Chirospecific Synthesis of (1S,3R)-1-Amino-3-(hydroxymethyl)cyclopentane, a Precursor for Carbocyclic Nucleoside Synthesis. Intramolecular Aziridine Cyclizations

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Carbocyclic nucleosides are important isosteres of nucleosides. Both chemically and enzymatically they are more stable than nucleosides, and they possess a variety of antiviral and antineoplastic activities.[1] The chiral synthesis of carbocyclic nucleosides has been reviewed recently[2,3] and we have reported an asymmetric synthesis of a key precursor of carbocyclic nucleosides, (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane, via a Dieckmann cyclization of an α-amino acid.[4] Now we report another method for the synthesis of this important precursor that involves the intramolecular cyclization of an ester enolate onto an activated aziridine to form a substituted cyclopentane ring. While reactions of aziridines with nucleophiles are well known,[5-7] intramolecular cyclizations of this type have not been reported. The desired aziridine was to be obtained from the appropriate amino alcohol, in turn derived from α-aminoadipic acid which was to be prepared from aspartic acid.

Prior to starting our synthesis of the aziridine the choice of the substituent on the nitrogen needed to be addressed. This group must activate the aziridine toward nucleophilic attack, but not react with the nucleophile (in our case an ester enolate) itself.[5-7]

We chose to protect the nitrogen of the aziridine as an arylsulfonate (Scheme I). The arylsulfonate offers the advantage of adequately activating the aziridine toward ring opening, while remaining unreactive toward the carbon anion. The use of other activating groups on the nitrogen (acyl or alkyl/Lewis acid) was not examined. The diacid was then converted to anhydride **2** which was converted to lactone **3** by first reducing with sodium borohydride followed by cyclizing in ethanolic HCl.[8] Lactone **3** was reduced to lactol **4** in 78% yield using DIBAL-H in methylene chloride; other solvents (Et_2O, THF) gave significant amounts of diol, or the lactone precipitated from solution (toluene) at low temperature. The lactol **4** is not stable to prolonged storage due to decomposition, including lactone formation; thus it should be used as soon as prepared. Two homologated esters of lactol **4** were prepared, the methyl and *tert*-butyl. The methyl ester was the initial choice, but lower yields later in the synthesis prompted examination of the *tert*-butyl ester.

Treatment of lactol **4** with the Wittig reagents [(methoxycarbonyl)methylene]triphenylphosphorane or [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane[9] gave the esters **5a** and **5b**. The low yields in this reaction were primarily due to a Michael addition of the alcohol on to the α,β-unsaturated ester to yield tetrahydrofuran **8**.[10] By changing to methyl diethylphosphonoacetate[11] with LiCl/iPr_2NEt,[12] unsaturated ester **5c** was obtained in better yield. Reduction of the double bond to hexanoate **6** followed by alcohol activation and cyclization gave the desired aziridines **7**. The aziridine could be formed by either of two methods. Method A uses Mitsunobu conditions to give **7a** in 62% yield and **7b** in 59% yield. Method B involves treatment of the alcohol with methanesulfonyl chloride and excess triethylamine to give a slightly higher yield of **7a** and **7b**.

Since we also wished subsequently to prepare functionalized cyclopentanes and cyclopentenes using this method, the α,β-unsaturated ester aziridine **9** also was prepared. We considered that deconjugative cyclization of this compound might lead to the cyclopentene **12**. The cyclization of the amido alcohol **5c** to an aziridine proved troublesome. The use of basic conditions to cyclize **5c** to **9** gave little or no product, and Mitsunobu conditions gave aziridine **9** in 51% yield.

The cyclization of the aziridines is shown in Scheme II. Cyclization of methyl ester **7a** could be effected in THF with KHMDS to yield cyclopentane **10a** as an inseparable 1/1 mixture of the two diastereomers in only 35% yield.

It seemed possible that the low yield of **10a** might be due to intermolecular condensations of the methyl ester. Thus the *tert*-butyl ester **7b** would provide a better yield of cyclized material since intermolecular condensations of the *tert*-butyl ester would be disfavored. Treatment of **7b** with KHMDS indeed gave the corresponding cyclopentane **10b** in 68% yield as a 1/1 mixture of diastereomers. The use of LDA as the base gave **10b** in 65% yield as a 2/1 mixture of cis/trans diastereomers. Unfortunately the cis and trans diastereomers of **10b** were difficult to separate. Needed was a process to obtain the cis dias-

(1) (a) Robins, R. K.; Revankar, G. R. In *Antiviral Drug Development*; De Clerq, E., Walker, R. T., Eds.; Plenum: New York, 1988; p 11. (b) MacCoss, M.; Robins, M. J. In *The Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie and Sons: U.K., 1990; pp 261–299.

(2) (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Marquez, V. E.; Lim, M.-I. *Med Res. Rev.* **1986**, *6*, 1.

(3) (a) Lister, J. H. In *Fused Pyrimidines*; Brown, D. W., Ed.; Wiley: New York, 1971; Part II, p 31. (b) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153. (c) Shaw, G.; Warrener, R. W. *J. Chem. Soc.* **1958**, 157. (d) See also ref 2a as well as refs cited in ref 4.

(4) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.

(5) Examples of aziridine opening in which the nitrogen substituent is alkyl or aryl: (a) Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153. (b) Bouayad, Z.; Chanet-Ray, J.; Ducher, S.; Vessiere, R. *J. Heterocycl. Chem.* **1991**, *28*, 1757. (c) Dureault, A.; Greck, C.; Depezay, J. C. *Tetrahedron Lett.* **1986**, *27*, 4157. (d) Dureault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, *54*, 5324.

(6) Examples of aziridine opening in which the nitrogen substituent is an acyl (aryl, *O*-alkyl, *N,N*-dialkyl) group: (a) Stamm, H.; Weiss, R. *Synthesis* **1986**, 395. (b) Stamm, H.; Weiss, R. *Synthesis* **1986**, 392. (c) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788. (d) Stamm, H.; Assithianakis, P.; Buchholz, B.; Weiss, R. *Tetrahedron Lett.* **1982**, *23*, 5021.

(7) Examples of aziridine opening in which the nitrogen substituent is arylsulfonyl: (a) Onistschenko, A.; Buchholz, B.; Stamm, H. *Chem. Ber.* **1986**, *119*, 2678. (b) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204. (c) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc. Chem. Commun.* **1989**, 1852.

(8) Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020.

(9) Knorr, U.; Knorr, H.; Ried, W.; Schuckmann, W. *Chem. Ber.* **1976**, *109*, 3869.

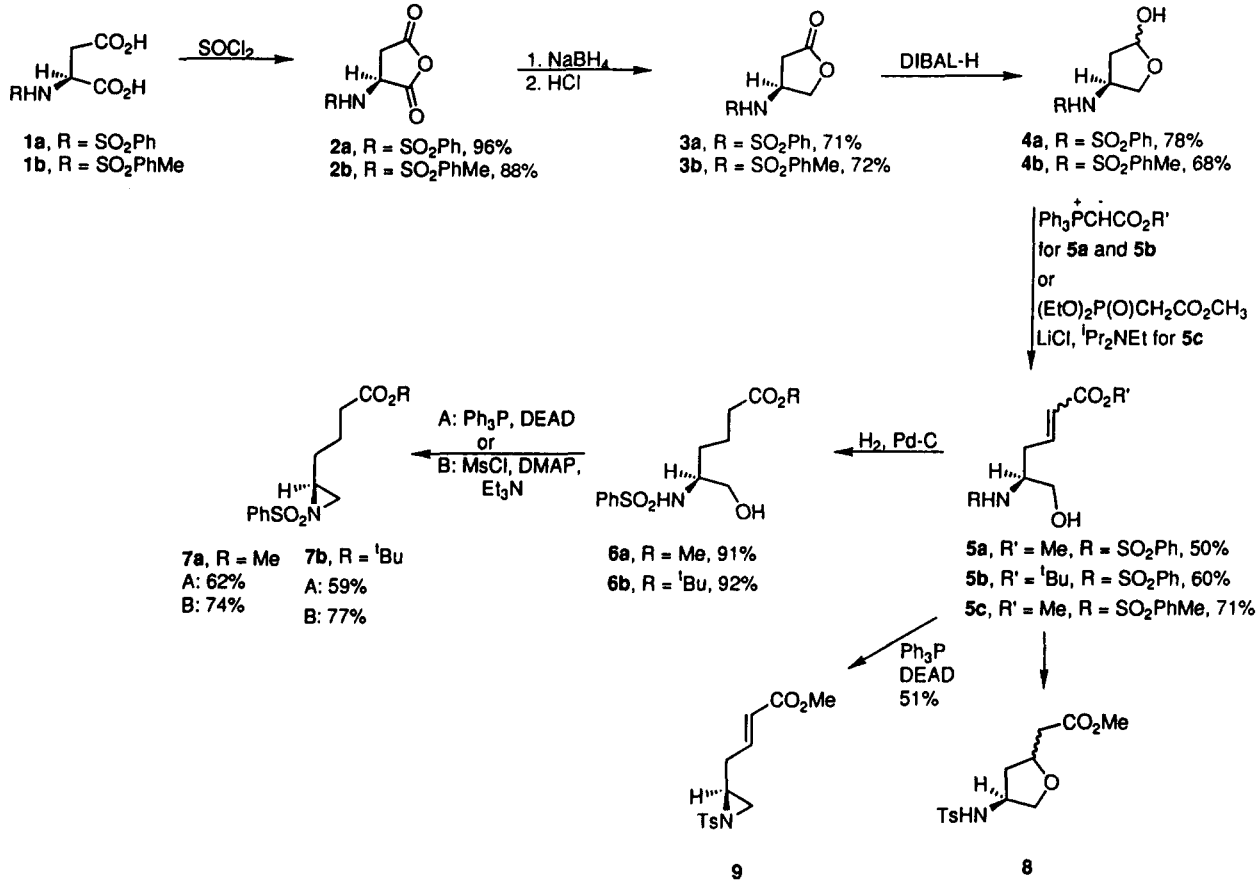
(10) Another example of this type of cyclization is reported in Ohuri, H.; Jones, G. H.; Moffat, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.

(11) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

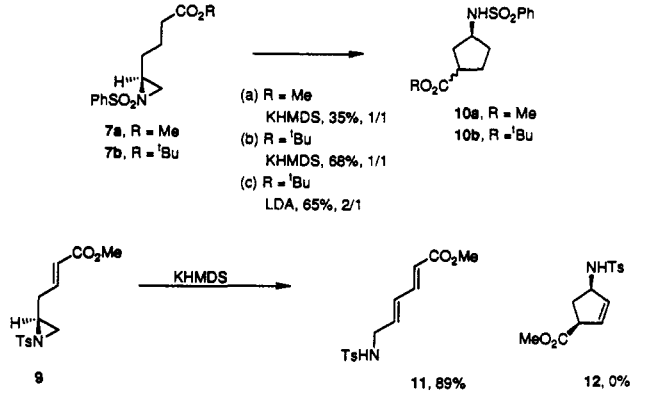
(12) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

0022-3263/93/1958-5019$04.00/0

Scheme I. Preparation of Aziridines from Aspartic Acid



Scheme II. Cyclization of Aziridines



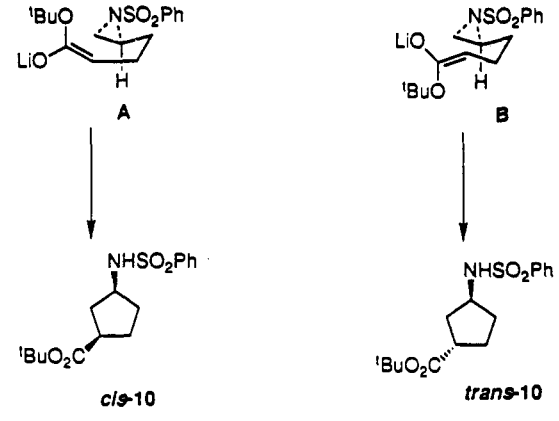


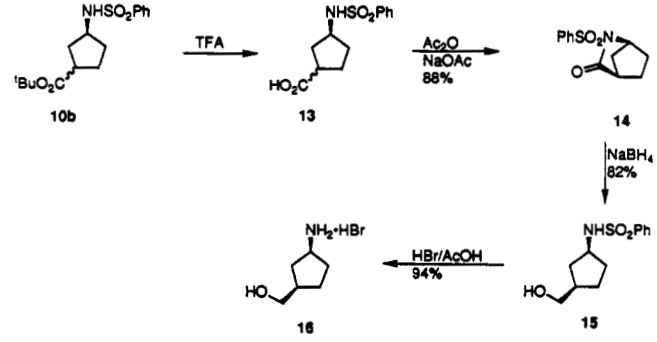
Figure 1. Proposed transition state for the cyclization of aziridine 7.

tereomer exclusively. Several attempts were made to improve the selectivity of the cyclization. Among these were adding $MgBr_2$, changing the reaction temperature, using Et_2O as solvent, and adding HMPA or DMPU. Also attempts were made to prepare the ketene acetal followed by cyclization. All these variations proved fruitless. A qualitative examination of a model of the enolate (Figure 1) shows no compelling reason for either isomer **A** (leading to the cis) or isomer **B** (leading to the trans) to be favored over the other.

Exposure of the α,β-unsaturated ester **9** to cyclization conditions did not give the desired cyclopentene **12** but only the diene **11**. This aziridine opening to yield diene proceeded at −78 °C, much milder conditions than that used in the previous cyclizations to form the cyclopentane.

Further attempts to influence the diastereomeric ratio of **10b** were abandoned and we turned to a strategy previously used to convert a mixture of diastereomers of an amino ester to a single bicyclic lactam.[4] Following this protocol, the ester **10b** (as a 2/1 mixture of diastereomers) was treated with TFA to give the crude acid **13** which was treated with acetic anhydride and sodium acetate to yield the lactam **14** in 88% yield from the ester **10b** (Scheme III). In our previous report, this type of reaction was carried out with an *N*-(9-phenylfluorenyl) group on the nitrogen. This example (**10b**→**14**) extends that reaction to a sulfonamide nitrogen, a much less basic nitrogen. Additionally, the product of this reaction is an imide, rather than the amide that was prepared in our previous report. This imide then was readily reduced to the sulfonamido alcohol **15** by $NaBH_4$. The benzenesulfonyl group could be easily removed in 94% yield with HBr/AcOH to yield aminocyclopentane hydrobromide **16**.[13]

Scheme III. Epimerization and Conversion of 10 to (1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (16)



The process we have presented provides a method for the converion of aspartic acid to the target (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane (**16**). This method involves the intramolecular cyclization of an ester enolate on to an activated aziridine ring to form a cyclopentane. The cyclopentane **10b** was formed as a mixture of diastereomers which was converted to a single diastereomer via the intermediacy of the bicyclic lactam **14**.

Experimental Section[14]

(*S*)-*N*-(Phenylsulfonyl)aspartic Anhydride (2a). Thionyl chloride (47.6 g, 400 mmol) was added to a suspension of **1a**[15] (10.9 g, 40 mmol) in EtOAc (60 mL) and stirred for 1 h. The resulting clear solution was concentrated to give 9.8 g (96%) of **2a** as a yellow solid: mp 116–118 °C; $[\alpha]^{25}_D$ –3.8° (*c* 1.4, EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.31 (d, *J* = 9.2, 1H), 7.83 (d, *J* = 7.3, 1H), 7.68 (m, 1H), 7.62 (m, 2H), 4.87 (m, 1H), 3.05 (dd, *J* = 18.1, 9.8, 1H), 2.70 (dd, *J* = 18.1, 6.9, 1H); ^{13}C NMR (DMSO-d_6) δ 171.1, 168.0, 140.8, 133.0, 129.5, 126.4, 52.2, 35.6. Anal. Calcd for $C_{10}H_9NO_5S$: C, 47.1; H, 3.5; N, 5.5. Found: C, 47.4; H, 3.5; N, 5.5.

(*S*)-4-(Tolylsulfonyl)aspartic Anhydride (2b) was prepared as for **2a** using 12.3 g of **1b** to give 10.0 g (88%) of **2b** as a white solid: mp 145–147 °C; $[\alpha]^{25}_D$ +1.3° (*c* 2.4, EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.20 (d, *J* = 9.1, 1H), 7.69 (d, *J* = 7.9, 2H), 7.41 (d, *J* = 7.9, 2H), 4.81 (m, 1H), 2.66 (dd, *J* = 18.1, 6.8, 1H), 2.57 (dd, *J* = 16.3, 6.7, 1H), 2.57 (dd, *J* = 16.3, 6.7, 1H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.0, 168.8, 143.3, 137.9, 129.8, 126.5, 52.2, 35.5, 21.0. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.1; H, 4.1; N, 5.2. Found: C, 49.1; H, 4.2; N, 5.2.

(*S*)-4-[(Phenylsulfonyl)amino]-γ-butyrolactone (3a). A solution of anhydride **2a** (9.6 g, 37.6 mmol) in THF (60 mL) was slowly added to a suspension of $NaBH_4$ (1.4 g, 38 mmol) in THF (50 mL), keeping the temperature below 20 °C. After the addition was complete the reaction was stirred at room temperature for 1.5 h, EtOH (7.5 mL) and concentrated HCl (7.5 mL) were added, and the reaction mixture was heated at reflux for 16 h. It then was cooled to room temperature and concentrated to one-half volume, diluted with brine, and extracted with EtOAc (2 × 100 mL). Evaporation and chromatography (40% EtOAc/hexane) gave 6.4 g (71%) of lactone **3a**: mp 89–91 °C; $[\alpha]^{25}_D$ –22° (*c*, 1.0, EtOH); ^{1}H NMR δ 7.85 (d, *J* = 7.4, 2H), 7.61 (m, 1H), 7.54 (m, 2H), 5.88 (bs, 1H), 4.37 (m, 1H), 4.15 (m, 2H), 2.65 (dd, *J* = 18.0, 7.5, 1H), 2.36 (dd, *J* = 18.0, 4.8, 1H); ^{13}C NMR δ 174.9, 139.7, 133.4, 129.5, 127.0, 73.2, 49.8, 34.8. Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8. Found: C, 49.7; H, 4.3; N, 5.6.

(*S*)-4-[(Tolylsulfonyl)amino]-γ-butyrolactone (3b) prepared as for **3a** using 5.0 g of **2b** which gave 3.4 g (72%) of **3b**: mp 111–113 °C; $[\alpha]^{25}_D$ –13° (*c*, 1.0, EtOH); ^{1}H NMR δ 7.73 (d, *J* = 8.1, 2H), 7.32 (d, *J* = 8.3, 2H), 5.88 (d, *J* = 7.1, 1H), 4.37 (m, 1H), 4.13 (m, 2H), 2.63 (dd, *J* = 18.0, 7.8, 1H), 2.44 (s, 3H), 2.37 (dd, *J* = 18.0, 4.9, 1H); ^{13}C NMR δ 175.4, 144.1, 136.5, 129.9, 126.9, 72.9, 49.6, 34.4, 21.4. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.7; H, 5.1; N, 5.5. Found: C, 51.4; H, 5.2; N, 5.4.

(1*R*/*S*,4*S*)-4-[(Phenylsulfonyl)amino]-2-hydroxytetrahydrofuran (4a). To a solution of lactone **3a** (6.8 g, 28.2 mmol) in CH_2Cl_2 (500 mL) at –78 °C was added DIBAL-H (36.7 mL of a 1.0 M solution in toluene, 36.7 mmol) over 1.5 h. After the addition was complete the mixture was stirred at –78 °C for an additional 2 h. Methanol (5.4 mL) was added, the mixture was warmed to room temperature, EtOAc (33 mL) and saturated aqueous $NaHCO_3$ solution (6 mL) were added, and the reaction was stirred for 6 h. After addition of Na_2SO_4 and Celite and filtration, concentration and chromatography (50% EtOAc/hexane) gave 5.3 g (78%) of lactol **4a** as a thick oil that decomposed upon storage: ^{1}H NMR δ 7.85 (m, 2H), 7.50 (m, 3H), 5.95 (d, *J* = 9.4, 0.7H), 5.75* (d, *J* = 7.7, 0.3H), 5.51* (m, 0.3H), 5.43 (m, 0.7H), 4.00 (m, 2H), 3.79 (dd, *J* = 9.4, 2.9, 0.7H), 3.56* (dd, *J* = 9.2, 3.0, 0.3H), 1.95 (m, 2H), 1.67 (d, *J* = 13.8, 1H); ^{13}C NMR δ 140.5*, 140.1, 132.8, 132.7*, 129.2, 126.9, 98.1*, 97.7, 73.4*, 71.4, 53.0, 52.4*, 40.5, 39.3* (* indicates a signal from the minor isomer). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.4; H, 5.4; N, 5.8. Found: C, 48.9; H, 5.4; N, 5.7.

***tert*-Butyl (*S*)-5-[(Phenylsulfonyl)amino]-6-hydroxyhex-2-enoate (5b).** A solution of **4a** (5.3 g, 21.9 mmol) and [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane (10.7 g, 28.5 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 20 h and then evaporated, and the concentrated residue was chromatographed (35% EtOAc/hexane) to give 4.5 g (60%) of **5b** as a cloudy semisolid which was a 1/8 mixture of cis/trans isomers by ^{1}H NMR: ^{1}H NMR δ 7.85 (m, 2H), 7.54 (m, 1H), 7.47 (m, 2H), 6.53 (m, 0.8H), 5.90* (d, *J* = 7.4, 0.2H, NH), 5.81* (m, 0.2H), 5.64 (d, *J* = 15.6, 0.8H), 5.57* (d, *J* = 11.5, 0.2H), 5.51 (d, *J* = 7.9, 0.8H, NH), 3.54 (m, 2H), 3.38 (m, 1H), 2.74 (t, *J* = 5.7, 1H, OH), 2.66* (m, 0.2H), 2.62* (m, 0.2H), 2.30 (m, 1.6H), 1.44* (s, 1.8H), 1.42 (s, 7.2H); ^{13}C NMR δ 166.8,* 165.4, 142.1, 142.0, 140.6, 140.3, 132.8, 132.6, 129.1, 129.0, 127.0, 126.3, 124.5, 81.7,* 80.5, 64.1,* 63.8, 54.6,* 34.2, 30.9,* 28.0 (* indicates a signal from the minor cis isomer). Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.3; H, 6.8; N, 4.1. Found: C, 56.2; H, 6.8; N, 3.8.

Methyl (*S*)-4-[(Tolylsulfonyl)amino]-6-hydroxyhex-2-enoate (5c). (1*R*/*S*,4*S*)-4-[(Tolylsulfonyl)amino]-2-hydroxytetrahydrofuran (**4b**) was prepared as for **4a** using 1.1 g of **3b** which gave 750 mg (68%) of crude **4b**: ^{1}H NMR δ 7.75 (m, 2H), 7.34 (m, 2H), 5.99 (d, *J* = 10.0, 1H), 5.53 (m, 1H), 5.45 (m, 1H), 4.02–3.88 (m, 2H), 3.81 (dd, *J* = 9.2, 3.0, 0.5H), 3.70–3.68 (m, 0.5H), 2.42 (s, 3H), 2.03–1.91 (m, 1H), 1.69 (d, *J* = 14.1, 1H); ^{13}C NMR δ 143.5, 137.8, 137.5, 129.7, 129.6, 97.9, 97.6, 73.1, 7.13, 52.9, 52.4, 40.5, 39.3, 21.3. It was used directly without further purification. Methyl diethylphosphonoacetate (1.3 g, 6.3 mmol) was added to a suspension of LiCl (267 mg, 6.3 mmol), followed by iPr_2NEt (813 mg, 6.3 mmol). To this now clear solution was added a solution of crude **4b** (2.0 g, 6.3 mmol) in CH_3CN (10 mL). After stirring for 2 h the reaction mixture was evaporated and the residue was dissolved in water and then extracted with EtOAc (4 × 20 mL). The extracts were washed with water, 1 M HCl, and brine and then evaporated. Chromatography (30% EtOAc/hexane) of the residue gave 1.2 g (71%) of **5c**: ^{1}H NMR δ 7.75 (d, *J* = 8.3, 2H), 7.30 (d, *J* = 8.2, 2H), 6.67 (dt, *J* = 15.6, 7.8, 1H), 5.76 (dt, *J* = 15.7, 1.2, 1H), 5.45 (bs, 1H), 3.70 (s, 3H), 3.60 (dd, *J* = 11.2, 4.1, 1H), 3.53 (dd, *J* = 11.2, 4.8, 1H), 3.40 (m, 1H), 2.65 (bs, 1H), 2.43 (s, 3H), 2.35 (m, 2H); ^{13}C NMR δ 166.7, 143.9, 143.6, 137.3, 129.7, 127.0, 123.9, 63.9, 54.3, 51.5, 34.3, 21.5. Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.7; H, 6.1; N, 4.5. Found: C, 53.2; H, 6.2; N, 4.4. When NaH was used as a base, the major product (89%) was tetrahydrofuranacetate **8**: ^{1}H NMR δ 7.74 (d, *J* = 8.0, 2H), 7.30 (d, *J* = 8.5, 2H), 5.48 (d, *J* = 8.3, 0.5H), 5.20 (d, *J* = 7.5, 0.5H), 4.40–4.35 (m, 0.5H), 4.14–4.07 (m, 0.5H), 3.94–3.84 (m, 1H), 3.67 (s, 1.5H), 3.66 (s, 1.5H), 3.60 (m, 0.5H), 3.45 (dd, *J* = 9.4, 3.7, 0.5H), 2.60 (d, *J* = 5.9, 1H), 2.56–2.41 (m, 2H), 2.42 (s, 3H), 2.35–2.28 (m, 0.5H), 2.02–1.96 (m, 0.5H), 1.80–1.72 (m, 0.5H), 1.55–1.49 (m, 0.5H).

(13) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.

(14) All reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted. Immediately prior to use tetrahydrofuran was distilled from sodium/benzophenone ketyl; acetonitrile, methylene chloride, triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride, and acetic anhydride was distilled from P_2O_5. Sodium acetate, at rt, and LiCl, at 150 °C, were dried under high vacuum before use. NMR spectra were recorded in $CDCl_3$ unless otherwise noted. Final solutions before evaporation were dried over $MgSO_4$.

(15) Ghosh, N. N.; Nandi, M. M. *Ind. J. Chem.* **1975**, *13*, 596.

***tert*-Butyl (*S*)-5-[(Phenylsulfonyl)amino]-6-hydroxyhexanoate (6b).** A mixture of unsaturated ester **5b** (4.2 g, 12.2 mmol) and 10% Pd/C (800 mg) in EtOAc (36 mL) was stirred under a H_2 atmosphere for 16 h. The mixture was filtered through Celite topped with 1 cm of silica gel, and the filtrate was concentrated to give 3.8 g (92%) of **6b**: $[\alpha]^{25}_D$ +2° (*c*, 2.0, $CHCl_3$); ^1H NMR δ 7.85 (d, J = 7.1, 2H), 7.47 (m, 3H), 5.61 (d, J = 8.0, 1H, NH), 3.48 (m, 2H), 3.20 (m, 1H), 2.93 (t, J = 5.6, 1H, OH), 2.02 (t, J = 6.8, 2H), 1.44–1.32 (m, 4H); ^{13}C NMR δ 172.8, 140.7, 132.5, 129.0, 126.9, 80.4, 64.4, 55.3, 34.7, 30.8, 28.0, 20.7. Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 56.0; H, 7.3; N, 4.1. Found: C, 55.8; H, 7.3; N, 3.8.

***tert*-Butyl (*S*)-*N*-(Phenylsulfonyl)-5,6-iminohexanoate (7b).** Methanesulfonyl chloride (180 mg, 1.6 mmol) was added to a −23 °C solution of **6b** (370 mg, 1.1 mmol), triethylamine (380 mg, 3.8 mmol), and DMAP (24 mg, 0.2 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 1 h then warmed to 0 °C and stirred for 18 h. It was diluted with Et_2O/petroleum ether (1/1, 20 mL), washed with water, 1 M HCl, and brine, and evaporated and chromatographed (20% EtOAc/hexane), to give 270 mg (77%) of **7b**: $[\alpha]^{25}_D$ +8.4° (*c*, 3.2, $CHCl_3$); ^1H NMR δ 7.95 (d, J = 7.2, 2H), 7.64 (t, J = 7.5, 1H), 7.55 (t, J = 7.9, 2H), 2.76 (m, 1H), 2.67 (d, J = 7.0, 1H), 2.17 (t, J = 7.3, 2H), 2.09 (d, J = 4.6, 1H), 1.65–1.48 (m, 4H), 1.42 (s, 9H); ^{13}C NMR δ 172.2, 138.0, 133.5, 129.0, 127.8, 80.2, 39.8, 34.5, 33.7, 30.5, 28.0, 22.1. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.0; H, 7.1; N, 4.3. Found: C, 58.7; H, 7.3; N, 4.1.

Methyl (*S*)-*N*-(Tolylsulfonyl)-5,6-iminohex-2-enoate (9). Diethyl azodicarboxylate (66 mg, 0.38 mmol) was added dropwise to a −40 °C solution of **5c** (108 mg, 0.35 mmol) and Ph_3P (91 mg, 0.35 mmol) in THF (35 mL). The reaction was stirred for 2 h, poured into brine, and extracted with EtOAc (2 × 25 mL). Evaporation and chromatography of the residue gave 52 mg (51%) of **9** as a white solid: mp 75–77 °C; ^1H NMR δ 7.81 (d, J = 8.3, 2H), 7.33 (d, J = 8.2, 2H), 6.67 (dt, J = 15.7, 7.0, 1H), 5.82 (d, J = 15.7, 1H), 3.71 (s, 3H), 2.81 (m, 1H), 2.70 (d, J = 6.9, 1H), 2.45 (s, 3H), 2.43 (m, 1H), 2.31 (m, 1H), 2.13 (d, J = 4.4, 1H); ^{13}C NMR δ 166.1, 144.7, 142.3, 134.6, 129.6, 127.9, 123.4, 51.4, 37.9, 33.4, 32.8, 21.6. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.9; H, 5.8; N, 4.7. Found: C, 56.8; H, 5.7; N, 4.5.

***tert*-Butyl (1*S*/*R*,3*S*)-3-[(Phenylsulfonyl)amino]-cyclopentanecarboxylate (10b).** KHMDS (0.86 mL of a 1.1 M solution in THF, 0.95 mmol) was added to a −78 °C solution of aziridine **7b** (258 mg, 0.79 mmol) in THF (8 mL) and stirred for 1 h. The mixture was then diluted with THF (71 mL, precooled to −78 °C) and then warmed to room temperature and after stirring for 6 h was quenched with 1 M KH_2PO_4 (1 mL). Evaporation and chromatography (25% EtOAc/hexane) gave 175 mg (68%) of **10b** as a 1/1 mixture: ^1H NMR δ 7.90–7.88 (m, 2H), 7.54–7.48 (m, 3H), 5.66 (d, J = 8.3, 0.5H, NH), 5.29 (d, J = 6.9, 0.5H, NH), 3.76–3.70 (m, 1H), 2.76–2.70 (m, 0.5H), 2.72–2.62 (m, 0.5H), 2.00–1.45 (m, 6h), 1.42 (s, 4.5H), 1.39 (s, 4.5H); ^1C NMR δ 176.3, 174.8, 144.1, 140.5, 132.5, 132.3, 129.0, 128.9, 127.8, 126.9, 126.8, 80.7, 54.9, 54.6, 42.6, 42.3, 36.4, 36.2, 33.3, 33.1, 27.9, 27.3. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.0; H, 7.1; N, 4.3. Found: C, 58.9; H, 7.1; N, 4.6.

Methyl (2*E*,4*E*)-6-[(Tolylsulfonyl)amino]hexa-2,4-dienoate (11). KHMDS (61 mL of a 1.1 M solution in THF, 0.06 mmol) was added to a −78 °C solution of **9** (18 mg, 0.06 mmol) in THF (12 mL). The reaction was stirred for 3 h and then poured into saturated NH_4Cl solution and extracted with EtOAc. Concentration and chromatography gave 16 mg (89%) of **11** as a white solid: mp 125–127 °C; ^1H NMR δ 7.74 (d, J = 8.3, 2H), 7.31 (d, J = 8.1, 2H), 7.15 (dd, J = 15.4, 11.0, 1H), 6.23 (dd, J = 15.2, 11.3, 1H), 5.91 (dt, J = 15.2, 5.9, 1H), 5.81 (d, J = 15.4, 1H), 4.76 (t, J = 6.0, 1H), 3.74 (s, 3H), 3.71 (m, 2H), 2.43 (s, 3H); ^{13}C NMR δ 167.1, 143.8, 143.1, 136.8, 136.4, 130.1, 129.8, 127.1, 121.7, 51.6, 44.7, 21.5. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.9; H, 5.8; N, 4.7. Found: C, 56.9; H, 5.7; N, 4.5.

(1*S*,4*R*)-*N*-(Phenylsulfonyl)-2-azabicyclo[2.2.1]heptan-3-one (14). Trifluoroacetic acid (4 mL) was added to a solution of ester **10b** (256 mg, 0.79 mmol) in CH_2Cl_2 (4 mL), the solution was stirred for 16 h and then evaporated, and the residue was dissolved in Ac_2O (8 mL). Sodium acetate (650 mg, 7.9 mmol) was added, and the mixture was heated at reflux for 6 h, cooled, evaporated, and chromatographed (25% EtOAc/hexane) to give 173 mg (88%) of **14** as a thick oil: $[\alpha]^{25}_D$ +34° (*c*, 1.0, $CHCl_3$); ^1H NMR δ 8.02 (d, J = 8.3, 2H), 7.65–7.62 (m, 1H), 7.55–7.53 (m, 2H), 4.76 (bs, 1H), 2.85–2.84 (m, 1H), 2.06–1.94 (m, 1H), 1.93–1.73 (m, 3H), 1.52–1.47 (m, 2H); ^{13}C NMR δ 174.5, 139.3, 133.7, 129.0, 127.4, 62.0, 46.5, 39.1, 28.4, 23.0; HRMS (EI) calcd for $C_{12}H_{14}NO_3S^+$: 252.0694. Found: 252.0697.

(1*S*,3*R*)-1-[(Phenylsulfonyl)amino]-3-(hydroxymethyl)-cyclopentane (15). To an ice-cooled solution of **14** (128 mg, 0.51 mmol) in MeOH (5 mL) was added $NaBH_4$ (97 mg, 2.5 mmol) and the mixture was stirred for 2 h. The mixture was evaporated, the residue was partitioned between 1 M HCl and EtOAc (3 × 15 mL), and the combined organic extracts were washed with brine, evaporated, and chromatographed (55% EtOAc/hexane) to give 107 mg (82%) of **15**: $[\alpha]^{25}_D$ −4.5° (*c*, 1.5, $CHCl_3$); ^1H NMR δ 7.88 (d, J = 7.5, 2H), 7.57–7.28 (m, 3H), 5.90 (d, J = 7.8, 1H, NH), 3.65–3.61 (m, 1H), 3.50 (d, J = 5.2, 2H), 2.11–2.07 (m, 1H), 1.96–1.89 (m, 1H), 1.70–1.60 (m, 1H), 1.52–1.43 (m, 2H), 1.24–1.19 (m, 1H); ^{13}C NMR δ 140.9, 132.3, 128.9, 126.9, 65.6, 54.8, 38.8, 36.3, 33.3, 25.6. Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.4; H, 6.7; N, 5.5. Found: C, 56.2; H, 6.7; N, 5.6.

(1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (16). A solution of **15** (78 mg, 0.31 mmol) in EtOAc (3 mL) was added in 3 portions over 3 h to a mixture of phenol (0.9 g, 9.25 mmol) and 32% HBr in AcOH (9 mL). The reaction was stirred for an additional 18 h, diluted with water (10 mL), and washed with EtOAc (3 × 5 mL). The aqueous layer was evaporated to give 57 mg (94%) of **16** as a glass whose spectra were identical with those previously reported.[4]

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