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Asymmetric Synthesis of Highly Substituted β-Lactones via Nucleophile-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes

Jonathan E. Wilson and Gregory C. Fu*

Department of Chemistry,

Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

I. General

THF was purified by passing it through a neutral alumina column. Zinc metal (Strem) was activated with hydrochloric acid. Benzaldehyde (Aldrich), *p*-trifluoromethylbenzaldehyde (Aldrich), *p*-tolualdehyde (Aldrich), and 2-bromo-2-methylpropanoylbromide (Aldrich) were distilled prior to use. Quinidine (Avocado), $LiClO_4$ (Alfa Aesar), 2-napthaldehyde (Aldrich), 4-acetylbenzaldehyde (Aldrich), DIBAL-H (1.0 M in THF; Aldrich), sodium azide (Alfa Aesar), DMSO (Aldrich), and *n*-propylamine (Aldrich) were used as received. Non-commercially available α-bromoacid bromides were synthesized according to a literature procedure.[1] Catalysts **1**,[2] **2**,[3] and *O*-TMS-quinidine[4] were prepared as previously reported.

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated.

II. Synthesis of Ketenes

Diethylketene. A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2-ethylbutanoylbromide (128 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (51.0 mg, 64%), which was identified by ^{1}H NMR to be 2-ethyl-*N*-propylbutyramide [551906-54-8].

Dimethylketene. A stirred slurry of Zn^0 (82 mg, 1.25 mmol) in THF (0.50 mL) in a Schlenk tube at –78 °C was treated with a solution of 2-bromo-2-methylpropanoyl-bromide (115 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was stirred for 10 minutes at –78 °C and then 20 minutes at 0 °C, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (63.0 mg, 97%), which was identified by ^{1}H NMR to be 2-methyl-*N*-propylpropanamide [CAS 108122-11-8].

Hexamethyleneketene. A sonicated slurry of Zn^0 (118 mg, 1.80 mmol) in THF (0.60 mL) in a Schlenk tube was treated with a solution of 1-bromocycloheptanoylbromide (170 mg, 0.600 mmol) in THF (0.60 mL). THF (0.30 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at 0 °C, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (86.7 mg, 79%), which was identified as *N*-propylcycloheptanamide.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (broad, 1H), 3.19-3.12 (m, 2H), 2.23-2.14 (m, 1H), 1.87-1.80 (m, 2H), 1.77-1.68 (m, 2H), 1.65-1.36 (m, 10H), 0.88 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.5, 47.7, 41.1, 31.9, 28.2, 26.8, 23.0, 11.5. FTIR (NaCl) 3281, 3083, 2927, 2857, 1640, 1558, 1456, 1384, 1235, 1155 cm^{-1}. HRMS (ESI, M+H) calc. for $C_{11}H_{22}NO$ 184.1696, found 184.1695. mp = 68° C.

Isopropyl methyl ketene. A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2,3-dimethylbutanoylbromide (129 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (500 μL, 6.08 mmol). Evaporation of the solvent and the excess amine furnished a white solid (48.0 mg, 64%), which was identified as 2,3-dimethyl-*N*-propylbutyramide.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (s, 1H), 3.27-3.08 (m, 2H), 1.89-1.73 (m, 2H), 1.49 (m, 2H), 1.07 (d, J=7.0 Hz, 3H), 0.91-0.86 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.5, 48.8, 41.1, 31.5, 23.1, 21.2, 19.7, 15.3, 11.5. FTIR (NaCl) 3296, 3087, 2874, 1644, 1557, 1461, 1371, 1235, 1157, 1086, 978, 709. HRMS (ESI, M+H) calc. for $C_9H_{20}NO$ 158.1539, found 158.1534. mp = 50° C.

Cyclopentyl methyl ketene. A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2-cyclopentylpropanoylbromide (142 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL)

was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (500 μL, 6.08 mmol). Evaporation of the solvent and the excess amine furnished a white solid (70.0 mg, 76%), which was identified as 2-cyclopentyl-*N*-propylpropanamide.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 (s, 1H), 3.27-3.07 (m, 2H), 1.96-1.84 (m, 2H), 1.82-1.65 (m, 2H), 1.61-1.43 (m, 6H), 1.16-1.00 (m, 5H), 0.88 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.7, 47.7, 44.0, 41.1, 31.4, 30.7, 25.2, 25.1, 23.1, 17.2, 11.5. FTIR (NaCl) 3291, 1634, 1557, 1455, 1232, 1156, 711 cm^{-1}. HRMS (ESI, M+H) calc. for $C_{11}H_{22}NO$ 184.1696, found 184.1691.

III. Catalytic Asymmetric Synthesis of β-Lactones via Cycloadditions of Disubstituted Ketenes with Aldehydes (Table 1)

Table 1, entry 1. A solution of diethylketene (38 mg, 0.38 mmol) in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (33 μL, 0.33 mmol) in toluene (0.75 mL) at –78 °C. A solution of (–)-**1** (6.0 mg, 0.016 mmol) in toluene (0.75 mL) was added dropwise over 5 min to the solution of ketene and benzaldehyde at –78 °C. The reaction mixture was stirred at –78 °C for 20 h, and then it was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O / pentane), which furnished 62.5 mg (94%) of a clear oil. HPLC analysis: 88% ee [Diacel CHIRALCEL AD-H column; 1.0 mL / min; solvent system: 3% isopropanol in hexanes; retention times: 8.3 min (major), 9.9 min (minor)].

Second run: (–)-**1** (3.0 mg, 0.0080 mmol), diethylketene (19 mg, 0.19 mmol), and benzaldehyde (17 μL, 0.17 mmol). 87% yield, 89% ee.

Table 1, entry 2. See the procedure in Section IV for Table 2, entry 1.

Table 1, entry 3. A solution of diethylketene (38 mg, 0.38 mmol) in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (40 μL, 0.39 mmol) and quinidine (6.5 mg, 0.020 mmol) in toluene (1.5 mL) at –78 °C. The resulting solution was immediately placed into a 0 °C ice-water bath, which warmed to room temperature over ~2 h. After 20 h at room temperature, the reaction mixture was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O / pentane), which furnished 2.0 mg of β-lactone (<5%).

Second run: Quinidine (6.5 mg, 0.020 mmol), diethylketene (38 mg, 0.38 mmol), and benzaldehyde (40 μL, 0.39 mmol). <5% yield.

Table 1, entry 4. A solution of diethylketene (38 mg, 0.38 mmol) in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C. The resulting solution was immediately placed into a 0 °C ice-water bath, which warmed to room temperature over ~2 h. After 20 h at room temperature, the reaction mixture was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O / pentane), which furnished 15.6 mg of a mixture of the desired β-lactone and an unidentified side product.

The mixture was treated with a solution of DIBAL-H in THF (1.0 M; 0.5 mL). After stirring for 6 h at room temperature, the reaction mixture was quenched with NaOH (1.0 N; 0.6 mL). The aqueous layer was extracted with Et_2O (5 x 1 mL), and the combined extracts were filtered through a short pad of silica gel with Et_2O washings. The solvent was removed, and the 1,3-diol was purified by silica gel chromatography (10% → 40% Et_2O / pentane), which furnished 9.0 mg (22%) of the 1,3-diol as a clear oil. HPLC analysis: 1% ee [Daicel CHIRALCEL AD-H column; 1.0 mL / min; solvent system: 10.0% isopropanol in hexanes; retention times: 9.6 min (minor), 12.6 min (major)].

Second run: Diethylketene (38 mg, 0.38 mmol), benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol). Mixture of the desired β-lactone and the unidentified side product: 15.3 mg; 1,3-diol: 8.1 mg (20%; 0% ee).

IV. Catalytic Asymmetric Synthesis of β-Lactones via Cycloadditions of Disubstituted Ketenes with Aldehydes (Table 2)

Table 2, entry 1. 3,3-Diethyl-4-phenyloxetan-2-one. General Procedure for Table 2. A solution of (+)-**1** (6.0 mg, 0.016 mmol) in THF (0.40 mL) was added dropwise over 5 min to a –78 °C solution of diethylketene (38 mg, 0.38 mmol) and benzaldehyde (32 μL, 0.32 mmol) in THF (1.5 mL). The reaction mixture was stirred at –78 °C for 5.5 h, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O / pentane), which furnished 61.0 mg (93%) of a clear oil. HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL / min; solvent system: 3.5% isopropanol in hexanes; retention times: 6.4 min (minor), 7.4 min (major)].

Second run: (–)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and benzaldehyde (32 μL, 0.32 mmol). 92% yield, 92% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.24 (m, 5H), 5.38 (s, 1H), 1.98 (m, 2H), 1.48-1.36 (m, 1H), 1.31-1.19 (m, 1H), 1.13 (t, J=7.5 Hz, 3H), 0.77 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 135.4, 128.7, 128.5, 125.7, 80.9, 64.5, 24.7, 21.9, 8.7, 7.9. FTIR (NaCl) 1824, 1454, 1248, 1102, 942 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{13}H_{16}NaO_2$ 227.1043, found 227.1046. $[\alpha]^{21.6}_D$ = +62° (c= 0.19, CH_2Cl_2; from reaction with (+)-**1**).

Table 2, entry 2. 3,3-Diethyl-4-(2-naphthyl)oxetan-2-one. The general procedure was followed: (+)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 2-napthaldehyde (50.0 mg, 0.320 mmol). Reaction time: 5.5 hours. Purified by silica gel chromatography (toluene), which provided 61.0 mg (75%) of a white solid. HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; solvent system: 3.5% isopropanol in hexanes; retention times: 6.8 min (minor), 9.4 min (major)].

Second run: (–)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), 2-napthaldehyde (50.0 mg, 0.320 mmol). 80% yield, 89% ee. $[\alpha]^{21.6}_{D}$ = –2.9° (c= 0.48, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91-7.84 (m, 4H), 7.56-7.52 (m, 2H), 7.36-7.32 (m, 1H), 5.54 (s, 1H), 2.03 (m, 2H), 1.53-1.40 (m, 1H), 1.34-1.22 (m, 1H), 1.19 (t, J=7.5 Hz, 3H), 0.77 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 133.2, 133.2, 132.9, 128.5, 128.2, 128.0, 126.8, 126.6, 125.0, 123.2, 81.0, 64.8, 24.7, 21.9, 8.3, 8.0. FTIR (NaCl) 1824, 1458, 1247, 1101 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{17}H_{18}NaO_2$ 277.1199, found 277.1204. $[\alpha]^{21.6}_{D}$ = –2.9° (c= 0.48, CH_2Cl_2; from reaction with (+)-**1**). mp = 59° C.

Table 2, entry 3. 3,3-Diethyl-4-(4-trifluoromethyl)phenyloxetan-2-one. The general procedure was followed: (+)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-trifluoromethylbenzaldehyde (44 μL, 0.32 mmol). Reaction time: 5.5 hours. Purified by silica gel chromatography (0% → 20% Et_2O / pentane), which provided 66.6 mg (76%) of a clear oil. HPLC analysis: 80% ee [Daicel CHIRACEL OJ column; 1.0 mL / min; solvent system: 3.5% isopropanol in hexanes; retention times: 7.6 min (minor), 10.7 min (major)].

Second run: (–)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-trifluoromethylbenzaldehyde (44 μL, 0.32 mmol). 72% yield, 79% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J=8.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 5.41 (s, 1H), 2.08-1.90 (m, 2H), 1.43-1.31 (m, 1H), 1.28-1.17 (m, 1H), 1.13 (t, J=7.5 Hz, 3H), 0.78 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 139.6, 130.7(q), 126.0(d), 125.8(d), 125.7(d), 80.0, 65.2, 24.6, 22.1, 8.8, 8.0. FTIR (NaCl) 1831, 1622, 1461, 1418, 1326, 1127, 1068, 943, 899 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{14}H_{15}F_3NaO_2$ 295.0916, found 295.0926. $[\alpha]^{21.7}_{D}$ = +31° (c=0.65, CH_2Cl_2; from reaction with (+)-**1**).

Table 2, entry 4. 3,3-Diethyl-4-(4-acetyl)phenyloxetan-2-one. The general procedure was followed: (+)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-acetylbenzaldehyde (47 mg, 0.32 mmol). Reaction time: 5.5 hours. Purified by

silica gel chromatography (5% → 10% acetone / pentane), which provided 59.3 mg (75%) of a clear oil. HPLC analysis: 82% ee [Daicel CHIRACEL AD column; 1.0 mL / min; solvent system: 3.5% isopropanol in hexanes; retention times: 14.3 min (minor), 18.9 min (major)].

Second run: (–)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-acetylbenzaldehyde (47 mg, 0.32 mmol). 77% yield, 80% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J= 8.5 Hz, 2H), 7.38 (d, J=8.5 Hz, 2H), 5.40 (s, 1H), 2.61 (s, 3H), 1.97 (dq, J=2.0 Hz, J=7.5 Hz, 2H), 1.26 (m, 2H), 1.11 (t, J=7.5 Hz, 3H), 0.75 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 173.6, 140.7, 137.1, 128.7, 125.9, 80.2, 65.2, 26.8, 24.6, 22.0, 8.8, 8.0. FTIR (NaCl) 1825, 1684, 1610, 1459, 1412, 1360, 1267, 1099 cm $^{-1}$. HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_3$ 269.1148, found 269.1140. $[\alpha]^{21.5}_D$ = +36° (c=0.34, CH_2Cl_2; from reaction with (+)-**1**).

Table 2, entry 5. 3,3-Diethyl-4-(4-methyl)phenyloxetan-2-one. The general procedure was followed: (–)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and *p*-tolualdehyde (38 μL, 0.32 mmol). Reaction time: 24 hours. Purified by silica gel chromatography (10% Et_2O / pentane; the remaining aldehyde was removed under vacuum), which provided 48.1 mg (69%) of a clear oil. The β-lactone was reduced to the diol with DIBAL-H for HPLC analysis (for the procedure, see Part IV). HPLC analysis (1,3-diol): 89% ee [Daicel CHIRACEL AD-H column; 1.0 mL / min; solvent system: 10% isopropanol in hexanes; retention times: 6.5 min (major), 8.9 min (minor)].

Second run: (+)-**1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and *p*-tolualdehyde (38 μL, 0.32 mmol). 64% yield, 88% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.16 (m, 4H), 5.34 (s, 1H), 2.38 (s, 3H), 1.96 (q, J=7.5 Hz, 2H), 1.50-1.37 (m, 1H), 1.31-1.18 (m, 1H), 1.11 (t, J=7.5 Hz, 3H), 0.76 (t, J= 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 138.4, 132.4, 129.4, 125.7, 81.1, 64.4, 24.7, 21.9, 21.4, 8.5, 8.0. FTIR (NaCl) 1825, 1459, 1101, 943, 890 cm^{-1}. HRMS (ESI, M+Na) calc. for

$C_{14}H_{18}NaO_2$ 241.1199, found 241.1199. $[\alpha]^{21.7}_D = -28°$ (c=0.49, CH_2Cl_2; from reaction with (–)-**1**).

Table 2, entry 6. 3,3-Dimethyl-4-phenyloxetan-2-one. [52178-66-2] A solution of (–)-**1** (12.5 mg, 0.034 mmol) in THF (0.6 mL) was added dropwise over 8 min to a –78 °C solution of dimethylketene (33 mg, 0.48 mmol) and benzaldehyde (58 μL, 0.57 mmol) in THF (1.75 mL). The reaction mixture was stirred at –78 °C for 22 h, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The filtrate was immediately treated with LAH (4.8 mmol; 1.0 M in THF), and the resulting mixture was stirred for 1 h at room temperature. The solution was then quenched with 1 N NaOH (5 mL) and H_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic extracts were combined, concentrated under vacuum, and then purified by silica gel chromatography (20% → 50% Et_2O / pentane), which furnished 55.0 mg (64%) of a white solid (1,3-diol; [33950-46-8]). HPLC analysis: 78% ee [Daicel CHIRALCEL AD-H column; 1.0 mL / min; solvent system: 5.0% isopropanol in hexanes; retention times: 14.5 min (minor), 15.8 min (major)].

Second run: (–)-**1** (18.7 mg, 0.050 mmol), dimethylketene (50 mg, 0.71 mmol), and benzaldehyde (86 μL, 0.85 mmol). 71% yield, 74% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.30 (m, 5H), 4.64 (s, 1H), 3.61 (d, J=11.0 Hz, 1H), 3.53 (d, J=11.0 Hz, 1H), 2.59 (s, 2H), 0.90 (s, 3H), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6, 127.9, 127.8, 127.7, 82.4, 72.3, 39.2, 23.0, 19.1. HRMS (ESI, M+Na) calc. for $C_{11}H_{12}NaO_2$ 199.0730, found 199.0732. $[\alpha]^{20.9}_D = -19.6°$ (c=0.73, CH_2Cl_2; from reaction with (–)-**1**).

Table 2, entry 7. 3,3-Spirocycloheptyl-4-phenyl-oxetan-2-one. A solution of (+)-**1** (10.9 mg, 0.029 mmol) in THF (0.9 mL) was added dropwise over 8 min to a –78 °C solution of hexamethyleneketene (60 mg, 0.48 mmol) and benzaldehyde (59 μL, 0.58 mmol) in THF (1.5 mL). The reaction mixture was stirred at –78 °C for 22 hours, and then it was filtered through a short pad of silica gel with copious washings with Et_2O.

The solvent was removed, and the product was purified by silica gel chromatography (0% → 6% Et_2O / hexane), which provided 74.5 mg (68%) of a clear oil. HPLC analysis: 83% ee [Daicel CHIRALCEL AD column; 1.0 mL / min; solvent system: 2.0% isopropanol in hexanes; retention times: 7.2 min (minor), 9.3 min (major)].

Second run: (–)-**1** (10.9 mg, 0.029 mmol), hexamethyleneketene (60 mg, 0.48 mmol), and benzaldehyde (59 μL, 0.58 mmol). 73% yield, 80% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.27 (m, 5H), 5.31 (s, 1H), 2.31-2.22 (m, 1H), 2.18-2.11 (m, 1H), 1.97-1.81 (m, 1H), 1.68-1.50 (m, 4H), 1.48-1.19 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 135.5, 128.8, 128.7, 125.9, 84.3, 64.0, 35.4, 30.4, 29.2, 29.2, 23.8, 22.9. FTIR (NaCl) 1821, 1497, 1457, 1355, 1112, 939 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_2$ 253.1199, found 253.1199. $[\alpha]^{21.6}_D$ = +18° (c=0.57, CH_2Cl_2; from reaction with (+)-**1**).

Table 2, entry 8. *cis*-3-Isopropyl-3-methyl-4-phenyloxetan-2-one. A solution of (–)-**1** (7.0 mg, 0.019 mmol) in THF (0.5 mL) was added dropwise over 5 min to a –78 °C solution of isopropyl methyl ketene (36 mg, 0.37 mmol) and benzaldehyde (113 μL, 1.11 mmol) in THF (1.5 mL). The reaction mixture was stirred for 22 hours, during which time it slowly warmed from –78 °C to –10 °C, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The crude reaction mixture was analyzed by ^{1}H NMR to determine the diastereoselectivity (4.1:1 cis:trans). The product was purified by silica gel chromatography (1% → 5% Et_2O / pentane), which provided 22.5 mg of the cis diastereomer (crystalline solid) and 14.5 mg of a mixture of diastereomers (49% yield, total). The major isomer was determined by X-ray crystallography to be the cis isomer (see Part VI). HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL / min; solvent system: 2.0% isopropanol in hexanes; retention times (cis diastereomer): 6.7 min (major), 8.7 min (minor)].

Second run: (+)-**1** (7.0 mg, 0.019 mmol), isopropyl methyl ketene (36 mg, 0.37 mmol), and benzaldehyde (113 μL, 1.11 mmol). 46% yield, 4.3:1 cis:trans, 92% ee (cis diastereomer).

Major diastereomer (cis): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.34 (m, 5H), 5.26 (s, 1H), 2.02 (sept, J=7.0 Hz, 1H), 1.50 (s, 3H), 1.02 (d, J=7.0 Hz, 3H), 0.38 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.0, 135.0, 129.1, 128.6, 127.0, 84.3, 63.7, 27.4, 17.7, 15.9, 14.8. FTIR (NaCl) 1821, 1456, 1111, 1078, 939 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{13}H_{16}NaO_2$ 227.1043, found 227.1045. $[\alpha]^{21.7}_D$ = +33° (c=0.20, CH_2Cl_2; from reaction with (+)-**1**). mp = 76° C.

Table 2, entry 9. *cis*-3-Cyclopentyl-3-methyl-4-phenyloxetan-2-one. A solution of (+)-**1** (8.5 mg, 0.023 mmol) in THF (0.75 mL) was added dropwise over 8 min to a –78 °C solution of cyclopentyl methyl ketene (56 mg, 0.45 mmol) and benzaldehyde (137 μL, 1.35 mmol) in THF (1.5 mL). The reaction mixture was stirred at –78 °C for 72 hours, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (1% → 2% Et_2O / pentane), which provided 43.3 mg of the major diastereomer and 9.6 mg of the minor diastereomer (51%, 4.5:1 cis:trans). HPLC analysis: 88% ee (cis diastereomer), 47% ee (trans diastereomer) [Daicel CHIRALCEL AD column; 1.0 mL / min; solvent system: 2.0% isopropanol in hexanes; retention times: cis diastereomer, 6.5 min (minor), 7.1 min (major); trans diastereomer, 6.3 min (minor), 7.6 min (major)].

Second run: (+)-**1** (8.5 mg, 0.023 mmol), cyclopentyl methyl ketene (56 mg, 0.45 mmol), and benzaldehyde (137 μL, 1.35 mmol). 55% yield, 4.7:1 cis: trans, 88% ee (cis diastereomer).

Major diastereomer (cis): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.31 (m, 5H), 5.31 (s, 1H), 2.08-1.97 (m, 1H), 1.55 (s, 3H), 1.53-1.30 (m, 5H), 1.29-1.18 (m, 1H), 1.15-1.03 (m, 1H), 1.00-0.89 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 135.6, 128.6, 128.5, 126.1, 83.7, 63.3, 39.8, 28.2, 26.7, 25.8, 25.6, 17.0. FTIR (NaCl) 1823, 1454, 1382, 1264, 1101, 945, 873 cm^{-1}. HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_2$ 253.1199, found 253.1193. $[\alpha]^{21.7}_D$ = +31° (c=0.29, CH_2Cl_2; from reaction with (+)-**1**).

Minor diastereomer (trans): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.32 (m, 3H), 7.27-7.25 (m, 2H), 5.40 (s, 1H), 2.30 (m, 1H), 2.03-1.84 (m, 2H), 1.83-1.53 (m, 5H), 1.51-1.36 (m, 1H), 0.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 135.8, 128.8, 128.5, 125.6, 79.6, 63.5, 44.5, 28.5, 28.1, 25.7, 25.6, 15.8. FTIR (NaCl) 1825, 1454, 1070, 942 cm^{-1}. $[\alpha]^{21.4}_{D}$ = +5.0° (c=0.68, CH_2Cl_2; from reaction with (+)-**1**).

V. Derivatization of the β-Lactones (Figure 1)

1-Phenyl-2,2-diethyl-1,3-propanediol. [63834-79-7] A solution of DIBAL-H in THF (1.0 M; 0.30 mL, 0.30 mmol) was added to a 0 °C solution of 3,3-diethyl-4-phenyloxetan-2-one (20.0 mg, 0.098 mmol; 91% ee) in THF (0.30 mL). Upon completion of the addition, the reaction mixture was warmed to room temperature over 2 h. Then, a solution of NaOH (1.0 N; 0.40 mL) was added. The aqueous layer was extracted with Et_2O (3 x 5 mL), and the combined extracts were washed with water and then brine. The organic layer was concentrated, and the residue was purified by column chromatography (10% → 40% Et_2O / pentane), which furnished 18.0 mg (88%) of a clear oil. HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL / min; solvent system: 10.0% isopropanol in hexanes; retention times: 7.0 min (minor), 8.9 min (major)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.26 (m, 5H), 4.73 (d, J=5.5 Hz, 1H), 3.57 (dd, J=11.5 Hz, J=3.5 Hz, 1H), 3.49 (d, J=4.5 Hz, 1H), 3.44 (dd, J=10.5 Hz, J=5.5 Hz, 1H), 3.24 (dd, J=6.0 Hz, J=4.0 Hz, 1H), 1.84-1.60 (m, 2H), 0.99 (m, 2H), 0.93 (t, J=7.5 Hz, 3H), 0.78 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 128.0, 127.8, 127.6, 80.6, 66.8, 43.3, 22.7, 22.6, 7.7, 7.6.

2,2-Diethyl-3-hydroxy-3-phenylpropanoic acid. [59697-81-3] A solution of KOH (1.0 N; 0.28 mL) was added to a solution of 3,3-diethyl-4-phenyloxetan-2-one (28.4 mg, 0.139 mmol; 92% ee) in wet THF (0.50 mL). The reaction mixture was sealed and heated to 60 °C for 5 h, and then it was cooled to room temperature and treated with HCl (1.0 N; 0.30 mL). The aqueous layer was extracted with EtOAc / Et_2O (1:1; 5 x 3 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered through a short plug of silica gel, and concentrated to a white solid (29.1 mg, 94%). The ee was determined by reducing the β-hydroxyacid to the 1,3-diol with $LiAlH_4$ in THF (15 equiv). HPLC analysis: 91% ee [Daicel CHIRALCEL AD-H column; 1.0 mL / min;

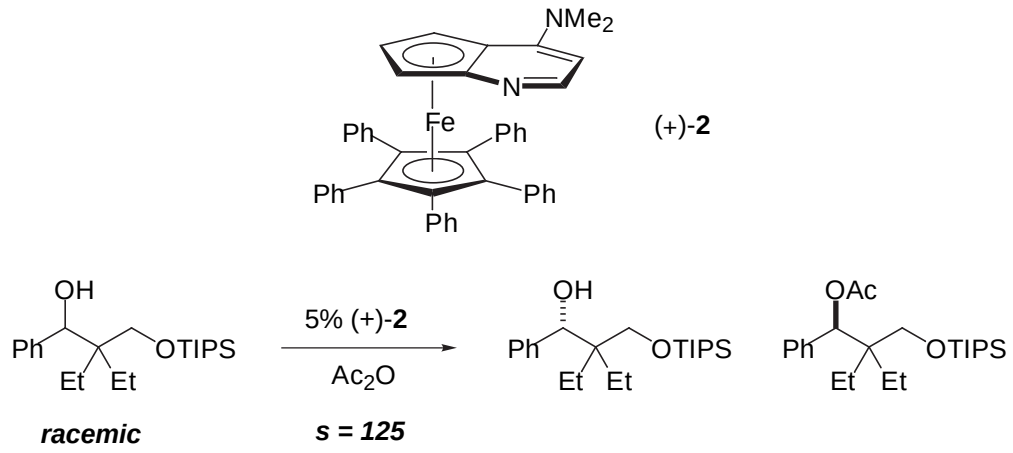
solvent system: 10.0% isopropanol in hexanes; retention times: 7.2 min (major), 9.2 min (minor)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.32 (m, 5H), 4.89 (s, 1H), 1.79 (m, 2H), 1.73 (dq, J=15.0 Hz, J=7.5 Hz, 1H), 1.41 (dq, J=15.0 Hz, J=7.5 Hz, 1H), 0.97 (t, J=7.5 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.3, 140.2, 128.4, 128.3, 127.4, 77.1, 54.8, 25.8, 23.4, 8.94, 8.92.

2,2-Diethyl-3-azido-3-phenylpropanoic acid. Sodium azide (21.0 mg, 0.323 mmol) was added to a solution of 3,3-diethyl-4-phenyloxetan-2-one (33.0 mg, 0.162 mmol; 92% ee) in DMSO (1.0 mL). The reaction vessel was sealed and heated to 65 °C for 48 h. The reaction was then quenched with HCl (1.0 N; 1.0 mL) and H_2O (1.0 mL). The aqueous layer was extracted with EtOAc (4 x 5 mL), and the organic extracts were combined and washed with H_2O and then brine. The extracts were concentrated, and the residue was purified by column chromatography (1% → 4% MeOH / CH_2Cl_2), which furnished 34.0 mg (85%) of the azide. To assay the ee, the acid was converted to the methyl ester by treatment with excess diazomethane in Et_2O . HPLC analysis: 92% ee [Daicel CHIRALCEL OJ-H column; 1.0 mL / min; solvent system: 5.0% isopropanol in hexanes; retention times: 7.1 min (minor), 7.6 min (major)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.40 (br s, 1H), 7.41-7.31(m, 5H), 4.94 (s, 1H), 1.82-1.58 (m, 4H), 0.95 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.8, 136.2, 128.7, 128.6, 128.5, 70.6, 54.5, 25.4, 24.2, 9.3, 8.9. FTIR (NaCl) 2973 (broad), 2103, 1699, 1453, 1252, 914, 742 cm^{-1}. HRMS (ESI, M–H) calc. for $C_{13}H_{16}N_3O_2$ 246.1248, found 246.1244. $[\alpha]^{21.4}_{D}$ = +123° (c=0.18, CH_2Cl_2; from reaction with (–)-**1**)

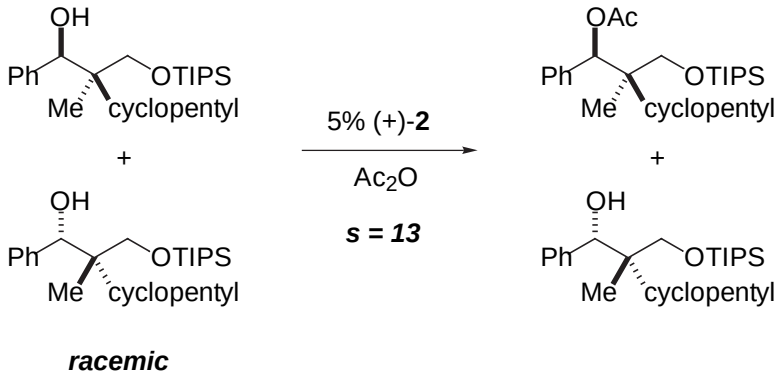
VI. Determination of the Absolute Stereochemistry of the β-Lactones



Kinetic resolution of (±)-2,2-diethyl-3-phenyl-1-triisopropylsiloxy-3-propanol. Ac_2O (6.8 μL, 0.072 mmol) was added to a stirred solution of the racemic alcohol (35 mg, 0.096 mmol), NEt_3 (6.6 μL, 0.072 mmol), and (+)-**2** (3.0 mg, 0.0050 mmol) in *t*-amyl alcohol (0.25 mL) at 0 °C.[5] The reaction mixture was stirred for 7 days at 0 °C, and then the reaction was quenched with MeOH (0.50 mL). The reaction mixture was filtered through a pad of silica gel and concentrated. The ^{1}H NMR spectrum of the unpurified reaction mixture indicated ~33% conversion. Purification by silica gel chromatography (0.5% → 2.0% Et_2O / pentane) yielded 13.0 mg of the acetate and 14.0 mg of the alcohol. HPLC analysis of the alcohol: 48% ee [Daicel CHIRALCEL AD-H column; 1.0 mL / min; solvent system: 5.0% isopropanol in hexanes; retention times: 3.9 min (minor), 7.8 min (major)].

A sample of 2,2-diethyl-3-phenyl-1-triisopropylsiloxy-3-propanol was then prepared from an enantioenriched sample of 3,3-diethyl-4-phenyloxetan-2-one (obtained from a reaction conducted with (–)-**1**). This sample was enriched (HPLC analysis: 90% ee) in the opposite enantiomer of the alcohol to that obtained from the kinetic resolution. On this basis, we assign the absolute stereochemistry of the product of the reaction

illustrated in entry 1 of Table 2. The stereochemistry of entries 2-7 are assigned by analogy (note that the HPLC elution order is the same for all entries: the major enantiomer elutes more slowly).

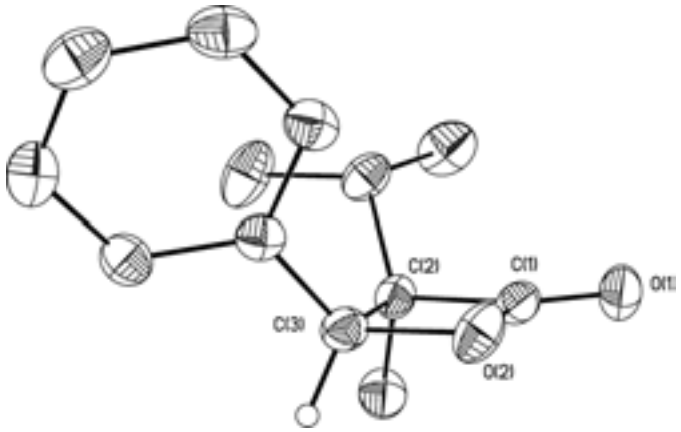


Kinetic resolution of (±)-2-cyclopentyl-2-methyl-3-phenyl-1-triisopropylsiloxy-3-propanol (illustrated diastereomer). Ac_2O (4.6 μL, 0.049 mmol) was added to a stirred solution of the racemic alcohol (29.5 mg, 0.076 mmol), NEt_3 (4.5 μL, 0.049 mmol), and (+)-**2** (2.5 mg, 0.0040 mmol) in *t*-amyl alcohol (0.40 mL). The reaction mixture was stirred for 2 days at room temperature, and then additional NEt_3 (4.5 μL, 0.049 mmol) and Ac_2O (4.6 μL, 0.049 mmol) were added. After five more days, the reaction was quenched with MeOH (0.5 mL). The reaction mixture was filtered through a pad of silica gel and concentrated. The ^1H NMR spectrum of the unpurified reaction mixture indicated a 17% conversion. Purification by silica gel chromatography (2.5% → 5.0% Et_2O / pentane) yielded 5.0 mg of the acetate and 21.0 mg of the partially resolved alcohol. HPLC analysis of the alcohol: 17% ee [Daicel CHIRALCEL AD-H column; 1.0 mL / min; solvent system: 10.0% isopropanol in hexanes; retention times: 3.5 min (minor), 5.5 min (major)].

A sample of 2-cyclopentyl-2-methyl-3-phenyl-1-triisopropylsiloxy-3-propanol was then prepared from an enantioenriched sample of diastereomerically pure *cis*-3-

cyclopentyl-3-methyl-4-phenyloxetan-2-one (obtained from a reaction conducted with (–)-**1**). This sample was enriched (HPLC analysis: 89% ee) in the opposite enantiomer of the alcohol to that obtained from the kinetic resolution. On this basis, we assign the absolute stereochemistry of the product of the reaction illustrated in entry 9 of Table 2.

VII. Determination of cis Relative Stereochemistry: X-ray Crystal Structure (Table 2, entry 8)



A colorless ether / pentane (1:1) solution of the β-lactone was prepared. Crystals suitable for X-ray structural analysis were obtained by solvent evaporation.

A colorless block of dimensions 0.41 x 0.29 x 0.19 mm^3 was mounted under STP and transferred to a Bruker AXS / CCD three-circle diffractometer equipped with a cold stream of N_2 gas. An initial unit cell was determined by harvesting reflections $I > 20\ \sigma(I)$ from 45 x 10-s frames of 0.30° ω scan data with monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The cell thus determined was orthorhombic.

A hemisphere of data was then collected using ω scans of 0.30° and 10-s frames. The raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. The data that were collected (8734 total reflections, 2926 unique, R_{int} = 0.0454) had the following Miller index ranges: –5 to 10 in h, –14 to 14 in k, and –17 to 17 in l. No absorption correction was performed.

All aspects of the solution and refinement were handled by SHELXTL NT version 5.10. The structure was solved by direct methods in the orthorhombic space group P2(1)2(1)2(1), a = 8.1417(5) Å; b = 10.8215(6) Å; c = 13.4224(8) Å; α = 90°; β = 90°; γ = 90°,

and refined using standard difference Fourier techniques. Final, full-matrix least-squares refinement (2926 data for 140 parameters) on F^2 yielded residuals of R_1 and wR_2 of 0.0408 and 0.1112 for data $I > 2\sigma(I)$, and 0.0442 and 0.1140, respectively, for all data. During the final refinement, all non-hydrogen atoms were treated anisotropically. Hydrogen atoms were included in calculated positions and refined isotropically on a riding model. Residual electron density amounted to a maximum of 0.202 e / Å^3 and a minimum of –0.219 e / Å^3.

The data have been deposited with the CCDC.

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