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Chiral induction in cyclopentyl-derived 1,3-*meso*-diesters: enantioselective hydrolyses with electric eel acetylcholinesterase

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Abstract

Eight 1,3-*meso*-diesters derived from a common cyclopentyl backbone were exposed to the hydrolase enzyme acetylcholinesterase from *Electrophorus electricus*. All eight compounds were hydrolyzed by the enzyme. The overall enantioselectivities were quite high, and the resulting e.e.s were generally >90%. The absolute configurations of the product monoesters were determined through stereochemical correlation. These data revealed that the preferred site for enzymatic hydrolysis in seven of the substrates was the *pro-S* ester function, with *pro-R* cleavage detected in the eighth.

1. Introduction

Enantiomerically pure cyclopentanoids are important building blocks for the preparation of biologically active molecules such as prostaglandins and carbocyclic nucleosides. Recently, we described[1] the formal synthesis of the carbocyclic nucleoside (−)-aristeromycin from the optically active starting material (1*R*,4*S*)-(+)-4-hydroxycyclopent-2-enyl acetate ((+)-**2**), a cyclopentanoid that shares the same absolute configuration found in natural nucleosides. A search for an efficient synthetic route to (+)-**2** led us to the discovery that the enzyme acetylcholinesterase from *Electrophorus electricus* (electric eel; EeAChE) could differentiate enantiotopically between *pro-R* and *pro-S* acetoxy groups on *meso*-diester **1** to afford chiral (*S*)-hydroxy ester **2** with a selectivity of 96% e.e. (>99% e.e. after one recrystallization)

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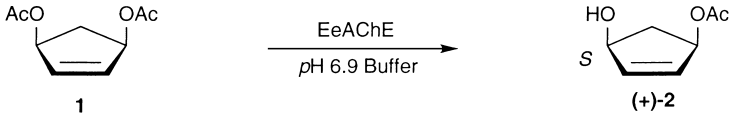
and a chemical yield of 94% (Scheme 1).[2] This enantioselective hydrolysis has been carried out on a 10 gram scale without difficulty.[3]



Scheme 1.

Since our inaugural work on this system, others have also reported successful chiral inductions with EeAChE on different *meso*-diester substrates.[4–8] In each case, the researchers found that EeAChE posted impressive enantioselectivities that ranged from 92 to 100% e.e. These findings have prompted us to explore further the scope and limitations of using EeAChE for the preparation of chiral, nonracemic cyclopentanoids. Herein, we report on the remarkable substrate enantioselectivity that EeAChE exhibits toward a series of structurally related *meso*-diesters derived from 1,3-cyclopentanediols. Enzyme enantioselectivity was also measured against structural variations in the acyl moieties. Details of the enzyme's substrate specificities and stereoselectivities gleaned from this study may eventually prove useful in the development of an experimental active-site model of predictive merit.

2. Results and discussion

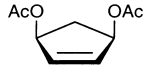
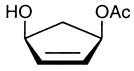
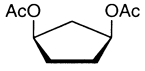
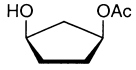
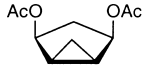
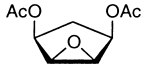
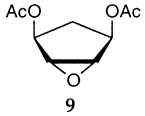
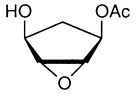
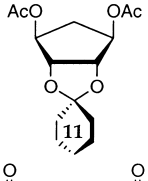
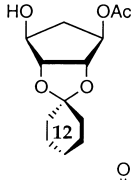
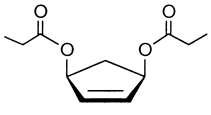
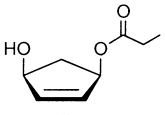
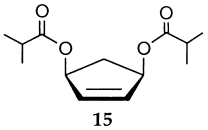
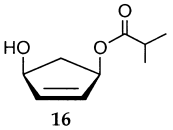
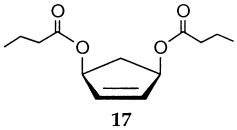
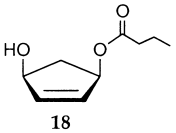
2.1. Substrate preparation

Table 1 illustrates the structurally related series of cyclopentanoid 1,3-*meso*-diester substrates used in this study. With the exception of diacetates **3** and **11**, all *cis*-diester substrates were constructed from their monoprotected racemic counterparts using standard acylation technology. Accordingly, the unsaturated hydroxyesters **2**, **14**, **16**, and **18**, precursors to *meso*-diesters **1**, **13**, **15**, and **17**, respectively, were conveniently prepared in a single step via the palladium-catalyzed reaction between cyclopentadiene monoepoxide and the appropriate carboxylic acid.[9,10]

Monoacetate **2** also served as the starting point for bicyclo-diesters **5**, **7**, and **9**. Hydroxyl-directed cyclopropanation of **2** via the Simmons–Smith reagent[11] yielded the expected β-cyclopropane monoacetate **6** which, upon acetylation with acetic anhydride in pyridine, produced the desired *meso*-diacetate **5**. β-Epoxy diacetate **7** was synthesized from **2** by a two-step procedure: stereoselective MCPBA epoxidation of the double bond[12] followed by acetylation. The preparation of the α-epoxy diacetate **9** necessitated that both hydroxyl functions be protected with the bulky *t*-butyldimethylsilyl group to discourage epoxidation from the β-face of the cyclopentanoid. Hence, the acetoxy group on **2** was hydrolyzed with K_2CO_3 in MeOH to give an intermediate *meso*-diol which was immediately disilylated with TBDMSCl. Epoxidation with purified MCPBA gave satisfactory yields of the required α-product.[12] Subsequent removal of the protecting groups with tetrabutylammonium fluoride (TBAF) and diacetylation with acetic anhydride and catalytic DMAP then afforded *meso*-diacetate **9**.

Finally, diacetates **3** and **11** were fashioned directly from the unsaturated diacetate **1**. Catalytic hydrogenation of **1** with 10% palladium on carbon provided the corresponding saturated diester **3** in useful yield. Alternatively, stereoselective osmylation of **1** followed by ketalization of the putative *cis*-diol with cyclohexanone and catalytic PTSA led to the desired spiral acetal **11**.

Table 1
Enantioselective hydrolysis of cyclopentanoid 1,3-*meso*-diesters with EeAChE

Entry	Substrate	Major Product	% Yield[a]	% e.e.[b]	Config.
1[c]	 **1**	 **2**	94	96[d]	*(S)* - OH
2	 **3**	 **4**	70 (86)	93	(S) - OH[e]
3	 **5**	 **6**	60 (74)	99	*(R)* - OH
4	 **7**	 **8**	72	67	*(S)* - OH
5	 **9**	 **10**	40 (96)	82	*(S)* - OH
6	 **11**	 **12**	61 (64)	80	*(S)* - OH
7	 **13**	 **14**	91	98	*(S)* - OH
8	 **15**	 **16**	48 (72)	>99	*(S)* - OH
9	 **17**	 **18**	49	97	*(S)* - OH

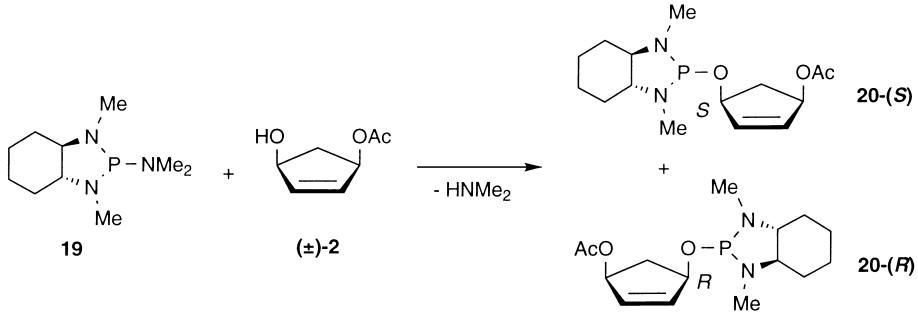
[a] Not Optimized. Numbers in parentheses are yields based upon recovered starting material.
[b] Determined by ^{31}P NMR measurement.
[c] Reference 2.
[d] Derivatized as Mosher's ester and determined by GC measurement.
[e] See Table 2, footnote c.

2.2. Enzymatic hydrolysis

Exposure of the sparingly water-soluble substrates to EeAChE in an aqueous pH 6.9 phosphate buffer initially afforded a two-phase system, but that gradually converged to a single phase as the diester was converted into the more soluble monohydroxy product. The hydrolyses were monitored by TLC. In most examples, hydrolysis of the second ester group was insignificant. The chiral hydroxyesters were isolated from the aqueous media via multiple extractions with an emulsion-suppressing solvent system consisting of 1:1 ether:ethyl acetate. The crude material was chromatographed over silica gel and fully characterized spectroscopically.

2.3. Determination of enantiomeric excess

Enantiomeric purities were determined by ^{31}P NMR measurements[13] on the diastereomeric pairs (e.g., 20-(*S*) and -(*R*)) generated from reaction of the chiral alcohols with optically active phosphorylating agent **19** (Scheme 2). The two phosphorus singlets that arise from the diastereomeric pairs have ^{31}P $\Delta\delta$ that range from 0.5 to 2.9 ppm and are thus easily resolved and integrated on high-field NMR spectrometers. The major advantage of this method is operational simplicity. The reaction and analysis are carried out directly in the NMR tube making isolation or purification of the derivatized alcohols unnecessary. All *meso*-diesters proved to be substrates for the enzyme and gave impressive enantioselectivities after hydrolysis (Table 1). The accuracy of the ^{31}P NMR technique was verified by comparison with the GC-analyzed e.e. value[2,3] for the Mosher-derived ester of (+)-**2**. A 1% margin of error was observed.



Scheme 2.

Interestingly, a correlation was found in this system between the relative ^{31}P absorption frequency of the derivatized chiral alcohols and the absolute configuration of the cyclopentanoid. In every example analyzed, the derivatized (*S*)-hydroxycyclopentanoids were found to adsorb at slightly higher field than their diastereomeric (*R*)-hydroxy counterparts (Table 2). This observation may prove valuable when assigning absolute configurations across a similar series of analogs.

2.4. Stereochemical correlations

The absolute configurations of the chiral monohydroxy esters were assigned through stereochemical correlation with the exception of α-epoxide **10**, which was deduced from comparison with the literature rotation.[12] The thoroughly documented[2] (1*R*,4*S*)-(+)-4-hydroxycyclopent-2-enyl acetate (+)-**2** served as the asymmetric benchmark upon which the absolute configurations for **4**, **6**, **8**, and **12** were based. Catalytic hydrogenation of (+)-**2** with 10% Pd on activated carbon cleanly afforded authentic (1*R*,3*S*)-(+)-3-hydroxycyclopentyl acetate (+)-**4**. (*S*)-Hydroxy acetates (+)-**6** and (+)-**8** were synthesized from (+)-**2**

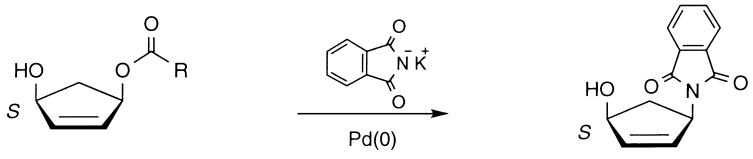
Table 2
Diastereomeric ^{31}P NMR absorption frequencies for the phosphorylated cyclopentanols used to determine enantiomeric purity[a,b]

Config.	2	4[c]	6	8	10	12	14	16	18
(S)-OH	**131.4**	**135.6**	133.6	**137.3**	**132.1**	**133.5**	**134.8**	**134.9**	**134.7**
(R)-OH	132.4	136.2	**135.4**	137.7	135.0	134.5	135.7	135.7	135.4

[a]In ppm.
[b]Emboldened values indicate the predominant enantiomer formed.
[c]The proper *R,S* -designation has been reversed in this example to maintain clarity and consistency. The enzymatically hydrolyzed acetoxy function in **4** is analogous to the site of hydrolysis in all the other *S*-hydroxyesters, yet the IUPAC convention would dictate that the opposing and misleading *R*-assignment be used.

as described earlier for their racemic analogs. Cyclohexylidene acetal (−)-**12** was prepared from (+)-**2** using the aforementioned osmylation–ketalization sequence.

The three unsaturated chiral esters **14**, **16**, and **18** were converted into the known[14] (+)-(1*S*,4*R*)-4-phthalimido-2-cyclopenten-1-ol **21** via a palladium-catalyzed allylic substitution reaction with potassium phthalimide (Scheme 3). This stereospecific substitution conserves the chirality of the stereocenter over the course of the reaction. In each case, the cyclopentylphthalimide **21** obtained rotated polarized light in the positive direction, which implies the (*S*)-arrangement about the hydroxyl function in esters **14**, **16**, and **18**.



14; R = Et
16; R = *i*-Pr
18; R = Pr

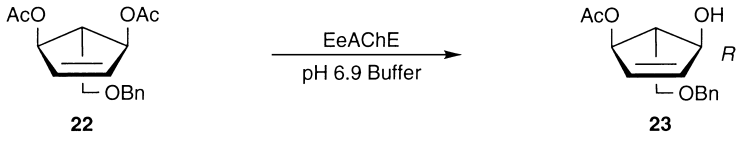
Scheme 3.

3. Conclusions

A few salient points have emerged from this study. Most startling is the singular reversal in enzyme stereoselectivity within the series of related cyclopentanoid analogs. Breach occurred when the cyclopentyl ring was symmetrically fused with a β-cyclopropyl functionality (entry 3). In this example, the *pro*-(*R*)-acetoxy group on **5** was preferentially hydrolyzed to supply the (*R*)-hydroxy enantiomer **6** in 99% e.e. This result is in sharp contrast to the skeletally analogous, yet more polar β-epoxy cyclopentane (entry 4) which yielded the (*S*)-hydroxy compound **8** predominantly, albeit with diminished selectivity (67% e.e.). These data suggest that polarity can influence the selection of opposing enantioselective pathways.

Still, this substrate-induced reversal in enzyme enantioselectivity on a cyclopentanoid is not an isolated event with EeAChE. Griffith and Danishefsky[6,15] experienced a similar outcome during their impressive synthetic study on the potent chitinase inhibitor allosamadin. They reported that desymmetrization of *meso*-diacetate **22** with EeAChE gave the unexpected (*R*)-hydroxy[16] product **23** in >95% e.e. (Scheme 4).

Since the substitution pattern on **22** is quite unlike those found on the substrates encountered in this study, it would be unwise to draw any conclusions based upon structural considerations. However, this is an area we plan to investigate in the future.



Scheme 4.

Also noteworthy is the finding that propionates, butyrates, and isobutyrates (entries 7, 8, and 9) also serve as substrates for this enzyme. Curiously, these three homologs induce slightly better enantioselectivities than the acetate group, the enzyme's evolutionary target. However, the larger ester moieties, especially the butyrates, suffered slower rates of enzymatic hydrolysis. For instance, the rate of monohydrolysis of dibutyrate **17** was in the order of days, while under identical conditions, diacetate **1** underwent the enzymatic hydrolysis in a matter of hours. This result was probably a manifestation of both the dibutyrate's decreased solubility in the aqueous buffer compared with the smaller, more polar acetoxy group and the spatial constraints imposed by the enzyme's acyl binding pocket. This latter point has been previously argued[17,18] to explain AChE's diminished activity towards butyrylcholine relative to the butyrylcholinesterase enzyme and is supported by site-specific mutagenesis and molecular modeling studies.

Finally, the enantioselectivities posted for **6**, **8**, and **10** (entries 3, 4, and 5) correlate with those obtained through Theil's[12] complementary approach of lipase-catalyzed transesterifications on *meso*-cyclopentane-1,3-diols. The three chiral monoacetates produced in this manner possessed absolute configurations opposite to those observed in the present study. Moreover, it was found that transesterifications across a range of substrate and lipase combinations always yielded (*R*)-hydroxy-enriched products except in the case of the β-cyclopropyl derivative **6**, which was formed preferentially in the (*S*)-hydroxy configuration. It is indeed curious that in both studies the cyclopropyl substrate was the sole outlier in an otherwise uniform stereochemical pattern of product formation.

4. Experimental

All non-aqueous reactions were carried in flame-dried glassware under a nitrogen atmosphere. The acetic, propionic, isobutyric, and butyric acids and their corresponding anhydrides were purchased from Aldrich Chemical Company. Tetrahydrofuran was distilled from a midnight blue sodium ketyl solution under nitrogen. Methylene chloride and pyridine were distilled from CaH_2 immediately prior to use. Chromatography solvents were purchased from VWR or Fischer and were used as received. Acetylcholinesterase (EeAChE, EC 3.1.1.7., 200 units/mg) was purchased from Sigma Chemical Company (C-3389) as a lyophilized powder. The 0.58 M NaH_2PO_4 buffer was prepared from sodium dihydrogen phosphate monohydrate obtained from Alpha Products (#307892) and adjusted to pH 6.9 with concentrated NaOH solution (MCB Reagent, SX0593-1).

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AC 200 or ARX 500 MHz spectrometers with $CDCl_3$ as solvent, except in the ^{31}P experiments where d_6-benzene was employed. Optical rotations were measured at 589 nm on a JASCO DIP-369 polarimeter with spectral grade solvents using a 1 mL capacity water-jacketed microcell connected to a constant temperature bath. FTIR spectra were obtained on NaCl plates with a Mattson 3050 Galaxy spectrometer operating at 10 scans and a resolution of 4 cm^{-1}. Preparative separations were performed by radial chromatography on a model 7924T Harrison

Research Chromatotron. Analytical TLC analyses were conducted on Baker Si 250 precoated glass plates (0.25 mm) and developed using either ethanolic *p*-anisaldehyde reagent or phosphomolybdic acid. New compounds were distilled bulb-to-bulb and submitted to UC Riverside Mass Spectrometry Facility for HRMS analysis. Sample homogeneity was verified by high signal-to-noise ^{13}C NMR spectra.

4.1. Preparation of cis-cyclopent-1,3-diyl diacetate **3**

A stirred suspension of 10% Pd on activated carbon (10 mg) and diacetate **1** (200 mg, 1.09 mmol) in 3.6 mL of absolute ethanol was cooled to −78°C and degassed (four times) under vacuum. The flask was fitted with a balloon containing hydrogen and allowed to return to room temperature. The reaction was quenched after two hours by passing the suspension through a plug of 1 g $MgSO_4$ and 2 g of SiO_2 with 25 mL of 1:1 hexane:ethyl acetate followed by 25 mL of ether. The filtrate was concentrated under vacuum and the residual oil was purified by SiO_2 radial chromatography with 3:1 hexane:ethyl acetate (R_f 0.25) to yield 38–61% of a colorless oil:[19] IR (film) 2979, 1739 (C=O), 1400, 1250, 1000 cm^{-1}; ^1H NMR (200 MHz) δ 5.07 (m, 2H), 2.31 (overlapping dt, *J*=15.4, 7.2 Hz, 1H), 2.01 (s, 6H), 1.70–1.95 (m, 5H); ^{13}C NMR δ 170.6, 74.6, 38.8, 30.6, 21.1.

4.2. Preparation of (±)-cis-3-hydroxycyclopentyl acetate **4**

The preparation of **4** was carried out as described for **3** substituting monoacetate **2** for the alkene substrate. Colorless oil:[20] IR (film) 3441 (br OH), 2971, 1725 (C=O), 1450, 1400, 1250, 1100 cm^{-1}; ^1H NMR (200 MHz) δ 5.12 (m, 1H), 4.29 (m, 1H), 2.13 (overlapping dt, *J*=14.9, 8.7 Hz, 1H), 2.01 (s, 3H), 1.89 (m, 5H); ^{13}C NMR δ 170.6, 75.7, 72.6, 41.9, 34.0, 30.6, 21.2; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 136.2 and 135.6.

4.3. Preparation of (1RS,2SR,4RS,5SR)-bicyclo[3.1.0]hex-2,4-diyl diacetate **5**

The preparation of **5** was carried out as described for **13** using **6** as the monohydroxy substrate and acetic anhydride as the acylating agent. The crude material was chromatographed over SiO_2 with 2:1 hexane:ethyl acetate (R_f 0.40) to yield 50% of a colorless oil:[12] IR (film) 2960, 1736 (C=O), 1400, 1362, 1250, 1238, 1021 cm^{-1}; ^1H NMR (200 MHz) δ 5.21 (dt, *J*=8.5, 3.4 Hz, 2H), 2.43 (overlapping dt, *J*=13.6, 8.0 Hz, 1H), 2.01 (s, 6H), 1.76 (m, 2H), 1.27 (overlapping dt, *J*=13.6, 8.8 Hz, 1H), 0.93 (m, 1H), 0.59 (m, 1H); ^{13}C NMR δ 170.9, 73.0, 30.2, 21.0, 20.1, 3.5.

4.4. Preparation of (1RS,2SR,4RS,5SR)-(±)-4-hydroxybicyclo[3.1.0]hex-2-yl acetate **6**

A stirred suspension of zinc–copper couple[21,22] (365 mg, 2.8 mmol), CH_2I_2 (114 μL, 1.41 mmol) in ether (1 mL) was heated to reflux for 15 min. A solution of **2** (100 mg, 0.70 mmol) dissolved in ether (0.5 mL) was then added to the flask in one portion. After 3 h, the reaction was quenched by the addition of sat. aq. NH_4Cl and then passed through a plug of Celite with 50 mL of ethyl acetate. The organic layer was washed successively with water (3×20 mL), sat. aq. $NaHCO_3$ (3×20 mL), water (3×10 mL), and brine (3×10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified over SiO_2 by radial chromatography using 2:3 hexane:ethyl acetate as the eluent (R_f 0.30) to yield 7–38% of a colorless oil:[12] IR (film) 3409 (br OH), 2928, 1729 (C=O), 1378, 1254, 1025 cm^{-1}; ^1H NMR (200 MHz) δ 5.15 (dt, *J*=8.4, 4.5 Hz, 1H), 4.46 (dt, *J*=8.2, 4.5 Hz, 1H), 2.32 (overlapping dt, *J*=13.3, 7.8 Hz, 1H), 2.01 (s, 3H), 1.70 (m, 2H), 1.17 (overlapping dt, *J*=13.4, 8.8 Hz,

1H), 0.92 (m, 1H), 0.54 (m, 1H); ^{13}C NMR δ 170.9, 73.2, 70.1, 33.0, 22.7, 20.9, 19.9, 2.2; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 135.4 and 133.6.

*4.5. Preparation of (1*RS,*2*SR,*4*RS,*5*SR*)-6-oxabicyclo[3.1.0]hex-2,4-diyl diacetate **7***

The preparation of **7** was carried out as described for **13** using **8** as the monohydroxy substrate and acetic anhydride as the acylating agent. Chromatographed over SiO_2 with 2:1 hexane:ethyl acetate (R_f 0.56, 1:1 hexane:ethyl acetate) to give a 70% yield of a white solid:[12] IR (KBr) 2925, 1732 (C=O), 1460, 1364, 1250, 1072, 1031 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.00 (t, *J*=8.2 Hz, 2H), 3.66 (s, 2H), 2.39 (overlapping dt, *J*=12.7, 7.9 Hz, 1H), 2.09 (s, 6H), 1.51 (overlapping dt, *J*=12.7, 8.6 Hz, 1H); ^{13}C NMR δ 170.4, 71.3, 54.7, 27.8, 20.6.

*4.6. Preparation of (1*RS,*2*SR,*4*RS,*5*RS*)-(±)-4-hydroxy-6-oxabicyclo[3.1.0]hex-2-yl acetate **8***

To an ice-cold stirred solution of **2** (48 mg, 0.341 mmol) in 10 mL of CH_2Cl_2 was added MCPBA (141 mg, 0.811 mmol) portionwise. The ice bath was removed and the reaction mixture was heated at reflux overnight. The solid material was removed from the reaction mixture by gravity filtration and rinsed with hexane (2×1 mL). The filtrate was washed sequentially with fresh sat. $Na_2S_2O_3$ (3×5 mL) and sat. $NaHCO_3$. The aqueous layers were then combined, treated with brine, and extracted with 1:1 ether:ethyl acetate (10×3 mL), then with pure ethyl acetate (20×3 mL) until TLC analysis showed no epoxide product remaining in the aqueous layer. The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was chromatographed over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.18) to give a 38% yield of a colorless oil:[12] IR (film) 3450 (br OH), 3057, 1734 (C=O), 1374, 1247, 1064, 1032 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.94 (dt, *J*=8.5, 1.4 Hz, 1H), 4.16 (br t, *J*=7.8 Hz, 1H), 3.64 (dd, *J*=2.9, 1.3 Hz, 1H), 3.54 (dd, *J*=2.9, 1.4 Hz, 1H), 2.35 (overlapping dt, *J*=12.8, 7.8 Hz, 1H), 2.10 (s, 3H), 1.34 (overlapping dt, *J*=12.8, 8.4 Hz, 1H); ^{13}C NMR δ 170.8, 71.8, 69.7, 57.3, 55.4, 31.0, 20.6; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 137.7 and 137.3.

*4.7. Preparation of (1*RS,*2*RS,*4*SR,*5*SR*)-6-oxabicyclo[3.1.0]hex-2,4-diyl diacetate **9***

The preparation of **9** is a modification of the procedure used by Theil et al.[12] To a stirred solution of **2** in methanol (7.1 mL) and ether (1.8 mL) was added K_2CO_3 (195 mg, 20 mol%). The hydrolysis reaction was monitored by TLC. After 4 h, the reaction mixture was passed through a plug of SiO_2 and $MgSO_4$ and then concentrated under vacuum to yield 644 mg of thick oil which was used without further purification. The crude diol was dissolved in CH_2Cl_2 (32.3 mL) and triethylamine (3.2 mL) and then treated with excess TBDMSCl (3.9 g, 25.8 mmol) and catalytic DMAP (78.8 mg, 10 mol%). The reaction proceeded for 1 h and was then quenched by addition of H_2O. The mixture was extracted with ether, washed with sat. $NaHCO_3$, and evaporated under aspirator pressure. The crude material was passed through a plug of SiO_2 and $MgSO_4$ with a solution of 40:1 hexanes:ethyl acetate. After removal of the solvent, 634 mg (30% yield) of reasonably pure *cis*-1,3-disilylated-4-cyclopentene remained behind and was judged satisfactory for the next epoxidation step. Dissolution of the TBDMS-diprotected diol (634 mg, 1.93 mmol) in CH_2Cl_2 (6.4 mL) was followed by the addition of freshly purified MCPBA (567 mg, 6.8 mmol) and $NaHCO_3$ (1.16 g, 6.8 mmol). The reaction proceeded for three days before being terminated by passing the mixture through an SiO_2–$MgSO_4$ plug with hexanes. The filtrate was concentrated under vacuum and the residual oil purified via radial chromatography over SiO_2 to yield 167.8 mg (25%) of the desired α-epoxy product and 162.1 mg (24.5%) of the diastereomeric β-epoxide:

R_f (35:1 hexanes:ethyl acetate) α-isomer=0.33; β-isomer=0.29. Deprotection of the hydroxyl groups was accomplished as follows: the α-epoxide (165 mg, 0.48 mmol) was dissolved in THF (0.5 mL) and subjected to the slow addition of 4 equiv. (2 mL) of 2 M tetrabutylammonium fluoride (TBAF) in THF. The reaction was complete in 5 min as visualized by TLC. Removal of the solvent and subsequent diacetylation of the crude diol with acetic anhydride provided, after chromatographic separation over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.59), a 57% yield of crystalline **9**:[12] IR (KBr) 2979, 2925, 2854, 1739 (C=O), 1427, 1376, 1239, 1077 cm^{-1}; ^1H NMR (200 MHz) δ 5.21 (br d, *J*=6.1 Hz, 2H), 3.62 (br s, 2H), 2.11 (dt, *J*=17.4, 6.1 Hz, 1H), 2.01 (s, 6H), 1.78 (d, *J*=17.4 Hz, 1H); ^{13}C NMR δ 170.2, 72.5, 56.6, 35.4, 20.9.

4.8. *Preparation of (1*RS,*2*RS,*4*SR,*5*RS*)-(±)-4-hydroxy-6-oxabicyclo[3.1.0]hex-2-yl acetate **10***

To a 10 mL flask was added diacetate **9** (40 mg, 0.2 mmol) in 5 mL of dry methanol. The flask was cooled in an ice bath and finely powdered K_2CO_3 was added in one portion. The stirred suspension was held at 0°C and monitored closely by TLC until the appearance of diol became evident (~13 min). The reaction mixture was immediately passed through a plug of SiO_2 with 10 mL of methanol. Excess solvent was removed under vacuum to give a yellowish oil. Purification of the monohydroxy compound was performed by radial chromatography over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.22) to give a 29% yield of a colorless oil:[12] IR (film) 3456 (br OH), 2953, 1736 (C=O), 1374, 1244, 1082 cm^{-1}; ^1H NMR (200 MHz) δ 5.19 (d, *J*=6.3 Hz, 1H), 4.30 (d, *J*=6.1 Hz, 1H), 3.59 (br d, *J*=7.3 Hz, 2H), 2.45 (br s, 1H), 2.03 (s, 3H), 2.00 (overlapping dt, *J*=15.5, 6.4 Hz, 1H), 1.68 (d, *J*=15.8 Hz, 1H); ^{13}C NMR δ 170.1, 73.3, 70.8, 58.3, 56.0, 37.7, 21.1; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 135.0 and 132.1.

4.9. *Preparation of (1*RS,*2*RS,*3*SR,*4*SR*)-2,3*-O-*cyclohexylidenecylopent-1,4-diyl diacetate **11***

To a 25 mL flask equipped with a glass-coated stir bar were added diacetate **1** (194 mg, 1.00 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (234 mg, 2.0 mmol), and 12.5 mL of an 8:1 acetone:water solution. Three millilitres of a 2% OsO_4 in water were added in one portion and the *cis*-hydroxylation reaction was allowed to proceed for 24 h at rt. The reaction was quenched by the addition of Na_2SO_3. The reaction mixture was passed through a 5×30 mm plug of SiO_2 with 100 mL of ether. The filtrate was concentrated under vacuum to give a semicrystalline oil which was used in the ketalization step without further purification. The crude diol was transferred to a dry 15 mL flask, dissolved in 1.86 mL (2 mmol) of freshly distilled cyclohexanone, and exposed to a small crystal of PTSA. The flask was heated at an oil-bath temperature of 75°C until TLC analysis indicated the starting material no longer remained (~20 h). The reaction mixture was passed through a plug of SiO_2 with ether and the solvent was removed under vacuum. The crude oil was purified over SiO_2 with 9:1 hexanes:ethyl acetate using radial chromatography to afford 82.4 mg (30% yield) of a colorless oil: R_f 0.6, 1:1 hexane:ethyl acetate; IR (film) 2938, 2861, 1740 (C=O), 1371, 1250, 1021 cm^{-1}; ^1H NMR (200 MHz) δ 5.06 (br dd, *J*=5.4, 1.2 Hz, 2H), 4.57 (d, *J*=1.6 Hz, 2H), 2.38 (dt, *J*=15.7, 5.4 Hz, 1H), 2.01 (s, 6H), 1.95 (dt, *J*=15.7, 1.24 Hz, 1H), 1.3–1.65 (m, 10H); ^{13}C NMR δ 169.7, 111.9, 83.8, 78.7, 36.2, 34.4, 33.5, 25.0, 23.8, 23.5, 20.9; HRMS (CI, NH_3) calcd for $C_{15}H_{23}O_6$ ($M+H^+$) 299.1495, found 299.1479.

4.10. Preparation of (1RS,2RS,3RS,4SR)-(±)-2,3-O-cyclohexylidene-4-hydroxycyclopentyl acetate **12**

The preparation of **12** was carried out as described for **11** substituting **2** as the alkene substrate. Colorless oil: R_f 0.28, 1:1 hexane:ethyl acetate; IR (film) 3449 (br OH), 2937, 1721 (C=O), 1371, 1250, 1021 cm^{-1}; ^1H NMR (200 MHz) δ 5.15 (d, *J*=5.3 Hz, 1H), 4.59 (m, 2H), 4.22 (m, 1H), 2.31 (dt, *J*=15.2, 5.2 Hz, 1H), 2.01 (s, 3H), 1.85 (br d, *J*=15.2 Hz, 1H), 1.65–1.3 (m, 10H); ^{13}C NMR δ 169.6, 111.5, 85.9, 83.8, 79.7, 36.4, 36.2, 33.4, 25.0, 23.8, 23.5, 21.0; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 134.5 and 133.5; HRMS (DCI, NH_3) calcd for $C_{13}H_{21}O_5$ ($M+H^+$) 257.1389, found 257.1379.

4.11. Preparation of cis-cyclopent-2-en-1,4-diyl dipropionate **13**

Into a dry 10 mL flask equipped with a magnetic stir bar was added (±)-*cis*-4-hydroxycyclopent-2-enyl propionate ((**14**) 74.9 mg, 0.749 mmol) and 0.5 mL of pyridine. The solution was cooled to 0°C with an ice-water bath. Following the dropwise addition of propionic anhydride (0.2 mL, 1.5 mmol) via syringe, the ice bath was removed and the reaction was monitored by TLC (2:1 hexane:ethyl acetate). After 24 h, the reaction mixture was recooled to 0°C, layered with ether, and quenched with ice water. The organic layer was washed consecutively with sat. $CuSO_4$ (three times), NH_4Cl (three times), and brine. The organic phase was then filtered through a plug comprised of $MgSO_4$ (1 g) and SiO_2 (2 g) with 25 mL of 1:1 hexane:ethyl acetate followed by 25 mL of ether. The solution was concentrated under vacuum and the crude oil chromatographed over SiO_2 using radial chromatography with 2:1 hexane:ethyl acetate (R_f 0.68) to give a 74% yield of a colorless oil:[23] IR (film) 2983, 1739 (C=O), 1351, 1353, 1190, 1081 cm^{-1}; ^1H NMR (200 MHz) δ 6.05 (s, 2H), 5.53 (dd, *J*=7.5, 3.9 Hz, 2H), 2.86 (overlapping dt, *J*=15.0, 7.5 Hz, 1H), 2.30 (q, *J*=7.5 Hz, 2H), 1.65 (dt, *J*=15.0, 3.8 Hz, 1H), 1.11 (t, *J*=7.5 Hz, 3H); ^{13}C NMR δ 173.9, 134.5, 76.9, 37.2, 27.5, 8.9.

4.12. Preparation of (±)-cis-4-hydroxycyclopent-2-enyl propionate **14**

Into a dry 25 mL flask equipped with a magnetic stir bar was added 6.25 mL of THF. The stirred solution was cooled in an ice-water bath and 1 mol% $Pd(PPh_3)_4$ was added in one portion. After dissolution of the catalyst, propionic acid (0.326 mL, 6.10 mmol) was added to the flask. This was immediately followed by a 5 min dropwise addition of a solution of cyclopentadiene monoepoxide (0.5 mL, 6.109 mmol) dissolved in 2 mL of THF. The reaction was monitored by TLC (1:1 hexane:ethyl acetate) and quenched after 15 min by passing the solution through a plug of SiO_2 (2 g) and $MgSO_4$ (1 g) with sufficient ether to ensure all of the product had been eluted. The solvent was removed by rotary evaporation and the residue was dissolved in ether and washed (three times) with sat. $NaHCO_3$. The aqueous layer was back-extracted several times with 1:1 ether:ethyl acetate. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and the residual oil chromatographed over SiO_2 using radial chromatography with 2:1 hexane:ethyl acetate (R_f 0.21) to give a 44% yield of a colorless oil:[24] IR (film) 3423 (br OH), 2981, 1731 (C=O), 1191 (C–O) cm^{-1}; ^1H NMR (200 MHz) δ 6.10 (m, 1H), 5.99 (ddd, *J*=5.5, 2.0, 1.1 Hz, 1H), 5.51 (m, 1H), 4.72 (m, 1H), 2.81 (overlapping dt, *J*=14.6, 7.3 Hz, 1H), 2.32 (q, *J*=7.5 Hz, 2H), 1.87 (br s, 1H), 1.64 (dt, *J*=14.6, 3.8 Hz, 1H), 1.14 (t, *J*=7.5 Hz, 3H); ^{13}C NMR δ 174.1, 138.4, 132.6, 76.9, 74.8, 40.6, 27.7, 9.0; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 135.7 and 134.8.

4.13. Preparation of cis-cyclopent-2-en-1,4-diyl diisobutyrate **15**

The preparation was carried out as described for **13** using **16** as the monohydroxy substrate and isobutyric anhydride as the acylating agent. Chromatographed over SiO_2 with 2:1 hexane:ethyl acetate (R_f 0.65) to give a 70% yield of a colorless oil: IR (film) 2975, 1735 (C=O), 1470, 1351, 1258, 1189, 1154, 1071 cm^{-1}; ^1H NMR (200 MHz) δ 6.08 (br d, *J*=0.7 Hz, 2H), 5.56 (ddd, *J*=0.7, 4.0, 7.5 Hz, 2H), 2.87 (overlapping dt, *J*=14.8, 7.5 Hz, 1H), 2.54 (septet, *J*=7.0 Hz, 1H), 1.67 (dt, *J*=14.8, 4.0 Hz, 1H), 1.15 (d, *J*=7.0 Hz, 6H); ^{13}C NMR δ 176.6, 134.6, 76.3, 37.4, 33.9, 18.8, 18.7; HRMS (CI, NH_3) calcd for $C_{13}H_{24}NO_4$ ($M+NH_4^+$) 258.1705, found 258.1710.

4.14. Preparation of (±)-cis-4-hydroxycyclopent-2-enyl isobutyrate **16**

Chromatographed over SiO_2 with 2:1 hexane:ethyl acetate (R_f 0.27) to give a 47% yield of a colorless oil: IR (film) 3411 (br OH), 2976, 1729 (C=O), 1159 (C–O) cm^{-1}; ^1H NMR (200 MHz) δ 6.07 (m, 1H), 5.92 (m, 1H), 5.50 (m, 1H), 4.72 (m, 1H), 3.44 (br s, 1H), 2.82 (overlapping dt, *J*=14.6, 7.3 Hz, 1H), 2.52 (septet, *J*=7.0 Hz, 1H), 1.60 (dt, *J*=14.6, 3.9 Hz, 1H), 1.15 (d, *J*=7.0 Hz, 6H); ^{13}C NMR δ 176.9, 138.4, 132.3, 76.9, 74.6, 40.5, 33.9, 18.8; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 135.7 and 134.9; HRMS (CI, NH_3) calcd for $C_9H_{18}NO_3$ ($M+NH_4^+$) 188.1287, found 188.1283.

4.15. Preparation of cis-cyclopent-2-en-1,4-diyl dibutyrate **17**

The preparation was carried out as described for **13** using **18** as the monohydroxy substrate and butyric anhydride as the acylating agent. Chromatographed over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.96) to give a 70% yield of a colorless oil: IR (film) 2966, 2877, 1737 (C=O), 1176 cm^{-1}; ^1H NMR (200 MHz) δ 6.06 (d, *J*=0.8 Hz, 2H), 5.54 (ddd, *J*=7.5, 3.9, 0.8 Hz, 2H), 2.86 (overlapping dt, *J*=14.9, 7.5 Hz, 1H), 2.26 (t, *J*=7.4 Hz, 4H), 1.66 (m, 5H), 0.95 (t, *J*=7.3 Hz, 6H); ^{13}C NMR δ 173.0, 134.5, 76.3, 37.3, 36.1, 18.3, 13.5; HRMS (CI, NH_3) calcd for $C_{13}H_{24}NO_4$ ($M+NH_4^+$) 258.1705, found 258.1703.

4.16. Preparation of (±)-cis-4-hydroxycyclopent-2-enyl butyrate **18**

Chromatographed over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.48) to give a 36–49% yield of a colorless oil: IR (film) 3422 (br OH), 2966, 2877, 1730 (C=O), 1183 cm^{-1}; ^1H NMR (200 MHz) δ 6.08 (m, 1H), 5.95 (m, 1H), 5.46 (m, 1H), 4.69 (m, 1H), 2.78 (overlapping dt, *J*=14.6, 7.3 Hz, 1H), 2.25 (t, *J*=7.2 Hz, 2H), 1.71 (br s, 1H), 1.57 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H); ^{13}C NMR δ 177.3, 138.4, 132.3, 76.8, 74.5, 40.5, 36.2, 18.3, 13.4; ^{31}P data for the diastereomeric pair derived from **19**, ^{31}P NMR δ 135.4 and 134.6; HRMS (CI, NH_3) calcd for $C_9H_{18}NO_3$ ($M+NH_4^+$) 188.1287, found 188.1286.

4.17. General procedure for the enzymatic hydrolysis of meso-diesters

Into a 10 mL round-bottom flask equipped with a stir bar free of any metal filings is added the *meso*-diester (~180–200 mg). The substrate is suspended in 6 mL of a 0.58 M NaH_2PO_4 buffer that had been adjusted to pH 6.9. A trace amount of NaN_3 was added to discourage bacterial growth. A small flake of lyophilized EeAChE (1 mg enzyme/g substrate) was added to the gently stirred mixture by means of a microspatula. The course of the reaction was monitored closely by TLC analysis (2:1 hexane:ethyl acetate). Diacetate substrates react between 4 and 24 h, with butyrates taking substantially longer. As the diester is consumed, the initially two-phase system converges into a single aqueous layer. The reaction is

quenched by the addition of sat. NH_4Cl and the hydrolyzed products are isolated by repeated extraction with 1:1 ether:ethyl acetate until TLC analysis of the aqueous phase indicates the monohydroxyester is no longer present. The combined extracts are dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue is further purified by chromatography over SiO_2.

*4.17.1. (1*S,*3*R*)-(+)-3-Hydroxycyclopentyl acetate (+)-**4***

Colorless oil: 70% yield (86% yield based upon recovered starting material); $[\alpha]_D^{28}$=+35.8 (*c* 0.52, $CHCl_3$); 93% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 135.5.

*4.17.2. (1*R,*2*S,*4*R,*5*S*)-(−)-4-Hydroxybicyclo[3.1.0]hex-2-yl acetate (−)-**6***

Colorless oil: 60% yield (74% yield based upon recovered starting material); rotation of 99% e.e. *ent*-**6** (prepared from 99% e.e. (+)-**2**): $[\alpha]_D^{24}$=+46.9 (*c* 1.25, $CHCl_3$); calculated rotation $[\alpha]_D^{24}$=−46.9 (*c* 1.25, $CHCl_3$) for 99% e.e., based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 135.4.

*4.17.3. (1*S,*2*R,*4*S,*5*S*)-(+)-4-Hydroxy-6-oxabicyclo[3.1.0]hex-2-yl acetate (+)-**8***

Colorless oil: 72% yield; $[\alpha]_D^{25}$=+32.0 (*c* 1.32, $CHCl_3$); 67% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 137.3.

*4.17.4. (1*R,*2*R,*4*S,*5*R*)-(+)-4-Hydroxy-6-oxabicyclo[3.1.0]hex-2-yl acetate (+)-**10***

Colorless oil: 40% yield (95% yield based upon recovered starting material); $[\alpha]_D^{25}$=+15 (*c* 0.865, $CHCl_3$); 82% e.e. based upon lit. value[12] for 82% e.e. $[\alpha]_D^{20}$=+15.0 (*c* 1.0, $CHCl_3$); ^{31}P data for derivative with **19**, ^{31}P NMR δ 135.5.

*4.17.5. (1*R,*2*R,*3*R,*4*S*)-(−)-2,3-*O*-Cyclohexylidene-4-hydroxycyclopentyl acetate (−)-**12***

Colorless oil: 61% yield (64% yield based upon recovered starting material); rotation of 99% e.e. (−)-**12** (prepared from 99% e.e. (+)-**2**): $[\alpha]_D^{25.6}$=−7.24 (*c* 2.4, $CHCl_3$); $[\alpha]_D^{26}$=−5.9 (*c* 0.29, $CHCl_3$); 81% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 133.4.

*4.17.6. (1*R,*4*S*)-(+)-4-Hydroxycyclopent-2-enyl propionate (+)-**14***

Colorless oil: 91% yield; $[\alpha]_D^{25}$=+63.1 (*c* 1.045, $CHCl_3$); 98% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 134.8.

*4.17.7. (1*R,*4*S*)-(+)-4-Hydroxycyclopent-2-enyl isobutyrate (+)-**16***

Colorless oil: 48% yield (72% yield based upon recovered starting material); $[\alpha]_D^{25}$=+66.8 (*c* 1.315, $CHCl_3$); >99% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 134.9.

*4.17.8. (1*R,*4*S*)-(+)-4-Hydroxycyclopent-2-enyl butyrate (+)-**18***

Colorless oil: 49% yield; $[\alpha]_D^{25}$=+57.0 (*c* 1.02, $CHCl_3$); 97% e.e. based upon ^{31}P data for derivative with **19**, ^{31}P NMR δ 134.6.

*4.18. The conversion of monohydroxy esters **14**, **16**, and **18** into (+)-(1*S,*4*R*)-4-phthalimidocyclopent-2-en-1-ol **21***

The preparation of **21** was carried out as previously described[14] substituting **14**, **16**, and **18** for (+)-**2**. Purification by chromatography over SiO_2 with 1:1 hexane:ethyl acetate (R_f 0.47) gave a colorless solid: mp 69–71°C; $[\alpha]_D^{26}$=+276 (*c* 1.03, $CHCl_3$); IR (KBr) 3398 (br OH), 1697 (C=O), 1380, 720 cm^{-1}; ^1H

NMR (200 MHz) δ 7.90–7.65 (m, 4H), 6.22 (m, *J*=5.5 Hz, 1H), 5.72 (dd, *J*=5.5, 2.5 Hz, 1H), 5.23 (m, *J*=9.6, 2.2 Hz, 1H), 4.74 (m, 1H), 4.07 (br s, 1H), 2.82 (ddd, *J*=15.4, 9.6, 7.8 Hz, 1H), 1.97 (br d, *J*=15.4 Hz, 1H); ^{13}C NMR δ 168.4, 138.4, 134.2, 131.8, 130.1, 123.3, 75.8, 53.0, 38.2.

*4.19. General method for the determination of enantiomeric excess with reagent **19***

The chiral derivatizing agent **19** was prepared from *trans*-1,2-diaminocyclohexane as reported by Alexakis.[13] This reagent was stored at −20°C as a 0.20 M solution in benzene with 10% C_6D_6. To determine the enantiomeric ratios, 0.11 mmol of **19** and 0.10 mmol of the chiral alcohol were added to a 5 mm NMR tube. The mixture was allowed to stand until no dimethylamine was detected with a litmus paper held at the mouth of the tube. No isolation or purification of the derivatized chiral alcohol was needed for this analysis. The sample was locked on deuterated benzene and the ^{31}P signals recorded. The signals were integrated to calculate the e.e. values reported in this paper.

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