Total Synthesis of (±)- and (+)-Valienamine via a Strategy Derived from New Palladium-Catalyzed Reactions

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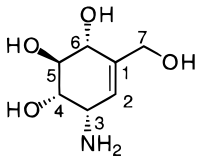
Abstract: A new strategy toward glycosidase inhibitors, represented by valienamine, which is such an inhibitor itself as well as a critical unit of pseudooligosaccharides that function this way, evolved from two newly developed palladium-catalyzed reactions. The applicability of a palladium(0)-catalyzed net regioselective cis-hydroxyamination derives from the reaction of vinyl epoxides with isocyanates. The utilization of a cocatalyst in this reaction is required in this case and may prove generally useful. A bidentate phosphite proved to be the most effective ligand. The requisite substrate was available via a Diels−Alder protocol and allowed the obtention of (±)-valienamine in only seven steps. The inability to perform the Diels−Alder reaction asymmetrically led to a different asymmetric synthesis of the pivotal epoxide intermediate in enantiomerically pure form, which derived from asymmetric palladium-catalyzed reactions. Using the desymmetrization of meso enedicarboxylates, the net equivalence of an asymmetric cis-hydroxycarboxylation led to the enantiomerically pure desired epoxide. (+)-Valienamine was available in 14 steps by this route.

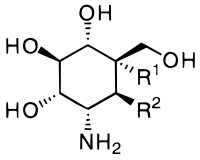
The development of a new methodology offers the opportunity to open new strategies for the total synthesis of complex natural products. We had developed a reaction that, combined with epoxidation, allows the net equivalent of a chemo-, regio-, and diastereoselective cis-hydroxyamination.[1] Similarly, our efforts in developing asymmetric allylic alkylations have led to a sequence effecting the net equivalent of an asymmetric cis vicinal hydroxycarboxylation.[2] These methods appear to be particularly suitable for the synthesis of glycosidase inhibitors.

The importance of polysaccharides in a myriad of cellular functions including energy transfer and storage, intercellular communication and recognition, and intramolecular protein and lipid function makes their processing an interesting target for the design and development of therapeutic agents. Pseudooligosaccharides represented by acarbose,[3] adiposin,[4] trestatin,[5] and amylostatin,[6] are potent glycosidase inhibitors and have therapeutic value. For example, acarbose inhibits degradation of sucrose and starch, the former leading to its use as an oral antidiabetic.[7] Additionally, the validamycin A complex is an antifungal used in the treatment of rice sheath blight.[8]

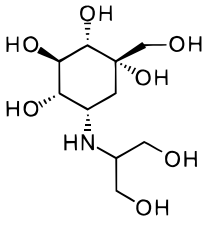
Common to all of these pseudooligosaccharides is the aminocyclitol unit valienamine (**1**).[9] Derivatives related to valienamine including validamine, valiolamine, and hydroxyvalidamine are also found as components of pseudooligosaccharides.[4,10] It has also been shown that these aminocyclitols are potent glycosidase inhibitors in their own right. The N-alkylated valiolamine AO-128 is also undergoing clinical trials for use as an oral antidiabetic. Their potent activity and the success of analogues stimulated much synthetic activity. Valienamine has been synthesized in both racemic and enantiomerically pure form. In all but three cases, the stereochemistry of the oxygens at carbons 4, 5, and 6 is derived from D-glucose.[11] In the other instances, the stereochemistry derived from the cyclitol quebrachitol[12] or from resolution of a Diels−



valienamine 1



$R^1 = R^2 = H$ validamine
$R^1 = OH$, $R^2 = H$ valiolamine
$R^1 = H$, $R^2 = OH$ hydroxy validamine



AO-128

(1) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.
(2) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.
(3) Schmidt, D.; Frommer, W.; Junge, B.; Müller, K.; Wingender, W.; Trutsheit, E. *Naturwissenschaften* **1977**, *64*, 536.
(4) Kameda, Y.; Asano, N.; Yoshikawa, M.; Mabui, K.; Horii, S.; Fukawase, H. *J. Antibiot.* **1983**, *36*, 1157.
(5) Itoh, J.; Omoyo, S.; Shomura, T.; Ogino, H.; Iwamatsu, K.; Inouye, S. *J. Antibiot.* **1981**, *34*, 1424, 1429.
(6) Sakairi, N.; Kuzuhara, H. *Tetrahedron Lett.* **1982**, *23*, 5327.
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(10) Horri, S.; Fukase, H.; Matsuo, T.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038.

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Scheme 1. Retrosynthesis of (+)-Valienamine

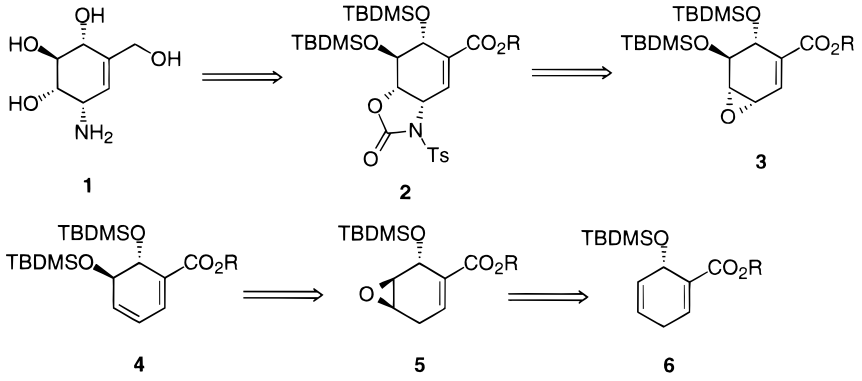
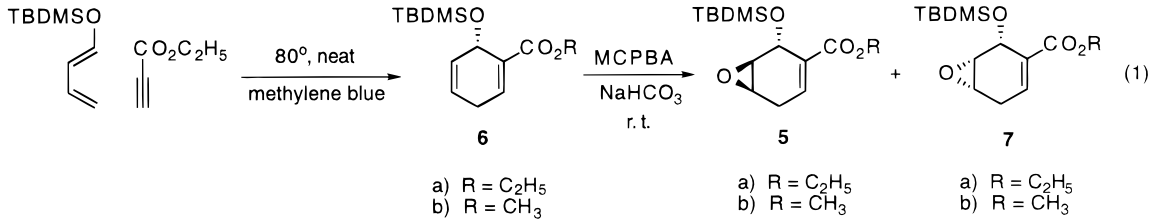


Chart 1



Alder adduct.[13] A significant drawback of many of these routes arises from lengthy protecting group manipulation. We wish to record a new strategy for the synthesis of (±)- and (+)-valienamine that provides an efficient approach to racemic valienamine and the ability to convert this strategy into an asymmetric synthesis. In the course of these studies, a new protocol invoking the importance of cocatalysis for the palladium-based cis-hydroxyamination sequence and a new application of the asymmetric palladium-catalyzed hydroxycarboxylation[15] sequence evolved.

Retrosynthesis

Scheme 1 presents a retrosynthetic analysis. A key aspect of this strategy is the installation of the amino alcohol unit via an opening of an allylic epoxide with net retention of configuration (transformation **3** → **2**).[14] The relative stereochemistry of the oxygen substituents of **3** derives from steric control by the allylic silyl ethers during epoxidation of **4** and **6**. This sequence translates into an asymmetric synthesis if **6** can be made enantiomerically pure.

Synthesis of (±)-Valienamine

The synthesis of **5** followed the literature precedent for the synthesis of the triethylsilyl derivative via a Diels−Alder reaction followed by epoxidation as in eq 1 (Chart 1).[16] To minimize aromatization in the Diels−Alder reaction, the reaction was performed without solvent and at 80 °C. Methylene blue was added to minimize polymerization of the reactants. In some runs, small amounts of ethyl benzoate and the silyl ether of ethyl salicylate could be detected by GC and ^{1}H NMR. Because of the sensitivity of **6**, it was generally used directly in the next step without purification. Chemoselective epoxidation with *m*-CPBA in methylene chloride gave a 78% yield of a 9:1 ratio of **5a**:**7a**. Almost identical results were obtained in benzene, but the workup proved more facile using methylene chloride. The major isomer was assigned as depicted based upon consideration of molecular modeling and precedent.[16] As depicted in Figure 1, the nearly planar nature of the cyclohexadiene ring places the siloxy group virtually orthogonal to that plane and suggests a bias for the epoxidizing agent to approach trans to the siloxy group. The 9:1 mixture was not resolvable and thus was employed in the next step.

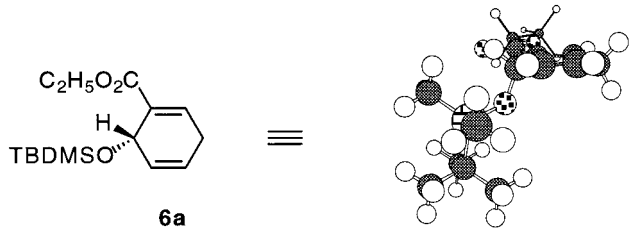


Figure 1. Molecular modeling of **6a**.

Base-promoted E_2 elimination in the presence of a silyl chloride simultaneously ring opened the epoxide and silylated the alcohol to give the cyclohexadiene **8a** (eq 2, Chart 2). DBU assisted by a catalytic amount of DMAP at room temperature gave a 76% yield in methylene chloride and a 74% yield in benzene. Aromatization was avoided by the use of ambient temperature and only a small excess of base. After flash

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(12) Paulsen, H.; Heiker, F. R. *Annalen* **1981**, 2180.

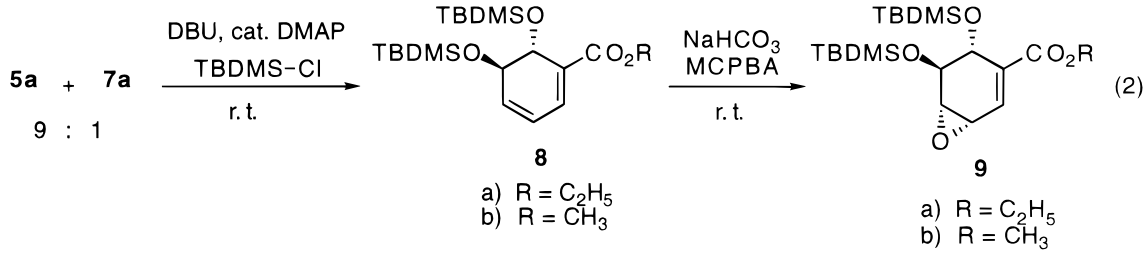
(13) (a) Knapp, S.; Naughton, A. B. J.; Dhar, T. G. M. *Tetrahedron Lett.* **1992**, *33*, 1025. (b) Ogawa, S.; Shibata, Y.; Nose, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3387. (c) Ogawa, S.; Iwasawa, T.; Nose, T.; Suami, S.; Ito, M.; Saito, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 903.

(14) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. Trost, B. M.; Hurnaus, R. *Tetrahedron Lett.* **1989**, *28*, 375.

(15) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.

(16) (a) Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 2. (b) After our work, the Diels−Alder utilized herein was reported; see: Kozlowski, M. C.; Tom, N. J.; Seto, C. T.; Sefler, A. M.; Bartlett, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2128. Kozlowski, M. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 5897.

Chart 2



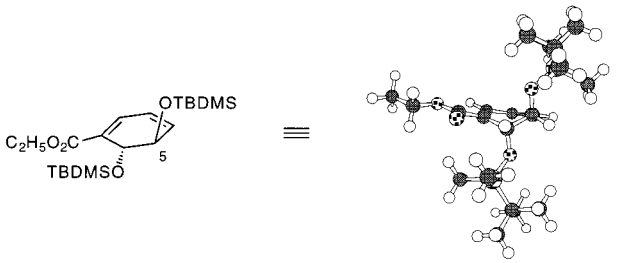


Figure 2. Molecular modeling of **8a**.

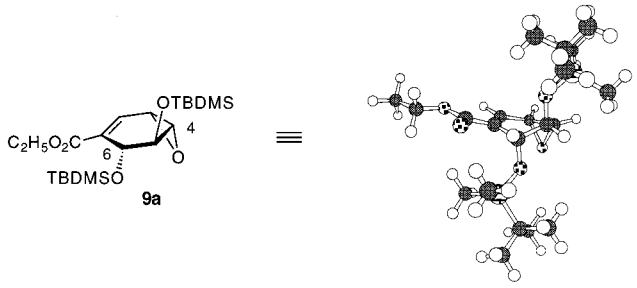


Figure 3. Molecular modeling of **9a**.

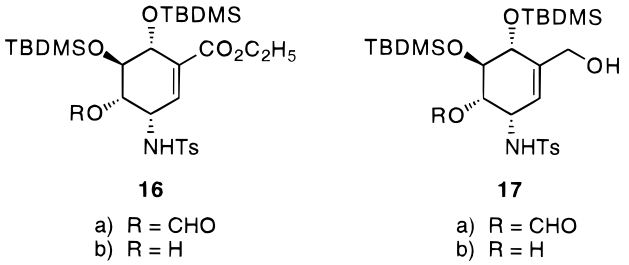
chromatography, only the trans diastereomer **8a** was isolated. The loss of the minor diastereomer **7a** may derive from a faster base-catalyzed aromatization since small amounts of an aromatic product could be detected in the crude reaction product.

Figure 2 depicts the most stable conformation of **8a** based upon a molecular mechanics calculation. This model indicates that the orthogonality of both siloxy groups with respect to the plane of the cyclohexadiene hinders both faces for chemoselective epoxidation. The greater proximity of the 5-siloxy group to the double bond suggests its effect should be larger. Gratifyingly, epoxidation with *m*-CPBA proceeded at room temperature in 86% yield to give a single diastereomer assigned as **9a**. The trans-diaxial nature of the siloxy groups is confirmed by the 2.1-Hz coupling of the vicinal hydrogens at C-5 and C-6. More significantly, a W-type long-range 2.1-Hz coupling between C-4 and C-6 supports the stereochemistry of the epoxidation as depicted (see Figure 3). The epoxide **9a** is quite stable as suggested by the fact it can be distilled at 200 °C at 0.05 Torr without decomposition.

The key step is the ring opening of the epoxide **9** with a nitrogen nucleophile at the allylic position with retention of configuration. We turned to the palladium-catalyzed addition of isocyanates with vinyl epoxides as illustrated in eq 3 (Chart 3). Treatment of epoxide **9a** under the previously employed conditions of $(dba)_3Pd_2{\cdot}CHCl_3$ and triisopropyl phosphite gave no reaction. A number of variations summarized in a table in the supporting information, involving changes of ligands and palladium, led to either no reaction, the product of hydrogen shift **12**, or uncharacterized products.

Addition of camphorsulfonic acid to promote ionization and stabilize the intermediate **13** by protonation led to the desired capture with ring closure at O rather than N to give **11a** in modest yield. Assuming that N-protonated **15** was the species cyclizing, a Lewis acid that might preferentially coordinate at O rather than at N was employed. Indium acetylacetonate[17] proved ineffective. On the other hand, use of trimethyltin acetate[18] was successful but still produced both **10** and **12** with triisopropyl phosphite as the ligand. The optimum conditions employed 5 mol % of palladium acetate, 15 mol % of bidentate ligand **14** (to minimize hydrogen shift), and 10 mol % of trimethyltin acetate to produce a 54% yield of **10a** in addition to a 19% yield of **11a**. It should be noted that the O-alkylated product **11a** can isomerize to the thermodynamically more stable N-alkylated product **10a**.

Adjustment of the ester oxidation level simultaneously cleaves the oxazolidinone. LAH proved too indiscriminate. DIBAL-H served well. The oxazolidinone was more reactive than the ester. Thus, with 2 equiv of DIBAL-H, a 1.6:1 ratio of **17a** and **16a** was obtained in addition to recovered starting material.



No products wherein the ester but not the oxazolidinone was reduced were detected. On the other hand, the "ate" complex between DIBAL-H and *n*-butyllithium produced a 1.4:1 ratio of **16b**:**16a**; i.e., no reduction of the ester was observed. Employing 5.5 equiv of DIBAL-H produced **17b** predominantly with some amount of the formate **17a**. For the best yields, quenching of the reaction proved important. Addition of a mixture of 30% aqueous potassium tartrate and triethanolamine was efficaceous. It was best to treat the crude mixture of **17a** and **17b** with methanolic sodium methoxide. In this way, a 76% yield of **17b** was obtained from **10a**.

The final stage involves removal of the protecting groups. In the first iteration, the tosyl group of **17b** was first removed using sodium in liquid ammonia, but only a 40% yield (brsm) of the amine **18** was obtained (eq 4, Chart 4). Desilylation of **18** using TBAF gave (±)-valienamine (**1**), which was characterized as its pentaacetate **20** in 50% yield. A more satisfactory sequence inverted the two steps. Desilylation of **17b** with TBAF gave a 55% yield of *N*-tosylvalienamine (**19**), which improved to 82% upon use of aqueous HF in acetonitrile. Dissolving

(17) Cf.: Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7904. Trost, B. M.; Sharma, S.; Schmidt, T. *Tetrahedron Lett.* **1993**, *34*, 7183.

(18) Cf.: Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

Chart 3

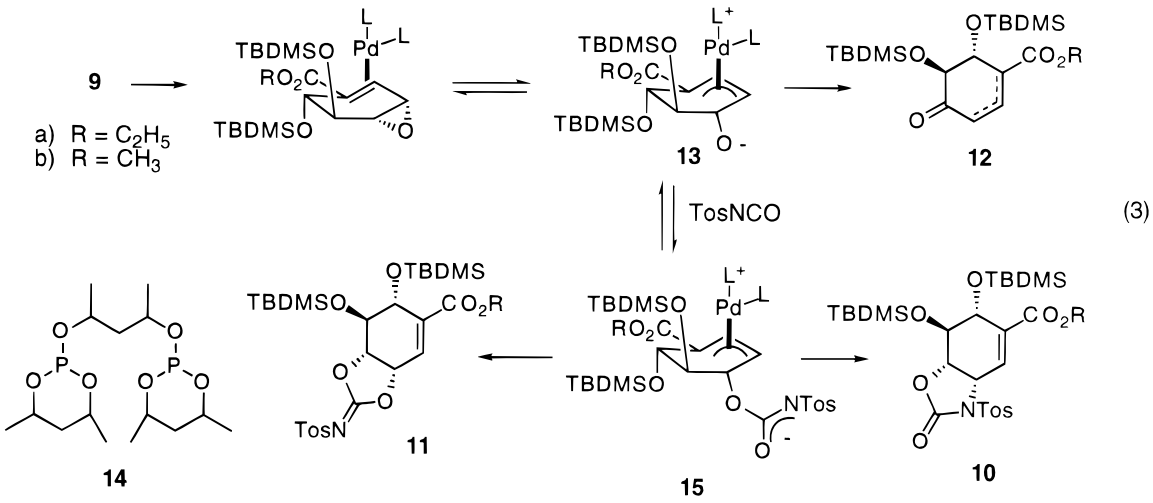


Chart 4

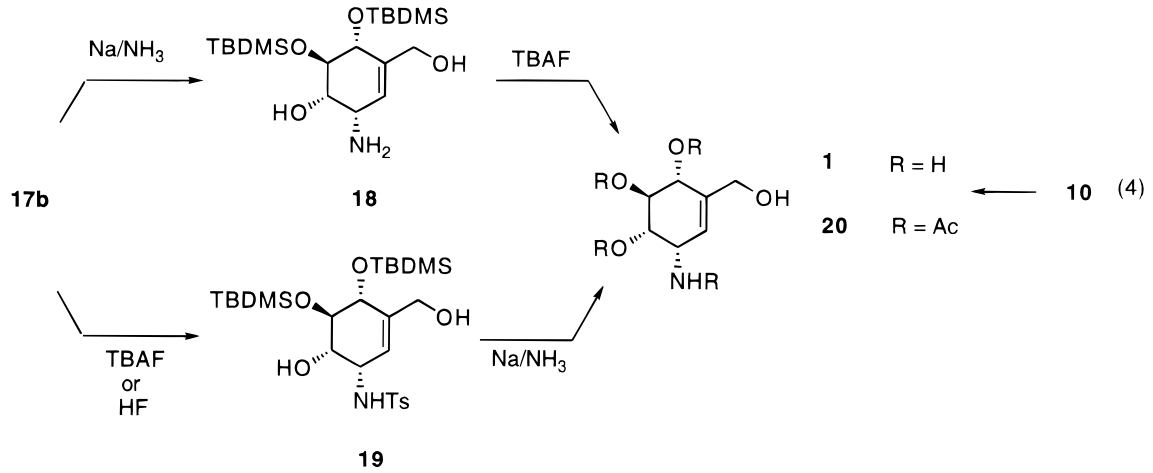
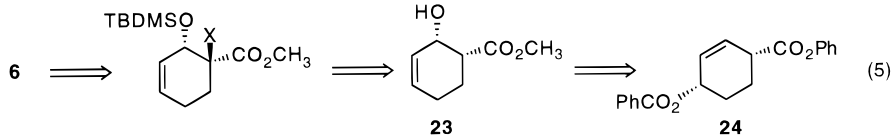


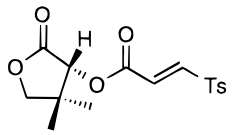
Chart 5



metal reduction of **19** provided (±)-valienamine, which was characterized as its pentaacetate in 56% yield. A more convenient operation started with oxazolidinone **10** through the four steps without purification of any intermediates to deliver the pentaacetate **20** in 33% overall yield (average 76% per step), which is identical with what is obtained wherein each step begins with purified material. Thus, this sequence requires seven steps to (±)-valienamine and proceeds in 10−15% overall yield from ethyl propiolate and 1-(*tert*-butyldimethylsiloxy)-1,3-butadiene, the latter being available in one step from crotonaldehyde.[19]

Asymmetric Synthesis

An asymmetric synthesis of cyclohexadiene **6** converts the above sequence into an asymmetric synthesis of valienamine. The most direct method would be an asymmetric Diels−Alder reaction. In contrast to the case of acrylate-type dienophiles, the propiolate type have not been examined very extensively and the reported studies have not been encouraging.[20] We examined the use of a diene containing a chiral auxiliary, 1-(*O*-methylmandeloxy)-1,3-butadiene,[19,21] unsuccessfully. Use of an acrylate synthon of a propiolate such as the sulfones **21** and **22** in order to examine a chiral auxiliary as well as a chiral Lewis acid-catalyzed reaction did not give encouraging results.



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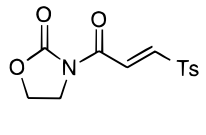


22

A completely different strategy emerges from the consideration of the introduction of a double bond α to the ester of **23** (eq 5, Chart 5). An asymmetric synthesis of **23** via an

(19) Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Org. Chem.* **1997**, *62*, 736.

(20) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H.; Ohashi, S.; Inagaki, S. *J. Org. Chem.* **1997**, *62*, 3026.

(21) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630 and earlier references therein.

Chart 6

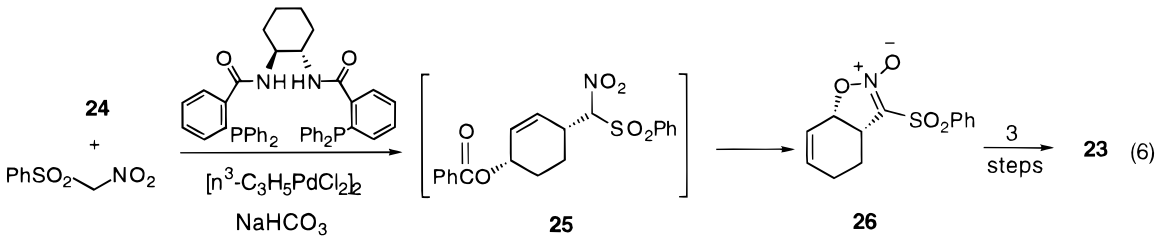
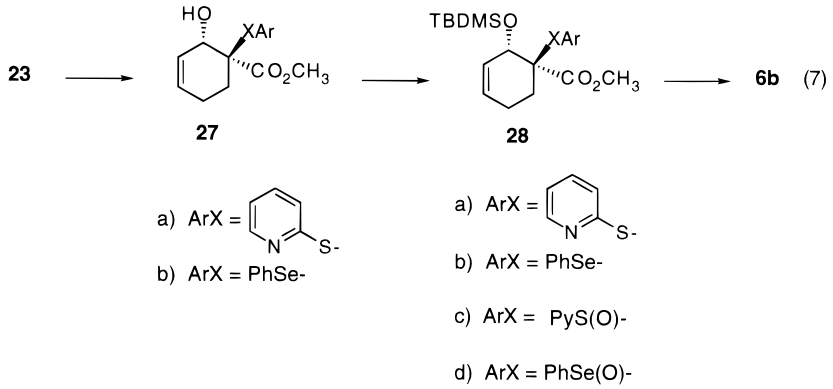


Chart 7



asymmetric Diels−Alder reaction is a potentially more traditional approach. However, this asymmetric Diels−Alder reaction has not been recorded.[22] An alternative strategy from dibenzoate **24**, however, also looked very attractive, especially since **24** is available in one step from cyclohexa-1,3-diene.[23]

Larger scale asymmetric alkylations of the dibenzoate with (phenylsulfonyl)nitromethane at 0.8 M (with respect to **24**) were best performed in 3:1 THF−water rather than pure THF to maintain homogeneity (eq 6, Chart 6). Under these conditions, alkylation to form **25** was complete within 15 min with less than 0.25 mol % of the palladium catalyst. The second stage of the alkylation leading to the cyclized product **26** requires a "mismatched" ionization and was therefore considerably slower. Thus, it proved effective to add an achiral catalyst at this stage, tetrakis(triphenylphosphine)palladium, to complete the cyclization in a shorter time frame. In this way, isoxazoline-*N*-oxide **26** was reproducibly obtained in 87% yield and with >99% ee. The product was deoxygenated with stannous chloride, solvolyzed to the methoxy derivative, and reduced with molybdenum hexacarbonyl as previously described[15] to give **23** enantiomerically pure. In the isoxazole reduction, it was essential to adsorb the crude reaction onto silica gel and expose it to air overnight for good yields, presumably to aid decomplexation of the metal from the product.[24] Sulfenylation of the dianion[25] generated from **23** with 2,2-dipyridyl disulfide[26] gave a 4:1 separable mixture of diastereomers (eq 7, Chart 7). The major one was assigned as depicted in **27a** based upon delivery of the sulfenylating agent trans to the alkoxy group. The fact that this new stereocenter is subsequently lost led us not to rigorously establish this stereochemistry. After protection of the free hydroxyl group to form **28a**, oxidation gave a 1:1 mixture of diastereomers of the sulfoxide **28c**. Thermolysis in toluene effected elimination of one diastereomer to **6b**. Attempts to force the less reactive sulfoxide to eliminate by increasing the reaction time or temperature gave mostly aromatized product. Attempts to influence the ratio of sulfoxide diastereomers by changing the oxidizing agent were not extensively made because the use of selenium results in a resolution of the problem.

Because selenoxides are more labile than sulfoxides and also epimerize at selenium rather rapidly, whereas sulfoxides do not,[27] we anticipated the above difficulty would be circumvented. Selenylation proceeded equivalently to sulfenylation to give a 5:1 ratio of diastereomers that readily separated, the major one being depicted as **27b**. Silylation to **28b** and oxidation with *m*-CPBA at −78 °C forms the selenoxide **28d**. Warming to 0 °C at this point only effected aromatization. On the other hand, addition of 2-methoxypropene as a selenenic acid trap prior to warming did produce the desired diene **6b**. Both selenide diastereomers participate equally well in the elimination. Thus, the mixture of selenide diastereomers was normally employed for the elimination. As before, the sensitivity of this cyclohexadiene, which requires only the elimination of a silanol to aromatize, led us to effect direct epoxidation to give the stable epoxides **5b** and **7b** in a 9:1 ratio as before.

The sequence from the epoxide **5b** generally follows that used for racemic substrates in the ethyl ester series with the yields being somewhat higher in most cases. The yield of the silylative oxide ring opening to **8b** improved to 90% by adding the epoxide to a mixture of the silyl chloride, DMAP, and DBU. Its epoxidation to **9b** proceeded in 88% yield. The critical conversion of the epoxide **9b** to the oxazolidinone **10b** occurred in 70% yield with only a small amount of the O-alkylated compound **11b** being observed by changing the order of addition (see Experimental Section). Transformation of oxazolidinone to (+)-valienamine, isolated as its pentaacetate, was performed without isolation of the intermediates in 31% overall yield for four steps (average 75% yield per step). Comparison of the

(22) For an asymmetric reaction of 1-acetoxy-1,3-butadiene using a chiral auxiliary, see: Mayer, S. C.; Pfizenmayer, A. J.; Jouillié, M. M. *J. Org. Chem.* **1996**, *61*, 1655.

(23) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chim. Scand.* **1990**, *44*, 492.

(24) Guarna, A.; Guidi, A.; Gote, A.; Drandi, A.; Desarlo, F. *Synthesis* **1989**, 175.

(25) Hermann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *26*, 2429.

(26) Trost, B. M.; Parquette, J. F. *J. Org. Chem.* **1993**, *58*, 1579.

(27) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1.

spectral properties to those recorded confirms its identity. Our $[\alpha]_D$ +23.8 (c = 0.5, $CHCl_3$) compares favorably to the literature, $[\alpha]_D$ +23.4 (c = 0.77, $CHCl_3$)[13a] and +24 (c = 1, $CHCl_3$).[11b] The asymmetric synthesis requires 14 steps from dibenzoate **24** to give valienamine in 1−2% overall yield.

Conclusions

The palladium-catalyzed ring opening of epoxides in the presence of isocyanates constitutes a useful entry to *cis*-amino alcohols, a common feature in many biologically important systems. The palladium-initiated ionization of the epoxide requires stabilization of the developing alkoxide anion. Apparently, the isocyanate was insufficient in playing this role in this case. In some cases, protonic solvents such as alcohols or water can play this role[28] but are incompatible with the isocyanate. The sensitivity of the palladium catalyst toward decomposition and the direct decomposition of the epoxide with typical Lewis acids preclude the use of common Lewis acids to promote this process. Trimethyltin acetate nicely balances reactivity so that only the desired catalytic reaction occurred. This cocatalyst had previously been successfully used in catalyzing the additions of TMM−PdL_2 to carbonyl groups[18] and may prove to be a generally useful cocatalyst for catalysts derived from sensitive low-valent homogeneous complexes.

The superior performance of the bidentate phosphite ligand **14** should also be noted.[29] Phosphite ligands have proven their effectiveness in a number of palladium-catalyzed allylic alkylations, presumably because they are both σ-donors and π-acceptors. Thus, they can be particularly effective at facilitating both the ionization event as well as the nucleophilic addition. Use of a bidentate phosphite like **14** can have a number of effects including minimization of undesirable hydrogen shift processes.

The asymmetric synthesis of the cyclohexadiene **6** is also noteworthy. The sensitivity of this compound makes a strategy invoking an asymmetric Diels−Alder reaction that relies on Lewis acid catalysis rather doubtful. Indeed, the conditions for the thermal reaction of ethyl propiolate and 1-siloxy-1,3-butadiene must be very carefully controlled to prevent aromatization. Any attempt to catalyze the reaction by Lewis acid catalysis led to aromatization. This belief was further borne out by some efforts to use enantiocontrolled Diels−Alder reactions either by asymmetric catalysis or by use of a chiral auxiliary. The racemic synthesis is the shortest to date. Resolution of one of the intermediates could obviously convert it into an asymmetric synthesis as well. The only asymmetric syntheses not starting from carbohydrates, one of which started with the racemic O-acetate ester corresponding to **23**, employed resolutions and required more than 16 steps[13a] compared to 7 here. The need to manipulate the multifunctionality of carbohydrates makes asymmetric syntheses from these enantiomeric precursors sufficiently long that the asymmetric synthesis reported herein compares favorably in length even though it begins with an achiral building block. This report represents the first asymmetric synthesis from achiral starting materials not employing a resolution. Modification of this route should also be able to provide access to interesting analogues and other members of this family of glycosidase inhibitors. The intermediates reported herein also constitute the equivalent of asymmetric syntheses of numerous targets including senepoxide, crotepoxide, pipepoxide,[16a] and an isochorismate synthase inhibitor[16b] as well as cyclitols and aminocyclitols in general.

Experimental Section

Reactions were generally conducted under a positive pressure of dry nitrogen within flame-dried glassware. Reactions were sealed with red rubber septa and magnetically stirred. THF and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Methylene chloride and acetonitrile were distilled from calcium hydride prior to use. Methanol was distilled from magnesium methoxide prior to use. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed ICN silica gel (Kiesselgel 60, 230−400 mesh). Analytical TLC was performed with 0.2-mm coated commercial silica plates (E. Merck, DC−Platten Kieselgel 60 F_{254}). NMR spectra were obtained from Gemini GEM-200 (200-MHz) or Gemini GEM-300 (300-MHz) instruments at the frequencies indicated. ^{1}H NMR chemical shifts are reported in ppm from residual $CDCl_3$ (7.24 ppm) or acetone-d_6 (29.8 ppm). ^{13}C NMR chemical shifts are reported in ppm from residual $CDCl_3$ (77.0 ppm). IR spectra were obtained using a Perkin-Elmer paragon 500 FT-IR spectrometer. Melting points were determined on a Thomas−Hoover oil bath apparatus and were not corrected. Analytical gas chromatography was performed on a Varian star 3600 gas chromatograph with a 10-m × 0.25-mm poly(dimethylsiloxane) column. Mass spectral analyses were performed by the NIH Mass Spectral Facility at the School of Pharmacy, University of California−San Francisco on a Kratos MS-90 instrument with an ionizing current of 98 mA and an ionizing voltage of 70 eV. Microanalyses were performed by M−H−W Laboratories, Phoenix, AZ. Optical rotation data were acquired with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated. Chiral HPLC was performed on Chiralpak AD and Chiralcel OD columns.

(−)-(1*S*,2*S*)-Bis[(diphenylphosphino)benzamido]cyclohexane. The title compound was prepared as previously reported from scalemic (1*S*,2*S*)-diaminocyclohexane of 94% ee. Scalemic bis amide (7.0 g) was heated in 95:5 ethanol:water (145 mL) until dissolved. After aging at 4 °C overnight, the crystalline ligand was isolated by filtration and dried under house vacuum overnight to give 6.65 g (95% recovery) of ligand of >99% ee as determined by chiral HPLC using a Chiracel OD column eluting with 90:10 heptane:2-propanol containing 0.1% diethylamine.

(3a*R*,7a*S*)-3-(Benzenesulfonyl)-*cis*-3a,5,6,7a-tetrahydro-4*H*-cyclohex[*d*]isoxazole-2-oxide (26). *cis*-(1,4-Dibenzoyloxy)-2-cyclohexene (**24**) (6.44 g, 20 mmol), (phenylsulfonyl)nitromethane (4.25 g, 21.1 mmol), π-allylpalladium chloride dimer (0.0207 g, 0.055 mmol), (1*S*,2*S*)-bis[(diphenylphosphino)benzamido]cyclohexane (0.139 g, 0.2 mmol), and sodium bicarbonate (3.6 g, 42.8 mmol) were placed in a flask under argon. A solution of THF:water (3:1, 25 mL; degassed by three freeze−thaw cycles under Ar) was added. The reaction progressed from colorless to yellow in 1 h, indicative of the completion of the first alkylation. At this time, (dibenzylideneacetone)palladium (0.0998 g, 0.092 mmol) and triphenylphosphine (0.191 g, 0.73 mmol) dissolved in 5 mL of THF for 20 min were added. After heating at 60 °C for 4 h, the reaction was cooled and ethyl acetate (100 mL) and water (50 mL) were added. The organic layer was extracted with NaOH (5% aqueous, 3 × 60 mL) and brine (60 mL). The combined aqueous phases were extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude solids were chromatographed on silica gel with a 20−30% ethyl acetate in hexane gradient to give the product (4.85 g, 17.4 mmol, 87%), $[\alpha]_D^{27}$ −126.4° (c = 1.16, CH_2Cl_2), mp = 96−98 °C (ether). Alternatively, the product was isolated by crystallization of the crude solid from hot hexanes. IR (neat): 1607, 1587, 1447, 1339 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 7.7 Hz, 2 H), 7.72 (dd, J = 7.7, 7.3 Hz, 1 H), 7.60 (dd, J = 8.1, 7.3 Hz, 2 H), 6.27 (m, 1 H), 5.76 (dd, J = 10.2, 1.8 Hz, 1 H), 5.04 (dd, J = 7.7, 1.7 Hz, 1 H), 3.75 (m, 1 H), 2.25 (m, 2 H), 1.81 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 136.5, 135.2, 129.7, 129.4, 121.8, 120.3, 73.6,

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42.7, 22.7, 22.6. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.60; H, 4.47; N, 4.91; S, 11.35.

(3a*R*,7a*S*)-3-(Phenylsulfonyl)-*cis*-3a,5,6,7a-tetrahydro-4*H*-cyclohex[*d*]isoxazole (6). To a solution of the nitronate **26** (5.65 g, 20.3 mmol) in acetonitrile (30 mL) was added $SnCl_2 \cdot H_2O$ (9.5 g, 42.1 mmol). After the pink solution was stirred for 24 h at room temperature, the acetonitrile was removed in vacuo and ether (250 mL) and KF (14 g, 241 mmoL) were added. After the solution was stirred for 120 min, the supernatant was diluted with ether (350 mL) and extracted with water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow solid (4.51 g) which was used without further purification. On smaller scales, chromatography on silica gel with 5:1 ethyl acetate:hexanes provided the title compound in 88% yield. $[\alpha]_D^{27}$ −167.7° (*c* = 1.01, CH_2Cl_2). IR (neat): 1584, 1560, 1448, 1329, 1311 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.1 Hz, 2 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.62 (dd, *J* = 7.6, 7.1 Hz, 2 H), 6.22 (m, 1 H), 5.86 (m, 1 H), 5.03 (dd, *J* = 8.8, 2.6 Hz, 1 H), 3.69 (ddd, *J* = 8.8, 4.9, 4.3 Hz, 1 H), 2.15 (m, 3 H), 1.85 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.1, 138.6, 135.3, 134.9, 129.9, 129.4, 121.7, 80.5, 44.3, 22.2, 21.9. HRMS Calcd for $C_7H_6NO_3S$ ($M^+ - C_6H_7O$): 184.0068. Found: 184.0047. HRMS Calcd for C_6H_8 ($M^+ - C_7H_5NO_4$): 80.0626. Found: 80.0626.

(3a*R*,7a*S*)-3-Methoxy-*cis*-3a,5,6,7a-tetrahydro-4*H*-cyclohex[*d*]isoxazole. The crude yellow solid from nitronic ester reduction and potassium carbonate (14 g, 101 mmol) in 100 mL of methanol were heated at reflux for 1 h. After the mixture was cooled to room temperature, methylene chloride (150 mL) and water (150 mL) were added. The organic layer was extracted with brine (10 mL) and the solvent removed in vacuo. The resultant oil was chromatographed on silica gel with 1:6 ethyl acetate:petroleum ether to give the title compound (1.76 g, 11.5 mmol, 57% for two steps), $[\alpha]_D^{27}$ +127.7° (*c* = 0.68, CH_2Cl_2). On smaller scales, the product was obtained in 86% yield for a 76% overall yield for the two steps. IR (neat): 1622, 1452, 1395, 1379, 1343 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.05 (ddd, *J* = 10.1, 4.0, 4.0 Hz, 1 H), 5.72 (dddd, *J* = 10.1, 3.8, 1.8, 1.7 Hz, 1 H), 4.85 (ddd, *J* = 8.6, 2.4, 1.1 Hz, 1 H), 3.83 (s, 3 H), 3.18 (ddd, *J* = 12.5, 7.1, 5.3 Hz, 1 H), 1.96 (m, 3 H), 1.75 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 133.3, 124.2, 77.2, 57.5, 42.3, 22.0, 20.6. HRMS Calcd for $C_8H_{11}NO_2$: 153.07898. Found: 153.0790.

(1*S*,2*R*)-Methyl *cis*-2-Hydroxy-3-cyclohexene-1-carboxylate (23). After purging a solution of the above isoxazole (2.0 g, 13.05 mmol), molybdenum hexacarbonyl (3.5 g, 13.25 mmol), and boric acid (2.45 g, 39.6 mmol) in acetonitrile (90 mL) and methanol (45 mL) and water (1.5 mL) with a stream of Ar for 15 min, it was heated at reflux for 3 h. The black reaction was cooled and poured into a recrystallization dish. Silica gel was added until a thick slurry formed. The slurry was dried open to air for 24 h. The silica gel was washed with ether to extract the product as a dark oil. Kugelrohr distillation (110 °C at 5 mmHg) gave the product as a water clear oil (1.25 g, 8.0 mmol, 61%), $[\alpha]_D^{26}$ +203.18° (*c* = 1.27, CH_2Cl_2). On a smaller scale, the product was obtained in 77% yield by flash chromatography on silica gel eluting with a gradient of 3:1 to 1:1 hexanes:ethyl acetate. IR (neat): 3455, 1730, 1655, 1436, 1304 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (m, 2 H), 4.45 (d, *J* = 4.6 Hz, 1 H), 3.76 (s, 3 H), 2.75 (d, *J* = 6.1 Hz, 1 H), 2.63 (m, 1 H), 2.25−1.94 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 131.9, 128.2, 64.3, 52.1, 45.4, 25.2, 19.6. HRMS Calcd for $C_8H_{12}O_3$ (M^+): 156.0786. Found: 156.0808.

(1*S*,2*S*)-Methyl 2-Hydroxy-1-(phenylselenenyl)cyclohex-3-enecarboxylate (27) and (1*R*,2*S*)-Methyl 2-Hydroxy-1-(phenylselenenyl)-cyclohex-3-enecarboxylate. Alcohol **23** (0.156 g, 1.0 mmol) in THF (1 mL) was added to LDA (2.4 mmol in 1.5 mL of hexane and 2.5 mL of THF) at −78 °C. The yellow solution was stirred at −78 °C for 40 min and then at 0 °C for 10 min. Solid diphenyldiselenide (0.319 g,1.02 mmol) was added. After 3 h at 0 °C, the reaction was diluted with ether and washed with $NaHSO_4$ (10% aqueous, 1 × 10 mL), NaOH (5% aqueous, 1 × 10 mL), and brine (1 × 5 mL). The organic phase was dried ($MgSO_4$), the solvent removed in vacuo, and the residue chromatographed on silica gel with a 15−30% ethyl acetate:petroleum ether gradient to give a major diastereomer (0.141 g, 0.45 mmol, 45%) and a minor diastereomer (0.027 g, 0.09 mmol, 9%). Major diastereomer $[\alpha]_D^{28}$ +46.5° (*c* = 0.66, CH_2Cl_2). IR (neat): 3469, 1728, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.1 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 1 H), 7.30 (dd, *J* = 7.4, 8.1 Hz, 2 H), 5.86 (m, 2 H), 4.40 (m, 1 H), 3.57 (s, 3 H), 3.24 (d, *J* = 7.4 Hz, 1 H), 2.27 (m, 1 H), 2.2−1.9 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 138.2, 130.3, 129.5, 128.8, 127.1, 125.8, 68.7, 54.3, 51.8, 25.2, 23.6. HRMS Calcd for $C_{14}H_{16}O_3Se$ (^{80}Se): 312.0264. Found: 312.02547. HRMS Calcd for $C_{14}H_{16}O_3Se$ (^{78}Se): 310.0272. Found: 310.0273.

Minor diastereomer $[\alpha]_D^{28}$ +28.70° (*c* = 0.54, CH_2Cl_2). IR (neat): 3470, 1728, 137, 1260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.1 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.30 (dd, *J* = 7.4, 8.1 Hz, 2 H), 5.82 (dt, *J* = 10.5, 2.8 Hz, 1 H), 5.74 (dm, *J* = 10.5 Hz, 1 H), 4.52 (br s, 1 H), 3.52 (s, 3 H), 3.30 (d, *J* = 3.2 Hz, 1 H), 2.30 (m, 1 H), 2.2−1.9 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 138.1, 129.5, 128.9, 127.3, 126.0, 67.6, 57.4, 51.9, 25.7, 23.6.

(1*S*,2*S*)-Methyl 2-[(*tert*-Butyldimethylsilanyl)oxy)-1-(phenylselenenyl)cyclohex-3-enecarboxylate (28b). *tert*-Butyldimethylsilyl chloride (0.88 g, 5.8 mmol), imidazole (0.5 g, 7.3 mmol), and *N*,*N*-dimethyl-4-aminopyridine (0.03 g, 0.25 mmol) were dissolved in CH_2Cl_2 (5 mL) and the resulting solids removed by filtration. The solution (0.8 mL, 0.94 mmol) was added to alcohol **15** (0.145 g, 0.47 mmol) and stirred at room temperature for 44 h. The solution was filtered through silica gel to remove solids and the solvent removed in vacuo. The residue was chromatographed with 0−3% ethyl acetate:petroleum ether gradient to give a clear oil (0.173 g, 0.41 mmol, 86.5%), $[\alpha]_D^{20}$ +155.1° (*c* = 2.15, CH_2Cl_2): IR (neat): 1732, 1474, 1438, 1253, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2 H), 7.35 (dd, *J* = 7.2 Hz, 1 H), 7.28 (dd, *J* = 7.2, 8.3 Hz, 2 H), 5.88 (dt, *J* = 9.6, 2.8 Hz, 1 H), 5.78 (m, 1 H), 4.42 (d, *J* = 5.1 Hz, 1 H), 3.47 (s, 3 H), 2.45 (m, 1 H), 2.25−2.1 (m, 2 H), 1.94 (dd, *J* = 5.7, 12.3 Hz, 1 H), 0.79 (s, 9 H), 0.03 (s, 3 H), −0.01 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 139.2, 132.5, 130.7, 130.3, 128.0, 127.6, 68.9, 57.8, 52.9, 27.1, 25.3, 23.7, 19.3, −2.3, −3.7. Anal. Calcd for $C_{20}H_{30}O_3SeSi$: C, 56.45; H, 7.11. Found: C, 56.68; H, 6.91.

The 1*R*,2*S* diastereomer was prepared from the minor selenenylation product in the same manner as above. $[\alpha]_D^{27}$ +103.2° (*c* = 0.48, CH_2Cl_2); mp 72−73 °C (petroleum ether). IR (neat): 1726, 1472, 1738, 1261, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2 H), 7.35 (dd, *J* = 7.2 Hz, 1 H), 7.28 (dd, *J* = 7.2, 8.3 Hz, 2 H), 5.75 (m, 2 H), 4.75 (d, *J* = 2.4 Hz, 1 H), 3.27 (s, 3 H), 2.45 (m, 1 H), 2.3 (m, 1 H), 2.08 (m, 2 H), 0.96 (s, 9 H), 0.22 (s, 3 H), 0.13 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 138.2, 130.4, 129.0, 128.6, 128.1, 127.7, 67.7, 58.3, 51.3, 27.0, 25.8, 24.9, 18.2, −3.7, −4.8. Anal. Calcd for $C_{20}H_{30}O_3SeSi$: C, 56.45; H, 7.11. Found: C, 56.36; H, 7.05.

Preparation of *rac*-3-(*tert*-Butyldimethylsiloxy)-2-carboethoxycyclohexa-1,4-diene (6a). A neat mixture of 1-(*tert*-butyldimethylsiloxy)buta-1,3-diene (1.84 g, 10.0 mol), ethyl propiolate (1.12 g, 11.4 mmol), and one crystal of methylene blue was subjected to three freeze−thaw cycles. After the tube was sealed, the mixture was heated at 80 °C for 5 days. Any volatile compound was removed in vacuo for 2 h and the resultant product (2.56 g, 9.06 mmol, 91%) used directly in the next step. IR (film): 1715, 1473, 1463, 1396 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.00 (m, 1 H), 5.88 (br s, 2 H), 5.10 (m, 1 H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1 H), 2.94 (m, 1 H), 2.70 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 0.86 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 137.3, 132.2, 128.4, 125.0, 61.5, 60.3, 27.1, 25.6, 17.9, 14.1, −4.5, −4.7. HRMS Calcd for $C_{15}H_{26}O_3Si$ (M^+): 282.1651. Found: 282.1664.

Preparation of *rac*-5a and (+)-5b. *rac*-5a. *m*-CPBA (1.21 g, 7.0 mmol) was added portionwise to a mixture of diene **6a** (0.988 g, 3.50 mmol) and sodium bicarbonate (0.890 g, 10.5 mmol) in 15 mL of benzene. After 9 h at room temperature, the reaction was filtered and the supernatant diluted with benzene. The organic layer was washed with saturated aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine. After drying ($MgSO_4$), filtration, and evaporation, flash chromatography (5:1 hexane:ether) gave a colorless oil (840 mg, 2.81 mmol, 80% yield). IR (film): 1713, 1472, 1463, 1415, 1371 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.74 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1 H), 5.05 (qd, *J* = 4.5, 1.5 Hz, 1 H), 4.25 (dq, *J* = 11.5, 5.0, 2.5 Hz, 1 H), 5.05 (qd, *J* = 4.5, 1.5 Hz, 1 H), 4.25 (dq, *J* = 11.5, 7.1 Hz, 1 H), 4.14 (dq, *J* = 11.5, 7.1 Hz, 1 H), 3.30 (m, 2 H), 2.73 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.18 (s, 3 H), 0.10 (s, 3 H). ^{13}C

NMR (75 MHz, $CDCl_3$): δ 166.4, 135.2, 129.7, 62.7, 60.5, 54.2, 49.2, 25.7, 25.6, 17.9, 14.0, −4.9, −5.0. HRMS Calcd for $C_{14}H_{26}O_4Si$: C, 60.37; H, 8.78. Found: C, 60.19; H, 8.53.

(+)-5b. To a mixture of phenylselenide **28b** (0.173 g, 0.406 mmol) and $CaCO_3$ (0.17 g, 1.7 mmol) in dichloromethane (12.5 mL) at −78 °C was added *m*-CPBA (0.081 g, 0.469 mmol) in dichloromethane (2.5 mL). After 15 min, 2-methoxypropene (0.377 g, 5.22 mmol) was added. After an additional 15 min at −78 °C, the reaction was removed from the cooling bath and stirred 45 min. The solvent was removed in vacuo. The residue was chromatographed immediately with 5:95 ethyl acetate:petroleum ether to give semipure diene **6b** (0.10 g). This compound was immediately epoxidized as above using sodium bicarbonate (0.206 g, 2.24 mmol) and *m*-CPBA (0.14 g, 0.81 mmol) in 1.5 mL of dichloromethane. After 20 h at room temperature, water, sodium bisulfite, and ethyl acetate were added. After the organic layer ($MgSO_4$) was dried, the solvent was removed in vacuo and the residue was chromatographed with 5:95 ethyl acetate:petroleum ether to give scalemic epoxide **5b** (0.053 g, 0.2 mmol, 48.3% for two steps), $[\alpha]_D^{25}$ +1.60° (c = 2.57, CH_2Cl_2).

Preparation of *rac*-8a and (−)-8b. *rac*-8a. DBU (0.760 g, 5.50 mmol) in 1 mL of dichloromethane was added to a solution of epoxide **5a** (1.18 g, 3.95 mmol), TBDMS-Cl (0.72 g, 4.78 mmol), and DMAP (0.048, 0.41 mmol) in 7 mL of dichloromethane. After stirring 24 h at room temperature, the reaction was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was flash chromatographed (19:1 hexane:ethyl acetate) to give *rac*-**8a** (1.24 g, 3.00 mmol, 76% yield). IR (film): 1712, 1587, 1472, 1463, 1405 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (dd, J = 5.1, 1.5 Hz, 1 H), 6.20 (dd, J = 9.4, 4.9 Hz, 1 H), 6.15 (ddd, J = 9.4, 5.2, 1.0 Hz, 1 H), 4.57 (br s, J = 1.3 Hz, 1 H), 4.28 (dq, J = 10.9, 7.1 Hz, 1 H), 4.18 (dq, J = 10.9, 7.1 Hz, 1 H), 4.10 (dd, J = 4.8, 1.6 Hz, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 0.86 (s, 9 H), 0.82 (s, 9 H), 0.16 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 133.0, 132.7, 129.8, 123.8, 69.8, 67.8, 60.3, 25.6, 25.5, 17.9, 17.8, 14.1, −4.5, −4.7, −4.8, −5.2. HRMS Calcd for $C_{15}H_{24}O_3Si$ (M^+ − TBDSOH): 280.1495. Found: 280.1485.

(−)-8b Epoxide. Epoxide (+)-**5b** (0.056 g, 0.19 mmol) was added to a 0 °C solution of TBDMS-Cl (0.037 g, 0.25 mmol), DBU (0.038 g, 0.25 mmol), and DMAP (0.0025 g, 0.020 mmol) in 0.5 mL of dichloromethane. The cooling bath was removed, the reaction performed, and the product purified (99.6:0.4 petroleum ether:ethyl acetate) as above to give (−)-**8b** (0.066 g, 0.17 mmol, 90%), $[\alpha]_D^{28}$ −305.1° (c = 3.29, CH_2Cl_2). IR (neat): 1715, 1651, 1589, 1463, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.07 (dd, J = 1.3, 9.4 Hz, 1 H), 6.15 (m, 2 H), 4.54 (s, 1 H), 4.08 (d, J = 4.4 Hz, 1 H), 3.75 (s, 3 H), 0.84 (s, 9 H), 0.80 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 133.1, 132.9, 129.4, 123.6, 69.9, 68.0.0, 51.5, 25.7, 25.6, 18.0, 17.9, −4.3, −4.7, −5.0. HRMS Calcd for $C_{20}H_{38}O_4Si_2$ (M^+): 398.2309. Found: 398.2306.

Preparation of *rac*-9a and (−)-9b. *rac*-9a. *m*-CPBA was added portionwise to a mixture of diene **8a** (2.82 g, 6.83 mmol) and sodium bicarbonate (1.72 g, 20.5 mmol) in 17 mL of methylene chloride. After stirring 3 h at room temperature, the reaction was filtered and diluted with ether. The resultant organic layer was washed with saturated aqueous sodium bisulfite, sodium bicarbonate, and brine. After drying ($MgSO_4$) and evaporation in vacuo, the residue was flash chromatographed (12:1 hexane:ethyl acetate) or distilled (bp 175−200 °C at 0.025 Torr, bath temperature) to give *rac*-**9a** (1.71 g, 3.99 mmol, 86% yield). IR (film): 1720, 1475, 1473, 1395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 4.2 Hz, 1 H), 4.57 (dd, J = 2.1 Hz, 1 H), 4.27 (dq, J = 10.9, 7.1 Hz, 1 H), 4.25 (m, 1 H), 4.15 (dq, J = 10.9, 7.1 Hz, 1 H), 3.51 (dt, J = 3.8, 2.4 Hz, 1 H), 3.40 (t, J = 4.0 Hz, 1 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.84 (s, 18 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), −0.01 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 137.4, 134.4, 69.3, 67.9, 60.7, 57.9, 45.1, 25.5, 25.4, 17.8, 17.7, 14.0, −4.6, −4.9, −5.0, −5.3. HRMS Calcd for $C_{20}H_{37}O_5Si_2$: C, 58.83; H, 9.40. Found: C, 58.71; H, 9.20

(−)-9b. Diene **8b** (0.067 g, 0.17 mmol), sodium bicarbonate (0.84 g, 1 mmol), and *m*-CPBA (0.061 g, 0.36 mmol) in 0.5 mL of dichloromethane as above gave, after flash chromatography eluting with 1−3% ethyl acetate:petroleum ether, (−)-**9b** (0.061 g, 0.15 mmol, 88%), $[\alpha]_D^{20}$ −140.26° (c = 3.05, CH_2Cl_2). IR (neat): 1721, 1473 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J = 4.2 Hz, 1 H), 4.56 (dd, J = 2.1 Hz, 1 H), 4.25 (dd, J = 2.1 Hz, 1 H), 3.76 (s, 3 H), 3.53 (m, 1 H), 3.42 (dd, J = 4.0 Hz, 1 H), 0.86 (br s, 18 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 137.6, 134.0, 69.3, 68.1, 58.0, 51.8, 45.1, 25.6, 17.9, 17.8, −4.5, −4.8, −4.9, −5.1. HRMS Calcd for $C_{20}H_{38}O_5Si_2$ (M^+): 414.2258. Found: 414.2248.

Preparation of 10a and 10b. *rac*-10a. A solution of the active catalyst was generated by sequential addition to 1 mL of THF of palladium acetate (11.2 mg, 0.05 mmol), phosphite **14** (50.8 mg, 0.30 mmol), and *n*-butyllithium (66.7 μL, 0.10 mmol, 1.5 M in hexanes). After 30 min at room temperature, epoxide **9a** (0.428 g, 1.0 mmol) in 1 mL of THF, *p*-toluenesulfonylisocyanate (0.59 g, 3.0 mmol), and trimethyltin acetate (22.3 mg, 0.10 mmol) were added. Heating at reflux for 42 h, concentration in vacuo, and direct flash chromatography (10:1 hexane:ethyl acetate) gave **10a** (337.2 mg, 0.54 mmol, 54% yield) and **11a** (56.1 mg, 0.09 mmol, 9% yield). **10a**: IR (film): 1791, 1722, 1598, 1472, 1464, 1367 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (br d, J = 8.5 Hz, 2 H), 7.28 (br d, J = 8.5 Hz, 2 H), 5.14 (dd, J = 8.6, 4.5 Hz, 1 H), 4.52 (br s, 1 H), 4.58−4.55 (m, 1 H), 4.35 (dq, J = 10.9, 7.2 Hz, 1 H), 4.23 (dq, J = 10.9, 7.2 Hz, 1 H), 4.12 (dd, J = 3.2, 2.4 Hz, 1 H), 2.40 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H), 0.81 (s, 9 H), 0.63 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), −0.13 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 150.4, 145.5, 135.5, 135.1, 132.5, 129.7 (2 C), 128.8 (2 C), 73.6, 68.8, 64.9, 61.3, 52.0, 25.3, 25.1, 21.4, 17.6, 17.4, 14.0, −5.2, −5.3, −5.5. HRMS Calcd for $C_{28}H_{44}NO_8SSi_2$ (M^+ − CH_3): 610.2326. Found: 610.2315. **11a**: IR (film): 1718, 1638, 1472, 1464, 1363 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 6.5 Hz, 2 H), 7.24 (d, J = 7.9 Hz, 2 H), 6.88 (d, J = 4.7 Hz, 1 H), 5.50 (dd, J = 8.1, 4.8 Hz, 1 H), 4.77 (ddd, J = 8.1, 2.5, 1.5 Hz, 1 H), 4.64 (dd, J = 3.1, 1.5 Hz, 1 H), 4.32 (dq, J = 10.8, 7.1 Hz, 1 H), 4.27 (t, J = 2.9 Hz, 1 H), 4.22 (dq, J = 10.7, 7.1 Hz, 1 H), 2.30 (s, 3 H), 1.33 (t, J = 7.1 Hz, 3 H), 0.81 (s, 9 H), 0.80 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 158.6, 143.3, 138.9, 137.5, 129.3 (2 C), 128.4 (2 C), 127.2, 77.2, 77.1, 68.7, 65.0, 61.5, 25.4, 25.3, 21.3, 17.7, 17.6, 13.9, −5.0, −5.3 (2 C). HRMS Calcd for $C_{25}H_{38}NO_8SSi_2$ (M^+ − t-C_4H_9): 568.1857. Found: 568.1873.

10b. The catalyst was prepared as above from recrystallized palladium acetate (11 mg, 0.05 mmol), phosphite **14** (51 mg, 0.14 mmol), and *n*-butyllithium (0.075 mL, 1.35 M in hexane, 0.101 mmol) in 2 mL of THF. Tosyl isocyanate (0.29 g, 1.48 mmol) and an aliquot of the palladium solution (0.5 mL, 0.0125 mmol) were added sequentially to epoxide **9b** (0.061 g, 0.15 mmol) and trimethyltin acetate (0.018 g, 0.08 mmol) under Ar. After heating and workup as above, **10b** [0.064 g, 0.11 mmol, 70% yield, $[\alpha]_D^{20}$ −32.6° (c = 1.0, CH_2Cl_2)] was obtained. IR ($CDCl_3$): 1788, 1721, 1472, 1438, 1363 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2 H), 7.27 (m, 3 H), 5.12 (dd, J = 4.7, 8.5 Hz, 1 H), 4.55 (m, 2 H), 4.11 (m, 1 H), 3.83 (s, 3 H), 2.41 (s, 3 H), 0.81 (s, 9 H), 0.65 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), −0.12 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 150.1, 145.4, 134.9, 132.4, 129.6, 128.7, 73.6, 68.8, 65.1, 52.2, 25.5, 25.3, 17.8, 17.6, −4.9, −5.0, −5.1, −5.2. HRMS Calcd for $C_{24}H_{36}NO_8SSi_2$ (M^+ − t-C_4H_9): 554.1700. Found: 554.1714.

Preparation of (3*S*,4*S*,5*R*,6*R*)-5,6-Bis(*tert*-Butyldimethylsiloxyl)-1-(hydroxymethyl)-3-[*N*-(*p*-toluenesulfonyl)amino]cyclohex-1-en-4-ol (17b). DIBAL-H (2.75 mL, 1.0 M in hexane, 2.75 mmol) was added over 30 min to a −78 °C solution of oxazolidinone **10a** (0.313 g, 0.50 mmol) in 1.5 mL of dichloromethane. After 2 h at −78 °C, methanol was added and the reaction allowed to warm to room temperature, at which point 30% aqueous sodium potassium tartrate and triethanolamine were added until a clear solution resulted. After extraction with ethyl acetate, the resulting organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in 5 mL of methanol containing a catalytic amount of sodium methoxide and the resultant solution stirred overnight at room temperature. After concentration in vacuo and flash chromatography (3:1 hexane:ethyl acetate), *rac*-**17b** (212 mg, 0.38 mmol, 76% yield) was obtained. In the same way, oxazolidinone **10b** (0.064 g, 0.10 mmol)

was converted to the crude enantiomerically pure aminodiol **17b**, which was taken directly onto the next step. IR (film): 3481, 1472, 1464, 1331 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 7.9 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 2 H), 5.61 (q, J = 1.7 Hz, 1 H), 5.39 (br d, J = 9.6 Hz, 1 H, exchangeable), 4.50 (m, 2 H), 3.99 (m, 1 H), 3.96 (br s, 1 H), 3.92 (dd, J = 4.2, 2.5 Hz, 1 H), 3.75 (d, J = 10.1 Hz, 1 H, exchangeable), 3.26 (dtt, J = 10.1, 4.2, 1.4 Hz, 1 H), 2.41 (s, 3 H), 0.86 (s, 9 H), 0.78 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), −0.01 (s, 3 H), −0.11 (s, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 143.5, 138.3, 137.2, 129.9 (2 C), 127.3 (2 C), 125.6, 70.1, 69.3, 67.8, 63.9, 50.6, 25.4, 25.3, 21.3, 17.5, −4.9, −5.2, −5.4, −5.5. Anal. Calcd for $C_{24}H_{38}NO_6SSi_2$ ($M^+ - CH_4CH_3H_2$): 524.1958. Found: 524.1922.

***N*-(*p*-Toluenesulfonyl)valienamine (19).** Aqueous hydrofluoric acid (0.13 mL, 10 M in water, 2.6 mmol) was added to a solution of diol **17b** (147 mg, 0.26 mmol) in 2.6 mL of acetonitrile. After 16 h at room temperature, the precipitate, which formed, was removed by filtration. The filtrate was concentrated in vacuo and the resulting residue purified by flash chromatography (4:1 methanol:chloroform) to give 20.9 mg of **19**. The initial precipitate was neutralized by dissolving in methanol and adding calcium carbonate. After the solution was filtered and concentrated, the residue was purified by flash chromatography to give an additional 50 mg of **19** for a total of 70.9 mg (0.21 mmol, 82% yield). More conveniently, after stirring the initial reaction mixture for 16 h, the reaction was added to methanol containing potassium carbonate. Workup consisted of adding brine and extraction with ethyl acetate followed by purification as above. For the enantiomerically pure substrate, the crude product was used directly in the next step. IR (KBr): 3500, 3380, 1451 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 7.79 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 6.26 (br d, J = 8.1 Hz, 1 H), 5.35 (br s, 1 H), 4.30−3.50 (m, 10 H), 2.41 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 141.6, 139.9, 130.1 (2 C), 127.2 (2 C), 120.0, 72.0, 70.0, 69.8, 61.8, 51.8, 21.2. Anal. Calcd for $C_{14}H_{19}NO_6S$: C, 51.05; H, 5.81; N, 4.25; S, 9.73. Found: C, 50.79; H, 6.02; N, 4.10; S, 9.46.

Preparation of Valienamine (1) and Its Pentaacetate (20). Small pieces of sodium were added to a solution of tetraol **19** (0.049 g, 0.15 mmol) in 10 mL of liquid ammonia at −78 °C until the blue color persisted, at which point ammonium chloride was added until the blue color disappeared. Evaporation of the ammonia gave racemic valienamine **1**, which was characterized as its pentaacetate. Valienamine was dissolved in a mixture of 2 mL of pyridine and 10 mL of acetic anhydride at room temperature. After stirring overnight, the reaction was diluted with dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate (caution: foaming) followed by brine. After drying ($MgSO_4$), filtration, and concentration, the residue was flash chromatographed (gradient from 1:1 hexane:ethyl acetate to pure ethyl acetate) to give **20** (32.4 mg, 0.084 mmol, 56% yield), mp 178−180 °C (ether−ethanol) [lit.[11g] mp 180−181 °C]. The above was repeated using crude enantiomerically pure tetraol **19** to give (+)-valienamine pentaacetate (**20**) (0.012 g, 0.031 mmol, 31%) in four steps from **10b**, $[\alpha]_D^{28}$ +23.8° (c = 0.5, $CHCl_3$), mp 90.5−93 °C (ether−ethanol) [lit.[8] mp 95 °C]. IR ($CDCl_3$): 1745, 1709, 1502, 1477, 1371 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.89 (q, J = 1.4 Hz, 1 H), -5.69 (br d, J = 8.7 Hz, 1 H), 5.46 (dd, J = 9.4, 6.4 Hz, 1 H), 5.36 (db, J = 6.7 Hz, 1 H), 5.11 (d, J = 4.6 Hz, 1 H), 5.09−4.98 (m, 1 H), 4.65 (dq, J = 13.2, 1.1 Hz, 1 H), 4.39 (d, J = 13.3 Hz, 1 H), 2.07 (s, 9 H), 2.06 (s, 3 H), 2.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.5, 170.3, 170.2, 170.1, 134.2, 126.2, 70.7, 68.9, 68.2, 62.7, 44.6, 22.9, 20.6, 20.4 (3 C). Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 53.00; H, 5.96; N, 3.55.

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Supporting Information Available: Table and accompanying text for the variation of catalyst conditions for epoxide and isocyanate addition (2 pages). See any current masthead page for ordering and Internet access instructions.

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