mL/min, with monitoring at 220 nm. Isocratic elution with 50% solvent B delayed the peptide substantially and resulted in resolution of impurities. For purification, the lyophilized peptide-containing salts were dissolved in 0.2 N AcOH (50 mL) and applied to a preparative Dynamax-60A (8 μm, C_{18}, Rainin) column (2.14 × 25 cm), with a 5-cm guard module. A gradient was run from 0 to 50% B over 30 min, eluting at a rate of 4 mL/min, with monitoring of the eluent at 280 nm. Center portions of the main component eluted after ca. 1.5 h. The purer fractions, determined by analytical HPLC, were pooled and lyophilized, yielding antagonist 11 (41 mg). Analogue purity was established by thin-layer chromatography (TLC) in four separate solvent systems (Table I), by analytical HPLC and by amino acid analysis (Table II).

For amino acid analyses (Table II) a standard of Pmp-SS-Cys was prepared[10] and was derivatized with PITC at the same time as the hydrolysis product of the analogue and a standard amino acid mixture (Pierce Chemical Co.), in order to form the PTC-amino acids for analysis by the Picotag method.[37] An aliquot of the PTC-derivative of Pmp-SS-Cys was injected into the Picotag column and eluted with the normal protocol, in order to determine its UV absorption and elution time, and in a separate run, it was coinjected with the PTC-amino acid standard into the Picotag column, in order to verify its position of elution. PTC-Pmp-SS-Cys has UV absorption similar to and coelutes with PTC-Ile; hence, for peptide hydrolyzates we report the combined values for Pmp-SS-Cys and Ile. The value of Pmp-SS-Cys is somewhat low for the Pmp component, because symmetric disulfide, Pmp-SS-Pmp, can also form. The value of Cys added to the value estimated for Pmp-SS-Cys gives an estimate for Cys. Except for tryptophan, all analogues gave the expected amino acid analysis ratios ± 10%. Tryptophan, was estimated in peptides by UV spectrophotometry at 280 nm, and Trp(For) was estimated at 300 nm. The lower values found for tryptophan suggest that the peptide may have several moles of AcOH, TFA, and H_2O, as we have observed with other peptides.[10,38] 1-Adamantaneacetic acid in hydrolysates was quantified by HPLC using a standard of this acid and monitoring at 220 nm.

This procedure, with only minor variations, was used to prepare all the antagonists (Table I) except for analogues 10 and 12, shown below.

Pmp-D-Trp-Ile-Gln-Asn-Cys-Pro-Arg-Trp(For)-NH_2, [Pmp^1,D-Trp^2,Arg^8,Trp(For)^9]OT (12, Table I). Pmp(S-Meb)-D-Trp-Ile-Gln-Asn-Cys(Meb)-Pro-Arg(Tos)-Trp(For)-MBHA-resin assembled by the SP method as described above (0.25 mmol) was treated with anisole (1 mL) and liquid HF[34] (9 mL) for 60 min at 0 °C. After removal of HF under vacuum, the residue was extracted four times with petroleum ether and then three times with 50% AcOH (10 mL). Following the usual oxidative cyclization as described above, HPLC purification yielded purified analogue 12 (36 mg).

Pmp-D-Trp-Ile-Gln-Asn-Cys-Pro-Trp-Gly-NH_2, [Pmp^1,D-Trp^2,Trp^3]OT (10, Table I). Pmp(*S*-Meb-D-Trp-Ile-Gln-Asn-Cys(Meb)-Pro-Trp-Gly-NH_2 (200 mg), obtained by the SP method was treated with sodium in liquid ammonia, as described above, the residue was dissolved in 50% AcOH (20 mL) and the solution was added to distilled water (600 mL). Since a cloudiness appeared, acetone (200 mL) was added until a clear solution resulted and then distilled water (1200 mL) was added. This solution was subjected to oxidative cyclization as described for antagonist 11 except that after concentrating in a vacuum to remove acetone, the solution was lyophilized. The residue obtained was dissolved in the smallest possible volume of 50% acetic acid and was applied to a Sephadex G-15 column (115 × 2.7 cm) and eluted with the same solvent at a rate of about 50–60 mL/h.[36] The eluate was monitored in a UV spectrophotometer at 254 nm. The fractions corresponding to the major peak were monitored by analytical HPLC, eluting isocratically with 75% solvent B, and the purer ones were pooled and lyophilized, yielding desalted peptide (80 mg). During analytical HPLC, isocratic elution with 55% solvent B delayed the peptide about 25 min and resulted in resolution of impurities. The peptide was dissolved in 50% AcOH (3 mL) and was diluted with water (9–15 mL) until faintly cloudy, the cloudiness being cleared with an additional drop of glacial AcOH. The solution was applied to a preparative Dynamax-60A (8 μm, C_{18}, Rainin) column (2.14 × 25 cm), with a 5-cm guard module. A gradient was run from 0 to 50% B over 30 min, eluting at a rate of 5 mL/min, with monitoring of the eluent at 280 nm. Center portions of the main component eluted after ca. 3 h. The purer fractions, determined by analytical HPLC, were pooled and lyophilized, yielding purified antagonist 10 (37 mg). The structures of the antagonists prepared are as follows: [Ac-Trp^1,D-Trp^2,Val^6,Arg^8]OT (1); [Pmp^1,Trp^2,Arg^8]OT (2), [Pmp^1,D-Trp^2,Trp^3,Arg^8]OT (3); [Pmp^1,D-Trp^2,Trp^4,Arg^8]OT (4), [Pmp^1,D-Trp^2,Trp^5,Arg^8]OT (5), [Aaa^1,D-Trp^2,Trp^6,Arg^8]OT (6), [Aaa^1,D-Trp^2,Val^6,Arg^8]OT (7), [Pmp^1,D-Trp^2,Ica^7,Arg^8]OT (8), [Pmp^1,D-Trp^2,Trp^7,Arg^8]OT (9), [Pmp^1,D-Trp^2,Trp^8]OT (10), [Pmp^1,D-Trp^2,Arg^8,Trp^9]OT (11), [Pmp^1,D-Trp^2,Arg^8,Trp(For)^9]OT (12). The physicochemical properties, amino acid analyses, and biological properties of these analogues are shown on Tables I–III, respectively.

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Registry No. 1, 133869-59-7; 2, 133851-41-9; 3, 133851-42-0; 4, 133851-43-1; 5, 133851-44-2; 6, 133851-45-3; 7, 133851-46-4; 8, 133851-47-5; 9, 133851-48-6; 10, 133851-49-7; 11, 133851-50-0; 12, 133851-51-1; OT, 50-56-6; AVP, 113-79-1; Boc-Ica, 133851-52-2; Ica, 78348-24-0; Pmp(*S*-Meb)-D-Trp-Ile-Gln-Asn-Cys(Meb)-Pro-Arg(Tos)-Trp-NH_2, 133851-53-3; Pmp(*S*-Meb)-D-Trp-Ile-Gln-Asn-Cys(Meb)-Pro-Trp-Gly-NH_2, 133851-54-4.

Stereospecific Synthesis of (*R*)- and (*S*)-*S*-Adenosyl-1,8-diamino-3-thiooctane, a Potent Inhibitor of Polyamine Biosynthesis. Comparison of Asymmetric Induction vs Enantiomeric Synthesis

Chin Liu and James K. Coward*

Departments of Medicinal Chemistry and Chemistry, The University of Michigan, Ann Arbor, Michigan 48109.
Received November 1, 1990

Two diastereomers of the potent spermidine synthase inhibitor *S*-adenosyl-1,8-diamino-3-thiooctane have been prepared in high (>96% de) stereochemical purity. Two synthetic routes were investigated, one based on asymmetric induction and the other involving an enantiomeric synthesis. The latter route gave the desired products in >96% de, whereas the synthesis based on asymmetric induction resulted in only 80% de in the final product. Evaluation of the two diastereomers as inhibitors of spermidine synthase showed that the *R* diastereomer is a more potent inhibitor than the *S* diastereomer.

The polyamines spermidine and spermine are synthesized in vivo by a pair of closely related aminopropyltransferases (APT), spermidine synthase (putrescine aminopropyltransferase, PAPT, EC 2.5.1.16) and spermine

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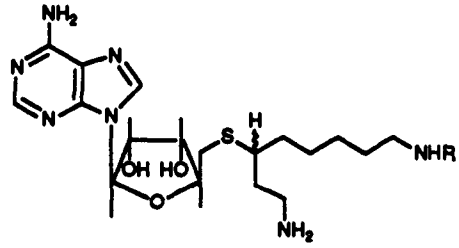
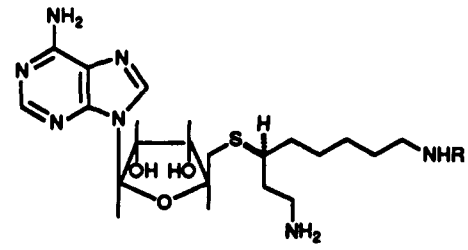
synthase (spermidine aminopropyltransferase, SAPT, EC 2.5.1.22).[1] Overall, nucleophilic attack at the electrophilic methylene carbon of decarboxylated S-adenosylmethionine (dcAdoMet) leads to transfer of an aminopropyl group to putrescine or spermidine leading to the formation of spermidine or spermine, respectively. Using chirally labeled substrates with spermidine synthase from *E. coli*, we have demonstrated that the transfer of the aminopropyl group occurs via direct nucleophilic attack (single displacement) rather than through an aminopropylated enzyme intermediate.[2] Thus, the transition state for the APT-mediated transfer of an aminopropyl group involves a simple S_N2 attack by the nucleophilic amine putrescine or spermidine on the electrophilic sulfonium salt dcAdoMet. We have previously described the synthesis of two multisubstrate adduct inhibitors of PAPT and SAPT, S-adenosyl-1,8-diamino-3-thiooctane (AdoDATO, **1a**) and



1

a, R = H
b, R = $CH_2CH_2CH_2NH_2$

S-adenosyl-1,12-diamino-3-thio-9-azadodecane (AdoDATAD, **1b**), respectively.[3,4] These two compounds are specific and potent inhibitors of the target aminopropyltransferase and have been extremely useful in studying the regulation of polyamine biosynthesis in mammalian cells.[5-7] As shown in structure **1**, these compounds are racemic at the methine carbon α to the sulfur atom. While there are many examples of strict stereospecificity in enzyme-catalyzed reactions, the transition state for enzyme-catalyzed alkyl transfer such as that mediated by the aminopropyltransferases involves a transition state approaching a planar carbocation.[2] It is not obvious whether stereospecificity would be observed in a molecule such as **1** which is designed to mimic the binding of the two substrates during approach to a planar transition state. However, it seems reasonable to expect that binding of the two substrates would occur with a set spatial relationship at the active site of the enzyme. In order to examine the stereospecificity of binding of compounds of this type to alkyltransferase, we have synthesized the two diastereomers of AdoDATO with S (**2a**) and R (**3a**) configurations at the methine carbon of interest. Preliminary inhibition studies using spermidine synthase from *E. coli* have demonstrated a marked difference between **2a** and **3a**, with **3a**



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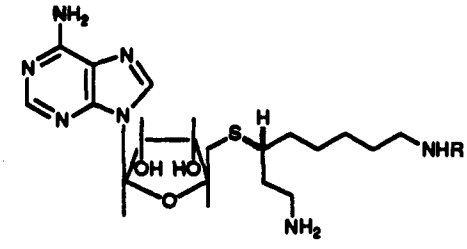


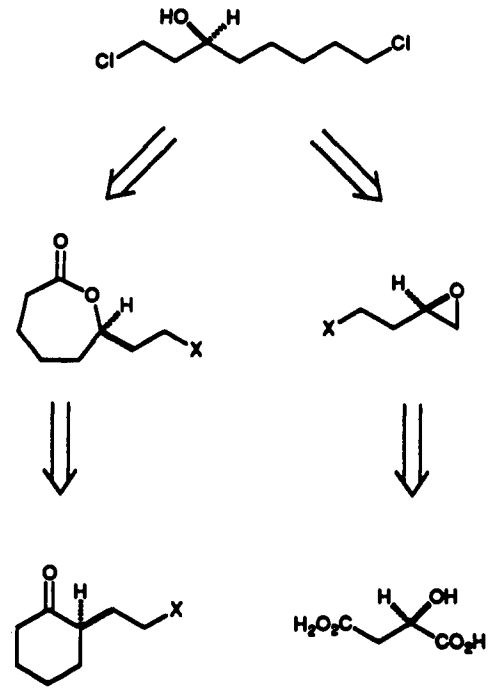
3

a, R = H
b, R = $CH_2CH_2CH_2NH_2$

being the more potent inhibitor. In addition, the synthetic route employed should allow for the general elaboration of structures of this type, including the two diastereomers of AdoDATAD, **2b** and **3b**.

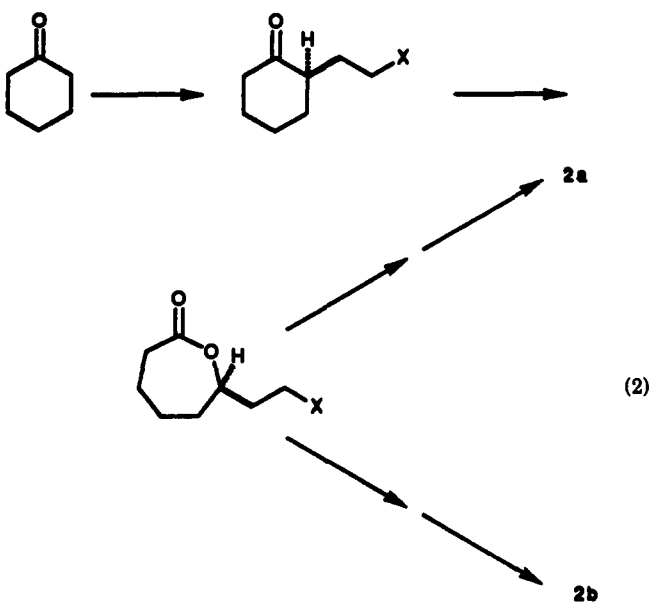
Chemistry

The initial retrosynthetic analysis (eq 1) suggested two possible approaches in order to obtain 1,8-dichloro-3-octanol, a known intermediate in the synthesis of racemic AdoDATO (**1a**),[3] in high stereochemical purity. A synthetic route based on asymmetric induction would involve alkylation of cyclohexanone using a chiral auxiliary as described by Meyers and colleagues.[8] Alternatively, an enantiomeric synthesis could be envisioned starting with malic acid. As shown in eq 2, the asymmetric induction route offers the possibility of proceeding via a common



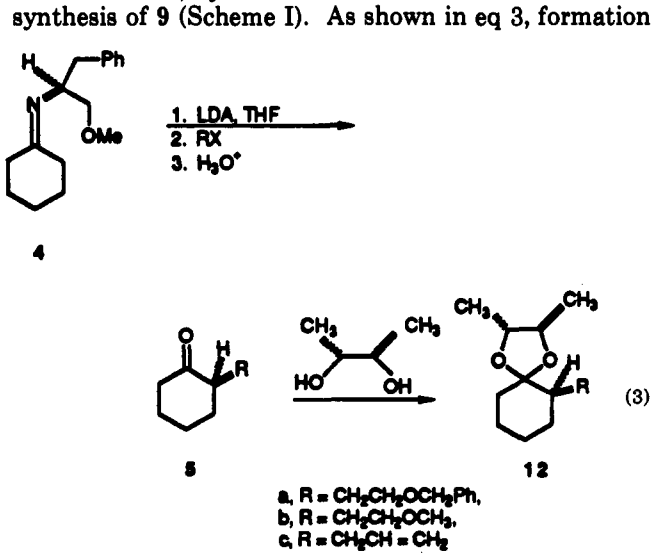
(1)

(1) Williams-Ashman, H. G.; Pegg, A. E. In *Polyamines In Biology and Medicine*; Morris, D. R., Marton, L., Eds.; Marcel Dekker: New York, 1981; pp 3-73.
(2) Orr, G. R.; Danz, D. W.; Pontoni, G.; Prabhakaran, P. C.; Gould, S. J.; Coward, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 5791.
(3) Tang, K.-C.; Mariuzza, R.; Coward, J. K. *J. Med. Chem.* **1981**, *24*, 1277.
(4) Woster, P. M.; Black, A. Y.; Duff, K. J.; Coward, J. K.; Pegg, A. E. *J. Med. Chem.* **1989**, *32*, 1300.
(5) Pegg, A. E.; Tang, K.-C.; Coward, J. K. *Biochemistry* **1982**, *21*, 5082.
(6) Pegg, A. E.; Wechter, R.; Poulin, R.; Woster, P. M.; Coward, J. K. *Biochemistry* **1989**, *28*, 8446.
(7) Pegg, A. E. *Cancer Res.* **1988**, *48*, 759.
(8) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.



lactone intermediate to chirally pure AdoDATO (**2a**) and AdoDATAD (**2b**). If this proved to be an effective synthetic route, the other stereoisomer in both series, **3a** and **3b**, could be obtained simply by using the enantiomeric chiral auxiliary.

The synthetic route to the desired dichlorooctanol **9** using the asymmetric induction approach is shown in Scheme I. In this case, the use of a chiral amine, (*S*)-(−)-2-amino-1-methoxy-3-phenylpropane,[8] to prepare chiral imine **4** should provide **9** with *R* configuration. Conversion of **9** prepared by this method to the corresponding Mosher ester[9] for analysis of stereochemical purity (Figure 1, discussed below) led to the unexpected finding that the chiral alcohol was obtained in only 80% ee. This was contrary to results reported in the literature[8] in which very high percent ee's (99% in several cases) were claimed by using this route to α-substituted cyclohexanones. Therefore, we analyzed the chiral purity of α-substituted cyclohexanone **5**, synthesized as an intermediate in the synthesis of **9** (Scheme I). As shown in eq 3, formation



of chiral ketal **12** is readily accomplished and allows one to analyze the stereochemical purity of this type of compound.[8,10] Analysis by ^{13}C NMR (see the Experimental Section) revealed that the initial alkylation product **5** was

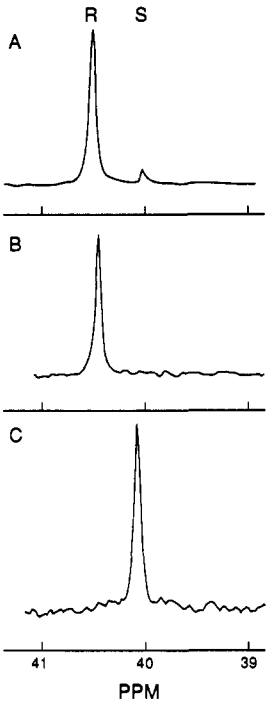


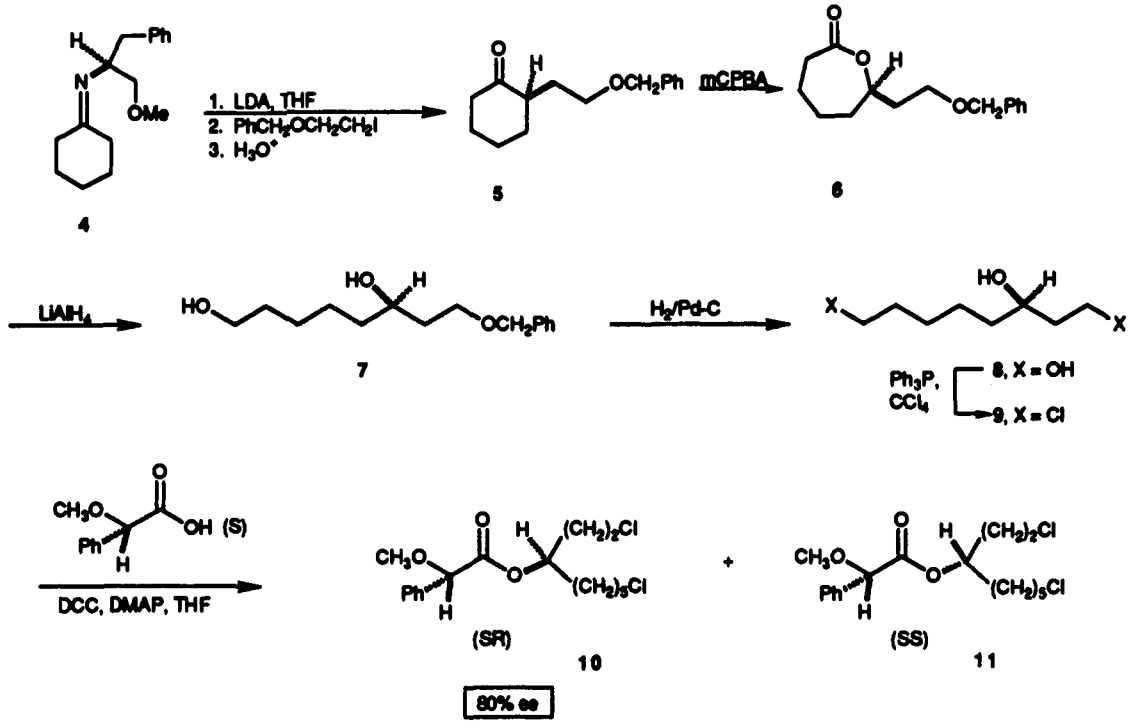
Figure 1. A portion of the ^{13}C NMR spectra of the Mosher esters **10** and **11** derived from 1,8-dichlorooctanol (**9**) prepared by (A) asymmetric induction (Scheme I), (B) enantiomeric synthesis (Scheme II), or (C) enantiomeric synthesis (Scheme II) via the *R* enantiomer of **16**.

obtained with only modest stereochemical control (80% ee). To be sure that this was not unique to the alkyl halide used in Scheme I, we repeated one of the alkylation reactions reported by Meyers et al.[8] using allyl bromide and obtained the α-substituted cyclohexanone with only 80% ee whereas the literature reports 99% ee based on optical rotation data.[8]

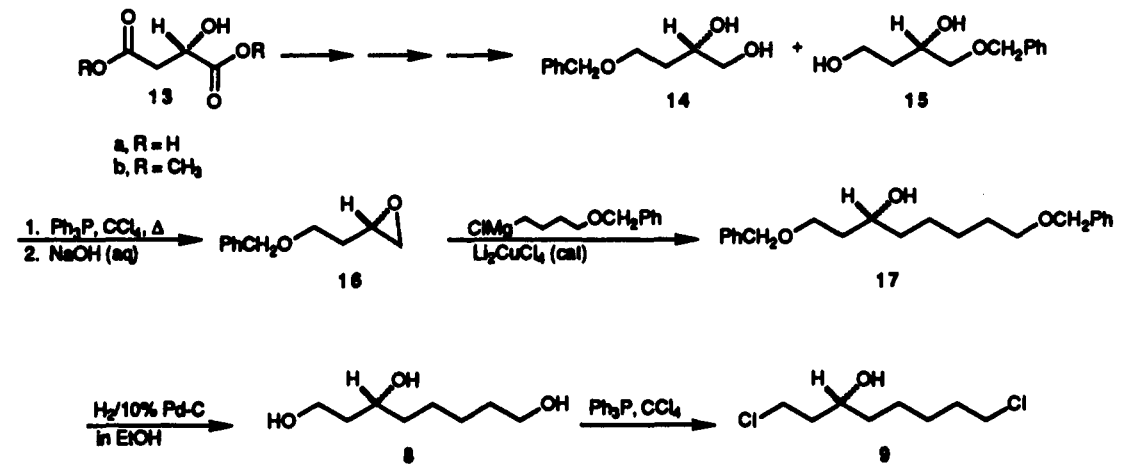
Faced with the disappointingly low stereocontrol in the asymmetric induction route (Scheme I), we turned our efforts to an enantiomeric synthesis of the desired dichlorooctanol **9**. We envisioned that homologation of an oxirane via nucleophilic attack with an appropriately substituted alkane would provide the dichlorooctanol. As shown in Scheme II, we chose oxirane **16** for this purpose. The synthesis of **16** has been reported in the literature, including a synthesis from L-malic acid (**13**).[11] Unfortunately, these routes lead to oxirane **16** with only 80% ee due to a lack of regiocontrol in the conversion of **14** to the monosulfonate ester prior to cyclization to the oxirane. We have recently described a simple conversion of **14** to **16** with very high stereochemical purity (>96% ee) under mild conditions, i.e., CCl_4/Ph_3P, followed by base-mediated cyclization.[12] Using **16** prepared in this way, we have successfully synthesized dichlorooctanol **9** by the route shown in Scheme II. Although the route shown depicts the formation of *R* isomer **9**, the same chemistry allows for the synthesis of the *S* isomer from the (*R*)-oxirane. The dichlorooctanols obtained by either asymmetric induction (Scheme I) or enantiomeric synthesis (Scheme II) were converted to their Mosher esters[9] and analyzed for stereochemical purity by ^{13}C NMR. In Figure 1 are shown portions of the ^{1}H NMR spectra for the esters derived from *R* isomer **9**, prepared by asymmetric induction (panel A) vs enantiomeric synthesis (panel B). As noted above, this

(9) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(10) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, 4883.
(11) Van der Eycken, E.; DeWilde, H.; Deprez, L.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 4759.
(12) Liu, C.; Coward, J. K. *J. Org. Chem.* **1991**, *56*, 2262–2264.

Scheme I



Scheme II



analysis leads to a value of 80% ee for the material prepared by asymmetric induction. In contrast, we observe >96% ee for the material prepared by enantiomeric synthesis. The *S* isomer, prepared by enantiomeric synthesis, was also converted to its Mosher ester, and analysis of the pertinent portion of its ^{13}C NMR spectrum (panel C) demonstrates that this material is of high stereochemical purity (>96% ee).

Since we had previously used racemic 1,8-dichloro-3-octanol in the synthesis of AdoDATO,[3] the only remaining question was if stereochemical integrity at the methine carbon of **9** (or its enantiomer) would be maintained during the multistep synthesis of **2a** and **3a**. Initially we used **9** which had been obtained by the asymmetric induction route (Scheme I) and established that **2a** could be obtained as shown in Scheme III with identical stereochemical purity of 80% de as observed in the starting material **9**. With the same synthetic route (Scheme III), target compounds **2a** and **3a** were then obtained in >96% de from **9** and its enantiomer prepared by enantiomeric synthesis (Scheme II). Although it is possible to show magnetic nonequivalence of the C-8 protons of **2a** and **3a**, there is not sufficient resolution of these signals in the NMR spectra to allow for a quantitative assessment of the stereochemical purity of these two diastereomers. No other resonances of **2a** and **3a** are sufficiently different to allow even a qualitative analysis of stereochemical purity. Analysis of the penultimate compound, *S*-adenosyl-1,8-diazido-3-thiooctane, showed that it is possible to assess stereochemical purity of this final intermediate by analysis of the ^{13}C NMR spectra. As shown in Figure 2, inspection of two portions of the spectra allow one to readily establish the stereochemical purity of the product. From comparison of the racemic material (panel A) with the *R* isomer (panel B) or *S* isomer (panel C), we conclude that the diazido pre-

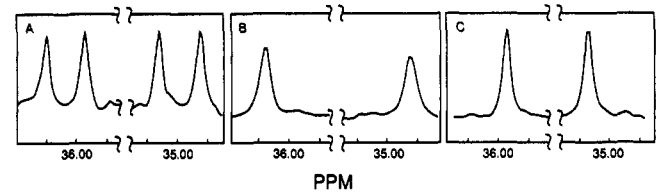
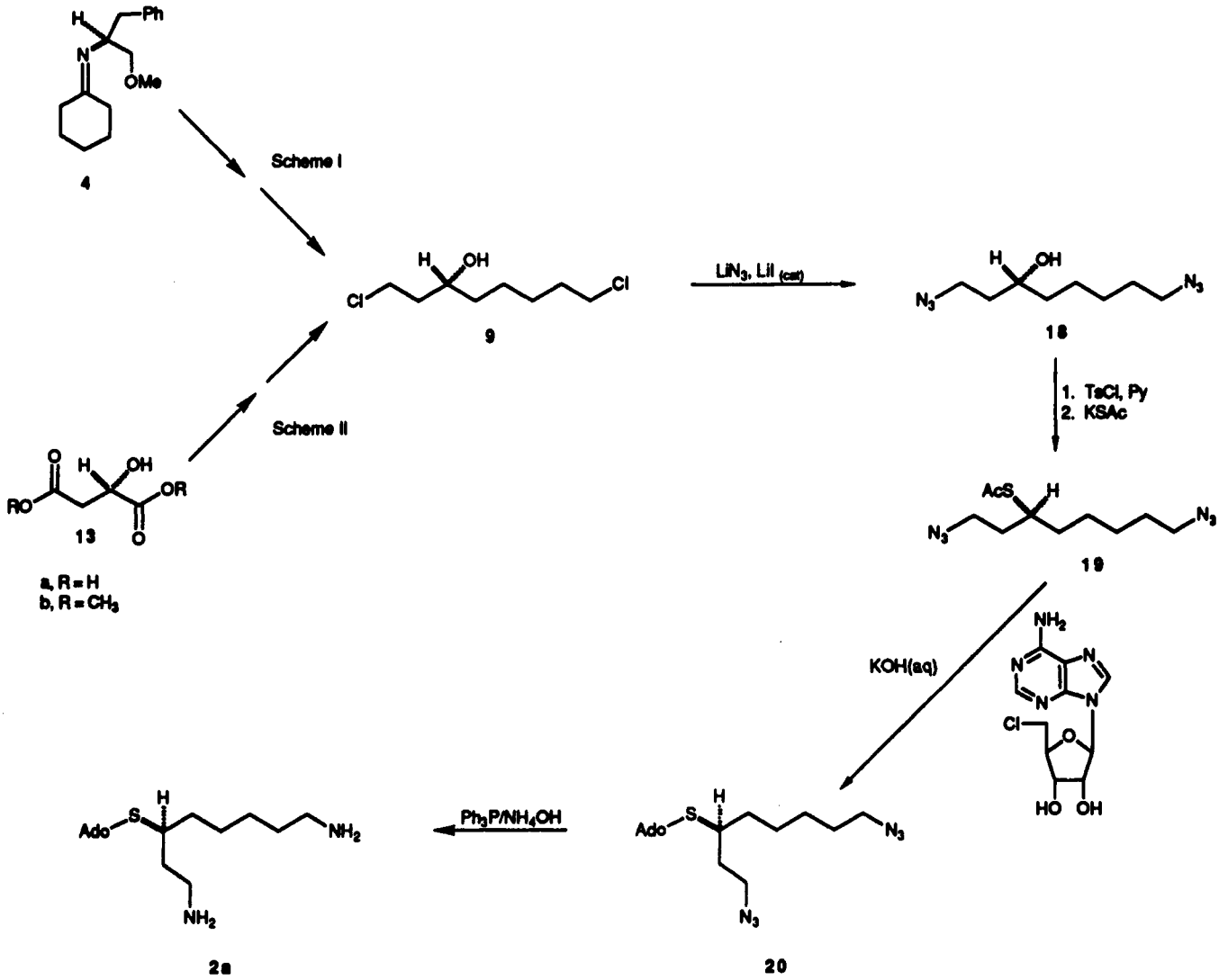


Figure 2. A portion of the ^{13}C NMR spectra of **20** (Scheme III) and its stereoisomers, precursors of **1** (*R,S*),[3] **3a** (*R*), and **2a** (*S*) in panels A–C, respectively. See text for details.

Scheme III



cursors of **2a** and **3a** have been prepared with very high (>96% de) stereochemical purity.

Biological Results and Discussion

Compounds **2a** and **3a** were studied as inhibitors of spermidine synthase from *E. coli*, isolated, and assayed as described previously.[2] In Figure 3 are shown the data obtained from these preliminary experiments. *R* isomer **3a** is a slightly more potent inhibitor of spermidine synthase than is **2a**. The observed difference between **2a** ($I_{50} \approx 1.2$ μM) and **3a** ($I_{50} \approx 0.5$ μM) is modest and a more detailed examination of the inhibition kinetics is currently underway in our laboratory. It should be noted that the value of I_{50} obtained for **3a** is similar to that previously obtained by us for inhibition by racemic AdoDATO of spermidine synthase from rat prostate[13] or *E. coli* (Szalma, J., unpublished data). It is not clear why the racemic material should be similar to the more inhibitory of the two pure isomers. However, it is possible that these compounds act as so-called slow-binding inhibitors[14] and a single time point assay, such as used in this work, might not detect significance differences between **3a** and the racemic material in formation (k_{on}) or dissociation (k_{off}) of the E·I complex. A thorough investigation of the inhibition kinetics employing various incubation times will be required in order to adequately investigate this possibility.

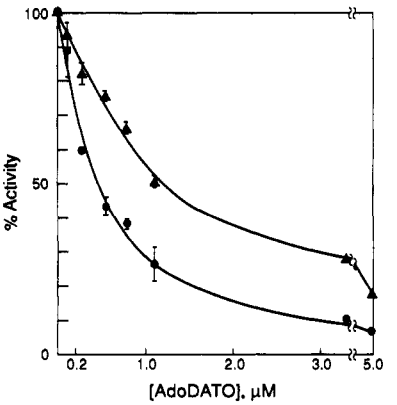
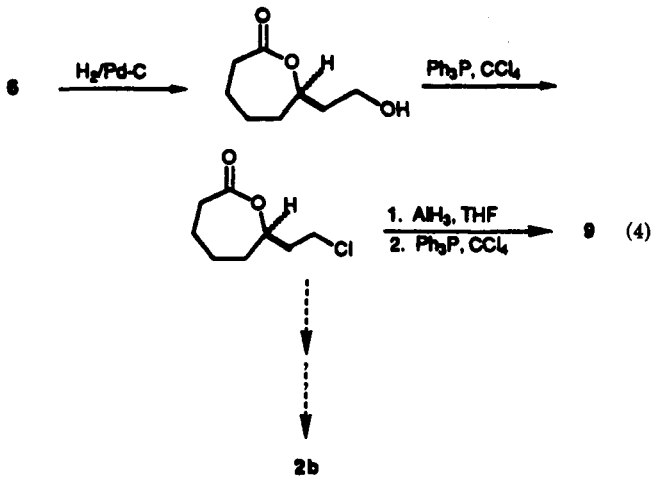


Figure 3. Inhibition of *E. coli* spermidine synthase by *S* diastereomer **2a** (▲), and R diastereomer **3a** (●). Error bars indicate deviation from the mean; where no error bar is indicated, the error is less than 0.5%.

In terms of synthetic methodology, the routes described in this paper are amenable to use in the synthesis of related compounds in high stereochemical purity. As noted above, the synthesis of isomers **2b** and **3b** should be accessible from the chiral lactone **6**. Preliminary experiments outlined in eq 4 suggest that this is a feasible route. Thus,

(13) Tang, K.-C.; Pegg, A. E.; Coward, J. K. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 1371.
(14) (a) Morrison, J. F.; Walsh, C. T. *Adv. Enzymol.* **1987**, *61*, 201. (b) Schloss, J. V. *Acc. Chem. Res.* **1988**, *21*, 348.



conversion of **6** to the free alcohol and then to ϵ-(2-chloroethyl)-ϵ-caprolactone[4] has been effected in an earlier synthesis of **9** (Liu, C., unpublished results). We have previously shown that aminolysis of the racemic (chloroethyl)caprolactone can be effected in an alternate synthesis of racemic AdoDATAD.[4] Unfortunately, the low stereochemical purity of **6** obtained thus far limits the value of this approach. However, homologation of **16** with a Grignard reagent derived from 4-chlorobutyraldehyde diethyl acetal followed by reductive amination of the corresponding free aldehyde with *O*-benzyl-3-amino-1-propanol should provide the key suitably blocked amino alcohol of high stereochemical purity. This product, an aminopropylated homologue of **17**, should be suitable for use in the synthesis of **2b** by the method previously described for the racemic material.[4]

Experimental Section

All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, D_2O, or CD_3OD with chemical shifts reported in ppm downfield from tetramethylsilane as an internal standard. ^1H NMR spectra were recorded at 300 or 360 MHz. ^{13}C NMR spectra were recorded at 75 or 90 MHz. Infrared spectra were measured with a Nicolet FT-IR spectrometer or Perkin-Elmer 1310 spectrophotometer. Analytical thin-layer chromatography was done on silica gel plates (EM Science, 5554-7) with 254 nm fluorescent indicator or Eastman cellulose plates with fluorescent indicator. Flash chromatography refers to liquid chromatography on silica gel according to the method of Still et al.[15] Optical rotations were measured in a Perkin-Elmer 241 polarimeter with a 1-dm path length in a constant-temperature jacket. Mass spectra were obtained on a Hewlett-Packard 5987A GC/MS instrument. High performance liquid chromatography (HPLC) was performed with an Altex Model 153 instrument and a Vydac C-18 reverse-phase column under ion-pair conditions as described by Wagner et al.[16] Ultraviolet spectra were obtained with a Perkin-Elmer Model 552 spectrophotometer.

All experiments were carried out in oven-dried or flame-dried glassware and reaction solutions were magnetically stirred. Reactions involving air- or moisture-sensitive material were carried out under a positive pressure of dry nitrogen. All chemical reagents used in this work were commercially available, were generally of >98% purity, and were used without further purification. The cyclohexanone imine of (*S*)-(−)-2-amino-1-methoxy-3-phenylpropane,[8] 5′-deoxy-5′-chloroadenosine,[3] and benzyl δ-chlorobutyl ether[17] were synthesized following literature procedures. Tetrahydrofuran (THF) and diethyl ether were distilled over $LiAlH_4$ prior to use. Carbon tetrachloride, methylene chloride, hexamethylphosphoric triamide (HMPA), and dimethyl sulfoxide were distilled over CaH_2 prior to use. Pyridine and dimethylformamide were dried over KOH pellets and distilled. KSAc, obtained from Kodak, was triturated with 2-butanone and dried in vacuo prior to use. Commercial tosyl chloride was recrystallized from petroleum ether/benzene prior to use.

Thin layer chromatography (TLC) was run on silica gel unless otherwise indicated using the following solvent systems and visualization methods: (A) solvent systems (ss), (1) hexane/ethyl acetate = 9/1, (2) hexane/ethyl acetate = 20/3, (3) hexane/ethyl acetate = 5/3, (4) $CHCl_3$/MeOH = 10/1, (5) cyclohexane/ethyl acetate = 5/3, (6) $CHCl_3$/MeOH = 4/1; (B) visualization methods (vm), (1) UV, (2) I_2, (3) phosphomolybdic acid solution.

2-Iodoethyl Benzyl Ether. To a stirred solution of 2-iodoethanol (12.0 g, 69.5 mmol) and benzyl 2,2,2-trichloroacetimidate (21.0 g, 83.2 mmol) in a mixture of cyclohexane (60 mL) and dichloromethane (30 mL) was added, under an argon atmosphere, trifluoromethanesulfonic acid (1 mL). The reaction mixture was stirred at room temperature for 18 h. The crystalline trichloroacetamide was removed by filtration and the filtrate washed with $NaHCO_3$ (saturated) and H_2O, followed by drying ($MgSO_4$) and concentration in vacuo. Purification of the crude material by column chromatography (silica gel, ss 1, vm 1, R_f = 0.45) gave product **2** in 87% yield (15.8 g): ^1H NMR ($CDCl_3$) δ 7.52–7.28 (m, 5 H), 4.57 (s, 2 H), 3.73 (t, 2 H), 3.27 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.78, 128.44, 127.81, 127.72, 72.84, 70.73, 2.87; IR (neat, cm^{-1}) 3086, 3065, 3030, 1764, 1497, 1455, 1356, 1110, 738, 695; MS *m/e* 262, 155, 135, 91 (100), 79, 65, 51, 39.

(*R*)-2-[2-(Benzyloxy)ethyl]cyclohexanone (5). An oven-dried 200-mL flask equipped with a magnetic stirring bar, a pressure-equalized addition funnel, and a rubber septum was charged with 30 mL of anhydrous THF under a nitrogen atmosphere. Freshly distilled diisopropylamine (0.590 g, 5.83 mmol) was added via syringe and the solution cooled to 0 °C for 15 min and then cooled to −20 °C (CCl_4/CO_2). Chiral imine (*S*)-4[8] (1.36 g, 5.56 mmol) was added over 15 min and allowed to stir for 1.5 h. The solution was then cooled to −78 °C (acetone/CO_2) and the alkyl iodide prepared above (2.98 g, 16 mmol) in THF (15 mL) was added over a period of 30 min and the mixture allowed to stir at −78 °C for additional 1 h. The cold, light yellow solution was poured into 100 mL of saturated NaCl (aqueous) solution and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine, then dried (Na_2SO_4) and concentrated in vacuo, and the amber oil was subjected to immediate hydrolysis. A buffer solution comprised of sodium acetate (4.95 g), acetic acid (12 mL), and water (52.5 mL) was added to the crude imine in 100 mL of pentane and shaken for 30 min. The aqueous layer was washed with pentane; the pentane solutions were combined and washed with 1 N HCl, H_2O, 5% $NaHCO_3$, H_2O, and brine. The pentane solution was then dried (Na_2SO_4), filtered, concentrated, and the oily residue was passed through a short column (silica gel, ss 2, vm 3, R_f = 0.24) to give **5** (1.17 g, 90%) as a light yellow liquid: ^1H NMR ($CDCl_3$) δ 7.36–7.25 (m, 5 H), 4.47 (s, 2 H), 3.50 (m, 2 H), 2.53–1.26 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 212.90, 138.53, 128.29, 127.59, 127.47, 72.19, 68.01, 47.34, 42.10, 34.19, 29.50, 28.05, 25.04; IR (neat, cm^{-1}) 3065, 3023, 1708 (C=O), 1455, 1363, 1103, 730, 695; MS *m/e* 232, 188, 141, 125, 98, 91 (100), 83, 65, 55, 41; *m/e* $(M + NH_4)^+$, 250 (100), 233, 125; $[\alpha]_D$ = −2.35° (*c* = 3.39, $CHCl_3$). HRMS calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1455. Anal. ($C_{15}H_{20}O_2$) C, H.

(*R*)-ϵ-[2-(Benzyloxy)ethyl]-ϵ-caprolactone (6). Ketone **5** (1.10 g, 4.74 mmol) was dissolved in 50 mL of CH_2Cl_2 and 3 equiv of mCPBA (2.45 g, 14.22 mmol) was added into the solution in one pot. The resulting mixture was stirred at room temperature for 5 days and an equal volume of saturated $NaHSO_3$ was then added into the reaction mixture. Following overnight stirring, the organic layer was washed successively with saturated $NaHCO_3$ and 5% KOH and dried over $MgSO_4$. Concentration and column chromatography (silica gel, ss 2, vm 1 and 2, R_f = 0.37) gave lactone **6** in 62% yield (730 mg) as a pale yellow liquid: ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5 H), 4.49 (s, 2 H), 4.47 (m, 1 H), 3.65 (td, *J* = 9.23 and 4.61 Hz, 1 H), 3.56 (td, *J* = 7.24 and 5.04 Hz, 1 H), 2.64 and 2.63 (2 sets triplet overlap, 2 H), 2.01–1.55 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 175.42, 138.27, 128.70, 127.61, 76.99, 73.08, 66.01, 36.52, 34.81, 34.60, 28.08, 22.93; IR (neat, cm^{-1}) 3086, 3065, 3030, 2931, 2861, 1729 (C=O), 1497, 1455, 1363, 1356, 1321, 1286, 1258, 1173, 1082, 1012, 745, 695; $[\alpha]_D$ = −49.54° (*c* = 2.57, $CHCl_3$). HRMS

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) Wagner, J.; Danzin, C.; Mamont, P. *J. Chromatogr.* **1982**, *227*, 349.
(17) Bennett, G. M.; Hock, A. L. *J. Chem. Soc.* **1927**, 472.

calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1411. Anal. ($C_{15}H_{20}O_3 \cdot H_2O$) C, H.

(*R*)-1-*O*-Benzyl-1,3,8-octanetriol (7). A solution of lactone **6** (378 mg, 1.52 mmol) in dry ether (5 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (57.8 mg, 1.52 mmol) in dry ether (25 mL) at 0–5 °C. The mixture was stirred for 30 min at room temperature and then heated under reflux for 3 h. The excess $LiAlH_4$ was then destroyed by addition of EtOAc (3 mL). Subsequent addition of H_2O (5 mL), 4 N NaOH (5 mL), and H_2O (5 mL) to the stirred and ice-cooled mixture was followed by 1 h stirring at room temperature. Then the mixture was filtered and the filter cake was thoroughly washed with ether. The combined Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired diol in 84% yield (322 mg) as a pale yellow liquid (silica gel, ss 4, vm 3, R_f = 0.42): ^1H NMR ($CDCl_3$) δ 7.36–7.22 (m, 5 H), 4.55 (s, 2 H), 3.78 (m, 1 H), 3.69 (m, 1 H), 3.64 (m, 1 H), 3.59 (t, 2 H), 3.14 (br s, 1 H, OH), 2.11 (br s, 1 H, OH), 1.75–1.33 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 137.95, 128.35, 127.62, 127.57, 73.24, 71.02, 69.02, 62.61, 37.31, 36.49, 32.63, 25.72, 25.27; IR (neat, cm^{-1}) 3367 (OH); $[\alpha]_D$ = −9.54° (c = 2.44, $CHCl_3$). HRMS calcd for $C_{15}H_{24}O_3$ (MH^+) 253.1803, found 253.1802. Anal. ($C_{15}H_{24}O_3$) C, H.

(*R*)-1,3,8-Octanetriol (8). Method A. A mixture of 5.38 g (21.3 mmol) of the 1-*O*-benzyl triol **7** and 200 mg of 10% Pd/C in 50 mL of 95% absolute ethanol was hydrogenated at room temperature and 54 psi for 48 h. The mixture was filtered, and the filtrate concentrated and chromatographed (silica gel, ss 3, vm 2 or 3, R_f = 0.05) to give 3.22 g (93% yield) of triol **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.88 (m, 3 H), 3.65 (t, 2 H), 2.60 (br s, 1 H, OH), 2.48 (br s, 1 H, OH), 1.75–1.38 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 72.19, 62.85, 61.92, 38.35, 37.72, 32.61, 25.70, 25.24; IR (neat, cm^{-1}) 3338, 2931, 2856, 1713, 1463, 1375, 1050; $[\alpha]_D$ = −4.21° (c = 1.64, EtOH); HRMS calcd for $C_8H_{18}O_3$ (MH^+) 163.1334, found 163.1329.

Method B. A mixture of dibenzyloxyoctanol **17** (see below) (2.22 g, 6.48 mmol) and 200 mg of 10% Pd/C in 30 mL of absolute ethanol was hydrogenated at room temperature and 50 psi for 50 h. The reaction mixture was filtered and concentrated to give a light yellow oil. The oily residue was then purified by plug filtration to give 1.05 g (quantitative yield) of octanetriol **8**. The ^1H and ^{13}C NMR spectra are similar to those described above for the material prepared via method A; $[\alpha]_D$ = −4.62° (c = 1.72, EtOH).

(*S*)-1,3,8-Octanetriol. The *S* isomer of **8** was synthesized by method B from the isomer of **17** (see below); yield 965 mg (87%). All spectral data (IR, ^1H NMR, ^{13}C NMR) are identical with the data obtained for *R* isomer **8**; $[\alpha]_D$ = +4.58° (c = 1.66, EtOH).

(*R*)-1,8-Di-*O*-benzyl-1,3,8-octanetriol (17). Magnesium (5.34 g, 26.9 mmol), benzyl δ-chlorobutyl ether (719 mg, 29.6 mmol), and a few drops of 1,2-dibromoethane in 25 mL of dry ether were gently warmed until reaction commenced. The reaction mixture was then stirred at room temperature for 12 h and then cooled to −78° C. A solution of lithium tetrachlorocuprate (0.8 mL, 0.08 mmol) in THF was introduced into the reaction mixture. After a further 1 h of stirring, *S*-[2-(phenylmethoxy)ethyl]oxirane **16**[12] (1.20 g, 6.72 mmol) in 15 mL of THF was added dropwise. The mixture was stirred at −78 °C for an additional 3 h and was then allowed to warm to room temperature overnight. The contents of the flask were then quenched with cold (0 °C) saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was subsequently dried ($MgSO_4$) and concentrated to give a light yellow oil. The oily residue was then chromatographed to give 2.14 g (93% yield) of **17** as a colorless liquid (silica gel, ss 3, vm 2 and 3, R_f = 0.41): ^1H NMR ($CDCl_3$) δ 7.33–7.24 (m, 10 H), 4.51 (s, 2 H), 4.49 (s, 2 H), 3.79–3.60 (m, 3 H), 3.46 (t, 2 H), 2.89 (s, 1 H, OH), 1.74 (q, 2 H), 1.65–1.38 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 138.81, 138.09, 128.39, 128.27, 127.60, 127.54, 127.38, 73.33, 72.87, 71.16, 70.43, 69.11, 37.46, 36.61, 29.76, 26.30, 25.43; IR (neat, cm^{-1}) 3452, 3086, 3065, 3030, 3009, 2931, 2861, 1954, 1877, 1806, 1736, 1602, 1581, 1497, 1455, 1364, 1307, 1251, 1202, 1103, 1026, 738, 695. $[\alpha]_D$ = −3.81° (c = 3.65, $CHCl_3$). HRMS calcd for $C_{22}H_{30}O_3$ 343.2273; found 343.2281. Anal. ($C_{22}H_{30}O_3$) C, H.

(*S*)-1,8-Di-*O*-benzyl-1,3,8-octanetriol. The *S* isomer of **17** was synthesized from the *R* isomer of **16**[12] as described above; yield 2.77 g (87%). All spectral data (IR, ^1H NMR, ^{13}C NMR) are identical with the data obtained for *R* isomer **17**: $[\alpha]_D$ = +3.31° (c = 4.12, $CHCl_3$).

(*R*)-1,8-Dichloro-3-octanol (9). To triphenylphosphine (2.63 g, 10 mmol) in CCl_4 (50 mL) was added 1.48 g (9.1 mmol) of **8** in one portion. After the addition was completed, the reaction temperature was raised to effect reflux. After 2 h at reflux temperature, another 2.63 g (10 mmol) of Ph_3P was added to the reaction mixture and stirring was continued at refluxing temperature for 16 h. During this time, the reaction was monitored by TLC until all the triol **8** was consumed. The resultant mixture was allowed to cool to room temperature; dry pentane (30 mL) was added and stirred for 15 min. The precipitated Ph_3PO was removed by filtration and washed with 10 mL of pentane. The combined organic solvent was evaporated and the residue was chromatographed (silica gel, ss 3, vm 3, R_f = 0.48) to give 1.07 g (59% yield) of dichloro alcohol **9** as a colorless liquid. IR and ^1H NMR spectra are identical with those obtained with racemic material previously synthesized in this laboratory;[3] ^{13}C NMR ($CDCl_3$) δ 68.74, 44.87, 41.84, 39.76, 37.27, 32.45, 26.75, 24.78; $[\alpha]_D$ = −21.55° (c = 2.17, $CHCl_3$); HRMS calcd for $C_8H_{16}Cl_2O$ (MH^+) 216.0920, found 216.0920.

(*S*)-1,8-Dichloro-3-octanol. The *S* isomer of **9** was synthesized from the *S* isomer of **8** as described above; yield 750 mg (65%). All spectral data (IR, ^1H NMR, ^{13}C NMR) are identical with the data obtained for *R* isomer **9**; $[\alpha]_D$ = +23.58° (c = 1.77, $CHCl_3$).

(*R*)-1,8-Diazido-3-hydroxyoctane (18). 1,8-Dichloro derivative **9** was converted to **18** as previously described for the racemic material.[3] Purification of the crude product by flash chromatography gave 1.02 g (94%) of pure **18** (silica gel, ss 3, vm 2 or 3, R_f = 0.46): IR (neat, cm^{-1}) 3402, 2938, 2861, 2509, 2095, 1455, 1258, 1103, 1047, 1005, 948; ^1H NMR ($CDCl_3$) δ 3.74 (m, 1 H), 3.47 (m, 2 H), 3.28 (t, 2 H), 1.76–1.37 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 69.29, 51.32, 48.57, 37.48, 35.99, 28.74, 26.64, 25.06; $[\alpha]_D$ = −9.08° (c = 1.68, $CHCl_3$).

(*S*)-1,8-Diazido-3-hydroxyoctane. The *S* isomer of **18** was synthesized from the *S* isomer of **9** as described above; yield 695 mg (87%). All spectral data (IR, ^1H NMR, ^{13}C NMR) are identical with the data obtained for *R* isomer **18**; $[\alpha]_D$ = +9.15° (c = 1.71, $CHCl_3$).

(*S*)-1,8-Diazido-3-(thioacetyl)octane (19). The 3-*O*-tosyl derivative was prepared from **18** as previously described for the racemic material:[3] yield 2.22 g (quantitative) (silica gel, ss 3, vm 1 and 2, R_f = 0.59); ^1H NMR ($CDCl_3$) δ 7.36 (AA'BB', 2 H), 7.80 (AA'BB', 2 H), 4.65 (m, 1 H), 3.31 (m, 2 H), 3.21 (t, 2 H), 2.49 (s, 3 H), 1.90–1.75 (m, 2 H), 1.63–1.49 (m, 4 H), 1.32–1.22 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 144.88, 134.29, 129.82, 127.73, 80.45, 51.21, 47.19, 34.38, 33.54, 28.56, 26.30, 24.14, 21.56. This product was sufficiently pure for use in further synthetic work.

Thioacetyl derivative **19** was prepared from the tosylate as previously described for the racemic material:[3] yield 912 mg (71%) (silica gel, ss 3, vm 1 and 2, R_f = 0.70); IR (neat) 3367, 2938, 2861, 2509, 2095, 1694, 1455, 1349, 1258, 1117, 948, 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (m, 1 H), 3.36 (m, 2 H), 3.26 (t, 2 H), 2.34 (s, 3 H), 1.96–1.37 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 195.14, 51.29, 49.02, 41.72, 34.86, 34.08, 30.73, 28.66, 26.40, 26.29; $[\alpha]_D$ = −4.89° (c = 2.11, $CHCl_3$); HRMS calcd for $C_{10}H_{18}N_6OS$ ($M + NH_4$)$^+$ 288.1606, found 288.1599.

(*R*)-1,8-Diazido-3-(thioacetyl)octane. The *R* isomer of **19** was synthesized from the *S* isomer of **18**, via the *O*-tosyl derivative (1.34 g, 88% crude yield), as described above; yield 548 mg (73%). All spectral data (IR, ^1H NMR, ^{13}C NMR) are identical with the data obtained for *S* isomer **19**; $[\alpha]_D$ = +4.97° (c = 2.09, $CHCl_3$).

(*S*)-*S*-Adenosyl-1,8-diamino-3-thiooctane (2a). The diazido thioacetyl derivative **19** was coupled to 5'-deoxy-5'-chloroadenosine under basic conditions to give the fully blocked diazido nucleoside **20** as previously described for the racemic material:[3] yield 191 mg (91%) (silica gel, ss 6, vm 1 and 2, R_f = 0.56); ^1H NMR (CD_3OD) δ 8.21 (s, 1 H), 8.12 (s, 1 H), 5.90 (d, 2 H), 4.23 (t, 1 H), 4.09 (m, 1 H) 3.33 (m, 2 H) 3.14 (t, 2 H), 2.94 (m, 2 H), 1.71–1.18 (m, 11 H); ^{13}C NMR (CD_3OD) δ 157.41, 153.96, 150.74, 141.57, 120.73, 90.34, 85.98, 74.75, 74.25, 52.38, 50.16, 44.94, 35.97 (*S* diastereomer, C2), 35.16 (*S* diastereomer, C4), 33.83, 29.76, 27.52, 27.33; $[\alpha]_D$ = +6.67° (c = 1.73, MeOH); HRMS calcd for $C_{18}H_{27}N_{11}O_3S$ (MH^+) 478.2097; found 478.2084. The blocked diazido nucleoside was converted to the target compound **2a** as described previously for the racemic material:[3] yield 176 mg (79%); IR

spectrum is identical with that reported for the racemic material;[3] ^{1}H NMR (D_2O) δ 8.21 (s, 1 H), 8.05 (s, 1 H), 5.92 (d, 1 H), 4.32 (t, 1 H), 4.20 (q, 1 H), 2.93–2.59 (m, 7 H), 1.59–1.05 (m, 10 H) [The peak of $H_{2'}$ was obscured by the HOD signal (4.84–4.69)]; ^{13}C NMR (D_2O) δ 155.53, 152.92, 148.97, 140.24, 118.85, 87.87, 83.84, 73.38, 72.60, 40.15, 38.24, 36.16, 33.85, 32.16, 29.58, 25.76, 25.63; HPLC[16] t_R = 23.8 min; $[\alpha]_D$ = −21.2° (c = 0.33, DMSO); HRMS calcd for $C_{18}H_{31}N_7O_3S$ 426.2287, found 426.2263.

(*R*)-*S*-Adenosyl-1,8-diamino-3-thiooctane (3a). *R* isomer **3a** was synthesized from the *S* isomer of **19** via the intermediate diazido nucleoside as described above; yield 197 mg (74%). All spectral data for the intermediate diazido nucleoside are identical with those obtained for the S isomer except for the following ^{13}C NMR data: 36.22 (*R* diastereomer, C2), 34.89 (*R* diastereomer, C4); $[\alpha]_D$ = −8.91 (c = 1.12, MeOH). The blocked intermediate was converted to **3a** as described above for **2a**: yield 125 mg (75%); all spectra data (IR, ^{1}H and ^{13}C NMR) are similar with the data obtained for S isomer **2a**; HPLC[16] t_R = 23.8 min; $[\alpha]_D$ = −30° (c = 0.3, DMSO); HRMS calcd for $C_{18}H_{31}N_7O_3S$ 426.2287, found 426.2272.

Cyclic Ketal of (*R*)-2-[2-(Benzyloxy)ethyl]cyclohexanone and (2*R*,3*R*)-2,3-butanediol (12). The procedure described by Meyers et al[8] was followed, with the exception that excess diol (2.5 equiv) was used to prevent any kinetic resolution during the ketalization reaction. After TLC analysis showed that the reaction was complete, standard workup afforded the desired product in 90% crude yield. ^{13}C NMR spectra revealed a clear separation of signals for C-2 and C-6 for the two diastereomers. The percent ee of (*R*)-2-(2-benzyloxyethyl)cyclohexanone (**5**) was determined by integration of the peaks observed at δ 42.50 vs 41.72 (C-2) and δ 37.10 vs 36.49 (C-6). This analysis led to a value of 80% ee for **5** synthesized as described herein (Scheme I).

Preparation of Mosher Esters 10 and 11 from (*S*)-*O*-Methylmandelic Acid and (*R*,*S*)-1,8-Dichloro-3-octanol. Following the procedure of Trost et al.,[18] 150 mg (0.75 mmol) of the racemic dichloro alcohol (or *R* (**9**) or *S* enantiomer) was dissolved in 5 mL of THF together with 125 mg (0.75 mmol) of (*S*)-*O*-methylmandelic acid and 186 mg (0.75 mmol) DCC. DMAP (10 mg, 0.08 mmol) was then added in one portion and the reaction solution was stirred for 18 h at ambient temperature. Dicyclohexylurea was removed by filtration, the filter cake washed with hexanes (3 × 50 mL), and the combined filtrates were washed successively with 1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and saturated brine (2 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography (silica gel, ss 3, vm 1 and 3, R_f = 0.71) to give 229 mg (88%) of the desired Mosher esters **10** and **11**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.27 (m, 5 H), 5.06 (m, 1 H), 4.80 (s, 1 H), 3.57–3.36 (m, 6 H), 3.14–3.00 (m, 1 H), 1.97–1.22 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 170.31, 136.33, 128.83 and 128.63, 127.11 and 127.08, 82.64 and 82.56, 72.20 and 72.13, 57.24, 44.75 and 44.65, 40.52 and 40.10, 37.14 and 36.97, 33.92 and 33.75, 32.29 and 32.20, 26.51 and 26.34, 24.30 and 23.80. Although it was not possible to determine the percent ee from the ^{1}H NMR spectra, ^{13}C NMR spectra were effective in determining the stereochemical purity of **9** and its enantiomer. Thus, integration of the two well-separated peaks at 40.52 (**10**) vs. 40.10 (**11**), and 24.30 (**11**) vs 23.80 (**10**) allowed for the accurate determination of percent ee in **9** and the *S* enantiomer (See Figure 1 and text); HRMS calcd for $C_{17}H_{24}Cl_2O_3$ (M^+) 346.1103, found 346.1102. Anal. ($C_{17}H_{24}Cl_2O_3$) C, H.

Enzyme Assays. Spermidine synthase was isolated from *E. coli* and partially purified as previously described.[2] The enzyme was assayed by the method of Raina et al.,[19] using [^{35}S]dcAdoMet as the radiolabelled substrate and an incubation time of 30 min at 37 °C. The concentrations of putrescine (0.44 mM) and dcAdoMet (20 μM) were saturating (ca. 10–30 K_m).

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Registry No. 2a, 134053-22-8; **3a**, 134053-25-1; **4**, 77857-35-3; **5**, 134005-33-7; **6**, 134005-34-8; **7**, 134005-35-9; (*R*)-**8**, 134053-20-6; (*S*)-**8**, 134053-21-7; (*R*)-**9**, 134005-38-2; (*S*)-**9**, 134005-39-3; **10**, 134005-45-1; **11**, 134005-46-2; **12a** (isomer 1), 134005-44-0; **12** (isomer 2), 134053-26-2; (*R*)-**16**, 115114-87-9; (*S*)-**16**, 85960-55-0; (*R*)-**17**, 134005-37-1; (*S*)-**17**, 134005-36-0; (*R*)-**18**, 134005-40-6; (*S*)-**18**, 134005-41-7; (*R*)-**19**, 134005-43-9; (*S*)-**19**, 134005-42-8; (*R*)-**20**, 134053-24-0; (*S*)-**20**, 134053-23-9; $PhCH_2OCH_2CH_2I$, 54555-84-9; benzyl δ-chlorobutyl ether, 50873-93-3; 5′-deoxy-5′-chloroadenosine, 892-48-8; (*S*)-*O*-methylmandelic acid, 26164-26-1; spermidine synthase, 37277-82-0.

(18) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.

(19) Raina, A.; Eloranta, T.; Pajula R.-L. *Methods Enzymol.* **1983**, *94*, 257.