Supporting information

Highly Diastereoselective Michael Addition of α-Hydroxy Acid Derivatives and Enatioselective Synthesis of (+)-Crobarbatic Acid

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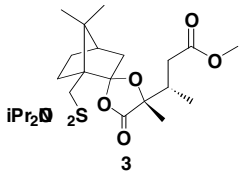
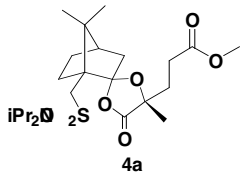
General procedure for Michael addition of 2a, 2b. A solution of LDA in THF (3.8 mL) was prepared under argon from diisopropylamine (1.1 mL, 7.67 mmol) and *n*-BuLi solution (2.5 M solution in hexane, 2.84 mL, 7.08 mmol) at 0 ^{o}C. After stirring for 30 min, the solution was cooled to –100 ^{o}C. A solution of dioxolanone **2** (5.90 mmol) in THF (11.0 mL) was added over 20 min, and the mixture was stirred for 30 min, then the solution of appropriate α,β-unsaturated ester (8.85 mmol) in THF (1 mL) was added slowly. The mixture was warm to –78 ^{o}C, and stirred for 3 h. Solution of 2% $H_2C_2O_{4(aq)}$ (2 mL) was added to the reaction mixture and the temprature was raised to 0^{o}C then neutralized with additional 2% $H_2C_2O_{4(aq)}$ to pH=6~7. The aqueous layer was extracted with EtOAc (3 x 20mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), evaporated *in vacuo* and the residue was purified by column chromatography on silica gel enluting with EtOAc/Hxane (1:5) to furnish the desired compound.



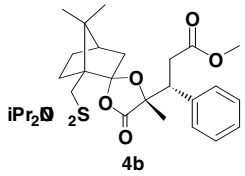
(1*S*,2*S*,5′*R*,1′′*S*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′,5′-(2′′-carbo-methoxy-1′′-methyl)ethylmethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-yl methanesulfonamide (3). White solid. mp = 110.5-110.8 ^{o}C; $[\alpha]_D^{23}$ +2.8 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2954, 2886, 1791, 1738, 1337, 1137, 979, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (heptet, *J*=6.8 Hz, 2H), 3.64 (s, 3H), 3.27 (d, *J*=13.6 Hz, 1H,), 2.90 (dd, *J*=16, 3.2 Hz, 1H), 2.45-2.39 (m, 1H), 2.34-2.29 (m, 2H), 2.08-2.01 (m, 2H), 1.86-1.80 (m, 3H), 1.44-1.25 (m, 2H), 1.40 (s, 3H), 1.29 (s, 6H), 1.27 (s, 6H), 1.06 (d, *J*=7.2 Hz, 3H), 1.02 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7

MHz) δ 173.3, 172.1, 115.1, 81.6, 54.2, 51.6, 51.3, 50.3, 47.9, 46.3, 44.0, 35.6, 35.3, 26.2, 25.5, 22.4, 21.3, 20.2, 19.9, 16.0, 13.6; HRMS calcd for $C_{24}H_{41}NO_7S$: 487.2604 Found: 487.2604; Anal. Calcd for $C_{24}H_{41}NO_7S$: C, 59.11; H, 8.47; N, 2.87; S, 6.58. Found: C, 59.08; H, 8.37; N, 2.77; S, 6.59.



4a

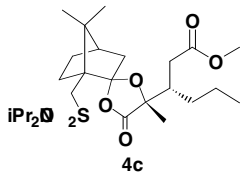
(1*S*,2*S*,5′*R*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′-(2′′-carbomethoxy) ethylmethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-ylmethanesulfonamide (4a). White solid. mp = 79.4-79.6 °C; $[\alpha]_D^{23}$ –6.3 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2949, 2881, 1796,1739, 1336, 1120, 979, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.69 (heptet, *J*=6.8 Hz, 2H), 3.67 (s, 3H), 3.26 (d, *J*=13.6 Hz, 1H), 2.57 (d, *J*=13.6 Hz, 1H), 2.57-2.39 (m, 2H), 2.36-2.28 (m, 2H), 2.07-1.97 (m, 3H), 1.84-1.76 (m, 3H), 1.51 (s,3H), 1.39-1.30 (m, 1H), 1.29 (s, 6H), 1.27 (s, 6H), 1.00 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 173.1, 172.1, 114.8, 78.9, 53.7, 51.2, 51.0, 50.0, 47.5, 46.0, 43.6, 32.0, 27.5, 25.9, 25.2, 22.0, 21.2, 19.8, 19.54, 19.51; HRMS calcd for $C_{23}H_{39}NO_7S$: 473.2477 Found: 473.2447; Anal. Calcd for $C_{23}H_{39}NO_7S$: C, 58.33; H, 8.30; N, 2.96; S, 6.77. Found: C, 58.36; H, 8.28; N, 2.89; S, 6.80.



4b

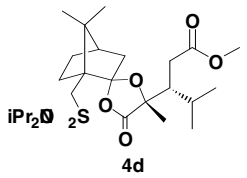
(1*S*,2*S*,5′*R*,1′′*R*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′,5′-(2′′-carbo-methoxy-1′′-phenyl)ethylmethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-yl methanesulfonamide (4b). White solid. mp = 77.4-77.7 °C; $[\alpha]_D^{23}$ +14.69 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2949, 2881, 1789, 1739, 1336, 1120, 979, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.26 (m, 5H), 3.72-3.67 (m, 1H), 3.63 (heptet, *J*=6.8 Hz, 2H), 3.53 (s, 3H), 3.20 (dd, *J*=16.2, 4.8 Hz, 1H), 3.11 (d, *J*=14 Hz, 1H), 2.97 (dd, *J*=17.0, 9.6 Hz, 1H), 2.57-2.53 (m, 1H), 2.54 (d, *J*=14 Hz,1H), 2.27-2.20 (m, 1H), 2.14-2.03 (m, 1H), 1.84-1.76 (m, 3H), 1.45 (s, 3H), 1.40-1.32 (m, 1H), 1.24 (d, *J*=6.8 Hz, 6H), 1.22 (d, *J*=6.8 Hz, 6H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7

MHz) δ 172.9, 171.5, 137.5, 129.2, 127.7, 127.1, 116.0, 81.8, 54.3, 51.4, 51.2, 50.2, 47.8, 46.5, 46.0, 44.0, 34.2, 26.0, 25.2, 22.5, 21.4, 20.3, 19.6, 18.8; HRMS calcd for $C_{29}H_{43}NO_7S$: 549.2760 Found: 549.2760; Anal. Calcd for $C_{29}H_{43}NO_7S$: C, 63.36; H, 7.88; N, 2.55; S, 5.83. Found: C, 63.34; H, 7.90; 2.54, N, ; S, 5.72.



4c

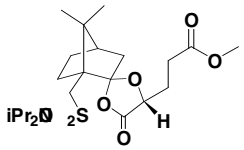
(1*S*,2*S*,5′*R*,1′′*S*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′,5′-(2′′-carbomethoxy-1′′-propyl)ethylmethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-yl methanesulfonamide (4c). White solid. mp = 113.3-113.5 °C; $[\alpha]_D^{23}$ +8.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2949, 2880, 1789, 1739, 1336, 1120, 979, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.68 (heptet, *J*=6.8 Hz, 2H), 3.63 (s, 3H), 3.25 (d, *J*=13.6 Hz, 1H), 2.82 (dd, *J*=16.6, 4.8 Hz, 1H), 2.59 (d, *J*=13.6 Hz, 1H), 2.45-2.39 (m, 1H), 2.33-2.26 (m, 2H), 2.12 (dd, *J*=13.6, 4.8 Hz, 1H), 2.08-2.00 (m, 1H), 1.90 (d, *J*=13.6 Hz, 1H), 1.83-1.76 (m, 2H), 1.68-1.62 (m, 2H), 1.42-1.19 (m, 3H), 1.40 (s, 3H), 1.28 (s, 6H), 1.27 (s, 6H), 1.02, (s, 3H), 0.91 (s, 3H), 0.90 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 173.6, 172.9, 115.3, 82.0, 54.4, 51.8, 51.5, 50.4, 48.1, 46.5, 44.2, 40.0, 34.2, 32.2, 26.3, 25.6, 22.6, 21.8, 20.51, 20.48, 20.0, 17.0, 14.2; HRMS calcd for $C_{26}H_{45}NO_7S$: 515.2917 Found: 515.2916; Anal. Calcd for $C_{26}H_{45}NO_7S$: C, 60.55; H, 8.80; N, 2.72; S, 6.22. Found: C, 60.52; H, 8.81; N, 2.77; S, 6.30.



4d

(1*S*,2*S*,5′*R*,1′′*S*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′,5′-(2′′-carbomethoxy-1′′-isopropyl)ethylmethyl-1′,3′-dioxolane-4′-one]} bicyclo[2.2.1]hept-1-ylmethanesulfonamide (4d). White solid. mp = 120.2-120.5 °C; $[\alpha]_D^{23}$ –0.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2949, 2881, 1791, 1939, 1336, 1120, 979, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ3.68 (heptet, *J*=6.8 Hz, 2H), 3.64 (s,3H), 3.26 (d, *J*=13.6 Hz, 1H), 2.72 (dd, *J*=16.8, 5.6 Hz, 1H), 2.59 (d, *J*=13.6 Hz, 1H), 2.40-2.36 (m, 1H), 2.35-2.32 (m, 1H), 2.31-2.23 (m, 2H), 2.19-2.10 (m, 1H),

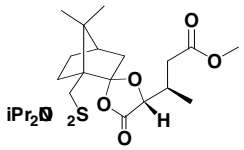
2.07-1.99 (m, 1H), 1.95 (d, *J*=13.6Hz, 1H), 1.82-1.75 (m, 2H), 1.44 (s, 3H), 1.42-1.34 (m, 1H), 1.28 (s, 6H), 1.26 (s, 6H), 1.02 (s, 3H), 0.97 (d, *J*=7.2 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 173.4, 173.1, 115.0, 82.1, 54.2, 51.6, 51.4, 50.3, 47.9, 46.1, 44.5, 44.1, 30.2, 26.9, 26.1, 25.5, 23.6, 22.4, 21.6, 20.4, 19.9, 19.3, 17.4; HRMS calcd for $C_{26}H_{45}NO_7S$: 515.2917 Found: 515.2916; Anal. Calcd for $C_{26}H_{45}NO_7S$: C, 60.55; H, 8.80; N, 2.72; S, 6.22. Found: C, 60.42; H, 8.76; N, 2.71; S, 6.23.



5e

(1*S*,2*S*,5′*R*,1′′*S*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′-(2′′-carbomethoxy) ethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-ylmethanesulfonamide (5e).

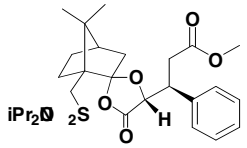
White solid. mp = 77.8-78.2 °C; $[\alpha]_D^{23}$ –9.43 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2949, 2886, 1796, 1737, 1336, 1153, 974, 774, 657 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.57 (d, *J*=7.8, 5.2 Hz, 1H), 3.68 (heptet, *J*=6.8 Hz, 2H), 3.66 (s, 3H), 3.27 (d, *J*=13.6 Hz, 1H), 2.56 (d, *J*=13.6 Hz, 1H), 2.53-2.43 (m, 2H), 2.35-2.24 (m, 2H), 2.20-2.11 (m, 1H), 2.07-1.98 (m, 1H), 1.92-1.77 (m, 3H), 1.38-1.32 (m, 1H), 1.283 (d, *J*=6.8 Hz, 6H), 1.275 (d, *J*=6.8 Hz, 6H), 1.00-0.90 (m, 1H), 0.98 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 172.4, 172.0, 117.5, 74.7, 54.6, 52.1, 51.3, 50.9, 48.0, 46.7, 43.6, 29.3, 27.5, 26.3, 25.5, 22.2, 21.8, 20.2, 19.8; HRMS calcd for $C_{22}H_{37}NO_7S$: 459.2291 Found: 459.2290; Anal. Calcd for $C_{22}H_{37}NO_7S$: C, 57.49; H, 8.11; N, 3.05; S, 6.98. Found: C, 57.33; H, 8.14; N, 3.10; S, 6.90.



5f

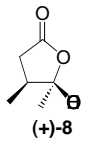
(1*S*,2*S*,5′*R*,1′′*R*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′-(2′′-carbomethoxy-1′′-methyl)ethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-yl methanesulfonamide (5f). White solid. mp = 64.9-65.2 °C; $[\alpha]_D^{23}$ –13.31 (*c* 1.0,

$CHCl_3$); IR (KBr) 2973, 2886, 1797, 1732, 1336, 1202, 1158, 1139, 974 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.46 (d, *J*=5.6 Hz, 1H), 3.69 (heptet, *J*=6.8 Hz, 2H), 3.65 (s, 3H), 3.27 (d, *J*=13.6 Hz, 1H), 2.59 (dd, *J*=15.6, 5.2 Hz, 1H), 2.57 (d, *J*=13.6 Hz, 1H), 2.48-2.38 (m, 1H), 2.33-2.25 (m, 3H), 1.94-1.75 (m, 4H), 1.38-1.22 (m, 1H), 1.29 (d, *J*=6.8 Hz, 6H), 1.28 (d, *J*=6.8 Hz, 6H), 1.08 (d, *J*=6.8 Hz, 3H), 0.98 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 172.1, 171.1, 117.2, 78.7, 54.8, 52.1, 51.2, 50.9, 48.1, 46.6, 43.5, 36.3, 32.5, 26.3, 25.3, 22.2, 21.8, 20.2, 19.7, 15.0; HRMS calcd for $C_{23}H_{39}NO_7S$: 473.2447 Found: 473.2447; Anal. Calcd for $C_{23}H_{39}NO_7S$: C, 58.33; H, 8.30; N, 2.96; S, 6.77. Found: C, 58.18; H, 8.23; N, 2.99; S, 6.78.



5g

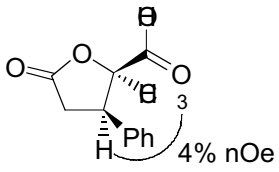
(1*S*,2*S*,5′*R*,1′′*S*)-*N*,*N*-Diisopropyl-{7,7-dimethyl-2-spiro-2′-[5′-(2′′-carbomethoxy-1′′-phenyl)ethyl-1′,3′-dioxolane-4′-one]}bicyclo[2.2.1]hept-1-yl methanesulfonamide (5g). White solid. mp = 165.6-165.8 °C; $[\alpha]_D^{23}$ –4.32 (*c* 1.0, $CHCl_3$); IR (KBr) 2983, 2954, 2886, 1791, 1723, 1329, 1149, 974 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.23 (m, 5H), 4.85 (d, *J*=4.4 Hz, 1H), 3.68-3.60 (m, 1H), 3.65 (heptet, *J*=6.8 Hz, 2H), 3.57 (s, 3H), 3.25 (d, *J*=13.6 Hz, 1H), 3.09 (dd, *J*=16.6, 6.8 Hz, 1H), 2.91 (dd, *J*=16.4, 8.4 Hz, 1H), 2.52 (d, *J*=13.6 Hz, 1H), 2.20-2.13 (m, 1H), 1.85-1.78 (m, 1H), 1.72-1.63 (m, 1H), 1.57-1.50 (m, 3H), 1.27 (s, 6H), 1.25 (s, 6H), 1.20-1.13 (m, 1H), 0.91 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 172.1, 171.3, 139.1, 128.8, 128.5, 127.6, 117.9, 79.1, 55.0, 52.4, 51.6, 51.1, 48.4, 45.6, 43.7, 43.5, 34.7, 26.3, 25.4, 22.6, 22.0, 20.5, 20.1; HRMS calcd for $C_{28}H_{41}NO_7S$: 535.2604 Found: 535.2603; Anal. Calcd for $C_{28}H_{41}NO_7S$: C, 62.78; H, 7.71; N, 2.61; S, 5.99. Found: C, 62.69; H, 7.72; N, 2.68; S, 5.99.



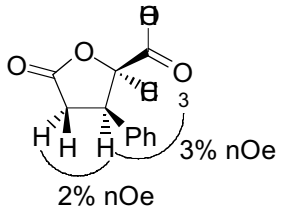
(+)-8

(2*R*,3*S*)-2,3-Dimethyl-5-oxo-tetrahydrofuran-2-carboxylic acid ((+)-crobarbatic acid 8). A solution containing **3** (0.5 g) in MeOH (4 mL) and 2*N* $NaOH_{(aq)}$ (1 mL)

was heated at 60 °C for 3h. After the solution was cooled, methanol was evaporated *in vacuo*. The residue was diluted with water (5 mL), and extracted with EtOAc (2_10mL). The organic phases were dried (Na_2SO_4) and concentrated to recover **1** (0.305 g), 91% yield. The pH value of aqueous layer was adjusted to 2 with concentrated $HCl_{(aq)}$, and water was evaporated in reduced pressure. The residue was dissolved in ether (10 mL) and filtered to remove salt (NaCl). The resulting solution was dried with $Na_2SO_{4(s)}$ and concentrated. *p*-TSA (0.1 g) and CH_2Cl_2 (5 mL) were added to the obtained residue. After stirring for 24h at ambient temperature, water (10 mL) was added to reaction mixture and aqueous layer was extracted with EtOAc (3_10mL). The combined organic phases were dried with $Na_2SO_{4(s)}$ and evaporated *in vacuo* to give white solid (0.136 g) of **8**, 86% yield. mp = 178.4-180.3 °C; $[\alpha]_D^{25}$ +3.56 (*c* 1.4, H_2O); IR (KBr) 3205(b), 2993, 2920, 2852, 1756, 1737, 1261, 1181, 965 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (dd, J=15.6, 6.8 Hz, 1H), 2.54-2.40 (m, 2H), 1.64 (s, 3H), 1.14 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 175.6, 174.8, 40.7, 35.7, 29.7, 21.8, 14.3; HRMS calcd for $C_7H_{10}O_4$: 158.0579 Found: 158.0580;



10a

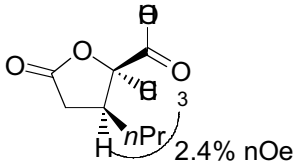


10a

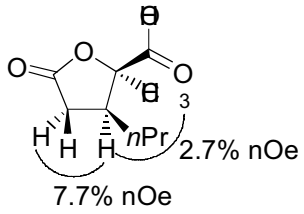
Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.05; H, 6.32.

(2*R*,3*R*)-2-methyl-3-phenyl-5-oxo-tetrahydrofuran-2-carboxylic acid (10a).

White solid. mp = 76.9-77.1 °C; $[\alpha]_D^{24}$ –222.04 (*c* 1.0, $CHCl_3$); IR (KBr) 3070, 3032, 2993, 2944, 1767, 1735, 1450, 1416, 1382, 1314, 1101 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.20 (m, 5H), 3.65 (dd, *J*=11.2, 8.8 Hz, 1H), 3.19 (dd, *J*=17.6, 11.6 Hz, 1H), 2.88 (dd, *J*=17.4, 8.8 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 176.0, 173.3, 133.8, 128.7, 128.3, 127.4, 87.9, 51.5, 33.6, 21.7; HRMS calcd for $C_{12}H_{12}O_4$: 220.0736 Found: 220.0740; Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 64.09; H, 5.70.



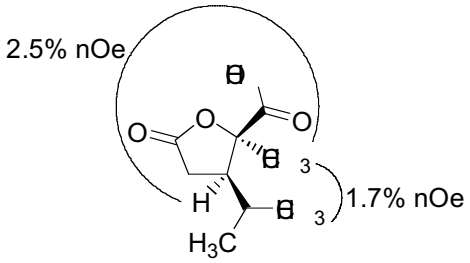
10b



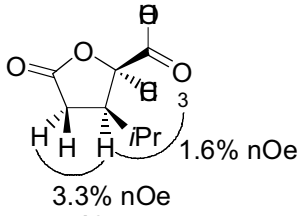
10b

(2*R*,3*S*)-2-methyl-3-propyl-5-oxo-tetrahydrofuran-2-carboxylic acid (10b).

White solid. mp = 98.2-98.4 °C; $[\alpha]_D^{25}$ +14.8 (*c* 1.0, $CHCl_3$); IR (KBr) 2959, 2934, 2876, 1767, 1736, 1231, 1090 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.66 (dd, *J*=16.4, 8.0 Hz, 1H), 2.47-2.32 (m, 2H), 1.65 (s, 3H), 1.61-1.53 (m, 1H), 1.42-1.16 (m, 3H), 0.93 (t, *J*=7.2, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 176.6, 174.6, 86.8, 45.8, 34.0, 31.5, 21.8, 21.1, 13.7; Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.63; H, 7.67.



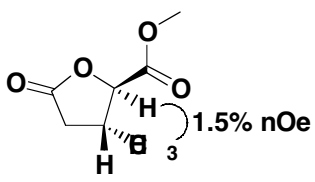
10c



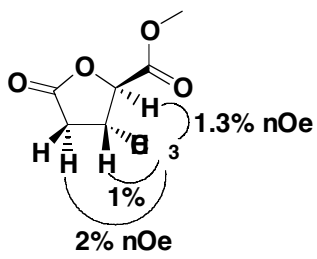
10c

(2*R*,3*R*)-3-isopropyl-2-methyl-5-oxo-tetrahydrofuran-2-carboxylic acid (10c).

Pale yellow oil. $[\alpha]_D^{25}$ –118.06 (*c* 1.0, $CHCl_3$); IR (KBr) 2973, 2915, 2881, 1767, 1747, 1241, 1090 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.67-2.51 (m, 2H), 2.18-2.11 (m, 1H), 1.71 (s, 3H), 1.69-1.61 (m, 1H), 1.05 (d, *J*=6.4 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.7 MHz) δ 176.8, 173.3, 87.3, 53.2, 33.9, 29.4, 23.6, 21.8, 21.4, HRMS calcd for $C_9H_{14}O_4$: 186.0892 Found: 186.0896.



11



11

(2*R*,3*R*)-3-methyl-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (11).

Pale yellow oil. $[\alpha]_D^{25}$ –13.37 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.49 (d, *J*=4.4 Hz, 1H), 3.79 (s, 3H), 2.77 (dd, *J*=17.4, 8.4 Hz, 1H), 2.74-2.58 (m, 1H), 2.18 (dd, *J*=17.4, 5.6, 1H), 1.27 (d, *J*=6.8 Hz, 3H).