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Synthesis of D- and L-2,3-*trans*-3,4-*cis*-4,5-*trans*-3,4-Dihydroxy-5-hydroxymethylproline and Tripeptides Containing Them

Antonio J. Moreno-Vargas,*[,†,‡] Inmaculada Robina,[‡] Elena Petricci,[†] and Pierre Vogel[†]

Laboratoire de Glycochimie et de Synthèse Asymétrique, Swiss Federal Institute of Technology (EPFL), BCH, CH-1015 Lausanne-Dorigny, Switzerland, and Departamento de Química Orgánica de la Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain

ajmoreno@us.es

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Enantiomerically pure (−)-(1*R*,4*R*,5*R*,6*S*)- and (+)-(1*S*,4*S*,5*S*,6*R*)-7-(*tert*-butoxycarbonyl)-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]hept-2-one ((−)-**3** and (+)-**3**) have been obtained from the Diels−Alder adduct of *N*-(*tert*-butoxycarbonyl)pyrrole and 2-bromo-1-(*p*-toluenesulfonyl)acetylene, including the Alexakis optical resolution of ketone (±)-**3** via formation of cyclic aminals with (1*R*,2*R*)-diphenylethylenediamine. Compounds (−)-**3** and (+)-**3** were converted into D- and L-2,3-*trans*-3,4-*cis*-4,5-trans-*N*-(*tert*-butoxycarbonyl)-5-hydroxymethyl-3,4-isopropylidenedioxyprolines (−)-**4** and (+)-**4**, respectively. Applying the Boc and Fmoc strategies of peptide synthesis, these compounds were used to construct two tripeptides containing the D- or L-2,3-*trans*-3,4-*cis*-4,5-*trans*-3,4-dihydroxy-5-hydroxymethylproline.

Introduction

To discover new peptide-based drugs, many structurally rigid non-peptide scaffolds have been designed. Insertion of these moieties in appropriate sites, a common approach to restrict the conformational degrees of freedom in small peptides, produces the specific three-dimensional structures required for binding to their receptors.[1] Hydroxylated prolines have been shown to significantly influence polypeptide secondary structure in antibiotics.[2] Dihydroxyprolines are present in adhesive proteins produced by marine organisms.[3] It should be recalled that the properties of peptides, and especially their water solubility, are modified by their degree of hydroxylation. Additional hydroxyl groups do not affect the general structure of the peptide containing them.[4] The incorporation of 3- or 4-hydroxyproline and of 3,4-dihydroxyproline moieties into fucopeptides that mimic the structure of sialyl Lewis X increases the interaction with E-selectin.[5] Also, L-proline and derivatives[6] have shown to be efficient organocatalysts in asymmetric aldol reactions. All these observations have stimulated the synthesis of several polyhydroxylated proline derivatives.[7]

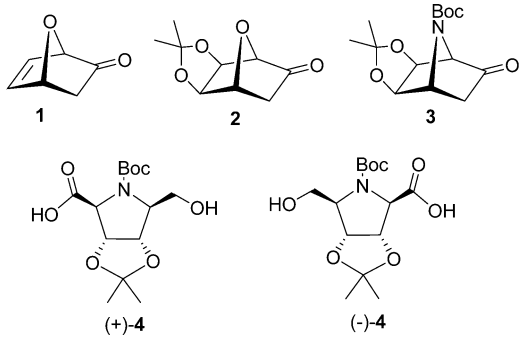

FIGURE 1.

† Swiss Federal Institute of Technology (EPFL).
‡ Universidad de Sevilla.

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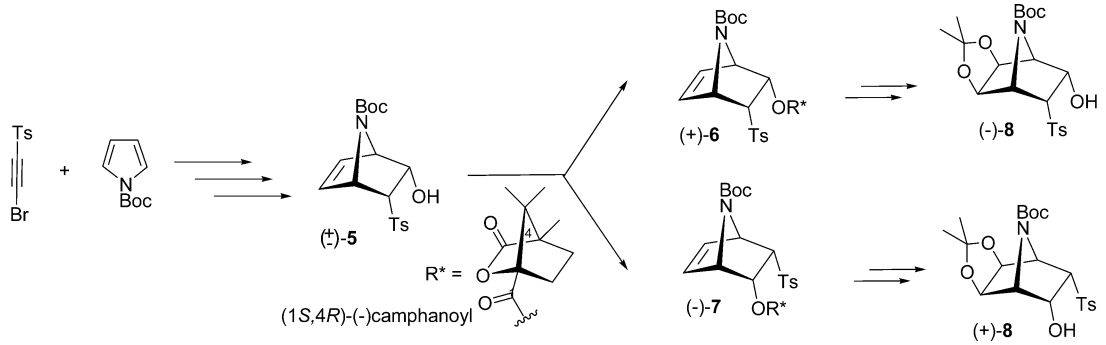
SCHEME 1[10a]

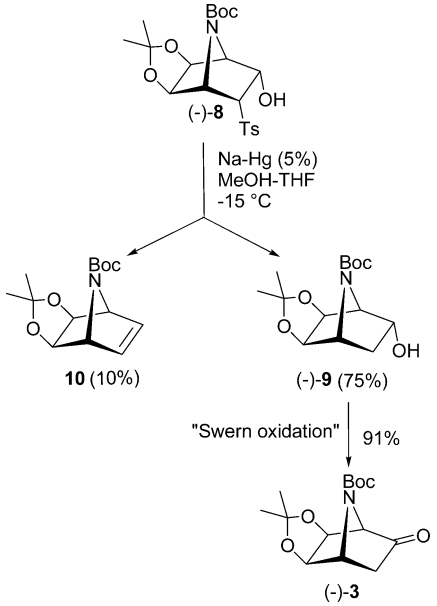


Our research group has developed the "naked sugar" methodology[8] which transforms furan into enantiomerically pure intermediates **1**[9a] and **2**,[9b] as examples. The latter has been converted into a large variety of sugars and rare analogues.[9] As part of our studies on the chemistry of 7-azabicyclo[2.2.1]heptanes,[10] we report herein the synthesis of enantiomerically pure 7-azanorbornanones (+)-**3** and (−)-**3**, two new compounds that are expected to become key intermediates for the synthesis of products of biological interest ("naked aza-sugar" chemistry). They can be easily transformed into the new polyhydroxyproline derivatives (−)-**4** and (+)-**4**. We shall also show that the latter can be used in the synthesis of peptides containing them.

Results and Discussion

We previously reported the synthesis of enantiomerically pure β-hydroxysulfone **8**[10a] via optical resolution of alcohol **5** using camphanic acid as chiral auxiliary (Scheme 1). Desulfonylation of hydroxysulfone (−)-**8** was attempted in different ways. When Bu_3SnH/AIBN in toluene at reflux was employed, the starting material was recovered. Using SmI_2/HMPA in THF at room temperature, the desired desulfonylated compound (−)-**9** was obtained in 39% yield. However, the use of Na(Hg) (5%) in dry MeOH−THF at −15 °C increased the yield of (−)-**9** up to 75%. The symmetric byproduct **10**[11] was formed in 10% yield (Scheme 2). Desulfonylation of β-hydroxysulfones by applying these conditions corresponds to the second step of the Julia olefination,[12] and usually, olefins are obtained in good yields. Swern oxidation of alcohol (−)-**9** led to 7-azanorbornanone derivative (−)-**3** in 91% yield. Starting from the enantiomerically pure alcohol

SCHEME 2



(+)-**8**, the corresponding enantiomerically pure 7-azanorbornanone (+)-**3** was easily synthesized in the same way.

Recently, we reported the facile optical resolution of 7-azanorbornenone **11**[10c] and 7-oxanorbornenone **1**[13] via formation of cyclic aminals with commercially available (1*R*,2*R*)-diphenylethylenediamine.[14] We thus envisaged the synthesis of enantiomerically pure ketone (−)-**3** starting from (−)-**11** by dihydroxylation of its alkene unit using OsO_4/NMO in acetone/H_2O (Scheme 3). To our surprise, the reaction never met with success: a complex mixture of products was obtained instead of the expected diol. We then decided to resolve (±)-**3** with the Alexakis method.[14] The diastereoisomeric aminals (+)-**12** and (−)-**13** are thus formed in nearly quantitative yield by reaction of racemic (±)-**3** with (1*R*,2*R*)-diphenylethylenediamine in CH_2Cl_2 containing MS 4 Å (20 °C, 24 h). The aminals (+)-**12** and (−)-**13** could be only separated by flash chromatography on silica gel ($\Delta R_F = 0.25$) doped with triethylamine (4%). The diastereomerically pure aminals were then hydrolyzed by treatment with 0.1 M H_3PO_4−THF affording enantiomerically pure (+)-**3** and

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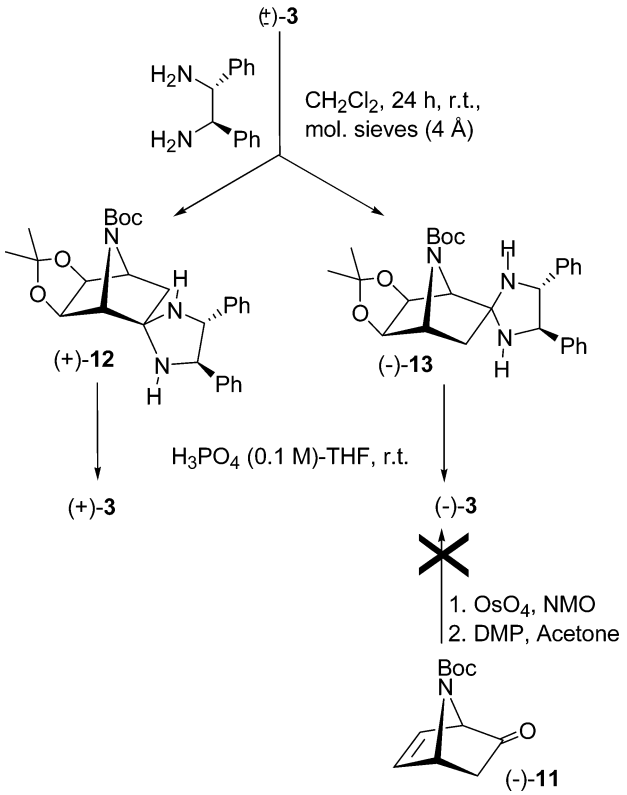
SCHEME 3



(−)-**3** in almost quantitative yield. The chiral diamine was also recovered nearly quantitatively.[13]

This resolution method is much more convenient than the one reported earlier[10a] for (±)-**8**, and enantiomerically pure ketones (+)-**3** and (−)-**3** are readily obtained.

To demonstrate the potential of 7-azanorbornanone derivatives (+)-**3** and (−)-**3** as suitable building blocks in the synthesis of new pyrrolidine-based scaffolds, we studied the opening of the bicyclic moiety following the chemistry developed previously in our group with oxa-analogues.[15] Treatment of (−)-**3** with 4 equiv of Et_3N and *N*-[(*tert*-butyl)dimethylsilyl]-*N*-methyltrifluoroacetamide gave the silyl enol ether (−)-**14** in 86% yield (Scheme 4). Ozonolysis of (−)-**14** at −78 °C in MeOH/CH_2Cl_2, followed by reduction of the ozonide and the aldehyde intermediate with $NaBH_4$ (−78 to +20 °C), gave (−)-**4** in 88% yield. To our delight and contrary to the result obtained with the oxa-analogue,[15] the acidic workup (pH 2−3) of the latter reaction mixture did not lead to the lactonization of (−)-**4**.

To confirm the relative configuration of (−)-**4** and to determine if any epimerization occurred at C-5 during the ozonolysis and further reductive workup processes, we carried out the reduction of acid (−)-**4** employing borane dimethyl sulfide complex in THF under reflux which gave diol **15** in 59% yield. The ^1H and ^{13}C NMR spectra showed the C_s symmetry of this compound. The 2,5-syn configuration was unambiguously assigned for (−)-**4** and **15** by the NMR data (Experimental Section). Deprotection of **15** under acidic conditions gave the known[16] *meso*-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine hydrochloride **16** in quantitative yield.

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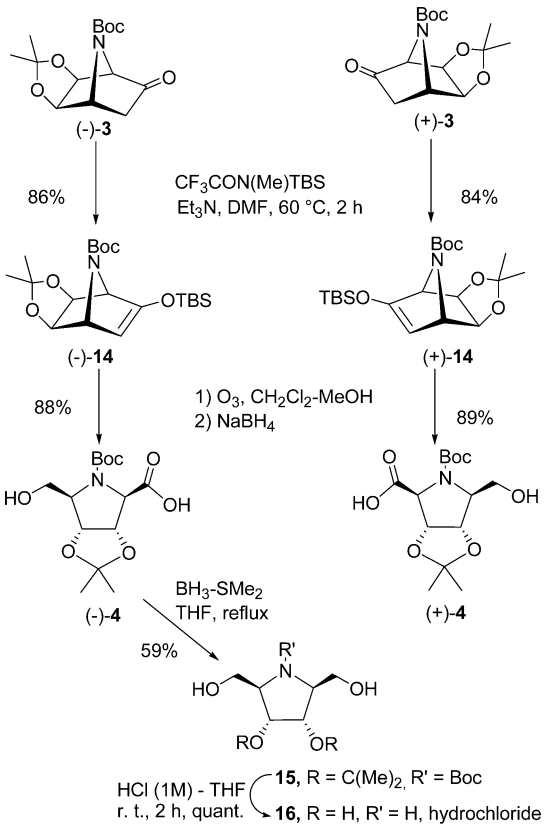
SCHEME 4



Finally, we explored the possibility of incorporating polyhydroxylated prolines into peptides with the goal to generate highly water soluble and conformationally restricted peptides. We first carried out the incorporation of polyhydroxylated proline (+)-**4** into a tripeptide following the Boc strategy for peptide synthesis. The coupling of (+)-**4** with glycine benzyl ester in the presence of PyBOP (benzotriazolyloxytrispyrrolidinophosphonium hexafluorophosphate) as condensating reagent followed by deprotection of the Boc group using 20% TFA in CH_2Cl_2 gave **17** in 63% overall yield (Scheme 5). The coupling of **17** with *N*-Boc-L-phenylalanine presented some difficulties: (1) the hindered nature of the secondary amine, (2) the rigidity of the cyclic system, and (3) the inductive effect of the oxy substituents of the pyrrolidine ring make the trihydroxyproline derivative **17** a poor nucleophile. When PyBOP was used as promoter, only traces of the desired tripeptide were detected. Using BOPCl,[17] a more powerful condensating reagent than PyBOP, the corresponding tripeptide was isolated in 25% yield. Finally, the use of PyAOP[18] (azabenzotriazolyloxytrispyrrolidinophosphonium hexafluorophosphate) was necessary to isolate tripeptide **19** in a good yield (72% after deprotection of the Boc group using 20% TFA in CH_2Cl_2).

We have also carried out the incorporation of polyhydroxylated proline (−)-**4** into a tripeptide following the

(17) (a) For a review in coupling methods for *N*-alkyl amino acids, see: Humphrey, J. M.; Chamberlin, R. A. *Chem. Rev.* **1997**, *97*, 2243. (b) For the use of BOPCl in difficult couplings, see: Halab, L.; Lubell, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 2474.
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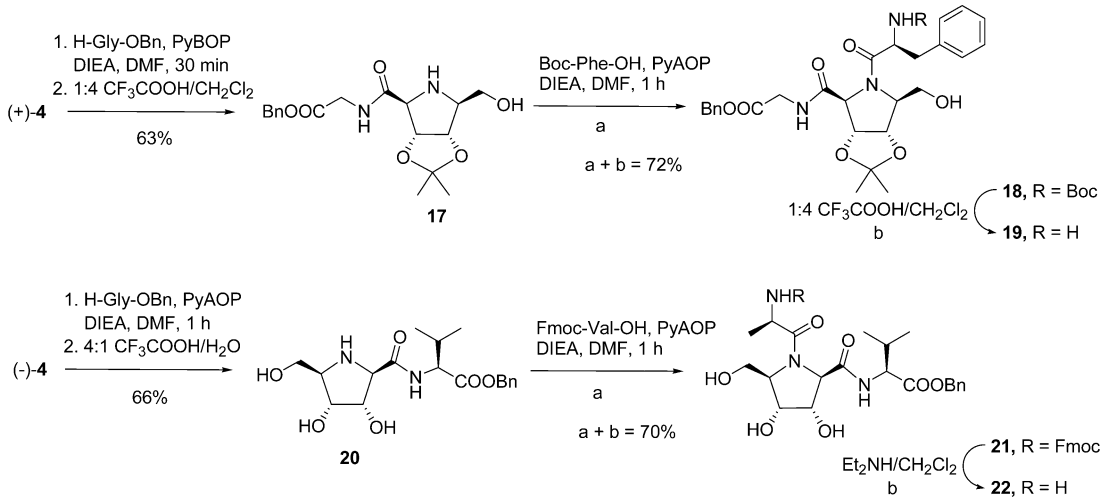
SCHEME 5



Fmoc strategy for peptide synthesis. The coupling of (−)-**4** with L-valine benzyl ester in the presence of PyBOP gave the corresponding dipeptide in only 40% yield. However, when PyAOP was used as promoter the yield was increased significantly as the corresponding dipeptide was obtained in 66% yield after deprotection of the Boc and acetonide groups with 80% CF_3COOH in H_2O. Removal of the protective groups such as Boc and acetonide, allows the peptide elongation to continue without the use of acidic conditions thanks to the Fmoc strategy. Subsequent coupling reaction of **20** with Fmoc-L-alanine, using PyAOP/DIEA as activating reagent, gave the corresponding tripeptide **21** in 70% yield. Tripeptide **21** was characterized as unprotected compound **22**, after deprotection of the Fmoc group under standard conditions (Et_2NH/CH_2Cl_2), in nearly quantitative yield. The coupling reaction was accomplished without protection of the triol moiety of the dipeptide **20**.

Conclusion

In summary, by following reaction schemes of the "naked sugars" methodology, we have performed the syntheses of previously unreported D- and L-3,4-diol-5-hydroxymethylproline derivatives starting from pyrrole. The method implies an efficient optical resolution of the (±)-7-*tert*-butoxycarbonyl-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]hept-2-one ((±)-**3**). We have demonstrated that the new polyfunctional prolines can be used to prepare peptides containing them, using either the Fmoc or the Boc strategy for the peptide synthesis. Work is undergoing to use our new proline derivatives as tridimensional scaffolds using not only their amino acid moiety but also their 5-hydroxymethyl group (primary alcohol) and 3,4-*cis*-diol moiety.

Experimental Section

(±)-7-*tert*-Butoxycarbonyl-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]heptane-2-*endo*-ol ((−)-9) and 7-*tert*-Butoxycarbonyl-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]hept-2-ene (10).[11] To a solution of alcohol (−)-**8** (548 mg, 1.24 mmol) in anhydrous MeOH (20 mL)−THF (20 mL) cooled at −15 °C was added finely crushed 5% sodium mercury amalgam (4.7 g, 12.4 mmol) in one portion under N_2 atmosphere. The mixture was vigorously stirred for 30 min and cooled to −15 °C. Then, the solution was filtered through Celite, concentrated in vacuo, and purified by column chromatography on silica gel (ether/petroleum ether, 1:1 → 3:1), eluting first **10** (34 mg, 10%) and second (−)-**9** (266 mg, 75%) as a white solid and a colorless oil, respectively. Data for (−)-**9**: $[\alpha]_D$ −8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) δ 4.90 (br s, 1 H), 4.71 (d, 1 H, ^3J = 5.6 Hz), 4.24 (d, 1 H), 4.07 (dt, 1 H), 3.99 (d, ^3J = 5.9 Hz), 3.97 (d, ^3J = 4.8 Hz), 2.02 (ddd, 1 H, ^3J = 9.8 Hz, ^2J = 13.0 Hz), 0.86 (dd, 1 H); ^{13}C NMR (100.5 MHz, DMSO-d_6, 363 K) δ 152.5, 108.3, 80.1, 77.3, 75.9, 66.2, 61.0, 58.4, 32.4, 27.2, 24.6, 23.4; HRCIMS *m*/*z* 286.1650, calcd for $C_{14}H_{23}NO_5$ + H 286.1654. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.95; H, 8.07; N, 4.91. Found: C, 58.76; H, 8.30; N, 4.70.

(1*R*,2*R*,3*S*,4*S*,4′*R*,5′*R*)- and (1*S*,2*S*,3*R*,4*R*,4′*R*,5′*R*)-4′,5′-Diphenylspiro[2,3-*exo*-isopropylidenedioxy-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2,2′-imidazoline] (+)-12 and (−)-13. (*R*,*R*)-Diphenylethylenediamine (158 mg, 0.74 mmol) was added under N_2 to a solution of ketone (±)-**3** (195 mg, 0.71 mmol) in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves. The reaction mixture was stirred for 24 h. Et_3N (0.5 mL) was added, and the molecular sieves were eliminated by filtration. The filtrate was concentrated and the resultant residue purified by flash chromatography (ether/petroleum ether:Et_3N, 10:15:1 → 15:10:1) affording first **12** (150 mg, 44%) and then **13** (141 mg, 42%), both as syrups. **Data for (+)-12:** $[\alpha]_D$ +73 (*c* 1.65, $CHCl_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$−Et_3N, 298 K, δ ppm, mixture of rotamers 1.2:1) (major rotamer) δ 155.0, 141.3, 139.6, 128.1−126.9 (10 C), 111.0, 81.7, 80.8, 78.6, 79.6, 70.2, 69.2, 66.3, 59.2, 43.0, 28.3, 25.5, 24.1, (minor rotamer) δ 154.9, 141.3, 139.4, 128.1−126.9 (10 C), 111.0, 81.5, 81.4, 78.7, 79.7, 70.2, 69.3, 67.5, 58.3, 42.7, 28.3, 25.5, 24.1; HRCIMS *m*/*z* found 477.2626, calcd for $C_{28}H_{35}N_3O_4$ 477.2628. **Data for (−)-13:** $[\alpha]_D$ −38 (*c* 1.65, $CHCl_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$−Et_3N, 298 K, mixture of rotamers 3.5:1) (major rotamer) δ 154.7, 141.8, 138.8, 128.7−126.1 (10 C), 110.8, 83.4, 81.3, 79.6, 78.6, 71.8, 69.2, 67.8, 58.4, 41., 28.4, 25.6, 24.3; (minor rotamer) δ 154.7 (CO), 141.0, 140.9, 128.7−126.1 (10 C), 110.8, 82.9, 81.6, 79.5, 78.5, 79.5, 71.3, 69.3, 67.1, 59.7, 42.6, 28.3, 25.6, 24.3; HRCIMS *m*/*z* 477.2620, calcd for $C_{28}H_{35}N_3O_4$ 477.2628.

(−)-7-*tert*-Butoxycarbonyl-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]hept-2-one ((−)-3). Method a. See the Supporting Information. **Method b.** A solution of (−)-**13** (50 mg, 0.10 mmol) in 0.1 M H_3PO_4−THF (2:1, 9 mL) was stirred for 30 min at 20 °C. Then, the mixture was diluted with H_2O and extracted with ether. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash chromatography (ether/petroleum ether, 2:1) affording (−)-**3** (27 mg, 91%) as white solid: mp = 85−87 °C;

$[\alpha]_D$ −51.9 (*c* 1.11, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 313 K) δ 4.67 (d, 1H, ^3J = 5.4 Hz), 4.41 (d, 1 H, ^3J = 5.4 Hz), 4.37 (d, 1 H), 4.34 (s, 1 H), 2.40 (dd, 1 H, ^2J = 17.8 Hz), 1.80 (d, 1 H), 1.47 (s, 12 H), 1.2 (s, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 313 K) δ 206.2, 154.1, 113.4, 81.8, 80.8, 78.0, 68.0, 59.2, 39.3, 28.2, 25.6, 24.4; HREIMS *m*/*z* 283.1422, calcd for $C_{14}H_{21}NO_5$ 283.1420.

(−)-7-*tert*-Butoxycarbonyl-2-[[(*tert*-butyl)dimethylsilyl]oxy]-5,6-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-hept-2-ene ((−)-14). Et_3N (68 mL, 0.92 mmol) and *N*-[(*tert*-butyl)dimethylsilyl]-*N*-methyltrifluoroacetamide (64 mL, 0.46 mmol) were added to a stirred solution of (−)-**3** (66 mg, 0.46 mmol) in dry DMF under Ar. The mixture was heated to 60 °C for 6 h. The solution was evaporated at 50 °C/0.05 Torr, and the residue was purified by column chromatography on silica gel (petroleum ether/AcOEt, 1:6) to give (−)-**14** (79 mg, 86%) as a colorless oil: $[\alpha]_D$ −38.2 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 4.86, 4.79 (2 br s, 1 H), 4.55, 4.46 (2 br s, 1 H), 4.46 (d, 1 H, ^3J = 5.4 Hz), 4.38 (d, 1 H), 4.26, 4.15 (2 br s, 1 H), 1.43, (s, 12 H), 1.30 (s, 3 H), 0.89, 0.88 (2 br s, 9 H), 0.15, 0.12 (2 s, 6 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 162.9, 161.7, 155.0, 154.9, 116.2, 116.1, 104.5, 103.1, 83.0, 82.5, 80.3, 80.0, 80.2, 65.4, 64.7, 63.4, 62.8, 28.7, 26.7, 25.9, 25.7, 25.6, 18.5, −4.4, −4.5, −4.6, −4.7; CIMS *m*/*z* 398 [20, $(M + H)^+$]. Anal. Calcd for $C_{20}H_{35}NSiO_5$: C, 60.42; H, 8.87; N, 3.52. Found: C, 60.22; H, 8.96; N, 3.46.

D-2,3-*trans*-3,4-*cis*-4,5-*trans*-*N*-(*tert*-Butoxycarbonyl)-5-hydroxymethyl-3,4-isopropylidenedioxyproline (Boc-D-Thyp(CMe$_2$)-OH)[19] ((−)-4). Compound (−)-**14** (98 mg, 0.24 mmol) was dissolved in anhydrous CH_2Cl_2/MeOH (1:1, 4 mL) and cooled to −78 °C. A stream of O_3 (3% in O_2, 50 mL/h) was bubbled through the solution for 25 min until persistence of a blue color. Then $NaBH_4$ (37 mg, 0.96 mmol) was added and the mixture allowed to warm to 20 °C under stirring. After 2 h at 20 °C, the solution was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of citric acid. The organic layer was separated, concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1 → 4:1) to give (−)-**4** (69 mg, 88%) as a syrup:. $[\alpha]_D$ −44 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 4.67 (dd, 1 H, ^3J = 5.9 Hz, ^3J = 1.5 Hz), 4.64 (d, 1 H), 4.14 (br s, 1 H), 3.92 (t, 1 H), 3.72 (dd, 1 H, $^2J_{Ha,Hb}$ = 11.4 Hz, ^3J = 4.3 Hz), 3.44 (dd, 1 H, ^3J = 3.2 Hz), 1.40 (s, 9 H), 1.38, 1.29 (2 s, 3 H each); ^{13}C NMR (100.5 MHz, DMSO-d_6, 373 K) δ 173.9, 153.2, 110.2, 83.0, 81.7, 77.6, 68.4, 66.0, 60.8, 27.2, 26.1, 24.3; CIMS *m*/*z* 318 [5, $(M + H)^+$], *m*/*z* 217 [20, $(M - Boc + 2H)^+$].

Boc-L-Phe-L-Thyp(CMe$_2$)-Gly-OBn (18). To a solution of compound **18** (26 mg, 0.071 mmol) in dry DMF (1.5 mL) were added *N*-Boc-L-phenylalanine (23 mg, 0.085 mmol), diisopropylethylamine (51 μL, 0.284 mmol), and PyAOP (45 mg, 0.085 mmol). The solution was stirred for 1 h and evaporated to dryness, and the crude was purified by flash chromatography (ether/petroleum ether, 2:1 → ether) to give **18** (31 mg, 0.051 mmol, 72% yield) as a white solid. Compound **18** was characterized as the unprotected tripeptide **19**.

H-L-Phe-L-Thyp-Gly-OBn (19). Tripeptide **18** (24 mg, 0.039 mmol) was dissolved in TFA (20%)−DCM (2 mL), and the mixture was stirred for 30 min. Then, the solution was concentrated and the crude coevaporated with Et_3N. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 30:1) to give **19** (16 mg, 0.032 mmol, 82%) as a colorless oil: $[\alpha]_D$ +36.2 (*c* 0.65, CH_3OH); ^1H NMR (400 MHz, CD_3OD, 298 K, mixture of rotamers) (major rotamer) δ 7.41−7.20 (m, 10 H), 5.21 (s, 2 H), 4.81 (dd, 1 H, ^3J = 5.8 Hz, ^3J = 2.2 Hz), 4.70 (br d, 1 H), 4.32 (t, 1 H, ^3J = 3.9 Hz), 4.25 (d, 1 H), 4.10 (d, 1 H, ^2J = 17.5 Hz), 4.05 (d, 1 H), 3.88 (dd, 1 H, ^2J = 11.5 Hz, ^3J = 4.8 Hz), 3.70 (dd, 1 H, ^3J = 3.1 Hz), 3.67 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 5.8 Hz), 2.99 (dd, 1 H, ^2J = 13.2 Hz), 2.85 (dd, 1 H), 1.28, 1.26 (2 s, 3 H each), (minor rotamer) δ 7.41−7.20 (m, 10 H), 5.21 (s, 2 H), 4.85 (dd, 1 H, ^3J = 5.7 Hz, ^3J = 2.7 Hz), 4.68 (d, 1 H), 4.66 (d, 1 H), 4.42 (t, 1 H, ^3J = 4.9 Hz), 4.06 (d, 1 H, ^2J = 17.6 Hz), 3.99 (d, 1 H), 3.91−3.89 (m, 1 H), 3.32 (dd, 1 H), 3.24 (dd, 1 H, ^2J = 11.9 Hz, ^3J = 5.3 Hz), 3.14 (dd, 1 H, ^2J = 12.8 Hz, ^3J = 7.4 Hz), 2.81 (dd, 1 H, ^3J = 6.5 Hz), 1.47, 1.33 (2 s, 3 H each).^{13}C NMR (100.5 MHz, CD_3OD, mixture of rotamers) (major rotamer) δ 177.3, 174.6, 171.8, 139.7−128.7 (12 C), 114.2, 85.8, 83.3, 70.9, 68.9, 68.3, 62.3, 56.3, 43.1, 42.6, 28.5, 26.2, (minor rotamer) δ 177.6, 174.3, 171.6, 139.0−128.7 (12 C), 114.2, 84.9, 83.8, 70.4, 68.9, 67.9, 64.3, 55.9, 43.7, 43.1, 28.4, 26.2; HRCIMS *m*/*z* 512.2401, calcd for $C_{27}H_{33}N_3O_7$ + H 512.2397.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all the new compounds. Experimental data for preparation of compounds **15**−**17** and **20**−**22**. ^1H and ^{13}C NMR data with detailed signal assignments, detailed MS data, complete list of α values, and IR data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) To use the nomenclature of peptides, the abbreviation H-D-Thyp-OH was chosen for the trihydroxyproline moiety in analogy to the D-hydroxyproline (H-D-Hyp-OH).