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Diastereoselective Synthesis of 4,5′-Bis-proline Compounds via Reductive Dimerization of *N*-Acyloxyiminium Ions

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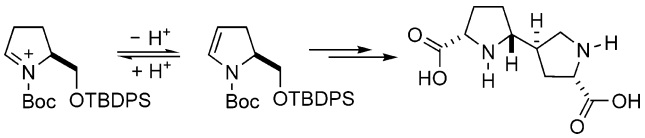

A short, practical synthesis of novel, unsymmetrical 4,5′-bis-proline compounds has been achieved, highlighted by the application of an unprecedented samarium diiodide-driven regio- and diastereocontrolled reductive dimerization of *N*-acyloxyiminium ions generated from readily available 2-methoxy-5-silyloxymethyl-*N*-Boc pyrrolidines. The title proline dimers proved to be pertinent metal-free catalysts in aldol and Mannich reactions.

Carbon−carbon-linked bis-proline compounds exemplified by the formulas **1**−**4** in Figure 1 may be of interest for several reasons. Their dual array of secondary amine and carboxylic functionalities embodied onto a flexible bis-pyrrolidine scaffold holds the prospect of binding to functional molecules and metal ions provided that proper alignment of the donor and acceptor sites is attainable. Also, should an orthogonal protection of the amino and carboxyl termini be realized, grafting such dimeric diamino diacid units onto specific peptide sequences would alter the regular folding patterns of the biomolecule eliciting unpredictable yet useful levels of structural and operational complexity.[1] Furthermore, coexistence within a single structure of two stereochemically defined proline subunits which are pertinent to recognition and catalysis could illuminate the important theme of molecular synergism and co-operativity.[2]

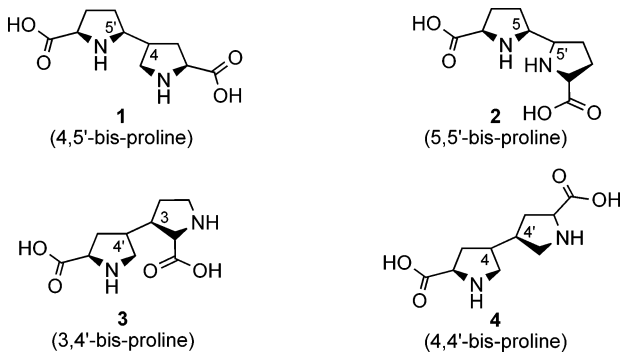

FIGURE 1. Representative members of the carbon−carbon-linked bis-proline family. Atom numbering refers to proline nucleus.

However, in spite of the intriguing nature of this compound class and the considerable promise offered by them, it is quite surprising that the synthesis and use of these entities have been substantially neglected.

Herein, we define a streamlined route to unsymmetrical bis-proline structures of type **1** by exploiting a samarium diiodide-driven regio- and diastereocontrolled reductive dimerization of *N*-acyloxyiminium ions.[3]

In order to join the two pyrrolidine nuclei of our targets with a robust carbon−carbon bond, we were inspired by the notorious enamine−iminium ion coupling reaction that Nature exploits to forge diverse bicyclic and polycyclic alkaloidal architectures.[4] We set about this project with protected 5(*S*)-configured hemiaminal **6**, whose access from L-glutamic acid-derived hydroxymethylpyrrolidinone **5** is illustrated in Scheme 1 (85% yield over four steps).

We surmised that treatment of an hemiaminal structure of type **I** with a Lewis acid promoter would generate a transient *N*-acyloxyiminium species **II** that rapidly equilibrates to ene−carbamate **III** via deprotonation (Scheme 2). If conditions were found for the donor and acceptor partners **II** and **III** to couple each other, rapid access to bis-pyrrolidine systems of type **IV** would be at hand. However, to stop the reaction cascade at the level of the bicyclic adducts, a reductant would have to be added to the reaction system prior to hydrolytic quenching, which irreversibly traps the binuclear iminium educt **IV**, eventually producing neutral 2,3′-linked bis-pyrrolidines of type **V**.

Although the first attempts to put into practice this subtle operation proved elusive (Table 1, entries 1−3), optimal conditions were finally established (entry 8) consisting of adopting a short silyl triflate-initiated equilibrium period which

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(1) For excellent reviews on peptidomimetic chemistry, see: (a) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; JAI Press: Stamford, CT, 1999; Vol. 2. (b) Synthesis of Peptides and Peptidomimetics. In *Houben-Weyl, Methods of Organic Chemistry*, 4th ed.; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme Verlag: Stuttgart, 2003; Vol. E22c.

(2) (a) Wright, D.; Usher, L. *Curr. Org. Chem.* **2001**, *5*, 1107−1131. (b) Gianneschi, N. C.; Masar, M. S., III; Mirkin, C. A. *Acc. Chem. Res.* **2005**, *38*, 825−837.

(3) Few examples of enamine−iminium ion dimerization reactions have been reported: (a) Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, H.; Matsubara, R. *Org. Lett.* **2006**, *8*, 4923−4925. (b) Hong, B.-C.; Wu, M. F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217−2220. (c) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082−2087. See also: Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.

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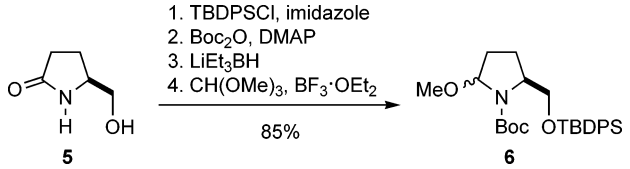
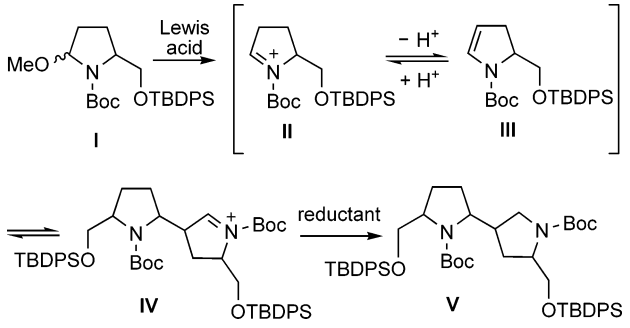
SCHEME 1. Preparation of Hemiaminal 6



SCHEME 2. Access to Carbon−Carbon-Linked Bis-pyrrolidine Systems via Reductive Dimerization of Pyrrolidinium Species



was followed by in situ reductive blockage with samarium diiodide in THF and final quenching.[5,6]

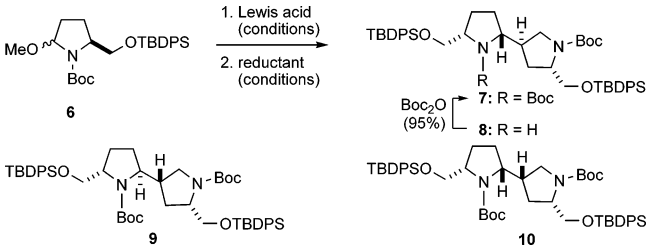
In the event, we were pleased to find that by strictly adhering to this protocol, the reductive dimerization of hemiaminal **6** occurred with high margins of regio- and diastereocontrol to produce (2*R*,3′*R*,5*S*,5′*S*)-2,3′-bipyrrolidine **7** predominantly (55% isolated yield), accompanied by minor amounts of partially deprotected counterpart **8** (15%), which could nicely converted to **7** by simple reprotection (Boc_2O, Et_3N, 95%). Marginal amounts of two other diastereoisomers were also recovered, to which stereostructures **9** and **10** were attributed as shown.

Inspection of the results in Table 1 reveals that balancing of reaction time and temperature is critical for the success of the reaction. In particular, the reaction gave the best results using a 5 min iminium ion equilibrium period at −15 °C before addition of the reducing samarium reagent in order for unsaturated dimers or saturated monomeric byproducts to be minimized (entries 4−7 vs 8).

The structural assignment of the *N*-Boc-protected binuclear pyrrolidines **7** and **8** by NMR analyses proved troublesome due to the occurrence of multiple backbone rotamers; therefore, removal of the carbamoyl fragments was planned. Gratifyingly, the *N*,*N*-deprotected counterpart, which quantitatively derived from **7** and **8** by TFA treatment, furnished readable 1D- and 2D-NMR spectra from which a firm stereostructural assignment was secured (Figure S1, Supporting Information).[7]

Apparently, during the crucial carbon−carbon coupling reaction, both the ene−carbamate component and the *N*-acyloxyiminium ion approached each other in a facially selective manner to avoid repulsive interactions with the bulky silyloxymethyl and carbamoyl substituents. Consistent with open transition-state models in Figure 2, for the donor ene−carbamate component a simple 1,3-asymmetric induction operates to favor the attack on the *re* face, whereas in the acceptor component a 1,2-induction is favored probably arising from the transmittal of the stereodirecting information of the stereogenic center onto the proximal carbamate protecting group (*si* face attack preferred).[8] In addition, in the preferred model, one can envision a favorable antiperiplanar attack of the enecarbamate moiety to the iminium ion which would allow good orbital overlap.

TABLE 1. Optimizing the Reductive Dimerization of Hemiaminal 6



entry	Lewis acid (conditions)	reductant (conditions)	yield[a] (%) 7	yield[a] (%) 8	dr 7 + 8: 9:10
1	TBSOTf, 1.0 equiv (THF, −15 °C, 20 min)	$NaBH_4$, 2.0 equiv (−15 °C, 60 min)		10[b]	
2	BF_3·OEt_2, 1.0 equiv (THF, −15 °C, 20 min)	$NaBH_4$, 2.0 equiv (−15 °C, 60 min)	3[c]		
3	TBSOTf, 1.0 equiv (THF, −15 °C, 20 min)	H_2, Pd/C (−10 °C, 120 min)			
4	TBSOTf, 1.0 equiv (THF, −15 °C, 20 min)	SmI_2, 2.0 equiv[d] (−15 °C, 120 min)	19[b]	30	6:1.5:1
5	TBSOTf, 1.0 equiv (THF, −80 °C, 20 min)	SmI_2, 2.0 equiv[d] (−80 to −30 °C, 90 min)	*b*,*c*		
6	TBSOTf, 1.0 equiv (THF, rt, 10 min)	SmI_2, 2.0 equiv[d] (rt, 30 min)		40[b]	
7	TBSOTf, 1.0 equiv (THF, −15 °C, 1 min)	SmI_2, 2.0 equiv[d] (−15 °C, 5 min)	50[b,c]	5	6:1.6:1
8	TBSOTf, 1.5 equiv (THF, −15 °C, 5 min)	SmI_2, 1.5 equiv[d] (−15 °C, 5 min)	55	15	20:2:1

[a] Isolated yields. [b] Mixtures of dimeric unsaturated compounds (m/z = 875.5) were also detected, whose identification was not pursued. [c] Significant amounts of (*S*)-1-(*tert*-butoxycarbonyl)-2-(*tert*-butyldiphenylsilanyloxymethyl)pyrrolidine formed. [d] Quenching procedure: aq $Na_2S_2O_3$ was added to the reaction mixture, and the aqueous phase was extracted with EtOAc. See the Experimental Section for details.

With the preparation of bis-pyrrolidine **7** secured, advancement to bis-proline **14** only required minimal structural modification, that is oxidation of the two primary carbinol ends to carboxylic functions and dismantling of the two pyrrolidine *N*-Boc protective groups. Thus, as depicted in Scheme 3, dimer **7** was almost quantitatively desilylated to diol **11**, which was subjected to conventional Swern oxidation.[9] Stable bis-aldehyde **12** was formed (91% isolated yield) that was further oxidized to protected diacid **13** ($NaClO_2$, NaH_2PO_4; 90% yield). Finally, acidic treatment (6 N aq HCl, dioxane) quantitatively converted **13** into the targeted bis-proline **14**, which was isolated as its water-soluble bis-hydrochloride salt. Preparation of the free

(5) While various Lewis acids may be successfully employed to generate iminium ions in situ from *N*,*O*-acetals (e.g., TBSOTf, TMSOTf, BF_3·OEt_2), the choice of the reducing agent (SmI_2) proved to be critical, as shown in Table 1.

(6) Unsatisfactory results were obtained when other solvents mixtures with coordinating additives were employed (e.g., THF/HMPA, THF/DMPU).

(7) Similarly, the stereostructures of minor isomers **9** and **10** were ascertained by 1D- and 2D-NMR analysis of the corresponding N,N-deprotected compounds. See the Supporting Information.

(8) For a description of the chiral relay principle, see: (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501−1506. (b) Hopman, J. C. P.; van den Berg, E.; Ollero Ollero, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315−4318. (c) Clayden, J.; Lund, A.; Vellverdù, L.; Helliwell, M. *Nature* **2004**, *431*, 966−971.

(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

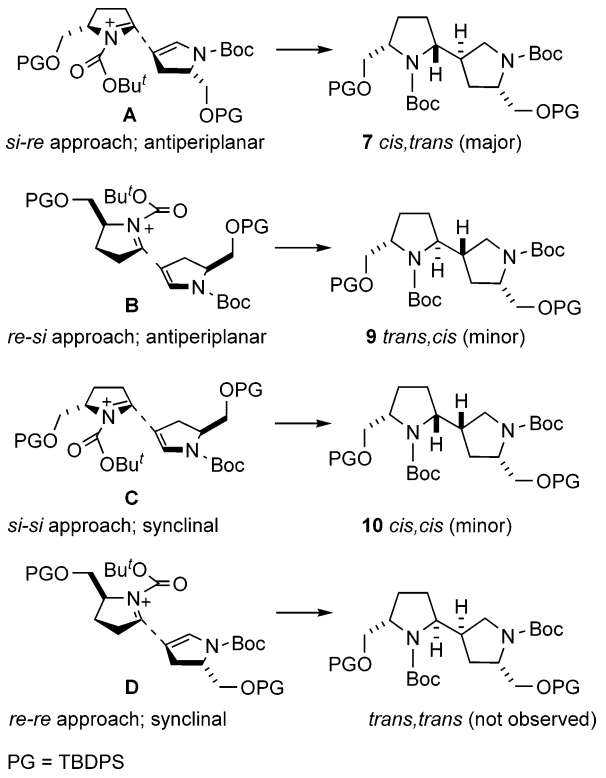
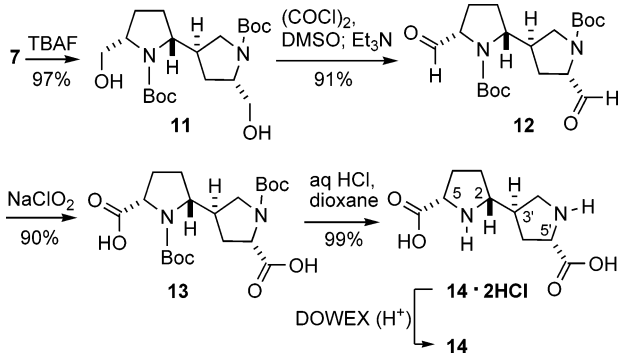


FIGURE 2. Transition states for the ene-carbamate/iminium ion coupling reaction leading to the corresponding stereoisomeric products.

SCHEME 3. Preparation of Bis-proline 14[a]



[a] Atom numbering refers to IUPAC nomenclature.

diamino diacid was cleanly effected by passing an aqueous solution of the HCl salt onto a DOWEX column (H^+ form) eluting with 1.5% aqueous ammonia solution.

Confirmation of the stereostructure of **14** as well as its conformational behavior for solutions in water (90:10 H_2O/D_2O) were made on the basis of 2D NMR experiments. The three-dimensional structure of **14** was calculated from 15 interproton distance restraints, using the simulated annealing calculations.[10] The 10 structures with the lowest energy were selected as a representative ensemble for the structure of **14** (Figure 3). The two proline residues were clearly found to be *trans*-disposed, with H2 and H3′ located on opposite sides within the molecule ($J_{2,3'}$ = 10.2 Hz; H2−C2−C3′−H3′ dihedral angle = 180 ± 40°).

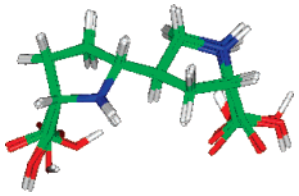
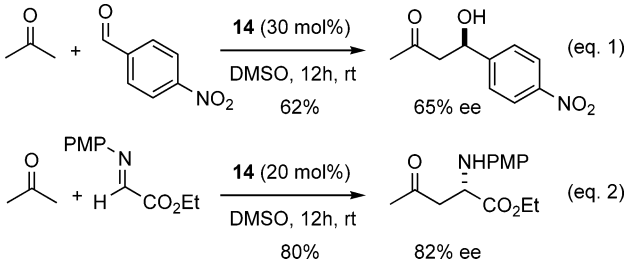


FIGURE 3. Ensemble of 10 lowest energy structures of bis-proline **14**. Color code: green, carbon; red, oxygen; blue, nitrogen; gray, hydrogen.

SCHEME 4. Examples of Crossed Aldol and Mannich Reactions Catalyzed by Bis-Proline 14



Paralleling exactly the synthesis protocol to (2*S*,4*R*,2′*S*,5′*R*)-configured proline dimer **14**, the enantiomeric (2*R*,4*S*,2′*R*,5*S*)-counterpart *ent*-**14** (not shown) was assembled by starting with commercially available, D-glutamic acid-derived (5*R*)-hydroxymethylpyrrolidin-2-one (48% overall yield for nine steps).

The ability of bis-proline compound **14** to catalyze asymmetric crossed aldol and Mannich reactions was investigated vis-à-vis certain previously established proline-catalyzed processes.[11,12] Here, the question was: does proline dimer **14** also catalyze these fundamental reactions, and if so, is its efficacy comparable with, or does it even override the notorius organocatalytic ability of proline itself? To address these questions, we evaluated the aldol addition of acetone to *p*-nitrobenzaldehyde (Scheme 4, eq 1). The reaction, catalyzed by 30 mol % of **14** in DMSO at 25 °C, afforded the corresponding cross-aldol product in a 62% yield and in 65% ee after 12 h.[13] Under similar conditions, the use of (*S*)-proline as the catalyst afforded the aldol product in comparable yield and slightly higher enantioselectivity (72% ee), while maintaining the same sense of enantioinduction (see the Supporting Information for details).[12a] A quite similar behavior was observed in the aldol coupling between cyclohexanone and *p*-nitrobenzaldehyde, where comparable yields and levels of simple diastereoselection and enantioinduction were obtained (61% yield, 60/40 anti/syn dr, 90% and 76% ee).[12b]

Application of bis-proline **14** vis-à-vis (*S*)-proline in a Mannich reaction was examined using acetone and *N*-*p*-methoxyphenyl-protected α-imino ethyl glyoxylate (Scheme 4, eq 2). The reactions were accomplished within 12 h with a

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(13) Lowering the catalyst loading to 10 mol % resulted in a prolonged reaction time and diminished enantioselectivity.

catalyst loading of 20 mol % in both instances, giving the corresponding Mannich adduct in high yields and enantioselectivities (80% yield, 82% ee).[12c,13] On the basis of these results, we surmized that unsymmetric bis-proline compounds of type **14** arising from conjugation of two proline nuclei through a direct carbon−carbon linkage prove to be organocatalysts as good as their monomeric proline counterparts.

In summary, short, diastereoselective syntheses of 4,5′-bisproline enantiomers **14** and *ent*-**14** have been accomplished in 47−48% overall yields and nine steps from commercially available L- and D-glutamic acid-derived hydroxymethylpyrrolidin-2-ones **5** and *ent*-**5**. Our strategy features a SmI_2-driven reductive dimerization of chiral *N*-acyloxyiminium ions for accessing the unprecedented carbon−carbon-linked bis-pyrrolidine substructures of these compounds. Bis-proline **14** proved to be a competent metal-free catalyst in direct asymmetric crossed-aldol and Mannich reactions.

Experimental Section

(2*R*,3′*R*,5*S*,5′*S*)-1,1′-Di-*tert*-butoxycarbonyl-5,5′-bis(*tert*-butyldiphenylsilanyloxymethyl)-2,3′-bipyrrolidine (7). To a stirring solution of hemiaminal **6** (0.70 g, 1.49 mmol) in dry THF (20 mL), cooled to −15 °C under argon, was slowly added *tert*-butyldimethylsilyl triflate (TBSOTf, 0.51 mL, 2.24 mmol). After 5 min, a dark blue solution of SmI_2 (0.1 M in THF, 22.4 mL, 2.24 mmol) was slowly added, and the resulting mixture immediately turned to yellow and was stirred at the same temperature for additional 5 min. The reaction mixture was quenched with solid $Na_2S_2O_3$ (120 mg) and water (50 mL) and extracted with EtOAc (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure giving a crude residue which was purified by silica gel flash chromatography (hexanes/EtOAc 90:10−0:100) to afford bipyrrolidine **7** (360 mg, 55%), along with minor amounts of stereoisomeric compounds **9** (36 mg, 5.5%) and **10** (16 mg, 2.5%), as well as partially deprotected bipyrrolidine **8** (87 mg, 15%).

Bipyrrolidine 7: colorless oil; $[\alpha]^{25}_D$ −20.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 7.64 (m, 8H), 7.37 (m, 12H), 3.8−4.1 (m, 4H), 3.4−3.8 (m, 3H), 3.0−3.4 (m, 2H), 2.30 (m, 1H), 1.8−2.2 (m, 5H), 1.60 (m, 1H), 1.47 (s, 9H), 1.31 (s, 9H), 1.07 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (Cq), 154.5 (Cq), 135.6 (8C, CH), 133.7 (4C, Cq), 129.7 (4C, CH), 127.7 (8C, CH), 79.5 (Cq), 79.2 (Cq), 64.7 (2C, CH_2), 60.1 (CH), 58.4 (2C, CH), 49.7 (CH_2), 41.4 (CH), 32.2 (CH_2), 29.9 (CH_2), 28.6 (3C, CH_3), 28.4 (3C, CH_3), 26.9 (3C, CH_3), 26.8 (4C, CH_3 and CH_2), 19.3 (Cq), 19.2 (Cq). Anal. Calcd for $C_{52}H_{72}N_2O_6Si_2$: C, 71.19; H, 8.27; N, 3.19. Found: C, 70.99; H, 8.36; N, 3.04.

Bipyrrolidine 8: colorless oil; $[\alpha]^{25}_D$ −13.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.67 (m, 8H, Ph), 7.41 (m, 12H, Ph), 3.85−4.05 (m, 1H, H6′$_A$), 3.71 (m, 2H, H6$_A$ and H6′$_B$), 3.63 (dd, J = 10.2, 5.4 Hz, 1H, H6$_B$), 3.53 (m, 1H, H5′), 3.4−3.5 (m, 1H, H2′$_A$), 3.30 (m, 1H, H5), 3.0−3.1 (m, 1H, H2′$_B$), 2.92 (m, 1H, H2), 2.2−2.4 (m, 1H, H3′), 1.7−1.9 (m, 4H, H3$_A$, H4′$_A$, H4′$_B$, and H4$_A$), 1.62 (m, 1H, H4$_B$), 1.35 (m, 1H, H3$_B$), 1.33 (s, 9H, Bu^t), 1.07 (s, 9H, Bu^t), 1.04 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (C═O), 135.6 (4CH, Ph), 135.5 (4CH, Ph), 133.6 (4Cq, Ph), 129.6 (4CH, Ph), 127.6 (8CH, Ph), 79.1 (Cq, OBu^t), 67.0 (C6), 64.6 (C6′), 62.3 (C2), 59.9 (C5), 58.7 (C5′), 49.9 (C2′), 42.2 (C3′), 32.9 (C4′), 30.4 (C3), 28.4 (3CH_3, Bu^t), 27.5 (C4), 26.9 (3CH_3, Bu^t), 26.8 (3CH_3, Bu^t), 19.3 (Cq, SiBu^t), 19.2 (Cq, SiBu^t). Anal. Calcd for $C_{47}H_{64}N_2O_4Si_2$: C, 72.63; H, 8.30; N, 3.60. Found: C, 72.88; H, 8.04; N, 3.75.

Conversion of **8** to **7** was effected as follows. To a stirring solution of bipyrrolidine **8** (80 mg, 0.10 mmol) in dry CH_2Cl_2 (10 mL) were sequentially added Boc_2O (27 mg, 0.12 mmol) and Et_3N (17 μL, 0.12 mmol). After 2 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting crude product was purified by flash chromatography (hexanes/EtOAc 90:10) to afford bipyrrolidine **7** in a 95% yield.

(2*R*,3′*R*,5*S*,5′*S*)-2,3′-Bipyrrolidine-5,5′-dicarboxylic Acid Dihydrochloride (14·2HCl). To solution of protected diacid **13** (136 mg, 0.32 mmol) in dioxane (3 mL) at room temperature was added 6 N aq HCl (2 mL), and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure to furnish **14·2HCl** (95 mg, 99%) as a white solid: mp >250 °C dec; $[\alpha]^{25}_D$ −42.9 (*c* 1.0, H_2O); IR (neat) 2886, 2736, 2545, 1726, 1205 cm^{-1}; ^{1}H NMR (600 MHz, D_2O) δ 4.51 (dd, J = 9.6, 4.8 Hz, 1H, H5′), 4.39 (dd, J = 9.6, 5.4 Hz, 1H, H5), 3.63 (dd, J = 11.4, 7.2 Hz, 1H, H2′$_A$), 3.60 (td, J = 10.2, 6.6 Hz, 1H, H2), 3.08 (dd, J = 12.0, 9.6 Hz, 1H, H2′$_B$), 2.69 (qt, J = 9.6, 7.2 Hz, 1H, H3′), 2.53 (ddd, J = 13.2, 7.8, 4.2 Hz, 1H, H4′$_A$), 2.32 (m, 1H, H4$_A$), 2.15−2.25 (m, 3H, H4′$_B$, H4$_B$ and H3$_A$), 1.68 (m, 1H, H3$_B$); ^{13}C NMR (150 MHz, D_2O) 171.4 (CO_2H), 171.1 (CO_2H), 62.4 (C2), 59.9 (C5), 59.6 (C5′), 47.8 (C2′), 38.8 (C3′), 32.2 (C4′), 27.7 (C3), 27.2 (C4). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O_4$: C, 39.88; H, 6.02; N, 9.30. Found: C, 39.77; H, 6.26; N, 9.24.

(2*R*,3′*R*,5*S*,5′*S*)-2,3′-Bipyrrolidine-5,5′-dicarboxylic Acid (14). Crude diacid **14·2HCl** (95 mg, 0.32 mmol) was dissolved in a 1.5% aqueous solution of NH_4OH and passed through DOWEX 650C ion-exchange resin (H^+ form). Elution of the resin with 1.5% aq NH_4OH furnished free amino acid **14** (72 mg, 100%) as a white solid: mp >250 °C dec; $[\alpha]^{25}_D$ −73.7 (*c* 0.6, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 4.15 (dd, J = 9.6, 4.2 Hz, 1H, H5′), 4.03 (dd, J = 9.6, 4.2 Hz, 1H, H5), 3.58 (dd, J = 12.0, 7.8 Hz, 1H, H2′$_A$), 3.47 (td, J = 10.2, 6.0 Hz, 1H, H2), 2.99 (dd, J = 11.4, 10.2 Hz, 1H, H2′$_B$), 2.60 (qt, J = 9.6, 7.2 Hz, 1H, H3′), 2.40 (ddd, J = 12.6, 6.6, 4.2 Hz, 1H, H4′$_A$), 2.19 (m, 1H, H4$_A$), 2.04−2.12 (m, 3H, H4$_B$, H4′$_B$ and H3$_A$), 1.57 (m, 1H, H3$_B$); ^{13}C NMR (150 MHz, D_2O) 174.3 (CO_2H), 173.7 (CO_2H), 62.5 (C2), 61.7 (C5), 61.1 (C5′), 47.8 (C2′), 39.4 (C3′), 33.1 (C4′), 28.5 (C3), 28.1 (C4); HRMS (ESI) found $[M + H]^+$ 229.1196, $C_{10}H_{17}N_2O_4$ requires 229.1188. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.54; H, 7.10; N, 12.30.

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Supporting Information Available: Experimental procedures, analytic and spectral data for intermediary compounds, NOE-derived structure of N,N-deprotected **7**, NMR-derived structural parameters of **14**, and copies of ^{1}H and ^{13}C NMR spectra of selected key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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