A Novel Stereodivergent Synthesis of Optically Pure *cis*- and *trans*-3-Substituted Proline Derivatives

N. André Sasaki,* Michael Dockner, Angèle Chiaroni, Claude Riche, and Pierre Potier

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

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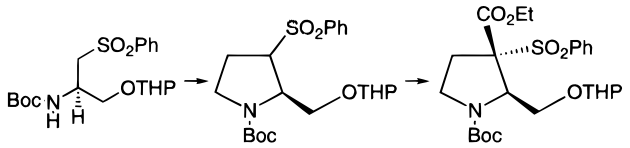
Introduction

During the last several years, a number of optically active *cis*- and *trans*-2,3-disubstituted pyrrolidines have been synthesized for the preparation of appropriate starting materials in the syntheses of indolizidine[1] and pyrrolizidine alkaloids[2] and in search of potent ligands for the NMDA receptor.[3] More recently, effort in the synthesis of 2,3-disubstituted pyrrolidines has been reinforced in terms of the synthesis of 3-substituted prolines, which have been viewed as conformationally constrained analogues of natural α-amino acids bridged by an ethylene group between the α-nitrogen and the β-carbon.[4] Introduction of rigidity into bioactive peptides has been considered as a useful means to study conformational prerequisites for their biological activities. One of the easily conceivable ways of inducing conformational constrains is to replace a natural amino acid with a 3-monosubstituted proline. Despite a growing interest in this type of α-amino acids, there are as yet very few practical methods for their preparation in optically pure form.[4c,5]

Previously, we have reported that nucleophilic attack of the sulfonyl carbanion of **2**, derived from **1** by one-step pyrrolidine ring formation, takes place with very high diastereofacial selectivity, as shown in Scheme 1.[3a]

This prompted us to raise the question as to whether the same trend of high diastereoselectivity could be observed in the alkylation on the carbanion of **2** with other alkylating groups. And if this is the case, can the stereochemistry of the alkyl group at C-3 be diverted by reversing the order of alkylation, namely, by first alkylating on the C-3 position and then by forming heterocyclic ring so as to obtain a C-3 diastereomer?

Scheme 1



As a continuation of our studies in developing a novel methodology for the synthesis of optically pure disubstituted pyrrolidines,[6] we have been interested in investigating the above question to explore a new stereodivergent route to enantio- and diastereoselective synthesis of 3-substituted proline derivatives in optically pure form. In this paper, we describe our new findings.

Result and Discussion

We chose *trans*- and *cis*-3-allyl-L-proline derivatives **8a** and **8c**, respectively, as our target molecules. This choice was based on the anticipation that in the course of syntheses, ^{1}H and ^{13}C NMR spectra of the allyl group might provide some useful information concerning its stereochemical relationship with the neighboring functionalities. Allyl is also a masked group to be transformed into another functionality. In addition, *N*-Boc-*trans*-3-allyl-L-proline, **8a**, was reported by Holladay *et al.* in the synthesis of a highly potent analogue of C-terminal tetrapeptide of cholecystokinin, which contains *trans*-3-*n*-propyl-L-proline in place of L-methionine.[4b, 5a]

Upon treatment of **1**[7] with freshly prepared 2-bromoethyl triflate in THF at −78 °C, the pyrrolidine **2**[8] was generated and purified by flash chromatography (EtOAc−heptane = 1:2) (92%). Alkylation of the monolithiate of **2** with 1.2 equiv of allyl bromide in THF at −78 °C afforded an inseparable mixture of **4a** and the corresponding C-3 diastereomer **4b** in 85% yield (route A) after purification by flash chromatography on silica gel (EtOAc−heptane = 1:2). Removal of THP by treatment with PPTS in ethanol gave a mixture of **5a**/**5b** in excellent yield. HPLC analysis of this mixture showed the ratio of the diastereomers to be 6:94.[9] Then, we reversed the order of alkylation on the sulfonyl carbanion. The dilithiated anion of **1** was treated with allyl bromide at −78 °C to give **3** in 95% yield after chromatographic purification. Allylic sulfone **3** was treated with 2 equiv of *n*-BuLi in THF at −78 °C, and then 1.2 equiv of 2-bromoethyl triflate was added. After standard workup, a mixture of pyrrolidine products **4a**/**4b** was purified by flash chromatography (EtOAc−heptane = 1:2) (route B). Treatment of this mixture with a catalytic amount (0.1

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(9) HPLC conditions for the determination of the ratio of **5a** and **5b**: column, Novapack Si 4 μm; column size, 3.9 × 150 mm; eluent, heptane/AcOEt/AcOH = 80/20/0.1; flow rate 1 mL/min; detector, refractometer R 410 (Waters); retention time, (**5a**) 9.45 min, (**5b**) 10.75 min.

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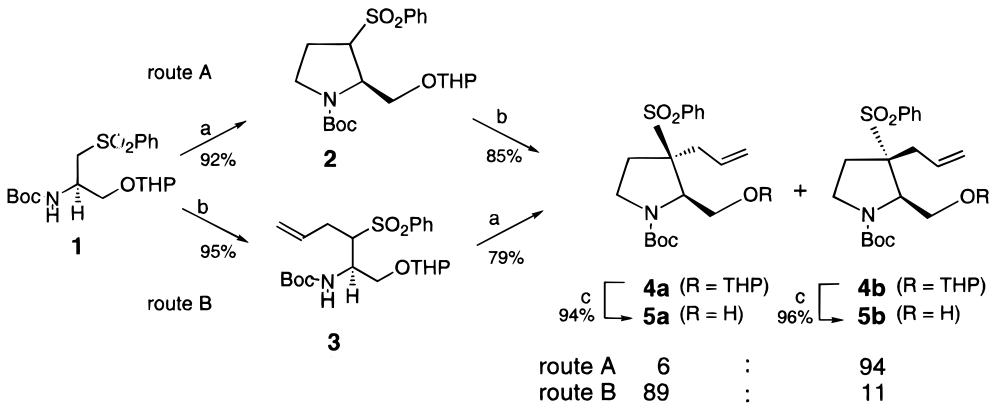
Scheme 2[a]



[a] Reaction conditions: (a) *n*-BuLi/THF, $BrCH_2CH_2OTf$, −78 °C; (b) *n*-BuLi/THF, allylbromide, −78 °C; (c) PPTS/EtOH, 50 °C.

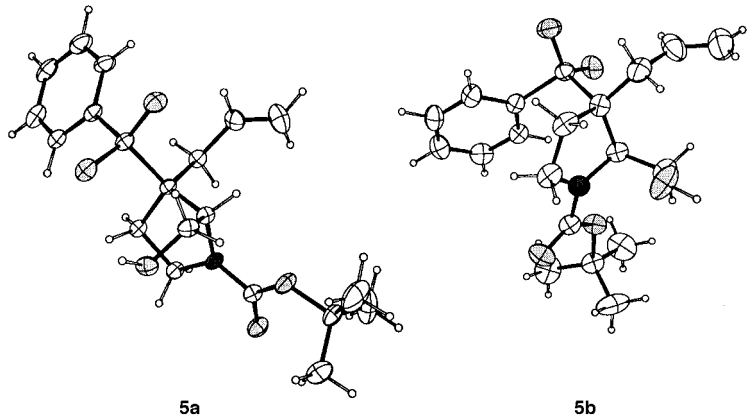


Figure 1. ORTEP drawings of **5a** and **5b**.

mol equiv) of PPTS in EtOH at 50 °C provided an 89:11 mixture of **5a**/**5b** (Scheme 2). Analytically pure **5b** and **5a** were easily available by recrystallization of the **5a**/**5b** mixutures obtained *via* routes A and B, respectively. It is noteworthy that ^{1}H and ^{13}C NMR spectra of **5a** and **5b** are indicative of their C-3 configuration. While **5a** exhibits a multiplet centered at 6.08 ppm that is attributed to one of the allylic protons, its counterpart of **5b** appears somewhat upfield centered at 5.70 ppm, suggesting a *cis* relationship between the allyl and the hydroxymethyl groups. In ^{13}C NMR spectra, signals at 40.0, 40.5, 120.0, and 130.7, 131.0 ppm are attributed to the allylic carbons in **5a**. Equally, ^{13}C NMR spectrum of **5b** shows corresponding signals at 34.8, 119.1, and 132.4 ppm. These characteristic differences in allylic signals serve as a useful indication for the evaluation of approximative diastereomeric purity of the derivatives of 5**a** and **5b**.

Finally, the absolute stereochemistry of **5a** and **5b** was determined by single-crystal X-ray analysis, which unambiguously demonstrates diastereomeric relationship between (3*R*)-**5a** and (3*S*)-**5b** as shown in Figure 1.[10]

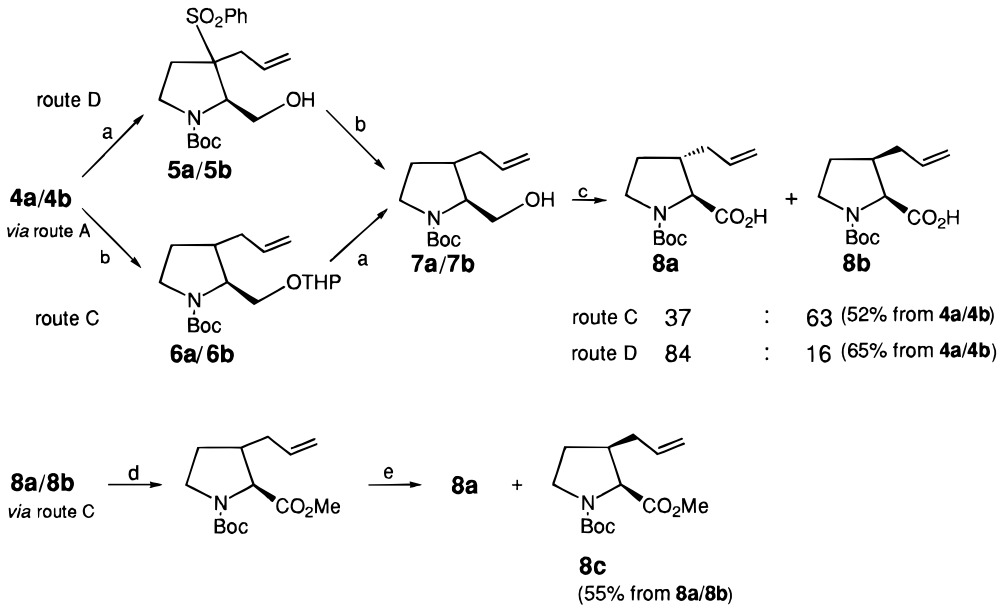
Desulfonylation of the mixtue of **4a**/**4b** obtained *via* route A with 6% Na−Hg in methanol, followed by removal of THP and subsequent Jones oxidation in acetone, provided a 37:63 mixture of **8a** and **8b** in 52% overall yield from **4a**/**4b** (route C). This ratio of the diastereomeric mixture was determined on the basis of HPLC analysis of the derived (*R*)-(+)-α-methylbenzylamides.[11] Treatment of the thus obtained mixture of **8a**/**8b** with diazomethane followed by selective saponification resulted in an easily separable mixture of *cis*-methyl ester **8c** (55% overall yield from **8a**/**8b**) and *trans*-acid **8a** (10% recovery). On the other hand, when the mixture of **5a**/**5b** obtained *via* route A was subjected to the sequential desulfonylation−Jones oxidation procedure (route D), the diastereomeric ratio of **8a** and **8b** (65% overall yield from **4a**/**4b**) turned out to be 84:16. This result indicates that, whereas the protonation (direct or mediated by the solvent) of the desulfonylated anion species of **5b** provides thermodynamically favored *trans* product **7a**, that of the desulfonylated anion species of **4b** takes place from the sterically less hindered side of the molecule so as to provide **6b** as a major kinetic product (Scheme 3).

As far as the mixture of **5a**/**5b** obtained *via* route B is concerned, desulfonylation by 6% Na−Hg in methanol afforded a single diastereomeric alcohol **7a** in 80% yield. This was then oxidized by Jones reagent in acetone to provide **8a** in 73% yield. The optical purity of **8a** was assessed to be more than 98% based on the HPLC analysis of its amide prepared from (*R*)-(+)-α-methylbenzylamine.[11] Catalytic hydrogenation of **8a** on Pd/C

(10) **5a**: torsional angle, $S-C_2-C_3-C_3-c_{allyl} = +71°$. **5b**: torsional angle, $S-C_2-C_3-C_3-c_{allyl} = -69°$. Positive sign is characteristic for the *R* configuration. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

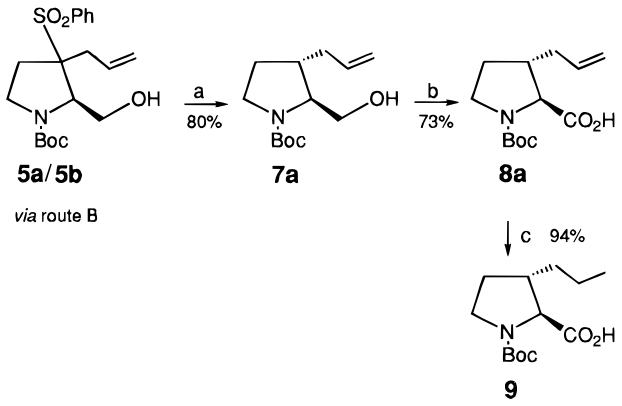
(11) A mixture of **8a**/**8b** was converted to (*R*)-(+)-α-methylbenzylamides according to the method described by Chung *et al.*[5a] HPLC conditions for the determination of the ratio of (*R*)-(+)-α-methylbenzylamide of **8a** and **8b**: column, Novapack Si 4 μm; column size, 3.9 × 150 mm; eluent, heptane/AcOEt/AcOH = 80/20; flow rate 1 mL/min; detector, refractometer R 410 (Waters); retention time ((*R*)-(+)-α-methylbenzylamide of **8a**) 9.66 min, ((*R*)-(+)-α-methylbenzylamide of **8b**) 10.80 min.

Scheme 3[a]



[a] Reaction conditions: (a) PPTS, EtOH, 50 °C; (b) 6% Na−Hg/Na_2HPO_4, MeOH; (c) Jones oxidation; (d) CH_2N_2; (e) 1 N NaOH, MeOH, 24 h.

Scheme 4[a]



[a] Reaction conditions: (a) 6% Na−Hg, MeOH, Na_2HPO_4; (b) Jones oxidation; (c) H_2, Pd/C.

afforded optically pure N-Boc-*trans*-3-*n*-propyl-L-proline, **9**[5a] (Scheme 4).

Thus, this sequence provides an efficient entry into enantiomerically and diastereomerically pure *cis*- and *trans*-2,3-disubstituted pyrrolidines.

In order to find out whether or not this high diastereoselectivity is due to an intramolecular chelation of the lithium atom in a lithiosulfone to oxygen in the neighboring functionality, which renders the phenyl group to such an orientation that incoming electrophile takes *anti* approach to the phenyl group, as depicted in Figure 2,[12,13] preparation of **5a** and **5b** was carried out starting from **10**, the *tert*-butyldimethylsilyl analogue of **1**. This is demonstrated in Scheme 5.

Although the diastereoselectivity *via* route B was less significant in this case, we observed that, to our surprise, allylation of **11** was a highly diastereoselective process. Taking into account of the absence of chelation with

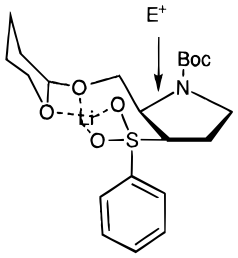


Figure 2.

silyloxy groups,[14] we postulate that the stereochemical outcome of the above reaction is due to a preferred pyramidal sulfonyl carbanion configuration controlled by the geometry and disposition of substituents at C-2. In the lithiated species of **2** and **11**, *trans* orientation of the adjacent protected hydroxymethyl and phenylsulfonyl groups is supposed to be the cause of the observed high stereofacial selectivity.

Conclusions

A novel stereodivergent method has been developed for the synthesis of optically pure *cis*- and *trans*-3-substituted proline derivatives starting from readily available **1** (or its antipode [7]) simply by reversing the order of double alkylation on sulfonyl carbanion. This relatively short step approach can provide access to all four possible diastereomers in a stereocontrolled manner. The extension of this methodology for the preparation of other constrained α-amino acids and for the synthesis of 2,3-disubstituted piperidines continues in our laboratory.

Experimental Section

General Methods. All melting points are uncorrected. Unless otherwise noted, all reagents obtained from commercial sources were used without further purification. THF was distilled from sodium benzophenone ketyl. All other organic solvents were dried and distilled prior to use. Flash chroma-

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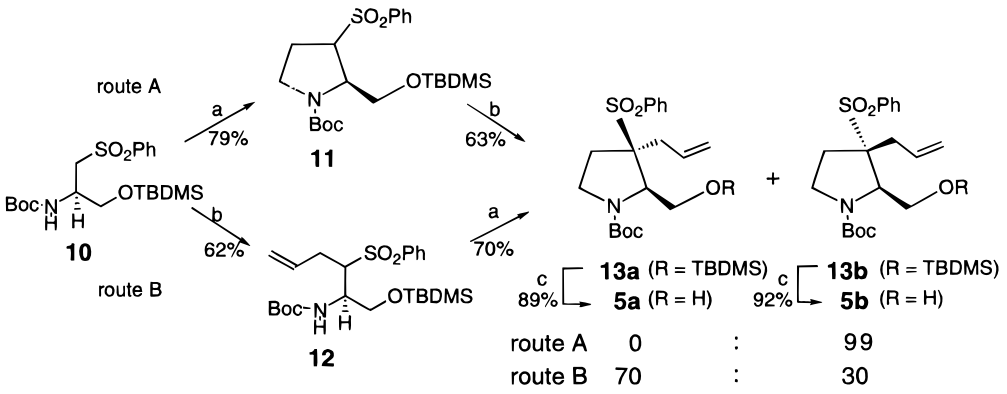
Scheme 5[a]



[a] Reaction conditions: (a) *n*-BuLi/THF, $BrCH_2CH_2OTf$, −78 °C; (b) *n*-BuLi/THF, allylbromide, −78 °C; (c) *n*-Bu4N$^+$F$^-$/THF, rt.

tography was performed using 230−400 mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on plates precoated with 0.25 mm of silica gel containing 60F-254 indicator. ^{1}H NMR spectra were recorded at 300, 250, and 200 MHz, and ^{13}C NMR spectra were recorded 75.5 MHz with chemical shifts reported in ppm (δ) downfield from TMS (internal reference) for ^{1}H and relative to the center line of the triplet of $CDCl_3$ at 77.14 ppm for ^{13}C, unless otherwise specified. Mass spectra were obtained by CI (isobutane), and the high-resolution mass spectrum was obtained by CI (methane). Elemental analyses were carried out by the microanalytical laboratory at the ICSN.

(2*R*)-1-(*tert*-Butyloxycarbonyl)-2-[[(2-tetrahydropyranyl)oxy]methyl]-3-allyl-3-(phenylsulfonyl)pyrrolidine (4a/4b) (*via* Route A). To a solution of **2** (3.50 g, 8.2 mmol) in THF (35 mL) was added dropwise *n*-BuLi (5.2 mL, 1.6 M in hexane) at −78 °C under dry nitrogen. The mixture was stirred for 30 min at −50 °C and then cooled back to −78 °C to add allyl bromide (1.2 g, 9.8 mmol) in THF (2 mL). The reaction mixture was allowed to warm to 0 °C while being stirred for 3 h and then diluted with EtOAc (30 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, and concentrated. Purification of the crude product was effected by flash chromatography on silica gel, eluting with EtOAc/heptane (1:2). Evaporation of the solvent afforded 3.25 g of a mixture of **4a**/**4b** in 85% yield: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.25−1.90 (m, 6H), 2.12−2.40 (m, 1H), 2.40−3.05 (m, 3H), 3.05−3.35 (m, 1H), 3.37−4.15 (m, 5H), 4.30−4.66 (m, 2H), 5.00−5.27 (m, 2H), 5.45−5.80 (m, 0.1H), 6.07−6.33 (m, 0.9H), 7.40−7.73 (m, 3H), 7.80−8.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.53, 18.75, 19.48, 25.30, 28.46, 30.37, 30.79, 31.35, 36.00, 44.44, 45.03, 60.06, 60.58, 60.93, 62.52, 64.83, 65.41, 66.22, 66.99, 79.91, 96.98, 100.09, 118.32, 128.97, 129.39, 129.66, 129.90, 133.61, 134.01, 137.28: MS (CI) *m*/*z* 466 ((M + H)$^+$, base), 382, 326, 143, 101. Anal. Calcd for $C_{24}H_{35}NO_6S$: C, 61.91; H, 7.57; N, 3.00; S, 6.88. Found: C, 62.04; H, 7.55; N, 2.83; S, 6.83.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-2-(hydroxymethyl)-3-allyl-3-(phenylsulfonyl)pyrrolidine (5b). A solution of 3.10 g (6.6 mmol) of the mixture of **4a**/**4b** in ethanol (25 mL) was warmed to 50 °C for 4 h in the presence of 0.1 equiv of PPTS. After evaporation of ethanol, the residue was diluted with CH_2Cl_2, washed with H_2O, and then dried and concentrated to provide 2.43 g of a mixture of **5a** and **5b** in 96% yield. The ratio of the **5a**/**5b** mixture was determined to be 6:94 by HPLC.[9]. Recrystallization (twice from EtOAc/heptane) provided 2.10 g of pure **5b**: mp 122−122.5 °C; $[\alpha]^{25}_D$ = +7.9° (*c* 1.0, CH_3OH); $[\alpha]^{25}_D$ = +3.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.10−2.24 (m, 1H), 2.44−2.92 (m, 3H), 3.21−3.41 (m , 1H), 3.55−3.95 (m, 3H), 4.35 (m, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 5.94−6.18 (m, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.45, 30.22, 34.81,45.08, 62.59, 63.34, 73.47, 80.59, 119.18, 129.19, 130.18, 132.58, 134.19, 136.29; MS (CI) *m*/*z* 382 (M + H)$^+$, 326 (base), 282. Anal. Calcd for $C_{19}H_{27}NO_5S$: C, 59.81; H, 7.13; N, 3.67; S, 8.40. Found: C, 59.81; H, 7.17; N, 3.54; S, 8.34.

(2*R*)-1-[(2-Tetrahydropyranyl)oxy]-2-[(*tert*-butyloxycarbonyl)amino]-3-(phenylsulfonyl)-5-hexene (3). To a solution of **1** (4.0 g, 10 mmol) in THF (40 mL) at −78 °C was added dropwise *n*-BuLi (12.6 mL, 1.6 M in hexane) under dry nitrogen, and the reaction mixture was stirred at −78 °C for 15 min while allyl bromide (1.45 g, 12 mmol) in THF (2 mL) was added. The reaction mixture was allowed to warm to 0 °C while being stirred for 2.5 h and then concentrated under reduced pressure. The residue was diluted with EtOAc and washed with H_2O. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated. Flash chromatography on silica gel (EtOAc/hexane = 1:2) afforded 4.20 g (9.56 mmol) of **3** in 95% yield: viscous oil; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.40−1.85 (m, 6H), 2.50−2.65 (m, 2H), 3.40−3.55 (m, 2H), 3.60−4.05 (m, 4H), 4.34−4.47 (m, 1H), 4.55−4.67 (m, 1H), 5.04−5.18 (m, 2H), 5.30 (m, 1H), 5.55−5.83 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18. 86, 18.94, 19.22, 25.05, 27.74, 28.06, 30.14, 30.27, 30.52, 30.73, 49.04, 49.25, 49.55, 61.75, 62.00, 62.16, 62.74, 62.95, 63.22, 64.77, 65.17, 66.23, 66.64, 67.29, 79.35, 97.81, 98.31, 98.90, 118.40, 118.52, 128.04, 128.14, 128.46, 128.97, 132.95, 133.13, 133.38, 133.57, 138.43, 139.56, 155.07; MS (CI) *m*/*z* 440 ((M + H)$^+$, base), 356, 300. Anal. Calcd for $C_{22}H_{33}NO_6S$: C, 60.11; H, 7.56; N, 3.18; S, 7.29. Found: C, 60.29; H, 7.66; N, 3.04; S, 7.21.

(2*R*)-1-(*tert*-Butyloxycarbonyl)-2-[[(2-tetrahydropyranyl)oxy]methyl]-3-allyl-3-(phenylsulfonyl)pyrrolidine (4a/4b) (*via* Route B). To a solution of **3** (4.16 g, 9.47 mmol) in THF (40 mL) was added dropwise *n*-BuLi (12.0 mL, 1.6 M in hexane) at −78 °C under dry nitrogen. The mixture was stirred for 30 min at −50 °C and then cooled back to −78 °C to add freshly prepared 2-bromoethyl triflate[15] (2.92 g, 11.3 mmol) in THF (4 mL). The reaction mixture was allowed to warm to 0 °C while being stirred for 2.5 h and then concentrated under reduced pressure. The residue was diluted with EtOAc (30 mL), washed with H_2O (10 mL), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product was effected by flash chromatography on silica gel, eluting with EtOAc−heptane (1:2). Evaporation of the solvent afforded 3.43 g of a mixture of **4a**/**4b** in 79% yield: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.15−1.95 (m, 7H), 2.02−2.41 (m, 2H), 2.88−3.14 (m, 1H), 3.33−3.65 (m, 3H), 3.65−3.82 (m, 0.5H), 3.77−3.4.04 (m, 1.5H), 4.10−4.40 (m, 2H), 4.70 (br s, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 9.5 Hz, 1H), 5.60−5.90 (m, 1H), 7.54−7.64 (m, 2H), 7.65−7.71 (m, 1H), 7.85−7.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.56, 25.03, 25.27, 28.16, 30.05, 30.28, 30.67, 31.03, 39.88, 40.23, 43.50, 44.20, 60.65, 61.03, 65.11, 65.79, 71.74, 79.62, 97.90, 119.38, 128.86, 129.09, 131.46, 133.69; MS (CI) *m*/*z* 466 (M + H)$^+$, 382 (base), 326, 143.

(2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-2-(hydroxymethyl)-3-allyl-3-(phenylsulfonyl)pyrrolidine (5a). A solution of 3.43 g (7.37 mmol) of the mixture of **4a**/**4b** obtained *via* route B in ethanol (30 mL) was warmed to 50 °C for 4 h in the presence of 0.1 equiv of PPTS. After evaporation of ethanol, the residue was diluted with CH_2Cl_2 (30 mL), washed with H_2O, and then dried and concentrated to provide 2.64 g of a mixture of **5a**/**5b** in 94% yield. The ratio of the **5a**/**5b** mixture was determined

(15) Subramanian, P. K.; Woodard, R. W. *J. Org. Chem.* **1987**, *52*, 15.

to be 89:11 by HPLC.[9] Recrystallization (twice from EtOAc/heptane) provided 2.11 g of pure **5a**: mp 133−134 °C; $[\alpha]^{25}_D$ = +74.5° (*c* 1.0, CH_3OH); $[\alpha]^{25}_D$ = +64.5° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.63−1.82 (m, 1H), 2.04−2.24 (m, 1H), 2.33 (dd, *J* = 15.0, 4.5 Hz, 0.5H), 2.48 (dd, *J* = 15.0, 4.5 Hz, 0.5H), 2.73−3.01 (m, 1H), 3.30−3.52 (m, 1H), 3.58−3.72 (m, 1H), 3.92−4.22 (m, 2H), 4.26−4.38 (m, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 5.12 (d, *J* = 9.8 Hz, 1H), 5.59−5.85 (m, 1H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.35, 31.67, 40.27, 40.77, 44.37, 44.88, 61.97, 62.29, 63.73, 64.53, 72.20, 72.46, 80.11, 120.11, 120.18, 129.29, 129.46, 130.70, 131.06, 134.43; MS (CI) *m*/*z* 382 ((M + H)$^+$, base), 326, 282. Anal. Calcd for $C_{19}H_{27}NO_5S$: C, 59.81; H, 7.13; N, 3.67; S, 8.40. Found: C, 59.66; H, 7.21; N, 3.56; S, 8.26.

(2*S*)-1-(*tert*-Butyloxycarbonyl)-2-[[(2-tetrahydropyranyl)oxy]methyl]-3-allylpyrrolidine (6a/6b). To a solution of **4a**/**4b** obtained *via* route A (2.12 g, 4.56 mmol) and Na_2HPO_4 (1.94 g, 13.68 mmol) in HPLC-grade MeOH (30 mL) was added 6% Na−Hg (5.2 g, 13.5 mmol). The mixture was vigorously stirred for 1 h at room temperature. After concentration of the solution, the residue was dissolved in CH_2Cl_2 (30 mL), washed with H_2O (4 × 10 mL), dried over $MgSO_4$, and concentrated. Flash chromatography of the crude product on silica gel, eluting with EtOAc/heptane (1:4), afforded a mixture of 1.14 g of **6a**/**6b** in 77% yield: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.40−1.65 (m, 6H), 1.60−2.10 (m, 2H), 1.92−2.45 (m, 2H), 3.19−3.63 (m, 4H), 3.50−4.05 (m, 4H), 4.50−4.66 (m, 1H), 4.92−5.14 (m, 2H), 5.70−5.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.64, 18.96, 19.23, 19.61, 25.43, 28.36, 28.46, 29.35, 30.27, 30.53, 30.72, 31.38, 31.53, 34.02, 38.09, 40.94, 41.66, 41.82, 45.47, 45.78, 58.41, 58.77, 60.85, 61.42, 61.59, 61.89, 62.46, 65.04, 65.42, 65.83, 66.57, 67.55, 68.15, 69.75, 79.06, 97.29, 97.84, 98.49, 99.09, 99.53, 114.77, 115.49, 116.25, 136.48, 137.27, 138.03; MS (CI) *m*/*z* 326 ((M + H)$^+$, base), 270, 242, 226, 186, 142. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.42; H, 9.60; N, 4.30. Found: C, 66.43; H, 9.47; N, 4.11.

(2*S*,3*S*)-1-(*tert*-Butyloxycarbonyl)-2-(hydroxymethyl)-3-allylpyrrolidine (7a). To a solution of a mixture of **5a**/**5b** obtained *via* route B (2.87 g, 7.52 mmol) and Na_2HPO_4 (3.20 g, 22.6 mmol) in HPLC-grade MeOH (30 mL) was added 6% Na−Hg (8.6 g, 22.4 mmol). The mixture was vigorously stirred for 1 h at room temperature. After concentration of the solution, the residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (4 × 15 mL), dried over $MgSO_4$, and concentrated. Flash chromatography of the crude product on silica gel, eluting with EtOAc/heptane (1:1), afforded 1.50 g of **7a** in 83% yield: viscous oil; $[\alpha]^{25}_D$ = −20.5° (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.74−2.40 (m, 5H), 3.15−3.35 (m, 1H), 3.42−3.88 (m, 3H), 4.92 (br s, 1H), 5.05 (d, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 13.7 Hz, 1H), 5.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.50, 29.58, 37.46, 41.05, 46.38, 64.53, 65.32, 66.96, 80.27, 116.84, 135.93; MS (CI) *m*/*z* 242 ((M + H)$^+$, base), 186, 142. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.69; H, 9.60; N, 5.80. Found: C, 64.95; H, 9.47; N, 5.79.

(2*S*,3*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-allylproline (8a). To a solution of **7a** (1.28 g, 5.3 mmol) in acetone (120 mL) was added Jones reagent (5.5 mL, 2 equiv). The mixture was vigorously stirred for 1 h at room temperature. After evaporation of acetone under reduced pressure, the residue was diluted with EtOAc (10 mL). The organic phase was washed with H_2O (3 × 10 mL) and extracted with 1 N NaOH (8 mL). The resultant solution was extracted with EtOAc (20 mL) and then was acidified to pH 2 with 1 N HCl. The precipitate was extracted into CH_2Cl_2 (20 mL), and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The combined CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was dried under reduced pressure over P_2O_5 to give 1.17 g of **8a** in 86% yield: viscous oil; $[\alpha]^{25}_D$ = −2.3° (*c* 1.0, CH_3OH); $[\alpha]^{25}_D$ = −27.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (two conformers) δ 1.41 (s, 6H), 1.45 (s, 3H), 1.56−1.68 (m, 1H, 4-H), 2.00−2.09 (m, 1H, 4-H), 2.09−2.20 (m, 1H, allyl), 2.30−2.45 (m, 1H, allyl), 2.35−2.50 (m, 1H, 3-H), 3.37−3.55 (m, 1H, 5-H), 3.45−3.63 (m, 1H, 5-H), 3.89 (d, *J* = 4.5 Hz, 0.6H, 2-H), 3.95 (d, *J* = 4.1 Hz, 0.4H, 2-H), 5.08 (d, *J* = 10.5 Hz, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 5.70−5.86 (m, 1H), 7.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.37, 29.22, 29.55, 37.35 ($CH_2CH{=}CH_2$), 42.25, 44.04, 45.51, 45.86, 63.95, 80.56, 80.83, 117.47 ($CH{=}CH_2$), 135.24 ($CH{=}CH_2$), 154.10, 155.53, 176.91, 178.71; MS (CI) *m*/*z* 256 (M + H)$^+$, 200 (base), 156. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.48. Found: C, 61.12; H, 8.35; N, 5.46.

(2*S*,3*R*)-*N*-(*tert*-Butyloxycarbonyl)-3-allylproline Methyl Ester (8c). A mixture of **8a**/**8b** (285 mg, 1.11 mmol) obtained *via* route C was esterified with CH_2N_2 in ether. After evaporation of ether, the residue was dissolved in MeOH (1.5 mL) and was treated with 1 N NaOH (1.2 mL) with stirring at room temperature for 24 h. The solution was concentrated to remove MeOH and then extracted with EtOAc (3 × 2 mL). The extracts were dried over $MgSO_4$, filtered, and concentrated to afford 163 mg of **8c** in 54% yield: viscous oil; $[\alpha]^{25}_D$ = +25.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (two conformers) δ 1.41 (s, 5H), 1.46 (s, 4H), 1.65−1.82 (m, 1H), 1.76−1.91 (m, 1H), 1.91−2.04 (m, 1H), 2.17−2.44 (m, 1H), 2.44−2.48 (m, 1H), 3.25−3.36 (m, 1H), 3.58−3.75 (m, 1H), 3.72 (s, 3H), 4.25 (d, *J* = 8.6 Hz, 0.6H), 4.35 (d, *J* = 8.3 Hz, 0.4H), 5.00−5.11 (m, 2H), 5.70−5.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.30, 28.43, 28.95, 29.71, 34.43, 34.48, 42.54, 45.63, 51.52, 61.96, 62.49, 79.87, 116.46, 116.54, 135.82, 172.37; MS (CI) *m*/*z* 270 ((M + H)$^+$, 204 (base), 170. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.43; H, 8.53; N, 5.14.

(2*S*,3*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-*n*-propylproline (9). Catalytic hydrogenation of **8a** (60 mg, 0.23 mml) in MeOH (1.5 mL) on palladium on activated carbon (5 mg, 10% Pd/C) was carried out for 30 min to afford 55 mg of **9** in 89% yield: mp 88−90 °C (lit.[5a] mp 88−89 °C); $[\alpha]^{25}_D$ = −17.8° (*c* 1.0, MeOH); $[\alpha]^{25}_D$ = −42.5° (*c* 1.0, $CHCl_3$) [lit.[5a] $[\alpha]^{25}_D$ = −42.5° (*c* 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) (two conformers) δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.28−1.69 (m, 14H), 2.00−2.18 (m, 1H), 2.20−2.48 (m, 1H), 3.34−3.70 (m, 2H), 3.84 (d, *J* = 6.2 Hz, 0.4H), 3.98 (d, *J* = 4.4 Hz, 0.6H); ^{13}C NMR ($CDCl_3$) δ 14.07, 20.88, 28.39, 30.10, 30.28, 35.63, 42.48, 44.72, 45.83, 46.12, 64.70, 80.50, 153.95, 155.95, 176.53, 179.06; MS (CI) *m*/*z* 258 ((M + H)$^+$, 219 (base), 202, 158. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.67; H, 9.00; N, 5.44. Found: C, 60.81; H, 8.89 ; N, 5.25.

(2*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*tert*-butyloxycarbonyl)amino]-3-(phenylsulfonyl)propane (10). Prepared from (2*S*)-2-[(*tert*-butyloxycarbonyl)amino]-3-(phenylsulfonyl)-1-propanol[7] in 88% yield according to the standard procedure:[16] viscous oil; $[\alpha]^{25}_D$ = −0.8° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 1.40 (s, 9H), 3.30−3.42 (m, 2H), 3.55−3.64 (m, 1H), 3.70−3.81 (m, 1H), 3.91−4.03 (m, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.03, 25.67, 28.17, 48.28, 56.32, 63.62, 79.69, 127.84, 129.17, 133.61, 139.49, 154.62; MS (CI) *m*/*z* 430 ((M + H)$^+$, base), 374, 330, 143. Anal. Calcd for $C_{20}H_{35}NO_5SSi$: C, 55.90; H, 8.21; N, 3.26; S, 7.46. Found: C, 55.81; H, 8.38; N, 3.09; S, 7.35.

(2*R*)-1-(*tert*-Butyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-(phenylsulfonyl)pyrrolidine (11). To a solution of **10** (860 mg, 2 mmol) in THF (10 mL) was added n-BuLi (2.7 mL, 1.6 M in hexane) at −78 °C under dry nitrogen. The mixture was stirred for 30 min at −78 °C while 2-bromoethyl triflate (620 mg, 2.4 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to 0 °C while being stirred for 2 h and then concentrated under reduced pressure. The residue was diluted with EtOAc (10 mL) and was washed with H_2O (3 × 5 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel eluting with EtOAc/heptane (1:2) provided 650 mg of **11** in 71% yield: viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.02, 0.03 (s, 6H), 0.84 (s, 4.2H), 0.89 (s, 2.8H), 0.91 (s, 2H), 1.45 (s, 6.5H), 1.51 (s, 2.5H), 2.15−2.51 (m, 2H), 3.17−3.30 (m, 1H), 3.35−3.50 (m, 1.5H), 3.50−3.88 (m, 2.5H), 4.24−4.38 (m, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −5.51, 18.11, 24.99, 25.32, 25.81, 28.35, 28.46, 45.60, 46.08, 59.20, 59.49, 62.95, 63.75, 65.19, 65.86, 79.72, 80.02, 128.01, 128.79, 129.40, 133.78, 133.95, 134.08, 137.71; HRMS (CI) calcd for $C_{22}H_{38}NO_5SSi$ (M + H)$^+$ 456.2239, found 456.2226.

(2*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*tert*-butyloxycarbonyl)amino]-3-(phenylsulfonyl)-5-hexene (12). To a solution of **10** (1.28 g, 2.97 mmol) in THF (20 mL) at −78 °C was added dropwise *n*-BuLi (3.8 mL, 1.6 M in hexane) under dry nitrogen, and the reaction mixture was stirred at −78 °C

(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

for 20 min when allyl bromide (430 mg, 3.56 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to 0 °C while being stirred for 2 h and then concentrated under reduced pressure. The residue was diluted with EtOAc (25 mL) and washed with H_2O (3 × 5 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated. Flash chromatography on silica gel (EtOAc/hexane = 1:2) gave 865 mg (1.84 mmol) of **12** in 62% yield: viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.02, 0.03 (s, 6H), 0.86 (s, 9H), 1.45 (s, 9H), 2.43−2.70 (m, 2H), 3.50 (m, 1H), 3.70 (m, 1H), 3.80 (m, 1H), 4.25 (m, 1H), 4.96−5.18 (m, 3H), 5.78 (m, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −5.74, 17.76, 25.49, 28.02, 30.71, 31.13, 50.94, 51.24, 62.37, 63.97, 79.24, 117.78, 118.50, 127.95, 128.50, 128.64, 128.88, 128.92, 133.49, 133.69, 138.04, 139.36, 155.01; MS (CI) m/z 470 ((M + H)$^+$, base), 414, 370. Anal. Calcd for $C_{23}H_{39}NO_5SSi$: C, 58.81; H, 8.36; N, 2.98; S, 6.82. Found: C, 58.82; H, 8.23; N, 2.81; S, 6.76.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-allyl-3-(phenylsulfonyl)pyrrolidine (13b) (*via* Route A). To a solution of **11** (1.22 g, 2.6 mmol) in THF (15 mL) was added dropwise *n*-BuLi (1.7 mL, 1.6 M in hexane) at −78 °C under dry nitrogen. The mixture was stirred for 30 min at −50 °C and then cooled back to −78 °C to add ally bromide (0.38 g, 3.1 mmol) in THF (1 mL). The reaction mixture was allowed to warm to 0 °C while being stirred for 3 h and then diluted with EtOAc (10 mL) and was washed with H_2O (3 × 5 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product was effected by flash chromatography on silica gel, eluting with EtOAc/heptane (1:2). Evaporation of the solvent afforded 0.82 g of **13b** in 63% yield: viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.02, 0.03 (s, 6H), 0.84, 0.85 (s, 9H), 1.35 (s, 3.6H), 1.45, 1.46 (s, 5.4H), 2.14−2.35 (m, 1H), 2.43−2.62 (m, 1H), 2.53−2.71 (m, 1H), 2.82−2.96 (m, 2H), 3.12−3.25 (m, 1H), 3.64−3.72 (m, 1H), 3.75−3.86 (m, 0.6H), 3.97−4.04 (m, 0.4H), 4.35−4.40 (m, 1H), 5.04−5.21 (m, 2H), 6.18−6.33 (m, 1H), 7.58 (t, J = 7.5 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.86−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.69, −5.60, −5.46, −5.37, 17.96, 25.79, 25.85, 28.49, 28.67, 31.36, 31.70, 35.75 ($CH_2CH{=}CH_2$), 35.94 ($CH_2CH{=}CH_2$), 44.63, 45.18, 61.22, 75.27, 79.50, 79.87, 118.17 ($CH{=}CH_2$), 128.90, 129.02, 129.24, 129.71, 129.96, 133.83 ($CH{=}CH_2$), 134.06 ($CH{=}CH_2$), 137.36, 153.10; MS (CI) m/z 496 ((M + H)$^+$, base), 440, 414. Anal. Calcd for $C_{25}H_{41}NO_5SSi$: C, 60.56; H, 8.33; N, 2.82; S, 6.46. Found: C, 60.34; H, 8.18; N, 2.71; S, 6.33.

(2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-allyl-3-(phenylsulfonyl)pyrrolidine (13a). For the comparison of its NMR spectra with those of **13b**, **13a** was prepared. To a mixture of **13a**/**13b** (580 mg, 1.1 mmol)-in tetrahydrofuran (10 mL), prepared from **3** in 70% yield using the same procedure as described for the preparation of **4a**/**4b** *via* route A, was added tetrabutylammonium fluoride (2 mL, 2 mmol, 1.0 M in THF). The mixture was stirrred at room temperature and the progress of the reaction monitored by TLC. After 30 min, the solution was treated with H_2O (20 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a 70:30 mixture of **5a**/**5b** (assessed by HPLC[9]) in 92% yield. The residue was recrystallized three times from EtOAc/hexane to afford **5a** (252 mg). To a solution of **5a** (120 mg, 0.3 mmol) in DMF (1.5 mL) at room temperature were added *tert*-butyldimethylsilyl chloride (60 mg, 0.4 mmol) and imidazole (54 mg, 0.8 mmol). After 48 h, diethyl ether (10 mL) was added and the mixture washed with saturated NH_4Cl solution (6 mL). The organic layer was separated and dried over $MgSO_4$, and the solvents were evaporated *in vacuo*. The crude product was purified by flash chromatography (EtOAc/heptane = 1:1) to provide 130 mg of **13a** in 83% yield: viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.03, 0.06 (s, 6H), 0.89 (s, 9H), 1.40 (s, 9H), 1.55−1.70 (m, 1H), 1.95−2.25 (m, 2H), 2.97 (q, J = 9.7 Hz, 1H), 3.30−3.52 (m, 2H), 4.00−4.23 (m, 3H), 4.82−5.05 (m, 2H), 5.66−5.82 (m, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ -5.65, −5.50, 18.31, 25.96, 28.48, 31.12, 40.37 ($CH_2CH{=}CH_2$), 40.57 (CH_2-$CH{=}CH_2$), 44.43, 44.85, 61.21, 61.91, 62.56, 62.89, 72.00, 79.86, 119.54 ($CH{=}CH_2$), 129.11, 129.34, 131.81, 133.87 ($CH{=}CH_2$), 138.29; MS (CI) m/z 496 ((M + H)$^+$, base), 440, 414. Anal. Calcd for $C_{25}H_{41}NO_5SSi$: C, 60.56; H, 8.33; N, 2.82; S, 6.46. Found: C, 60.29; H, 8.28; N, 2.69; S, 6.41.

X-ray Structure Analysis of 5a. Crystal data: $C_{19}H_{27}NO_5S$, molecular weight 381.49; colorless crystal of 0.03 × 0.20 × 0.53 mm monoclinic system; space group $P2_1$, Z = 2, a = 10.723(5) Å, b = 7.110(3) Å, c = 12.992(5) Å, β = 101.15(2)°, V = 971.8(7) Å^3, d_{calc} = 1.30 g cm^{-3}, F (000) = 408, λ (Cu Kα) = 1.5418 Å, μ = 1.68 mm^{-1}. Intensity data were measured on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the ($\theta - 2\theta$) scan technique up to θ = 65°. From the 2553 collected reflexions ($-12 \le h \le 12$, $-6 \le k \le 8$, $0 \le l \le 15$), 2430 were independent (R_{int} = 0.05), and 2255 were considered as observed with $I \ge 3\sigma(I)$. Cell parameters were refined from 25 well-centered reflexions with $9.7 \le \theta \le 23.9°$. The structure was solved by direct methods using *SHELX*S86[17] and refined by full-matrix least-squares methods with *SHELX*76,[18] minimizing the function $\sum w(F_o - |F_c|)^2$. The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions (d(C−H) = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.053 and R_w = 0.069 (with $R_w = [\sum w(F_o - |F_c|)^2/\sum wF_o^2]^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.0043F_o^2]$. The residual electron density in the final difference map was located between 0.98 and −0.39 e Å^{-3}. An intermolecular hydrogen bond links the hydroxy group O_7 to the carbonyl of the Boc group (O_7-H···O_{12} = 2.889(6) Å).

X-ray Structure Analysis of 5b. Crystal data: $C_{19}H_{27}NO_5S$, molecular weight 381.49; colorless crystal of 0.02 × 0.10 × 0.20 mm, monoclinic system; space group $P2_1$, Z = 4, a = 7.020(6) Å, b = 11.608(6) Å, c = 26.313(16) Å, β = 105.54(5)°, V = 2065(2) Å^3, d_{calc} = 1.23 g cm^{-3}, F(000) = 816, λ (Cu Kα) = 1.5418 Å, μ = 1.58 mm^{-1}. Intensity data were measured on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the ($\theta - 2\theta$) scan technique up to θ = 64°. From the 3667 collected reflections ($-8 \le h \le 7$, $0 \le k \le 13$, $0 \le l \le 30$), 3602 were independent (R_{int} = 0.11), and 3071 were considered as observed with $I \ge 3\sigma(I)$. Cell parameters were refined from 25 well-centered reflexions with $10.2 \le \theta \le 19.9°$. The structure was solved by direct methods using SHELXS86 [17] and refined by full-matrix least-squares methods with *SHELX*76,[18] minimizing the function $\sum w(F_o - |F_c|)^2$. The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions (d(C−H) = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.072 and R_w = 0.089 (with $R_w = [\sum w(F_o - |F_c|)^2/\sum wF_o^2]^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.008F_o^2]$. The residual electron density in the final difference map was located between −0.87 and +0.59 e Å^{-3}. The two molecules of the asymmetric unit are linked through a hydrogen bond between the hydroxy group O_7 (molecule B) and the carbonyl of the Boc group O_{12} of molecule A (O_7−H···O_{12} = 2.733(8) Å). The hydroxy O_7−H (A) is linked in a similar manner to the carbonyl O_{12} of a neighboring molecule (B, 1 + x, y, z), 2.742(8) Å).

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**, **2**, **3**, **4a**,**b**, **5a**,**b**, **6a**, **7a**, **8a**,**c**, **9**−**12**, and **13a**,**b**, ^{13}C NMR spectra for compounds **1**, **5a**,**b**, **7a**, **8a**,**c**, **9**−**11**, **13a**,**b**, and 2D ^{1}H−^{1}H, ^{1}H−^{13}C spectra for compounds **5a**, **8a**,**c**, **9**, **11**, and **13b** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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