# Valence Tautomerism in Titanium Enolates: Direct Catalytic Radical Haloalkylation and Application to the Total Synthesis of Neodysidenin.

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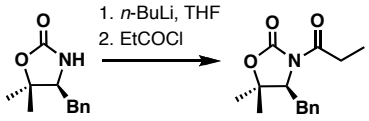
**SUPPORTING INFORMATION**

**General Information.** All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether ($Et_2O$) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine, pyridine, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride in a still under and atmosphere of argon. Di-*iso*-propylethylamine (Hunig's Base) were distilled from calcium hydride under an inert atmosphere of dry argon and stored over calcium hydride. Reaction temperatures were controlled by IKA-brand fuzzy thermo couples. Room temperature reactions were carried out between 20-25 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 $F_{254}$ (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 200, 400, and 500 MHz on Varian Mercury Vx, Varian Unity Inova, and Varian Unity Inova spectrometers, respectively. Carbon magnetic resonance spectra were recorded at 50 MHz, 100 MHz, and 125 MHz on Varian Mercury Vx, Varian Unity Inova, and Varian Unity Inova spectrometers, respectively. All Chemical shifts were reported in δ units relative to tetramethylsilane using residual solvent as reference. Optical Rotations were measured on a Jasco DIP-1000 polarimeter. High Resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.

**Typical procedure for the synthesis of *N*-propionyl oxazolidinones (procedure 1).**

A solution of an oxazolidinone (1.0 mmol) in dry tetrahydrofuran (5 ml) under argon was cooled to −78 °C in a dry ice-acetone bath. At this temperature, *n*-butyllithium in hexane (2.5 M in hexanes, 0.42 ml, 1.05 mmol) is added dropwise. The reaction mixture is allowed to stir at this temperature for 25 min and propionyl chloride (91 μl, 1.05 mmol) is added dropwise. The reaction mixture is stirred at −78 °C for 30 min then quenched with saturated aqueous ammonium chloride solution. The reaction mixture is transferred to a separatory funnel and the organic phase is collected. The aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with brine. Drying with anhydrous sodium sulfate, filtration, and removal of the solvent under reduced pressure on a rotary evaporator afforded the crude product as a light yellow oil. The oil is purified by silica gel column chromatography to provide *N*-propionyl oxazolidinone.

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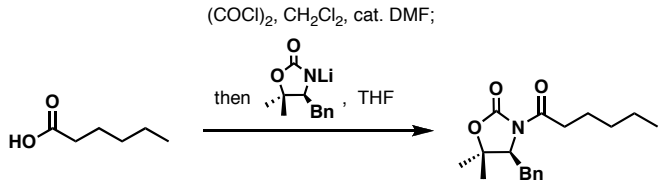
**Oxazolidinone 1.** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.209 g, 0.800 mmol, 99 %) after purification by silica gel column chromatography (hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -32.3° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.26-7.14 (m, 5H); 4.44 (dd, J1=9.6 Hz, J2=4.0 Hz, 1H); 3.08 (dd, J1=14.4 Hz, J2=4.0 Hz, 1H); 2.86 (q, J=7.2 Hz, 2H); 2.81 (dd, J1=14.4 Hz, J2=9.6 Hz, 1H); 1.30 (s, 3H); 1.29 (s, 3H); 1.07 (t, J=7.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 174.3, 152.8, 137.1, 129.2, 128.7, 126.9, 82.2, 63.6, 35.4, 29.4, 28.6, 22.4, 8.5. HRMS (ESI) calcd for $C_{15}H_{19}NO_3Na$ [M+Na] 284.1263, found 284.1262.

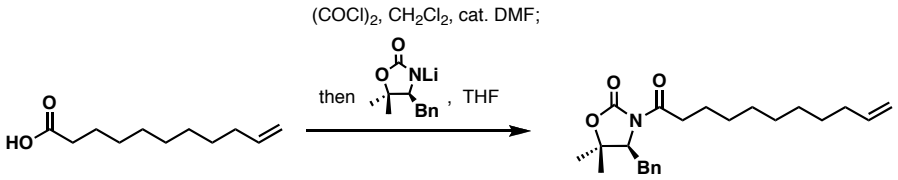
**Typical procedure for the synthesis of other *N*-acyl oxazolidinones (procedure 2).**

DMF (~30 μl) was added to a solution of carboxylic acid (1.0 mmol), oxalyl chloride (1.2 mmol), and dry dichloromethane (5 ml) at 0 ◦C. After 30 min, the solution was warmed to room temperature and stirred for 1 h. The solution was concentrated under reduced pressure on a rotary evaporator. In a separate flask, *n*-butyllithium (2.0 M in hexane, 0.5 ml, 1.0 mmol), was added to a solution of oxazolidinone (1.2 mmol) in THF (5 ml) at -78 ◦C under argon. The solution was stirred for 1 h at -78 ◦C. A solution of the crude acyl chloride in THF (5.0 ml total with rinses) was added dropwise at -78 ◦C. After stirring at -78 °C for 1 h and at room temperature for 30 min, the reaction mixture was quenched with aqueous ammonium chloride (15 ml). The aqueous layer was extracted with ethyl acetate (3x25 ml). The combined organic layers were washed with a mixture of brine (5 ml) and saturated aqueous bicarbonate (5 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant oil was purified by column chromatography to give the corresponding imide.

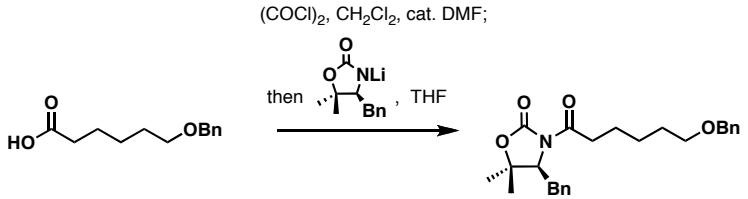



**Oxazolidinone (Table 1, entry 4).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.381 g, 73%) after purification by silica gel column chromatography

(hexanes:EtOAc 4:1). $[\alpha]_D^{23}$ -31.6° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$); δ(ppm): 7.32-7.20 (m, 5 H); 4.50 (dd, J1=11.5 Hz, J2=4.0 Hz, 1H); 3.14 (dd, J1=14.4 Hz, J2=4.0 Hz, 1H); 2.92-2.85 (m, 3H); 1.67-1.58 (m, 2H); 1.37 (s, 3H); 1.35 (s, 3H); 1.35-1.25 (m, 4H); 0.90 (t, J=7.2 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 173.9, 152.8, 137.2, 129.3, 128.9, 127.0, 82.3, 63.7, 35.8, 35.6, 31.5, 28.8, 24.3, 22.6, 22.5, 14.1. HRMS (ESI) calcd for $C_{18}H_{25}NO_3Na$ [M+Na] 326.1732, found 326.1728.

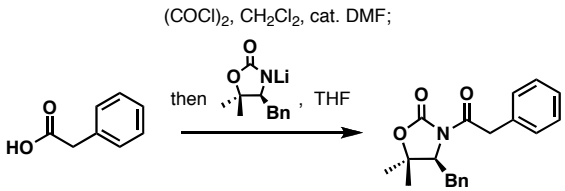



**Oxazolidinone (Table 1, entry 5, entry 6).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.757 g, 79%) after purification by silica gel column chromatography (hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -26.9° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.21 (m, 5 H); 5.85-5.77 (m, 1H); 4.99 (d, J=17.0 Hz, 1H); 4.92 (d, J=10.0 Hz, 1H); 4.50 (dd, J1=9.5 Hz, J2=3.5 Hz, 1H); 3.13 (dd, J1=14.5 Hz, J2=3.5 Hz, 1H); 2.92-2.85 (m, 3H); 2.06-2.01 (m, 2H); 1.65-1.59 (m, 2H); 1.37 (s, 3H); 1.35 (s, 3H); 1.38-1.26 (m, 10H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 173.8, 152.9, 139.4, 137.2, 129.3, 128.9, 127.0, 114.3, 82.3, 63.7, 35.9, 35.6, 34.0, 29.5, 29.5, 29.3, 29.3, 29.1, 28.8, 24.6, 22.5. HRMS (ESI) calcd for $C_{23}H_{33}NO_3Na$ [M+Na] 394.2358, found 394.2364.

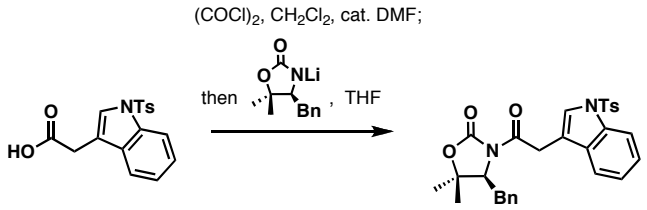



**Oxazolidinone (Table 1, entry 7).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.662 g, 63%) after purification by silica gel column chromatography (Hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -23.2° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$); δ(ppm): 7.36-7.20 (m, 10 H); 4.50 (s, 2H); 4.49 (dd, J1=9.6 Hz, J2=4.0 Hz, 1H); 3.47 (t, J=6.8 Hz, 2H); 3.13 (dd, J1=14.4 Hz, J2=4.0 Hz, 1H); 2.91 (q, J=7.2 Hz, 2H); 2.87 (dd, J1=14.4 Hz, J2=9.6 Hz, 1H); 1.69-1.58 (m, 4H); 1.47-1.39 (m, 2H); 1.37 (s, 3H); 1.35 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 173.7, 152.9, 138.8, 137.2, 129.3, 128.9, 128.6, 127.8,

127.7, 127.0, 82.3, 73.1, 70.4, 63.7, 35.8, 35.6, 29.7, 28.7, 25.9, 24.4, 22.5. HRMS (ESI) calcd for $C_{25}H_{31}NO_4Na$ [M+Na] 432.2151, found 432.2154.



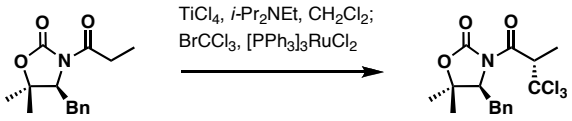

**Oxazolidinone (Table 1, entry 8).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.540 g, 65%) after purification by silica gel column chromatography (Hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -23.1° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.36-7.20 (m, 10 H); 4.50 (dd, J1=9.6 Hz, J2=4.0 Hz, 1H); 4.30 (d, J=17.2 Hz, 1H); 4.26 (d, J=17.2 Hz, 1H); 3.14 (dd, J1=14.4 Hz, J2=4.0 Hz, 1H); 2.86 (dd, J1=14.4 Hz, J2=9.6 Hz, 1H); 1.37 (s, 3H); 1.32 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 171.7, 152.8, 137.0, 133.9, 129.9, 129.3, 128.9, 128.8, 127.4, 127.0, 82.5, 64.0, 42.0, 35.4, 28.7, 22.5. HRMS (ESI) calcd for $C_{20}H_{21}NO_3Na$ [M+Na] 346.1419, found 346.1413.




**Oxazolidinone (Table 1, entry 9).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (1.36 g, 64%) after purification by silica gel column chromatography (Hexanes:EtOAc 7:3). $[\alpha]_D^{23}$ -7.9° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.98 (d, J=8.0 Hz, 1H); 7.76 (d, J=8.5 Hz, 2H); 7.62 (s, 1H); 7.49 (d, J=8.0 Hz, 1H); 7.31 (t, J=8.0 Hz, 1H); 7.24-7.17 (m, 8 H); 4.49 (dd, J1=9.0 Hz, J2=4.0 Hz, 1H); 4.32 (s, 2H); 3.07 (dd, J1=14.5 Hz, J2=4.0 Hz, 1H); 2.83 (dd, J1=14.5 Hz, J2=9.0 Hz, 1H); 2.32 (s, 3H); 1.37 (s, 3H); 1.29 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 170.1, 152.8, 145.0, 136.8, 135.5, 135.1, 130.8, 130.0, 129.2, 128.8, 127.0, 127.0, 125.6, 125.0, 123.5, 120.0, 114.9, 113.8, 82.7, 63.7, 35.5, 32.2, 28.6, 22.4, 21.7. HRMS (ESI) calcd for $C_{29}H_{28}N_2O_5SNa$ [M+Na] 539.1617, found 539.1611.

**Standard procedure for the trichloromethylation reaction.**

To a solution of oxazolidinone (0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.2 mL) was added a 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $BrCCl_3$ (0.15 mL, 1.5 mmol, 3.0 equiv.) was then added, followed by $RuCl_2(PPh_3)_3$ (34 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated in a sealed vial at 45 °C for 12 h. The reaction was quenched with $H_2O$ (3 ml) and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography of the crude material afforded the corresponding compound.

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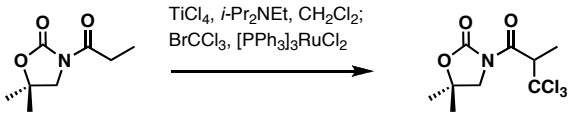
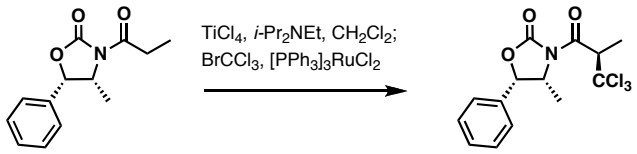
**Oxazolidinone 2.** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.186 g, 98%, dr>98:2) after purification by silica gel column chromatography (hexanes:EtOAc 95:5). $[\alpha]_D^{23}$ -47.4° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.29-7.24 (m, 4H); 7.22-7.17 (m, 1H); 5.28 (q, J=6.5 Hz, 1H); 4.53 (dd, J1=10.5 Hz, J2=3.0 Hz, 1H); 3.27 (dd, J1=14.5 Hz, J2=3.0 Hz, 1H); 2.81 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.60 (d, J=6.5 Hz, 3H); 1.34 (s, 3H); 1.30 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 170.1, 152.3, 136.8, 129.2, 128.9, 127.1, 99.5, 82.7, 64.3, 55.8, 34.7, 28.9, 22.6, 15.8. HRMS (ESI) calcd for $C_{16}H_{18}{}^{35}Cl_3NO_3Na$ [M+Na] 400.0250, found 400.0244.

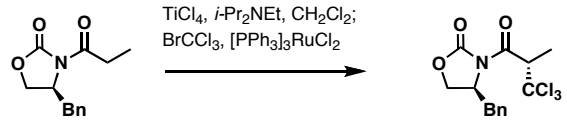



**Oxazolidinone (Table 1, entry 1).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.137 g, 95%) after purification by silica gel column chromatography (hexanes:EtOAc 4:1). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 5.25 (q, J=7.0 Hz, 1H); 3.80 (d, J=11.0 Hz, 1H); 3.72 (d, J=11.0 Hz, 1H); 1.56 (d, J=7.0 Hz, 1H); 1.51 (s, 3H); 1.48 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 169.6,

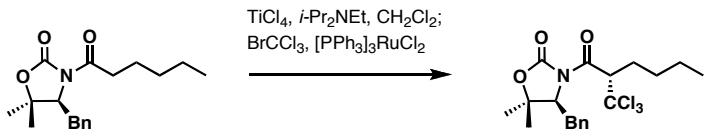
152.3, 99.3, 79.2, 55.3, 54.6, 27.3, 27.1, 15.6. HRMS (ESI) calcd for $C_9H_{12}{}^{35}Cl_3NO_3Na$ [M+Na] 309.9780, found 309.9785.




**Oxazolidinone (Table 1, entry 2).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.156 g, 89%) after purification by silica gel column chromatography (hexanes:EtOAc 4:1). $[\alpha]_D^{23}$ +33.7° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.43-7.34 (m, 3H); 7.30 (d, J=7.5 Hz, 2H); 5.70 (d, J=7.0 Hz, 1H); 5.36 (q, J=6.5 Hz, 1H); 4.85 (qu, J=7.0 Hz, 1H); 1.63 (d, J=6.5 Hz, 3H); 0.93 (d, J=7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 169.3, 152.7, 133.0, 129.1, 128.9, 125.8, 99.4, 79.0, 55.3, 55.2, 15.8, 14.4. HRMS (ESI) calcd for $C_{14}H_{14}{}^{35}Cl_3NO_3Na$ [M+Na] 371.9937, found 371.9935.

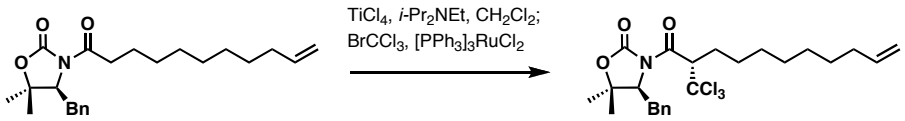



**Oxazolidinone (Table 1, entry 3).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.151 g, 86%, dr>98:2) after purification by silica gel column chromatography (Hexanes:EtOAc 4:1). $[\alpha]_D^{23}$ -13.4° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.29-7.24 (m, 4H); 7.22-7.17 (m, 1H); 5.28 (q, J=6.5 Hz, 1H); 4.53 (dd, J1=10.5 Hz, J2=3.0 Hz, 1H); 3.27 (dd, J1=14.5 Hz, J2=3.0 Hz, 1H); 2.81 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.60 (d, J=6.5 Hz, 3H); 1.34 (s, 3H); 1.30 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 170.1, 152.3, 136.8, 129.2, 128.9, 127.1, 99.5, 82.7, 64.3, 55.8, 34.7, 28.9, 22.6, 15.8. HRMS (ESI) calcd for $C_{16}H_{18}{}^{35}Cl_3NO_3Na$ [M+Na] 400.0250, found 400.0244.

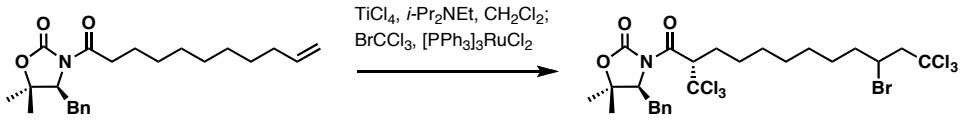



**Oxazolidinone (Table 1, entry 4).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.209 g, 99%, dr>98:2) after purification by silica gel column

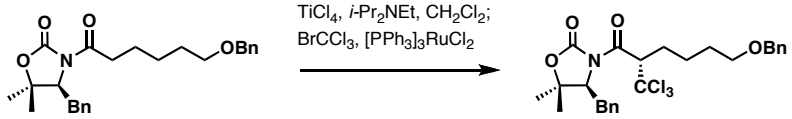
chromatography (hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -13.9° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.29 (m, 4H); 7.26-7.21 (m, 1H); 5.47 (dd, J1=6.5 Hz, J2=, 1H); 5.47 (dd, J1=11.0 Hz, J2=3.0 Hz, 1H); 4.61 (dd, J1=11.0 Hz, J2=2.5 Hz, 1H); 3.29 (dd, J1=14.5 Hz, J2=2.5 Hz, 1H); 2.86 (dd, J1=14.5 Hz, J2=11.0 Hz, 1H); 2.27-2.19 (m, 1H); 2.10-2.04 (m, 1H); 1.44-1.34 (m, 3H); 1.36 (s, 3H); 1.35 (s, 3H); 0.92 (t, J=7.0 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 169.6, 152.3, 137.0, 129.1, 128.9, 127.1, 98.9, 82.3, 64.5, 59.8, 34.9, 30.9, 29.1, 28.8, 22.7, 22.5, 14.0. HRMS (ESI) calcd for $C_{19}H_{24}{}^{35}Cl_3NO_3Na$ [M+Na], 442.0719 found 442.0708.



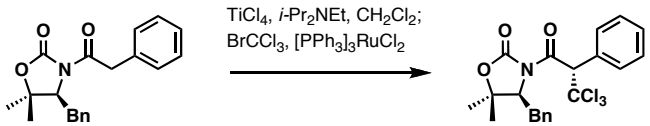

**Oxazolidinone (Table 1, entry 5).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone (0.186 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.3 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $BrCCl_3$ (50 μL, 0.5 mmol, 1.0 equiv.) was then added, followed by $RuCl_2(PPh_3)_3$ (34 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 45 °C for 12h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 95:5) of the crude material afforded the title compound as a colorless oil (0.155 g, 63%, dr>98:2). $[\alpha]_D^{23}$ -5.8° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.31-7.29 (m, 4H); 7.24-7.21 (m, 1H); 5.83-5.75 (m, 1H); 5.47 (dd, J1=11.0 Hz, J2=2.5 Hz, 1H); 4.98 (d, J=17.0 Hz, 1H); 4.92 (d, J=10.5 Hz, 1H); 4.60 (dd, J1=11.0 Hz, J2=2.5 Hz, 1H); 3.28 (dd, J1=14.5 Hz, J2=2.5 Hz, 1H); 2.86 (dd, J1=14.5 Hz, J2=11.0 Hz, 1H); 2.52-2.18 (m, 1H); 2.08-2.05 (m, 4H); 1.64-1.58 (m, 1H); 1.41-1.25 (m, 15H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 169.6, 152.3, 139.2, 137.0, 129.1, 128.9, 127.0, 114.4, 98.9, 82.3, 64.5, 59.8, 34.8, 33.9, 31.1, 29.5, 29.3, 29.1, 29.0, 28.9, 27.0, 22.5. HRMS (ESI) calcd for $C_{24}H_{32}{}^{35}Cl_3NO_3Na$ [M+Na], 510.1345 found 510.1351.




**Oxazolidinone (Table 1, entry 6).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.333 g, 97%, dr>98:2) after purification by silica gel column chromatography (hexanes:EtOAc 95:5). $[\alpha]_D^{23}$ -5.3° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.31-7.28 (m, 4H); 7.25-7.21 (m, 1H); 5.47 (dd, J1=11.0 Hz, J2=3.0 Hz, 1H); 4.61 (dd, J1=11.0 Hz, J2=3.0 Hz, 1H); 4.31 (sext, J = 5.0 Hz, 1H); 3.44 (dd, J1=16.0 Hz, J2=5.0 Hz, 1H); 3.28 (dd, J1=14.5 Hz, J2=2.5 Hz, 1H); 3.21 (dd, J1=16.0 Hz, J2=5.5 Hz, 1H); 2.86 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 2.25-2.19 (m, 1H); 2.08-1.98 (m, 2H); 1.95-1.88 (m, 1H); 1.61-1.52 (m, 1H); 1.50-1.44 (m, 1H); 1.42-1.25 (m, 12H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 169.6, 152.2, 137.0, 129.1, 128.9, 127.0, 98.8, 97.3, 82.3, 64.5, 62.8, 59.8, 49.2, 39.6, 34.8, 31.0, 29.4, 29.2, 28.8, 28.7, 27.3, 26.9, 22.5. HRMS (ESI) calcd for $C_{25}H_{32}Br^{35}Cl_6NO_3Na$ [M+Na] 705.9594, found 705.9562.

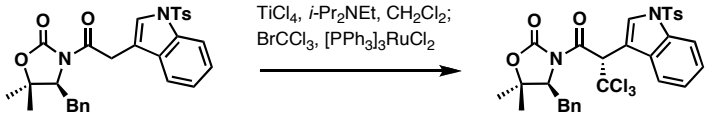



**Oxazolidinone (Table 1, entry 7).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.229 g, 87%, dr>98:2) after purification by silica gel column chromatography (hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ -5.3° (c 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$); δ(ppm): 7.35-7.21 (m, 10H); 5.50 (dd, J1=10.8 Hz, J2=2.8 Hz, 1H); 4.58 (dd, J1=10.8 Hz, J2=2.4 Hz, 1H); 3.48 (t, J=6.4 Hz, 2H); 3.29 (dd, J1=14.4 Hz, J2=2.4 Hz, 1H); 2.85 (dd, J1=14.4 Hz, J2=10.8 Hz, 1H); 2.32-2.22 (m, 1H); 2.13-2.05 (m, 1H); 1.75-1.63 (m, 2H); 1.56-1.42 (m, 2H); 1.33 (s, 3H); 1.28 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 169.5, 152.2, 138.6, 137.0, 129.1, 128.9, 128.5, 127.8, 127.7, 127.0, 98.8, 82.4, 73.1, 69.7, 64.5, 59.8, 34.8, 30.9, 29.6, 28.7, 23.8, 22.5. HRMS (ESI) calcd for $C_{26}H_{30}{}^{35}Cl_3NO_4Na$ [M+Na] 548.1138, found 548.1135.

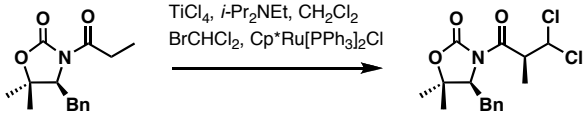



**Oxazolidinone (Table 1, entry 8).** The title compound was prepared following the standard procedure and was obtained as a colorless oil

(0.201 g, 91%, dr>98:2) after purification by silica gel column chromatography (Hexanes:EtOAc 9:1). $[\alpha]_D^{23}$ +77.2° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.68-7.66 (m, 2H); 7.42-7.37 (m, 3H); 7.32-7.31 (m, 4H); 7.26-7.23 (m, 1H); 6.38 (s, 1H); 4.49 (dd, J1=10.0 Hz, J2=3.0 Hz, 1H); 3.28 (dd, J1=14.5 Hz, J2=3.0 Hz, 1H); 2.95 (dd, J1=14.5 Hz, J2=10.0 Hz, 1H); 1.32 (s, 3H); 1.03 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 167.6, 152.0, 136.7, 132.0, 131.2, 129.7, 129.3, 129.0, 128.5, 127.1, 101.9, 82.9, 65.3, 64.3, 35.4, 28.4, 22.3. HRMS (ESI) calcd for $C_{21}H_{20}{}^{35}Cl_3NO_3Na$ [M+Na] 462.0406, found 462.0400.

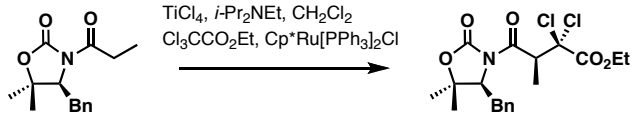



**Oxazolidinone (Table 1, entry 9).** The title compound was prepared following the standard procedure and was obtained as a colorless oil (0.193 g, 61%, dr>98:2) after purification by silica gel column chromatography (Hexanes:EtOAc 4:1). $[\alpha]_D^{23}$ +84.0° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$); δ(ppm): 8.06 (s, 1H); 7.96 (d, J=9.0 Hz, 1H); 7.83 (d, J=9.0 Hz, 1H); 7.76 (d, J = 10.5 Hz, 2H); 7.35-7.30 (m, 5H); 7.29-7.24 (m, 3H); 7.21 (d, J=10.5 Hz, 2H); 6.89 (s, 1H); 4.51 (dd, J1=12.5 Hz, J2=4.0 Hz, 1H); 3.32 (dd, J1=18.0 Hz, J2=4.0 Hz, 1H); 2.93 (dd, J1=18.0 Hz, J2=12.5 Hz, 1H); 2.34 (s, 3H); 1.32 (s, 3H); 1.00 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 167.2, 152.2, 145.4, 136.7, 135.1, 134.6, 130.3, 130.2, 129.3, 129.2, 129.0, 127.2, 127.1, 125.3, 124.0, 120.8, 113.7, 113.6, 98.3, 82.8, 64.3, 56.9, 35.2, 28.5, 22.5, 21.8. HRMS (ESI) calcd for $C_{30}H_{27}{}^{35}Cl_3N_2O_5SNa$ [M+Na] 655.0604, found 655.0587.

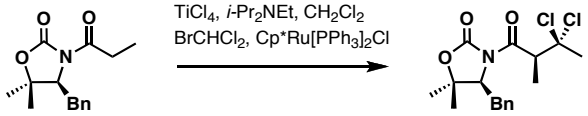



**Oxazolidinone (Table 2, entry 1).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.0 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $BrCHCl_2$ (0.41 mL, 5.0 mmol, 10 equiv.) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 45 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and

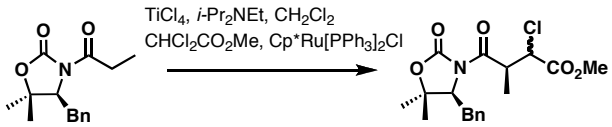
the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as a colorless oil (0.110 g, 64%, dr>98:2). $[\alpha]_D^{23}$ -54.2° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.27 (m, 4H); 7.25-7.22 (m, 1H); 6.06 (d, J=7.5 Hz, 1H); 4.53 (dt, J1=7.5 Hz, J2=7.0 Hz, 1H); 3.22 (dd, J1=14.5 Hz, J2=2.5 Hz, 1H); 2.85 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.44 (d, J=7.0 Hz, 3H); 1.38 (s, 3H); 1.32 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 172.2, 152.3, 136.8, 129.1, 129.0, 127.1, 82.9, 73.8, 64.1, 49.6, 35.0, 28.9, 22.6, 14.5. HRMS (ESI) calcd for $C_{16}H_{19}{}^{35}Cl_2NO_3Na$ [M+Na] 366.0640, found 366.0646.




**Oxazolidinone (Table 2, entry 2).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.15 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $Cl_3CCOOEt$ (0.20 mL, 1.5 mmol, 3.0 equiv.) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 60 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as a colorless oil (0.173 g, 83%, dr>98:2). $[\alpha]_D^{23}$ -9.9° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.30-7.25 (m, 4H); 7.22-7.18 (m, 1H); 4.89 (q, J=7.0 Hz, 1H); 4.30 (dd, J1=10.5 Hz, J2=2.5 Hz, 1H); 4.29 (q, J = 7.0 Hz, 2H); 3.18 (dd, J1=14.5 Hz, J2=2.5 Hz, 1H); 2.85 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.61 (d, J=7.0 Hz, 3H); 1.33 (s, 3H); 1.32 (s, 3H); 1.31 (t, J=7.0 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 172.3, 165.9, 152.0, 129.1, 128.9, 128.8, 127.0, 84.8, 82.2, 64.3, 64.2, 49.9, 34.7, 28.8, 22.4, 13.9, 13.8. HRMS (ESI) calcd for $C_{19}H_{23}{}^{35}Cl_2NO_5Na$ [M+Na] 438.0851, found 438.9839.



**Oxazolidinone (Table 2, entry 3).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.15 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. 1,1,1-trichloroethane (0.15 mL, 1.5 mmol, 3.0 equiv.) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 45 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as a colorless oil (0.127 g, 71%, dr>98:2). $[\alpha]_D^{23}$ -60.4° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.28 (m, 4H); 7.24-7.21 (m, 1H); 4.97 (d, J=7.0 Hz, 1H); 4.54 (dd, J1=10.0 Hz, J2=2.5 Hz, 1H); 3.29 (dd, J1=14.5 Hz, J2=3.5 Hz, 1H); 2.83 (dd, J1=14.5 Hz, J2=10.0 Hz, 1H); 2.26 (s, 3H); 1.47 (d, J=7.0 Hz, 3H); 1.36 (s, 3H); 1.31 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 172.4, 152.4, 137.0, 129.1, 128.9, 127.0, 90.4, 82.3, 64.3, 51.6, 34.8, 34.3, 28.8, 22.6, 15.1. HRMS (ESI) calcd for $C_{17}H_{21}{}^{35}Cl_2NO_3Na$ [M+Na] 380.0796, found 380.0791.

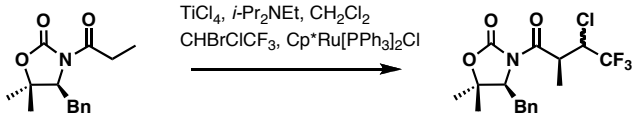



**Oxazolidinone (Table 2, entry 4).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.15 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $Cl_2CHCOOMe$ (0.52 mL, 5.0 mmol, 10 equiv.) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 60 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 95:15) of the crude material afforded 2 diastereoisomers (dr 1.3:1).

Diastereoisomer 1: colorless oil (81 mg, 44 %). $[\alpha]_D^{23}$ -13.2° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.26 (m, 4H); 7.22 (t, J =

7.0 Hz, 1H); 4.62 (d, J=9.0 Hz, 1H); 4.46 (dd, J1=11.0 Hz, J2=3.0 Hz, 1H); 4.34 (dq, J1=9.0 Hz, J2= 7.0 Hz, 1H); 3.75 (s, 3H); 3.13 (dd, J1=15.0 Hz, J2=3.0 Hz, 1H); 2.87 (dd, J1=15.0 Hz, J2=11.0 Hz, 1H); 1.40 (d, J=7.0 Hz, 3H); 1.34 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 174.7, 169.5, 152.0, 137.2, 129.1, 128.9, 126.9, 82.7, 63.9, 58.1, 53.3, 42.8, 34.8, 29.0, 26.6, 14.6. HRMS (ESI) calcd for $C_{18}H_{22}{}^{35}ClNO_5Na$ [M+Na] 390.1084, found 390.1081.

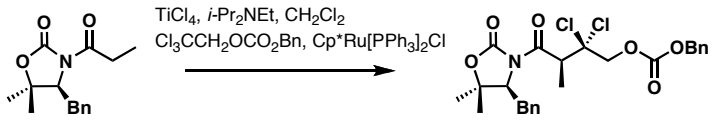
Diastereoisomer 2: colorless oil (57 mg, 31 %). $[\alpha]_D{}^{23}$ -52.0° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.32-7.28 (m, 4H); 7.24-7.21 (m, 1H); 4.63 (d, J=9.5 Hz, 1H); 4.54-4.48 (m, 2H); 3.80 (s, 3H); 3.28 (dd, J1=14.5 Hz, J2=3.0 Hz, 1H); 2.87 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.37 (s, 3H); 1.32 (s, 3H); 1.27 (d, J=7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 173.3, 168.6, 152.3, 137.0, 129.2, 128.9, 127.0, 82.7, 64.3, 57.8, 53.3, 43.2, 34.9, 28.9, 22.6, 15.0. HRMS (ESI) calcd for $C_{18}H_{22}{}^{35}ClNO_5Na$ [M+Na] 390.1084, found 390.1083.



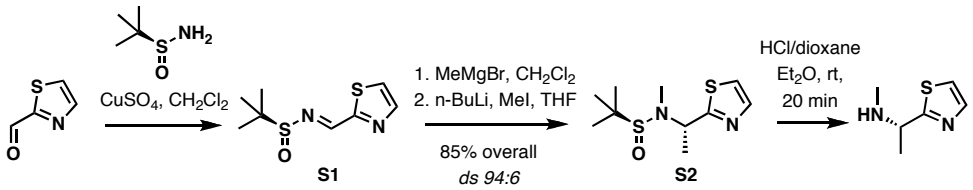

**Oxazolidinone (Table 2, entry 5).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.15 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. $BrClCHCF_3$ (0.53 mL, 5.0 mmol, 10 equiv.) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 60 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as a mixture of diastereomers (0.134 g, 71%, dr 1.6:1).

Diastereoisomer 1: $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.33-7.27 (m, 5H); 4.77 (qu, J=6.5 Hz, 1H); 4.53 (dd, J1=10.0 Hz, J2=3.0 Hz, 1H); 4.43 (qu, J=6.5 Hz, 1H); 3.19 (dd, J1=14.0 Hz, J2=3.0 Hz, 1H); 2.83 (dd, J1=14.0 Hz, J2=10.0 Hz, 1H); 1.39 (d, J=6.5 Hz, 3H); 1.37 (s, 3H); 1.34 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 172.4, 152.3, 136.8, 129.1, 129.0, 127.1, 124.0 (q, J=280.2 Hz), 83.0, 64.1, 58.2 (q, J=32.9 Hz), 39.1, 34.9, 28.9, 22.6, 13.4.

Diastereoisomer 2: $^{1}$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.33-7.27 (m, 5H); 4.63-4.52 (m, 3H); 3.26 (dd, J1=14.0 Hz, J2=3.0 Hz, 1H); 2.86 (dd, J1=14.0 Hz, J2=10.0 Hz, 1H); 1.38 (d, J=6.5 Hz, 3H); 1.38 (s, 3H); 1.34 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 172.8, 152.2, 136.9, 129.1, 129.0, 127.1, 124.1 (q, J=280.2 Hz), 82.8, 64.2, 57.8 (q, J=33.0 Hz), 42.4, 34.9, 28.9, 22.6, 15.2. HRMS (ESI) calcd for $C_{17}H_{19}{}^{35}ClF_3NO_3Na$ [M+Na] 400.0903, found 400.0903.



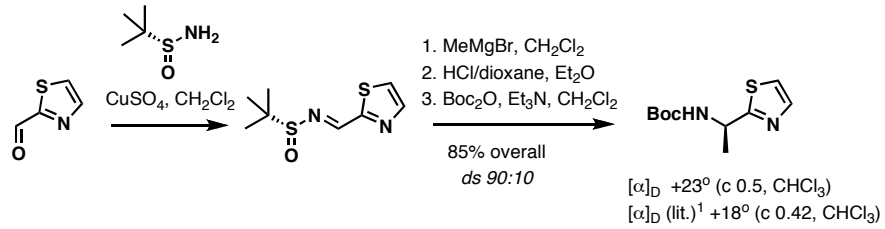

**Oxazolidinone (Table 2, entry 6).** A 0.5 M solution of $TiCl_4$ in $CH_2Cl_2$ (1.05 mL, 0.525 mmol, 1.05 equiv.) was added to a solution of oxazolidinone **1** (0.131 g, 0.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (1.15 mL) at 0 °C. After 5 min at 0 °C, diisopropylethylamine (90 μL, 0.525 mmol, 1.05 equiv.) was added. The resulting dark-red solution was stirred at 0 °C for 40 min. 1,1,1-trichloroethyl benzyl carbonate (0.850 g, 3.0 mmol, 6.0 equiv.) in $CH_2Cl_2$ (0.20 mL) was then added, followed by $Cp^*Ru[PPh_3]_2Cl$ (28 mg, 0.035 mmol, 7 mol%) and the reaction mixture was heated at 45 °C for 12 h in a sealed vial. The reaction was quenched with $H_2O$ and the layers were separated. The aqueous layer was then extracted with dichloromethane and the combined organic layers dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as a colorless oil (0.187 g, 73%, dr>98:2). $[\alpha]_D^{23}$ -43.4° (c 1.0, $CH_2Cl_2$). $^{1}$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.39-7.33 (m, 5H); 7.30-7.20 (m, 5H); 5.22 (d, J=14.0 Hz, 1H); 5.19 (d, J=14.0 Hz, 1H); 4.96 (q, J=7.0 Hz, 1H); 4.85 (d, J=11.5 Hz, 1H); 4.71 (d, J=11.5 Hz, 1H); 4.49 (dd, J1=10.5 Hz, J2=3.0 Hz, 1H); 3.28 (dd, J1=14.5 Hz, J2=3.0 Hz, 1H); 2.77 (dd, J1=14.5 Hz, J2=10.5 Hz, 1H); 1.53 (d, J=7.0 Hz, 3H); 1.33 (s, 3H); 1.32 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 171.5, 154.4, 152.3, 137.0, 134.9, 129.1, 128.9, 128.8, 128.8, 128.6, 127.0, 89.2, 82.6, 72.8, 70.5, 64.4, 48.3, 34.7, 28.7, 22.5, 15.0. HRMS (ESI) calcd for $C_{25}H_{27}{}^{35}Cl_2NO_6Na$ [M+Na] 530.1113, found 530.1110.



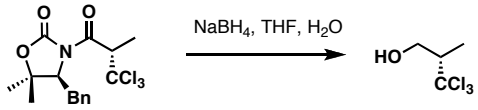

**(*R*)-2-(1-*N*-methylamino)ethylthiazole.** Copper(II) sulfate pentahydrate (0.60 g, 2.40 mmol) was carefully flame-dried under vacuum in the reaction flask. After cooling, the flask was filled with argon, and dry dichloromethane (2.7 ml) and 2-thiazolecarboxaldehyde (Aldrich, 0.10 ml, 1.14 mmol) were added followed by (*S*)-tert-butanesulfinamide (0.138 g, 1.14 mmol). The mixture was stirred for at room temperature for 12 h, and then filtered through Celite and concentrated on a rotary evaporator to furnish 0.238 g of the crude product. This material was dissolved in dry dichloromethane (5.5 ml) cooled to -50 °C under argon, and methylmagnesium bromide (3M in $Et_2O$, 0.75 ml, 2.25 mmol) was added dropwise. The mixture was stirred at -50 °C for 4 h and allowed to warm to room temperature overnight. Quenching with saturated aqueous ammonium chloride, extraction with dichloromethane, drying with sodium sulfate, and concentration afforded crude product (0.266 g), which was used without purification. The crude material was dissolved in dry THF (6.0 ml), cooled to -78 °C, and *n*-butyllithium (2.53M in hexanes, 0.48 ml, 1.21 mmol) was added dropwise. After 5 min, iodomethane (0.40 ml, 6.4 mmol) was added. After 15 min, the mixture was warmed to 0 °C and stirred for 1.5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layers were dried with sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by column chromatography (90%, the 100% ethyl acetate — hexanes) to afford the desired product (0.240 g, 0.974 mmol, 85% overall).

Hydrogen chloride (4M in dioxane, 0.49 ml, 1.96 mmol) was added to a solution of the *N*-methylsulfinamide (0.240 g, 0.974 mmol) in dry MeOH (1.5 ml) at 0 °C. The resulting mixture was stirred at room temperature for 20 min (complete by TLC) and concentrated. The residue was partitioned between dichloromethane and 1 M aqueous sodium hydroxide, the organic layer was dried with sodium sulfate and concentrated. The residue was purified by column chromatography (10% MeOH — $CH_2Cl_2$) to provide the pure amine (0.135 g, 0.949 mmol, 98%). The enantiomeric ratio of 94:6 was established by chiral HPLC of the corresponding *N*-Boc derivative (Daicel Chiralcel 4.6×250 mm OD-H column, 2% MTBE — hexane, 1.0 ml/min, $t_R$ 31.4 min (*R*-enantiomer), 34.3 min (*S*-enantiomer)). $[\alpha]_D^{23}$ -23.6° (c 1.0, $CHCl_3$), $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.69 (d, J=3.5 Hz, 1H); 7.24 (d, J=3.5 Hz, 1H); 4.07 (q, J=6.5 Hz, 1H); 2.43 (s, 3H); 1.48 (d, J=6.5 Hz, 3H). $^{13}$C NMR

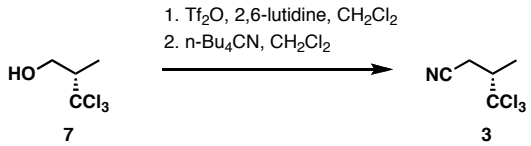
(125 MHz, $CDCl_3$); δ(ppm): 177.3, 142.5, 118.7, 58.2, 34.7, 23.1. **Absolute configuration** was confirmed by the preparation of the (*R*)-*N*-Boc derivative as shown in the following Scheme:




The optical rotation of this *N*-Boc derivative matched the material thoroughly characterized previously by Dondoni and co-workers.[1]



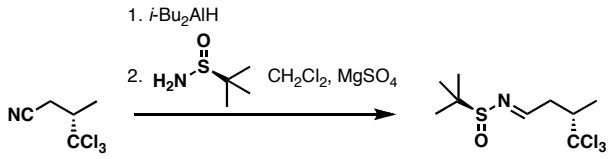

**Alcohol 7.** Sodium borohydride (3.60 g, 95.1 mmol) was added to a solution of oxazolidinone **2** (12.0 g, 31.7 mmol) in THF (260 mL) and $H_2O$ (84 mL) at 0 °C. The solution was warmed at room temperature and stirred for 2 h. After cooling to 0 °C, the reaction mixture was quenched with 1 M aqueous HCl (100 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL). The organic layers were combined and washed with brine, dried with anhydrous sodium sulfate, and concentrated carefully under reduced pressure. Purification by column chromatography (hexanes:EtOAc 3:2) of the crude material afforded the title compound as a colorless oil (3.40 g, 61%). $[\alpha]_D^{23}$ -12.5° (c 0.57, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 4.15 (dd, J1=11.5 Hz, J2=4.0 Hz, 1H); 3.66 (dd, J1=11.5 Hz, J2=7.5.0 Hz, 1H); 2.75-2.69 (m, 1H); 1.41 (d, J=6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 103.3, 64.6, 56.8, 14.8.




**Nitrile 3.** 2,6-Lutidine (5.56 mL, 47.9 mmol, 2.5 equiv) was added to a solution of alcohol **7** (3.40 g, 19.16 mmol, 1.0 equiv.) in $CH_2Cl_2$ (9 mL). Trifluoromethanesulfonic anhydride (4.0 mL, 23.95 mmol, 1.25 equiv.) was then added to the mixture at -15 °C. The solution was stirred at -15 °C for 2 h. The reaction was diluted with dichloromethane (15 mL) washed with 1 M aqueous HCl (2*15 mL) and saturated $NaHCO_3$ (15mL). The organic layer was

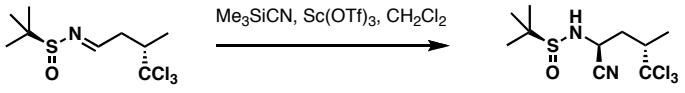
[1] Dondoni, A.; Merchan, F. L.; Merino, P.; Rojo, I.; Tejero, T. *Synthesis* **1996**, 641–646.

dried over sodium sulfate, filtered and concentrated. To a solution of the crude triflate in dichloromethane (64 mL) was added tetraethylammonium cyanide (4.5 g, 28.74 mmol, 1.5 equiv.) at -15 °C. The reaction mixture was stirred 2 h at -15 °C. The reaction was diluted with dichloromethane (15 mL) washed with 1 M aqueous HCl (2*15 mL) and saturated $NaHCO_3$ (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:EtOAc 95:5) of the crude material afforded the title compound as a colorless oil (2.53 g, 71%). $[\alpha]_D^{23}$ -28.2° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$); δ(ppm): 3.07 (dd, J1=16.8 Hz, J2=4.0 Hz, 1H); 3.00-2.92 (m, 1H); 2.57 (dd, J1=16.8 Hz, J2=10.4 Hz, 1H); 1.54 (d, J=6.4 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 117.3, 102.8, 51.6, 21.9, 16.6. HRMS (CI) calcd for $C_5H_7{}^{35}Cl_3N$ [M+H] 185.9644, found 185.9652.

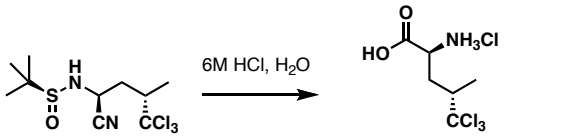



3 4

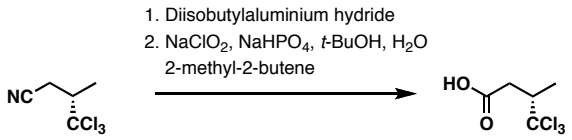
**Sulfinimine 4.** Diisobutylaluminum hydride (neat, 1.34 mL, 7.5 mmol, 1.4 equiv) was added to a solution of nitrile **3** (1.00 g, 5.36 mmol, 1.0 equiv) in $CH_2Cl_2$ (32 mL) at -78 °C. The solution was stirred at -78 °C for 2 h. 40 mL of 1 M aqueous HCl and 20 mL of $H_2O$ were then added and the reaction mixture was warmed up at room temperature and stirred 2 h. The organic layer was then washed with Rochelle salt and dried over sodium sulfate, filtered and concentrated. (*S*)-(-)-*tert*-butanesulfinamide (0.715 g, 5.90 mmol, 1.1 equiv), pyridinium *p*-toluenesulfonate (67 mg, 0.27 mmol, 0.05 equiv), $MgSO_4$ (6.45 g, 53.6 mmol, 10 equiv) were added to a solution of the crude aldehyde in dichloromethane (5.4 mL) at room temperature. The reaction mixture was then stirred for 48 h at room temperature. The crude mixture was filtered through a pad of celite and concentrated. Purification by column chromatography (hexanes:EtOAc 9:1) of the crude material afforded the title compound as white solid (1.06 g, 67%, dr>98:2) along with the corresponding unreacted aldehyde (0.195 g, 1.03 mmol, 19%). $[\alpha]_D^{23}$ +139.8° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 8.10 (dd, J1=5.0 Hz, J2= 3.5 Hz, 1H); 3.22 (ddd, J1=17.0 Hz, J2=4.0 Hz, J3=3.5 Hz, 1H); 3.16-3.01 (m, 1H); 2.67 (ddd, J1=17.0 Hz, J2=9.5 Hz, J=5.0 Hz, 1H); 1.38 (d, J=6.5 Hz, 3H); 1.21 (s, 9H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 166.4, 105.0, 57.2, 51.8, 40.0, 22.6, 17.2. HRMS (ESI) calcd for $C_9H_{16}{}^{35}Cl_3NOSNa$ [M+Na] 313.9916, found 313.9919.




**Amino-nitrile 8.** Trimethylsilane (0.31 mL, 2.33 mmol, 2.0 equiv) and $Sc(OTf)_3$ (86 mg, 0.175 mmol, 0.15 equiv) were added to a solution of sulfinimine **4** (0.341 g, 1.16 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.7 mL) at 0 °C. The solution was stirred at 0 °C for 48 h. The crude mixture was concentrated, and purification of the residue by column chromatography (hexanes:EtOAc 7:3 to 1:1) afforded the title compound as white solid (0.345 g, 93%, dr 94:6). $[\alpha]_D^{23}$ -23.3° (c 1.0, $CH_2Cl_2$). $^1H$ NMR (500 MHz, $CDCl_3$); δ(ppm): 4.58 (d, J=9.5 Hz, 1H); 4.19 (ddd, J1=9.5 Hz, J2=9.5 Hz, J3=4.5 Hz, 1H); 2.73-2.66 (m, 1H); 2.64-2.59 (m, 1H); 1.93 (ddd, J1=14.0 Hz, J2=9.5 Hz, J3=4.5 Hz, 1H); 1.35 (d, J=6.5 Hz, 3H); 1.23 (s, 9H). $^{13}C$ NMR (125 MHz, $CDCl_3$); δ(ppm): 119.4, 104.7, 57.6, 51.0, 44.6, 38.4, 22.8, 16.3. HRMS (ESI) calcd for $C_{10}H_{17}{}^{35}Cl_3N2OSNa$ [M+Na] 341.0025, found 341.0004.

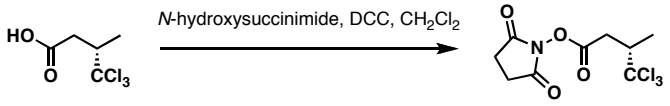



**(2*S*,4*S*)-5,5,5-Trichloroleucine.** A solution of amino-nitrile **8** (0.250 g, 0.782 mmol, 1.0 equiv) in 6 M aqueous HCl (4 mL) was heated at reflux for 2.5 h. The reaction mixture was diluted with $H_2O$ (5 mL), washed with $Et_2O$ (2×5 mL) and the aqueous phase evaporated. A slurry of Dowex 50x8-100 ion exchange resin (approximately 2 g of resin per 10 mg of the crude mixture) in 2 M aqueous HCl was placed in a flash column and washed with distilled $H_2O$ until the eluent was neutral (pH 7). The crude amino acid HCl salt was neutralized (pH 7) with 1.5% aqueous $NH_4OH$ then applied to the column. Distilled $H_2O$ (4-5 void volumes) was eluted through the resin, followed by elution with 1.5% aqueous $NH_4OH$. Fractions were collected and those containing the amino acid (TLC: $SiO_2$/4:1 MeOH:$H_2O$, visualized with ninhydrin) were dried under vacuum. Saturated hydrogen chloride in $Et_2O$ was finally added to the neutral amino acid to give the pure amino acid HCl salt as a white solid (0.186 g, 88%, dr>98:2). $[\alpha]_D^{23}$ -15.3° (c 1.0, $H_2O$). $^1H$ NMR (500 MHz, $D_2O$); δ(ppm): 3.87 (dd, J1=10.5 Hz, J2=4.0 Hz, 1H); 2.85-2.80 (m, 1H); 2.52-2.47 (m, 1H); 2.11 (ddd, J1=14.5 Hz, J2=10.5 Hz, J3=4.0 Hz, 1H); 1.43 (d, J=6.5, 3H). $^{13}C$ NMR (125 MHz, $D_2O$:$CD_3OD$ 2:1); δ(ppm): 172.2, 105.1, 52.2, 51.7, 34.9, 16.8. HRMS (ESI) calcd for $C_6H_{11}{}^{35}Cl_3NO_2$ [M+H] 233.9844, found 233.9855.




3 9

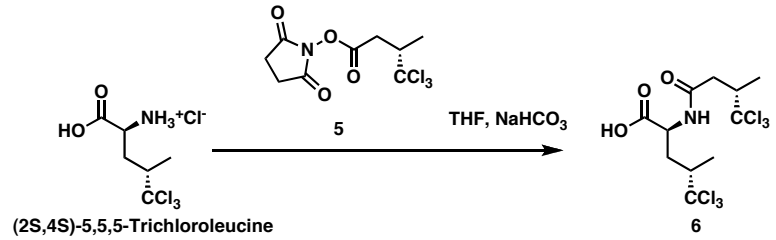
**Carboxylic acid 9.** Diisobutylaluminum hydride (neat, 0.67 mL, 3.75 mmol, 1.4 equiv) was added to a solution of nitrile **3** (0.500 g, 2.68 mmol, 1.0 equiv) in $CH_2Cl_2$ (16 mL) at -78 °C. The solution was stirred at -78 °C for 2 h. 1 M Aqueous HCl (20 mL) and 10 mL of $H_2O$ were then added and the reaction mixture was warmed up at room temperature and stirred 2 h. The organic layer was then washed with Rochelle salt and dried over sodium sulfate, filtered and concentrated. $NaClO_2$ (1.21 g, 13.4 mmol, 5 equiv), $NaHPO_4$ (1.85 g, 13.4 mmol, 5 equiv), 2-methyl-2-butene (1.7 mL, 16.1 mmol, 6 equiv) were added to a solution of the crude aldehyde, *t*-BuOH (7.5 mL) and $H_2O$ (3.0 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for 20 min and then 3 h at room temperature. The crude mixture was diluted with $H_2O$ (10 mL) and extracted with dichloromethane (3*15 mL). Purification by column chromatography (dichloromethane:MeOH 97:3) of the crude material afforded the title compound as a white solid (0.459 g, 83%). $[\alpha]_D^{23}$ -19.5° (c 0.65, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 3.17 (dd, J1=16.0 Hz, J2=3.0 Hz, 1H); 3.15-3.10 (m, 1H); 2.47 (dd, J1=16.0 Hz, J2=9.5 Hz, 1H); 1.42 (d, J=6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 178.1, 104.8, 51.7, 38.5, 17.4. HRMS (ESI) calcd for $C_5H_6{}^{35}Cl_3O_2$ [M-H] 202.9433, found 202.9434.



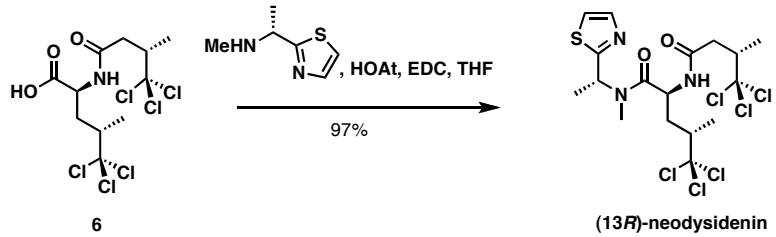

9 5

***N*-Hydroxysuccinimide ester 5.** Dicyclohexyl carbodiimide (DCC, 60.3 mg, 0.292 mmol, 1.2 equiv) and *N*-hydroxysuccinimide (33.6 mg, 0.292 mmol, 1.2 equiv) were added to a solution of carboxylic acid **9** (50 mg, 0.243 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 40 h. The crude mixture was filtered through a pad of celite and concentrated. Purification by column chromatography (dichloromethane : hexanes 4:1) of the crude material afforded the title compound as white solid (67 mg, 91%). $[\alpha]_D^{23}$ -21.2° (c 1.0, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 3.38 (dd, J1=16.0 Hz, J2=3.0 Hz, 1H); 3.20-3.13 (m, 1H); 2.85 (s, 4H); 2.71 (dd, J1=16.0 Hz, J2=10.5 Hz, 1H); 1.47 (d, J=6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm):

169.0, 166.8, 103.8, 51.7, 35.4, 25.7, 16.7. HRMS (ESI) calcd for $C_9H_{10}{}^{35}Cl_3NO_4Na$ [M+Na] 323.9573, found 323.9571.

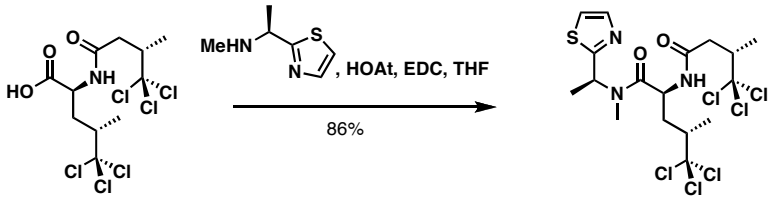



**Carboxylic acid 6.** Saturated aqueous $NaHCO_3$ (0.15 mL) and succinimide ester **5** (30 mg, 0.1 mmol, 1.0 equiv) were added to a suspension of (2*S*,4*S*)-5,5,5-trichloroleucine (27 mg, 0.1 mmol) in THF (0.15 mL) at room temperature. The reaction mixture was stirred for 14 h at room temperature. 1 M Aqueous HCl was added and the aqueous layer was extracted with ethyl acetate (3×5 mL). The organic layers were combined and washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 1:9, contains 0.5% acetic acid) of the crude material afforded the title compound as white solid (41.5 mg, 99%, dr>98:2). $[\alpha]_D^{23}$ -23.9° (c 1.0, MeOH). $^1$H NMR (500 MHz, $CD_3OD$); δ(ppm): 4.61 (dd, J1=12.0 Hz, J2=3.5 Hz, 1H); 3.18-3.13 (m, 1H); 3.05 (dd, J1=14.5 Hz, J2=3.5 Hz, 1H); 2.62-2.56 (m, 1H); 2.43 (dd, J1=14.0 Hz, J2=10.0 Hz, 2H); 2.03-1.97 (m, 1H); 1.41 (d, J=6.5 Hz, 3H); 1.35 (d, J=6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CD_3OD$); δ(ppm): 174.4, 173.3, 106.8, 106.3, 53.4, 53.3, 40.6, 36.4, 30.9, 17.1, 16.3. HRMS (ESI) calcd for $C_{11}H_{15}{}^{35}Cl_6NO_3Na$ [M+Na] 441.9081, found 441.9085.



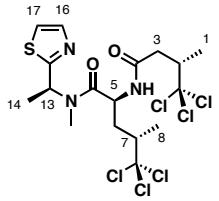

**(13*R*)-Neodysidenin.** EDC (18 mg, 0.094 mmol) was added to a solution of acid **6**(14.0 mg, 0.0332 mmol), (*R*)-2-(1-*N*-methylamino)ethylthiazole (12 mg, 0.084 mmol, 83:17 er) and HOAt (14 mg, 0.102 mmol) in THF (0.75 ml) and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and washed with 1 M aqueous HCl and brine. Drying of the organic layers with sodium sulfate and concentration afforded the crude product, which was purified by careful column

chromatography (40% ethyl acetate – hexanes) afforded (13*R*)-neodysidenin (17.7 mg, 0.0324 mmol, 97%) containing ~15% of inseparable 13*S*-diastereomer and about 20% of the amide bond rotamers. $[\alpha]_D^{23}$ +26.1° (c 0.50, $CHCl_3$), [lit.[2] $[\alpha]_D^{23}$ -52.1° (c 0.165, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.73 (d, J=3.0 Hz, 1H); 7.33 (d, J=3.0 Hz, 1H); 6.82 (bd, J=8.0 Hz, 1H); 6.13 (q, J=7.0 Hz, 1H); 5.08 (ddd, J1=10.5 Hz, J2=8.0 Hz, J3=2.5 Hz, 1H); 3.21 (ddq, J1=9.5 Hz, J2=6.5 Hz, J3=3.5 Hz, 1H); 3.06 (dd, J1=15.0 Hz, J2=2.5 Hz, 1H); 2.96 (s, 3H); 2.61 (m, 1H); 2.38 (m, 1H); 2.32 (m, 1H); 1.68 (m, 1H); 1.67 (d, J=7.0 Hz, 3H); 1.50 (d, J=6.5 Hz, 3H); 1.37 (d, J=6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$); δ(ppm): 171.5, 170.6, 169.2, 142.8, 120.1, 105.6, 105.1, 51.94, 51.87, 50.7, 47.8, 40.5, 37.3, 30.0, 17.0, 16.8, 16.7. $C_{17}H_{23}{}^{35}Cl_6N_3O_2SNa$ [M+Na] 565.9540, found 565.9543.




**Neodysidenin.** EDC (9 mg, 0.047 mmol) was added to a solution of acid **6** (7.0 mg, 0.0166 mmol), (*S*)-2-(1-*N*-methylamino)ethylthiazole (6.0 mg, 0.042 mmol, 82:8 er) and HOAt (7 mg, 0.050 mmol) in THF (0.40 ml) and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and washed with 1 M aqueous HCl and brine. Drying of the organic layers with sodium sulfate and concentration afforded the crude product, which was purified by column chromatography (40% ethyl acetate – hexanes) to afford neodysidenin (7.8 mg, 0.0143 mmol, 86%) containing about 20% of the amide bond rotamer that was also observed by Molinski and co-workers.[2] $[\alpha]_D^{23}$ -62.3° (c 0.20, $CHCl_3$) [lit.[2] $[\alpha]_D^{23}$ -52.1° (c 0.165, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) and $^{13}$C NMR (125 MHz, $CDCl_3$) See Table below. HRMS (ESI) calcd for $C_{17}H_{23}{}^{35}Cl_6N_3O_2SNa$[M+Na] 565.9540, found 565.9531.

[2] MacMillan, J. B.; Trousdale, E. K.; Molinski, T. F. *Org. Lett.* **2000**, *2*, 2721–2723.



neodysidenin

**Comparison of the $^{1}$H NMR data for the synthetic and natural neodysidenin** (major amide rotamer only)[2]

| $^{1}$H # | natural, δ (*J*) (at 300 MHz) | synthetic, δ (*J*) (at 500 MHz) | synthetic 13*R*-epimer, δ (*J*) (at 500 MHz) |
|---|---|---|---|
| 1 | 1.37 (d, 3H, 6.7 Hz) | 1.37 (d, 3H, 6.5 Hz) | 1.37 (d, 3H, 6.5 Hz) |
| 2 | 3.22 (m, 1H, 10.2, 6.7, 3.2 Hz) | 3.21 (ddq, 1H, 9.5, 6.5, 3.5 Hz) | 3.21 (ddq, 1H, 9.5, 6.5, 3.5 Hz) |
| 3a | 2.32 (m, 1H) | 2.32 (m, 1H) | 2.32 (m, 1H) |
| 3b | 3.09 (dd, 1H, 15.3, 2.4 Hz) | 3.07 (dd, 1H, 15.0, 2.5 Hz) | 3.06 (dd, 1H, 15.0, 2.5 Hz) |
| 5 | 5.06 (ddd, 1H, 11.1, 8.4, 2.4 Hz) | 5.08 (ddd, 1H, 10.5, 8.0, 2.5 Hz) | 5.08 (ddd, 1H, 10.5, 8.0, 2.5 Hz) |
| 6a | 1.67 (1H, overlap) | 1.67 (1H, overlap) | 1.67 (1H, overlap) |
| 6b | 2.38 (m, 1H) | 2.38 (m, 1H) | 2.38 (m, 1H) |
| 7 | 2.60 (m, 1H) | 2.61 (m, 1H) | 2.61 (m, 1H) |
| 8 | 1.48 (d, 3H, 6.7 Hz) | 1.49 (d, 3H, 7.0 Hz) | 1.50 (d, 3H, 6.5 Hz) |
| 13 | 6.17 (q, 1H, 7.1 Hz) | 6.16 (q, 1H, 7.0 Hz) | 6.13 (q, 1H, 7.0 Hz) |
| 14 | 1.67 (d, 3H, 7.1 Hz) | 1.67 (d, 3H, 7.0 Hz) | 1.67 (d, 3H, 7.0 Hz) |
| 16 | 7.74 (d, 1H, 3.3 Hz) | 7.73 (d, 1H, 3.0 Hz) | 7.73 (d, 1H, 3.0 Hz) |
| 17 | 7.34 (d, 1H, 3.3 Hz) | 7.33 (d, 1H, 3.0 Hz) | 7.33 (d, 1H, 3.0 Hz) |
| *N*-Me | 2.94 (s, 3H) | 2.94 (s, 3H) | 2.96 (s, 3H) |
| NH | 6.70 (bd, 1H, 8.4 Hz) | 6.73 (bd, 1H, 8.5 Hz) | 6.82 (bd, 1H, 8.0 Hz) |

**Comparison of the $^{13}$C NMR data for the synthetic and natural neodysidenin, 125 MHz** (major amide rotamer only)[2]

| natural, δ | synthetic, δ | synthetic 13*R*-epimer, δ |
|---|---|---|
| 171.2 | 171.4 | 171.5 |
| 170.4 | 170.6 | 170.6 |
| 169.4 | 169.6 | 169.2 |
| 142.6 | 142.8 | 142.8 |
| 119.9 | 120.2 | 120.1 |
| 105.3 | 105.5 | 105.6 |
| 104.9 | 105.1 | 105.1 |
| 51.74 | 51.92 | 51.94 |
| 51.71 | 51.89 | 51.87 |
| 50.6 | 50.7 | 50.7 |
| 47.5 | 47.7 | 47.8 |
| 40.3 | 40.5 | 40.5 |
| 36.9 | 37.1 | 37.3 |
| 29.8 | 30.0 | 30.0 |
| 16.8 | 17.0 | 17.0 |

| | | |
|---|---|---|
| 16.5 | 16.7 | 16.8 |
| 16.3 | 16.5 | 16.7 |