ANGEWANDTE CHEMIE
A Journal of the Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z50084

69451 Weinheim, Germany

Enantiopure β-Hydroxy Morpholine Amides From Terminal Epoxides via Carbonylation at 1 Atm

Steven N. Goodman and Eric N. Jacobsen

Materials: 4-(trimethylsilyl)morpholine is available from Aldrich, or can be readily synthesized by the procedure outlined below. Morpholine, triethylamine, *N,N*-diisopropylamine and resolved epoxides were distilled from CaH_2 prior to use. EtOAc was dried over $MgSO_4$ and distilled, and diethyl ether and THF were distilled from sodium/benzophenone. Reactions were monitored by GC or TLC analysis.

Synthesis of 4-(trimethylsilyl)morpholine: To a oven-dried 1 L flask was added morpholine (22.0 mL, 0.252 mol), ether (250 mL), and triethylamine (37.0 mL, 0.265 mol). The rapidly stirred solution was cooled to 0 °C and TMSCl (32.7 mL, 0.258 mol) was added dropwise. The reaction mixture, which rapidly became a thick, white slurry, was allowed to stir overnight at room temperature. The mixture was then filtered, rinsed with pentane, and the solvent removed in vacuo. Additional triethylammonium hydrochloride which precipitated upon concentration was filtered off, and the crude material purified by fractional distillation through a 15 cm Vigreux column to afford 26.4 g (66%) of 4-(trimethylsilyl)morpholine: b.p. 80-84 °C (49 mmHg) [lit. b.p. 57-60 °C (20 mmHg)].[1]

General carbonylation procedure: To an oven-dried 10 mL Schlenk flask equipped with a stirbar and septum was added $[Co_2(CO)_8]$ (8.5 mg, 0.025 mmol) under a nitrogen atmosphere. The atmosphere was exchanged for CO (vacuum/fill 3x) from a double balloon affixed to the stopcock sidearm. Ethyl acetate (1.5 mL) was added, and the solution stirred for ten minutes. Trimethylsilylmorpholine (0.23 mL, 1.3 mmol) and epoxide (1.0 mmol) were added sequentially, and the septum was replaced with a greased glass stopper. The reaction mixture was stirred at the desired temperature for the specified length of time, at which point 3 N HCl (aq) (1.5 mL) was added to the reaction at room temperature. After

stirring for ten minutes, the layers were separated, the aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers washed with brine (2 mL). The aqueous layers were further extracted with EtOAc (2 x 15 mL each). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide the β-hydroxy morpholine amide as a clear to yellow oil.

(*S*)-3-Hydroxy-1-morpholin-4-yl-butan-1-one (Table 1, entry 1). $[\alpha]_D^{26}$ +51.4 (*c* = 1.08 in $CHCl_3$); FTIR (film) 3426 cm^{-1} (OH), 1623 cm^{-1} (C=O); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 4.20 (m, 1H; C*H*(OH)), 4.16 (bs, 1H; OH), 3.63 (m, 5H), 3.58 (m, 1H), 3.42 (m, 2H), 2.42 (dd, ^3J(H,H) = 1.2, 16.2 Hz, 1H; CH(OH)CH_2C(O)), 2.30 (dd, ^3J(H,H) = 9.6, 16.2 Hz, 1H; CH(OH)CH_2C(O)), 1.21 (d, ^3J(H,H) = 6.6 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 171.3, 66.8, 66.5, 64.2, 45.7, 41.8, 40.7, 22.2; MS (CI, NH_3): m/z (%): 174 (100) [M^+ + H].

(*S*)-1-Morpholin-4-yl-3-(trimethyl-silanyloxy)-butan-1-one (Table 1, entry 2). $[\alpha]_D^{24}$ +2.4 (*c* = 1.00 in $CHCl_3$); b.p. 81-84 °C (0.01 mmHg); FTIR (film) 1643 cm^{-1} (C=O); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 4.30 (ddt, ^3J(H,H) = 1.2, 6.0, 6.0 Hz, 1H; C*H*(OSi(CH_3)$_3$)), 3.64 (m, 5H), 3.60 (m, 1H), 3.51 (m, 2H), 2.59 (dd, ^3J(H,H) = 7.2, 14.4 Hz, 1H; CH(OH)CH_2C(O)), 2.29 (dd, ^3J(H,H) = 5.4, 14.4 Hz, 1H; CH(OH)CH_2C(O)), 1.20 (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3), 0.08 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 170.0, 66.8, 66.7, 66.6, 46.5, 42.5, 41.8, 24.3, 0.1; MS (APCI): m/z (%): 174 (100) [M^+ + H – $SiMe_3$].

(*R*)-3-Hydroxy-1-morpholin-4-yl-pentan-1-one (Table 1, entry 3). $[\alpha]_D^{24}$ –42.7 (*c* = 1.03 in $CHCl_3$); FTIR (film) 3437 cm^{-1} (OH), 1624 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 4.02 (bs, 1H; OH), 3.97 (m, 1H; C*H*(OH)), 3.68 (m, 5H), 3.61 (m, 1H), 3.45 (m, 2H), 2.47 (dd, ^3J(H,H) = 2.5, 16.5 Hz, 1H; CH(OH)CH_2C(O)), 2.31 (dd, ^3J(H,H) = 9.0, 16.5 Hz, 1H; CH(OH)CH_2C(O)), 1.57 (m, 1H; C$H_2$$CH_3$), 1.49 (m, 1H; C$H_2$$CH_3$), 0.98 (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 171.2, 69.1, 66.5, 66.2, 45.5, 41.5, 38.6, 29.1, 9.7; MS (ESI): m/z (%): 188 (100) [M^+ + H].

(*S*)-3-Hydroxy-1-morpholin-4-yl-heptan-1-one (Table 1, entry 4). $[\alpha]_D^{26}$ +34.6 (*c* = 1.02 in $CHCl_3$); FTIR (film) 3428 cm^{-1} (OH), 1625 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 4.04 (m, 1H; C*H*(OH)), 4.01 (bs, 1H; OH), 3.68 (m, 5H), 3.62 (m, 1H), 3.45 (m, 2H), 2.47 (dd, ^3J(H,H) = 2.5, 16.5 Hz, 1H; CH(OH)CH_2C(O)), 2.31 (dd, ^3J(H,H) = 9.0, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 1.55 (m, 1H), 1.44 (m, 2H), 1.35 (m, 3H), 0.91 (dt, ^3J(H,H) = 3.0, 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 171.2, 67.9, 66.7, 66.4, 45.6, 41.7, 39.2, 36.1, 27.7, 22.6, 14.0; MS (APCI): m/z (%): 216 (100) [M^+ + H].

(*R*)-3-Hydroxy-1-morpholin-4-yl-hept-6-en-1-one (Table 1, entry 5). $[\alpha]_D^{24}$ –46.4 (*c* = 1.07 in $CHCl_3$); FTIR (film) 3421 cm^{-1} (OH), 1625 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 5.84 (m, 1H; C*H*=CH_2), 5.05 (ddd, ^3J(H,H) = 2.0, 3.5, 17.0 Hz, 1H; CH=CH_2), 4.97 (ddd, ^3J(H,H) = 1.5, 3.5, 10.5 Hz, 1H; CH=CH_2), 4.07 (m, 1H; C*H*(OH)), 4.02 (bs, 1H; OH), 3.67 (m, 5H), 3.60 (m, 1H), 3.45 (m, 2H), 2.47 (dd, ^3J(H,H) = 2.5, 16.5 Hz, 1H; CH(OH)CH_2C(O)), 2.33 (dd, ^3J(H,H) = 9.5, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 2.25 (m, 1H; CH_2CH=CH_2), 2.18 (m, 1H; CH_2CH=CH_2), 1.65 (m, 1H; CH(OH)C$H_2$$CH_2$), 1.52 (m, 1H; CH(OH)C$H_2$$CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 171.2, 138.2, 114.8, 67.3, 66.7, 66.4, 45.6, 41.7, 39.2, 35.5, 29.7; MS (APCI): m/z (%): 214 (100) [M^+ + H].

(*S*)-3-Hydroxy-4-isopropoxy-1-morpholin-4-yl-butan-1-one (Table 1, entry 6). $[\alpha]_D^{24}$ –36.7 (*c* = 1.03 in $CHCl_3$); FTIR (film) 3440 cm^{-1} (OH), 1628 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 4.19 (m, 1H; C*H*(OH)), 3.85 (d, ^3J(H,H) = 3.0 Hz, 1H; OH), 3.68 (m, 5H), 3.62 (m, 2H), 3.49 (m, 4H), 2.56 (dd, ^3J(H,H) = 3.5, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 2.49 (dd, ^3J(H,H) = 8.5, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 1.17 (dd, ^3J(H,H) = 1.0, 6.5 Hz, 6H; (CH_3)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 171.0, 72.3, 71.3, 67.7, 66.9, 66.7, 46.1, 42.0, 36.4, 22.2; MS (CI, NH_3): m/z (%): 232 (100) [M^+ + H].

(*S*)-4-Benzyloxy-3-hydroxy-1-morpholin-4-yl-butan-1-one (Table 1, entry 7). $[\alpha]_D^{24}$ –31.4 (*c* = 1.04 in $CHCl_3$); FTIR (film)

3422 cm^{-1} (OH), 1627 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 7.31 (m, 5H; C_6H_5), 4.55 (s, 2H; $PhCH_2$), 4.24 (m, 1H; CH(OH)), 3.91 (d, ^{3}J(H,H) = 3.0 Hz, 1H; OH), 3.63 (m, 5H), 3.5-3.6 (m, 3H), 3.43 (m, 2H), 2.53 (dd, ^{3}J(H,H) = 3.6, 16.2 Hz, 1H; CH(OH)CH_2C(O)), 2.47 (dd, ^{3}J(H,H) = 8.4, 16.2 Hz, 1H; CH(OH)CH_2C(O)); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 170.4, 137.8, 128.1, 127.5, 127.5, 73.1, 73.0, 67.1, 66.4, 66.2, 45.6, 41.5, 35.9; MS (APCI): m/z (%): 280 (100) $[M^+ + H]$.

(*S*)-4-Chloro-3-hydroxy-1-morpholin-4-yl-butan-1-one (Table 1, entry 8). $[\alpha]_D^{24}$ –40.3 (*c* = 1.04 in $CHCl_3$); FTIR (film) 3419 cm^{-1} (OH), 1625 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 4.26 (m, 2H; CH(OH)), 3.58-3.68 (m, 8H), 3.46 (m, 2H), 2.63 (dd, ^{3}J(H,H) = 3.0, 16.8 Hz, 1H; CH(OH)CH_2C(O)), 2.57 (dd, ^{3}J(H,H) = 8.4, 16.8 Hz, 1H; CH(OH)CH_2C(O)); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 170.2, 68.2, 66.8, 66.5, 48.1, 46.0, 42.0, 36.2; MS (APCI): m/z (%): 208 (100) $[M^+ + H]$.

(*R*)-Butyric acid 2-hydroxy-4-morpholin-4-yl-4-oxo-butyl ester (Table 1, entry 9). $[\alpha]_D^{26}$ +27.9 (*c* = 1.00 in $CHCl_3$); FTIR (film) 3435 cm^{-1} (OH), 1735 cm^{-1} (C=O), 1630 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 4.30 (m, 1H; CH(OH)), 4.18 (d, ^{3}J(H,H) = 4.0 Hz, 1H; OH), 4.14 (m, 2H; nPrCO$_2$CH_2O), 3.68 (m, 4H), 3.63 (m, 2H), 3.44 (m, 2H), 2.51 (dd, ^{3}J(H,H) = 3.5, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 2.45 (dd, ^{3}J(H,H) = 9.0, 16.0 Hz, 1H; CH(OH)CH_2C(O)), 2.34 (t, ^{3}J(H,H) = 7.5 Hz, 2H; $CH_2CH_2CO_2CH_2$), 1.67 (sept, ^{3}J(H,H) = 7.5 Hz, 2H; $CH_3CH_2CH_2$), 0.96 (t, ^{3}J(H,H) = 8.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 173.4, 170.0, 66.8, 66.6, 66.3, 66.3, 45.6, 41.7, 35.8, 35.6, 18.2, 13.5; MS (APCI): m/z (%): 260 (90) $[M^+ + H]$.

Representative procedure for the addition of enolates to morpholine amides: (*R*)-benzyl glycidyl ether (**3a**) (50 mmol, 8.21 g), 4-(trimethylsilyl)morpholine (65 mmol, 10.35 g) and $[Co_2(CO)_8]$ (2.5 mmol, 0.855 g, 2.5 mol %) were reacted in EtOAc (75 mL) for 24 h at room temperature, using the general procedure above. Upon completion of the reaction, the solvent was thoroughly removed in vacuo, and the brown mixture reconcentrated from THF (2 x 10 mL). To an oven-dried 1 L

flask containing *i*-Pr_2NH (24.5 mL, 0.175 mol) in THF (75 mL) was added *n*BuLi (66.4 mL of a 2.64 M solution in hexanes, 0.175 mol) within 30 min, maintaining an internal temperature between –8 °C and 0 °C. The solution was stirred an additional 15 min at 0 °C, then cooled to -45 °C. *tert*-Butyl acetate (23.0 mL, 0.175 mol) in THF (40 mL) was added dropwise over 30 min, stirred for an additional 30 min, then Et_2AlCl (neat, 22.0 mL, 0.175 mol) was added dropwise over 30 min. The mixture was stirred 30 min, then the crude carbonylation mixture in THF (50 mL) was added via cannula over 30 min. The resulting solution was stirred at -45 °C until completion of the reaction (3-5 h, as indicated by GC), then carefully quenched at this temperature with the addition of 200 mL of a saturated aqueous solution of K,Na-tartrate [CAUTION! Care must be taken to control the exotherm and ethane gas evolution involved with this quench.] EtOAc (200 mL) was added, and the solution stirred until the solid material had dissolved. The phases were separated, and the aqueous layer extracted with an additional 200 mL EtOAc. The combined organic layers were washed with 1 N HCl (3 x 100 mL), brine (3 x 75 mL), dried over Na_2SO_4, and concentrated to afford 14.0 g of a pale brown oil (91% recovery) consisting predominantly of the desired δ-hydroxy-β-ketoester. Column chromatography (eluting with 90:10 to 70:30 hexanes:EtOAc) provided pure **2a** (9.75 g, 63% yield) as a 95:5 mixture of keto:enol tautomers by ^1H NMR ($CDCl_3$).

(*S*)-6-Benzyloxy-5-hydroxy-3-oxo-hexanoic acid tert-butyl ester (2a). $[\alpha]_D^{26}$ -15.5 (*c* = 1.03 in $CHCl_3$); FTIR (film) 3495 cm^{-1} (OH), 1733 cm^{-1} (C=O), 1713 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 7.33 (m, 5H; C_6H_5), 4.57 (d, ^3J(H,H) = 12.0 Hz, 1H, PhCH_2), 4.54 (d, J = 12.0 Hz, 1H; PhCH_2), 4.29 (m, 1H; C*H*OH), 3.51 (dd, ^3J(H,H) = 4.5, 10.0 Hz, 1H; BnOCH_2CH(OH)), 3.46 (dd, ^3J(H,H) = 6.0, 10.0 Hz, 1H; BnOCH_2CH(OH)), 3.39 (s, 2H; C(O)CH_2CO_2tBu), 2.84 (d, ^3J(H,H) = 4.5 Hz, 1H; OH), 2.76 (d, ^3J(H,H) = 6.5 Hz, 2H; CH(OH)CH_2C(O)CH_2), 1.46 (s, 9H; *t*Bu); **minor enol tautomer**: δ 12.35 (s, 1H, C(O*H*)CHCO_2tBu), 4.97 (s, 1H, C(OH)C*H*CO_2tBu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 203.1, 166.2, 137.8, 128.5, 127.8, 127.7, 82.2, 73.4, 73.1, 66.7, 51.2, 46.2, 28.0; MS (CI, NH_3): m/z (%): 326 (100) [$M^+ + NH_4$], 309 (10) [$M^+ + H$], 270 (65) [$M^+ + NH_4 - C_4H_8$].

(*S*)-6-(tert-Butyl-dimethyl-silanyloxy)-5-hydroxy-3-oxo-hexanoic acid tert-butyl ester (2b). $[\alpha]_D^{24}$ -15.4 (*c* = 1.03 in $CHCl_3$); FTIR (film) 3495 cm^{-1} (OH), 1730 cm^{-1} (C=O), 1713 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ 4.14 (ddddd, ^3J(H,H) = 6.0, 6.0, 6.0, 6.0, 6.0 Hz, 1H; C*H*OH), 3.64 (dd, ^3J(H,H) = 4.5, 10.0 Hz, 1H; TBSOCH_2CH(OH)), 3.57 (dd, ^3J(H,H) = 6.5, 10.0 Hz, 1H; TBSOCH_2CH(OH)), 3.44 (s, 2H; C(O)CH_2CO_2tBu), 2.81 (d, ^3J(H,H) = 4.5 Hz, 1H; OH), 2.75 (s, 1H; CH(OH)CH_2C(O)CH_2), 2.74 (d, ^3J(H,H) = 6.5 Hz, 2H; CH(OH)CH_2C(O)CH_2), 1.49 (s, 9H; CO_2tBu), 0.92 (s, 9H; *t*Bu(CH_3)$_2$Si), 0.093 (s, 3H; *t*Bu(CH_3)$_2$Si), 0.091 (s, 3H; *t*Bu(CH_3)$_2$Si); **minor enol tautomer**: δ 12.34 (s, 1H, C(O*H*)CHCO_2tBu), 5.01 (s, 1H, C(OH)C*H*CO_2tBu), 1.51 (s, 9H; ; CO_2tBu), 0.92 (s, 9H; *tBu*Me$_2$Si); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 203.0, 166.3, 82.1, 68.1, 66.2, 51.3, 36.0, 28.0, 25.9, 18.3, -5.4, -5.4; MS (CI, NH_3): m/z (%): 350 (100) [M^+ + NH_4], 333 (18) [M^+ + H], 294 (50) [M^+ + NH_4 – C_4H_8].

(*R*)-5-hydroxy-3-oxo-hexanoic acid *tert*-butyl ester. $[\alpha]_D^{26}$ +37.0 (*c* = 2.04 in $CHCl_3$) [lit.: $[\alpha]_D^{26}$ +37.3 (*c* = 2.03 in $CHCl_3$)]; FTIR (film) 3410 cm^{-1} (OH), 1730 cm^{-1} (C=O), 1712 cm^{-1} (C=O); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 4.23 (m, 1H; C*H*OH), 3.35 (d, ^3J(H,H) = 2.4 Hz, 2H; C(O)CH_2CO_2tBu), 2.84 (d, J = 3.6 Hz, 1H; OH), 2.71 (dd, ^3J(H,H) = 2.4, 18.0 Hz, 1H; CH(OH)CH_2C(O)CH_2), 2.62 (dd, ^3J(H,H) = 9.0, 17.4 Hz, 1H; CH(OH)CH_2C(O)CH_2), 1.45 (s, 9H; *t*Bu), 1.19 (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3); **minor enol tautomer**: δ 12.34 (s, 1H, C(O*H*)CHCO_2tBu), 4.95 (s, 1H, C(OH)C*H*CO_2tBu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 204.3, 166.2, 82.3, 63.8, 51.1, 51.0, 28.0, 22.4; MS (CI, NH_3): m/z (%): 220 (85) [M^+ + NH_4], 203 (15) [M^+ + H], 163 (100) [M^+ + NH_4 – C_4H_8].

References

[1] K. Itoh, S. Sakai, Y. Ishii, *J. Org. Chem*. **1966**, *31*, 3948-3951.