A Versatile Method for the Facile Synthesis of Enantiopure *trans*- and *cis*-2,5-Disubstituted Pyrrolidines

Qian Wang, N. André Sasaki,* Claude Riche, and Pierre Potier

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

Received June 30, 1999

Treatment of (2*S*)-1-*O*-benzylglycerol-2,3-bistriflate **(2)** with the trilithiated species of chiral building blocks **5**−**7** provided 2,3,5-trisubstituted pyrrolidines that were subjected to reductive desulfonylation to give *trans*-2,5-disubstituted pyrrolidines **11**−**13**, respectively. The same reaction sequence with the (2*R*)-bistriflate **4** and trilithiated **5** afforded the cis isomer **19**. This two-step synthetic mehodology can furnish any one of the four possible diastereomers of enantiopure 2,5-disubstituted pyrrolidines in 60−72% overall yields.

Introduction

Preparation of enantiopure polysubstituted pyrrolidine derivatives is quite a challenging subject. Among this class of compounds, 2,5-disubstituted pyrrolidines are particularly interesting due to the fact that many of them occur in nature and possess a broad range of physiological properties.[1] They often serve as pivotal key intermediates in the synthesis of pyrrolizidine and indolizidine derivatives.[2] Furthermore, *trans*-2,5-disubstituted pyrrolidines have proven to be of considerable importance as chiral auxiliaries.[3−5] This is demonstrated by a large number of reports focused on their asymmetric synthesis.[6] The most recent example is an efficient method developed by Katritzky et al.[7] that is based on the Husson's 2-cyano-6-oxazolopiperidine synthon methodology.[8] However, a majority of the methods reported so far has been plagued by the need of the separation of a diastereomeric mixture, which by no means is trivial. In the case of the pyrrolidine chiral auxiliaries, in particular, it is desirable to prepare both of the enantiopure 2*S*,5*S* and 2*R*,5*R* isomers. With this in mind, we have previously described two synthetic approaches starting from readily available chiral building block **6**[9a,10] and chiral glycidyl triflate or **7**[11] and chiral

(1) (a) Caro, M. R.; Derbes, V. J.; Jung, R. C. *Arch. Dermatol.* **1957**, *75*, 475. (b) Adrouny, G. A.; Derbes, V. J.; Jung, R. C. *Science* **1959**, *130*, 449. (c) Attygalle, A. B.; Morgan, E. D. *Chem. Soc. Rev.* **1984**, *13*, 245. (d) Jones, T. H.; Blum, M. S. In *Alkaloids, Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley: New York, 1983; Vol. 1, p 33−84. (e) Casier, P.; Lemaire, M.; J. L.; Clément, J.-L.; Basselier, J.-J.; Lange, C.; Célérier, J.-P.; Lhommet, G. Fr. Patent 84/06980. (e) Ronzani, N.; Lajat, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1131.

(2) (a) Grandjean, C.; Rosset, S.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1993**, *34*, 4517. (b) Oppolzer, W.; Jacobsen, E. J. *Tetrahedron Lett.* **1986**, *27*, 1141. (c) Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2072. (d) Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405. (e) Takahata, H.; Banda, H.; Momose, T. *Heterocycles* **1993**, *36*, 2777. (f) Bloch, R.; Brillet-Fernandez, C.; Kühn, P.; Mandville, G. *Heterocycles* **1994**, *38*, 1589. (g) Célimène, C.; Dhimane, H.; Le Bail, M.; Lhommet, G. *Tetrahedron Lett.* **1994**, *35*, 6105. (h) Fleurant, A.; Salion, C.; Célérier, J.-P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255. (i) Célimène, C.; Dhimane, H.; Saboureau, A.; Lhommet, G. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1585. (j) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1996**, *42*, 39. (k) Vo Thanh, G.; Célérier, J.-P.; Lhommet, G. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2211. (l) Vo Thanh, G.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1999**, *40*, 3713.

(3) *trans*-2,5-Dialkylpyrrolidines: (a) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. (b) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. (c) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (d) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (e) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 103. (f) Yamazaki, T.; Gimi, R.; Welch, J. T. *Synlett* **1991**, *8*, 573. (g) Genicot, C.; Ghosez, L. *Tetrahedron Lett.* **1992**, *48*, 7357. Zwaagstra, M.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1993**, *4*, 2163. (h) A recent application: Pearson, A.; Gontcharov, A.; Zhu, P. Y. *Tetrahedron* **1997**, *53*, 3849.

(4) *trans*-2,5-Dialkoxymethylpyrrolidines: (a) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi; M. *Tetrahedron Lett.* **1984**, *25*, 857. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015. (c) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343. (d) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807. (e) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403. (f) Uchikawa, M.; Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4577. (g) Ikegami, S.; Uchiyama, H.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333. (h) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1989**, *30*, 3805. (i) Marzi, M.; Misiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075. (j) Chen, L.-Y.; Ghosez, L. *Tetrahedron Lett.* **1990**. *31*, 4467. (k) Fuji, K.; Node, M.; Naniwa, Y.; Kawabata, T. *Tetrahedron Lett.* **1990**, *31*, 3175. (l) Gouverneur, V.; Ghosez, L. *Tetrahedron*: *Asymmetry* **1990**, *1*, 363. (m) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 5349. (n) Yamamoto, Y.; Ohmori, H.; Sawada, S. *Synlett* **1991**, *8*, 319. (o) Ghosez, L.; Genicot, C.; Gouverneur, V. *Pure Appl. Chem.* **1992**, *64*, 1849. (p) Marzi, M.; Minetti, P.; Misti, D. *Tetrahedron* **1992**, *48*, 10127. (q) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298. (r) Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165. (s) Giese, B.; Hoffmann, U.; Roth, M.; Veit, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445. (t) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375. (u) Sibi, M. P.; Lu, J. *Tetrahedron Lett.* **1994**, *35*, 4915. (v) Shi, M.; Satoh, Y.; Makihara, T.; Masaki, Y. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2109. (w) Kawanami, Y.; Moriya, H.; Goto, Y.; Tsukao, K.; Hashimoto, M. *Tetrahedron* **1996**, *52*, 565. (x) Takahata, H.; Takahashi, S.; Kouno, S.; Momose, T. *J. Org. Chem.* **1998**, *63*, 2224. (y) Recent applications: (z) Felice, E.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1999**, *40*, 4413. (aa) Donohoe, T. J.; Stevenson, C. A.; Helliwell, M.; Irshad, R.; Ladduwahetty, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1315.

(5) *trans*-Diferrocenylpyrrolidines: Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 3711.

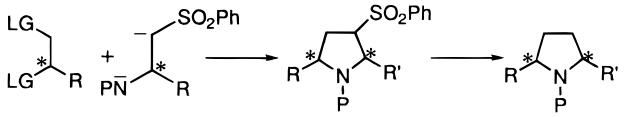
(6) (a) A recent review: Pichon, M.; Figadère, B. *Tetrahedron*: *Asymmetry* **1996**, *7*, 927 and references therein. (b) Vo Thanh, G.; Célérier, J.-P.; Fleurant, A.; Grandjean, C.; Rosset, S.; Lhommet, G. *Heterocycles* **1996**, *43*, 1381. (c) Chiesa, M. V.; Manzoni, L.; Scolastico, C. *Synlett* **1996**, 441. (d) Langlois, N.; Rojas-Rousseau, A.; Decavallas, O. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1095. (e) Beausoleil, E.; L'Archevêque, B.; Bélec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (f) Dhimane, H.; Vanucci, C.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 1415. (g) Arndt, H.-D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879. (h) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *Tetrahedron Lett.* **1998**, *39*, 1697. (i) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069. (j) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520.

(7) Katritzky, A. R.; Cui, X.-L.; Yang, B. Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979.

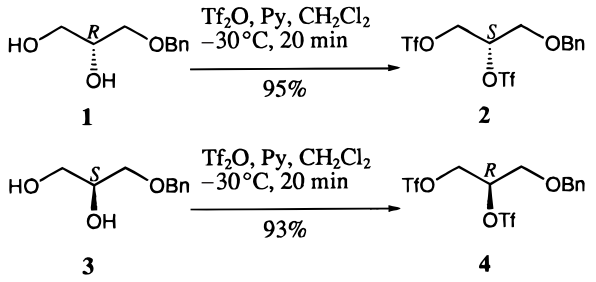
(8) (a) Huang, P. Q.; Arseniyadis, S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 547. (b) Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457.

10.1021/jo991052d CCC: $18.00
Published on Web 10/22/1999

Scheme 1



Scheme 2



2,3-*O*-isopropylideneglycerol triflate. Although these methods are efficient, the diastereomeric excess of the newly formed pyrrolidines according to the first protocol remains to be about 85%,[10] and the second one requires a multistep reaction sequence.[11] In this paper, we report a new and versatile one-step cyclization method that provides any one of the four possible stereoisomers of 2,5-disubstituted pyrrolidines in an enantiomerically pure form. The basic principle of this new approach is illustrated in Scheme 1.

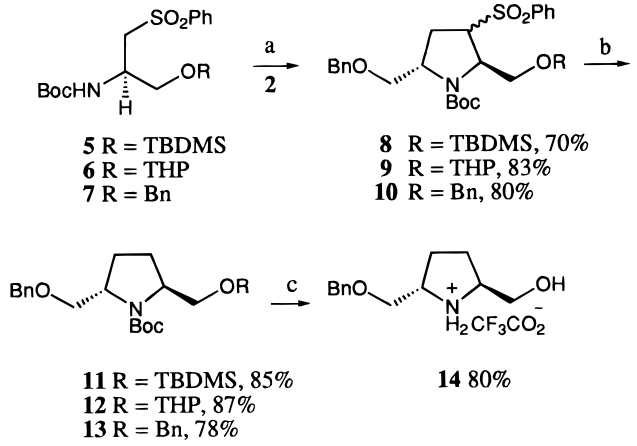
Results and Discussion

Synthesis of (2*S*,5*S*)-*trans*-2,5-Disubstituted Pyrrolidine Derivatives. The bistriflate of (*R*)-1-*O*-benzyl glycerol required for annulation process was prepared as shown in Scheme 2. Treatment of diol **1**, which was in turn prepared from (*S*)-(+)-2,3-*O*-isopropylideneglycerol by a two-step sequence,[12] with 2 equiv of trifluoromethanesulfonic anhydride in dichloromethane in the presence of 2.2 equiv of pyridine at −30 °C furnished the bistriflate **2** in 95% isolated yield.

The reaction temperature should be carefully controlled. In fact, when the reaction was carried out at 0 °C under otherwise identical conditions, the yield of bistriflate **2** dropped significantly. The bistriflate can be purified by flash chromatography and can be kept in the refrigerator for several months without decomposition. A similar procedure applied to (*S*)-diol **3** gave the (*R*)-bistriflate **4** in 93% yield.

With the bistriflate **2** and the chiral synthon **5** (R = TBDMS) in hand,[9b] the key coupling reaction was then investigated. Treatment of **5** with 2 equiv of *n*-BuLi (Scheme 3) generated the corresponding dianion, which was then trapped by the bistriflate **2** to give the pyrrolidine **8** in 58% overall yield together with 18% of recovered synthon **5** (Table 1, entry 1). The major byproducts isolated from this reaction derived from the bistriflate **2**. In fact, olefins **15**−**17** have been isolated

Scheme 3[a]



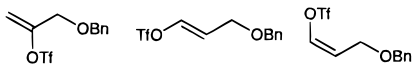
5 R = TBDMS
6 R = THP
7 R = Bn

8 R = TBDMS, 70%
9 R = THP, 83%
10 R = Bn, 80%

11 R = TBDMS, 85%
12 R = THP, 87%
13 R = Bn, 78%

14 80%

[a] Reagents and conditions: (a) BuLi (3 equiv), THF, −70 °C, 30 min then **2**, −70 °C, 1 h; (b) 6% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 2 h; (c) TFA, rt, 6 h.



15 **16** **17**

Figure 1.

Table 1. Survey of Annulation Conditions

entry	base (equiv)	solvent	*T* (°C)	**8** (% yield)	**5** (% recovery)
1	BuLi (2)	THF	−70	58	18
2	BuLi (2)	THF	−95	40	49
3	BuLi (2)	THF−HMPA	−70	0	83
4	BuLi (2)	Et_2O	−70	10	50
5	BuLi (2)	THF-Et_2O	−70	10	46
6	KHMDS (2)	THF	−70	0	80
7	KHMDS (2)	Et_2O	−70	0	85
8	BuLi (3)	THF	−70	70	21

and identified (Figure 1). To avoid this side reaction, a detailed survey of reaction conditions was carried out, and some of the results varying base (the counterion), reaction temperature, solvent, additive and equivalents of bases are summarized in Table 1. It is seen from these studies that the reaction is subjected to a significant countercation effect as the annulation did not proceed at all when KHMDS was used as a base. Addition of highly coordinating solvent (HMPA, 3 equiv) exhibited an adverse effect (Entry 3), while the reaction proceeded very slowly in Et_2O. Although most of the unreacted sulfone can be recovered, the uncoupled bistriflate was transformed completely to the olefins under all these conditions. Interestingly, acyclic coupling product was not isolated, which may indicate that the second S_N2 cyclization reaction proceeds relatively fast and that the overall efficiency of the annulation depends on the first intermolecular S_N2 reaction. Finally, under the optimal conditions found in our hands (3 equiv of BuLi, THF, −70 °C), the desired annulation process proceeded smoothly to afford the pyrrolidine **8** in 70% yield (89% based on 79% of conversion) as a mixture of two diastereoisomers (**8a** and **8b**, cf. Scheme 4) in a 2.7/1 ratio. About 21% of the starting sulfone was recovered, which accounted for the overall mass balance. We speculated that the trianion was formed under these conditions[13] and that the *gem*-dianion of sulfone was more nucleophilic favoring the attack of carbanion to the triflate leading to a high yield

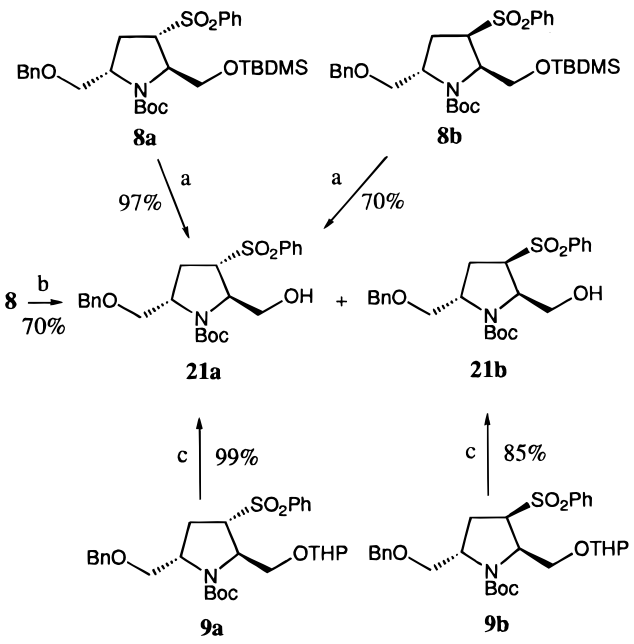
(9) (a) Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069. (b) Sasaki, N. A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P. *J. Org. Chem.* **1997**, *62*, 765. (c) Dockner, M.; Sasaki, N. A.; Riche, C.; Potier, P. *Liebigs Ann./Recuel.* **1997**, 1267. (d) Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron* **1998**, *54*, 15759.

(10) Sasaki, N. A.; Sagnard, I. *Tetrahedron* **1994**, *50*, 7093.

(11) Dockner, M.; Sasaki, N. A.; Potier, P. *Heterocycles* **1996**, *42*, 529.

(12) Iguchi, K.; Kitade, M.; Kashiwagi, T.; Yamada, Y. *J. Org. Chem.* **1993**, *58*, 5690.

Scheme 4[a]



[a] Reagents amd conditions: (a) Bu_4NF, THF, rt, 1 h; (b) 1% I_2/MeOH, reflux, 24 h; (c) PPTS, EtOH, 50 °C, overnight.

of pyrrolidine **8**. That the stereoisomerism of **8** was due to the newly formed chiral center at the α-position of the sulfone (C-3 of pyrrolidine) was proved during the subsequent chemical transformations (vide infra). It is worthy to note that the N-alkylation of triflate occurred exclusively in an S_N2 manner without the interference of the S_N1 mechanism, which is prone to epimerization.

In the previous paper,[14] we have reported that reaction of chiral synthon (*R*)- or (*S*)-**6** with 1-chloro-2-bromoethane can lead to the formation of either pyrrolidine or cyclopropane derivatives depending on the quantity of the base used. In the present case, the reaction was highly regioselective to give exclusively the pyrrolidine **8** without comcommitant formation of cyclopropane derivative even in the presence of 3 equiv of base.

The transformation of **8** to final 2,5-disubstituted pyrrolidine was straightforward. Desulfonylation of **8a** (6% Na−Hg in methanol at 0 °C) afforded compound **11** as two rotamers in 85% yield. Simultaneous removal of *N*-Boc and *O*-TBDMS groups under mild acidic conditions (TFA) furnished compound **14** as a single isomer. The same synthetic sequence applied to compound **8b** afforded a product identical in all respects with that obtained from **8a**, confirming that **8a** and **8b** were C-3 epimers. In practical synthesis, a mixture of two diastereomers **8a** and **8b** were used for the above-mentioned transformations without lowering the overall yields.

To provide further information about the stereoisomerism of **8a** and **8b**, an epimerization experiment through the protonation of intermediate sulfonyl stabilized carbanion was performed. Treatment of a mixture of **8a** and **8b** with 1 equiv of *n*-BuLi followed by quenching with aqueous NH_4Cl solution gave exclusively compound **8a**. This result can be account for on the basis of preferred pyramidal sulfonyl carbanion configuration as well as the

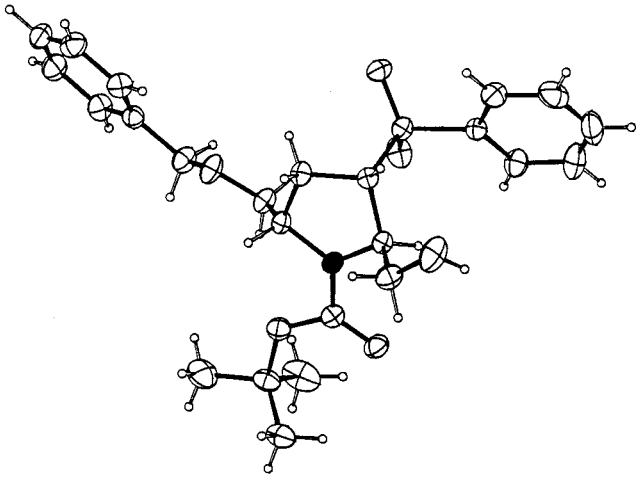


Figure 2.

preferred trans orientation of the adjacent C-2 protected hydroxymethyl group and phenyl sulfonyl group in the lithiated species of **8**. This control experiment is in accordance with our previous observations[9b] and paved the way for the projected stereoselective synthesis of 2,3,5-trisubstituted pyrrolidines. In this respect, an interesting observation has been made en route to compound **21a** from the two diastereomers **8a** and **8b**. Thus, treatment of diastereomerically pure compound **8a** or **8b** with tetrabutylammonium fluoride (TBAF) in THF gave the same desilylated product **21a**. Apparently, the basicity of these conditions (fluoride anion) is strong enough to epimerize the C-3 asymmetric center (Scheme 4). Desilylation while keeping the stereochemical integrity of compound **8b** could be realized by treatment with 1% of I_2 in methanol at reflux temperature.[15] The stereochemistry of **21a** was fully established by single-crystal X-ray analysis (Figure 2). While the stereochemistry of C-3 was of no consequence in the present studies as it will be destroyed in following transformation, it nevertheless provided important background information regarding the introduction of substituent at the C-3 position of pyrrolidine derivatives.

Applying the same synthetic sequence to chiral synthons **6** (R = THP) and **7** (R = Bn, Scheme 3),[9c] pyrrolidines **12** and **13** were synthesized in 72% and 62% overall yields, respectively. The stereochemistry of compounds **9a** and **9b** was determined by their conversion to the corresponding alcohols **21a** and **21b** by treatment with PPTS in EtOH at 50 °C (Scheme 4). The fact that different protective groups of the primary hydroxy group were tolerated enhances the generality of this efficient synthetic approach.

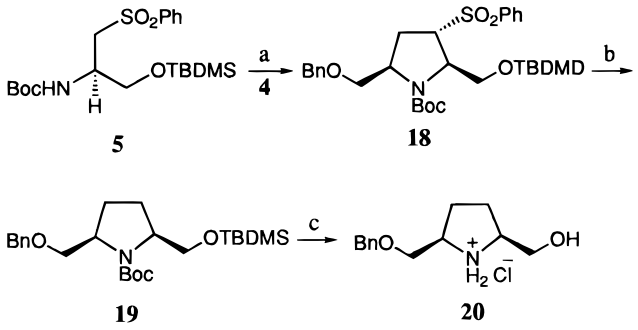
Synthesis of (2*S*,5*R*)-*cis*-2,5-Disubstituted Pyrrolidine Derivative. To access this type of compound, (*R*)-bistriflate **4** was required (Scheme 2). The coupling reaction of bistriflate (*R*)-**4** with the trianion of the synthon **5** proceeded cleanly to afford compound **18** in 89% yield (Scheme 5), and no trace of **8a** or **8b** was found from this reaction. Interestingly, only one diastereomer was observed in this case, indicating the much higher thermodynamic stability of **18** vs its C-3 epimer. Desulfonylation of **18** with 6% Na−Hg in methanol afforded (2*S*,5*R*)-*cis*-2,5-disubstituted pyrrolidine derivative **19** in

(13) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993; pp 158−172.

(14) Pauly, R.; Sasaki, N. A.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 237.

(15) Vaino, A. R.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1996**, 2351.

Scheme 5[a]



[a] Reagents and conditions: (a) BuLi (3 equiv), THF, −70 °C, 30 min then **4**, −70 °C, 1 h, 89%; (b) 6% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 3 h, rt, overnight, 78%; (c) TFA, rt, 6 h, then concd HCl, 100%.

78% yield as a mixture of two rotamers. The physical properties (IR, NMR, R_f) of compound **19** were completely different from those of **11**. This observation confirms that the synthetic sequences shown in Schemes 3 and 5 are free of epimerization. Treatment of **19** with TFA then HCl in methanol furnished compound **20** as a single isomer in quantitative yield.

Conclusion

We have developed a new, highly stereoselective synthesis of optically pure (2*S*,5*S*)-*trans*- and (2*S*,5*R*)-*cis*-2,5-disubstituted pyrrolidine derivatives from readily available chiral synthons. By docking two units with appropriate stereochemistry, all four diastereomers are readily accessible. The efficient and modulable approach described here should find application in the syntheses of pyrrolidine and indolizidine type natural products as well as pyrrolidine based C_2-symmetry chiral ligands.[10] The extension of this methodology for the synthesis of 2,3,5-trisubstituted pyrrolidine derivatives in a stereocontrolled manner is undergoing in our laboratory.

Experimental Section

General Methods. All reagents obtained from commercial sources were used without further purification. THF was distilled from sodium benzophenone ketyl. Flash chromatography 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. (*R*)- and (*S*)-2,3-*O*-isopropylideneglycerol (99% ee, CHEMI S.p.A., Italy) were used as received. ^{1}H NMR spectra were recorded at 300, 250, and 200 MHz, and ^{13}C NMR spectra were recorded at 75.5, 62.5, and 50 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 high-resolution mass spectrum was obtained by CI (methane). Elemental analyses were carried out by the microanalytical laboratory at the ICSN.

(2*S*)-1-*O*-Benzylglycerol-2,3-bistrifluoromethanesulfonate (2). To a solution of triflic anhydride (1.17 g, 0 70 mL, 4.16 mmol) in dry dichloromethane (40 mL) at −30 °C was added dropwise a solution of (*R*)-1-*O*-benzylglycerol **1** (379 mg, 2.08 mmol) and pyridine (362 mg, 369 μL, 4.58 mmol) in dry dichloromethane (2 mL) over a period of 10 min. After being stirred for 15 min, the reaction mixture was washed with ice-cold water and satd $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The light-brown residual oil was purified through silica gel (heptane/EtOAc = 2/1) to give the pure bistriflate **2** as a colorless oil (877 mg, 95%): $[\alpha]^{22}_D$ +21 (*c* 4.4, $CHCl_3$); IR ($CHCl_3$) 3035, 2871, 1497, 1455, 1428, 1366 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.30 (m, 5H), 5.15 (quintet, J = 4.8 Hz, 1H), 4.80−4.68 (m, 2H), 4.59 (s, 2H), 3.78 (d, J = 5.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.5, 128.7, 128.4, 128.0, 118.6 (q, J = 319 Hz), 118.5 (q, J = 319 Hz), 82.8, 74.0, 72.7, 67.0; MS (CI, NH_3) *m*/*z* 464 $[M + NH_4]^+$. Anal. Calcd for $C_{12}H_{12}O_7S_2F_6$: C, 32.29; H, 2.71; S, 14.61. Found: C, 32.24; H, 2.79; S, 14.11.

(2*R*)-1-*O*-Benzylglycerol-2,3-bistrifluoromethanesulfonate (4). Starting from (*S*)-1-*O*-benzylglycerol **3** (690 mg, 3.79 mmol), exactly the same procedure as described for the preparation of compound **2** furnished **4** (1.56 g, 93%): $[\alpha]^{22}_D$ −21 (*c* 5.2, $CHCl_3$); IR ($CHCl_3$) 3035, 2870, 1497, 1455, 1422, 1366 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.28 (m, 5H), 5.15 (quintet, J = 4.8 Hz, 1H), 4.81−4.68 (m, 2H), 4.59 (s, 2H), 3.78 (d, J = 5.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.6, 128.8, 128.4, 128.0, 118.7 (q, J = 319 Hz), 118.5 (q, J = 319 Hz), 82.9, 74.0, 72.8, 67.0; MS (CI, NH_3) *m*/*z* 464 $[M+NH_4]^+$. Anal. Calcd for $C_{12}H_{12}O_7S_2F_6$: C, 32.29; H, 2.71; S, 14.61. Found: C, 32.33; H, 2.78; S, 14.21.

(2*R*,3*S*,5*S*)- and (2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (8). To a solution of **5** (R = TBDMS) (140 mg, 0.33 mmol) in THF (5 mL) was added dropwise BuLi (1.6 M, 0.62 mL, 0.99 mmol) at −70 °C. After the solution was stirred for 30 min at the same temperature, a solution of **2** (189 mg, 0.42 mmol) in THF (1.5 mL) was added dropwise, and stirring was continued for 1 h before quenching by addition of saturated NH_4Cl. The reaction mixture was extracted with ether. The ether extracts were washed with brine, dried, and evaporated. Preparative TLC (silica gel, dichloromethane/acetone = 50/1) afforded **8** as a mixture of two isomers (132 mg, 70%; 89% based on 71% of conversion) and starting material **5** (29 mg, 21%) was recovered. Compounds **8a** and **8b** could be separated by PTLC (silica gel, heptane/EtOAc = 4/1)

(2*R*,3*S*,5*S*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (8a). Major isomer (two rotamers): $[\alpha]^{20}_D$ −20 (*c* 3.5, $CHCl_3$); IR ($CHCl_3$) 2956, 2931, 1688, 1475, 1450, 1394, 1369, 1306, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.85 (m, 2H), 7.68−7.53 (m, 3H), 7.36−7.27 (m, 5H), 4.65−4.47 (m, 2H), 4.40−4.31 (m, 1H), 4.19−3.79 (m, 3H), 3.76−3.71 (m, 1H), 3.64−3.17 (m, 2H), 2.69−2.24 (m, 2H), 1.46, 1.38 (two s, 9H), 0.82, 0.80 (two s, 9H), −0.016, −0.060, −0.068 (three s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.0, 138.3, 138.0, 133.9, 129.3, 128.7, 128.3, 127.7, 80.2, 73.2, 70.5, 70.0, 65.5, 65.2, 63.7, 62.2, 60.9, 60.3, 57.7, 57.5, 28.6, 28.4, 28.3, 25.8, 18.0, −5.6; MS (CI) *m*/*z* 576 $[M + H]^+$. Anal. Calcd for $C_{30}H_{45}NO_6SSi$: C, 62.58; H, 7.88; N, 2.43; S, 5.55. Found: C, 62.16; H, 8.08; N, 2.41; S, 5.42.

(2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (8b). Minor isomer (two rotamers): $[\alpha]^{20}_D$ −26 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 2929, 2857, 1696, 1654, 1559, 1456, 1394, 1306, 1255 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89−7.86 (m, 2H), 7.68−7.51 (m, 3H), 7.29−7.21 (m, 3H), 7.11−7.07 (m, 1H), 7.01−6.97 (m, 1H), 4.51−3.95 (m, 7H), 3.82 (dd, J = 9.7, 3.8 Hz, 0.5H), 3.54 (dd, J = 9.6, 4.7 Hz, 0.5H), 3.36 (dt, J = 9.5, 2.5 Hz, 1H), 2.97−2.75 (m, 1H), 1.89 (dd, J = 11.3, 6.6 Hz, 0.5 H), 1.74 (dd, J = 11.3, 6.6 Hz, 0.5H), 1.46, 1.40 (two s, 9H), 0.91, 0.90 (two s, 9H), 0.13, 0.092, 0.067, 0.036 (four s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.2, 153.1, 140.3, 140.2, 138.4, 138.1, 133.7, 129.3, 128.5, 128.4, 128.2, 127.8, 127.6, 127.5, 127.4, 80.2, 73.4, 73.2, 71.5, 70.4, 64.2, 63.6, 61.0, 59.5, 59.4, 59.2, 57.5, 57.1, 30.2, 29.7, 28.6, 28.6, 26.0, 18.2, −5.5, −5.6, −5.7; MS (CI) *m*/*z* 576 $[M + H]^+$.

(2*R*,3*S*,5*S*)- and (2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-tetrahydropyranyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (9). Starting from **6** (172 mg, 0.43 mmol), exactly the same procedure as described for the preparation of compound **5** furnished **9** as four isomers (195 mg, 83%), and 27 mg (16%) of the starting sulfone **7** was recovered.

(2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-tetrahydropyranyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (9a) (*β*-Sulfone). Less polar isomers, two isomers (four rotamers): IR ($CHCl_3$) 3019, 2977, 1688, 1522, 1477, 1423, 1393, 1368 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91−7.88 (m, 2H), 7.72−7.52 (m, 3H), 7.36−7.00 (m, 5H), 4.73−4.60 (m, 1H), 4.46−4.22 (m, 4H), 4.17−3.95 (m, 4H), 3.88−3.76 (m, 1H), 3.57−3.50 (m, 1H), 3.43−3.34 (m, 1H), 2.92−2.71 (m, 1H), 2.05−1.81 (m, 1H), 1.80−1.40 (m, 6H), 1.46, 1.39 (two s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.2, 140.1, 140.0, 138.2, 138.0, 133.7, 129.5, 129.3, 128.4, 128.4, 128.1, 127.7, 127.6, 127.4, 127.3, 99.3, 99.2, 97.7, 97.3, 80.3, 80.2, 73.3, 73.1, 71.3, 70.2, 65.5, 65.3, 63.9, 63.2, 61.0, 58.1, 57.0, 56.9, 30.6, 30.3, 29.8, 29.4, 28.5, 25.6, 18.7; MS (CI) *m*/*z* 546 $[M + H]^+$; HRMS calcd for $C_{29}H_{40}NO_7S$ (M + H) 546.2526, found 546.2519.

(2*R*,3*S*,5*S*)-1-*tert*-Butoxycarbonyl-2-tetrahydropyranyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (9b) (α-Sulfone). More polar isomers, two isomers (four rotamers): IR ($CHCl_3$) 3019, 2977, 1690, 1522, 1477, 1423, 1392 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89−7.86 (m, 2H), 7.66−7.51 (m, 3H), 7.37−7.29 (m, 5H), 4.68−4.38 (m, 4H), 4.22−3.27 (m, 8H), 2.84−2.40 (m, 2H), 1.57−1.38 (m, 6H), 1.47, 1.38 (two s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.1, 138.6, 138.4, 138.2, 138.0, 133.9, 129.4, 128.9, 128.4, 127.8, 127.6, 99.5, 98.1, 97.6, 80.4, 73.4, 70.6, 70.2, 67.3, 66.0, 65.8, 65.4, 62.6, 61.8, 61.6, 59.2, 58.5, 57.7, 57.2, 30.6, 30.2, 28.6, 28.4, 28.2, 25.3, 19.5, 19.3, 19.2, 18.9; MS (CI) *m*/*z* 546 $[M + H]^+$; HRMS calcd for $C_{29}H_{40}NO_7S$ (M + H) 546.2526, found 546.2539.

(2*R*,3*S*,5*S*)- and (2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (10). Starting from **7**(151 mg, 0.37 mmol), exactly the same procedure as described for the preparation of compound **5** furnished **10** as two isomers (165 mg, 80%) and 27 mg (18%) of the starting sulfone **7** was recovered. Compound **10**: IR ($CHCl_3$) 3015, 2978, 1688, 1496, 1478, 1455, 1393, 1368, 1251 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90−7.79 (m, 2H), 7.70−7.48 (m, 3H), 7.39−7.00 (m, 10H), 4.70−4.28 (m, 5H), 4.20−3.28 (m, 6H), 2.96−2.67, 2.52−2.34, 1.98−1.77 (m, 2H), 1.40, 1.39 (two s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.1, 153.0, 139.9, 138.4, 138.2, 137.9, 133.8, 133.7, 129.3, 129.2, 128.7, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 80.3, 80.1, 73.2, 73.0, 71.2, 70.3, 70.2, 68.8, 67.9, 66.6, 65.7, 65.1, 64.0, 63.4, 59.2, 58.5, 58.1, 58.0, 57.6, 57.3, 56.9, 56.6, 30.1, 29.5, 28.4; MS (CI) *m*/*z* 552 $[M + H]^+$; HRMS calcd for $C_{31}H_{38}NO_6S$ (M + H) 552.2420, found 552.2407.

(2*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-5-benzyloxymethylpyrrolidine (11). To a solution of the sulfone **8** (109 mg, 0.19 mmol) in HPLC-grade MeOH (4 mL) containing Na_2HPO_4 (215 mg, 1.52 mmol) was added 6% Na−Hg (437 mg, 1.14 mmol) at 0 °C. The mixture was vigorously stirred at 0 °C for 2 h. Mercury was removed by decanting the reaction mixture. After evaporation of MeOH in vacuo, the residue was dissolved in water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine, dried, and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 20/1) gave compound **11** as two rotamers (70 mg, 85%): $[\alpha]^{20}_D$ −71 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3006, 2963, 2931, 1681, 1475, 1456, 1394, 1369 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 4.58, 4.54, 4.49, 4.47 (four d, *J* = 12.0 Hz, 2H), 4.04−3.62 (m, 4H), 3.58 (dd, *J* = 8.9, 3.0 Hz, 0.5H), 3.46 (t, *J* = 7.7 Hz, 0.5H), 3.43 (t, *J* = 7.6 Hz, 0.5H), 3.27 (t, *J* = 8.6 Hz, 0.5H), 2.18−1.85 (m, 4H), 1.46, 1.40 (two s, 9H), 0.88, 0.87 (two s, 9H), 0.041, 0.030, 0.020 (three s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.8, 138.8, 138.5, 128.5, 128.4, 127.7, 127.6, 79.4, 79.3, 73.3, 70.8, 70.1, 63.4, 62.8, 59.1, 57.5, 28.7, 28.6, 27.2, 26.3, 26.0, 25.9, 18.3, −5.2, −5.3; MS (CI) *m*/*z* 436 $[M + H]^+$. Anal. Calcd for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.22; Found: C, 66.14; H, 9.21; N, 3.32.

(2*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-tetrahydropyranyloxymethyl-5-benzyloxymethylpyrrolidine (12). Starting from **9** (109 mg, 0.2 mmol), exactly the same procedure as described for the preparation of **11** furnished compound **12** as two isomers (four rotamers) (70 mg, 87%): $[\alpha]^{20}_D$ −83 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3009, 2947, 2870, 1683, 1476, 1455, 1394, 1368 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.60−4.45 (m, 3H), 4.02−3.25 (m, 8H), 2.08−1.43 (m, 10H), 1.46, 1.39 (two s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.9, 153.8, 138.8, 138.5, 128.5, 128.4, 127.6, 99.5, 98.8, 98.1, 79.5, 73.3, 70.8, 70.7, 70.1, 68.5, 67.7, 67.5, 66.7, 62.1, 61.9, 57.6, 57.4, 57.1, 30.7, 28.6, 27.1, 27.0, 26.8, 26.4, 26.2, 25.9, 25.6, 19.6, 19.5, 19.3; MS (CI) *m*/*z* 406 $[M + H]^+$. Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 67.85; H, 8.66; N, 3.24.

(2*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-5-benzyloxymethylpyrrolidine (13). Starting from **10** (127 mg, 0.23 mmol), exactly the same procedure as described for the preparation of **11** furnished compound **13** as two rotamers (75 mg, 78%): $[\alpha]^{21}_D$ −81 (*c* 2.25, $CHCl_3$); IR ($CHCl_3$) 3030, 2981, 1680, 1504, 1483, 1455, 1391, 1363 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 10H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.03−3.98 (m, 1H), 3.93−3.85 (m, 1H), 3.67 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.46 (dd, *J* = 9.1, 7.6 Hz, 1H), 3.29 (t, *J* = 8.6 Hz, 1H), 2.11−1.89 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.8, 138.7, 138.4, 128.4, 128.4, 127.5, 79.5, 73.2, 70.6, 69.9, 57.1, 28.5, 26.9, 25.9; MS (CI) *m*/*z* 412 $[M + H]^+$; HRMS calcd for $C_{25}H_{34}NO_4$ (M + H) 412.2488, found 412.2493.

(2*R*,5*S*)-2-Hydroxymethyl-5-benzyloxymethylpyrrolidine (14). A solution of **11** (73 mg, 0.17 mmol) in trifluoroacetic acid was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH = 10/1) to give compound **14** (45 mg, 80%): $[\alpha]^{22}_D$ +14 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3338, 3013, 2963, 2875, 1675, 1456, 1431, 1369 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 4.82 (br s, 3H, OH and NH_2^+), 4.55 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.68−3.51 (m, 6H), 2.01−1.85 (m, 2H), 1.71−1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 128.5, 128.0, 73.4, 69.3, 61.5, 58.9, 27.3, 26.5; MS (CI) *m*/*z* 278 [M + 57], 222 $[M + H]^+$; HRMS calcd for $C_{13}H_{20}NO_2$ (M + H) 222.1494, found 222.1489.

(2*R*,3*S*,5*S*)- and (2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (21). Compound **8** (110 mg, 0.19 mmol) was treated with a 1% (m/v) solution of iodine in methanol. The mixture was refluxed for 24 h. The solvent was removed, and the residue was dissolved into ether and aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with ether. The ether layer was washed with brine, dried over Na_2SO_4, and evaporated. Preparative TLC on silica gel (heptane/EtOAc = 1/2) gave alcohols **21a** (45 mg, 51%) **21b** (17 mg, 19%).

(2*R*,3*S*,5*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (21a). Major isomer (two rotamers): $[\alpha]^{20}_D$ −7.9 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3400, 3006, 2981, 1688, 1463, 1394, 1369 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.69−7.53 (m, 3H), 7.39−7.29 (m, 5H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.29 (m, 1H), 4.09−4.01 (m, 1H), 3.80 (m, 2H), 3.64−3.58 (m, 3H), 3.10 (br s, 1H, OH), 2.56 (m, 1H), 2.38−2.28 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.8, 138.3, 137.7, 134.1, 129.4, 128.8, 128.4, 127.7, 80.9, 73.2, 69.8, 65.0, 63.2, 61.0, 57.5, 28.3, 28.0; MS (CI) *m*/*z* 462 $[M + H]^+$; HRMS for $C_{24}H_{32}NO_6S$ (M + H) 462.1950, found 462.1928.

(2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (21b). Minor isomer (two rotamers): $[\alpha]^{20}_D$ −12 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3531, 3020, 2983, 1688, 1455, 1448, 1394, 1369 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91−7.84 (m, 2H), 7.77−7.56 (m, 3H), 7.30−7.00 (m, 5H), 4.41, 4.40, 4.34, 4.31 (four d, *J* = 12.0 Hz, 2H), 4.25−4.08 (m, 4H), 3.90 (dd, *J* = 9.8, 3.4 Hz, 0.5H), 3.60 (dd, *J* = 9.5, 4.2 Hz, 0.5H), 3.33 (dt, *J* = 9.7, 2.3 Hz, 1H), 3.21 (m, 0.5H), 3.02 (m, 0.5H), 2.79−2.58 (m, 1H), 1.90 (dd, *J* = 11.9, 6.0 Hz, 0.5H), 1.79−1.72 (m, 0.5H), 1.47, 1.41 (two s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.3, 152.9, 138.9, 138.3, 138.0, 134.3, 129.6, 128.6, 128.5, 128.2, 127.9, 127.7, 127.5, 127.4, 80.6, 73.4, 73.2, 71.3, 70.2, 64.1, 63.4, 61.4, 60.6, 60.5, 60.3, 56.7, 56.4, 31.0, 30.4, 28.6; MS (CI) *m*/*z* 462 $[M + H]^+$; HRMS for $C_{24}H_{32}NO_6S$ (M + H) 462.1950, found 462.1950.

(2*R*,3*S*,5*S*)- and (2*R*,3*R*,5*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (21). Major Isomer 21a. A solution of **9a** (12 mg, 0.022 mmol) in EtOH (2 mL) containing PPTS (0.6 mg, 0.0022 mmol) was stirred at 50 °C for 24 h. The solvent was evaporated. The residue was dissolved in dichloromethane, washed with water, saturated $NaHCO_3$, and brine, respectively, dried over Na_2SO_4, and evaporated. Preparative TLC on silica gel (heptane/EtOAc = 1/2) afforded cmpound **21a** (10 mg (99%).

The minor isomer **21b** was obtained from **9b** (25 mg, 0.046 mmol) by exactly the same procedure as described for the preparation of compound **21a** (18 mg, 85%).

(2*R*,3*S*,5*R*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-phenylsulfonyl-5-benzyloxymethylpyrrolidine (18). To a solution of **5** (185 mg, 0.43 mmol) in THF (5 mL) was added dropwise BuLi (1.6 M, 0.81 mL, 1.29 mmol) at −70 °C. After the mixture was stirred for 30 min at the same temperature, a solution of **4** (250 mg, 0.56 mmol) in THF (3 mL) was added dropwise, and stirring was continued for 1 h before quenching by addition of saturated NH_4Cl. The reaction mixture was extracted with ether. The ether extracts were washed with brine, dried, and evaporated. Preparative TLC (silica gel, toluene/EtOAc = 6/1) afforded **18** as a single isomer (two rotamers) (220 mg, 89%), and starting material **5** (40 mg, 22%) was recovered. Compound **18**: $[\alpha]^{20}_D$ +10 (*c* 3.2, $CHCl_3$); IR ($CHCl_3$) 2956, 2931, 2863, 1688, 1456, 1400, 1369, 1313, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92−7.89 (m, 2H), 7.66−7.54 (m, 3H), 7.32−7.26 (m, 5H), 4.51−4.40 (m, 2H), 4.30 (m, 1H), 4.08−4.00 (m, 1H), 3.83−3.77 (m, 1H), 3.66−3.33 (m, 4H), 2.69−2.27 (m, 2H), 1.48, 1.41 (two s, 9H), 0.80, 0.75 (two s, 9H), −0.069, −0.10, −0.12 (three s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.0, 153.7, 138.0, 137.6, 133.9, 129.3, 128.7, 128.6, 128.3, 127.4, 80.1, 73.1, 70.8, 70.2, 63.6, 62.8, 62.5, 61.7, 60.2, 56.9, 28.4, 28.3, 28.0, 27.3, 25.8, 18.1, −5.6; MS (CI, NH_3) *m*/*z* 576 $[M + H]^+$. Anal. Calcd for $C_{30}H_{45}NO_6SSi$: C, 62.58; H, 7.88; N, 2.43; S, 5.55. Found: C, 62.16; H, 7.85; N, 2.61; S, 5.52.

(2*R*,5*R*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-5-benzyloxymethylpyrrolidine (19). To a solution of the sulfone **18** (1.10 g, 1.91 mmol) in HPLC-grade MeOH (20 mL) containing Na_2HPO_4 (2.17 g, 15.28 mmol) was added 6% Na−Hg (4.39 g, 11.46 mmol) at 0 °C. The mixture was vigorously stirred at 0 °C for 3 h and then at room temperature overnight. Mercury was removed by decanting the reaction mixture. After evaporation of MeOH in vacuo, the residue was dissolved in water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine, dried over Na_2SO_4, and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 20/1) gave compound **19** as two rotamers (648 mg, 78%): $[\alpha]^{20}_D$ +1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3006, 2956, 2931, 1681, 1475, 1456, 1394, 1369 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32−7.25 (m, 5H), 4.50 (d, *J* = 2.6 Hz, 2H), 4.00−3.90 (m, 1H), 3.80−3.30 (m, 5H), 2.01−1.79 (m, 4H), 1.42 (s, 9H), 0.85 (s, 9H), −0.012, −0.015 (two s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 138.7, 128.4, 127.6, 79.4, 73.3, 71.5, 64.0, 63.0, 59.7, 57.9, 28.6, 27.4, 26.8, 26.1, 18.4, −5.2; MS (CI) *m*/*z* 436 $[M + H]^+$. Anal. Calcd for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.22. Found: C, 65.98; H, 9.54; N, 3.15.

(2*R*,5*R*)-2-Hydroxymethyl-5-benzyloxymethylpyrrolidine (20). A solution of **19** (44 mg, 0.10 mmol) in trifluoroacetic acid was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH = 10/1) to give the product as a salt of trifluoroacetic acid that was then treated with concd HCl in MeOH and evaporated to afford compound **20** (26 mg, 100%): $[\alpha]^{20}_D$ −4.2 (*c* 0.52, MeOH); IR (Nujol) 3401, 2924, 2854, 1641, 1586, 1500, 1454, 1378, 1366 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30−7.16 (m, 5H), 4.81 (br s, 3H, OH and NH_2^+), 4.51 (s, 2H), 3.78−3.55 (m, 6H), 2.06−2.04 (m, 2H), 1.76−1.75 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 138.8, 129.3, 128.9, 128.7, 74.2, 69.5, 63.3, 61.3, 61.1, 26.8, 26.4; MS (CI) *m*/*z* 278 $[M + 57]$, 222 $[M + H]^+$; HRMS calcd for $C_{13}H_{20}NO_2$ (M + H) 222.1494, found 222.1487.

2-Trifluoromethylsulfonyloxy-3-benzyloxypropene-1 (15): IR ($CHCl_3$) 3034, 2864, 1673, 1497, 1455, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.33 (m, 5H), 5.34−5.28 (m, 2H), 4.58 (s 2H), 4.10 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 137.1, 128.7, 128.2, 128.0, 118.6 (q, *J* = 320 Hz), 106.9, 72.8, 68.2; MS (CI, NH_3) *m*/*z* 314 $[M + NH_4]^+$.

(*E*)-1-Trifluoromethylsulfonyloxy-3-benzyloxypropene-1 (16): IR ($CHCl_3$) 3033, 2863, 1674, 1497, 1454, 1426 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43−7.27 (m, 5H), 6.78 (br d, *J* = 11.8 Hz, 1H), 5.88 (dt, *J* = 11.8, 5.8 Hz, 1H), 4.53 (s, 2H), 4.05 (dd, *J* = 5.8, 1.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.5, 128.4, 128.1, 127.9, 118.7 (q, *J* = 319 Hz), 118.5, 72.8, 64.9; MS (CI, NH_3) *m*/*z* 314 $[M + NH_4]^+$.

(*Z*)-1-Trifluoromethylsulfonyloxy-3-benzyloxypropene-1 (17): IR ($CHCl_3$) 3034, 2928, 1672, 1496, 1455, 1429 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 6.63 (br d, *J* = 5.8 Hz, 1H), 5.50 (q, *J* = 6.2 Hz, 1H), 4.52 (s, 2H), 4.21 (dd, *J* = 6.4, 1.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 136.4, 128.6, 128.0, 127.9, 118.7 (q, *J* = 319 Hz), 117.3, 72.9, 62.5; MS (CI, NH_3) *m*/*z* 314 $[M + NH_4]^+$.

X-ray Crystal Structure of 21a. Crystal data: $C_{24}H_{31}NO_6S$, M_w = 461.56; colorless crystal of 0.30 × 0.20 × 0.10 mm, monoclinic, space group *P*21, *Z* = 2, *a* = 12.600(4) Å, *b* = 5.781(2) Å, *c* = 16.649(8) Å, β = 96.32(2)°, *V* = 1205.4(8) Å^3, d_{calcd} = 1.272 g cm^{-3}, *F*(000) = 492, λ = 1.541 80 Å (Cu Kα), μ = 1.517 mm^{-1}, Nonius CAD-4 diffractometer, θ range: 2.67−67.97, 2920 collected reflections, 2675 unique (R_{int} = 0.0801), 2262 observed ($I > 2\sigma(I)$). Full-matrix least-squares (SHELXL93),[16] *R* = 0.0458 for 2262 observed reflections, wR_2 = 0.1313 for 2675 unique reflections, goodness of fit = 0.997. Residual electron density between −0.256 and 0.304 e A^{-3}. Absolute configuration was established by refinement of the Flack parameter[17] (−0.01(3), using the 329 most significative pairs of Frieded with θ < 32%) and examination of selected bijvoet pairs for which the absolute value of $\Delta F_c = (F(hkl) - F(-h\ -k\ -l)$ is greater than 1.0 e (maximum ΔF_c = 1.9 e). For these 68 pairs, only three are incorrectly predicted.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**, **4**, **8a**,**b**, **9a**,**b**, **10**−**20**, and **21a**,**b** and X-ray data for compound **21a**. This material is available free of charge via the Internet at http:/pubs.acs.org.

JO991052D

(16) Sheldrick, G. M. *SHELXL93*. Program for the solution of crystal structures; University of Göttingen: Germany, 1993.

(17) Flack, H. D. *Acta Crystallogr*. **1983**, *A38*, 876.