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Enantioselective Synthesis of Ceralure B_1, Ethyl *cis*-5-Iodo-*trans*-2-methylcyclohexane-1-carboxylate

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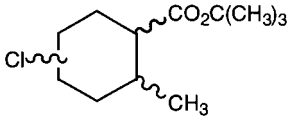
Abstract—Ethyl (1*R*, 2*R*, 5*R*)-5-iodo-2-methylcyclohexane-1-carboxylate is a potent attractant for the Mediterranean fruit fly. This compound was stereoselectively synthesized on a multigram scale in nine steps in 15% yield. Key steps of the synthesis involved an asymmetric Diels–Alder reaction, iodolactonization, stereoselective reduction of the carbonyl, and inversion of configuration with iodide. Published by Elsevier Science Ltd.

Introduction

The Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann) commonly known as the medfly, is a worldwide pest that feeds on 253 fruits and vegetables.[1] The establishment of this exotic pest into the continental United States would significantly increase pesticide use and curtail fruit and vegetable exports, a multi-billion dollar industry.[2] For more than 30 years trimedlure (TML), a mixture of sixteen regio- and stereoisomers of *tert*-butyl esters of 4 (and 5)-chloro-2-methylcyclohexane-1-carboxylate (**1**) has been widely used as an attractant in traps used to monitor and detect male medfly.[3] HPLC separation of these isomers made possible a field study of the relative attractiveness of these racemates toward the Mediterranean fruit fly.[4] Of these isomers, TML-C (**2**) was shown to be most active. Particularly noteworthy is the ability of the medfly to discriminate among the two enantiomers of TML-C, with the (1*S*, 2*S*, 4*R*) configuration being most attractive.[5,6]



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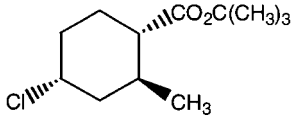

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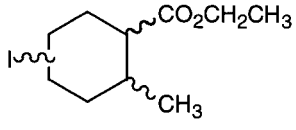
Recently, an iodo analog of trimedlure, ceralure (CER) (**3**), also a mixture of 16 regio- and stereoisomers of ethyl 4 (and 5)-iodo-2-methylcyclohexane-1-carboxylate has been found to be a more persistent and potent attractant than TML.[7] A field study designed to measure the relative attractiveness of these racemates, which were tediously separated by HPLC, demonstrated that ethyl *cis*-5-iodo-*trans*-2-methylcyclohexane-1-carboxylate (CER B_1) (**4**) is most active.[8]



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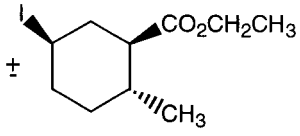

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We sought to develop an efficient enantioselective synthesis of CER B_1 which is amenable to multigram scale, for various reasons. Firstly, to our knowledge, despite various attempts, no stereoselective synthesis of the most active stereoisomer of CER or even TML has been developed. Secondly, we wanted to ascertain which enantiomer of CER B_1 is most attractive. Finally and most importantly, an efficient synthesis of the most active compound within the 16 component CER mixture should provide a significantly improved tool for monitoring infestations of the Mediterranean fruit fly.

Our synthetic plan for developing an enantioselective synthesis of **4** is shown in Scheme 1. We envisaged that the construction of the cyclohexane ring via an asymmetric Diels–Alder reaction between butadiene and (*E*)-crotonic acid would establish the *trans* stereochemistry between the carboxylate and the methyl group with absolute stereochemical control. Iodolactonization, followed by reduction and transesterification should in effect provide for

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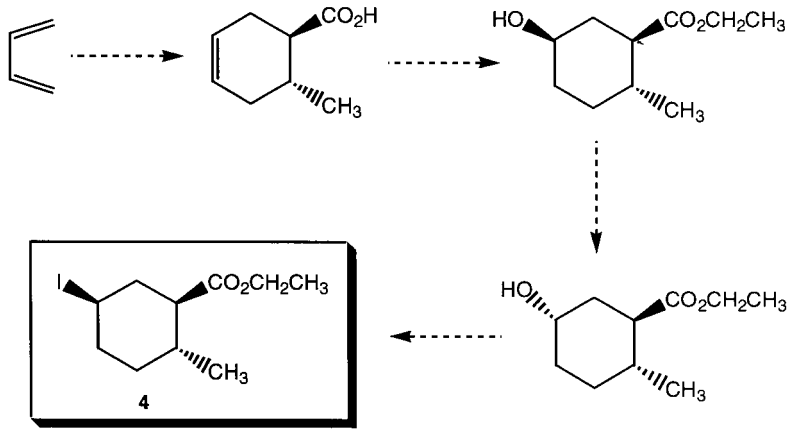


Scheme 1. Synthetic plan for enantioselective synthesis of **4**.

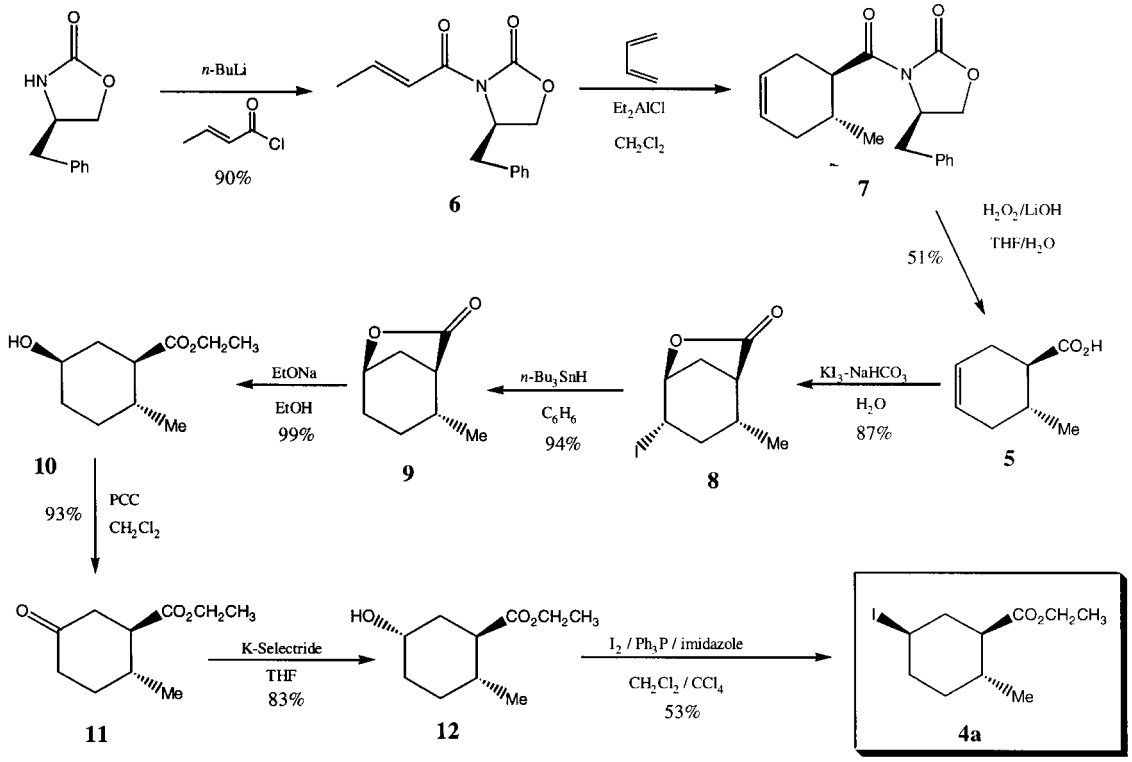
regioselective and stereoselective addition of water across the double bond. Inversion of configuration of the hydroxyl, followed by S_N2 displacement with iodide, should provide (**4**) in optically pure form.

Results and Discussion

We sought to utilize an asymmetric Diels–Alder reaction to obtain the enantiomers of sigluric acid **5**. This would avoid the tedious multistep chiral resolution of **5**, used previously for the synthesis of the enantiomers of TML.[6] Evans has described the asymmetric Diels–Alder technique with chiral α,β-unsaturated *N*-acyloxazolidinones.[9,10] Most appealing is the ready availability of both enantiomers of the benzyloxazolidinone chiral auxiliary. Hence, treatment of the chiral oxazolidinone derived from D-phenylalanine with *n*-butyllithium followed by addition of (*E*)-crotonyl chloride generated the chiral α,β-unsaturated *N*-acyloxazolidinone **6** in 90% yield. The asymmetric reaction of **6** with butadiene in the presence of 2.0 equiv. of the Lewis acid catalyst diethylaluminum chloride at −15°C generated the adduct **7** with high diastereoselectivity (ds>97:1). Galvinoxyl was employed in this procedure to prevent the polymerization of butadiene under the reaction conditions.[11] Without purification, **7** was subject to contrasteric carboximide hydrolysis with lithium hydroperoxide[12] to afford (1*R*, 6*R*)-6-methyl-3-cyclohexene-1-carboxylic acid **5** in 51% overall yield from **6**. The optical purity of **5** was judged to be 97% ee on a chiral cyclodextrin column. The chiral auxiliary was also recovered in 87% yield. The absolute configuration of **5** is based on precedent of analogous reactions documented by Evans.[9] Additionally, the literature value for the rotation of **5** ($[\alpha]_D=-84.2°$) confirms the stereochemical assignment.[6]

Iodolactonization of **5** with I_2, KI and $NaHCO_3$ provided **8** in a highly regioselective manner in 87% yield.[13,14] Attempted hydrogenolysis of the iodolactone with various heterogeneous metal catalysts, including Pd/C, Pt/C, or Pt/Al_2O_3, proved to be unsuccessful. Unreacted starting material or products resulting from over reduction were obtained. However, reduction of iodolactone **8** to lactone **9** proceeded smoothly in 94% yield with tributyltin hydride in the presence of catalytic azobisisobutyronitrile (AIBN) in refluxing benzene.[13] Finally, ring-opening of the lactone with sodium ethoxide in ethanol generated **10** in quantitative yield. Hence the synthetic sequence **5** to **10** was, in effect, equivalent to the regio- and stereoselective addition of water across the olefin. However, the configuration of the hydroxyl was opposite to that desired. Hence, inversion of the hydroxyl was required. Mitsunobu inversion of a hydroxyl in the cyclohexane ring was plagued with difficulties, due to the propensity of elimination as well as low reactivity resulting from steric hindrance of an approaching nucleophile. Accordingly, in an alternate approach, the hydroxyl in **10** was oxidized with PCC[15] in methylene chloride to generate the ketone (**11**) in high yield (95%). Stereoselective reduction of the ketone should provide the desired alcohol **12** with inverted stereochemistry. As the cyclohexanone ring in **11** should exist in a distorted chair conformation with the ethyl ester and methyl groups occupying equatorial positions, reduction of the ketone with hydride from an equatorial trajectory should provide the desired alcohol **12** with inverted stereochemistry. In fact, reduction of **11** with $NaBH_4$ gave predominantly **10** (ds=9:1), most likely as a result of approach of comparatively unhindered borohydride from the axial position. Interestingly, reduction of the ketone with the sterically encumbered reducing agent $LiAlH(OC(CH_3)_3)_3$ also gave a preponderance of **10** (ds>99:1). However, reduction of **11** with K-Selectride®[16] in THF at −78°C followed by oxidation of the trialkylborane with hydrogen peroxide under neutral conditions, generated the desired axial alcohol **12** with high stereoselectivity (ds>25:1). Alcohol **12** could then be isolated in pure form by simple flash chromatography (86%).

Activation of the hydroxyl, followed by nucleophilic displacement with iodide should generate the desired **4a** stereoisomer. However, this last step of the sequence proved to be quite difficult. A variety of conditions were attempted, including $Ph_3P/DEAD/CH_3I$, Ph_3P/N-iodosuccinimide, $Ph_3P/DEAD/ZnI_2$, I_2SiH_2, and *o*-phenylene phosphochloridite/I_2, all of which proved unsuccessful. In these instances, starting material was recovered, along with **4a** and elimination product. We attribute this to the steric hindrance of the axial hydroxyl in **12** for activation. If activation were to occur, facile E-2 elimination of the activated axial hydroxyl would compete with nucleophilic attack by iodide. Other



Scheme 2. Enantioselective synthesis of Ceralure B_1 (**4a**).

reagents, including P_2I_4, Me_3SiCl/NaI, Cl_3SiMe/NaI, and trimethylsilylpolyphosphate/NaI, did yield **4a**, albeit in poor stereoselectivity, most likely due to the highly ionic nature of the intermediates involved. After modification of previously reported conditions, we found that Ph_3P-imidazole-I_2[17] in a 2:1 carbon tetrachloride/methylene chloride mixture at room temperature did give CER B_1 (**4a**) in fair yield (55%) and in high stereoselectivity (ds>50:1) (Scheme 2). Fortunately, the elimination side product could easily be removed by flash chromatography. The ^1H and ^{13}C NMR spectra of **4a** synthesized in this manner were identical to those of an authentic racemic sample previously isolated from the mixture of CER stereoisomers by HPLC.[8] Synthesis of CER B_1 (**4a**) in high optical purity by this route, yielded material on a 6.0-g scale. The opposite enantiomer (**4b**) was also generated from the readily available benzyloxazolidinone chiral auxiliary derived from L-phenylalanine. Both enantiomers of CER B_1 (**4**) were determined to be 97% ee on a chiral GC column.

Conclusions

In summary, a convenient nine-step stereoselective synthesis of the enantiomers of CER B_1 (**4**) has been described. The synthesis was accomplished in 15% overall yield and is amenable to large scale. Preliminary field tests on cotton wicks conducted in Hawaii demonstrated that the 1*R*,2*R*,5*R* enantiomer (**4a**) is very attractive to the Mediterranean fruit fly and that the 1*S*,2*S*,5*S* enantiomer (**4b**) is significantly less active. Preliminary results demonstrate that **4a** caught as many as ten and twenty times more flies than the standard TML and CER mixtures, respectively. Thus the increased efficiency of trapping per dose of material may justify the use of this attractant as a replacement of TML that is annually used in over 100,000 baited detection traps for monitoring infestations of the Mediterranean fruit fly in the U.S.

Experimental

Melting points were uncorrected. ^1H NMR and $^{13}C\{^1H\}$NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ on a Bruker QE-300 spectrometer unless otherwise stated. ^1H NMR coupling constants are reported in Hz. Mass spectra were obtained with a Hewlett–Packard 5971 GC–MS equipped with a 30 m DB-5 (J&W Scientific) fused silica column. IR spectra were obtained with a Hewlett–Packard Series 6890 gas chromatograph (equipped with a 60-m DB-Waxter (J&W Scientific) fused silica column) coupled to a Bio Rad IRD II Infrared Detector. Optical rotations were recorded using a Perkin–Elmer Model 241 automatic polarimeter operated at the sodium-D (589 nm) wavelength. Gas chromatography was performed on a Shimadzu Model 14A gas chromatograph using hydrogen as the carrier gas. Combustion analyses were conducted by Galbraith Laboratories, Inc., Knoxville, TN.

Analytical thin layer chromatography (TLC) was carried out on silica gel (J. T. Baker IB-F). Flash chromatography was performed as previously described on E. Merck silica gel (230–400 mesh).[18] Tetrahydrofuran (THF) was distilled from sodium/benzophenone; methylene chloride and benzene were distilled from CaH_2 and purged with nitrogen before using. Unless otherwise noted, materials were obtained from commercial suppliers and were used without

further purification. All reactions were carried out under a nitrogen atmosphere. Mention of a proprietary company or product does not imply endorsement by the US Department of Agriculture.

(4*R*)-3-((*E*)-2-Butenoyl)-4-(phenylmethyl)-2-oxazolidinone (6) was synthesized according to a literature procedure.[9] The product was recrystallized from ethanol to yield a white solid (156.4 g, 90%). R_f 0.20 (ethyl acetate/hexane 1:9); mp 79–81°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.35 (m, 7H), 4.67–4.75 (m, 1H), 4.10–4.21 (m, 2H), 3.30 (dd, J=3.4 Hz, 13.2 Hz, 1H), 2.79 (dd, J=9.5 Hz, 13.2 Hz, 1H), 1.97 (d, J=5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 153.2, 146.3, 135.2, 129.2, 128.6, 127.0, 121.7, 65.8, 54.9, 37.5, 18.2; MS (EI) m/z 245 (M^+, 10), 230 (11), 154 (12), 133 (4), 91 (9), 69 (100), 41 (11); $[\alpha]_D$= −78.3° (c=3.83, $CHCl_3$).

(4*R*)-3-((4′*R*,5′*R*)-Cyclohexene-4′-carbonyl)-4-(phenylmethyl)-2-oxazolidinone (7).[10] In a fume hood, a 3 L, 3-neck round-bottomed flask equipped with a dry-ice condenser, was charged with oxazolidinone **6** (70.0 g, 0.286 mol), galvinoxyl (500 mg, 1.2 mmol), and 400 mL of methylene chloride. After cooling to −78°C, butadiene (800 mL, 9.6 mol), dried by passage through Drierite was condensed into the solution. Diethylaluminum chloride (0.570 mol, 1.8 M in toluene) was added over 10 min and the solution was stirred overnight at −15 to −10°C. The reaction was quenched by addition to 1 M HCl (1000 mL), and stirred for 60 min at room temperature to allow the butadiene to evaporate. The layers were separated and the aqueous layer was extracted with methylene chloride (4×250 mL). The combined organics were neutralized by stirring with solid $NaHCO_3$, dried ($MgSO_4$) and the volatiles were removed in vacuo to give a crude oil (103.9 g, 107% crude yield), that was carried onto the next step without purification. A portion of the sample was purified by flash chromatography (1:4 ethyl acetate/hexane), to give a solid; R_f 0.25 (1:9 ethyl acetate/hexane); mp 79–80°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.36 (m, 5H), 5.69–5.73 (m, 2H), 4.68–4.76 (m, 1H), 4.14–4.24 (m, 2H), 3.70 (dt, J=5.5 Hz, 10.2 Hz, 1H), 3.26 (dd, J=3.2 Hz, 13.5 Hz, 1H), 2.79 (dd, J=9.5 Hz, 13.5 Hz, 1H), 2.35–2.43 (m, 1H), 2.02–2.27 (m, 3H), 1.75–1.86 (m, 1H), 0.97 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 153.1, 135.3, 129.4, 128.9, 127.3, 126.3, 124.6, 66.0, 55.3, 44.2, 37.9, 33.0, 30.3, 29.0, 19.5; MS (EI) m/z 299 (M^+, 13), 284 (1), 178 (25), 122 (100), 95 (46), 79 (30); $[\alpha]_D$=−141.5° (c=1.48, $CHCl_3$).

(1*R*, 6*R*)-6-Methyl-3-cyclohexene-1-carboxylic acid (5).[6] To a cold (0°C) solution of **7** (103.9 g, 0.286 mol), in 4:1 THF/water (500 mL) was added 30% hydrogen peroxide (160 mL, 1.40 mol), followed by addition of solid lithium hydroxide (27.4 g, 0.652 mol). The resulting mixture was allowed to slowly warm to room temperature, and after 4 h the reaction was complete. The solution was cooled (0°C) and sodium sulfite (202 g, 1.6 mol) was added. The bulk of the THF was removed in vacuo, and the resulting mixture (pH 12–13) was extracted with methylene chloride (5×200 mL) to remove the chiral auxiliary. The combined methylene chloride extracts were dried ($MgSO_4$) and the volatiles were removed in vacuo to yield 44.0 g (87% yield) of the recovered benzyloxazolidinone auxiliary. The aqueous layer was acidified to pH 1–2 with 12 M HCl and extracted with ethyl acetate (5×300 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and the volatiles were removed in vacuo to yield an oil that was purified by flash chromatography (1:1 ethyl acetate/hexane, 0.3% acetic acid) to give **5** as a solid (20.2 g, 51% overall yield from **6**). The optical purity of the methyl ester of **5** was shown to be 97% ee (30 m Chiraldex BD-A column, 70°C isothermal, 25 psi, t_r major 31.4 min, t_r minor 33.0 min). R_f 0.40 (ethyl acetate/hexane 1:1); mp 65–66°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.2–11.8 (b, 1H), 5.61–5.69 (m, 2H). 2.12–2.33 (m, 4H), 1.89–2.00 (m, 1H), 1.67–1.77 (m, 1H), 1.02 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3, 126.3, 124.5, 46.8, 32.9, 30.3, 28.7, 19.7; MS (EI) m/z 140 (M^+, 21), 122 ($[M-H_2O]^+$, 16), 111 (14), 95 (100), 79 (75), 67 (49); $[\alpha]_D$=−99.0° (c=4.89, $CHCl_3$).

(1*R*,2*R*,4*S*,5*S*)-4-Iodo-2-methyl-6-oxabicyclo[3.2.1]octan-7-one (8).[14] To a solution of optically active **5** (16.8 g, 120 mmol) in methylene chloride (200 mL) and water (400 mL), were added $NaHCO_3$ (20.1 g, 240 mmol), KI (120 g, 720 mmol) and iodine (91.0 g, 360 mmol). The resulting mixture was protected from light and stirred for 24 h. The solution was cooled (0°C), and sodium thiosulfate was carefully added until the dark iodine color disappeared. It was then extracted with diethyl ether (4×300 mL). The combined organics were dried ($MgSO_4$) and the volatiles were removed in vacuo to give crude **8** as a yellowish solid (27.8 g, 87% yield). This was carried onto the next step without further purification. R_f 0.33 (ethyl acetate/hexane 1:9); mp 99–100°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (dd, J=3.6 Hz, 5.9 Hz, 1H), 4.35–4.38 (m, 1H), 2.90 (m, 1H), 2.63–2.73 (m, 1H), 2.49–2.52 (m, 1H), 2.20–2.36 (m, 2H), 1.95–2.00 (m, 1H). 1.38 (d, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 81.6, 43.8, 34.3, 29.3, 27.8, 19.5, 19.1; MS (EI) m/z 266 (M^+, 4), 139 ($[M-I]^+$, 80), 95 (100), 79 (16), 67 (26), 55 (29); $[\alpha]_D$=−3.60° (c=2.22, $CHCl_3$).

(1*R*,2*R*,5*R*)-2-Methyl-6-oxabicyclo[3.2.1]octan-7-one (9).[14] A solution of **8** (26.8 g, 101 mmol), tributyltin hydride (29.8 mL, 111 mmol), and AIBN (200 mg) in benzene (300 mL) was refluxed overnight. After removing the benzene in vacuo, diethyl ether (250 mL) and 10% aqueous KF (250 mL) were added. Stirring for 30 min precipitated a tributyltin flouride polymer. The polymer was removed by filtration, and the filtrate was extracted with methylene chloride (3×100 mL). The combined organics were dried ($MgSO_4$) and the volatiles were removed in vacuo to yield an oil that was purified by flash chromatography (using eluent gradient 1:20 ethyl acetate/hexane to 3:7 ethyl acetate/hexane) to give **9** as a yellowish solid (13.2 g, 94% yield). R_f 0.26 (ethyl acetate/hexane 1:9); mp 62–63°C; IR (gas phase) cm^{-1} 2975, 2888, 1811, 1347, 1156; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76–4.80 (m, 1H), 2.43–2.46 (m, 1H), 2.12–2.25 (m, 2H), 2.01–2.05 (m, 1H), 1.89–1.98 (m, 2H), 1.62–1.70 (m, 1H), 1.41–1.47 (m, 1H), 1.13 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 78.1, 44.5, 31.0, 28.1, 24.8, 24.4, 17.5; MS (EI) m/z 140 (M^+, 3), 112 ($[M-CO]^+$, 3), 97 (28), 81 (100), 70 (38), 55 (48); $[\alpha]_D$=+31.3° (c=0.96°, $CHCl_3$); Analysis calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.15; H, 8.60.

Ethyl (1*R*,2*R*,5*R*)-5-hydroxy-2-methyl-1-carboxylate (10). Sodium (5.0 g, 217 mmol) was dissolved in anhydrous ethanol (250 mL) at room temperature. Lactone **9** (13.2 g, 94.3 mmol) was added and the solution was allowed to stir at room temperature for one hour, whereupon the reaction was judged to be complete by TLC. The mixture was diluted with saturated ammonium chloride (300 mL) and extracted with methylene chloride (3×100 mL). The combined organics were dried ($MgSO_4$) and the volatiles were removed in vacuo to give **10** as a crude oil (17.3 g, 99% yield) that was carried onto the next step without further purification. R_f 0.25 (ethyl acetate/hexane 3:7); IR (gas phase) cm^{-1} 3650, 2941, 2869, 1748, 1244, 1171, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, J=7.2 Hz, 2H), 3.52–3.61 (m, 1H), 1.92– 2.08 (m, 4H), 1.69–1.78 (m, 1H), 1.56–1.69 (m, 1H), 1.39–1.50 (m, 1H), 1.26–1.36 (m, 1H), 1.23 (t, J=7.2 Hz, 3H), 0.97–1.11 (m, 1H), 0.86 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 69.8, 60.2, 49.7, 38.2, 35.0, 33.6, 32.4, 19.6, 14.2; MS (EI) m/z 186 (M^+, 3), 168 ($[M-H_2O]^+$, 57), 141 ($[M-OCH_2CH_3]^+$, 16), 129 (29), 95 (100), 73 (21), 55 (30); $[\alpha]_D$=−26.6° (c=1.10, CH_2Cl_2). Analysis calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.68; H, 9.51.

Ethyl (1*R*,2*R*)-2-methyl-5-one-1-carboxylate (11). To a suspension of pyridinium chlorochromate (36.0 g, 167 mmol) in methylene chloride (200 mL) was added **10** (17.27 g, 92.8 mmol), whereupon the mixture became a dark homogeneous solution. The reaction was stirred overnight. Diethyl ether (3×300 mL) was added, and the product was passed through a short column of Florisil® to remove the chromium salts. Removal of the solvent in vacuo gave **11** as an oil (15.9 g, 93% yield), that was carried onto the next step without further purification. R_f 0.61 (ethyl acetate/hexane 3:7); IR (gas phase) cm^{-1} 2972, 2940, 1744, 1166, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (dq, J=1.1 Hz, 7.2 Hz, 2H), 2.35–2.63 (m, 5H), 2.01–2.19 (m, 2H), 1.42–1.53 (m, 1H), 1.28 (t, J=7.2 Hz, 3H), 1.03 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 173.5, 60.6, 50.5, 42.7, 40.3, 33.4, 33.2, 19.0, 14.1; MS (EI) m/z 184 (M^+, 23), 169 ($[M-CH_3]^+$, 3), 155 ($[M-CH_2CH_3]^+$, 8), 139 ($[M-OCH_2CH_3]^+$, 8), 128 (35), 111 (100), 99 (46). 55 (50); $[\alpha]_D$=−46.9° (c=1.00, CH_2Cl_2). Analysis calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.06; H, 8.73.

Ethyl (1*R*,2*R*,5*S*)-5-hydroxy-2-methyl-1-carboxylate (12). To a cold (−78°C) solution of **11** (14.9 g, 80.8 mmol) in THF (250 mL) was added K-Selectride® (95.0 mmol, 1.0 M in THF). After addition was complete, the mixture was allowed to warm to −50°C and was stirred for an additional 4 h, whereupon the reaction was judged to be complete by TLC. The reaction was quenched by addition to 2.2 M NaH_2PO_4/K_2HPO_4 buffer (300 mL, pH 7). The mixture was cooled (0°C) and 30% hydrogen peroxide (42 mL, 370 mmol) was added and the mixture was allowed to stir overnight. The layers were separated and the aqueous layer was extracted with ethyl acetate (4×200 mL). The combined organics were washed with brine (300 mL), 1.0 M sodium sulfite (300 mL), dried ($MgSO_4$) and the volatiles were removed in vacuo to yield an oil that was further purified by flash chromatography (3:7 ethyl acetate/hexane) to give **12** as an oil (12.48 g, 83% yield). R_f 0.35 (ethyl acetate/hexane 3:7); IR (gas phase) cm^{-1} 3655, 2938, 2895, 1746, 1240, 1158, 1041; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45–4.54 (m, 1H), 4.10 (q, J=7.2 Hz, 2H), 2.34–2.44 (m, 1H), 2.00–2.30 (b, 1H), 1.26–1.91 (m, 7H), 1.22 (t, J=7.2 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 65.4, 60.0, 45.1, 35.8, 33.9, 32.0, 27.6, 20.2, 14.2; MS (EI) m/z 186 (M^+, 3), 168 ($[M-H_2O]^+$, 37), 141 ($[M-OCH_2CH_3]^+$, 25), 130 (12), 95 (100), 73 (27), 55 (34); $[\alpha]_D$=−27.4° (c=1.10, CH_2Cl_2). Analysis calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.19; H, 9.62.

Ethyl (1*R*,2*R*,5*R*)-5-iodo-2-methyl-1-carboxylate (4a). To a cold (0°C) solution of **12** (8.28 g, 44.5 mmol) in 1:2 methylene chloride/carbon tetrachloride (400 mL) was added triphenylphosphine (14.0 g, 53.4 mmol), imidazole (3.63 g, 53.4 mmol), and iodine (13.5 g, 54.4 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of saturated sodium thiosulfate (300 mL) and stirred until the solution became clear. The layers were separated and the aqueous layer was extracted with methylene chloride (2×200 mL). The combined organics were washed with sodium thiosulfate (200 mL), brine (200 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo to yield a solid that was purified by flash chromatography (toluene) to give **4a** as an oil (7.0 g, 53% yield). Analysis on a 60 m SPB-608 column[19] indicated production of **4a** in high diastereoselectvity (>40:1). R_f 0.76 (ethyl acetate/hexane 3:7); IR (gas phase) cm^{-1} 2961, 2936, 1748, 1319, 1279, 1180, 1140, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, ^{J}=7.2 Hz, 2H), 4.00–4.09 (m, 1H), 2.51–2.58 (m, 1H), 2.37–2.45 (m, 1H), 2.10–2.22 (m, 1H), 1.95–2.09 (m, 2H), 1.69–1.80 (m, 1H), 1.59–1.67 (m, 1H), 1.26 (t, J=7.2 Hz, 3H), 1.06–1.12 (m, 1H), 0.86 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 60.4, 53.3, 42.7, 39.9, 36.2, 33.1, 25.8, 20.0, 14.2; MS (EI) m/z 251 ($[M-OCH_2CH_3]^+$, 2), 169 ($[M-I]^+$, 21), 123 (11), 95 (100), 81 (8), 67 (14), 55 (17); $[\alpha]_D$=−29.0° (c=0.72, CH_2Cl_2).

Ethyl (1*S*,2*S*,5*S*)-5-iodo-2-methyl-1-carboxylate (4b) was produced in an analogous manner from the oxazolidinone derived from L-Phe. $[\alpha]_D$=+28.8° (c=0.65, CH_2Cl_2).

Ethyl (1*SR*, 2*SR*, 5*SR*)-5-iodo-2-methyl-1-carboxylate (4) was generated in an analogous manner from racemic (1*RS*, 6*RS*)-6-methyl-3-cyclohexene-1-carboxylic acid.

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