Enzymatic Resolution of Aminocyclopentenols as Precursors to D- and L-Carbocyclic Nucleosides

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Racemic *cis*-4-aminocyclopent-2-en-1-ols were synthesized in three steps utilizing hetero Diels−Alder chemistry. Starting from suitably protected hydroxylamines, oxidization with sodium periodate and trapping with cyclopentadiene afforded cycloadducts (±)-**5a**−**d**. The N−O bond of the cycloadducts was reduced with $Mo(CO)_6$ to afford (±)-*cis*-4-aminocyclopent-2-en-1-ols (±)-**6a**−**d**. These compounds, or their corresponding acetates, were kinetically resolved by enzymatic acetylation or hydrolysis, respectively. Enzymatic acetylation of *cis*-*N*-(benzylcarbamoyl)-4-aminocyclopent-2-enol [(±)-**6a**] with *Candida antarctica B* lipase and *Pseudomonas species* lipase gave the corresponding acetate (−)-**7a** in 90% and 92% ee, respectively, after 40% conversion. Enzymatic hydrolysis of *cis*-*N*-acetyl-4-aminocyclopent-2-enol 1-*O*-acetate (±)-**7d** with electric eel acetylcholine esterase was successful in providing both *cis*-*N*-acetyl-4-aminocyclopent-2-enols (+)-**6d** and (+)-**7d** in 92% ee (99% ee after a single recrystallization) after 40% conversion. Further synthetic transformations of these resolved synthetic building blocks and derivatives are also reported.

Introduction

Nucleosides have proven to be a functionally diverse class of compounds with a wide range of biological activity.[1] Several structural modifications have been applied to their basic framework, including the replacement of the furanose oxygen with a methylene unit, creating a new class of compounds termed carbocyclic nucleosides.[2] These cyclopentane versions of nucleosides have in some cases proven to be more biologically effective than their furanose counterparts due to increased resistance to enzymatic and hydrolytic degradation.[3] Several approaches toward the synthesis of optically active carbocyclic nucleosides have been reported over the past decade.[2,4] Many involve the production of typical 5′-(hydroxymethyl)cyclopentane derivatives, such as aristeromycin and carbovir[5] and, therefore, do not allow access to structurally diverse carbocyclic nucleosides such as the polyoxins and nikkomycins.[6]

With recent reports in the literature describing the syntheses of L-nucleosides,[7] the enantiomers of naturally occurring D-nucleosides, we recognized the need for a concise, inexpensive route to 4-aminocyclopent-2-enol precursors. These compounds could serve as chiral building blocks for D- and L-4-hydroxymethyl carbocyclic nucleosides as well as for structurally diverse carbocyclic nucleosides[6a] and aminocyclopentenol natural products.[8] Enantiomerically pure 4-aminocyclopent-2-enols were envisioned to be derived through an enzymatic route, which would alleviate the need for a chiral auxiliary (one for each enantiomer) as well as the need for cleavage of that auxiliary, resulting in improved atom efficiency. Also, utilization of a biocatalyst provides direct and immediate access to each enantiomer. Resolution of racemic *cis*-4-aminocyclopent-2-enol (±)-**1** would afford both enantiopure 4-aminocyclopent-2-enol derivatives (**1** and **2**) in an enantiodivergent synthesis (Scheme 1).

Herein, we report a successful enantiodivergent synthesis of 4-aminocyclopent-2-enols that can serve as building blocks for D- and L-carbocyclic nucleosides.

Results and Discussion

Several substrates for kinetic enzymatic resolution were prepared for both enzymatic acetylation and hydrolytic reactions (Scheme 2). Benzyl carbamate (±)-**6a**

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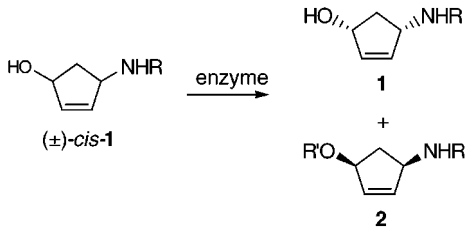
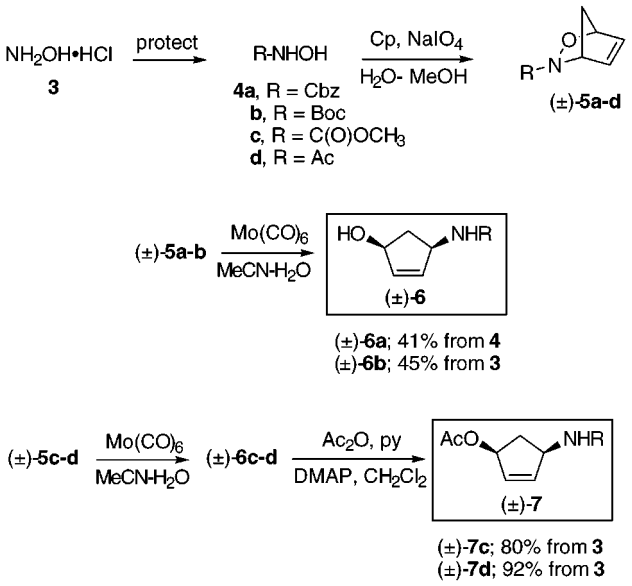
Scheme 1



Scheme 2



was prepared in two steps from benzyl *N*-hydroxycarbamate (**4a**) in 41% yield. *tert*-Butyl carbamate (±)-**6b** was prepared in three steps from hydroxylamine hydrochloride in 45% overall yield according to literature procedures.[4b] Thus, the N-protected hydroxylamines (**4a,b**) were oxidized with sodium periodate to the transient acylnitroso species in the presence of cyclopentadiene to form the corresponding hetero Diels−Alder cycloadducts (**5a,b**).[9] Subsequent N−O bond reduction[10] with $Mo(CO)_6$ in MeCN−H_2O provided (±)-**6a** and (±)-**6b** suitable for enzymatic kinetic resolution by acetylation. Two other substrates were designed to have higher solubility in aqueous media, which would allow for enzymatic resolution by esterase-catalyzed hydrolysis. Thus, methyl carbamate (±)-**7c** and acetamide (±)-**7d** were synthesized by a slightly modified method (compared to the synthesis of carbamates (±)-**6a** and (±)-**6b**) to enable efficient production of these water-soluble compounds (Scheme 2). Thus, hydroxylamine was protected as methylcarbamate **4c** and acetamide **4d** and then oxidized and trapped with cyclopentadiene in situ to yield cycloadducts (±)-**5c** and (±)-**5d**, respectively, in one-pot, two-step reactions. N−O bond reduction of the cycloadducts, followed by acetylation, gave methyl carbamate (±)-**7c** and acetamide (±)-**7d** in 80% and 92% overall yields, respectively, in four steps.

Two approaches in the search for an appropriate enzyme for the kinetic resolution by acetylation were pursued. The first approach involved wide screening with a large number of enzymes in order to find an appropriate biocatalyst for kinetic resolution of allylic alcohols (±)-**6a** and (±)-**6b**. A screening kit[11] containing 25 lipases was utilized for the determination of substrate compatibility with alcohol (±)-**6a**. Vinyl acetate was used as the acetylation reagent with CH_2Cl_2 as the solvent. Of the 25 lipases examined, several were found to successfully acetylate alcohol (±)-**6a**, and on the basis of commercial availability, four of these enzymes were selected for further testing: *Mucor meihei*, *Candida rugosa*, *Candida antarctica A*, and *Candida antarctica B*. *M. meihei* lipase was found not to catalyze the formation of allylic acetate **7a** on a larger scale even under "forcing" conditions (mg enzyme:mg substrate 1:2; 18 equiv of vinyl acetate). *C. rugosa* and *C. antarctica A* lipases were found to catalyze substrate turnover, but were sluggish. *C. antarctica B* lipase, however, was found to produce allylic acetate (−)-**7a** after 39% conversion of starting material (±)-**6a** (Scheme 3, Table 1). The resulting allylic acetate (−)-**7a** was hydrolyzed (K_2CO_3) and derivatized with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride for Mosher ester analysis (HPLC).[12] Thus, allylic acetate (−)-**7a** was found to be of 90% ee. The *E* value for *C. antarctica B* was calculated to be 34.[13] This *E* value indicates that the acetylation is selective enough for production of an enantiopure 4-aminocyclopent-2-enol but would require recrystallization of the acetylation product to increase the % ee. The absolute configuration of (−)-**7a** was determined by comparison of the optical rotation to that of a sample with known configuration.[14a]

N-Boc-protected aminocyclopentenol derivative (±)-**6b** was screened as a substrate for enzymatic kinetic resolution by acetylation with a kit containing eight lipases.[15] Isopropenyl acetate was used as the acetylation reagent with CH_2Cl_2 as solvent. It was found that two enzymes accepted (±)-**6b** as a substrate; *Burkholderia species* lipase and *Candida antarctica B* lipase. A larger scale

(9) For a review on acylnitroso hetero-Diels−Alder reactions, see: Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317.

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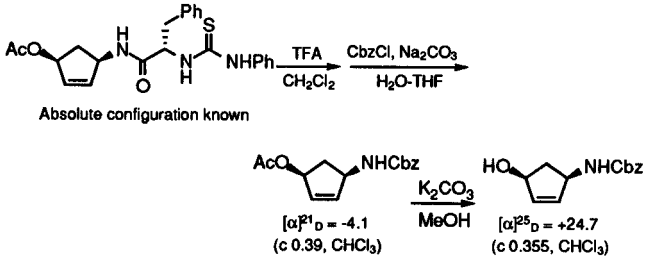
(14) (a) The absolute stereochemistry of acetate (−)-**7a** was determined by comparison of the optical rotations of this compound as well as its solvolysis product, alcohol (+)-**6a**, to samples of known configuration synthesized from an intermediate in the Edman degradation sequence as shown below. Acetamide (−)-**7d** was also synthesized by this method; $[\alpha]^{24}_D = -24.5$ (*c* 0.33, $CHCl_3$). See: Vogt, P. F.; Hansel, J.−G.; Miller, M. J. *Tetrahedron Lett.* **1997**, *38*, 2803. (b) Synthesis of (−)-**7b** from (−)-**7d** (Scheme 6) gave a standard for determination of the configuration of acetate (−)-**7b** derived from enzymatic resolution of (±)-**6b**. Methyl carbamate (+)-**6c** obtained from enzymatic hydrolysis was transformed to acetate (−)-**7b** by the synthetic route shown in Scheme 6 in order to determine its absolute configuration.



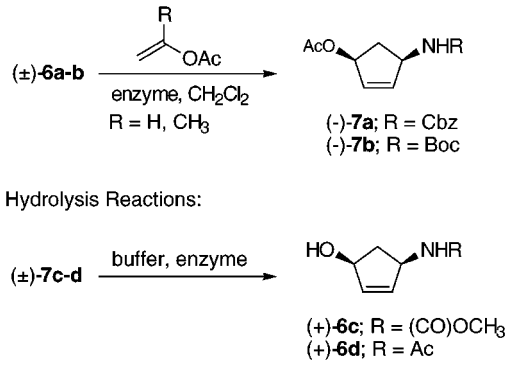
(15) Chirazyme Lipases and Esterases Screening Kit; Boehringer Mannheim.

Table 1. Kinetic Enzymatic Resolutions

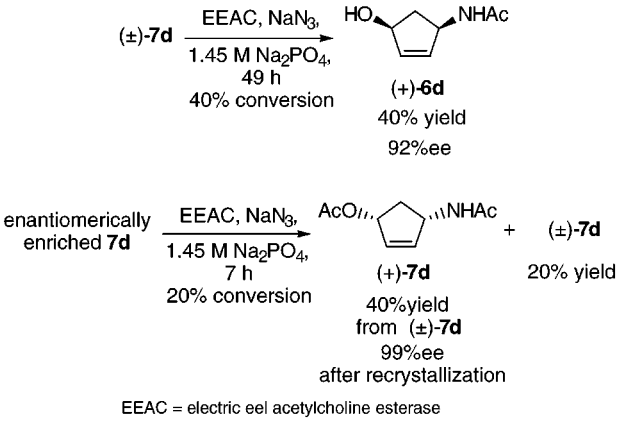
substrate	enzyme	product	% conversion	%ee[a]	*E*
		Acetylation Reactions			
(±)-**6a**	*C. antarctica B* lipase	(−)-**7a**	39	90	34
(±)-**6a**	*Pseudomonas* sp. lipase	(−)-**7a**	40	92	44.9
(±)-**6b**	*Burkholderia* sp. lipase	(−)-**7b**	39	55	4.8
(±)-**6b**	*C. antarctica B* lipase	(−)-**7b**	40	81	16.3
		Hydrolysis Reactions			
(±)-**7c**	electric eel acetylcholine esterase	(+)-**6c**	50	72	15.6
(±)-**7d**	electric eel acetylcholine esterase	(+)-**6d**	40	92	44.9

[a] Before recrystallization.

Scheme 3



Scheme 4



reaction with isopropenyl acetate in *tert*-butyl methyl ether (MTBE) with *Burkholderia* sp. afforded acetate (−)-**7b** in 55% ee after 39% conversion (% ee determined by Mosher ester analysis; ^{19}F NMR).[14b] Acetylation catalyzed by *C. antarctica B* lipase under the same conditions afforded acetate (−)-**7b** in 81% ee after 40% conversion.

The second approach utilized in locating an appropriate enzyme involved literature searching for analogous substrates that have been resolved enzymatically.[16] Enzymatic resolution of cyclopentene diol derivatives is well-known in the literature, but resolution of aminocyclopentenols is not as prevalent.[17] *Pseudomonas* sp. lipase has been shown to provide resolution of cyclopentene alcohols.[18] The similarities between such alcohols and alcohol (±)-**6a** led us to attempt kinetic resolution by similar methodology using *Pseudomonas* sp. lipase. Thus, alcohol (±)-**6a** was reacted with vinyl acetate in dichloromethane in the presence of *Pseudomonas* sp. lipase (Scheme 3, Table 1). After 6 h, 40% of alcohol (±)-**6a** had been transformed into the corresponding allylic acetate (−)-**7a**. The resulting allylic acetate (−)-**7a** was determined to be of 92% ee (determined by Mosher ester analysis; HPLC; calcd $E = 44.9$).[14a] A disadvantage of the use of this enzyme was the large enzyme-to-substrate ratio needed (mg enzyme:mg substrate 1:4.7), which may make large-scale synthesis impractical.

Electric eel acetylcholinesterase (EEAC), an enzyme that has high specificity for cyclopentene diacetates, was chosen for enzymatic hydrolysis of water-soluble acetates (±)-**7c** and (±)-**7d**.[19] It was reasoned that both of these compounds could resemble the meso diacetates previously resolved by this enzyme and should result in enantioselective recognition. Thus, acetate (±)-**7c** was subjected to EEAC in 1.45 M NaH_2PO_4, pH 6.9 buffer (Scheme 3, Table 1); after 50% conversion, alcohol (+)-**6c** was formed in 72% ee (Mosher ester analysis; ^{19}F NMR) with an *E* value of 15.6.[14b] With such a low *E* value for this reaction, it appears that although acetate (±)-**7c** is a good substrate for EEAC, the enzyme is not enantioselective in its choice of substrates.[20]

Acetate (±)-**7d** (0.15 g, 0.82 mmol) was subjected to EEAC (0.20 mg, 100 units) in 1.45 M NaH_2PO_4, pH 6.9 buffer, upon which 40% of the allylic acetate had been hydrolyzed to the alcohol in 9 h. Alcohol (+)-**6d** was found to be of 92% ee (Mosher ester analysis) with an *E* value of 44.9 (Scheme 3, Table 1).[14a] This reaction was conducted on a larger scale in which 4 g of acetate (±)-**7d** was resolved by EEAC (1.1 mg; 500 units) in 49 h (Scheme 4). Alcohol (+)-**6d** was found to be of 92% ee (Mosher ester analysis; 99% ee after a single recrystallization (EtOAc/hexanes)). The remaining enantiomerically enriched acetamide **7d** was then resubjected to EEAC, and after a 20% conversion the unreacted allylic acetate was isolated, saponified to the alcohol, and derivatized to its Mosher ester. Analysis by ^{1}H and ^{19}F NMR showed 92% ee of (+)-*N*-acetyl-4-aminocyclopent-2-enol 1-*O*-acetate (+)-**7d**. A greater than 99% ee of (+)-**7d** could be achieved through a single recrystallization (EtOAc/hexanes).

With these results in hand, we attempted to remove the Cbz and acetamide protecting groups from compounds **7a** and **7d** in order to gain entry into carbocyclic nucleoside syntheses. Cbz groups are normally removed under hydrogenation conditions, which would not be

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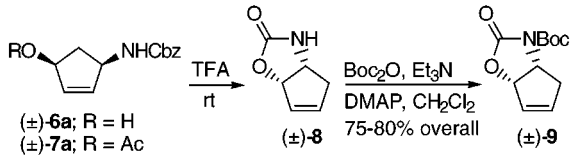
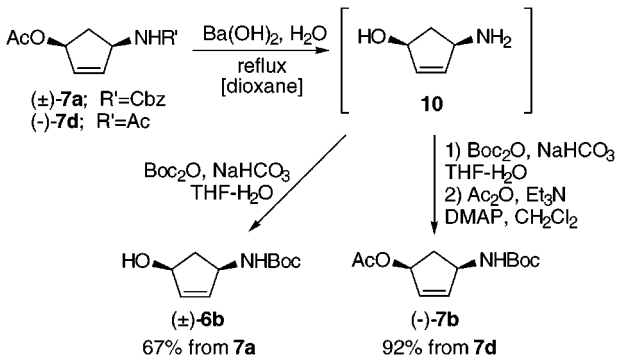
(20) Acetate (±)-**7a** was subjected to EEAC in aqueous buffer; apparently, insolubility of the substrate prevented hydrolysis from occurring even after addition of 10% MeOH or 10% EtOH (4 days reaction time).

Scheme 5



Scheme 6



compatible with the alkene moiety. Several methods appeared to be compatible with both esters and alkenes, but suitability of these methods for an allylic acetate moiety was unknown. It was found that all three of the reaction conditions tested (TMSI/CH_3CN/0−5 °C,[21] *B*-bromocatecholborane/CH_2Cl_2,[22] and TFA/rt) led to a rearranged oxazolidinone product **8**, although only TFA drove the reaction to completion (Scheme 5). Oxazolidinone **8** was immediately derivatized to Boc-carbamate **9** in 75−80% overall yield (via TFA). This rearrangement process to form **8** is equally successful with either alcohol **6a** or its acetate derivative **7a**. Oxazolidinones **8** and **9** have been previously reported by Muxworthy and co-workers.[23] Compound **8** was also produced by these authors via a rearrangement reaction (35% yield) but under basic conditions, therefore, presumably operating by a different mechanism.[24]

Although both Lewis and Brønsted acids were found to effect rearrangement of acetate (±)-**7a**, $Ba(OH)_2$ in H_2O/*p*-dioxane under refluxing conditions, conditions used to cleave *N*-acetamides,[25] was successful in removal of the *N*-benzyloxycarbamoyl protecting group of (±)-**7a**, as well as the *N*-acetamide of (−)-**7d** (Scheme 6). Without purification, the intermediate 4-aminocyclopent-2-enol (**10**) was reprotected with a Boc group to give alcohol (±)-**6b** in 67% yield from (±)-**7a**. Enantiomerically pure amino alcohol **10**, from (−)-**7d**, was also reprotected as the Boc-carbamate followed by subsequent *O*-acetylation to afford acetate (−)-**7b** in 92% yield for the three steps. Acetate (−)-**7b** may be more suitable for carbocyclic nucleoside syntheses that require a more easily removed *N*-protecting group, such as the Boc carbamate moiety, as well as provide an allylic acetate for Pd(0)-catalyzed[4c] nucleophilic additions. Alternatively, reaction of the enantiomerically pure intermediate amino alcohol **10**, from either (+)-**6d** or (−)-**7d**, with an appropriate heterocyclic moiety[26] would give direct entry to both D- and L-carbocyclic nucleoside syntheses.

Conclusions

cis-(±)-4-Aminocyclopent-2-enol derivatives were kinetically resolved by several enzymes to afford compounds of high enantiopurity. Selected enzymatic experiments based on literature precedence and broad screen testing of lipases were both useful approaches for the determination of appropriate biocatalysts. From these two approaches, amino alcohol (±)-**6a** was enantiomerically resolved to provide acetate (−)-**7a** in 90% and 92% ee with *C. antarctica B* and *Pseudomonas* sp., respectively. Also, acetate (±)-**7d** was enzymatically resolved with electric eel acetylcholinesterase to efficiently provide two enantiomerically pure *N*-acetyl cyclopentenol derivatives (+)-**6d** and (+)-**7d** as precursors in the enantiospecific syntheses of D- and L-carbocyclic nucleosides.

Experimental Section

General Methods. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 300, 75.4, and 282 MHz, respectively, in $CDCl_3$ unless otherwise noted. α,α,α-Trifluorotoluene was used as an internal standard for ^{19}F NMR and was defined as 0.0 ppm. In cases where both racemates and optically pure compounds were synthesized, the racemates were used for full characterization (excepting polarimetry data); all optically pure samples gave ^1H NMR spectra that matched that of racemates. The enzymes used in this study were obtained from the following sources and had the following activity: *Burkholderia* sp. lipase, Boehringer Mannheim, 225 U/mg; *C. antarctica B* lipase, Boehringer Mannheim, 130 U/mg; *Pseudomonas* sp. lipase, Sigma, 25 U/mg; electric eel acetylcholine esterase, Sigma, 263 U/mg. Instruments and general methods used have been described previously.[4a,27]

General Procedure for Cycloadduct N−O Bond Reduction. A 15:1 CH_3CN:H_2O solution of cycloadduct was charged with $Mo(CO)_6$ (1.1 equiv) and refluxed under Ar until the solution turned black. The heat was then removed and the solution allowed to cool to room temperature. $NaBH_4$ (1 equiv) was then added slowly (if the N-protecting group was a carbamate, $NaBH_4$ was not used), and the reaction was again refluxed. When complete as determined by TLC analysis, the mixture was concentrated in vacuo and the crude mixture was purified by column chromatography.

***N*-(Benzyloxycarbonyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene [(±)-5a].** This compound was prepared by a modified method as compared to that of Kirby et al.[28] *N*-(Benzyloxycarbonyl)hydroxylamine (1.02 g, 6.1 mmol) was dissolved in MeOH−H_2O (3:1, 40 mL) and cooled to 0−5 °C. Freshly distilled cyclopentadiene (1.4 mL, 17.4 mmol) and then $NaIO_4$

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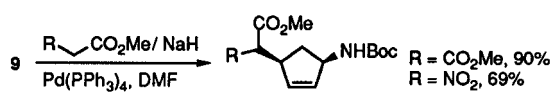
(23) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7539.

(24) Oxazolidinone **9** was reported[23] to undergo Pd(0) coupling with carbon nucleophiles ($MeCOCH_2Ts$). We also found that **9** underwent successful Pd(0) coupling with dimethyl malonate (90% yield) and methyl nitroacetate (69% yield) and in one case underwent coupling with Pd(II) (dimethyl malonate, 65% yield). Adenine coupling, however, was not successful under Pd(0)-coupling conditions, possibly indicative of the equilibrium between the closed and open forms of the urethane. This equilibrium has been previously reported with lactone substrates: Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192.



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(1.26 g, 5.9 mmol) were added, and the reaction was allowed to warm to room temperature and stirred 2 h. The reaction was cooled to 0−5 °C, more cyclopentadiene (1 mL, 12.5 mmol) and $NaIO_4$ (0.76 g, 3.5 mmol) were added, and the mixture was stirred for 30 min. The mixture was concentrated in vacuo to a slurry, H_2O was added, and the solution was extracted with EtOAc. The combined organic layers were washed with saturated sodium thiosulfate, H_2O, and brine, dried over $MgSO_4$, vacuum-filtered through Celite, and concentrated in vacuo to a tan oil. Spectral data of the crude material was consistent with that reported in the literature.[28] This material was used in the next reaction without further purification.

***cis*-*N*-(Benzylcarbamoyl)-4-aminocyclopent-2-enol [(±)-6a].** Cycloadduct (±)-**5a** was dissolved in MeCN−H_2O (15:1, 40 mL); $Mo(CO)_6$ (1.95 g, 7.4 mmol) was added, and the mixture was refluxed for 2 h. The reaction mixture was then concentrated in vacuo to a brown sludge, which was taken up in EtOAc, dried over $MgSO_4$, vacuum-filtered through Celite/silica, and concentrated in vacuo. Column chromatography (0−90% EtOAc−hexanes) provided 0.582 g of a white powder in 41% yield for two steps: ^{1}H NMR δ 1.55 (dt, J = 3.3, 14.4, 1H), 2.72 (dt, J = 8.1, 14.4, 1H), 3.07 (d, J = 6.6, 1H), 4.49 (broad m, 1H), 4.67 (broad m, 1H), 5.07 (s, 2H), 5.22 (d, J = 8.4, 1H), 5.83 (dt, J = 0.9, 5.4, 1H), 5.98 (d, J = 5.4), 7.30−7.36 (m, 5H); ^{13}C NMR δ 41.09, 55.17, 66.65, 75.02, 128.04, 128.11, 128.48, 133.80, 136.29, 155.77; IR (KBr) cm^{-1} 3319, 3062, 3032, 2892, 1682; HRMS (FAB) calcd for $C_{13}H_{16}NO_3$ (M + 1) 234.1130, obsd 234.1107.

***N*-(Methylcarbamoyl)-2-oxo-3-azabicyclo[2.2.1]hept-5-ene [(±)-5c].** This compound was previously prepared by Keck et al., although spectral data were not reported.[29] NH_2-OH·HCl (5.22 g, 74.5 mmol) was dissolved in EtOH (60 mL) and H_2O (30 mL) and cooled in an ice−water bath. $NaHCO_3$ (6.26 g, 74.5 mmol) was added slowly, and after the mixture was stirred for 15 min, dimethylpyrocarbonate (8 mL, 74.5 mmol) was added. The reaction was refluxed for 3 h (solution became homogeneous) and then stirred overnight at room temperature. The pH of the reaction was then adjusted from 7 to 5.5 by addition of 15% HCl. MeOH (50 mL) and H_2O (10 mL) were added followed by the addition of freshly distilled cyclopentadiene (25 mL, 298.0 mmol). $NaIO_4$ (16.0 g, 74.5 mmol) was dissolved in a minimal amount of water (10 mL) and added to the reaction mixture. The reaction was complete in 30 min as indicated by TLC analysis. The mixture was concentrated in vacuo and the slurry taken up into water and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, vacuum-filtered through Celite, and concentrated in vacuo to afford a tannish oil. The product was not stable if heated during concentration. Column chromatography (50% EtOAc−hexanes) afforded 11.5 g of cycloadduct (±)-**5c** as a light tan oil in 99% yield. This material was used in the next reaction without further purification: ^{1}H NMR δ 1.79 (d, J = 8.7 Hz, 1H), 2.03 (dt, J = 2.1, 8.7 Hz, 1H), 3.75 (s, 3H), 5.05 (s, 1H), 6.42 (m, 1H), 6.47 (m, 1H); HRMS (FAB) calcd for $C_7H_{10}NO_3$ (M + 1) 156.0661, obsd 156.0657.

***cis*-*N*-(Methylcarbamoyl)-4-aminocyclopent-2-enol [(±)-6c].** Cycloadduct (±)-**5c** was converted to the alcohol following the general procedure for N−O bond reduction. Cycloadduct (±)-**5c** (1.0 g, 6.45 mmol) was reduced [$Mo(CO)_6$ (2.04 g, 7.74 mmol), CH_3CN (20 mL), H_2O (1 mL)]; column chromatography (2−4% MeOH−CH_2Cl_2) afforded 800 mg of aminocylcopentenol (±)-**6c** as a yelow oil in 80% yield: ^{1}H NMR δ 1.56 (m, 1H), 2.74 (ddd, J = 7.5, 8.1, 14.4 Hz, 1H), 3.07 (bs, 1H), 3.66 (s, 3H), 4.48 (m, 1H), 4.69 (m, 1H), 5.16 (bs, 1H), 5.84 (m, 1H), 6.00 (m, 1H); ^{13}C NMR δ 40.87, 51.90, 54.90, 74.76, 133.76, 136.02, 156.46; IR (neat) cm^{-1} 3336, 3064, 2951, 1700, 1540; HRMS (FAB) calcd for $C_7H_{12}NO_3$ (M + 1) 158.0817, obsd 158.0829.

***N*-Acetyl-2-oxo-3-azabicyclo[2.2.1]hept-5-ene [(±)-5d].** This compound was prepared by a synthetic route different from that of Corrie[30] and Ranganathan et al.[31] NH_2OH·HCl (5.0 g, 72.0 mmol) was dissolved in EtOH (120 mL) and H_2O (60 mL) and cooled in an ice−water bath. $NaHCO_3$ (12.1 g, 144 mmol) was added slowly, and after the mixture was stirred for 15 min, Ac_2O (6.8 mL, 72.0 mmol) was added. The reaction was refluxed for 3 h (solution became homogeneous) and then stirred overnight at room temperature. The pH of the reaction was then adjusted from 7 to 5.5 by addition of 15% HCl. MeOH (150 mL) and H_2O (30 mL) were added followed by the addition of freshly distilled cyclopentadiene (28 mL, 350.0 mmol). $NaIO_4$ (15.0 g, 70 mmol) was dissolved in a minimal amount of water (50 mL) and added to the reaction mixture. The reaction was complete in 30 min as indicated by TLC analysis. The mixture was concentrated in vacuo and the slurry taken up into water and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, vacuum-filtered through Celite, and concentrated in vacuo to afford a light tan oil. The product was not stable if heated during concentration. Column chromatography (50% EtOAc−hexanes) afforded 9.7 g of cycloadduct (±)-**5d** as a light tan oil in 99% yield. This material was used in the next reaction without further purification: ^{1}H NMR δ 1.83 (bs, 1H), 1.86 (s, 1H), 1.98 (s, 3H), 5.28 (bs, 1H), 5.34 (bs, 1H), 6.37 (bs, 1H), 6.57 (bs, 1H); HRMS (FAB) calcd for $C_7H_{10}NO_2$ (M + 1) 140.0712, obsd 140.0697.

***cis*-*N*-Acetyl-4-aminocyclopent-2-enol [(±)-6d].** Cycloadduct (±)-**5d** was converted to the alcohol following the general procedure for N−O bond reduction. Cycloadduct (±)-**5d** (1.0 g, 7.2 mmol) was reduced [$Mo(CO)_6$ (2.28 g, 8.64 mmol), $NaBH_4$ (0.272 g, 7.2 mmol)]; column chromatography (2−8% MeOH−CH_2Cl_2) afforded 870 mg of aminocylcopentenol (±)-**6d** as a yelow oil in 92% yield: ^{1}H NMR δ 1.56 (ddd, J = 3.3, 3.3, 14.4 Hz, 1H), 1.96 (s, 3H), 2.71 (ddd, J = 7.5, 8.1, 14.4 Hz, 1H), 3.45 (bs, 1H), 4.72 (m, 2H), 5.83 (dd, J = 1.5, 5.6 Hz, 1H), 6.01 (m, 1H), 6.23 (bs, 1H); ^{13}C NMR δ 23.33, 40.83, 53.52, 74.97, 133.57, 136.47, 169.98; IR (neat) cm^{-1} 3296, 3011, 1635; HRMS (FAB) calcd for $C_7H_{12}NO_2$ (M + 1) 142.0868, obsd 142.0882. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.39; H, 7.81; N, 9.90.

General Procedure for Acetylation of *N*-Protected Aminocyclopentenols. A CH_2Cl_2 solution of aminocyclopentenol was charged with pyridine or triethylamine (6 equiv), Ac_2O (5 equiv), and (dimethylamino)pyridine (DMAP, 0.05 equiv) and stirred overnight under Ar at room temperature. For water-insoluble products [(±)-**7a** and (±)-**7b**], the reaction mixture was concentrated in vacuo, taken up in EtOAc, washed with dilute aqueous HCl, H_2O, and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, vacuum-filtered through Celite, and concentrated in vacuo to give the crude product. For water-soluble products [(±)-**7c** and (±)-**7d**], the reaction mixture was diluted with EtOAc and washed with 15% HCl until no pyridine remained. The combined aqueous layers were saturated with NaCl and back-extracted with EtOAc to remove any product. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The products were then purified as stated.

***cis*-*N*-(Benzylcarbamoyl)-4-aminocyclopent-2-enol 1-*O*-Acetate [(±)-7a].** To provide a standard for enzymatic assays; following the general procedure for acetylation, alcohol (±)-**6a** (0.327 g, 1.4 mmol) was acetylated [Ac_2O (0.16 mL, 1.7 mmol), triethylamine (1 mL, 7.2 mmol), DMAP (∼2 mg)] to give 0.43 g of a pale yellow solid in quantitative yield: ^{1}H NMR δ 1.56 (dt, J = 4.2, 15, 1H), 2.02 (s, 3H), 2.82 (overlapping dt, J = 7.8, 14.4, 1H), 4.73 (br s, 1H), 5.02 (d, J = 8.4, 1H), 5.10 (s, 2H), 5.51−5.53 (m, 1H), 5.94 (d, J = 5.7, 1H), 5.98 (d, J = 5.7, 1H), 7.27−7.36 (s, 5H); ^{13}C NMR δ 21.10, 38.46, 54.81, 66.79, 77.32, 128.16, 128.50, 132.46, 136.61, 136.53, 155.42, 170.53; IR (KBr) cm^{-1} 3315, 3068, 3037, 2953, 1734, 1687; HRMS (FAB) calcd for $C_{15}H_{17}NO_4$ (M + 1) 276.1236, obsd 276.1239.

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***cis-N*-(Methylcarbamoyl)-4-aminocyclopent-2-enol 1-*O*-Acetate [(±)-7c].** Following the general procedure for acetylation, alcohol (±)-**6c** (0.370 g, 2.36 mmol) was acetylated [Ac_2O (0.67 mL, 7.08 mmol), pyridine (0.76 mL, 9.44 mmol), DMAP (5 mg, 0.0460]; column chromatography (60% hexanes−EtOAc) afforded 471 mg (quantitative) of methyl carbamate (±)-**7c** as a white solid (recrystallized from EtOAc−hexanes): mp 62−63 °C; ^{1}H NMR δ 1.53 (ddd, J = 4.2, 4.2, 14.7 Hz, 1H), 2.05 (s, 3H), 2.82 (m, 1H), 3.68 (s, 3H), 4.75 (bs, 2H), 5.54 (m, 1H), 5.98 (m, 1H); ^{13}C NMR δ 21.05, 38.46, 52.04, 54.74, 77.29, 132.34, 136.54, 156.10, 170.49; IR (KBr) cm^{-1} 2952, 1726, 1530; HRMS (FAB) calcd for $C_9H_{14}NO_4$ (M + 1) 200.0923, obsd 200.0923.

***cis-N*-Acetyl-4-aminocyclopent-2-enol 1-*O*-Acetate [(±)-7d].** Following the general procedure for acetylation, alcohol (±)-**6d** (0.550 g, 3.9 mmol) was acetylated [Ac_2O (1.84 mL, 19.5 mmol), pyridine (1.9 mL, 23.4 mmol), DMAP (5 mg, 0.046 mmol)]; column chromatography (80% EtOAc−hexanes) afforded 700 mg of acetamide (±)-**7d** as a white solid in 98% yield (recrystallized from EtOAc−hexanes): mp 103−104 °C; ^{1}H NMR δ 1.53 (ddd, 3.9, 3.9, 14.7 Hz, 1H), 2.84 (ddd, J = 7.8, 7.8, 14.7 Hz, 1H), 1.99 (s, 3H), 2.05 (s, 3H), 4.98 (m, 1H), 5.55 (m, 1H), 5.66 (bs, 1H), 5.99 (m, 2H); ^{13}C NMR δ 21.08, 23.17, 38.16, 52.88, 77.49, 132.42, 136.48, 169.25, 170.44; IR (KBr) cm^{-1} 3438, 2986, 1732, 1666, 1509; HRMS (FAB) calcd for $C_9H_{14}NO_3$ (M + 1) 184.0974, obsd 184.0974.

Enzyme Screening of (±)-6a with Altus ChiroScreen-TE Kit. The directions contained within the kit were followed.

General Procedure for Enzymatic Resolutions by Acetylation. The alcohol to be kinetically resolved was dissolved in the appropriate solvent; the enzyme and the acetylation reagent were added. The flask was sealed, and the mixture was stirred at room temperature with initial qualitative monitoring by TLC and quantitative monitoring by ^{1}H NMR or by HPLC. After the % conversion reported, the reaction was filtered through silica to remove the enzyme and concentrated in vacuo.

General Procedure for Chemical Solvolysis of Acetates. Acetate (0.04 mmol) was dissolved in MeOH (∼2 mL), and K_2CO_3 (∼5 mg) was added. The reaction was stirred at room temperature for 3.5 h, at which time no starting material remained as determined by TLC. The reaction mixture was concentrated in vacuo, taken up in 10% MeOH−$CHCl_3$ (EtOAc for less polar saponification products), and washed with H_2O and brine. The solution was dried over $MgSO_4$, vacuum-filtered through Celite, and concentrated in vacuo.

General Procedure for Synthesis of Mosher Esters. The alcohol (0.038 mmol, crude) was placed in a flask, purged with Ar, and then dissolved in CH_2Cl_2 (dry, 2 mL). DMAP (15 mg, 0.12 mmol) and (*S*)-(+)-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.010 mL, 0.05 mmol) were added, and the reaction was stirred for 30 min at room temperature. TLC analysis indicated that no starting material remained. The mixture was concentrated in vacuo, and the residue was taken up in EtOAc, washed with H_2O and saturated $NaHCO_3$, dried over $MgSO_4$, vacuum-filtered through Celite, and concentrated in vacuo.

Enzymatic Resolution of Alcohol (±)-6a by Acetylation. (1) Alcohol (±)-**6a** (28.2 mg, 0.12 mmol) was reacted in CH_2Cl_2 (0.5 mL) with *C. antarctica B* lipase (5.2 mg) and vinyl acetate (0.04 mL, 0.43 mmol) with monitoring by HPLC (8% *i*-PrOH−hexanes; t_R acetate = 2.8 min; t_R alcohol = 5.1 min). The reaction was terminated after 31 h and 39% conversion. Preparative radial chromatography (25−75% EtOAc−hexanes) provided acetate (−)-**7a** (9.1 mg), $[\alpha]^{22}_D = -9.7$ (*c* 0.33, $CHCl_3$). The hydrolysis product (K_2CO_3/MeOH) was purified by column chromatography (25−75% EtOAc−hexanes), $[\alpha]^{24}_D = +64.9$ (*c* 0.205, $CHCl_3$). The Mosher ester was synthesized and analyzed by HPLC; 1% *i*−PrOH-hexanes t_R = 14.48 min (major), t_R = 14.87 (minor); major/minor 21:1 or 90% ee. These peaks matched that of the Mosher ester made from a racemic sample of alcohol (±)-**6a** and (*S*)-(+)-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.

(2) Alcohol (±)-**6a** (75 mg, 0.374 mmol) was reacted in CH_2Cl_2 (1.0 mL) with *Pseudomonas* sp. lipase (8 mg) and vinyl acetate (0.125 mL, 1.36 mmol) with monitoring by HPLC (see above conditions). The reaction was terminated after 6 h and 40% conversion. Column chromatography (20−33% EtOAc−hexanes) provided 40 mg of pure acetate. The acetate was hydrolyzed and the Mosher ester synthesized and analyzed by HPLC (as above); major/minor 23:1 or 92% ee.

Enzyme Screening of (±)-6b with Boehringer Lipase Kit. The amounts of enzymes used in this experiment are as follows: (L-1) 6.7 mg, (L-2) 2.9 mg, (L-3) 13.4 mg, (L-4) 4.1 mg, (L-5) 8.5 mg, (L-6) 7.2 mg, (L-7) 18 mg, (L-8) 38 mg. Each enzyme was added to a 20 mL scintillation vial containing a stir bar. Alcohol (±)-**6b** (53 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (17 mL); 2 mL of this solution was added to each vial (0.03 mmol of alcohol per vial). Isopropenyl acetate (2 drops) was added to each vial. The vials were capped and magnetically stirred at room temperature. The reactions were monitored at 1, 11, 18.5, and 35 h by TLC (50% EtOAc−hexanes) with comparison to an authentic sample of the racemic product. *Burkholderia* sp. (L-1) and *C. antarctica B* (L-2) lipases were found to produce significant amounts of acetylated products after 18.5−36 h.

Enzymatic Resolution of Alcohol (±)-6b by Acetylation. (1) Alcohol (±)-**6b** (62 mg, 0.314 mmol) was acetylated in MTBE (2.5 mL) with *Burkholderia* sp. lipase (9.3 mg) and isopropenyl acetate (0.14 mL, 1.27 mmol) with monitoring by ^{1}H NMR. The reaction was terminated after 5.3 h and 39% conversion. Preparative radial chromatography with 50% EtOAc−hexanes provided 23.1 mg of pure acetate (more acetate also isolated as a mixture), $[\alpha]^{23}_D = -14.94$ (*c* 0.46, $CHCl_3$). The acetate was hydrolyzed and the Mosher ester synthesized: ^{19}F NMR δ −8.82 (s), −8.76 (s); 3.47:1 ratio; therefore, 77.6% pure or 55% ee. These peaks matched that of the Mosher ester made from a racemic sample of alcohol (±)-**6b** and (*S*)-(+)-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

(2) Alcohol (±)-**6b** (47.1 mg, 0.24 mmol) was acetylated in MTBE (1.5 mL) with *C. antarctica B* lipase (9.7 mg) and isopropenyl acetate (0.15 mL, 1.4 mmol) with monitoring by ^{1}H NMR. The reaction was terminated after 21 h and 40% conversion. Preparative radial chromatography (35−50% EtOAc−hexanes) provided 19.9 mg of pure acetate, $[\alpha]^{22}_D = -22.6$ (*c* 0.40, $CHCl_3$). The acetate was hydrolyzed and the Mosher ester was synthesized: ^{19}F NMR δ −8.82 (s), −8.76 (s); 9.5:1 ratio; therefore, 81% ee.

Hydrolytic Enzymatic Resolution of (±)-6c. Methyl carbamate (±)-**6c** (0.163 g, 0.82 mmol) was dissolved in MeOH (minimum amount) and hydrolyzed with EEAC (250 units) in NaH_2PO_4 buffer solution.[32] After 3.5 h (50% conversion by HPLC) the reaction was terminated by removal of the solvent. The remaining slurry was extracted with 2:1 MeOH−EtOAc. The organic layers were combined and concentrated to a white solid. Column chromatography (5−8% MeOH−CH_2Cl_2) afforded 0.65 g (49%) of alcohol (+)-**6c** and 0.75 g (45%) of acetate (+)-**7c**. Alcohol **6c**: $[\alpha]^{22}_D = +66.4$ (*c* 0.13, $CHCl_3$). Acetate **7c**: $[\alpha]^{24}_D = +50.0$ (*c* 0.24, $CHCl_3$). Mosher ester analysis of (+)-**6c** was conducted by ^{19}F NMR: δ −8.73 (s), −8.78 (s); 6.14:1 ratio; therefore, 72% ee. These peaks matched that of the Mosher ester made from a racemic sample of alcohol (±)-**6c** and (*S*)-(+)-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

Hydrolytic Enzymatic Resolution of (±)-7d. Acetate (±)-**7d** (3.40 g, 18.56 mmol) was dissolved in MeOH (minimum amount) and hydrolyzed with electric eel acetylcholinesterase (500 units) in NaH_2PO_4 buffer solution.[32] After 49 h (40% conversion by HPLC), the reaction was concentrated to a slurry. The remaining slurry was extracted with 2:1 MeOH−EtOAc. The organic layers were combined and concentrated to a white solid. Column chromatography (5−8% MeOH−CH_2-

(32) The buffer was prepared by dissolution of 100 g of sodium dihydrogen phosphate monohydrate into 200 mL of distilled water. The pH of the solution was adjusted to 6.9 with the addition of concentrated sodium hydroxide solution, and then the solution was diluted to a final volume of 500 mL.

Cl_2) afforded 1.0 g of alcohol (+)-**6d** and 2.06 g of enantiomerically enriched acetate (+)-**7d**: $[\alpha]^{22}_D = +25.66$ (*c* 0.38, $CHCl_3$).

Enantiomerically enriched acetate **7d** (2.0 g, 10.92 mmol) was subjected to the same conditions (25 mL 1.45 M NaH_2PO_4 buffer, 38 mL H_2O, 1000 units EEAC, and 5 mg NaN_3) for 7 h (20% conversion). The reaction was worked up and chromatographed as described above to afford 1.60 g of diacetate (+)-**7d** and 0.30 g of (±)-**6d**. Alcohol (+)-**6d**: Mosher ester analysis of (+)-**6d**: ^{19}F NMR δ −8.24 (s), −8.11 (s); 96:4 ratio; therefore, 92% ee. These peaks matched that of the Mosher ester made from a racemic sample of alcohol (±)-**6d** and (*S*)-(+)-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Acetate (+)-**7d** was solvolyzed (MeOH, K_2CO_3) to alcohol (−)-**6d**, $[\alpha]^{24}_D = -90.0$ (*c* 0.10, $CHCl_3$). Alcohol (−)-**6d** was converted to its Mosher ester: ^{19}F NMR δ −8.12 (s), −8.24 (s); 96:4 ratio; therefore, 92% ee. Alcohol (−)-**6d** was recrystallized (EtOAc/hexanes) and then converted to its Mosher ester. ^{19}F NMR analysis of the Mosher ester indicated >99% purity of a single isomer; therefore, 99% ee.

1-(*tert*-Butylcarbamoyl)cyclopent-4-eno-*syn*-3a,6a-oxazolidin-2-one (9). Alcohol (±)-**6a** (1.13 g, 4.8 mmol) was dissolved in trifluoroacetic acid (10−12 mL). The reaction evolved a slight amount of heat during which time it was briefly cooled and the reaction turned dark brown. After being stirred at room temperature for 30 min, no starting material remained as determined by TLC (50% hexanes−EtOAc). Toluene−EtOAc (1:1) was added, and the mixture was concentrated in vacuo. This procedure was repeated several times. The crude, brown oil was stored at 0 °C overnight. Crystallization of a portion of oxazolidinone **8** occurred, giving colorless crystals that were collected on a Hirsch funnel and rinsed with toluene−hexanes, mp 118−121 °C. These crystals were recombined with the crude oil and taken on to the next synthetic step.

The crude oxazolidinone **8** was dissolved in CH_2Cl_2 (dry, ∼40 mL) under Ar. Triethylamine (∼3 mL) was added, and the mixture was cooled over an ice bath. Boc_2O (1.6 g, 7.3 mmol) and DMAP (∼5 mg) were added, and then the mixture was allowed to warm to room temperature. After 3.5 h, starting material remained as determined by TLC (100% EtOAc). Triethylamine (1.5 mL) was added, and the mixture was stirred for 22 h; TLC indicated that starting material still remained. Boc_2O (1.65 g, 7.6 mmol) was added, and the reaction was stirred at room temperature for an additional 22.5 h. The mixture was then concentrated in vacuo. The residue was taken up in EtOAc and washed with saturated aqueous $NaHCO_3$, water, and brine. The solution was dried over $MgSO_4$, vacuum filtered through Celite and silica, and concentrated in vacuo to a brown oil. Column chromatography (0−75% EtOAc−hexanes) provided 0.803 g of a light yellow solid in 76% overall yield: ^{1}H NMR δ 1.40 (br s, 10H), 2.49 (d of quintets, J = 2.4, 18.3, 1H), 2.77 (ddt, J = 2.4, 6.9, 18.6, 1H), 4.63 (t, J = 8.0, 1H), 5.27 (d, J = 8.1, 1H), 5.69−5.74 (m, 1H), 5.98 (dd, J = 2.1, 5.7, 1H); ^{13}C NMR δ 27.52, 40.11, 55.86, 81.13, 83.13, 127.26, 136.37, 148.89, 151.54; IR (KBr) cm^{-1} 3005, 2976, 2937, 1814, 1710; HRMS (FAB) calcd for $C_{11}H_{16}NO_4$ (M + 1) 226.1079, obsd 226.1098.

***cis*-*N*-(*tert*-Butylcarbamoyl)-4-aminocyclopent-2-enol [(±)-6b] from (±)-7a.** Acetate (±)-**7a** (0.35 g, 1.27 mmol) was dissolved in *p*-dioxane−H_2O (1:1, 24 mL) and Ba$(OH)_2$·$8H_2O$ (1.5 g, 4.8 mmol) was added. The mixture was refluxed for 55 h and then cooled to room temperature. The reaction was neutralized with solid CO_2 to pH 6−7 and then gravity-filtered and concentrated in vacuo to an oil. The oil was taken up in absolute EtOH, gravity-filtered, and concentrated in vacuo.

The crude 4-aminocyclopent-2-enol was dissolved in THF (20 mL) and then $NaHCO_3$ (0.26 g, 3.8 mmol) and Boc_2O (0.45 g, 2.1 mmol) were added and the mixture was stirred at room temperature for 9 h. More $NaHCO_3$ (0.2 g, 2.9 mmol) and Boc_2O (0.28 g, 1.3 mmol) were added, and the mixture was stirred for an additional 3 h. The mixture was concentrated in vacuo, taken up in EtOAc, and washed with saturated aqueous NH_4Cl, H_2O, saturated aqueous $NaHCO_3$, and brine. The solution was dried over $MgSO_4$, vacuum-filtered through Celite/silica, and concentrated in vacuo. Preparative radial chromatography gave 0.14 g of (±)-**6b** in 67% yield based on recovered starting material [(±)-**7a**]; 57 mg. Spectral data were consistent with literature values.[4b]

***cis*-*N*-(*tert*-Butylcarbamoyl)-4-aminocyclopent-2-enol 1-*O*-Acetate [(−)-7b] from (−)-7d.** Acetamide (−)-**7d** (0.814 g, 4.44 mmol) was dissolved in saturated aqueous Ba$(OH)_2$ (37 mL) and refluxed for 26.5 h. The reaction was then worked up as above. The crude 4-aminocyclopentenol was protected with an *N*-Boc group as above for (±)-**6b** from (±)-**7a**. Acetylation according to the general procedure described above followed by column chromatography (0−40% EtOAc−hexanes) gave 0.9805 g of a white solid in 92% yield. Spectral data were consistent with literature values,[6a] $[\alpha]^{23}_D = -16.7$ (*c* 0.59, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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