-cysteine methyl ester·HCl (3.61 g, 21.0 mmol) in one portion. The pH of the reaction mixture was adjusted to ca. 7 with 10% $NaHCO_3$ and the reaction was warmed to room temperature. The reaction was stirred for 16 h and the solvents were removed under vacuum. The resulting residue was dissolved in H_2O (50 mL) and this solution was extracted with EtOAc (2 × 100 mL). The pH of the aqueous layer was adjusted to 6 with 1 N HCl and then it was extracted with more EtOAc. To facilitate the partitioning of the thiazolidine product into the organic solvent, the aqueous layer was saturated with solid NaCl and then it was extracted with $CHCl_3$. This process was repeated three times with readjustment of the pH to 6 between extractions. The combined organic layers were dried over anhydrous Na_2SO_4 and then they were concentrated to give the diastereomeric mixture of crude thiazolidines as an off white foam (6.0 g, 75%). MS (ESI) *m/z* 411.2 $(M + Na)^+$; HRMS (ESI) *m/z* 389.1730, $C_{17}H_{28}N_2O_6S + H^+$ $[M + H]^+$ requires 389.1741.

Methyl (3′*S*,6′*R*,7′a*R*)-, (3′*S*,6′*S*,7′a*R*)-, (3′*S*,6′*S*,7′a*S*)-, or (3′*S*,6′*R*,7′a*S*)-1-(*tert*-Butoxycarbonyl)tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (4a−d). To a solution of the thiazolidine mixture **18** (3.0 g, 7.73 mmol) in freshly distilled CH_2Cl_2 (550 mL) was added 2-chloro-1-methylpyridinium iodide (2.17 g, 8.5 mmol) followed by Et_3N (2.37 mL, 17.0 mmol). The resulting pale yellow solution was heated at reflux for 8 h under an Ar atmosphere. The reaction mixture was cooled to room temperature and then it was extracted with 10% citric acid, 1 N $NaHCO_3$, and brine. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and subsequent removal of solvent gave a mixture of four diastereomers, **4a**−**d**, as a thick yellow oil (TLC (EtOAc/hexanes, 1:1) R_f 0.75, 0.58, 0.51 and 0.48), along with the byproduct of the Mukaiyama's catalyst 1-methyl-1*H*-pyridin-2-one. Separation of the isomers was carried out on a Ready Sep prepacked silica gel column by eluting with EtOAc/

hexanes (1:3). Isomer **4a** was obtained as a white solid (18%), which on recrystallization from hot hexane gave long white needles. Further elution gave isomer **4b** as a thick syrup (21%) followed by isomers **4c** (12%) and **4d** (10%) with each of the latter two contaminated with the byproduct of Mukaiyama's catalyst.

Isomer 4a: mp 116−119 °C; $[\alpha]^{20}_D$ +108.5 (*c* 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (d, 1H, J = 7.5 Hz), 5.13 (dd, 1H, J = 3.3 and 7.5 Hz), 3.90 (dt, 1H, J = 4.2 and 12.9 Hz), 3.29 (dd, 1H, J = 3.6 and 11.1 Hz), 3.71 (s, 3H), 3.22 (dd, 1H, J = 7.5 and 11.1 Hz), 2.83 (ddd, 1H, J = 4.2, 10.2, and 13.2 Hz), 2.44 (d, 1H, J = 13.8 Hz), 2.32 (dd, 1H, J = 7.8 and 13.8 Hz), 1.38 (s, 9H), 1.55−1.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 170.3, 155.1, 81.6, 63.2, 62.8, 59.4, 52.9, 42.8, 36.4, 34.5, 32.9, 28.5, 24.0, 18.9; HRMS (ESI) *m/z* 393.1458, $C_{17}H_{26}N_2O_5S + Na^+$ $[M + Na]^+$ requires 393.1455. Anal. Calcd for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56; S, 8.66. Found: C, 55.26; H, 7.14; N, 7.68; S, 8.46.

Isomer 4b: $[\alpha]^{20}_D$ +262.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (br s, 1H), 5.02 (t, 1H, J = 6.9 Hz), 3.84 (dt, 1H, J = 4.2 and 12.6 Hz), 3.69 (s, 3H), 3.48 (dd, 1H, J = 7.2 and 10.5 Hz), 3.25 (dd, 1H, J = 1.8 and 10.8 Hz), 2.79 (m, 1H), 2.67 (dd, 1H, J = 7.2 and 12.3 Hz), 2.19 (dd, 1 H, J = 6.6 and 12.3 Hz), 1.50−1.90 (m, 6H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 170.3, 155.6, 81.0, 65.5, 61.1, 58.9, 53.0, 43.2, 39.0, 35.3, 32.8, 28.6, 23.8, 19.4; HRMS (ESI) *m/z* 393.1439, $C_{17}H_{26}N_2O_5S + Na^+$ $[M + Na]^+$ requires 393.1455. Anal. Calcd for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56; S, 8.66. Found: C, 55.27; H, 7.20; N, 7.40; S, 8.41.

Isomer 4c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (t, 1H, J = 6.0 Hz), 4.32 (d, 1H, J = 6.9 Hz), 3.90 (dt, 1 H, J = 4.2 and 13.5 Hz), 3.76 (s, 3H), 3.57 (dd, 1 H, J = 7.5 and 12.6 Hz), 3.33 (dd, 1H, J = 2.4 and 12.6 Hz), 2.8−2.9 (m, 1H), 2.20−2.45 (m, 2H), 1.60−2.10 (m, 6H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 169.3, 155.5, 81.2, 65.7, 64.8, 57.2, 52.9, 42.9, 39.0, 35.8, 34.8, 28.6, 24.1, 18.8; MS (ESI) *m/z* 393.2 $[M + Na]^+$; HRMS (ESI) *m/z* 371.1648, $C_{17}H_{26}O_5N_2S + H^+$ $[M + H]^+$ requires 371.1656.

Isomer 4d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (t, 1H, J = 6.9 Hz), 3.99 (t, 1H, J = 6.9 Hz), 3.7−3.7 (m, 1H), 3.79 (s, 3H), 3.53 (dd, 1H, J = 7.2 and 11.1 Hz), 3.27 (dd, 1 H, J = 6.6 and 11.1 Hz), 2.90−3.10 (m, 1H), 2.53 (d, 1H, J = 7.2 Hz), 1.55−1.95 (m, 6H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 168.2, 155.2, 80.9, 66.1, 62.1, 59.2, 52.9, 42.5, 37.5, 36.1, 32.1, 28.7, 23.6, 18.6; MS (ESI) *m/z* 393.2 $[M + Na]^+$; HRMS (ESI) *m/z* 393.1452, $C_{17}H_{26}O_5N_2S + Na^+$ $[M + Na]^+$ requires 393.1455.

Methyl [3′*S*,6′*R*,7′a*R*]-1-[[1-(*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (19a). Compound **4a** (0.1 g, 0.27 mmol) was treated with 4 N HCl in dioxane under Ar for 3 h. Solvent and excess HCl were removed under vacuum. The white solid obtained was thoroughly dried and used for the following coupling reaction.

Method A. The amine HCl salt (83 mg, 0.27 mmol) was dissolved in dry DMF (3 mL) and to this solution was added Boc-L-Pro-OH (0.40 mg, 1.9 mmol), DCC (390 mg, 1.9 mmol), and HOBt·H_2O (255 mg, 1.9 mmol) followed by triethylamine (56 μL, 0.27 mmol). The reaction mixture was stirred under an Ar atmosphere for 4 days. The excess DMF was removed under reduced pressure and the residue remaining was dissolved in EtOAc. The solution was filtered to remove the undissolved solids and the filtrate was washed successively with 1 N $NaHCO_3$, H_2O, 10% citric acid, 1 N $NaHCO_3$, H_2O, and finally brine. The organic layer was dried over Na_2SO_4 and then it was evaporated under reduced pressure to give the crude product. This material was chromatographed on a silica gel column with 2% MeOH in EtOAc to give 55 mg (50%) of **19a** as a thick glassy syrup.

Method B. The amine HCl salt (60 mg, 0.195 mmol) was dissolved in dry DMF (5.0 mL). To this solution was added Mukaiyama's catalyst (124 mg, 0.49 mmol) followed by the addition of Boc-L-Pro-OH (105 mg, 0.49 mmol) and Hunig's base (204 μL, 1.17 mmol). The reaction mixture was stirred overnight under an inert atmosphere after which time it was concentrated to remove excess DMF. EtOAc was added to the residue and the mixture was filtered to remove the undissolved solids. The filtrate was dried over anhydrous Na_2SO_4 and then it was concentrated. The residue was purified by silica gel chromatography with 2% MeOH in EtOAc to give 64 mg (70%) of **19a** as a glassy syrup. $[\alpha]^{20}_D$ + 65.1 (*c* 2.2, $CHCl_3$). ^{1}H and ^{13}C NMR showed the presence of rotamers about the carbamate bond in a ratio of 7:3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (m, 1H) and 5.31 (m, 1H), 4.51 and 4.57 (dd, 1H, J = 3.3 and 8.0 Hz), 3.75 and 3.82 (m, 1H), 3.71 and 3.72 (s, 3H), 3.16−3.56 (m, 5H), 2.52 (m, 1H), 2.35 (m, 1H), 1.48−2.2 (m, 10H), 1.37 and 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 and 176.6, 174.3 and 173.4, 170.5 and 170.4, 154.8 and 153.8, 79.7 and 79.6, 63.3 and 63.2, 63.0, 59.3 and 59.1, 57.2 and 56.7, 53.2 and 53.1, 47.2 and 46.9, 43.2 and 44.2, 36.3, 33.8 and 33.5, 33.4 and 33.0, 31.1 and 30.4, 28.9 and 28.8, 24.8 and 23.9, 24.1 and 23.7, 18.6 and 18.0; HRMS (ESI) *m/z* 490.1991, $C_{22}H_{33}N_3O_6S + Na^+$ $[M + Na]^+$ requires 490.1983.

Methyl [3′*S*,6′*S*,7′a*R*]-1-[[1-(*tert*-Butoxycarbonyl)-2-(*S*)-pyrrolidinyl]carbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (19b). Compound **4b** (40 mg, 0.11 mmol) was treated with 4 N HCl in dioxane (2 mL) under Ar for 3 h. Solvent and excess HCl were removed under vacuum. The white solid obtained was thoroughly dried and used for the coupling reaction. The amine HCl salt (30 mg, 0.098 mmol) was dissolved in dry DMF (3.0 mL). Mukaiyama's catalyst (63.0 mg, 0.24 mmol) was added followed by the addition of Boc-L-Pro-OH (53 mg, 0.24 mmol) and Hunig's base (102 μL, 0.58 mmol). The reaction mixture was stirred overnight under an Ar atmosphere. The reaction was worked up as described for **19a**. Column chromatographic purification afforded 34.5 mg (75.5%) of pure **19b**. $[\alpha]^{20}_D$ +5.7 (*c* 2.52, $CHCl_3$). ^{1}H and ^{13}C NMR showed the presence of rotamers about the carbamate bond in a ratio of 9:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (d, 1H, J = 6.0 Hz), 5.05 (t, 1H, J = 7.2 Hz), 4.47 (dd, 0.9H, J = 3.9 and 8.7 Hz) and 4.64 (br d, 0.1H), 3.62 (s, 3H), 3.7 (m, 1H), 3.51 (dd, 1H, J = 6.9 and 10.5 Hz), 3.32−3.48 (m, 3H), 3.19 (dd, 1H, J = 1.2 and 10.5 Hz), 3.04 (dt, 1H, J = 6.9 and 12.9 Hz), 2.61 (dd, 1H, J = 7.5 and 12.9 Hz), 2.15 (dd, 1H, J = 6.3 and 12.9 Hz), 1.62−2.12 (m, 9H), 1.37 and 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer) δ 173.8, 172.4, 170.4, 154.3, 80.5, 64.8, 60.8, 59.9, 57.9, 52.9, 46.7, 42.6, 40.3, 34.8, 31.9, 30.0, 28.3, 23.9, 23.8, 18.2; HRMS (ESI) *m/z* 490.1979, $C_{22}H_{33}N_3O_6S + Na^+$ $[M + Na]^+$ requires 490.1983. Anal. Calcd for $C_{22}H_{33}N_3O_6S$: C, 56.51; H, 7.11; N, 8.99; S, 6.86. Found: C, 56.60; H, 6.94; N, 8.68; S, 6.47.

[3′*S*,6′*R*,7′a*R*]-1-[[(1-*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxamide (20a). Spiro bicyclic ester **19a** (55 mg, 0.12 mmol) was treated with a saturated solution of NH_3 (prepared by bubbling a stream of NH_3 into MeOH at −78 °C for about 15 min). The reaction mixture was closed with a balloon and the flask was warmed to room temperature where it was stirred until the reaction was complete. After about 8 h, Ar was bubbled through the reaction mixture to remove the excess NH_3. The solution was concentrated to give crude **20a**, which upon purification by silica gel chromatography with 2−5% MeOH in EtOAc as the eluting solvent gave 43 mg (81%) of **20a**. Mp 226−228 °C; $[\alpha]^{20}_D$ +56.1 (*c* 2.31, $CHCl_3$). ^{1}H and ^{13}C NMR showed the presence of rotamers about the carbamate bond in a ratio of 7:3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 and 7.28 (br s, 1H), 5.5 (br s, 1H), 5.05 (m, 1H), 4.8 (dd, 1H, J = 5.1 and 8.4 Hz), 4.5−4.65 (m, 1H), 3.8 (m, 1H), 3.10−3.66 (m, 5H), 2.43 (dd, 0.3H, J = 7.8 and 13.8 Hz) and 2.59 (dd, 0.7H, J = 7.8 and 13.8 Hz), 2.20 (dd, 0.7H, J = 3.9 and 14.1 Hz) and 2.31 (dd, 0.3H, J = 3.9 and 14.1 Hz), 1.46−2.16 (m, 10H), 1.35 and 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 and 174.1, 173.7 and 173.3, 172.3 and172.0, 153.8 and 154.6, 79.8 and 79.7, 65.3 and 64.9,

62.7 and 62.5, 57.8 and 57.7, 57.1 and 57.6, 44.2 and 46.8, 35.0 and 34.4, 36.2 and 36.4, 30.2 and 31.1, 28.8 and 28.9, 24.8 and 23.9, 24.3 and 23.6, 18.7 and 18.1; HRMS (ESI) *m/z* 475.2000, $C_{21}H_{32}N_4O_5S + Na^+$ $[M + Na]^+$ requires 475.1986. Anal. Calcd for $C_{21}H_{32}N_4O_5S$: C, 55.73; H, 7.13; N, 12.38; S, 7.09. Found: C, 55.43; H, 6.90; N, 12.38; S, 6.71.

[3′*S*,6′*S*,7′a*R*]-1-[[(1-*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxamide (20b). Spiro bicyclic ester **19b** (60 mg, 0.13 mmol) was treated with 30 mL of a saturated methanolic solution of NH_3 for 8 h. Concentration followed by column purification afforded 45 mg of pure product (77.5%) as a white solid. An analytically pure sample was prepared by crystallization from EtOAc and Et_2O. Mp 140−142 °C; $[\alpha]^{20}_D$ +42.6 (*c* 1.69, $CHCl_3$). ^1H and ^{13}C NMR showed the presence of rotamers about the carbamate bond in a ratio of 7:3. ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 and 7.06 (br s, 1H), 5.91 and 5.93 (br s, 1H), 4.98 (t, 1H, J = 6.9 Hz), 4.82−4.88 (m, 1H), 4.48 (dd, 0.7H, J = 3.9 and 8.4 Hz) and 4.60 (m, 0.3H), 3.28−3.62 (m, 4H), 3.03 (m, 1H), 2.62 (dd, 1H, J = 8.0 and 12.4 Hz), 1.59−2.4 (m, 12H), 1.39 and 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 and 175.4, 172.4 and 172.2, 172.0 and 171.7, 154.1 and 154.6, 80.4 and 80.2, 65.1 and 65.5, 61.3 and 61.7, 61.1 and 60.3, 57.8 and 57.9, 46.7 and 47.1, 42.8 and 43.1, 39.3 and 38.4, 34.3 and 34.8, 32.1 and 31.8, 29.9 and 28.9, 28.3 and 28.8, 23.9 and 24.3, 23.8 and 23.7, 18.4 and 18.6; HRMS (ESI) *m/z* 475.2001, $C_{21}H_{32}N_4O_5S + Na^+$ $[M + Na]^+$ requires 475.1986. Anal. Calcd for $C_{21}H_{32}N_4O_5S$: C, 55.73; H, 7.13; N, 12.38; S, 7.09. Found: C, 56.14; H, 6.97; N, 12.12; S, 6.92.

(3′*S*,6′*R*,7′a*R*)-1-[(2*S*)-2-Pyrrolidinylcarbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazoline]-3′-carboxamide Hydrochloride (21a). Spiro bicyclic amide **20a** (45 mg, 0.1 mmol) was treated with 4 N HCl in dioxane (3 mL) for 8 h under an Ar atmosphere. The solvent and excess HCl were removed in vacuo. The resulting residue was twice suspended in CH_2Cl_2 and the mixture was stripped of solvent. A white solid was obtained, which was dissolved in water and the solution then lyophilized to give a white hygroscopic solid in quantitative yield. $[\alpha]^{20}_D$ +93.6 (*c* 1.06, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 5.24 (dd, 1H, J = 2.7 and 7.8 Hz), 4.60−4.78 (m, 2H), 3.75 (dt, 1H, J = 4.5 and 13.5 Hz), 3.55 (dd, 1H, J = 8.4 and 11.4 Hz), 3.43 (dd, 1H, J = 5.4 and 11.4 Hz), 3.22−3.28 (m, 3H), 2.66 (d, 1H, J = 8.1 and 14.4 Hz), 2.52 (m, 1H), 2.47 (dd, 1H, J = 3.0 and 14.4 Hz), 1.52−2.05 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.5, 174.3, 170.6, 66.2, 64.4, 60.7, 39.9, 47.4, 44.7, 37.1, 35.1, 34.6, 30.1, 25.0, 24.4, 18.8; HRMS (ESI) *m/z* 353.1643, $C_{16}H_{24}N_4O_3S + H^+$ $[M + H]^+$ requires 353.1641.

(3′*S*,6′*S*,7′a*R*)-1-[(2*S*)-2-Pyrrolidinylcarbonyl]tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazoline]-3′-carboxamide Hydrochloride (21b). Spiro bicyclic amide **20b** (40 mg, 0.088 mmol) was treated with 4 N HCl−dioxane (3 mL) for 8 h under an N_2 atmosphere. The solvent and excess HCl were removed under reduced pressure. The residue was twice suspended in CH_2Cl_2 and the mixture stripped of solvent to give a white solid, which was dried under vacuum to give a white hygroscopic solid (35 mg, 100%). $[\alpha]^{20}_D$ +68.2 (*c* 0.61, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 5.15 (t, 1H, J = 7.2 Hz), 5.09 (dd, 1H, J = 2.4 and 6.6 Hz), 4.64 (t, 1H, J = 7.8 Hz), 3.76 (dt, 1H, J = 4.2 and 12.9 Hz), 3.48 (dd, 1H, J = 6.6 and 10.5 Hz), 3.28−3.42 (m, 3H), 3.23 (dd, 1H, J = 3.9 and 13.2 Hz), 2.89 (dd, 1H, J = 7.5 and 12.9 Hz), 2.48 (m, 1 H), 2.24 (dd, 1H, J = 6.6 and 12.6 Hz), 1.60−2.18 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 172.1, 169.5, 67.3, 61.9, 60.4, 60.3, 47.5, 43.9, 40.4, 35.2, 32.1, 29.3, 25.2, 24.1, 18.6; HRMS (ESI) *m/z* 353.1640, $C_{16}H_{24}N_4O_3S + H^+$ $[M + H]^+$ requires 353.1641.

Methyl [3′*S*,6′*R*,7′a*R*]-Tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (22). Compound **4a** (60 mg, 0.27 mmol) was treated with 4 N HCl in dioxane (0.5 mL) under Ar for 3 h. Solvent and excess HCl were removed under vacuum to give **22**·HCl. $[\alpha]^{20}_D$ + 180 (*c* 0.31, MeOH); ^1H NMR (300 MHz, MeOH-d_4) δ 5.29 (dd, 1H, J = 2.4 and 7.5 Hz), 5.07(dd, 1H, J = 5.1 and 8.4 Hz), 3.79 (s, 3H), 3.62 (dd, 1H, J = 8.7 and 11.7 Hz), 3.46 (dd, 1 H, J = 5.1 and 11.7 Hz), 3.39 (dt, 1H, J = 2.4 and 12.9 Hz), 3.1−3.24 (m, 1H), 2.81 (dd, 1 H, J = 7.8 and 15.3 Hz), 2.63 (dd, 1H, J = 2.4 and 15.3 Hz), 1.60−2.10 (m, 6H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 172.8, 170.8, 64.4, 63.8, 59.6, 53.5, 42.7, 37.1, 33.2, 32.5, 22.5, 18.9. The white hygroscopic solid obtained was suspended in EtOAc and Hunig's base was added until the pH of the reaction mixture was basic. The reaction mixture was concentrated and the residue was dried thoroughly. It was purified by column chromatography with 2% MeOH in EtOAc to give 43 mg (93%) of **22**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, 1H, J = 3.9 and 7.5 Hz), 5.05 (dd, 1H, J = 4.8 and 7.2 Hz), 3.74 (s, 3H), 3.30−3.45 (m, 2H), 3.05 (dt, 1H, J = 3.6 and 12.9 Hz), 2.66−2.78 (m, 1H), 2.57 (dd, 1H, J = 7.2 and 13.8 Hz), 2.2 (dd, 1H, J = 3.9 and 13.8 Hz), 1.4−2.0 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 170.2, 63.4, 63.1, 57.8, 53.2, 42.8, 38.4, 36.5, 34.5, 26.4, 20.8; HRMS (ESI) *m/z* 271.1123, $C_{12}H_{18}N_2O_3S + H^+$ $[M + H]^+$ requires 271.1111.

Methyl [3′*S*,6′*S*,7′a*R*]-Tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (23). A similar procedure to that used for the deprotection of **4a** was used. Compound **4b** (50 mg, 0.14 mmol) was treated with 0.5 mL of 4 N HCl/dioxane. Treatment with Hunig's base followed by column chromatographic purification with 2% MeOH in EtOAc gave 34 mg (89%) of **23** as pale brown thick syrup. $[\alpha]^{20}_D$ +173.6 (*c* 1.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.02−5.13 (m, 2H), 3.75 (s, 3H), 3.27−3.38 (m, 2H), 3.15 (dt, 1H, J = 4.2 and 13.2 Hz), 2.75 (dd, 1H, J = 6.9 and 13.2 Hz), 2.6 (m, 1H), 2.07 (dd, 1H, J = 6.0 and 12.9 Hz), 1.90 (br s, 1H), 1.40−1.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 170.1, 63.7, 62.5, 57.6, 53.2, 42.4, 41.4, 35.9, 33.2, 26.2, 21.2; HRMS (ESI) *m/z* 271.1120, $C_{12}H_{18}N_2O_3S + H^+$ $[M + H]^+$ requires 271.1111.

Methyl [3′*R*,6′*S*,7′a*R*]-Tetrahydro-5′-oxospiro[piperidine-2,6′-pyrrolo[2,1-*b*]thiazolidine]-3′-carboxylate (24). Fifty milligrams of **4c** (contaminated with 1-methyl-1*H*-pyridin-2-one) was treated with 4 N HCl/dioxane. The HCl salt obtained was dissolved in MeOH and an aqueous ammonia solution (0.1 mL) was added. The reaction was stirred overnight. The reaction mixture was concentrated and the residue was dried. Column chromatography of the residue with 2% MeOH in EtOAc gave 12 mg of **23** and 11 mg of **24**. $[\alpha]^{20}_D$ +16.7 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, 1H, J = 3.9 and 7.5 Hz), 5.05 (dd, 1H, J = 4.8 and 7.2 Hz), 3.74 (s, 3H), 3.30−3.45 (m, 2H), 3.05 (dt, 1H, J = 3.6 and 12.9 Hz), 2.66−2.78 (m, 1H), 2.57 (dd, 1H, J = 7.2 and 13.8 Hz), 2.2 (dd, 1H, J = 3.9 and 13.8 Hz), 1.4−2.0 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 170.2, 63.4, 63.1, 57.8, 53.2, 42.8, 38.4, 36.5, 34.5, 26.4, 20.8; HRMS (ESI) *m/z* 271.1099, $C_{12}H_{18}N_2O_3S + H^+$ $[M + H]^+$ requires 271.1111.

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Supporting Information Available: General experimental procedures; proton and carbon NMR spectra of **4a**−**d**, **8**, **9**, **11**, **14**, **15**, **17**, **19a**,**b**, **20a**,**b**, **21a**,**b**, **22**, **22**·HCl, **23**, and **24**; 2D-NOESY spectra of **4c** and **4d**; 1D NOE spectra for **24**; X-ray structure data for compounds **4a, 20a**, and **20b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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