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Enantioselective Desymmetrization of Diesters

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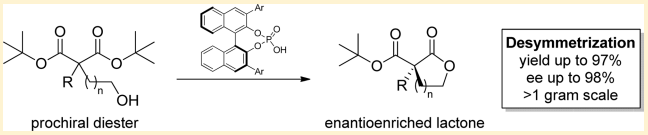
Supporting Information

ABSTRACT: The desymmetrization of prochiral diesters with a chiral phosphoric acid catalyst to produce highly enantioenriched lactones in excellent yield is reported. The process is easily scaled and accommodates a variety of substitution patterns, many of which result in the generation of an enantioenriched all-carbon quaternary center. Manipulation of lactone product to useful small building blocks is also described.



The desymmetrization of prochiral molecules to yield enantioenriched products is a powerful tool in asymmetric synthesis.[1] In particular, the desymmetrization of diesters through an enzyme-mediated partial hydrolysis is a strategy that has been widely used.[2] However, biocatalyzed reactions are often hampered by poor selectivity and catalyst instability as well as difficulties with recovery and reuse.

The lactone motif is seen in many biologically active molecules, and in particular, enantiopure lactones with a fully substituted carbon α to the carbonyl are common. (+)-Hopeahainol A (**1**),[3] which has proven to be an acetylcholinesterase inhibitor that is associated with Alzheimer's disease, and (*S*)-camptothecin (**2**),[4] which exhibits anticancer activity through topoisomerase I inhibition, are two examples (Figure 1).

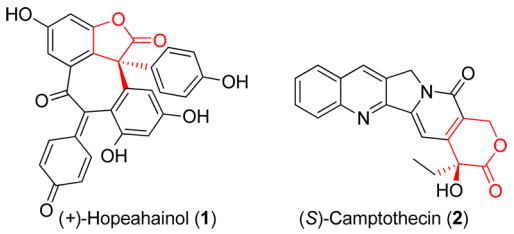
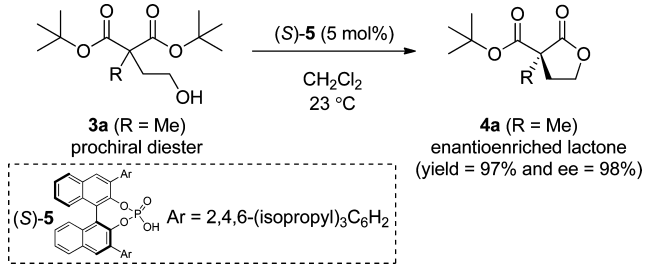


Figure 1. Lactone natural products with an α-chiral center.

Due to our ongoing interest in the development of enantioselective cyclizations, we have previously disclosed the desymmetrization of hydroxy diester **3a** to lactone **4a** in the presence of chiral Brønsted acid **5** in high yield and excellent enantioselectivity (Scheme 1).[5] Presumably, the reaction proceeds through selective activation of one of the esters with the chiral phosphoric acid followed by an intramolecular transesterification. On the basis of this encouraging initial result, we set out to explore the full scope of the desymmetrization process and the utilization of the lactone product.

Construction of enantioenriched α-carboxy-γ-lactones such as **4a** containing a quaternary center has been previously explored due to the high utility of such compounds. Acylation

Scheme 1. Previously Reported Desymmetrization of Diester



of silyl ketene acetals has been accomplished with chiral DMAP derivatives,[6] isothiourea,[7] or thiourea catalysts;[8] however, results are limited to aryl R groups and/or a need for disubstitution of the γ-carbon. Diastereoselective conjugate addition of an enolate equivalent is another strategy that has yielded some promising results, yet the scope of acceptable Michael acceptors is limited.[9] A recent desymmetrization of diynoic acids via bromolactonization has yielded interesting bromoenol lactones; however, scope of the reaction is again limited.[10] Most recently, a method for the enantioselective α-alkylation of α-*tert*-butoxycarbonyllactones through phase-transfer catalysis was revealed; however, substitution was limited to benzylic or allylic groups.[11] The methodology described here, whereby a chiral Brønsted acid **5** catalyzes the cyclization of a symmetric substrate to deliver an enantioenriched lactone, takes advantage of our previously established ester activation by a chiral acid and thus differentiation of the two enantiotopic groups. The lactone products obtained through variation of the methyl group to other substitution patterns are valuable compounds potentially carrying a challenging all-carbon quaternary center (when R ≠ H).

The synthesis of diester substrates such as **3a** begins with the monoalkylation of di-*tert*-butyl malonate (**6**) with sodium hydride and methyl iodide. A second alkylation with 2-

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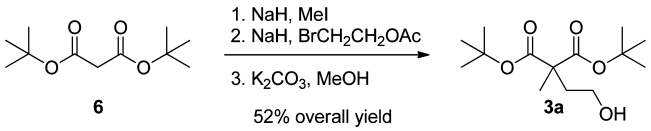
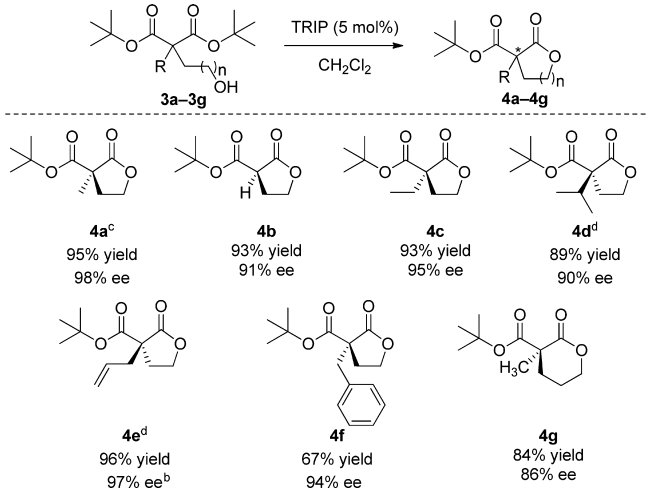
bromoethyl acetate and subsequent hydrolysis yields hydroxy diester **3a** in three short steps and 52% overall yield (Scheme 2).

Scheme 2. Preparation of Prochiral Substrates



Variuos substrates (Table 1, **3b**–**3g**) were studied, ranging in length and branching. Each substrate was prepared as substrate **3a**, but using the appropriate alkyl halide in the first alkylation step. Gratifyingly, modification of the original methyl group in **3a** with larger groups such as ethyl **3c**, isopropyl **3d**, allyl **3e**, and benzyl **3f** yielded enantioenriched lactones containing an all-carbon quaternary stereocenter that would be difficult to install using other methodologies in good to excellent yields (67–97%) and enantiopurity greater than 90%. Replacement of the methyl group with a proton **3b** generated lactone **4b** in excellent yield and good enantiopurity (93% yield and ee = 91%).

Table 1. Substrate Scope[a]



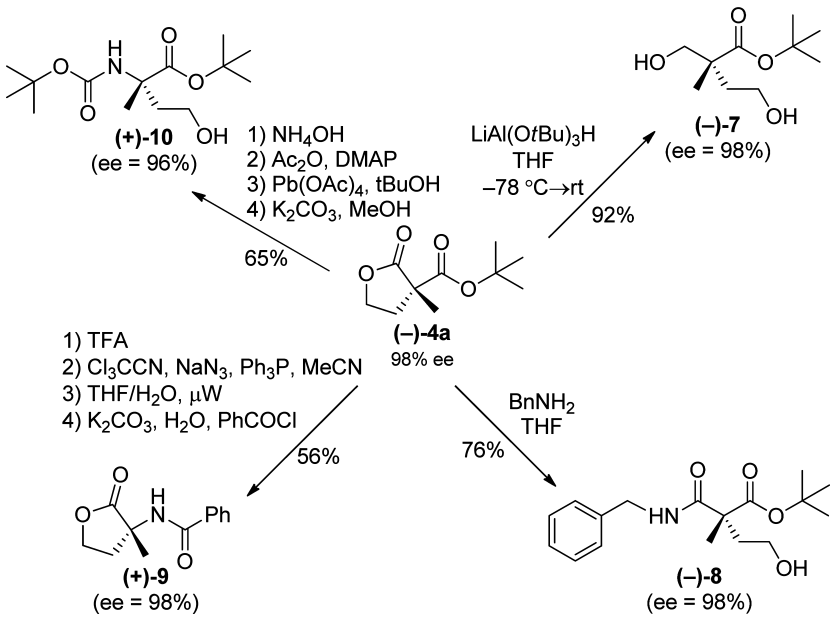
[a]Typical reaction conditions: 0.4 mmol **3**, 0.02 mmol catalyst (*S*)-**5**, in 5 mL of CH_2Cl_2 at set temperature and time. Yields are isolated yields and % ee's determined by GC analysis with a chiral support unless indicated otherwise. [b]Enantiomeric excess determined by HPLC analysis with a chiral support column. [c]Reaction carried out on 1.9 g of **4a** with 20 mg of catalyst (*S*)-**5**. [d]Catalyst used was (*R*)-**5**.

Based on the successful generation of enantioenriched γ-lactones, the desymmetrization was expanded to include preparation of a δ-lactone. Lactonization of the one-carbon homologated hydroxyl diester **3g**, which was prepared through hydroboration and oxidation of methyl, allyl di-*tert*-butyl malonate, occurred with the Brønsted acid chiral catalyst **5** in dichloromethane at room temperature to yield lactone **4g** in good yield (84%) and selectivity (86%).

In order to fully exploit the desymmetrization process, lactone **4a** was prepared on a 1.3 g scale from 1.9 g of **3a** and 20 mg of catalyst **5**, yielding lactone **4a** in 95% yield and 98% ee.

Lactones with enantioenriched all-carbon containing stereocenters such as **4a** prepared from prochiral diesters in good yield and enantioselectivity are prime candidates for incorporation into more complex molecules. The utility of these highly enantioenriched lactone substrates was shown through the transformation of lactone (−)-**4a** into a variety of highly functionalized building blocks (Scheme 3). Successful reduction of lactone (−)-**4a** with lithium tri-*tert*-butoxyaluminum hydride yielded diol (−)-**7** in 92% yield and without loss of enantiopurity (ee = 98%).[12] Amide ester (−)-**8** was formed upon treatment of lactone **4a** with the benzyl amine in 76% yield and retention of 98% ee.[13] Cleavage of the *tert*-butyl ester of lactone **4a** with TFA followed by conversion of the resulting carboxylic acid to the acyl azide and subsequent Curtius rearrangement yielded amido lactone (+)-**9** in 56% overall yield and 98% ee.[14] Treatment of lactone **4a** with aqueous ammonium hydroxide followed by acetylation of the resulting alcohol yielded an amide ester that then underwent a Hofmann

Scheme 3. Transformations



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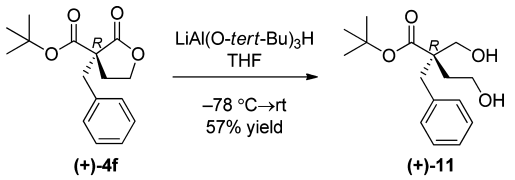
rearrangement with lead(IV) acetate and hydrolysis with potassium carbonate to give α-amino ester (+)-**10** in 65% overall yield and 96% ee.[15]

The absolute configuration of lactone products **4a**−**4g** was assigned through comparison of a known optical rotation value. Diol (+)-**11** is readily prepared from lactone (+)-**4f**, and the sign of rotation matches literature values for (*R*)-**11** (Scheme 4).

Scheme 4. Determination of Absolute Configuration



this paper: $[\alpha]_D^{23}$ = +4.1 (*c* = 1.3, $CHCl_3$)
previous:[11] $[\alpha]_D^{25}$ = +4.7 (*c* = 1.0, $CHCl_3$)

CONCLUSIONS

In summary, we have developed a highly generalized and scalable desymmetrization of hydroxy di-*tert*-butyl esters to produce enantioenriched lactones in high yields and selectivities, many of which contain a challenging all-carbon quaternary center that are difficult to prepare using other methods. The lactone products readily undergo transformations to generate highly functionalized small molecules that are potentially valuable intermediates in the synthesis of bioactive molecules.

EXPERIMENTAL SECTION

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 $CDCl_3$ as a solvent at rt. The NMR chemical shifts (δ) are reported in parts per million. 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 a 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.

Typical Procedure for Alkylations of Di-*tert*-butylmalonate. To a solution of sodium hydride (60% in mineral oil, 1 equiv) in THF (7 mL) was added di-*tert*-butyl malonate (1 equiv), and the solution was stirred until gas evolution was complete. To the reaction mixture was added alkyl halide (1 equiv), and the solution was stirred until reaction completion was determined by TLC analysis.[16] The reaction was quenched with saturated NH_4Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford monoalkylated malonate (yields up to 82%).

To a solution of sodium hydride (60% mineral oil, 2 equiv) in THF (7 mL) was added monoalkylated malonate intermediate, and the solution was stirred until gas evolution was complete. To the reaction mixture was added 2-bromoethyl acetate (2.5 equiv) at 0 °C, and the solution was stirred until reaction completion was determined by TLC analysis. The reaction was quenched with saturated NH_4Cl (6 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (5→15% EtOAc in hexanes) to afford dialkylated malonate (yields up to 90%).

To a solution of the dialkylated intermediate (1 equiv) in MeOH (7 mL) was added K_2CO_3, and the solution was stirred at rt until reaction completion was determined by TLC analysis. The reaction mixture was diluted with CH_2Cl_2 and was extracted with CH_2Cl_2 (2 × 15 mL) and H_2O (1 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to afford hydroxyl diester (yields up to 87%).

Compound ***3a:*** colorless oil (0.26 g, 78% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (t, *J* = 6.3 Hz, 2H), 2.07 (t, *J* = 6.3 Hz, 2H), 1.47 (s, 18 H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 81.4, 58.8, 38.1, 27.8, 20.1; IR (neat) cm^{-1} 3440, 2974, 2934, 1723, 1456, 1367, 1156, 1113, 847; HRMS ($C_{14}H_{26}O_5$, ESI) calcd 297.1677 [M + Na]$^+$, found 297.1667.

Compound ***3b:*** colorless oil (0.28 g, 54% yield); ^+H NMR (500 MHz, $CDCl_3$) δ 3.71 (m, 2H), 3.34 (t, *J* = 15.6 Hz, 1H), 2.07 (m, 2 H), 1.96 (bs, 1H), 1.45 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 81.8, 60.7, 51.3, 31.5, 28.0; IR (neat) cm^{-1} 3441, 2977, 2933, 1723, 1456, 1367, 1137, 843; HRMS ($C_{13}H_{24}O_5$, ESI) calcd 283.1521 [M + Na]$^+$, found 283.1523.

Compound ***3c:*** a white crystal (0.31 g, 87% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 3.65 (m, 2H), 2.07 (t, *J* = 6.6 Hz, 2H), 1.88 (m, q, *J* = 7.5 Hz, 2H), 1.44 (s, 18 H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 81.3, 59.1, 57.7, 34.7, 27.9, 25.9, 8.6; IR (neat) cm^{-1} 3434, 2975, 2934, 1745, 1474, 1365, 1154, 1117, 851; HRMS ($C_{15}H_{28}O_5$, ESI) calcd 311.1834 [M + Na]$^+$, found 311.1835.

Compound ***3d:*** colorless oil (0.09 g, 46% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (m, 2H), 2.23 (m, 1H), 2.01 (t, *J* = 6.5 Hz, 2H), 1.46 (s, 18 H), 0.96 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 82.1, 61.5, 59.5, 36.3, 33.3, 28.3, 18.2; IR (neat) cm^{-1} 3004, 2936, 2356, 1712, 1475, 1365, 1147, 1066, 852; HRMS ($C_{16}H_{30}O_5$, ESI) calcd 325.1990 [M + Na]$^+$, found 325.2001.

Compound ***3e:*** colorless oil (38 mg, 74% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.08 (m, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 2.58 (d, *J* = 7.4 Hz, 2H), 2.05 (t, *J* = 6.6 Hz, 2H), 1.43 (s, 18 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 132.4, 118.8, 81.6, 59.0, 56.9, 37.8, 35.3, 27.3; IR (neat) cm^{-1} 3010, 2943, 1736, 1477, 1364, 1260, 1142, 1074; HRMS ($C_{16}H_{28}O_5$, ESI) calcd 323.1834 [M + Na]$^+$, found 323.1826.

Compound ***3f:*** colorless oil (0.24 g, 42% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 5.03 (m, 5H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.21 (s, 2H), 2.00 (t, *J* = 6.6 Hz, 2H), 1.47 (s, 18 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 138.4 130.3, 128.2, 126.9, 82.1, 59.3, 30.1, 35.5, 28.0; IR (neat) cm^{-1} 3321, 2971, 2963, 1758, 1471, 1330, 1116, 1045, 879; HRMS ($C_{20}H_{30}O_5$, ESI) calcd 373.1990 [M + Na]$^+$, found 373.1987.

Compound ***3g:*** To a solution of sodium hydride (60% in mineral oil, 1.5 g, 38.2 mmol) in THF (10 mL) was added di-*tert*-butyl 2-methylmalonate intermediate dropwise (4.4 g, 19.1 mmol), and the solution was stirred for 10 min at rt. To the reaction mixture was added allyl bromide (4.2 mL, 47.8 mmol) dropwise, and the solution was stirred for 24 h at rt. The reaction was quenched with saturated NH_4Cl (7 mL) at 0 °C, phases were separated, and aqueous phase was extracted EtOAc (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the di-*tert*-butyl 2-allyl-2-methylmalonate intermediate): ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.07 (m, 2H), 2.52 (m, 2H), 1.43 (s, 18H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 133.1, 118.7, 81.1, 54.3, 40.1, 36.5, 27.9, 19.6.

The BH_3-THF (1 M in THF, 0.74 mmol) was diluted with THF (0.11 mL). To the solution was added di-*tert*-butyl 2-allyl-2-methylmalonate intermediate (0.4 g) at 0 °C and allowed to warm to rt. After 2.5 h, a NaOH solution (3 M, 0.89 mL) was added followed by hydrogen peroxide (30 wt % in water, 0.3 mL, 2.87 mmol) at 0 °C. The reaction mixture was stirred at 50 °C overnight. The reaction mixture was extracted with Et_2O (2 × 10 mL) and H_2O (1 ×

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10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes with 0.1% TEA) to afford compound **3g** as a colorless oil (0.13 g, 31% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (m, 2H), 1.79 (m, 2H), 1.51 (m, 2H), 1.42 (s, 18H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 81.1, 62.9, 54.34, 31.6, 27.9, 19.9; IR (neat) cm^{-1} 3442, 2970, 2929, 1720, 1457, 1366, 1150, 1112, 851; HRMS ($C_{15}H_{28}O_5$, ESI) calcd 311.1834 $[M + Na]^+$, found 311.1825.

Typical Procedure for Enantioselective Lactonization of Hydroxy Diester. To a solution of chiral acid catalyst **5** (0.05 mmol) in CH_2Cl_2 (5 mL) was added hydroxy diester (1.0 mmol), and the solution was stirred for the allocated time and temperature. The reaction was extracted with EtOAc (2 × 10 mL) and H_2O (1 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated.

The residue was purified by flash chromatography on silica gel (10→20% EtOAc in hexanes) to afford enantioenriched lactone (yields up to 97%).

Compound ***4a:*** Reaction was carried out at rt for 120 h to yield a white crystal (184 mg, 97% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (m, 2H), 2.64 (m, 1H), 2.13 (m, 1H), 1.47 (s, 9 H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 169.5, 83.0, 65.9, 50.6, 35.2, 27.8, 20.1; IR (neat) cm^{-1} 2980, 1735, 1448, 1372, 1235, 1043; HRMS ($C_{10}H_{16}O_4$, ESI) calcd 223.0946 $[M + Na]^+$, found 223.0934; $[\alpha]_D^{23}$ = −3.6 (c = 0.5, $CHCl_3$).

Compound ***4b:*** Reaction was carried out at 5 °C for 72 h to yield a colorless oil (188 mg, 93% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (m, 1H) 4.30 (m, 1H), 3.42 (m, 1H), 2.59 (m, 1H), 2.46 (m, 1H), 1.48 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 166.9, 83.1, 67.3, 47.0, 27.9, 26.5; IR (neat) cm^{-1} 2980, 1772, 1725, 1369, 1138, 1016; HRMS ($C_9H_{14}O_4$, ESI) calcd 185.0813, $[M - H]^-$, found 185.0807; $[\alpha]_D^{23}$ = +3.6 (c = 2.8, $CHCl_3$).

Compound ***4c:*** Reaction was carried out at rt for 120 h to yield a white crystal (94 mg, 93% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.63 (m, 1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.46 (s, 9 H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 168.7, 82.9, 66.1, 55.4, 31.3, 27.9, 27.1, 9.1; IR (neat) cm^{-1} 2979, 1741, 1466, 1370, 1236, 1043; HRMS ($C_{11}H_{18}O_4$, ESI) calcd 237.1102 $[M + Na]^+$, found 237.1105; $[\alpha]_D^{23}$ = +1.6 (c = 2.2, $CHCl_3$).

Compound ***4d:*** Reaction was carried out at 35 °C for 192 h to yield a white crystal (39.2 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.61 (m, 2H), 2.17 (m, 1H), 1.47 (s, 9 H), 0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 167.9, 82.8, 66.2, 59.8, 31.4, 27.7, 26.3, 17.9, 17.7; IR (neat) cm^{-1} 2970, 1734, 1414, 1383, 1201, 1044; HRMS ($C_{12}H_{20}O_4$, ESI) calcd 251.1259 $[M + Na]^+$, found 251.1259; $[\alpha]_D^{23}$ = −5.6 (c = 1.1, $CHCl_3$).

Compound ***4e:*** Reaction was carried out at 35 °C for 168 h to yield a white crystal (18 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.22 (m, 2H), 4.31 (m, 2H), 2.73 (m, 1H), 2.51 (m, 2 H), 2.33 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 168.2, 132.1, 120.0, 83.1, 66.2, 54.1, 37.9, 31.0, 27.7; IR (neat) cm^{-1} 2949, 1772, 1349, 1286, 1141, 1066; HRMS ($C_{12}H_{18}O_4$, ESI) calcd 249.1102 $[M + Na]^+$, found 249.1093; $[\alpha]_D^{23}$ = −4.7 (c = 0.5, $CHCl_3$).

Compound ***4f:*** Reaction was carried out at 35 °C for 155 h to yield a colorless oil (77 mg, 67% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.25 (m, 1H), 3.85 (m, 1H), 3.25 (m, 2H), 2.54 (m, 1H), 2.25 (m, 1H), 1.47 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 169.6, 135.7, 130.2, 128.7, 127.3, 83.3, 66.2, 56.1, 38.9, 30.6, 27.9; IR (neat) cm^{-1} 2979, 2360, 1771, 1721, 1454, 1368, 1145, 1029; HRMS ($C_{16}H_{20}O_4$, ESI) calcd 299.1259 $[M + Na]^+$, found 299.1261; $[\alpha]_D^{23}$ = +25.1 (c = 1.1, $CHCl_3$).

Compound ***4g:*** Reaction was carried out at rt for 144 h to yield a colorless oil (29.1 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (m, 1H), 2.42 (m, 1H), 1.91 (m, 2H), 1.63 (m, 1H), 1.46 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 171.1, 82.7, 68.7, 51.1, 30.8, 27.8, 23.1, 20.5; IR (neat) cm^{-1}; 2983, 1730, 1446, 1370, 1229, 1042; HRMS ($C_{11}H_{18}O_4$, ESI) calcd 237.1102 $[M + Na]^+$, found 237.1095; $[\alpha]_D^{23}$ +14.1 (c = 1.0, $CHCl_3$).

Compound ***7:*** To a solution of compound **4a** (110 mg, 0.5 mmol) in THF (5.0 mL) was added a solution of LiAl(OtBu)$_3$H (1.0 M in THF, 2 mL, 2.0 mmol) at −78 °C. The solution was allowed to warm to rt and react for 24 h. The reaction was quenched with saturated potassium sodium tartrate, phases were separated, and aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (20→40% EtOAc in hexanes) to afford compound **7** as a colorless oil (94 mg, 92% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.48 (d, J = 8.6 Hz, 1H), 3.23 (d, J = 8.0 Hz, 1H), 2.43 (m, 1H), 1.99 (m, 1H), 1.17 (s, 3H) 1.12 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.5, 73.6, 67.3, 65.9, 43.8, 32.8, 27.0, 20.3; IR (neat) cm^{-1} 3436, 2976, 2930, 1722, 1456, 1367, 1146, 1103, 846; HRMS ($C_{10}H_{20}O_4$, ESI) calcd 227.1259 $[M + Na]^+$, found 227.1250; $[\alpha]_D^{23}$ = −0.6 (c = 1.0, $CHCl_3$).

Compound ***8:*** To a solution of compound **4a** (100 mg, 0.5 mmol) in THF (5.0 mL) was added benzyl amine (0.27 mL, 2.5 mmol) at rt. The solution was allowed to react under reflux for 4 days. The reaction was acidified with 1 M HCl at 0 °C and extracted with Et_2O (2 × 10 mL) and H_2O (1 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→30% EtOAc in hexanes) to afford compound **8** as a colorless oil (90 mg, 77% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.44 (d, J = 5.7 Hz, 2H), 3.7 (m, 2H), 2.15 (m, 2H), 1.46 (m, 3H) 1.44 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 172.2, 138.1, 128.7, 127.7, 127.5, 82.3, 59.4, 52.9, 43.6, 39.2, 27.7, 22.1; IR (neat) cm^{-1} 3358, 2980, 2359, 1726, 1369, 1242, 1045; HRMS ($C_{17}H_{25}NO_4$, ESI) calcd 308.1861 $[M + H]^+$, found 308.1866; $[\alpha]_D^{23}$ = −3.3 (c = 1.5, $CHCl_3$).

Compound ***9:*** To a solution of compound **4a** (45 mg, 0.22 mmol) was added trifluoroacetic acid (9 mL) at rt. The solution was allowed to react at rt overnight. The reaction mixture was then concentrated. To the reaction residue were added NaN_3 (18 mg, 0.27 mmol) and PPh_3 (0.12 g, 0.44 mmol) at rt. MeCN (10 mL) was then added to the reaction mixture at 0 °C and stirred until homologous. Cl_3CCN (0.08 mL, 0.44 mmol) was added at 0 °C, and the solution was allowed to warm to rt and react for 30 h. The reaction mixture was partially concentrated and the residue dissolved in CH_2Cl_2 (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL) and H_2O (1 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to yield a yellow clear oil (43 mg).

The crude acyl azide intermediate (43 mg, 0.26 mmol) was dissolved in THF (1.5 mL) and heated to 100 °C for 20 min in a microwave reactor. The observance of an isocyanate peak (2283 cm^{-1}) by IR spectroscopy confirmed that the rearrangement had occurred. A mixture of K_2CO_3 (0.14 g, 1.02 mmol) in H_2O (0.3 mL) was added to the reaction mixture and allowed to stir for 20 min, and to it was added benzoyl chloride (0.027 mL, 0.24 mmol). The solution was allowed to react overnight at rt. The reaction was acidified with 1 M HCl, and the reaction mixture was extracted with EtOAc (2 × 10 mL) and H_2O (1 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (30→60% acetone in hexanes) to afford compound **9** as a white crystal (31 mg, 56% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.42 (m, 5H), 4.56 (m, 1H), 4.33 (m, 1H), 2.83 (m, 1H), 2.57 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 166.8, 133.5, 132.3, 130.2, 128.8, 65.9, 56.2, 35.0, 22.3; IR (neat) cm^{-1} 3296, 2982, 2361, 1763, 1632, 1527, 1319, 1107, 1023, 936; HRMS ($C_{16}H_{30}O_5$, ESI) calcd 325.1990 $[M + Na]^+$, found 325.2001; $[\alpha]_D^{23}$ = +2.0 (c = 1.0, $CHCl_3$).

Compound ***10:*** To a solution of compound **4a** (88.1 mg, 0.44 mmol) in dioxane (1.5 mL) was added concentrated NH_4OH (5 mL) at rt. The solution was allowed to react at rt overnight. The reaction mixture was then concentrated. The reaction mixture was dissolved in TEA (0.10 mL, 0.66 mmol) in CH_2Cl_2 (2 mL). DMAP (11 mg, 0.09 mmol) was added followed by Ac_2O (0.06 mL, 0.66 mmol) at rt, and the solution was allowed to react for 40 h. The reaction mixture was concentrated, and the residue dissolved in EtOAc (5 mL) and extracted with EtOAc (2 × 10 mL) and H_2O (10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (15→30% acetone in hexanes) to afford amide ester intermediate as a colorless oil (47

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mg, 41% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.1 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 2.00 (s, 3H), 1.46 (s, 9H) 1.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 173.3, 171.1, 82.6, 61.0, 52.2, 35.4, 27.7, 21.9, 20.9; IR (neat) cm^{-1} 3348, 2979, 2358, 1745, 1669, 1364, 1227, 1121, 1037; HRMS ($C_{12}H_{21}NO_5$, ESI) calcd 282.1317 $[M + Na]^+$, found 282.1326.

To a solution of the amide ester intermediate (28 mg, 0.108 mmol) in *t*BuOH (0.55 mL) was added $Pb(OAc)_4$ (95.9 mg, 0.216 mmol) at 70 °C. The solution was allowed to react overnight. To the reaction mixture were added Et_2O (4 mL) and $NaHCO_3$ (0.11 g) and allowed to stir for 10 min. The reaction mixture was filtered through SiO_2 and concentrated. The residue was purified by flash chromatography on silica gel (20→40% acetone in hexanes) to afford the amide intermediate as a colorless oil (20 mg, 57% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, J = 6.6 Hz, 2H), 2.2 (m, 1H), 2.15 (m, 1H), 2.00 (s, 3H) 1.50 (s, 3H), 1.46 (s, 9 H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 171.0, 154.2, 82.1, 79.4, 60.9, 58.1, 34.5, 28.4, 27.9, 24.2, 21.0; IR (neat) cm^{-1} 3358, 2980, 2359, 1726, 1369, 1242, 1045; HRMS ($C_{16}H_{29}NO_6$, ESI) calcd 354.1892 $[M + Na]^+$, found 354.1882.

To a solution of the amide intermediate (20 mg, 0.061 mmol) in MeOH (1.5 mL) was added K_2CO_3 (41 mg) at rt. The solution was allowed to react for 20 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and extracted with H_2O (1 × 5 mL). The organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solution was concentrated to yield compound **10** as a colorless oil (14 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.7 (m, 2H), 2.2 (m, 1H), 2.15 (m, 1H), 1.52 (s, 3H), 1.46 (s, 9 H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 154.7, 81.8, 79.4, 59.2, 58.5, 39.1, 28.4, 28.0, 23.8; HRMS ($C_{14}H_{27}NO_5$, ESI) calcd 312.1786 $[M + Na]^+$, found 312.1776; $[\alpha]_D^{23}$ = +10.0 (c = 0.9, $CHCl_3$).

Compound **11**: colorless oil (100 mg, 57% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 3.84 (d, J = 12.0 Hz, 1H), 3.69 (m, 2H), 3.54 (d, J = 12.0 Hz, 1H), 3.17 (b, 2H), 2.95 (d, J = 13.7 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 136.5, 130.5, 127.9, 126.8, 82.0, 65.4, 59.2, 51.7, 41.9, 38.9, 27.9; IR (neat) cm^{-1} 3433, 2974, 2932, 1773, 1725, 1453, 1369, 1145, 1104, 844; $[\alpha]_D^{23}$ = +4.1 (c = 1.3, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C spectra of new compounds and traces of enantioenriched products 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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