Sulfonation with Inversion by Mitsunobu Reaction: An Improvement on the Original Conditions

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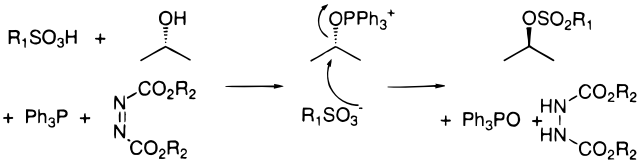
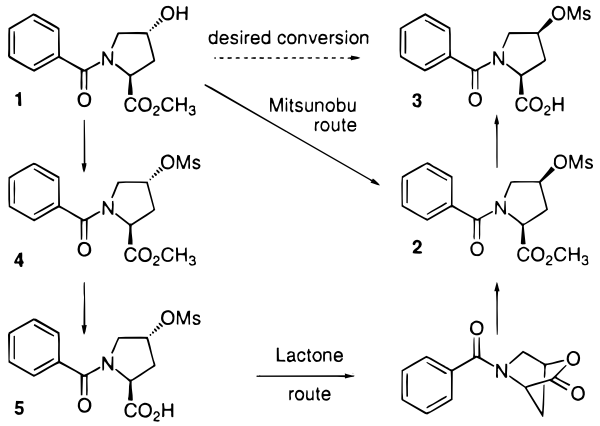
Received May 23, 1996

Sulfonation of a secondary alcohol with stereochemical inversion using Mitsunobu conditions was first described by Galynker and Still, using zinc tosylate.[1] The sulfonates produced have been displaced with inversion, resulting in new bond formation with net retention of stereochemistry.[2] The covalent nature of the zinc salts has been claimed as essential for clean sulfonation and similar displacements using Mitsunobu-like chemistry.[3] Typically the redox byproducts (triphenylphosphine oxide and the hydrazinedicarboxylate) are removed by chromatography,[4,5] which complicates scale-up operations.



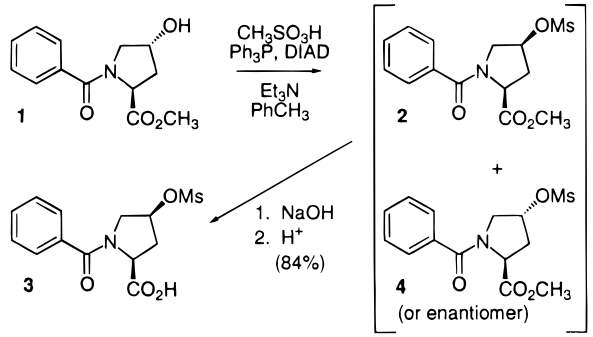
Results and Discussion

The *cis*-mesyloxy proline derivative **3** is a key intermediate for the marketed ACE inhibitor Fosinopril Sodium,[6] and the naturally occurring L-hydroxyproline derivative **1** was selected as starting material for the preparation of this bulk drug substance.[7] The lactone route below was initially used for the preparation of **3**, but was abandoned in favor of a more efficient process for eventual scale-up.



The Mitsunobu approach to **3** was viewed as an efficient alternative to the lengthy lactone approach. Several goals were set for cost-productive development of a suitable process: minimize the number of equivalents of the azodicarboxylate,[8] simplify conditions by avoiding the preparation of a zinc salt, and optimize isolation conditions to avoid purifying **3** by column chromatography.

Mesylation of **1** with clean inversion could be readily conducted with triphenylphosphine (1.2 equiv) methanesulfonic acid (1.2 equiv), diisopropyl azodicarboxylate (DIAD, 1.4 equiv), and triethylamine (0.4 equiv) in toluene. DIAD has been preferred to diethyl azodicarboxylate on scale-up, for safety reasons.[1d,9] The use of triethylamine was found to eliminate the need to prepare the zinc salt of methanesulfonic acid, and increasing the triethylamine charge led to increased levels of dehydroproline byproducts.[10] Typically the condensation was complete after about 3 h at 60−70 °C. Stereochemical inversion to **2** was clean, producing only 3% of the undesired *trans*-mesylate ester **4**.[11] To minimize byproduct formation, the optimal charging sequence was found to be triphenylphosphine, methanesulfonic acid, and DIAD, followed by **1** and triethylamine.[1d]



For economy of operations on scale, mesylate **2** was not isolated. (For analytical purposes a reference sample

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(1) (a) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461. For scope and mechanistic details on the Mitsunobu reaction, see: (b) Mitsunobu, O. *Synth.* **1981**, *1*, 1. (c) Hughes, D. L. The Mitsunobu Reaction. *Organic Reactions*; John Wiley and Sons, Inc.: 1992; Vol. 42, p 335. (d) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (e) Hughes, D. L. *Org. Prep. Proc. Int.* **1996,** *28*, 129. (f) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996,** *61*, 2967.

(2) (a) Emmer, G.; Grassberger, M. A.; Meingassner, J. G.; Schulz, G.; Schaude, M. *J. Med. Chem.* **1994**, *37*, 1908. (b) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Org. Chem.* **1992**, *57*, 3631. (c) Ladouceur, G.; Mais, D. E.; Jakubowski, J. A.; Utterback, B. G.; Robertson, D. W. *Biomed. Lett.* **1991**, *1*, 173. (d) Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096. (e) Iguchi, S.; Miyata, Y.; Miyake, H.; Arai, Y.; Okegawa, T.; Kawasaki, A. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1989**, *19*, 670. (f) Thierauch, K. H.; Sturzebecher, C. S.; Schillinger, E.; Rehwinkel, H.; Raduchel, B.; Skuballa, W.; Vorbruggen, H. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1989**, *19*, 655. (g) Thierauch, K. H.; Sturzebecher, C. S.; Schillinger, E.; Rehwinkel, H.; Raduchel, B.; Skuballa, W.; Vorbruggen, H. *Prostaglandins* **1988**, *35*, 855. (h) Iguchi, S.; Miyata, Y.; Okuyama, S.; Miyake, H.; Okegawa, T. *Chem. Pharm. Bull.* **1988**, *36*, 1128. (i) Mori, K.; Kuwahara, S. *Liebigs Ann. Chem.* **1987**, *6*, 555. (j) Pougny, J. R.; Rollin, P. *J. Carbohydr. Chem.* **1986**, *5*, 701. (k) Falck, J. R.; Manna, S.; Capedevila, J. *Tetrahedron Lett.* **1984**, *25*, 2443. (l) Laesecke, K.; Kohn, A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1983**, 1429.

(3) (a) Pianetti, P.; Rollin, P.; Pougny, J. R. *Tetrahedron Lett.* **1986**, *27*, 5853. (b) Rollin, P. *Synth. Commun.* **1986**, *16*, 611. (c) Ho, P. T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.

(4) For examples, see: (a) Smith, A. B., III; Hale, K. J.; Rivero, R. A. *Tetrahedron Lett.* **1986**, *27*, 5813. (b) Bowers-Nemia, M. M.; Joullié, M. M. *Heterocycles* **1983**, *20*, 817. Preparing the lactone from the carboxylic acid precursor of **1** would have added another step to the sequence.

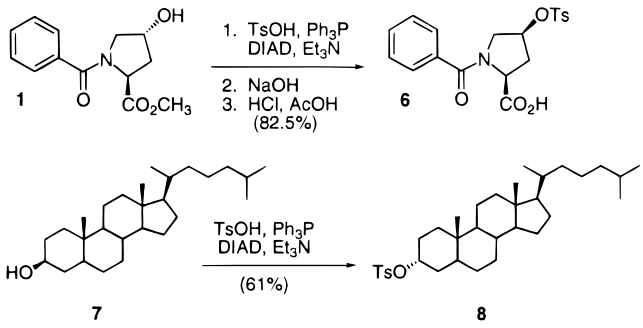
(5) The product has also been removed by pH-controlled extraction from the Mitsunobu byproducts: King, M. L.; Forman, A. L.; Orella, C.; Pines, S. H. *Chem. Eng. Prog.* **1985**, 36.

S0022-3263(96)00953-X CCC: $12.00

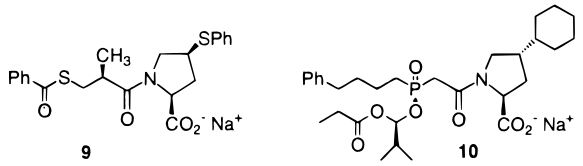
of **2** was prepared by esterification of **3**, as described in the Experimental Section.) When the Mitsunobu reaction was completed, hydrolysis was conducted by adding a small excess of aqueous sodium hydroxide and vigorously stirring the triphasic mixture at 5 °C for 1−2 h. After addition of hydrochloric acid to pH 6−7, solids were removed by filtration. These solids were found to be a 1:1 complex of triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate, as shown by single-crystal X-ray analysis.[12,13] On multikilo operations, 80−85% of the triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate present was routinely removed by filtration as this complex.

The aqueous phase of the biphasic filtrate was separated and acidified with hydrochloric acid to crystallize the product. A small amount of acetic acid was used to solubilize impurities during crystallization. The *cis*-mesylate acid **3** was isolated in 80−85% yield on multikilo scale. The product and the *trans*-isomer **5** are well resolved by HPLC analysis, and the stereochemistry of **3** was confirmed to be *cis* by single-crystal X-ray analysis.[13] Routinely no more than 0.1% of the *trans*-isomer **5** was detected in the isolated product. (For analytical purposes a reference sample of **5** was prepared by hydrolysis of **4** derived from L-proline, as described in the Experimental Section.) Without further purification the purity of **3** was at least 98% relative to a reference standard, with less than 0.1% each of triphenylphosphine oxide, reduced DIAD, or other impurities derived from **1**.

This procedure has been used to produce the *cis*-tosyloxy acid **6** and the tosylate **8**[1a] without chromatography. Slight modifications were undertaken: the water in *p*-toluenesulfonic acid monohydrate was removed by azeotropic distillation prior to the addition of triphenylphosphine and DIAD, as water consumes stoichiometric amounts of these reagents. The C3 methine signal in **8** was found at δ 4.74, in good agreement with that published for the α-tosylate **8**,[1a] thus indicating tosylation with inversion at this center. The protocol described should be applicable to the preparation of other sulfonates.



Conformational Preferences of 4-Substituted Prolines. The solid-state *cis*-diaxial conformation of **3** is very similar to that of zwitterionic *cis*-4-hydroxyproline.[14] Axial orientations of the 4-*cis* substituent are also favored for 4-phenoxy[15] and 4-cyano[16] derivatives. However, *cis*-4-alkyl[17,18] and *cis*-4-thio[19] substituents prefer an equatorial conformation, and we report here a similar preference for the 4-*cis*-phenylthio substituent in a crystal structure of the ACE inhibitor Zofenopril, **9**.[6,13] Although the pyrrolidine ring exhibits considerable conformational variation, 4-*trans*-monosubstituted prolines show similar preferences—aryl[6] and alkyl[18,20] groups favor an equatorial orientation—and we also report here a similar preference for the 4-*trans*-cyclohexyl substituent in a crystal structure of Fosinopril Sodium, **10**.[6,13] Axial orientations have been found for 4-*trans*-carboxylic acid[21] and hydroxylamine[22] derivatives and appear to be strongly favored by 4-*trans*-oxygen substituents in N-acylated and protonated derivatives.[23] This axial orientation in **1** may facilitate displacement of the activated phosphonium species to give the intermediate **2**.



Conclusion. We have developed improved conditions to sulfonate a secondary alcohol with inversion by using a modified Mitsunobu procedure. These conditions do not require the use or formation of zinc salts and use only a slight excesses of reagents (sulfonic acid, triphenylphosphine, and DIAD). Isolation of the product is facilitated by the prior crystallization and removal of the Mitsunobu

(6) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148.

(7) (a) Kronenthal, D. R.; Mueller, R. H.; Kuester, P. L.; Kissick, T. P.; Johnson, E. J. *Tetrahedron Lett.* **1990**, *31*, 1241. (b) Kronenthal, D.; Kuester, P. L.; Mueller, R. H. U.S. Pat. 4912231.

(8) Georges, M.; Mackay, D.; Fraser-Reid, B. *Can. J. Chem.* **1984**, *62*, 1539.

(9) For a discussion on safety considerations of azodicarboxylates, see: *Org. Synth.* **1995**, *73*, 278.

(10) Small amounts of the 3,4- and 4,5-dehydroproline impurities were detected, along with impurities similar to compound **4** in ref 1a.

(11) Refluxing overnight decreased the ratio to ca. 92:8, probably due to epimerization α to the methyl ester. The absolute stereochemistry of the *trans*-mesylate ester detected in this Mitsunobu reaction is not known.

(12) Conducting the Mitsunobu reaction in toluene probably promotes the crystallization of the complex, as toluene has been shown to be a suitable solvent for crystallization of weakly acidic compounds with triphenylphosphine oxide: Etter, M. C; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639.

(13) Coordinates for the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(14) Shamala, N.; Row, T. N. G.; Venkatesan, K. *Acta Crystallogr., B* **1976**, *32*, 3267 (AHLPRO). All referenced crystal structures were retrieved from the Cambridge Structural Database, April 1996 release (CSD: Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, G.F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comp. Sci.* **1991**, *31*, 187−204). CSD refcodes are included at the end of each reference.

(15) Palkowitz, A. D.; Steinberg, M. I.; Thrasher, K. J.; Reel, J. K.; Hauser, K. L.; Zimmerman, K. M.; Wiest, S. A.; Whitesitt, C. A.; Simon, R. L.; Pfeifer, W.; Lifer, S. L.; Boyd, D. B.; Barnett, C. J.; Wilson, T. M.; Deeter, J. B.; Takeuchi, K.; Riley, R.E.; Miller, W. D.; Marshall, W. S. *J. Med. Chem.* **1994** *37*, 4508 (YIHJEE).

(16) Webb, T. R.; Eigenbrot, C. *J. Org. Chem.* **1991,** *56*, 3009 (TALBUD).

(17) Cerrini, S.; Lamba, D.; Scatturin, A.; Rossi, C.; Ughetto, G. *Biopolymers* **1989**, *28*, 409 (JATZIN).

(18) Flippen-Anderson, J. L.; Gilardi, R.; Karle, I. L.; Frey, M. H.; Opella, S. J.; Gierasch, L. M.; Goodman, M.; Madison, V.; Delaney, N. G. *J. Am. Chem. Soc.* **1983,** *105*, 6609 (CEDREI and CEDRAE).

(19) Yanagi, K.; Takeuchi, Y.; Sunagawa, M. *Acta Crystallogr., Sect. C* **1992**, *48*, 1737 (VUCJEI).

(20) Leban, I.; Golic, L.; Resman, A.; Zmitek, J. *Acta Chim. Slov.* **1994**, *41*, 405 (SUPBIO).

(21) Dupont, L.; Lamotte, J.; Campsteyn, H.; Vermeire, M.; Welter, A. *Acta Crystallogr., Sect. B* **1978**, *34*, 850 (CXPROL).

(22) Bernardinelli, G.; Tronchet, J. M. J.; Jorand, C. *Z. Kristallogr.* **1991**, *195*, 129 (SIYYOO).

redox byproducts, eliminating the need for chromatography. No more than 0.1% of the *trans*-isomer is found in the product **3**. These conditions have been extended to the preparation of two other sulfonates.

Experimental Section

General Methods. Melting points are uncorrected. All reagents and solvents were reagent grade. All reactions were conducted under nitrogen, except for hydrolyses.

Mitsunobu Sulfonation. Method A. A slurry of methanesulfonic acid (7.8 mL, 120 mmol) and triphenylphosphine (32.8 g, 125 mmol) in 250 mL of toluene was cooled to about 20 °C, and DIAD[24] (27.1 g, 140 mmol) was added, keeping the temperature below 35 °C. Then the alcohol (100 mmol) was added, followed by triethylamine (5.5 mL, 40 mmol). The slurry was heated to 60−70 °C and held at that temperature until the formation of the sulfonate was complete by HPLC, generally about 3 h. The reaction was cooled to about room temperature for workup.

Mitsunobu Sulfonation. Method B. For use with hydrated sulfonic acids. The reactor was fitted with a Dean−Stark apparatus and condenser and charged with the sulfonic acid and toluene (2.1 mL/mmol). The mixture was refluxed under nitrogen until water removal was complete and cooled to about 20 °C. Thereafter the procedure was the same as in method A.

***N*-Benzoyl-4-*cis*-(methanesulfonyloxy)-L-proline (3).** Method A was used for the Mitsunobu condensation, with alcohol **1**[25] (25.0 g, 100 mmol). The orange-brown solution was cooled to 5 °C and mixed with aqueous NaOH (150 mmol, 90 mL). The triphasic mixture was stirred vigorously at 5 °C until hydrolysis was complete by HPLC assay,[26] about 2 h, and acidified to pH 6−7 with HCl (concentrated, ca. 8 mL). The suspension was stirred at 5 °C for 1 h, and the solids of triphenylphosphine oxide−diisopropyl hydrazinedicarboxylate (see experimental below) were filtered off and washed with cold water (2 × 35 mL). The organic layer of the filtrate was extracted with distilled water (2 × 15 mL). Glacial acetic acid was added in two portions to the combined aqueous phases, first to adjust to pH 3.8−3.9 at 25 °C (*ca.* 10 mL) to initiate crystallization. The crystal slurry was stirred at room temperature for 30 min and adjusted to pH 4 (glacial acetic acid, *ca.* 6 mL). The mixture was adjusted to pH 2 by the slow addition of HCl (concentrated, *ca.* 7 mL), held at 20−25 °C for 30 min, and stirred at 0−5 °C for 1 h. The product was isolated by filtration and washed with cold water (2 × 30 mL). Drying in a vacuum oven at 50 °C/30 mmHg returned 25.8 g (84%) of **3**. By HPLC analysis the purity of this material was at least 98% relative to a standard of **3**. No more than 0.1% each of the *trans*-isomer **5**, triphenylphosphine oxide, or other individual organic impurites was detectable. The product contained about 0.1−0.2% water and acetic acid.

A reference standard was prepared by recrystallization from 10 volumes of 1:1 EtOAc:95% EtOH to provide material with mp 172−174 °C (lit.[7a] mp 173−174 °C), $[\alpha]^{20}_D$ −55.0° (*c* = 1.0, MeOH) (lit.[7a] $[\alpha]^{20}_D$ −50.6° (*c* = 1.0, MeOH)). ^{1}H NMR (300 MHz, $CDCl_3$ + drop of CD_3OD) showed a mixture of rotamers due to the tertiary amide: δ 2.51−2.76 (m, 2H), 3.07 (s, 3H), {3.89 (d, *J* = 4.4 Hz), 3.98 (br s), 4.02 (br s), 4.17 (d, *J* = 5.3 Hz), 4.22 (d, *J* = 5.3 Hz), *ca.* 2H combined}, {4.52 (d, *J* = 8.4 Hz) and 4.88 (m, *J* = 4.2, 4.9 Hz), *ca.* 1H combined}, {5.24 (t, *J* = 4.5 Hz) and 5.40 (br m), 1H combined}, 7.43−7.56 (m, 5 H). ^{13}C NMR [75 MHz, $CDCl_3$ + drop of CD_3OD]: δ 34.7, 37.4, 37.7, 37.9, 52.3, 54.2, 56.7, 59.6, 77.1, 82.5, 126.5, 128.2, 129.9, 130.3, 134.8, 135.4, 170.3, 171.2, 172.0, 172.4. IR (KBr): 1745 (br), 1595, 1570, 1335, 1165 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_6S$: C, 49.83; H, 4.83; N, 4.47; S, 10.23. Found: C, 49.74; H, 4.73; N, 4.38; S, 10.38.

Triphenylphosphine Oxide−Diisopropyl Hydrazinedicarboxylate. This byproduct was generally not dried or characterized. A batch was found suitable for single-crystal X-ray analysis: mp 111−113 °C. ^{1}H NMR [400 MHz, $CDCl_3$]: δ 1.16 (d, 12H, *J* = 6.3 Hz), 4.88 (m, 2H, *J* = 6.3 Hz), 6.5 (brm, 2H), 7.62−7.19 (m, 15H). ^{13}C NMR [100 MHz, $CDCl_3$]: δ 21.9, 69.9, 128.4, 128.5, 131.88, 131.90, 132.1, 133.0, 156.4. IR (KBr): 3220 (br), 1710 (br), 1110 cm^{-1}. Anal. Calcd for $C_{26}H_{31}N_2O_5P$: C, 64.72; H, 6.48; N, 5.81; P, 6.42. Found: C, 64.75; H, 6.30; N, 5.78; P, 6.39.

***N*-Benzoyl-4-*cis*-(methanesulfonyloxy)-L-proline Methyl Ester (2).** The ester generated by the Mitsunobu reaction was not routinely isolated. A reference sample was prepared by adding **3** (40.0 g, 142 mmol) to a solution of thionyl chloride (11.2 mL, 154 mmol) in methanol (400 mL) that had been prepared at −15 °C and stirred 17 h at room temperature. The esterification was quenched into water (200 mL) at 10 °C and adjusted to pH 7.1 with aqueous $NaHCO_3$ (saturated, 520 mL). The slurry was cooled to 4 °C and filtered, and the product was washed with ice water (2 × 200 mL) and dried to afford 30.68 g (73.5%) of white solid: mp 90−91 °C, $[\alpha]^{20}_D$ −51.6° (*c* = 1.0, MeOH). ^{1}H NMR [400 MHz, $CDCl_3$, a mixture of rotamers due to the tertiary amide]: δ {2.59 and 2.67 (brm, 2H)}, 3.07 (s, 3H), 3.74−4.26 (brm, 2H), {3.86 (s) and 3.94 (s), 3H}, {4.57 (brm) and 5.00 (brm), 1H}, {5.26 (brm) and 5.40 (brm), 1H}, 7.48−7.59 (m, 5H). ^{13}C NMR [75 MHz, $CDCl_3$]: δ 35.0, 38.0, 38.4, 52.5, 54.3, 56.7, 59.6, 126.5, 126.9, 128.4, 130.1, 130.4, 135.2, 135.8, 169.5, 170.9, 171.2. IR (KBr): 1746, 1640, 1346, 1169 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.36; H, 5.23; N, 4.28; S, 9.79. Found: C 51.45; H, 5.00; N, 4.29; S, 9.49.

***N*-Benzoyl-4-*trans*-(methanesulfonyloxy)-L-proline (5) (Sodium Salt).** A suspension of **4**[7a] (200 g, 0.61 mol) in water (1 L) was treated with NaOH (10 M, 73.3 mL) at room temperature for 2.5 h and acidified to pH 1.5 with HCl (concentrated). The reaction was extracted with CH_2Cl_2 (3 × 500 mL), and the combined extracts were polish-filtered through Hyflo. The solvent was removed under reduced pressure, and the residue was taken up into absolute EtOH (1.0 L). Over 30 min sodium 2-ethylhexanoate (0.61 mol in absolute EtOH, 522 mL) was added, followed by absolute EtOH (0.50 L). The suspension was stirred at 0−4 °C for 1 h, and the product was filtered and washed with absolute EtOH (3 × 250 mL). The crystals were reslurried in absolute EtOH (1.5 L) at 4 °C for 1 h, filtered, washed with absolute EtOH (2 × 250 mL), and dried to afford 144.7 g (70.6%): mp 136 °C (endotherm, differential scanning calorimetry), $[\alpha]^{20}_D$ −79.5° (*c* = 1.0, H_2O). ^{1}H NMR [400 MHz, DMSO-d_6, a mixture of rotamers due to the tertiary amide]: δ 2.2−2.45 (brm, 2H), {3.16 (s) and 3.23 (s), (3H combined}, {3.51 (d, *J* = 12.1 Hz), 3.72 (d, *J* = 6.0 Hz), 3.76 (d, *J* = 6.0 Hz), 3.84−3.91 (m), 4.03 (dd, *J* = 4.1 and 4.2 Hz), 4.42 (t, *J* = 8.0 Hz), 5.22−5.25 (m), 4H total}, 7.34−7.50 (m, 5H). ^{13}C NMR [75 MHz, DMSO-d_6]: δ 35.8, 37.56, 37.64, 37.68, 39.7, 51.3, 55.3, 59.1, 61.8, 127.2, 127.9, 128.3, 128.5, 129.3, 129.9, 136.6, 137.0, 168.0, 169.2, 174.0, 174.3. IR (KBr): 1619, 1356, 1171 cm^{-1}. Anal. Calcd for $C_{13}H_{14}NO_6SNa\cdot0.5H_2O$: C, 45.35; H, 4.39; N, 4.07; S, 9.31; H_2O, 2.62. Found: C, 45.52; H, 4.19; N, 4.03; S, 9.46; H_2O, 2.52 (Karl Fischer titration).

***N*-Benzoyl-4-*cis*-(*p*-toluenesulfonyloxy)-L-proline (6).** Method B was used for the Mitsunobu condensation, with alcohol **1**[25] (25.0 g, 100 mmol). The reaction was stirred at 65 °C for 6 h and then without heat overnight. By HPLC[27] the ratio of intermediate tosylate ester to starting material was 40:1. The yellow solution was stirred vigorously with aqueous NaOH (0.15

(23) Seven of eight such *trans*-4-hydroxyproline structures have an axial OH (*e.g.* Koetzle, T. F.; Lehmann, M. S.; Hamilton, W. C. *Acta Crystallogr., Sect. B* **1973,** *29*, 231 (HOPROL12). Hospital, M.; Courseille, C.; Leroy, F.; Roques, B. P. *Biopolymers*, **1979,** *18*, 1141 (NAHYPL, or *N*-acetyl-*trans*-4-hydroxyproline). Garbay-Jaureguiberry, C.; Arnoux, B.; Prange, T.; Wehri-Altenburger, S.; Pascard, C.; Roques, B. P. *J. Am. Chem. Soc.* **1980,** *102*, 1827 (GLHPRC, or prolylhydroxyproline)). The last reference also contains the exception: the hydroxyl is pseudoequatorial in glycyl-L-4-hydroxyproline (GLHPRA). Intermediate conformations occur in two mono- and di-N-alkylated derivatives: Jones, G. P.; Naidu, B. P.; Paleg, L. G.; Tiekink, E. R. T. *Acta Crystallogr. Sect. C* **1988,** *44*, 2208 (GOJMAT and GOJMEX).

(24) DIAD purity may be determined by dissolving a standardized amount of triphenylphosphine in acetonitrile containing 0.2% acetic acid and titrating with DIAD until the yellow-orange color remains.

(25) Portoghese, P. S.; Turcotte, J. G. *Tetrahedron* **1971**, *27*, 961. The ester was dried to moisture levels of not more than 0.1%.

(26) Waters 30 cm μ-Bondapak C-18 column held at 31 °C, eluted at 1.0 mL/min with 28:72 methanol:(0.05 M KH_2PO_4 acidified to pH 3.0 with 3 M H_3PO_4), 215 nm. Typical retention times: **1**, 10.4 min; **2**, 16.7 min; **3**, 7.6 min; **4**, 18.0 min; **5**, 8.0 min.

(27) YMC Basic 25 cm column, eluted at 1.0 mL/min with 50:50 acetonitrile:0.01 M ammonium phosphate, acidified to pH 4 after mixing, monitored at 210 nm. Typical retention times: **1**, 3.7 min; ester intermediate, 8.5 min; **6**, 5.6 min.

mol, 90 mL) at room temperature for 21 h, and the solids were removed by filtration and washed with water (70 mL). The combined filtrates were acidified to pH 7.3 (concentrated HCl) and stirred at 4−5 °C for 45 min. A second crop of the TPPO−reduced DIAD complex was removed by filtration, and the filtrate was acidified to pH 5.4 with acetic acid (glacial, 2.5 mL). The suspension was stirred at room temperature for 45 min, acidified to pH 3.95 (glacial acetic acid, 7.5 mL, and concentrated HCl, 5.0 mL), and diluted with water (200 mL) and 95% EtOH (221 mL). The suspension was warmed to 50 °C, cooled to room temperature, and filtered. Product was washed with 20% EtOH in water (50 mL) and dried at ambient conditions to return 32.13 g of **6** (82.5%), mp 167−167.5 °C, 99.4% by HPLC analysis.[27] A sample was recrystallized from 95% EtOH (six volumes) to return material with mp 173−174 °C (lit.[25] mp 105−115 °C for *N*-benzoyl-*trans*-4-(*p*-toluenesulfonyloxy)-L-proline), $[\alpha]^{20}_D$ −60.6° (c = 1.0, MeOH). ^{1}H NMR [300 MHz, $CDCl_3$ + drop of CD_3OD, a mixture of rotamers due to the tertiary amide]: δ 2.31−2.58 (m, 2H), 2.45 (s, 3H), 3.73 (d, J = 4.7 Hz) and 3.77 (d, J = 3.2 Hz, 2H combined with prior peak), 4.42 (d, <1H, J = 8.3 Hz), 4.76 (m, 1H, J = 3.8, 5.2 Hz), 4.99 (t, 1H, J = 5.3 Hz), 7.33−7.48 (m, 7H), 7.75 (d, 2H, J = 8.1 Hz). ^{13}C NMR [75 MHz, $CDCl_3$ + drop of CD_3OD]: δ 21.4, 34.4, 37.6, 52.1, 53.9, 56.7, 59.7, 77.2, 78.1, 126.5, 126.8, 127.5, 128.3, 129.9, 130.1, 130.5, 132.8, 134.9, 145.3, 170.2, 171.0, 172.0. IR (KBr): 1738, 1600, 1440, 1360, 1192 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_6S$: C, 58.60; H, 4.92; N, 3.60; S, 8.23; Found: C, 58.55; H, 4.85; N, 3.54; S, 8.30.

3α-(*p*-Toluenesulfonyloxy)cholestane (8). Method B was used, with an input of 11.30 g (59.4 mmol) of *p*-toluenesulfonic acid monohydrate in toluene (124 mL total volume). Other inputs were charged proportionally, with 19.22 g (49.5 mmol) of dihydrocholesterol ("95%"). After stirring at 65 °C for 6.5 h, the reaction was incomplete by TLC, and the suspension was cooled to room temperature and recharged with triphenylphosphine (10.39 g, 39.6 mmol) and DIAD (9.1 mL, 46.2 mmol). After 6.5 h at 65 °C, the starting material was consumed, the reaction was cooled to 4 °C, and the byproduct was filtered and washed with toluene (2 × 50 mL). The combined filtrates were concentrated under reduced pressure to a residue and dissolved at 65 °C in MeOH−EtOAc (180 mL, 150 mL). The suspension was chilled at 2−4 °C, and the product was removed by filtration and washed with chilled MeOH−EtOAc (2 × 50 mL, ratio 18:15). Vaccum drying returned 16.48 g (61.3%), mp 124.5−125 °C. ^{1}H NMR [300 MHz, $CDCl_3$]: δ 0.63−1.97 (46H), 2.44 (s, 3H), 4.74 (m, 1H), 7.32 (d, 2H, J = 8.2 Hz), 7.79 (d, 2H, J = 8.2 Hz). ^{13}C NMR [75 MHz, $CDCl_3$]: δ 11.3, 12.0, 18.6, 20.7, 21.6, 22.5, 22.8, 23.8, 24.1, 26.8, 28.0, 28.1, 28.2, 31.7, 32.2, 33.4, 35.3, 35.4, 35.8, 36.1, 39.1, 39.5, 39.9, 42.5, 53.8, 56.1, 56.4, 80.3, 127.6, 129.7, 134.7, 144.2. Anal. Calcd for $C_{34}H_{54}O_3S$: C, 75.23; H, 10.03; S, 5.91. Found: C, 75.41; H, 10.19; S, 5.86. $[\alpha]^{20}_D$ +21.8° (c = 1.0, CH_2Cl_2). IR (KBr): 2938, 1365, 1348, 1188 cm^{-1}.

The combined filtrates from the first crop were concentrated to a residue and dissolved at 65 °C in MeOH−EtOAc (100 mL, 80 mL). The suspension was cooled and the product was collected by filtration to afford after drying 4.05 g (15.1%) of white solid, impure **8**.

Acknowledgment. We thank S. Riseman for developing the DIAD titration assay, R. Deshpande for identification of impurities, and V. Palaniswamy for assistance in obtaining the NMR spectra.

Supporting Information Available: Solid-state conformational drawings of **3**, **9**, **10**, and the triphenylphosphine oxide−diisopropyl hydrazinedicarboxylate complex (4 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.

JO9609539