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Asymmetric Synthesis of Hydroxy Esters with Multiple Stereocenters via a Chiral Phosphoric Acid Catalyzed Kinetic Resolution

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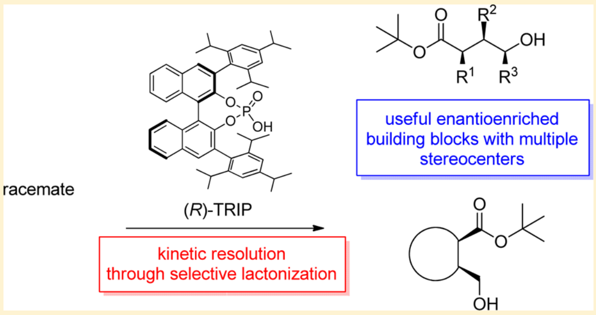
Supporting Information

ABSTRACT: The kinetic resolution of hydroxy *tert*-butyl esters through a Brønsted acid catalyzed lactonization is described. The resulting enantioenriched molecules have cyclic backbones and/or multiple stereocenters. DFT calculations explore how small changes in substrate structure can have a large impact on the selectivity of the process.



INTRODUCTION

The preparation of single enantiomer compounds for therapeutic use is a growing industry.[1] In 2006, enantiopure drug sales represented 37% of the total pharmaceutical market with an annual growth rate of 11%.[2] With the advanced interest in single enantiomer drugs, methods for the preparation of enantioenriched or enantiopure compounds have exploded. While the method of choice for preparation is often asymmetric synthesis, kinetic resolutions can still be an important option. Kinetic resolution takes advantage of the difference in the relative rate of reaction of the two enantiomers of a racemic mixture with a chiral reagent or catalyst. While it is true that since you start with a racemate, the greatest possible yield of a single enantiomer compound is 50%, kinetic resolutions have the distinct advantage that the enantiopurity of the desired compound can be increased by simply running the reaction to a higher percent conversion, with the eventual result of an essentially *enantiopure* compound.[3] Furthermore, kinetic resolutions can often be the practical choice for preparation of enantioenriched molecules if the racemates are readily available, catalyst loading is low, and the reaction can be done on a large scale.[4]

Small enantioenriched building blocks with multiple stereocenters are often key intermediates in the synthesis of biologically important molecules and natural products. In particular, α,γ-disubstituted hydroxy carbonyl compounds and γ-lactones such as (−)-**1** and (−)-**2** have been utilized as key building blocks in the synthesis of complex macrolides such as the geodiamolide and amphidinolide family as well as jaspamide (Scheme 1).[5] Also, bicyclic lactones and precursors such as (−)-**3** and (−)-**4** have been used as building blocks for the angiotensine converting enzyme (ACE) inhibitor Trandolapril marketed by Abbott Laboratories, as well as antifungals and GABA inhibitors.[6] This paper focuses on the use of an intramolecular lactonization event to form small enantioenriched building blocks with multiple stereocenters in one step.

Recently, we published a method for the preparation of enantioenriched α-substituted hydroxy esters through a kinetic resolution catalyzed by chiral phosphoric acids[7] (Scheme 2).[8] Bulky racemic esters were found to selectively lactonize in the presence of a chiral Brønsted acid to yield a recoverable enantioenriched hydroxy ester and lactone with selectivity factors up to 20. Herein, we sought to explore a broader scope of this reaction, including substrates with multiple stereocenters, and cyclic motifs.

RESULTS AND DISCUSSION

Hydroxy esters with α,β- and α,γ-disubstitution patterns (**10**–**15**) were prepared as diastereomeric mixtures from readily available starting materials (Scheme 3).[9] Relative configurations were assigned after purification of small quantities of each diastereomer, followed by lactonization and comparison of NMRs to known lactones.[10] Initial kinetic resolution screening of the diastereomeric mixtures was carried out in the presence of the previously optimized chiral Brønsted acid catalyst, TRIP (**7**, Table 1). Lactonization of the disubstituted hydroxy esters was executed in dichloromethane at the given temperature and time with reaction monitoring performed using an internal standard and GC analysis with a chiral support column. As is typically seen for intramolecular reactions, the current cyclizations were conducted under dilute conditions so as to

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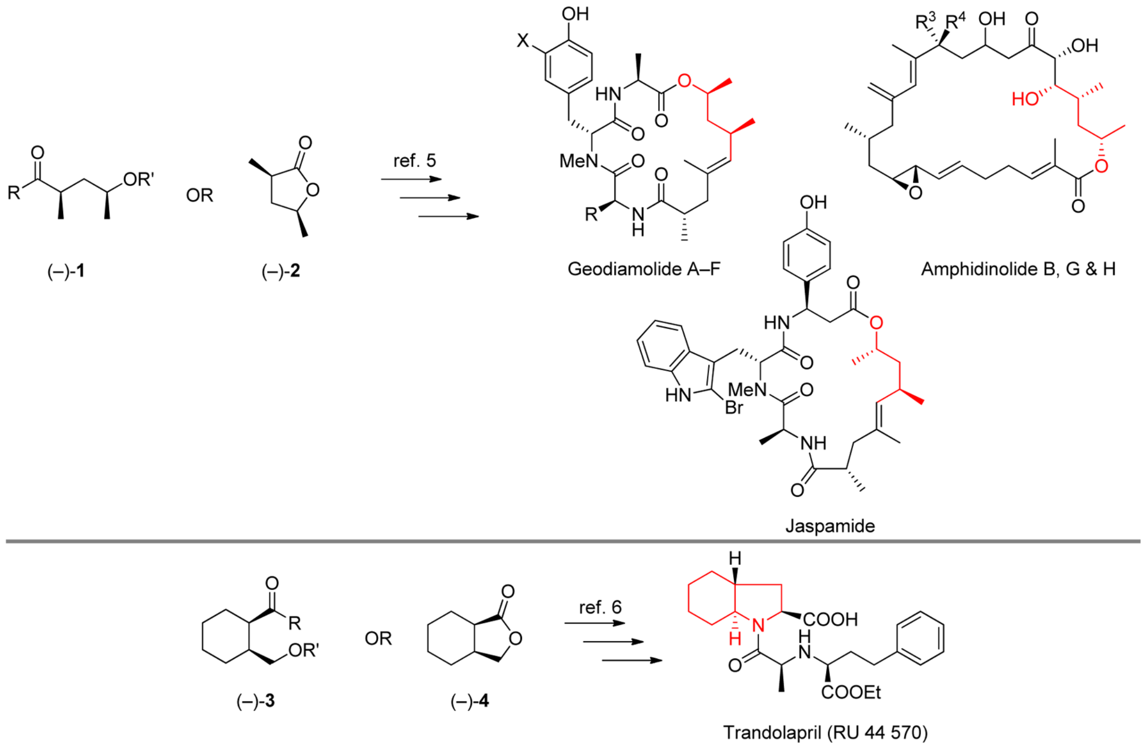
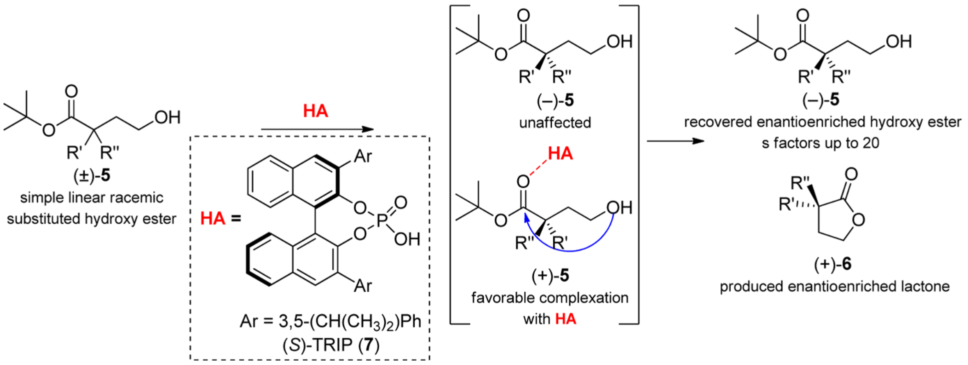
Scheme 1. Building Blocks with Multiple Stereocenters Used in the Synthesis of Natural Products and Drug Targets



Scheme 2. Previously Developed Kinetic Resolution



Scheme 3. Synthesis of Linear Disubstituted Hydroxy Esters

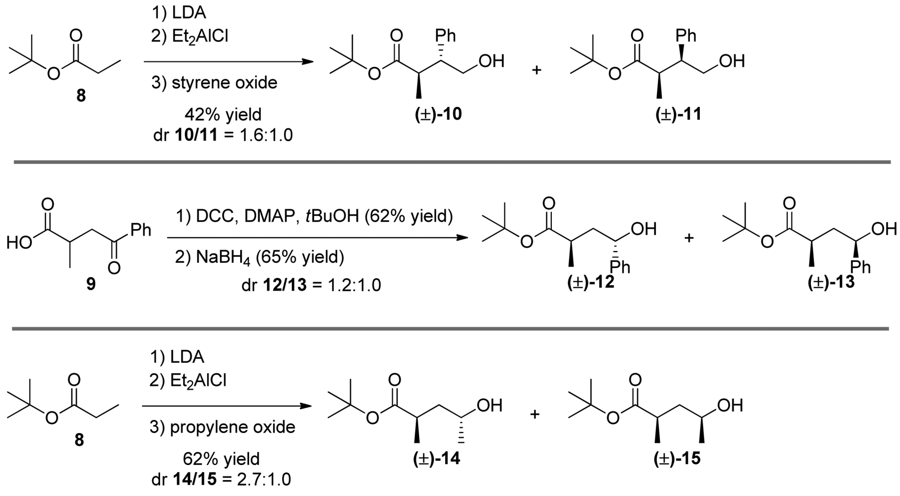
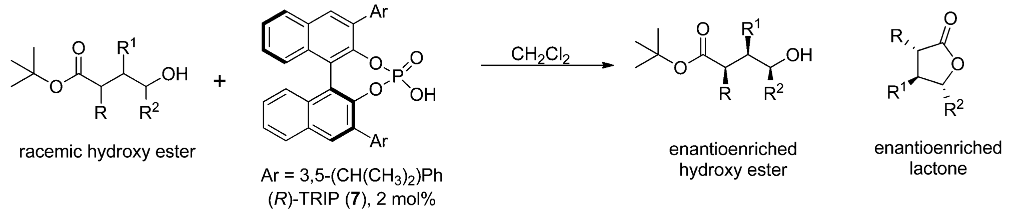
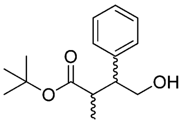
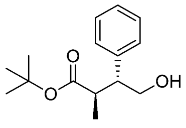
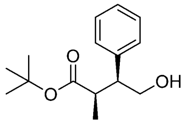
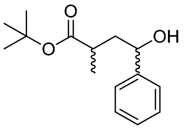
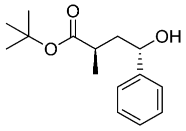
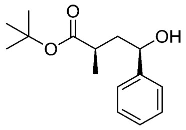
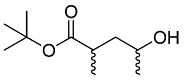
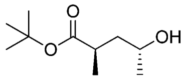
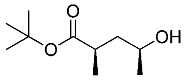


Table 1. Reaction Scope[a]



Entry	Substrate	Enantioenriched Hydroxy Ester	Temp (°C)	Time (h)	%conv	%ee$_{sm}$	%ee$_p$	s
1	 (±)-**10/11** (1.6:1.0)	 **10**	-5	20	74	50	8	2.2
2		 **11**	-5	20	44	10	3	1.4
3	 (±)-**12/13** (1.2:1.0)	 **12**	5	96	91	10	13	1.1
4		 **13**	5	96	58	15	21	1.4
5	 (±)-**14/15** (2.7:1.0)	 **14**	-5	48	70	21	1	1.4
6		 **15**	-5	24	44	62	13	15.8

[a]Reactions carried out using 10 mg of substrate in 10 mL of CH_2Cl_2 with 2 mol % of catalyst. Conversion determined using gas chromatography and an internal standard. ee determined by GC or HPLC analysis with a chiral support column. Selectivity factor (*s*) was determined using the equation: $s = k_{rel}(\text{fast/slow}) = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$, where c = conversion and ee_s.[12]

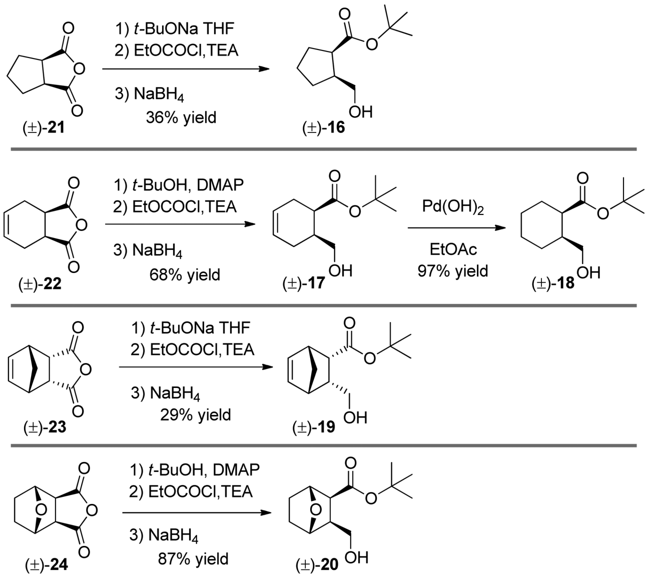
minimize intermolecular reactions.[11] As seen in Table 1, the selectivity factors for most lactonizations were very small (under 2.5) and enantioselectivities are only modest and or inconsistent.[12] The single exception was the *syn*-dimethyl substrate **15**, which had a selectivity factor of 15.8.

Racemic cyclic hydroxy esters (**16**−**20**) were synthesized in three steps from their bicyclic anhydrides (Scheme 4). Opening of the anhydride with *tert*-butanol (or its sodium salt) resulted in the ester/acid, the acid of which was selectively reduced with sodium borohydride after formation of the mixed anhydride. In contrast to the linear disubstituted esters, the cyclic hydroxy esters were overall much better kinetic resolution substrates (Table 2). The least selective esters (±)-**16** and (±)-**19** (entry 1, selectivity factor = 3.6, and entry 4, selectivity factor = 2.4) involve formation of a lactone with a fused 5,5 ring system. All others (**17**, **18**, and **20**; entries 2, 3, and 5) have selectivities factors above 10. We propose that the cyclic substrates are more selective due to the conformational restriction that places the alcohol in closer proximity to the ester, giving a more rigid transition state.

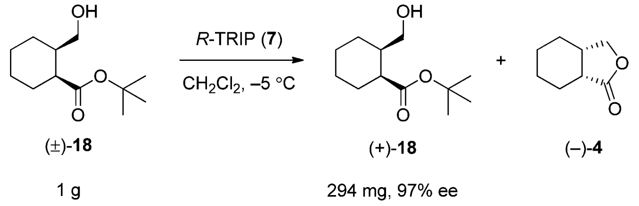
With our initial screenings in hand, the best substrate was subjected to kinetic resolution conditions on a larger scale (Scheme 5). One gram of 1,2-disubstituted *cis*-cyclohexane (±)-**18** yielded 294 mg of (+)-**18** (29% isolated yield) with an enantiopurity of 97%.

Intrigued by the disparity between the diastereomers **14** and **15**, a DFT study at the B3LYP/6-311+G(d) level of theory was performed. Two potential pathways were examined for a simplified catalyst system and a single enantiomer of monosubstituted hydroxy ester **5** (Scheme 6).[13] Path 1 (to form complex **CP1**) is a monocoordination model that involves activation of the ester of **RT** by the acidic proton of the phosphoric acid **CAT** and the hydrogen on the alcohol of **RT** by the same oxygen of **CAT**. In path 2, the complex **CP2** incorporates the dual functionality of the catalyst with the acidic proton activating the carbonyl of **RT** and the Lewis basic

Scheme 4. Synthesis of Cyclic Substrates



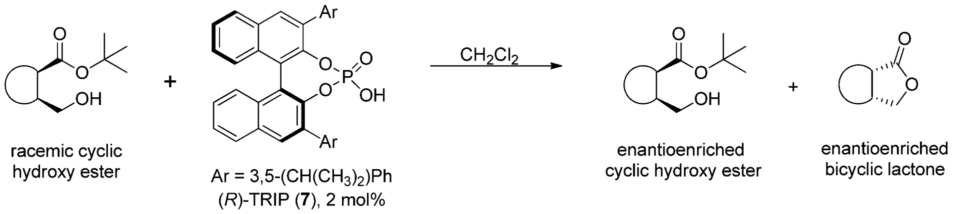
Scheme 5. Synthetic Scale

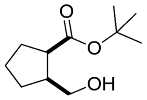
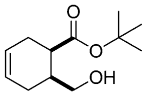
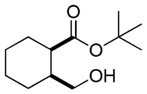
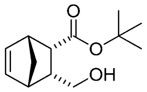
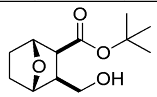


phosphoryl oxygen activating the hydroxy group of **RT**. For each pathway, the relative energies of the complexes (**CP1** and **CP2**) and the transition states (**TS1** and **TS2**) were calculated. The barrier height for **CP1** and **CP2** pathways is 22.0 and 16.6 kcal/mol, respectively, with the latter favored by 5.4 kcal/mol. This result unambiguously shows that **CP2** is the favorable pathway for the process.

With the dicoordination pathway established, we sought to explore the disparity of selectivity between (±)-**14** and (±)-**15** (Scheme 7). For each diastereomer, the catalyst complexes (**CP14a**/**CP14b** and **CP15a**/**CP15b**) and the transition potential transition states (**TS14a**/**TS14b** and **TS15a**/**TS15b**) were calculated. The relative energies and reaction barriers are plotted in Figure 1. The more selective

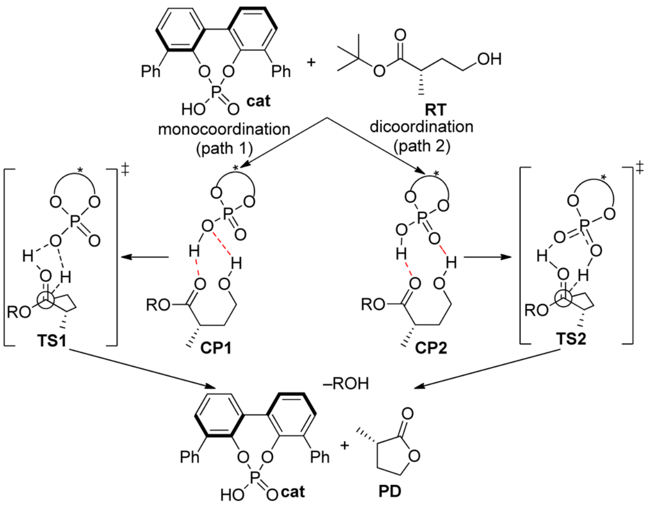
Table 2. Cyclic Substrates[a]



Entry	Substrate	Temp (°C)	Time (h)	%conv	%ee$_{sm}$	%ee$_p$	s
1	 (±)-**16**	−20	24	49	41	53	3.6
2	 (±)-**17**	-20	64	53	67	35	10.4
3	 (±)-**18**	0	20	60	95	33	15.7
4	 (±)-**19** (dr = 10:1)	5	48	70	50	5	2.4
5	 (±)-**20**	−20	12	62	74	55	12.4

[a] Reactions carried out using 10 mg of substrate in 10 mL of CH$_2$Cl$_2$ with 2 mol % of catalyst. Conversion determined using gas chromatography and an internal standard. ee determined by GC or HPLC analysis with a chiral support column. Selectivity factor (s) was determined using the equation: $s = k_{rel}(\text{fast/slow}) = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$, where c = conversion and ee$_s$.[12]

Scheme 6. Potential Reaction Pathways



diastereomer (±)-**15** had hydrogen-bonding complexes and transition states that were more stable than the enantiomers of (±)-**14**. Also, the difference between the barrier heights of the two enantiomers of (±)-**15** (3.1 kcal/mol) was much greater than the difference between the two enantiomers of (±)-**14** (0.7 kcal/mol). This larger difference of barrier heights for the two enantiomers of (±)-**15** is the origin of the better selectivity of this compound.

CONCLUSION

In summary, we have expanded the Brønsted acid catalyzed kinetic resolution of hydroxy *tert*-butyl esters to include substrates with multiple stereocenters. Good selectivity was seen for cyclic substrates. Theoretic studies were conducted to explore what role the chiral phosphoric acid **7** plays in the reaction. It was determined that the reaction favors a dicoordination model and that subtle differences in structure (diastereomers (±)-**14** versus (±)-**15**) can account for large differences in selectivity.

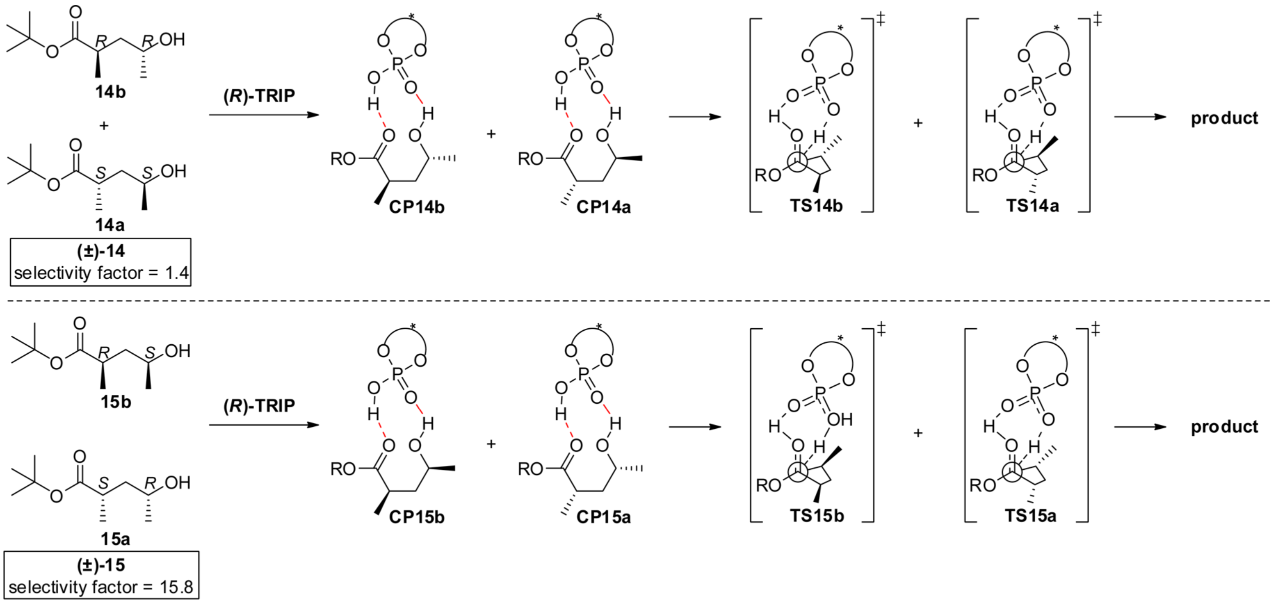
EXPERIMENTAL SECTION

Computational Studies. DFT calculations using B3LYP[14] were performed for the reaction sequences. To reduce the computational cost, a simplified TRIP model was employed to replace the 3,5-$(CH(CH_3)_2)Ph$ group with a phenyl group. The Pople's standard 6-311+G(d)[15] was used for all elements. For each compound, different conformations with different stereocenters were considered. For example, for **14**, we examined (*R*,*R*) and (*S*,*S*) conformations and, for **15**, we considered both (*R*,*S*) and (*S*,*R*) diastereomers. Calculations were performed with the Gaussian 09 DO1 package with tight SCF convergence and ultrafine integration grids.[16] For transition-state structure searches, we started from the molecular complex. The QST2 (the quadratic synchronous transit approach with the reactant and product structures as the input) technique was employed. After a transition-state search is accomplished, a single-point frequency calculation was performed to ensure that the final structure obtained (i) has only one imaginary frequency and (ii) the vibration mode of the negative frequency corresponds to the bond formation that is anticipated. In addition, intrinsic reaction coordinates (IRCs) were calculated to verify the relevance of transition-state structures.

General Methods. Unless noted, all solvents and reagents were obtained from commercial sources and used without further purification; anhydrous solvents were dried following standard procedures. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were plotted on 400 and 500 MHz spectrometers using $CDCl_3$ or acetone d_6 as a solvent at rt. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^1H NMR: s = singlet, d = doublet, m = multiplet, b = broad, t = triplet, q = quartet, p = pentet. The reactions were monitored by TLC using silica G F_{254} precoated plates. Flash chromatography was performed using flash grade silica gel (particle size: 40−63 μm, 230 × 400 mesh). Enantiomeric excess was determined by GC analysis and HPLC analysis. IR data were obtained with an FTIR spectrometer with frequencies reported in cm^{-1}. High-resolution mass spectra were acquired on an Orbitrap XL MS system. The specific rotations were acquired on an analytical polarimeter.

Compounds 10 and 11. Lithium diisopropylamide was prepared by dissolving distilled diisopropylamine (1.6 mL, 11.4 mmol) in dry THF (15 mL) in a flame-dried flask under argon at −78 °C. *n*-Butyllithium (1.6 M in hexanes, 7.1 mL, 11.4 mmol) was added dropwise, and the mixture was stirred for 15 min at −78 °C. *tert*-Butyl propionate (1.1 mL, 7.6 mmol) was then added dropwise, and the mixture was stirred for 15 min at −78 °C. Diethylaluminum chloride

Scheme 7. Closer Look at Diastereomers (±)-14 and (±)-15



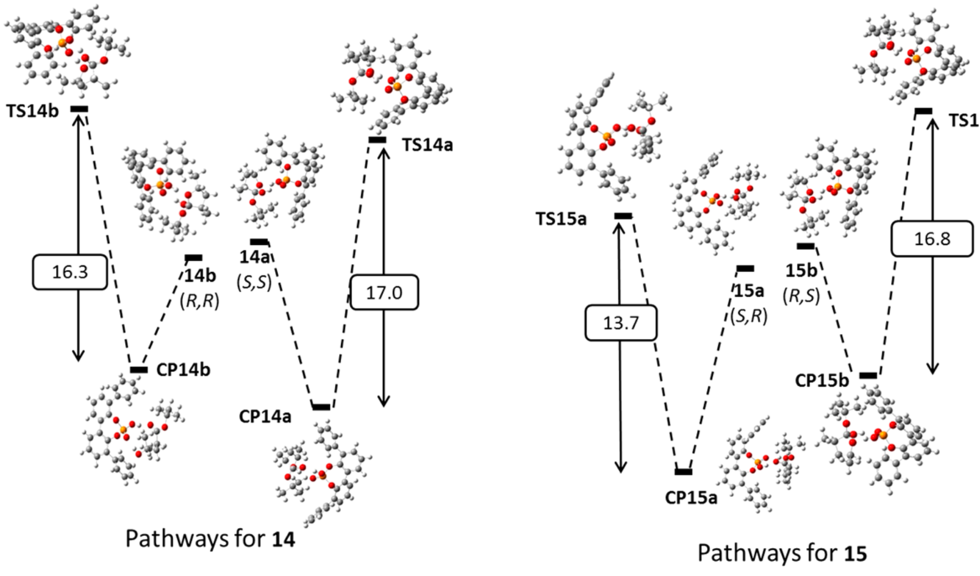


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Figure 1. Energy profiles of species involved in lactonizations of **14** and **15**. Numbers shown in boxes are the barrier heights of different pathways. Units in kcal/mol.

(1 M in hexanes, 7.6 mL, 7.6 mmol) was added dropwise, and the mixture was stirred for 15 min at −78 °C. Styrene oxide (0.43 mL, 3.8 mmol) was added dropwise, and the mixture was stirred for 2 h at −78 °C. The reaction was quenched with NH_4Cl and added to a beaker with 4 M HCl (20 mL) and ice (10 g). After the ice had melted, the aqueous mixture was extracted twice with ether and the organic layer was washed twice with 5% $NaHCO_3$, once with brine, dried, and concentrated in vacuo. Purification by column chromatography (10−20% EtOAc in hexanes) yielded a colorless oil as a mixture of diastereomers (0.40 g, 42% yield, dr 1.2:1). Small samples of each diastereomer were purified via chromatography for characterization purposes.

10. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.33 (m, 2H), 7.22 (m, 2H), 3.80 (m, 2H), 2.99 (ddd, *J* = 10.5, 7.2, 5.3 Hz, 1H), 2.65 (dq, *J* = 10.3, 7.2 Hz, 1H), 1.49 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 140.1, 128.8, 128.7, 127.2, 80.8, 65.9, 51.7, 43.2, 28.2, 16.3; IR (neat) cm^{-1} 3423, 2976, 2932, 1722, 1454, 1367, 1246, 1148, 1065, 846, 698; HRMS ($C_{15}H_{22}O_3$, ESI) [M + H]$^{+1}$, calculated 251.1642, found 251.1639.

11. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.23 (m, 3H), 3.91 (m, 1H), 3.82 (ddd, *J* = 9.6, 7.5, 5.1 Hz, 1H), 2.98 (m, 1H), 2.79 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 140.6, 128.8, 128.6, 127.2, 80.3, 64.4, 51.3, 42.8, 27.7, 15.6; IR (neat) cm^{-1} 3422, 2979, 2938, 1712, 1456, 1368, 1153, 848; HRMS ($C_{15}H_{22}O_3$, ESI) [M + H]$^{+1}$, calculated 251.1642, found 251.1637.

Compounds 12 and 13. 2-Methyl-4-oxo-4-phenylbutanoic acid (0.90 g, 4.7 mmol) was esterified with *tert*-butanol (1.3 mL, 14 mmol), DCC (1.16 g, 5.6 mmol), and DMAP (0.11 g, 0.93 mmol) in CH_2Cl_2 (23 mL). All reagents were placed in a flame-dried flask under argon and stirred for 4 h at −5 °C. The mixture was quenched with hexanes and filtered. The filtrate was concentrated in vacuo and purified via column chromatography (1.5″ × 6″ silica gel, 10−20% EtOAc in hexanes) to yield intermediate keto ester as a white solid (0.44 g, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 3.43 (m, 1H), 3.00 (m, 2H), 1.42 (s, 9H), 1.23 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 198.4, 175.3, 136.9, 133.2, 128.7, 128.1, 80.4, 42.0, 36.0, 28.1, 17.5; IR (neat) cm^{-1} 2967, 2933, 1728, 1674, 1596, 1447, 1365, 1218, 1150, 1004, 852, 763, 691; HRMS ($C_{15}H_{20}O_3$, ESI) [M + Na]$^{+1}$, calculated 271.1310, found 271.1301

The ketone was then reduced by dissolving sodium borohydride (0.27 g, 7.1 mmol) in dry methanol (6 mL) in a flame-dried round-bottom under argon in an ice bath. The ketone (0.45 g, 1.8 mmol) in dry methanol (2 mL) was then added dropwise at 0 °C. The reaction was allowed to warm to rt over 1 h and then was quenched with 1 M HCl (pH ∼ 2). The methanol was removed in vacuo, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried and concentrated in vacuo. Purification via column chromatography (20% EtOAC in hexanes) yielded a colorless oil as mixture of diastereomers (0.29 g, 65% yield, dr 1.5:1.0).

12/13. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.25 (m, 1H), 4.70 (m, 1H), 2.64 (bs, 1H), 2.50 (m, 1H), 2.10 (m, 1H), 1.68 (m, 1H), 1.45 (s, 9H), 1.14 (m, 3H);^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 176.5, 159.1 144.7, 136.4, 128.6, 127.7, 127.1, 126.0, 113.9, 80.6, 80.4, 73.4, 72.9, 55.4, 43.0, 38.1, 34.0, 32.1, 28.2, 28.1, 17.7; IR (neat) cm^{-1} 3429, 2975, 2934, 1723, 1454, 1366, 1149, 1028, 698; HRMS ($C_{15}H_{22}O_3$, ESI) [M + H]$^{+1}$, calculated 251.1642, found 251.1637.

Compounds 14 and 15. Lithium diisopropylamide was prepared by dissolving distilled diisopropylamine (1.6 mL, 11.4 mmol) in dry THF (15 mL) in a flame-dried flask under argon at −78 °C. *n*-Butyllithium (1.6 M in hexanes, 7.1 mL, 11.4 mmol) was added dropwise, and the mixture was stirred for 15 min at −78 °C. *tert*-Butyl propionate (1.1 mL, 7.6 mmol) was then added dropwise, and the mixture was stirred for 15 min at −78 °C. Diethylaluminum chloride (1 M in hexanes, 7.6 mL, 7.6 mmol) was added dropwise, and the mixture was stirred for 15 min at −78 °C. Propylene oxide (0.27 mL, 3.8 mmol) was added dropwise, and the mixture was stirred for 2 h at −78 °C. The reaction was quenched with NH_4Cl and added to a beaker with 4 M HCl (20 mL) and ice (10 g). After the ice had melted, the aqueous mixture was extracted twice with ether, and the organic layer was washed twice with 5% $NaHCO_3$, once with brine, dried, and concentrated in vacuo. Purification by column chromatography (10−20% EtOAc in hexanes) yielded a colorless oil as a mixture of diastereomers (0.89 g, 62% yield, dr 2.7:1.0). Small samples of each diastereomer were purified via chromatography for characterization purposes.

14. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (m, 1H), 2.54 (m, 1H), 1.68 (d, *J* = 3.7 Hz, 1H), 1.46 (dd, *J* = 9.2, 4.6 Hz, 1H), 1.40 (s, 9H), 1.14 (d, *J* = 6.4, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 80.5, 65.8, 43.2, 37.3, 28.1, 23.7, 17.9; IR (neat) cm^{-1} 3386, 2973, 2934, 1708, 1457, 1367, 1255, 1148, 1081, 1035, 848;

HRMS ($C_{10}H_{20}O_3$, ESI) [2M + Na]$^{+1}$, calculated 399.2701, found 399.1771.

15. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (m, 1H), 2.56 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H), 1.43 (s, 9H), 1.17 (d, J = 6.0, 3H), 1.12 (d, J = 7.3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 80.5, 65.9, 43.2, 37.3, 28.2, 23.7, 17.8; IR (neat) cm^{-1} 3389, 2976, 1710, 1455, 1359, 1255, 1144, 1029, 850; HRMS ($C_{10}H_{20}O_3$, ESI) [M + Na]$^{+1}$, calculated 211.1305, found 211.1300.

Compound (±)-16. *cis*-1,2-Cyclopentanecarboxylic anhydride (200 mg, 1.43 mmol) was added to a THF (8.0 mL) solution containing sodium *tert*-butoxide (151 mg, 1.57 mmol). The reaction mixture was stirred at rt for 16 h; then a citric acid solution (10 mL) was added. The reaction mixture was extracted with Et_2O (100 mL), and the ether layer was washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to yield the *tert*-butyl ester acid as a colorless oil, which was used in the next transformation without purification.

The above crude *tert*-butyl ester acid (1.43 mmol) was dissolved in dry THF (5 mL) and cooled in an ice water bath. After 10 min, triethylamine (0.21 mL, 1.7 mmol) was added via a syringe, followed by the addition of ethyl chloroformate (0.168 mL, 11.72 mmol). After 1 h, the white precipitate was removed via vacuum filtration through a pad of Celite and the filtrate was cooled in a dry ice acetone bath. After 10 min, ethanol (3.0 mL) was added, followed by $NaBH_4$ (108 mg, 2.86 mmol) in portions over 10 min. After TLC indicated the consumption of the mixed anhydride intermediate and the formation of a new polar spot, the reaction mixture was diluted with ether (20 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product as an oil, which was purified by column chromatography (CH_2Cl_2/acetone, 97:3) to afford the pure alcohol as a colorless liquid (100 mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (m, 2 H), 2.80 (m, 1H), 2.50 (bs, 1H), 2.40 (m, 1H), 2.7−2.9 (m, 4H), 1.55 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 81.0, 64.2, 47.2, 46.0, 29.0, 28.2, 24.1; IR (neat) cm^{-1} 3441, 2960, 2872, 1720, 1453, 1365, 1162, 1048; HRMS ($C_{11}H_{20}O_3$, ESI) [M + H]$^{+1}$, calculated 201.1485, found 201.1482.

Compound (±)-17. A mixture of *cis*-1,2,3,6-tetrahydrophthalic anhydride (12.2 g, 80 mmol), DMAP (1.0 g, 8.0 mmol), and *tert*-butanol (100 mL) was heated at reflux for 36 h. After cooling to rt, the reaction mix was diluted with ether (150 mL) and washed with 1 M HCl solution (2 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude *tert*-butyl ester acid as a white solid, which was used in the next transformation without purification.

The above *tert*-butyl ester acid (3.2 g, 14.15 mmol) was dissolved in dry THF (60 mL) and cooled in an ice water bath. After 10 min, triethylamine (2.4 mL, 17.0 mmol) was added via a syringe, followed by the addition of ethyl chloroformate (1.6 mL, 17 mmol). After 1 h, the white precipitate was remove via vacuum filtration through a pad of Celite and the filtrate was cooled in a dry ice acetone bath. After 10 min, ethanol (40 mL) was added, followed by $NaBH_4$ (650 mg, 17.0 mmol) in portions over 30 min. After TLC indicated the consumption of the mixed anhydride intermediate and the formation of a new polar spot, the reaction mixture was diluted with ether (20 mL) and washed with water (3 × 20 mL) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product as an oil, which was purified by column chromatography (hexane/dichloromethane/acetone, 10:5:1) to afford the compound **17** as a colorless liquid (2.2 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.7 (m, 2H), 3.7 (m, 1H), 3.5 (m, 1H), 2.7 (m, 1H), 1.9−2.4 (m, 6H), 1.5 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 125.3, 80.9, 63.8, 41.1, 37.1, 28.2, 27.1, 25.3; IR (neat) cm^{-1} 3417, 3025, 2977, 2930, 1723, 1584, 1366, 1243, 1160, 1038; HRMS ($C_{12}H_{20}O_3$, ESI) [M + H]$^{+1}$, calculated 213.1485, found 213.1480.

Compound (±)-18. A mixture of alkene **17** (2.1 g, 10.0 mmol), Pd/C (200 mg), and EtOAc (100 mL) was stirred under hydrogen pressure using a balloon for 16 h. The Pd/C was removed via filtration through a pad of Celite, and the filtrate was concentrated under vacuum to give the titled compound (2.05 g, 97% yield). ^{1}H NMR (500 MHz $CDCl_3$) δ 3.53 (m, 2H), 2.70 (m, 1H), 2.41 (m 1H), 2.02 (m, 1H), 1.91 (m, 1H), 1.72 (m, 2H), 1.63 (m, 3H), 1.48 (m, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 80.9, 64.6, 43.4, 40.9, 28.2, 26.7, 26.6, 23.9, 23.5; IR (neat) cm^{-1} 3412, 2931, 2858, 1723, 1449, 1366, 1254, 1151, 1040; HRMS ($C_{12}H_{22}O_3$, ESI) [M + H]$^{+1}$, calculated 215.1642, found 215.1637.

Compound (±)-19. *cis*-5-Norborane-*endo*-2,3-dicarboxylic anhydride (500 mg, 3.0 mmol) was added to a THF (15.0 mL) and *tert*-butanol (15.0 mL) solution containing sodium *tert*-butoxide (285 mg, 3.0 mmol). After the reaction mixture was stirred at rt for 16 h, a citric acid solution (20 mL) was added and the reaction mixture was extracted with Et_2O (150 mL). The ether layer was washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to the *tert*-butyl ester acid as a colorless oil, which was used in the next transformation without purification.

The above crude *tert*-butyl ester acid (3.0 mmol) was dissolved in dry THF (20.0 mL) and cooled in an ice water bath. After 10 min, triethylamine (0.4 mL, 3.3 mmol) was added via a syringe, followed by the addition of ethyl chloroformate (0.313 mL, 3.3 mmol). After 1 h, the white precipitate was removed via vacuum filtration through a pad of Celite and the filtrate was cooled in a dry ice acetone bath. After 10 min, ethanol (8 mL) was added, followed by $NaBH_4$ (228 mg, 6.0 mmol) in portions over 10 min. After TLC indicated the consumption of the mixed anhydride intermediate and the formation of a new polar spot, the reaction mixture was diluted with ether and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product as an oil, which was purified by column chromatography (CH_2Cl_2/hexanes/acetone, 12:6:1) to afford the pure alcohol as a colorless liquid (200 mg, 29% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, 1H, J = 5.8, 2.3 Hz), 6.08 (dd, J = 5.8and 2.9 Hz, 1H), 3.5 (dd, J = 12 and 5.2 Hz, 1H), 3.38 (bs, 1H), 3.08 (m, 2H), 2.85 (bs, 1H), 2.66 (m, 1H), 1.42 (s, 9H), 1.4 (dt, J = 8.6 and 2.3 Hz, 1H), 1.29 (d, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 136.2, 134.5, 81.2, 64.4, 48.7, 48.6, 47.6, 46.5, 46.1, 28.2. IR (neat) cm^{-1} 3273, 2976, 2934, 2879, 1715, 1459, 1368, 1350, 1336, 1245, 1028, 1005; HRMS ($C_{13}H_{20}O_3$, ESI) [M + H]$^{+1}$, calculated 225.1485, found 225.1479.

Compound (±)-20. A mixture of cantharidic anhydride (1.29 g, 7.5 mmol), DMAP (0.1 g, 0.8 mmol), and *tert*-butanol (30 mL) was heated at reflux for 36 h. After cooling to rt, the reaction mix was diluted with ether (150 mL) and washed with a diluted HCl solution (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude *tert*-butyl ester acid as a white solid, which was used in the next transformation without purification.

The above crude *tert*-butyl ester acid (242 mg, 1.0 mmol) was dissolved in dry THF (8 mL) and cooled in an ice water bath. After 10 min, triethylamine (0.16 mL, 1.2 mmol) was added via a syringe, followed by ethyl chloroformate (0.12 mL, 1.25 mmol). After 1 h, the white precipitate was removed via vacuum filtration through a pad of Celite and the filtrate was cooled in a dry ice acetone bath. After 10 min, ethanol (5.0 mL) was added, followed by $NaBH_4$ (76 mg, 2.0 mmol) in portions over 5 min. After TLC indicated the consumption of the mixed anhydride intermediate and the formation of a new polar spot, the reaction mix was diluted with ether (20 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product as an oil, which was purified by column chromatography (CH_2Cl_2/acetone, 97:3, as an eluent) to afford the pure alcohol as a white solid (200 mg, 87% yield). ^{1}H NMR (500 MHz, acetone d_6) δ 4.60 (d, J = 4.6 Hz, 1H), 4.48 (d, J = 5.7 Hz, 1H), 3.5 (m, 1H), 3.29 (m, 1H), 2.62 (d, J = 9.2 Hz, 1H), 2.25 (m, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 1.46 (m, 3H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, acetone d_6) δ 170.8, 79.8, 78.0, 60.6, 60.5, 50.7, 50.3, 50.3, 28.6, 29.4; IR (neat) cm^{-1} 3475, 2971, 2946, 1711, 1363, 1209, 1152, 1051, 1042; HRMS ($C_{12}H_{20}O_4$, ESI) [M + H]$^{+1}$, calculated 229.1434, found 229.1429.

General Procedure for Lactonization on GC Scale. To an oven-dried, screw-capped vial was introduced anhydrous solvent (10 mL), and hydroxyester (10 mg, 0.06 mmol). To the vial was added 1 mL of internal standard (226 mg of xylene in 500 mL of CH_2Cl_2). The vial was conditioned to the experiment temperature for 10 min, and an initial time point was taken, after which catalyst (1.0 mg, 0.001 mmol) was added and the reaction mixture was aged at experimental temperature. Aliquots were taken for chiral GC analysis.

Large-Scale Lactonization of Compound (+)-18. To an oven-dried RBF equipped with a septum and stir bar was introduced (±)-**18** (1.0 g, 4.67 mmol) and dichloromethane (250 mL) under argon. The reaction flask was cooled to −5 °C for 15 min, and then (*R*)-**7** (70 mg, 0.093 mmol) was added. After the reaction mixture was stirred for 16 h, Et_2O (20 mL) was added and the reaction mixture was concentrated under vacuum (bath was kept at 10 °C). The residue was purified by silica gel column chromatography (dichloromethane/acetone 95:5) to give enriched alcohol (+)-**18** as a colorless liquid (294 mg, 29% yield, 97% ee). $[\alpha]_D^{23} = +11.0°$ (c = 0.065, $CHCl_3$), and lactone (240 mg), $[\alpha]_D^{23} = -22.0°$ (c = 0.07, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C spectra of products, chromatographic data of hydroxy esters, and computational tables are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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