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An Enzymatic Approach to the Desymmetrization of Disubstituted Pyrrolines

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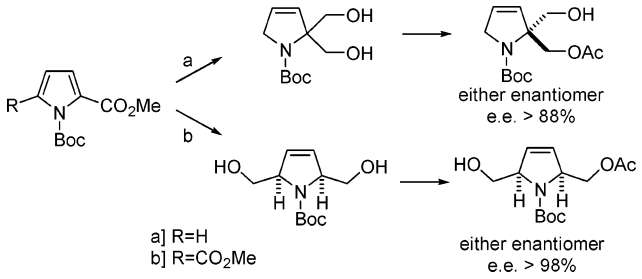
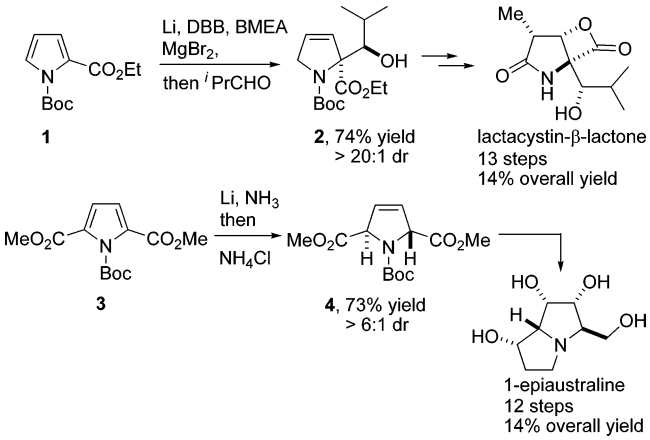


The enzymatic desymmetrization of 2,2- and 2,5-disubstituted pyrroline compounds is reported in a procedure which gives access to both enantiomers in excellent enantiomeric excess and good yield. The enzyme reaction precursors are formed easily from two readily available substituted pyrroles using both ammonia (Na/NH_3) and ammonia-free (Li/DBB) Birch reduction conditions.

We have previously reported studies into the partial reduction of mono- and disubstituted pyrroles using Birch reduction conditions (Na, NH_3) and, recently, an ammonia-free variant (Li, DBB, R_2NH).[1] Two such examples of this methodology are shown in Scheme 1: in the first example excellent *anti*-diastereoselectivity was achieved in the ammonia-free reductive aldol reaction of monosubstituted *N*-Boc pyrrole **1**. Initial reduction of **1** with LiDBB and BMEA (bismethoxy ethylamine), followed by transmetalation of the enolate thus formed and quenching with isobutyraldehyde gave pyrroline **2** (>20:1 anti/syn). The utility of this methodology was proven in our synthesis of the biologically active natural product lactacystin-

SCHEME 1



β-lactone.[2] In another development, we have also shown that the ammonia Birch reduction conditions allow transformation of disubstituted *N*-Boc pyrrole **3** in 73% yield and with 6:1 diastereoselectivity in favor of the *trans*-pyrroline **4** (Scheme 1). This chemistry was recently used as part of our route toward the polyhydroxylated pyrrolizidine natural products 1-epiaustraline and hyacinthacine A_1.[3] Both of these examples show the ready applicability of the stereoselective partial reduction methodology to natural product synthesis. Unfortunately, the syntheses shown both gave racemic material because neither partial reduction reaction is an enantioselective process. A certain degree of enantioselectivity has been obtained within the ammonia-free reduction first by the use of chiral auxiliaries[4] and then by the use of enantioselective protonation.[5] While both methods gave encouraging results, we have yet to achieve the levels of practicality or enantioselectivity required to fulfill the aim of developing this methodology to encompass the syntheses of enantiopure natural products based on the pyrrolidine structural motif. Therefore, an attractive option was to use an enzymatic approach to desymmetrize pyrroline compounds formed after the Birch reduction of both mono- and disubstituted pyrroles.

Following literature precedent, diol **7** was formed on a multigram scale in two steps from commercially available pyrrole **5** (Scheme 2).[6] A standard Birch reduction followed by an electrophilic quench using iodomethyl pivalate gave 2,2-disubstituted pyrrole **6** in 75% yield. This can then be doubly reduced using Altenbach's protocol with lithium borohydride

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(1) (a) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015−5018. (b) Donohoe, T. J.; House, D.; Ace, K. W. *Org. Biomol. Chem.* **2003**, *1*, 3749−3757. (c) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999−1002.

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(6) (a) Harbuck, J. W.; Rapoport, H.; *J. Org. Chem.* **1972**, *37*, 3618−3622. (b) Leroy, J.; Porhiel, E.; Bondon, A. *Tetrahedron* **2002**, *58*, 6713−6722. (c) Schieweck, F.; Altenbach, H.-J. *J. Carbohydr. Chem.* **2000**, *19*, 647−652.

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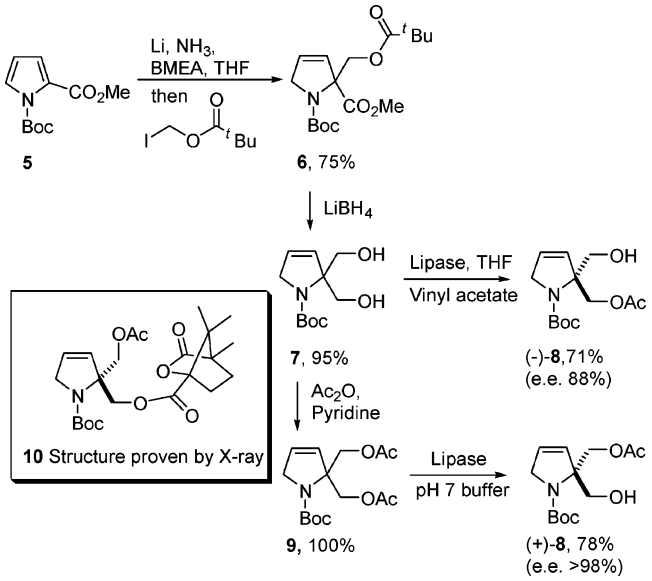
SCHEME 2



to give the required diol compound **7** in 95% yield.[7] The aim was to use lipase-catalyzed reactions to form both enantiomers of the monoacetylated pyrroline **8** by esterification of diol **7** or, alternatively, by hydrolysis of the corresponding diacetatylated derivative **9 (**Scheme 2).

A number of enzymes were screened for both the acetylation and hydrolysis reaction with the best results obtained using the enzyme lipoprotein lipase obtained from the *Pseudomonas* species.[8] Pleasingly, the esterification reaction gave monoacetate (−)-**8** (ee 85%)[9] in a yield of 54% (with 20% recovered starting material), but the rate of reaction was slow, and each reaction required 2 weeks at room temperature. The rate of reaction could be greatly increased by carrying out the reaction in an incubator at 37 °C. Under these conditions the acetylation (**7** → (−)-**8)** reaction gave a yield of 71% (ee 88%) after only 48 h. The hydrolysis of diacetate **9** was considerably faster than the acetylation reaction, and after 16 h at 37 °C, monoacetate (+)-**8** (ee > 98%) was isolated in a good yield of 78%. It should be noted that while the enzyme could be filtered, dried, and recovered for further use after the acetylation reaction, this was unfortunately not possible with the hydrolysis reaction because of the aqueous conditions used.

Having synthesized monoacetate (+)-**8** in high enantiomeric excess, it was necessary to determine its absolute stereochemistry. To achieve this, enantiopure monoacetate **(+)-8** was coupled with (1*S*)-(−)-camphanic chloride.[10] X-ray crystallography of the thus formed camphanoyl ester **10** proved the stereochemical assignment of **(+)-8** as shown. The stereochemistry of this adduct confirmed the sense of selectivity displayed by the enzyme, and this is consistent with previous literature reports concerning the stereoselectivity of lipoprotein lipase from *Pseudomonas* species.[11]

As mentioned previously, our investigations into the diastereoselective Birch reduction of 2,5-disubstituted pyrrole **3** have been reported, and by variation of the conditions, excellent control of diastereoselectivity to give either the *meso cis* compound or the *trans*-pyrroline was achieved.[1c] Importantly, disubstituted pyrrole **3** (Scheme 3) was formed in one step from commercially available *N*-Boc pyrrole in a double lithiation reaction using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as a base followed by a quench with methyl chloroformate. To obtain the *meso cis*-dihydropyrrole **11** selectively, an ammonia-free partial reduction was used quenching with the bulky proton source 2,6-di-*tert*-butylphenol giving pyrroline **11** in a greater than 10:1 (*cis*) selectivity. The experimental procedure reported here for the ammonia-free reduction of pyrrole **3** is a modified version of our previously reported technique and is no longer reliant upon the prior grinding of lithium wire into a powder to make it more reactive. This change allows the reaction to be carried out on a much larger scale (30−40 mmol) and makes the procedure both easier to carry out as well as safer to perform because powdered lithium is no longer formed at any point during the reaction.

Initial attempts to desymmetrize *cis*-pyrroline **11** focused on monohydrolysis of the diester to give the mixed acid/ester compound. However, this route gave only poor results (low conversion), and another approach was sought. Originally, the reduction of *cis*-diester **11** was performed using lithium borohydride to give the *cis*-diol compound **12**, but this reaction gave only moderate yields.[1c] A thorough screen of a variety of reducing reagents revealed that the best results were obtained by use of Red-Al which formed the *cis*-diol **12** in 84% yield (Scheme 3). As before, it was hoped to access both enantiomers of the monoacetylated pyrroline **13** either by esterification of *cis*-diol **12** or by hydrolysis of the corresponding *cis*-diacetate **14**. Accordingly, diacetate **14** could be formed from diol **12** in quantitative yield by reaction with acetic anhydride in pyridine.

Based upon the previous success using the enzyme lipoprotein lipase from *Pseudomonas* species the investigations began using this enzyme as a catalyst for the acetylation of **12** (Scheme 3). For the esterification reaction of *cis*-diol **12**, vinyl acetate (10 eq.) was used in THF at 37 °C. Pleasingly it was observed that these conditions resulted in formation of the monoacetylated pyrroline (+)-**13** (ee > 98%) in a yield of 90% on a 30 mmol scale. The enantiomeric excess was measured accurately by formation of the *para*-nitrobenzoate derivative **15** and then HPLC analysis against a racemic standard.[12] As before, the enzyme used in the acetylation reaction could be recovered and recycled. To determine the absolute stereochemistry of the enantiopure monoacetylated pyrroline **(+)-13** the camphanoyl ester of monoacetate (+)-**13** was formed and then reacted with TFA to remove the Boc protecting group and form TFA salt **16**; X-ray crystallography of TFA salt **16** proved the stereo-

(7) Schieweck, F.; Altenbach, H.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3409−3414.

(8) Lipoprotein lipase from *Pseudomonas* species supplied by a commercial supplier (62336, ≥160 units/mg).

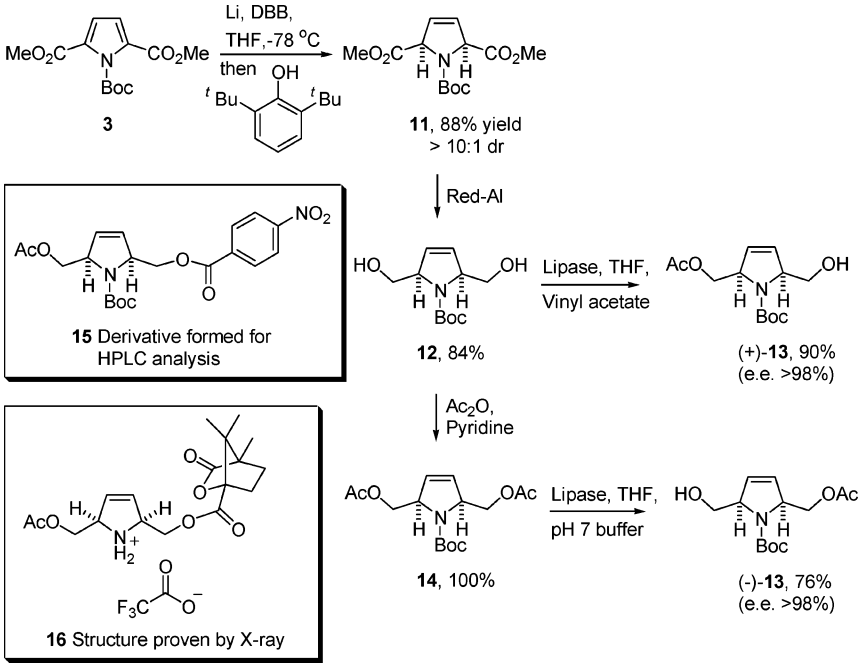
(9) As measured by HPLC against a racemic standard (Chiralpak AD, hexane/EtOH 93:7, 206 nm, 1 mL min^{-1}, t_R = 18.8 and 35.6 min) formed from diol **7** by reaction with acetic anhydride (10 equiv) and cerium (III) chloride (0.1 equiv) in THF. See Supporting Information for full experimental details.

(10) (1*S*)-(−)-Camphanic chloride has 99% ee by GLC.

(11) (a) Bianchi, D.; Cesti, P.; Battistel, E, *J. Org. Chem.* **1988**, *53*, 5531−5534. (b) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231−5239.

(12) As measured by HPLC (Chiralpak AD, hexane/EtOH 98:2, 254 nm, 1 mL min^{-1}, t_R = 31.1 and 38.0 min) against a racemic standard formed initially by reaction of diol **11** with acetic anhydride (10 equiv) and cerium-(III) chloride (0.1 equiv) in THF giving **(±)-13** and then conversion to the *para*-nitrobenzoate derivative **(±)-15** by reaction with *para*-nitrobenzoyl chloride (2 equiv) and DMAP (3 equiv) in dichloromethane. See Supporting Information for full experimental details.

SCHEME 3



chemical assignment of (+)-**13** to be as shown. Again, since the enzyme used, lipoprotein lipase from *Pseudomonas* species, is known to preferentially acetylate primary and secondary alcohol stereogenic centers of (*R*)-configuration, our findings are consistent with this sense of stereoselectivity.

The hydrolysis reaction of diacetate **14** was again accomplished using lipoprotein lipase from *Pseudomonas* species. The optimum conditions were found to be use of pH 7 buffer solution with 2-propanol as a cosolvent to aid dissolution of the diacetylated starting material. These conditions gave formation of monoacetylated pyrroline (−)-**13** (ee > 98%) in 76% yield as measured by HPLC against a racemic standard.

In conclusion, enantioselective and high yielding routes have been developed to both enantiomers of the monoacetylated 2,2-disubstituted *N*-Boc pyrroline **8** and the monoacetylated 2,5-disubstituted *N*-Boc pyrroline **13**. This has been achieved via desymmetrization of the corresponding pyrroline systems using lipoprotein lipase from *Pseudomonas* species either to selectively monoacetylate 1,3- and 1,5-diols or to selectively hydrolyze their corresponding diacetates. The resulting enantiopure building blocks have the potential for wide applicability in the synthesis of several heterocyclic natural products. It is hoped that this chemistry will now expedite enantioselective routes toward members of the alexine family of polyhydroxylated pyrrolizidines (from the 2,5-pyrroline system) or, alternatively, the oxazolomycin family of compounds using 2,2-disubstituted pyrroline compounds.

Experimental Section

Note: The majority of the proton and carbon spectra exhibit doubling of some signals because of the presence of Boc group rotamers.

(*R*)-2-(Acetoxymethyl)-*N*-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)-2,5-dihydropyrrole ((−)-8). Vinyl acetate (0.20 mL, 220 mmol) and lipoprotein lipase (10 mg) were added to a solution of diol **7** (50 mg, 0.218 mmol) in THF (2 mL). The reaction mixture was incubated at 37 °C (shaken at 150 rpm) and monitored by TLC. When conversion had been judged to be sufficient, the reaction mixture was filtered, and the enzyme was recovered for recycling. The solvent was removed under reduced pressure, and the crude mixture was purified by flash column chromatography [SiO_2, EtOAc-light petroleum (bp 40−60 °C), 1:2, then 1:1 after product obtained] to yield, in order of elution, diacetate **9** as a colorless oil (13 mg, 19%), the title compound as a colorless oil (42 mg, 71%, ee 88%), and then starting material (2 mg, 4%). $[\alpha]^{20}_D$ −32.3 (*c* 1.0, MeOH). IR (thin film) 3416 (br), 2976, 1745, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.00 (1 H × 0.2, m), 5.86 (1 H × 0.8, dt, *J* 6.6 and 1.8), 5.58 (1 H × 0.2, m), 5.49 (1 H × 0.8, dt, *J* 6.6 and 2.0), 4.89 (1 H, m), 4.61 (1 H × 0.8, d, J_{AB} 11.2), 4.53 (1 H × 0.8, d, J_{AB} 11.2), 4.40 (1 H × 0.2, d, J_{AB} 11.1), 4.36 (1 H × 0.2, d, J_{AB} 11.1), 4.19−4.22 (2 H × 0.2, m), 4.15 (1 H × 0.8, dt, J_{AB} 15.9, *J* 2.0), 4.10 (1 H × 0.8, dt, J_{AB} 15.9, *J* 2.0), 3.92 (1 H × 0.2, d, J_{AB} 11.3), 3.88 (1 H × 0.8, d, J_{AB} 12.0), 3.77 (1 H × 0.8, d, J_{AB} 12.0), 3.73 (1 H × 0.2, d, J_{AB} 11.3), 2.04 (3 H, s), 1.51 (9 H × 0.2, s), 1.48 (9 H × 0.8, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.7, 155.6, 129.4, 127.2, 80.9, 73.8, 67.1, 63.1, 55.5, 28.4, 20.9. ESI HRMS (*m*/*z*): 294.1314 [M + MeCN + Na]$^+$; $C_{13}H_{21}NO_5$ + Na^+ requires 294.1317.

(*S*)-2-(Acetoxymethyl)-*N*-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)-2,5-dihydropyrrole ((+)-8). Lipase (10 mg) was added to a mixture of diacetate **9** (50 mg, 0.16 mmol) in THF (0.05 mL) and pH 7 phosphate buffer (1.95 mL, 0.5 M). The reaction mixture was incubated at 37 °C (shaken at 150 rpm) and monitored by TLC. When conversion had been judged to be sufficient, the product was extracted with ethyl acetate (3 × 5 mL). The solvent was removed under reduced pressure to yield a crude mixture that was separated by flash column chromatography [SiO_2, EtOAc-light petroleum (bp 40−60 °C), 4:6] to yield the title compound as a colorless oil (34 mg, 78%, ee > 98%) which was spectroscopically identical to the racemic sample. $[\alpha]^{25}_D$ +39.2 (*c* 1.0, MeOH).

(2*R*,1′*S*)-2-(Acetoxymethyl)-*N*-(*tert*-butoxycarbonyl)-2-(camphanoyloxymethyl)-2,5-dihydropyrrole (10). (1*S*)-(−)-Camphanic chloride (128 mg, 590 μmol) in DCM (2 mL) was added dropwise to a stirred solution of (*S*)-(+)-pyrroline **8** (>95% ee) (44 mg, 150 μmol) and DMAP (2−4 mg) in DCM (8 mL) and triethylamine (62 μL, 440 μmol) under an atmosphere of argon at room temperature. The reaction was stirred for 16 h. The crude mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2, EtOAc-light petroleum (bp

40−60 °C), 3:17] to yield a white solid. Recrystallization from ethyl acetate−hexane yielded the title compound as colorless blocks (59 mg, 81%): mp 79−83 °C. IR (thin film): 2972, 1791, 1749, 1697, 1456, 1391, 1344 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$): δ_H 5.98 (1 H × 0.5, dt, *J* 6.3 and 1.8), 5.90 (1 H × 0.5, dt, *J* 6.3 and 1.8), 5.64 (1 H × 0.5, dt, *J* 6.3 and 2.0), 5.60 (1 H × 0.5, dt, *J* 6.3 and 2.0), 4.80 (1 H × 0.5, J_{AB} 11.1), 4.68 (1 H × 0.5, J_{AB} 11.1), 4.58 (1 H × 0.5, J_{AB} 11.1), 4.57 (1 H × 0.5, J_{AB} 11.1), 4.44 (1 H × 0.5, J_{AB} 11.1), 4.40 (1 H × 0.5 + 1 H × 0.5, J_{AB} 11.1), 4.34 (1 H × 0.5, J_{AB} 11.1), 4.19 (1 H, m), 4.13 (1 H, m), 2.42−2.31 (1 H, m), 2.05 (3 H × 0.5, s), 2.05 (3 H × 0.5, s), 2.03−1.86 (2 H, m), 1.72−1.63 (1 H, m), 1.50 (9 H × 0.5, s), 1.46 (9 H × 0.5, s), 1.11 (3 H, s), 1.02 (3 H × 0.5, s), 1.01 (3 H × 0.5, s), 0.93 (3 H × 0.5, s), 0.92 (3 H × 0.5, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.4, 167.1, 153.2, 129.0, 128.8, 127.6, 91.0, 90.7, 81.2, 80.0, 76.7, 71.3, 70.3, 65.1, 64.5, 64.2, 63.9, 55.4, 55.2, 54.8, 54.1, 54.0, 30.8, 30.6, 28.9, 28.4, 20.8, 20.7, 16.7, 16.6, 9.7. ESI HRMS (*m*/*z*): 352.1756 $[M - Boc + 2 H]^+$; $C_{18}H_{26}NO_6$ requires 352.1760.

(2*R*,5*S*)-*tert*-Butyl-2-(acetoxymethyl)-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate ((+)-13). Vinyl acetate (29 mL, 310 mmol) and lipoprotein lipase (300 mg) were added to a solution of diol **12** (7.0 g, 31 mmol) in THF (250 mL). The mixture was incubated at 37 °C for 16 h (shaken at 150 rpm). The enzyme was removed by filtration, and the filtrate was extracted into ethyl acetate (2 × 70 mL) and washed with brine (70 mL). The combined organic layers were dried over $MgSO_4$ and filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography [SiO_2, EtOAc-light petroleum (bp 40−60 °C), 1:1] to yield (+)-pyrroline **13** as a pale yellow oil (8.3 g, 90%, ee > 98%). $[\alpha]^{20}_D$ +71.1 (*c* 1.0, CH_2Cl_2). IR (thin film): 3445 (br), 2977, 1745, 1699 cm^{-1}. ^1H NMR (500 MHz, DMSO-D_6, 373 K): δ_H 5.96 (1H, d, *J* = 6.0), 5.80 (1H, d, *J* = 6.3), 4.61 (1H, m), 4.43 (2H, m), 4.25 (1H, dd, *J* = 10.8 and 3.9), 4.04 (1H, dd, *J* = 10.8 and 5.8), 3.69 (1H, m), 3.33 (1H, dt, *J* = 10.1 and 6.3), 2.00 (3H, s), 1.50 (9H, s). ^{13}C NMR (125 MHz, DMSO-D_6, 373 K): δ_C 170.3, 154.3, 130.6, 127.6, 79.7, 67.3, 65.2, 64.1, 64.0, 28.6, 20.9. ESI HRMS (*m*/*z*): 294.1312 $[M + Na]^+$; $C_{13}H_{21}NO_5 + Na^+$ requires 294.1318.

(2*S*,5*R*)-*tert*-Butyl-2-(acetoxymethyl)-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate ((−)-13). Diacetate **14** (50 mg, 0.16 mmol) was dissolved in 2-PrOH (0.05 mL). pH 7 buffer solution (1.95 mL, 0.5 M) was added followed by lipoprotein lipase (10 mg). The mixture was incubated at 37 °C for 15 h (shaken at 150 rpm) and then filtered through Celite. The Celite cake was then rinsed with ethyl acetate (15 mL). The combined ethyl acetate and reaction mixture solutions were dried over $MgSO_4$ and concentrated in vacuo before being purified by flash column chromatography [SiO_2, EtOAc-light petroleum (bp 40−60 °C), 1:4 then 2:3 then 4:1] to afford, in order of elution, diacetate **14** as a pale yellow oil (3 mg, 6%) and (−)-pyrroline **13** as a pale yellow oil (33 mg, 76%, ee > 98%) which was spectroscopically identical to the racemic sample. $[\alpha]^{20}_D$ −73.8 (*c* 1.0, CH_2Cl_2).

2-(Acetoxymethyl)-5-(((1*R*,4*S*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy)methyl)-2,5-dihydro-1*H*-pyrrolium-trifluoroacetate (16). (1*S*)-(−)-Camphanic chloride (240 mg, 1.11 mmol) in DCM (3 mL) was added dropwise to a stirred solution of (+)-pyrroline **13** (>98% ee) (150 mg, 0.55 mmol) and DMAP (10 mg) in DCM (15 mL) and triethylamine (0.23 mL, 1.66 mmol) under an atmosphere of argon at room temperature. The reaction was stirred for 16 h before addition of H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organics were washed once with 1 M HCl (20 mL), dried over $MgSO_4$, and concentrated in vacuo before being purified by flash column chromatography [SiO_2, EtOAc-light petroleum (bp 40−60 °C), 30:70] to yield a colorless oil which solidified upon standing over the course of 2 weeks (220 mg, 88%): mp 85−87 °C. $[\alpha]^{20}_D$ −18.3 (*c* 1.0, $CHCl_3$). IR (thin film): 2973, 1792, 1744, 1701 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$): δ_H 5.83−5.87 (2 H, m), 4.79−4.83 (1 H, m), 4.65−4.70 (1 H, m), 4.51−4.59 (1 H, m), 4.37−4.43 (1 H, m), 4.03−4.18 (2 H, m), 2.41−2,47 (1 H, m), 2.03−2.08 (4 H, m), 1.89−1.98 (1 H, m), 1.65−1.73 (1 H, m), 1.50 (9 H, s), 1.12 (3 H, s), 1.06 (3 H, s), 0.96 (3 H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 178.0, 170.6, 167.3, 154.1, 129.0, 128.4, 128.2, 91.0, 80.8, 66.8, 66.2, 64.8, 64.3, 64.0, 63.9, 63.3, 62.9, 54.8, 54.2, 30.7, 28.9, 28.4, 21.0, 20.9, 16.8, 14.2, 9.7. ESI HRMS (*m*/*z*): 474.2102 $[M + Na]^+$; $C_{23}H_{33}NO_8 + Na^+$ requires 474.2098. The camphanic protected pyrroline **(**25 mg, 0.055 mmol) was stirred in trifluoroacetic acid (0.1 mL) at room temperature for 10 min and then concentrated in vacuo to give a brown oil. The crude product was purified by flash column chromatography [SiO_2, MeOH-dichloromethane, 1:19] to yield a brown solid. Recrystallization from dichloromethane yielded the title compound as brown needles (23 mg, 89%): mp 116−120 °C. $[\alpha]^{20}_D$ −4.4 (*c* 1.25, CH_2Cl_2). IR (thin film) 2925, 1783, 1748, 1673 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$): δ_H 5.90 (1 H, d, *J* = 6.4), 5.87 (1 H, d, *J* = 6.4), 4.96 (1 H, br. s), 4.88 (1 H, br. s), 4.61 (1 H, dd, *J* = 12.3 and 6.5), 4.41−4.50 (2 H, m), 4.33−4.39 (1 H, m), 2.43 (1 H, ddd, *J* = 13.6, 10.5 and 4.0), 2.01−2.10 (4 H, m), 1.93 (1 H, td, *J* = 11.9 and 4.29), 1.69 (1 H, ddd, *J* = 13.1, 9.2 and 3.9), 1.11 (3 H, s), 1.06 (3 H, s), 0.95 (3 H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 178.3, 171.1, 167.3, 161.9 (m), 128.2, 126.9, 116.1 (q, *J* = 280), 91.0, 65.5, 64.7, 63.6, 62.2, 54.9, 54.6, 30.8, 28.9, 20.5, 16.6, 9.6. ESI HRMS (*m*/*z*): 352.1757 $[M - F_3CCO_2^-]^+$; $C_{18}H_{26}NO_6$ requires 352.1755.

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Supporting Information Available: Detailed experimental procedures for all compounds and spectroscopic data for all novel compounds in pdf and cif formats. This material is available free of charge via the Internet at http://pubs.acs.org.

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