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Design of a New Cascade Reaction For the Construction of Complex Acyclic Architecture: The Tandem Acyl–Claisen Rearrangement

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen or argon *via* syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), Bruker AMX-400 (400 MHz and 100 MHz, respectively), Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant

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[1]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43,* 2923.

(Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. (δ ppm). IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a CC-1701 (30 m x 0.25 mm) column from C&C Column Technologies. High performance liquid chromatography (HPLC) was performed on the Hewlett-Packard 1100 Series chromatographs using a 4.6 x 250 mm Zorbax Sil column.

General Procedure A: Preparation of the allylic diamines. According to a modified procedure of Werner,[3] to a solution of the triphenylphosphonium halide salt in THF was added *t*-BuOK portionwise. After 1 h, a solution of the diaminoketone in THF was added to the resulting orange mixture and heated to reflux. After 12 h, the crude reaction mixture was washed with 1 *N* HCl (50 mL). The resulting aqueous layer was then separated and washed with Et_2O (3 x 50 mL) and then carefully adjusted to pH 12 with 1 *N* NaOH (50 mL). The aqueous layer was then extracted with Et_2O (3 x 50 mL) and the organic layers combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by chromatography on grade I alumina (Et_2O) to furnish the title compounds.

Morpholin-4-yl-acetic acid ethyl ester (16). Morpholine (13.0 mL, 0.15 mol) was added dropwise to a solution of ethyl bromoacetate (10.5 g, 63.8 mmol) in toluene (100 mL). After 8 h, the resulting mixture was filtered through a plug of Celite® with Et_2O and

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[3]Werner, D. S.; Stephenson, G. *Liebigs Ann.* **1996**, 1705.

concentrated to provide **16** (10.2 g, 58.9 mmol) in 92% yield as a yellow oil, which was used without further purification. IR (CH_2Cl_2) 1745, 1455, 1297, 1197, 1166, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (q, *J* = 9.5 Hz, 2H, C**H**$_2$$CH_3$), 3.75 (t, *J* = 6.2 Hz, 4H, $O(CH_2)_2$), 3.19 (s, 2H, CH_2CO), 2.57 (t, *J* = 6.2 Hz, 4H, $N(CH_2)_2$, 1.27 (dt, *J* = 8.9, 0.8 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 66.6, 60.5, 59.6, 53.2, 14.1; LRMS (FAB) *m/z* 174 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_8H_{15}NO_3H)^+$ requires m/z 174.4113, found *m/z* 174.1135.

1,3-Di-morpholin-4-yl-propan-2-one (17). Following a modified version of the procedure described by McElvain,[4] a round bottom flask charged with **16** (10.0 g, 58.0 mmol) and NaOEt (2.0g, 29.0 mmol) was heated to 100 °C under reduced pressure (40 torr) with removal of EtOH by short path distillation. After the evolution of EtOH had ceased (2 h), the resulting black solid residue was dissolved in a hot solution of NaOH (64 g, 1.6 mol) and EtOH (240 mL) in H_2O (320 mL) and then heated to reflux. After 1.5 h, the resulting solution was cooled to 23 °C and the aqueous layer was removed, extracted with Et_2O (3 x 200 mL). The combined organic layers were then washed with brine (200 mL), dried (Na_2SO_4) and concentrated to afford (11.7 g, 51.3 mmol) of **17** as a yellow solid in 60% yield which was used without further purification: mp 62 °C; IR (CH_2Cl_2) 1455, 1366, 1293, 1116, 1004, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (t, *J* = 6.2 Hz, 8H, 2 x $O(CH_2)_2$), 3.26 (s, 4H, $(CH_2)_2CO$), 2.50 (t, *J* = 6.2 Hz, 8H, 2 x $N(CH_2)_2$); ^{13}C NMR (100 MHz) 205.4, 66.8, 66.2, 53.9; LRMS (FAB) *m/z* 229 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{11}H_{20}N_2O_3H)^+$ requires m/z 229.1552, found *m/z* 229.1555.

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[4] Thomas, W.B.; McElvain, S.M. *J. Am. Chem. Soc.* **1934,** *56,* 1806.

1,3-Dimorpholin-4-yl-2-ethylidene-propane (1). Prepared according to general procedure A from ethyltriphenylphosphonium bromide (11.3 g, 30.3 mmol), *t*-BuOK (3.4 g, 30.0 mmol) and ketone **17** (1.40 g, 6.00 mmol) in THF (30 mL) to provide **1** as a white solid (0.83 g, 3.5 mmol) in 58% yield: mp 41 °C; IR (CH_2Cl_2) 1455, 1366, 1293, 1116, 1004, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (q, *J* = 6.9 Hz, 1H, CH=C), 3.67 (m, 8H, 2 x $N(CH_2)_2$), 2.94 (s, 2H, C**H**$_2$C=CH), 2.88 (s, 2H, C**H**$_2$C=CH), 2.37 (bs, 8H, 2 x $O(CH_2)_2$), 1.66 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 126.3, 67.1, 67.1, 64.0, 55.7, 53.7, 53.6, 13.2; LRMS (FAB) *m/z* 240 $(M)^+$; HRMS (FAB) exact mass calc'd for $(C_{13}H_{24}N_2O_2)^+$ requires m/z 240.1838, found *m/z* 240.1907.

2-Chloromethylene-1,3-dimorpholin-4-yl-propane (12). Prepared according to general procedure A from chloromethyltriphenylphosphonium chloride (6.68 g, 22.1 mmol), *t*-BuOK (2.46 g, 21.9 mmol) and ketone **17** (1.00 g, 4.38 mmol) in THF (30 mL) to provide **12** as a yellow oil (0.79 g, 3.0 mmol) in 68% yield; IR (CH_2Cl_2) 2866, 2819, 1452, 1352, 1298, 1120, 1004, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1H, CH=C), 3.69 (t, *J* = 4.6 Hz, 8H, 2 x $O(CH_2)_2$), 3.25 (s, 2H, CH_2C=C), 3.01 (s, 2H, CH_2C=C), 2.18-2.45 (m, 8H, 2 x $N(CH_2)_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 118.2, 55.6, 53.6, 67.1, 61.1; LRMS (CI) *m/z* 261 $(M)^+$; HRMS (CI) exact mass calc'd for $(C_{12}H_{21}ClN_2O_2H)^+$ requires m/z 261.2369, found *m/z* 261.1370.

1,3-Dimorpholin-4-yl-2-phenylthiomethylene-propane (15). Prepared according to general procedure A from phenylthiomethyltriphenylphosphonium chloride (3.92 g, 9.31 mmol), *t*-BuOK (1.04 g, 9.31 mmol) and ketone **17** (1.00 g, 4.38 mmol) in THF (20 mL) to provide 1**5** as a yellow oil (0.10 g, 3.0 mmol) in 7% yield; IR (CH_2Cl_2) 2814, 2250, 1583, 1455, 1293, 1116, 1007, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.32 (m, 4H, Ph), 7.15-7.19 (m, 1H, Ph), 6.35 (s, 1H, CH=C), 3.63-3.66 (m, 8H, 2 x $O(CH_2)_2$), 3.09 (s, 2H,

$CH_2C{=}C$), 2.87 (s, 2H, $CH_2C{=}C$), 2.38-2.43 (m, 8H, 2 x $N(CH_2)_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.9, 129.0, 128.9, 126.3, 124.9, 67.0, 63.3, 57.8, 53.6, 53.5; LRMS (CI) *m/z* 335 $(MH)^+$; HRMS (CI) exact mass calc'd for $(C_{18}H_{26}N_2O_2SH)^+$ requires *m/z* 335.1793, found *m/z* 335.1784.

3-(-N-methyl-morpholinyl)-4-(-N-morpholinyl)-but-2-enenitrile (14). Prepared according to general procedure A from cyanomethyltriphenylphosphonium chloride (3.30 g, 11.0 mmol) and ketone **17** (500 mg, 2.19 mmol) in THF (22 mL) to provide **14** as a yellow oil (120 mg, 3.0 mmol) in 22% yield; IR (CH_2Cl_2) 2980, 2872, 2247, 1710, 1112, 1116, 730 cm^{-1}; ^1H NMR (400 MHz) δ 5.75 (s, 1H, CH=C), 3.69-3.72 (m, 8H, 2 x $O(CH_2)_2$), 3.25 (s, 2H, $CH_2C{=}C$), 3.13 (s, 2H, $CH_2C{=}C$), 2.45-2.46 (bs, 8H, 2 x $N(CH_2)_2$; ^{13}C NMR (100 MHz) δ 160.6, 116.3, 98.3, 66.7, 66.6, 61.1, 59.8, 53.5, 53.4; LRMS (CI) *m/z* 252 $(MH)^+$; HRMS (CI) exact mass calc'd for $(C_{13}H_{21}N_3O_2H)^+$ requires m/z 252.1712, found *m/z* 252.1712.

Benzoic acid-2-(-N-methyl-morpholinyl)-3-(-N-morpholinyl)-propenyl ester (13). Based upon a modified procedure of Boeckman[5], a solution of benzoic acid 2-methyl-propenyl ester[6] (64.3 g, 0.365 mol) and NBS (136.4 g, 0.766 mol) in CCl_4 (730 mL) at reflux was added benzoyl peroxide (1.06 g, 4.38 mmol). After 2 h, the reaction mixture was filtered through a plug of Celite® and concentrated to yield the dibromide, which was used without further purification. A solution of the crude dibromide in CH_2Cl_2 (3.2 L) was treated with *i*-Pr_2EtN (127 mL, 0.729 mol), followed by dropwise addition of morpholine (64 mL, 0.73 mol) at 4 °C. The reaction was then allowed to warm to 23 °C. After 1.3 h,

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[5] Boeckman, R. K.; Ko S.S. *J. Am. Chem. Soc.* **1982,** *104,* 1033.

[6] Olofson R. A.; Dang, V. A. *J. Org. Chem.* **1990,** *58,* 1.

the reaction mixture was washed with H_2O (3 x 600 mL), dried (Na_2SO_4), filtered, concentrated and purified on with grade I alumina (Et_2O) to afford the product **13** as a yellow solid (62.0 g, 9.24 mmol) in 50% yield; mp 80 °C; IR (CH_2Cl_2) 1729, 1455, 1293, 1274, 1251, 1116, 1004, 865 cm^{-1}; ^1H NMR (400 MHz) δ (d, *J* = 7.2 Hz, 2H, Ar), 7.63 (*app* t, *J* = 7.4 Hz, 1H, Ar), 7.50 (*app* t, *J* = 7.6 Hz, 2H, Ar), 7.42 (s, 1H, CH=C), 3.68-3.72 (m, 8H, 2 x $O(CH_2)_2$), 3.21 (s, 2H, CH_2C=C), 3.02 (s, 2H, CH_2C=C), 2.46-2.49 (m, 8H, 2 x $N(CH_2)_2$); ^{13}C NMR (100 MHz) δ 163.4, 135.3, 133.7, 129.9, 129.0, 128.6, 119.4, 67.1, 58.8, 54.0, 53.8, 53.6; LRMS (FAB) *m/z* 347 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{19}H_{26}N_2O_4H)^+$ requires m/z 347.1971, found *m/z* 347.1971.

1,3-Dipiperidin-2-ethylidene-1-yl-propane (11). According to Werner,[3] to a solution of the (ethyl)triphenylphosphonium bromide (5.00 g, 13.5 mmol) in Et_2O (50 mL) was added dropwise *n*-BuLi (5.50 mL of a 2.47 M solution in hexanes, 13.5 mmol). After 1 h, the resulting orange mixture was cooled to –78 °C and 1,3-dichloroacetone (1.70 g, 13.5 mmol) in Et_2O (50 mL) was added dropwise at which time a color change from dark orange to yellow was observed. The reaction mixture was then allowed to warm to 23 °C over 15 h and then Et_2O (100 mL) was added. The resulting mixture was then filtered through a pad of Celite© with Et_2O (200 mL). The organic layer was then separated, dried (Na_2SO_4), and then concentrated at 0 °C to provide 1-chloro-2-(chloromethyl)-2-butene (**18**) (0.70 g, 2.68 mmol) in 37% yield which was used without further purification. To a refluxing mixture of piperidine (0.70 mL, 6.71 mmol) and $NaHCO_3$ (300 mg, 5.36 mmol) in H_2O (1.0 mL) was added **18**. After 2.5 h, the resulting mixture was washed with 1 *N* HCl (20 mL). The aqueous layer was then separated and washed with Et_2O (3 x 20 mL) and then carefully adjusted to pH 12 with 1 *N* NaOH (20 mL). The aqueous layer was then extracted with Et_2O (3 x 50 mL) and the organic layers combined, washed with brine (20 mL), dried (Na_2SO_4), and then concentrated. The resulting residue was purified by chromatography on

grade I alumina (Et_2O) to furnish **11** as a yellow oil (300 mg, 1.27 mmol) in 47% yield. IR (film) 2935, 2757, 1444, 1298, 1151, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (q, *J* = 6.9 Hz, 1H, CH=C), 2.89 (s, 2H, C**H**$_2$C=CH), 2.86 (s, 2H, C**H**$_2$C=CH), 2.31 (bs, 8H, 2 x N(CH_2)$_2$), 1.66 (d, *J* = 6.9 Hz, 3H, CH_3), 1.28-1.58 (m, 3.67, 8H, (C**H**$_2$$CH_2$)$_2$N), 1.39-1.42 (m, 2H, C**H**$_2$$CH_2$$CH_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.6, 56.9, 55.1, 54.9, 26.5, 25.0, 24.9 13.7.

1,3-Dipyrrolin-1-yl-2-ethylidene-propane (10). To a solution of pyrrolidine (7.75 mL, 93.0 mmol) in THF (40.0 mL) at 23 °C was added 1-chloro-2-(chloromethyl)-2-butene (**18**) (2.85 g, 18.56 mmol)**.** After 5 h, the resulting mixture was extracted with 1 *N* HCl (aq) (40 mL). The resulting aqueous layer was washed with Et_2O (3 x 40 mL) and then carefeully adjusted to pH 12 with 1 *N* NaOH (40 mL). The aqueous layer was then extracted with Et_2O (3 x 50 mL) and the organic layers combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by chromatography on grade I basic alumina (Et_2O) to furnish **10** as a colorless oil (600 mg, 2.88 mmol) in 16% yield. IR (film) 2966, 2781, 1630, 1267, 1197 cm^{-1}; ^1H NMR (300 MHz) δ 5.58 (q, *J* = 6.9 Hz, 1H, CH=C), 3.09 (s, 2H, C**H**$_2$C=CH), 3.07 (s, 2H, C**H**$_2$C=CH), 2.46-2.47 (m, 8H, 2 x N(CH_2)$_2$), 1.71-1.80 (m, 8H, (C**H**$_2$$CH_2$)$_2$N), 1.71 (d, *J* = 4.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz) δ 64.6, 56.9, 55.1, 54.9, 26.5, 25.0, 24.9 13.7; LRMS (FAB) *m/z* 209 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{13}H_{24}N_2H)^+$ requires m/z 209.2015, found *m/z* 209.2018.

General Procedure B: To a flask charged with $TiCl_4$•$(THF)_2$ was added the allyl dimorpholine in CH_2Cl_2, followed by *i*-Pr_2NEt. The resulting solution was then cooled to –20 °C for 5 min before the acid chloride in CH_2Cl_2 was added dropwise over 1 min, unless noted otherwise. The resulting dark red solution was maintained at –20 °C until the allyl

dimorpholine was consumed (4-6 h) as determined by TLC analysis (EtOAc). The resulting solution was then diluted with EtOAc (20 mL) and then washed with aqueous 1*N* NaOH (20 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL), and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (EtOAc) to afford the title compounds.

General Procedure C: To a flask containing $Yb(OTf)_3$ was added the allyl dimorpholine in CH_2Cl_2, followed by *i*-Pr_2NEt at 23 °C. After 5 min a solution of the acid chloride in CH_2Cl_2 was added dropwise over 1 min. The resulting dark red solution was maintained at 23 °C until the allyl dimorpholine was consumed (4-6 h) as determined by TLC analysis (EtOAc). The reaction mixture was then diluted with EtOAc (20mL) and washed with aqueous 1*N* NaOH (20 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL), and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (EtOAc) to afford the title compounds.

(2*R,3*R**,6*R**)-1,7-Dimorpholin-4-yl-4-methylene-2,3,6-trimethyl-heptane-1,7-dione (9).** Prepared according to the general procedure C from **1** (50.0 mg, 0.208 mmol), $Yb(OTf)_3$ (258mg, 0.416 mmol), *i*-Pr_2NEt (0.15 mL, 0.83 mmol), and propionyl chloride (0.75 mL, 1 M solution in CH_2Cl_2, 0.75 mmol) in 4.0 mL of CH_2Cl_2 to provide the title compound as a colorless oil in 97% yield (71.4 mg, 0.203 mmol); 98:2 *syn–anti:anti–anti*. *Syn–anti* isomer: IR (CH_2Cl_2) 2976, 2864, 1733, 1637, 1463, 1436, 1374, 1247, 1116, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 2H, CH_2=C), 3.43-3.68 (m, 16H, 2 x $O(CH_2CH_2)_2N$), 2.90 (m, 1H), 2.72 (m, 1H), 2.49 (dd, *J* = 7.3, 14.6 Hz, 1H, C**H**(H)C=CH_2), 2.36 (m, 1H), 2.0 (dd, *J* = 6.4, 14.6, 1H, C**H**(H)C=CH_2), 1.07 (d, *J* = 6.5

Hz, 3H, CH_3), 1.04 (d, *J* = 4.5 Hz, 3H, CH_3), 1.00 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.7, 174.7, 152.2, 109.5, 67.0, 66.8, 46.1, 45.9, 42.1, 41.9, 40.6, 40.2, 40.0, 39.6, 33.4, 17.7, 17.3, 17.2, 15.3; LRMS (FAB) *m/z* 353 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{19}H_{32}N_2O_4H)^+$ requires m/z 353.2440, found *m/z* 353.2444. Diastereomer ratio was determined by GLC with a CC-1701 column (100 °C, 20 °C/min gradient, 25 psi); *syn–anti* adduct t_r = 43.0 min, *syn–syn* adduct t_r = 44.0 min, and *anti–anti* adduct t_r = 51.8 min.

(2*R,3*R**,6*R**)-1,7-Dipiperidin-1-yl-4-methylene-2,3,6-trimethyl-heptane-1,7-dione (Table 2, entry 3).** Prepared according to the general procedure C from **11** (50.0 mg, 0.212 mmol), $Yb(OTf)_3$ (258mg, 0.416 mmol), *i*-Pr_2NEt (0.15 mL, 0.85 mmol), and propionyl chloride (0.80 mL, 1 M solution in CH_2Cl_2, 0.80 mmol) in 4.0 mL of CH_2Cl_2 to provide the title compound as a colorless oil in 99% yield (73.4mg, 0.203 mmol); 96:4 *syn–anti:anti–anti*. *Syn–anti* isomer: IR (film) 3059, 2989, 2943, 2866, 2309, 1622, 1444, 1267, 911, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 1H, C**H**(H)=C), 4.69 (s, 1H, C**H**(H)=C), 3.33-3.58 (m, 8H, 2 x $N(CH_2)_2$), 2.71-2.81 (m, 1H, CH(CO)), 2.47 (dd, *J* = 7.1, 14.6 Hz, 1H, C**H**(H)C=CH_2), 2.32-2.51 (m, 1H), 1.98 (dd, *J* = 6.6, 14.7, 1H, C**H**(H)C=CH_2), 1.41-1.63 (m, 12 H, 2 x $CH_2CH_2CH_2$), 1.04 (d, *J* = 6.9 Hz, 3H, CH_3), 1.00 (d, *J* = 4.8 Hz, 3H, CH_3), 0.98 (d, *J* = 5.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz) δ 174.5, 174.3, 152.4, 109.5, 43.2, 43.1, 41.0, 40.3, 39.9, 26.1, 27.1, 26.1, 26.0, 25.0, 18.1, 17.3, 15.3; LRMS (FAB) *m/z* 350 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{21}H_{36}N_2O_2H)^+$ requires m/z 349.2855, found *m/z* 349.2854. Diastereomer ratio was determined by GLC with a CC-1701 column (100 °C, 20 °C/min gradient, 25 psi); *syn–anti* adduct t_r = 30.1min, *syn–syn* adduct t_r = 31.1min, and *anti–anti* adduct t_r = 36.6 min.

(2*R,3*R**,6*R**)-1,7-Dipyrrolidin-1-yl-4-methylene-2,3,6-trimethyl-heptane-1,7-dione (Table 2, entry 2).** Prepared according to the general procedure C from **10** (43.3mg, 0.208 mmol), $Yb(OTf)_3$ (258mg, 0.416 mmol), *i*-Pr_2NEt (0.30 mL, 1.72. mmol), and propionyl chloride (1.04 mL, 1 M solution in CH_2Cl_2, 0.80 mmol) added by syringe pump over 1 h in 4.0 mL of CH_2Cl_2 to provide the title compound as a colorless oil in 90% yield (65.3mg, 0.203 mmol); 95:5 *syn–anti:anti–anti.* *Syn–anti* isomer: IR (film) 3059, 2989, 2943, 2866, 2309, 1622, 1444, 1267, 911, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 1H, C**H**(H)=C), 4.69 (s, 1H, C**H**(H)=C), 3.33-3.58 (m, 8H, 2 x $N(CH_2)_2$) 2.71-2.81 (m, 1H, CH(CO)), 2.47 (dd, *J* = 7.1, 14.6 Hz, 1H, C**H**(H)C=CH_2), 2.32-2.51 (m, 1H), 1.98 (dd, *J* = 6.6, 14.7, 1H, C**H**(H)C=CH_2), 1.41-1.63 (m, 12 H, 2 x $CH_2CH_2CH_2$), 1.04 (d, *J* = 6.9 Hz, 3H, CH_3), 1.00 (d, *J* = 4.8 Hz, 3H, CH_3), 0.98 (d, *J* = 5.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz) δ 174.5, 174.3, 152.4, 109.5, 43.2, 43.1, 41.0, 40.3, 39.9, 26.1, 27.1, 26.1, 26.0, 25.0, 18.1, 17.3, 15.3; LRMS (FAB) *m/z* 350 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{21}H_{36}N_2O_2H)^+$ requires m/z 349.2855, found *m/z* 349.2854. Diastereomeric ratios were determined by GLC with a CC-1701 column (100 °C, 20 °C/min gradient, 25 psi); *syn–anti* adduct t_r = 30.1min, *syn–syn* adduct t_r = 31.1min, and *anti–anti* adduct t_r = 36.6 min.

(2*S,3*R**,6*R**)-3-Chloro-2,6-dimethyl-1,7-dimorpholin-4-yl-4-methylene-heptane-1,7-dione (Table 2, entry 4).** Prepared according to the general procedure C from **12** (57.0 mg, 0.219 mmol), $Yb(OTf)_3$ (258 mg, 0.416 mmol), *i*-Pr_2NEt (0.15 mL, 0.83 mmol), and propionyl chloride (0.75 mL, 1 M solution in CH_2Cl_2, 0.75 mmol) in 4.0 mL of CH_2Cl_2 to provide the title compound as a yellow oil in 98% yield (80.1 mg, 0.215 mmol); 99:1 *syn–anti:syn–syn* by GLC analysis. *Syn–anti* isomer: IR (CH_2Cl_2) 1640, 1463, 1436, 1235, 1116, 1031, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H, C**H**(H)=C), 4.89 (s, 1H, C**H**(H)=C), 4.58 (d, *J* = 10.0 Hz, 1H, CHCl), 3.46-3.68 (m, 16H, 2 x $O(CH_2CH_2,)_2N$), 3.14 (m, 1H, C**H**CHCl), 2.98 (m, 1H, COC**H**CH_2), 2.58 (dd, *J* = 8.4, 14.8 Hz, 1H,

C**H**(H)C=CH_2), 2.16 (dd, *J* = 5.2, 14.8, 1H, C**H**(H)C=CH_2), 1.34 (d, *J* = 12.4 Hz, 3H, CH_3), 1.11 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.3, 172.0, 146.1, 114.5, 67.0, 66.9, 66.8, 66.6, 46.1, 46.0, 42.1, 42.0, 40.9, 37.0, 36.6, 33.8, 18.2, 16.9; LRMS (FAB) *m/z* 373 $(M)^+$; HRMS (FAB) exact mass calc'd for $(C_{18}H_{29}ClN_2O_4)^+$ requires m/z 372.8868, found *m/z* 373.1901.

(2*S,3*R**,6*R**)-2,6-Dimethyl-1,7-dimorpholin-4-yl-4-methylene-3-phenylsulfanyl-heptane-1,7-dione (Table 2, entry 7).** Prepared according to the general procedure B from **15** (51.0 mg, 0.152 mmol), $TiCl_4$•$(THF)_2$ (102 mg, 0.305 mmol), *i*-Pr_2NEt (0.11 mL, 0.61 mmol), and propionyl chloride (0.46 mL, 1 M solution in CH_2Cl_2, 0.46 mmol) in 1.5 mL of CH_2Cl_2 to provide the title compound as a yellow oil in 70% yield (47.8 mg, 0.107 mmol); 93:7 *syn–anti:anti–anti* by ^{1}H NMR analysis. *Syn–anti* isomer: IR (film) 3491, 2974, 2858, 1637, 1437, 1359, 1305, 1236, 1112, 1027, 896, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.40 (m, 2H, Ar), 7.21-7.29 (m, 3H, Ar), 4.73 (s, 1H, C**H**(H)=C), 4.47 (s, 1H, C**H**(H)=C), 3.84 (d, *J* = 10.8 Hz, 1H, CHSPh), 3.39-3.68 (m, 16H, 2 x O(CH_2CH_2,)$_2$N), 3.14 (m, 1H, C**H**CHSPh), 2.98 (m, 1H, (CO)C**H**CH_2), 2.58 (dd, *J* = 8.4, 14.8 Hz, 1H, C**H**(H)C=CH_2), 2.16 (dd, *J* = 5.2, 14.8, 1H, C**H**(H)C=CH_2), 1.34 (d, *J* = 12.4 Hz, 3H, CH_3), 1.11 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.2, 173.2, 146.3, 134.7, 132.7, 128.7, 127.3, 112.2, 66.8, 66.6, 57.0, 45.9, 41.9, 38.7, 38.6, 33.6, 18.4, 17.2; LRMS (FAB) *m/z* 447 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{24}H_{34}N_2O_4SH)^+$ requires m/z 447.2318, found *m/z* 447.2315.

(2*R,3*R**,6*R**)-3-Cyano-2,6-dimethyl-1,7-dimorpholin-4-yl-4-methylene-heptane-1,7-dione (Table 2, entry 6).** Prepared according to the general procedure B from **14** (45.0 mg, 0.179 mmol), $TiCl_4$•$(THF)_2$ (120 mg, 0.359 mmol), *i*-Pr_2NEt (0.13 mL, 0.72 mmol), and propionyl chloride (0.54 mL, 1 M solution in CH_2Cl_2, 0.54 mmol) in 1.8 mL of

CH_2Cl_2 to provide the title compound in 78% yield (50.7 mg, 0.139 mmol) as a white solid; mp 92-94 °C; 97:3 *syn–anti:anti–anti* by ^{1}H NMR and ^{13}C NMR analysis. *Syn–anti* isomer: IR (film) 2794, 2920, 2858, 1637, 1444, 1359, 1267, 1112, 1035, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 1H, C**H**(H)=C), 4.95 (s, 1H, C**H**(H)=C), 3.75 (d, *J* = 9.2 Hz, 1H, CHCN), 3.47-3.67 (m, 16H, 2 x O(CH_2CH_2,)$_2$N), 3.10 (m, 1H, (C**H**CHCN), 2.92 (m, 1H, (CO)C**H**CH_2), 2.54 (dd, *J* = 8.6, 15.0 Hz, 1H, C**H**(H)C=CH_2), 2.14 (dd, *J* = 5.6, 15.2 Hz, 1H, C**H**(H)C=CH_2), 1.30 (d, *J* = 6.8 Hz, 3H, CH_3), 1.10 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 173.7, 171.0, 140.8, 116.1, 112.2, 66.8, 66.7, 66.6, 46.0, 45.9, 42.2, 42.0, 40.5, 37.8, 37.2, 33.6, 17.9, 16.4; LRMS (CI) *m/z* 363 $(M)^+$; HRMS (CI) exact mass calc'd for $(C_{19}H_{29}N_3O_4)^+$ requires m/z 363.2158, found *m/z* 363.2162.

(2*R,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-1,7-dimorpholin-4-yl-4-methylene-heptane-1,7-dione (Table 2, entry 5).** Prepared according to the general procedure C from **13** (72.1 mg, 0.208 mmol), $Yb(OTf)_3$ (258 mg, 0.416 mmol), *i*-Pr_2NEt (0.15 mL, 0.83 mmol), and propionyl chloride (0.75 mL, 1 M solution in CH_2Cl_2, 0.75 mmol) in 4.0 mL of CH_2Cl_2 to provide the title compound as a yellow oil in 86% yield (81.7 mg, 0.178 mmol); 91:9 *syn–anti:syn–syn*. *Syn–anti* isomer: IR (CH_2Cl_2) 2247, 1722, 1637, 1440, 1274, 1116, 1031, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H, Ar), 7.58 (t, *J* = 9.3, 1H, Ar), 7.45 (t, *J* = 9.5 Hz, 2H, Ar), 5.69 (d, *J* = 9.5 Hz, 1H, CHOBz), 5.19 (s, 1H, C**H**(H)=C), 4.98 (s, 1H, C**H**(H)=C), 3.47-3.70 (m, 16H, 2 x O(CH_2CH_2,)$_2$N), 3.25 (dt, *J* = 8.5, 17.5 Hz, 1H, C**H**CHOBz), 3.02 (app dt, *J* = 8.5, 20.4 Hz, 1H, (CO)C**H**CH_2), 2.55 (dd, *J* = 9.0, 18.0 Hz, 1H, C**H**(H)C=CH_2), 2.14 (dd, *J* = 8.5, 18.0 Hz, 1H, C**H**(H)C=CH_2), 1.24 (d, *J* = 8.5 Hz, 3H, CH_3), 1.07 (d, *J* = 8.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.6, 171.7, 165.3, 145.1, 133.0, 130.0, 129.5, 128.4, 114.2, 76.0, 66.8, 46.2, 45.9, 42.1, 38.8, 37.4, 33.9, 17.7, 13.8; LRMS (CI) *m/z* 459 $(MH)^+$; HRMS (CI) exact mass calc'd for $(C_{25}H_{34}N_2O_6H)^+$ requires m/z 459.2495, found *m/z* 459.2481. Diastereomer ratio was

determined by HPLC with a Zorbax SIL column (75:25 hexane:EtOH, 1.0 mL/min); *syn–anti* adduct t_r = 14.5 min, *anti–anti* adduct t_r = 16.8 min.

(2*R,3*S**,6*R**)-1,7-Dimorpholin-4-yl-2,6-diphthalamido-4-methylene-3-methyl-heptane-1,7-dione (Table 3, entry 3).** Prepared according to the general procedure C from **1** (106 mg, 0.441 mmol), $Yb(OTf)_3$ (516 mg, 0.882 mmol), *i*-Pr_2NEt (0.31 mL, 1.8 mmol), and phthalylglycyl chloride (1.5 mL, 1 M solution in CH_2Cl_2, 1.5 mmol) added over 2 h via syringe pump in 8.0 mL of CH_2Cl_2 to provide the title compound as a light yellow solid in 98% yield (266 mg, 0.432 mmol); 95:5 *syn–anti*:*anti–anti*. *Syn–anti* isomer: IR (CH_2Cl_2) 2972, 2864, 2254, 1776, 1718, 1656, 1382, 1116, 923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 3.2, 5.6 Hz, 2H, Phth), 7.84 (dd, *J* = 3.0, 5.6 Hz, 2H, Phth), 7.72 (d, *J* = 3.0 Hz, 2H, Phth), 7.70 (d, *J* = 3.2 Hz, 2H, Phth), 5.42 (dd, *J* = 4.2, 11.3 Hz, 1H, CH_2C**H**NPhth), 5.09 (s, 1H, C**H**(H)=C), 5.02 (s, 1H, C**H**(H)=C), 4.95 (d, *J* = 10.4 Hz, 1H, CHC**H**NPhth), 3.40-3.90 (m, 16H, 2 x $O(CH_2CH_2,)_2N$), 2.98 (dd, *J* = 3.7, 14.3 Hz, 1H, CHC**H**NPhth), 0.89 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ; 173.9, 171.0, 140.8, 116.1, 112.2, 66.8, 66.7, 66.6, 46.0, 45.9, 42.2, 42.0, 40.5, 37.8, 37.2, 33.6, 17.9, 16.4; LRMS (FAB) *m/z* 615 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{33}H_{34}N_4O_8)^+$ requires m/z 615.2455, found *m/z* 615.2453. Diastereomer ratio was determined by HPLC with a Zorbax SIL column (75:25 hexane:EtOH, 1.0 mL/min); *syn–anti* adduct t_r = 18.7 min, *anti–anti* adduct t_r = 21.0 min. Recrystallization from toluene/hexane afforded crystals suitable for single crystal X-ray diffraction (*vide infra)*.

(2*S,3*R**,6*S**)-2,6-Dibenzyl-1,7-dimorpholin-4-yl-3-methyl-4-methylene-heptane-1,7-dione (Table 3, entry 2).** Prepared according to the general procedure C from **1** (54.0 mg, 0.225 mmol), $Yb(OTf)_3$ (258 mg, 0.416 mmol), *i*-Pr_2NEt (0.15 mL, 0.86 mmol), and hydrocinnamoyl chloride (0.73 mL, 1 M solution in CH_2Cl_2, 0.73 mmol) in 4.0 mL of

CH_2Cl_2 to provide the title compound as a white solid in 99% yield (113 mg, 0.224 mmol); mp 125-126 °C; 92:8 *syn–anti:anti–anti*. *Syn–anti* isomer: IR (CH_2Cl_2) 2974, 1637, 1444, 1236, 1120, 1035, 888 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15-7.32 (m, 10H, Ph), 4.75(s, 1H, C**H**(H)=C), 4.73 (s, 1H, C**H**(H)=C), 3.71-3.78 (m, 1H), 3.60-3.66 (m, 1H), 3.53-3.57 (m, 1H), 3.45-3.49 (m,1H), 3,36-3.40 (m,1H), 3.18-3.34 (m, 5H), 3.06-3.15 (m, 3H), 2.90-3.06 (m,1H), 2.96 (m,1H), 2.75-2.91 (m, 5H), 2.62-2.70 (m, 1H), 2.54-2.61 (m, 2H), 2.46-2.51 (m, 1H), 2.23 (dd, *J* = 5.5, 15.0 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.7, 151.7, 139.6, 139.5, 129.1, 129.0, 128.4, 128.3, 126.5, 126.4, 109.7, 66.6, 66.4, 66.1, 65.9, 48.1, 45.9, 45.8, 41.9, 41.6, 41.5, 41.0, 39.6, 38.8, 37.2, 18.2; LRMS (FAB) *m/z* 505 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{31}H_{40}N_2O_4H)^+$ requires m/z 505.3066, found *m/z* 505.3069. Diastereomer ratio was determined by HPLC with a Zorbax SIL column (82:18 hexane/EtOH, 1.0 mL/min); *syn–anti* adduct t_r = 9.8 min, *anti–anti* adduct t_r = 9.2 min.

(2*R,3*S**,6*R**)-3-Benzoate-1,7-dimorpholin-4-yl-2,6-dipivaloate-4-methylene-heptane-1,7-dione (Table 3, entry 5).** Prepared according to the general procedure B from **13** (74.0 mg, 0.214 mmol), $TiCl_4$•$(THF)_2$ (271 mg, 0.812 mmol), *i*-Pr_2NEt (0.30 mL, 1.7 mmol), and α-pivaloxyacetylchloride (0.75 mL, 1 M solution in CH_2Cl_2, 0.75 mmol) in 4.2 mL of CH_2Cl_2 at 23 °C to provide the title compound as a colorless oil in 71% yield (95.9 mg, 0.152 mmol); 92:8 *syn–anti:anti–anti* by ^1H and ^{13}C NMR analysis. *Syn–anti* isomer: IR (film) 3059, 2981, 2255, 1730, 1661, 1452, 1267, 1151, 911, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4, 2H, Ar), 7.57 (m, 1H, Ar), 7.44 (m, 2H, Ar), 5.77 (dd, *J* = 8.0, 24.8 Hz, 2H), 5.56 (dd, *J* = 6.0, 8.0 Hz, 1H), 5.46 (s, 1H, C**H**(H)=C), 5.31 (s, 1H, C**H**(H)=C), 3.53-3.82 (m, 16H, 2 x $O(CH_2CH_2,)_2N$), 2.63-2.65 (m, 2H), 1.11 (s, 18H, 2 x $C(CH_3)_3$)**;** ^{13}C NMR (125 MHz) δ 177.6, 177.5, 168.1, 165.0, 164.8, 140.2, 133.4, 129.6, 129.2, 128.4, 118.9, 73.2, 69.8, 67.6, 66.7, 66.6, 46.2, 45.9, 42.4, 38.7, 38.4, 36.2, 26.8;

LRMS (FAB) *m/z* 631 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{33}H_{46}N_2O_{10}H)^+$ requires m/z 631.3231, found *m/z* 631.3237.

(2*R,3*S**,6*R**)-1,7-Dimorpholin-4-yl-2,6-dipivaloate-3-methyl-4-methylene-heptane-1,7-dione (Table 3, entry 4).** Prepared according to the general procedure B from **1** (59.4 mg, 0.247 mmol), $TiCl_4$•$(THF)_2$ (316 mg, 0.946 mmol), *i*-Pr_2NEt (0.34 mL, 2.0 mmol), and α-pivaloxyacetylchloride (0.86 mL, 1 M solution in CH_2Cl_2, 0.86 mmol) in 4.9 mL of CH_2Cl_2 at 23 °C to provide the title compound after purification by silica gel chromatography (85:15 EtOAc/Hexane) as a yellow oil in 97% yield (126 mg, 0.240 mmol); >97:3 *syn–anti:anti–anti* by ^{1}H NMR and ^{13}C NMR analysis. *Syn–anti* isomer: IR (film) 3059, 2981, 1730, 1653, 1444, 1267, 1159, 911, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 4.0, 9.6 Hz, 1H, CH_2C**H**OPv), 5.07 (d, *J* = 8.0 Hz, 1H, CHC**H**OPv), 5.01 (s, 1H, C**H**(H)=C), 4.99 (s, 1H, C**H**(H)=C), 3.39-3.61 (m, 16H, 2 x $O(CH_2CH_2,)_2N$), 2.68 (app t, *J* = 7.4 Hz, 1H, C**H**CH_3), 2.47 (dd, *J* = 9.8, 14.2 Hz, 1H, CH_2=C C**H**(H)), 2.37 (dd, *J* = 3.8, 14.6 Hz, 1H, CH_2=C C**H**(H)), 1.15 (s, 9H, $C(CH_3)_3$), 1.14 (s, 9H, $C(CH_3)_3$), 1.06 (d, *J* = 7.2 Hz, 3H, CH_3)**;** ^{13}C NMR (100 MHz) δ 177.9, 177.7, 167.7, 167.7, 144.8, 115.4, 72.2, 67.4, 66.7, 46.3, 45.9, 42.4, 38.9, 38.6, 38.5, 38.1, 27.0, 26.9, 16.3; LRMS (FAB) *m/z* 525 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{27}H_{44}N_2O_8H)^+$ requires m/z 525.3176, found *m/z* 525.3175.

(2*R,3*S**,6*R**)-3-Chloro-1,7-dimorpholin-4-yl-2,6-dipivaloate-4-methylene-heptane-1,7-dione (Table 3, entry 6).** Prepared according to the general procedure B with **12** (77.0 mg, 0.295 mmol), $TiCl_4$•$(THF)_2$ (374 mg, 1.12 mmol), *i*-Pr_2NEt (0.41 mL, 2.4 mmol), and α-pivaloxyacetylchloride (1.0 mL, 1 M solution in CH_2Cl_2, 1.0 mmol) in 6.0 mL of CH_2Cl_2 at 23 °C to provide the title compound as an orange oil in 84% yield (135 mg, 0.248 mmol); >95:5 *syn–anti:anti–anti* by ^{1}H NMR and ^{13}C NMR. *Syn–anti* isomer:

IR (film) 2974, 2927, 2866, 1730, 1653, 1452, 1274, 1151, 1074, 1027 cm^{-1}; ^1H NMR (300 MHz) δ 5.62 (d, *J* = 9.2 Hz, 1H, C**H**CHCl), 5.49 (t, *J* = 7.0 Hz, 1H, (CO)C**H**CH_2), 5.39 (s, 1H, C**H**(H)=C), 5.25 (s, 1H, C**H**(H)=C), 4.83 (d, *J* = 9.2 Hz, 1H, CHCl), 3.40-3.70 (m, 16H, 2 x O$(CH_2CH_2)_2$N), 2.63 (d, *J* = 6.9 Hz, 2H, H_2C=CC**H**$_2$), 1.24 (s, 9H, C$(CH_3)_3$), 1.21 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (125 MHz) δ 177.8, 177.4, 167.5, 165.2, 139.9, 120.1, 70.7, 67.4, 66.7, 66.6, 61.2, 59.8, 46.0, 42.6, 42.5, 38.9, 38.6, 36.0, 35.8, 27.0, 20.9, 20.3; LRMS (FAB) *m/z* 545 $(MH)^+$; HRMS (FAB) exact mass calc'd for $(C_{26}H_{41}ClN_2O_8H)^+$ requires m/z 545.2630, found *m/z* 545.2736.

General Procedure D: Regioselective hydrolysis of the α,β-disubstituted amide carbonyl of the tandem adducts by iodolactonization–reductive ring opening. Following the Metz protocol,[7] to a solution of the 1,7-di-morpholin-1,7-dione in 1:1 DME/H_2O at 23 °C was added I_2 and the resulting solution maintained in the absence of light for 3 h. At this point the solution was diluted with EtOAc (30 mL), and the resulting mixture was washed successively with $Na_2S_2O_3$ (10 % aq., 20mL), and brine (20 mL), and then dried (Na_2SO_4) and concentrated to provide the corresponding iodolactone which was used without further purification. The resulting residue was dissolved in AcOH, treated with Zn dust and then heated at 65 °C for 2 h. At this pont the reaction mixture was cooled to 23 °C and 1 *N* HCl (20 mL) was added. After extraction with EtOAc (3 x 30 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was purified by chromatography on silica gel (99:1 EtOAc/AcOH) to furnish the title compounds.

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[7] Metz, P. *Tetrahedron* **1993,** *49,* 6367.

(2*R,3*R**,6*R**)-4-Methylene-7-morpholin-4-yl-2,3,6-trimethyl-heptanoic acid (19).** Prepared according to the general procedure D from **9** (49.0 mg, 0.139 mmol), I_2 (100 mg, 0.42 mmol), and 0.70 mL 1:1 DME/H_2O followed by Zn (91 mg, 1.39 mmol) and AcOH (0.30 mL) to yield **19** as a white solid (32.8 mg, 0.115 mmol) in 83% yield; 92:8 regioselectivity by GLC analysis. Major isomer (α,β-disubstituted acid): IR (film) 2974, 2927, 1722, 1614, 1452, 1375, 1236, 1112, 1035, 904 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H, C**H**(H)=C), 4.77 (s, 1H, C**H**(H)=C), 3.57-3.69 (m, 8H, 2 x $O(CH_2CH_2)_2N$), 2.89-2.96 (m, 1H, CH(COOH)), 2.60-2.67 (m, 1H, CH(CON)), 2.41-2.53 (m, 2H), 2.05-2.12 (dd, *J* = 7.3, 14.6 Hz, 1H, C**H**(H)C=CH_2), 1.13 (d, *J* = 5.2 Hz, 3H, CH_3), 1.09 (d, *J* = 5.6 Hz, 3H, CH_3), 1.02 (d, *J* = 5.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz) δ 180.3, 149.5, 111.0, 66.9, 66.7, 46.1, 42.8, 42.3, 41.6, 37.8, 33.5, 29.6, 17.5, 15.0, 12.7; LRMS (CI) *m/z* 284 $(MH)^+$; HRMS (CI) exact mass calc'd for $(C_{15}H_{25}NO_4H)^+$ requires m/z 284.1862, found *m/z* 284.1868.

(2*S,3*R**,6*S**)-2,6-Dibenzyl-3-methyl-4-methylene-7-morpholin-4-yl-heptanoic acid (20).** Prepared according to the general procedure D from (2*S**,3*R**,6*S**)-2,6-Dibenzyl-4-methylene-3-methyl-1,7-dimorpholin-4-yl-heptane-1,7-dione (Table 3, entry 2), (47.1 mg, 0.108 mmol), I_2 (88.0 mg, 0.373 mmol), and 0.70 mL 1:1 DME/H_2O followed by Zn (53.0 mg, 0.811 mmol) and AcOH (1.0 mL) to yield **20** as a white solid (35.8 mg, 0.095 mmol) in 82% yield: 92:8 regioselectivity by ^1H NMR analysis. Major isomer (α,β-disubstituted acid): IR (film) 3028, 2943, 2866, 2248, 1730, 1599, 1452, 1112, 911, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06-7.23 (10 H, Ar), 4.87 (s, 1H, C**H**(H)=C), 4.76 (s, 1H, C**H**(H)=C), 3.42-3.57 (m, 2H), 3.18-3.28 (m, 2H), 3.03-3.13 (m, 2H), 2.46-2.86 (m, 10H), 2.23 (dd, *J* = 5.3, 15.5 Hz, 1H, CH_2=C C**H**(H)), 1.07 (d, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (125 MHz) δ 178.0., 174.1, 149.3, 139.9, 139.4, 129.5, 129.3, 129.0, 128.8, 128.5, 128.3, 127.2, 126.7, 126.2, 109.7, 66.8, 66.2, 51.9, 46.6, 42.4, 42.8, 40.0, 37.6, 34.0, 33.7,

30.1, 16.7; LRMS (ES) *m/z* 458 $(M+Na)^+$; HRMS (ES) exact mass calc'd for $(C_{27}H_{33}NO_4+Na)^+$ requires m/z 458.2307, found *m/z* 458.2318.

(2*S,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-4-methylene-7-morpholin-4-yl-heptanoic acid (21).** Prepared according to the general procedure D from (2*R**,3*R**,6*R**)-3-Benzoate-2,3-dimethyl-4-methylene-1,7-di-morpholin-4-yl-heptane-1,7-dione (Table 2, entry 5), (27.8 mg, 60.6 μL), I_2 (60.0 mg, 0.254 mmol), and 1.2 mL 1:1 DME/H_2O, followed by Zn (40 mg, 0.61 mmol) and AcOH (1 mL) to yield **21** as a white solid (20.7 mg, 53.3 μmol) in 88% yield: 83:17 regioselectivity by ^{1}H NMR analysis. Major isomer (α,β-disubstituted acid): IR (film) 2981, 2935, 2866, 1722, 1637, 1452, 1274, 1112, 1027, 966, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H, Ar), 7.58 (*app* t, *J* = 9.3, 1H, Ar), 7.45 (*app* t, *J* = 9.5 Hz, 2H, Ar), 5.69 (d, *J* = 5.0 Hz, 1H, CHOBz), 5.09 (s, 1H, C**H**(H)=C), 4.98 (s, 1H, C**H**(H)=C), 3.49-3.76 (m, 8H, 2 x O(CH_2CH_2,)$_2$N), 2.99-3.05 (m, 2H), 2.61 (dd, *J* = 7.0, 14.5 Hz, 1H, C**H**(H)C=CH_2), 2.18 (dd, *J* = 6.5, 15.0 Hz, 1H, C**H**(H)C=CH_2), 1.28 (d, *J* = 7.0 Hz, 3H, CH_3), 1.13 (d, *J* = 8.5 Hz, 3H, CH_3); ^{13}C NMR (125 MHz) δ 176.8, 175.2, 165.3, 143.5, 133.2, 129.6, 128.5,128.4, 113.9, 75.6, 66.8, 66.7, 46.1, 42.4, 41.8, 36.9, 34.0, 17.8, 10.9; LRMS (CI) *m/z* 389.1 $(M)^+$; HRMS (CI) exact mass calc'd for $(C_{21}H_{27}NO_6)^+$ requires m/z 389.1838, found *m/z* 389.1845. The solid was recrystallized from toluene/hexanes to afford crystals suitable for single crystal X-ray diffraction (*vide infra).*

(2*R,3*R**,6*R**)-2,3,6-Trimethyl-4-methylene-7-morpholin-4-yl-heptanoic acid (19)**

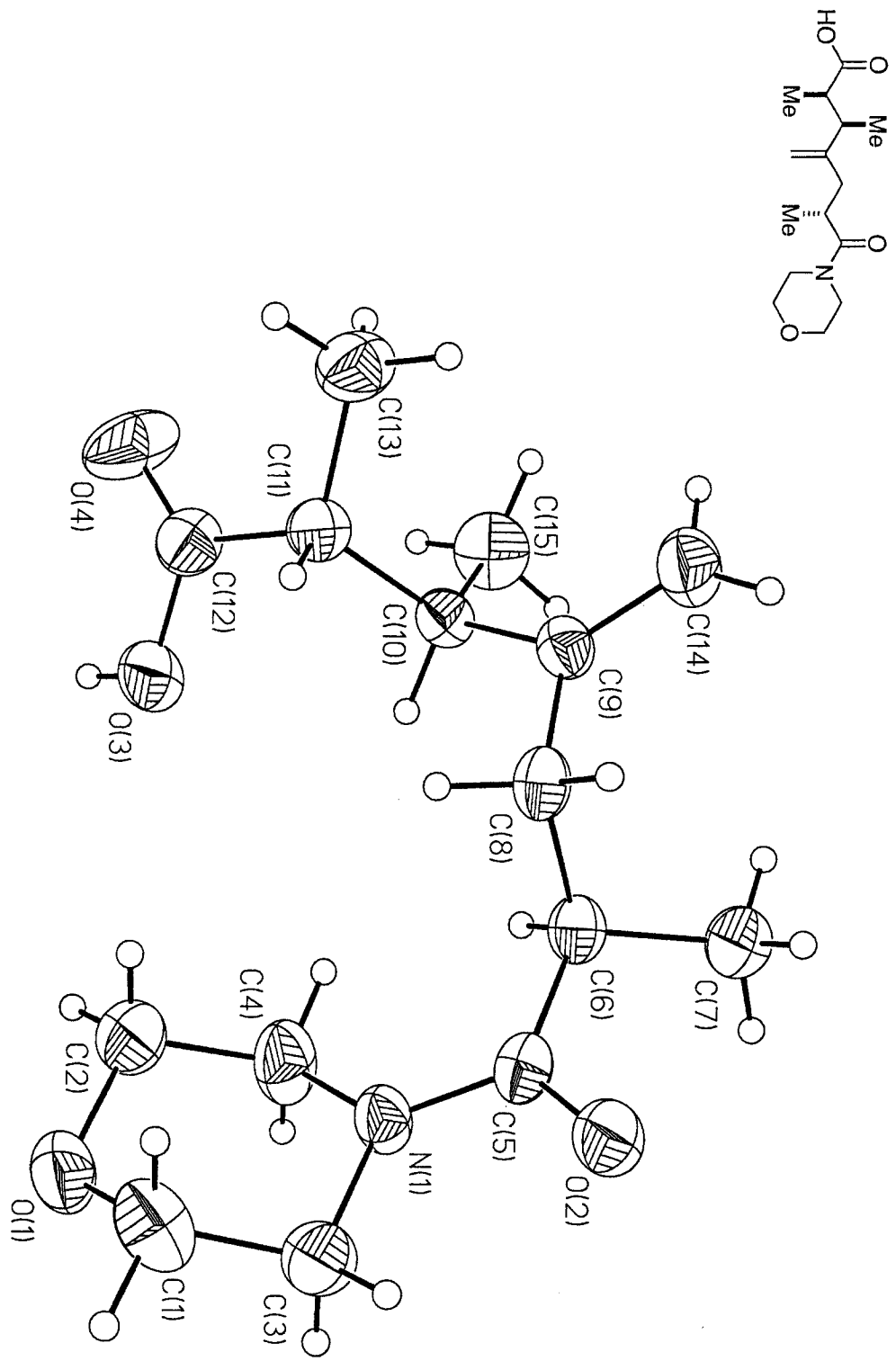


Table S-1. Crystal data and structure refinement for 1.

Identification code	vmd1d
Empirical formula	$C_{15}H_{25}NO_4$
Formula weight	283.36
Temperature	149 K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P21/n
Unit cell dimensions	a = 8.6695(9) Å alpha = 90° b = 11.4469(12) Å beta = 92.8340(10)° c = 15.785(2) Å gamma = 90°
Volume, Z	1564.6(3) $Å^3$, 4
Density (calculated)	1.203 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	616
Crystal size	0.48 x 0.08 x 0.07 mm
Crystal color and habit	colorless needle
θ range for data collection	2.20 to 25.94°
Limiting indices	$-10 \le h \le 10$, $-13 \le k \le 12$, $-18 \le l \le 16$
Reflections collected	7536
Independent reflections	2750 (R_{int} = 0.0753)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2750 / 0 / 186
Goodness-of-fit on F^2	0.849
Final R indices [I>2σ(I)]	R1 = 0.0431, wR2 = 0.0769
R indices (all data)	R1 = 0.1290, wR2 = 0.0946
Extinction coefficient	0.0027(9)
Largest diff. peak and hole	0.133 and -0.146 $eÅ^{-3}$

Table S-2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-2747(2)	3846(1)	7814(1)	50(1)
O(2)	-7179(2)	5990(1)	6717(1)	49(1)
O(3)	191(2)	6312(2)	5839(1)	48(1)
O(4)	1377(2)	6600(2)	4645(1)	70(1)
N(1)	-4782(2)	5643(2)	7250(1)	36(1)
C(1)	-4322(3)	3610(2)	7594(2)	54(1)
C(2)	-2226(3)	4777(2)	7300(2)	53(1)
C(3)	-5311(3)	4651(2)	7738(2)	46(1)
C(4)	-3134(3)	5870(2)	7415(2)	49(1)
C(5)	-5796(3)	6266(2)	6756(1)	34(1)
C(6)	-5202(2)	7265(2)	6239(1)	32(1)
C(7)	-6361(3)	8265(2)	6178(1)	44(1)
C(8)	-4838(2)	6775(2)	5359(1)	34(1)
C(9)	-3977(3)	7638(2)	4843(1)	31(1)
C(10)	-2259(2)	7708(2)	5057(1)	31(1)
C(11)	-1400(2)	6704(2)	4608(1)	34(1)
C(12)	209(3)	6541(2)	5012(2)	41(1)
C(13)	-1330(3)	6864(2)	3657(1)	51(1)
C(14)	-4703(3)	8296(2)	4262(2)	48(1)
C(15)	-1540(3)	8893(2)	4893(2)	52(1)

Table S-3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.418(3)	O(1)-C(2)	1.427(3)
O(2)-C(5)	1.238(2)	O(3)-C(12)	1.333(3)
O(4)-C(12)	1.193(3)	N(1)-C(5)	1.350(3)
N(1)-C(3)	1.459(3)	N(1)-C(4)	1.462(3)
C(1)-C(3)	1.492(3)	C(2)-C(4)	1.494(3)
C(5)-C(6)	1.510(3)	C(6)-C(7)	1.523(3)
C(6)-C(8)	1.545(3)	C(8)-C(9)	1.502(3)
C(9)-C(14)	1.322(3)	C(9)-C(10)	1.513(3)
C(10)-C(15)	1.521(3)	C(10)-C(11)	1.559(3)
C(11)-C(13)	1.516(3)	C(11)-C(12)	1.516(3)

C(1)-O(1)-C(2)	109.3(2)	C(5)-N(1)-C(3)	120.2(2)
C(5)-N(1)-C(4)	127.7(2)	C(3)-N(1)-C(4)	112.0(2)
O(1)-C(1)-C(3)	111.4(2)	O(1)-C(2)-C(4)	111.9(2)
N(1)-C(3)-C(1)	110.0(2)	N(1)-C(4)-C(2)	110.2(2)
O(2)-C(5)-N(1)	119.7(2)	O(2)-C(5)-C(6)	121.4(2)
N(1)-C(5)-C(6)	118.9(2)	C(5)-C(6)-C(7)	111.2(2)
C(5)-C(6)-C(8)	107.6(2)	C(7)-C(6)-C(8)	112.3(2)
C(9)-C(8)-C(6)	112.2(2)	C(14)-C(9)-C(8)	121.3(2)
C(14)-C(9)-C(10)	123.7(2)	C(8)-C(9)-C(10)	115.0(2)
C(9)-C(10)-C(15)	114.6(2)	C(9)-C(10)-C(11)	110.3(2)
C(15)-C(10)-C(11)	111.8(2)	C(13)-C(11)-C(12)	110.5(2)
C(13)-C(11)-C(10)	113.9(2)	C(12)-C(11)-C(10)	110.5(2)
O(4)-C(12)-O(3)	122.6(2)	O(4)-C(12)-C(11)	125.0(2)
O(3)-C(12)-C(11)	112.4(2)		

Symmetry transformations used to generate equivalent atoms:

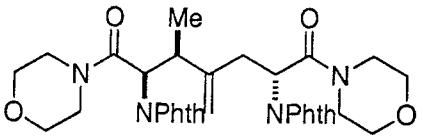
Table S-4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1)	42(1)	49(1)	60(1)	13(1)	-1(1)	11(1)
O(2)	27(1)	65(1)	55(1)	18(1)	-3(1)	-2(1)
O(3)	26(1)	70(1)	48(1)	14(1)	-5(1)	3(1)
O(4)	28(1)	134(2)	48(1)	-15(1)	5(1)	-2(1)
N(1)	26(1)	36(1)	45(1)	9(1)	-2(1)	0(1)
C(1)	60(2)	43(2)	58(2)	9(1)	-9(1)	-2(2)
C(2)	35(2)	63(2)	61(2)	16(2)	9(1)	7(2)
C(3)	34(2)	57(2)	49(2)	10(1)	1(1)	-2(1)
C(4)	30(2)	49(2)	66(2)	8(1)	-7(1)	2(1)
C(5)	27(2)	36(2)	39(2)	-2(1)	-1(1)	4(1)
C(6)	28(1)	31(1)	36(2)	-2(1)	-3(1)	0(1)
C(7)	46(2)	42(2)	45(2)	0(1)	5(1)	7(1)
C(8)	26(1)	33(1)	42(2)	-2(1)	-4(1)	2(1)
C(9)	32(1)	30(1)	30(1)	-1(1)	-3(1)	3(1)
C(10)	30(1)	31(1)	32(2)	3(1)	0(1)	-5(1)
C(11)	29(1)	41(2)	33(2)	-1(1)	-1(1)	-3(1)
C(12)	39(2)	46(2)	39(2)	-6(1)	-2(1)	0(1)
C(13)	41(2)	72(2)	39(2)	-6(1)	0(1)	2(2)
C(14)	42(2)	52(2)	49(2)	2(1)	-5(1)	7(1)
C(15)	51(2)	43(2)	62(2)	0(1)	2(1)	-12(1)

(2*R,3*S**,6*R**)-3-Methyl-4-methylene-1,7-dimorpholin-4-yl-2,6-diphthalamido-heptane-1,7-dione (Table 3, entry 3)**



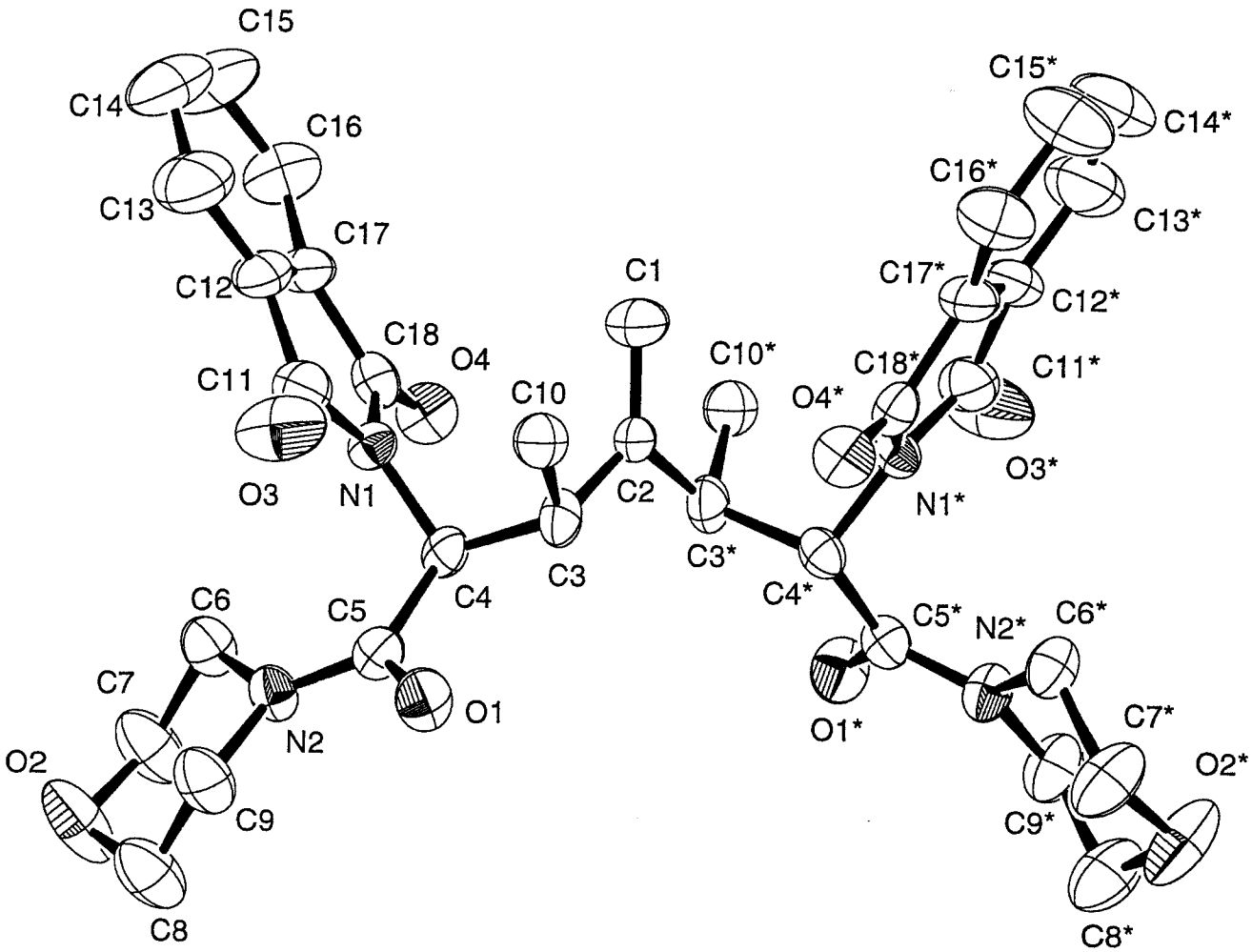


Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy

atom	x	y	z	B_{eq}	occ
O(1)	0.02813(10)	0.11376(9)	0.65702(18)	3.63(6)	
O(2)	-0.15110(10)	0.02443(11)	0.5240(2)	5.58(8)	
O(3)	-0.01496(13)	0.05595(11)	0.8987(2)	5.73(8)	
O(4)	-0.13970(9)	0.21242(10)	0.88262(18)	3.52(6)	
N(1)	-0.06916(11)	0.13982(11)	0.8690(2)	2.31(7)	
N(2)	-0.06608(12)	0.08398(11)	0.6498(2)	2.71(7)	
C(1)	0.0000	0.2500	0.9840(5)	6.3(2)	1/2
C(2)	0.0000	0.2500	0.8786(4)	2.76(13)	1/2
C(3)	0.01787(13)	0.19685(13)	0.8137(3)	2.86(9)	
C(4)	-0.03762(13)	0.16379(12)	0.7764(3)	2.38(8)	
C(5)	-0.02272(16)	0.11759(14)	0.6906(3)	2.74(10)	
C(6)	-0.12778(15)	0.08394(14)	0.6822(3)	3.28(10)	
C(7)	-0.16676(15)	0.07491(16)	0.5863(3)	4.76(12)	
C(8)	-0.09251(17)	0.03150(16)	0.4855(3)	4.88(12)	
C(9)	-0.04964(15)	0.03635(15)	0.5763(3)	3.90(10)	
C(10)	0.0573(3)	0.1615(3)	0.8921(6)	3.19(15)	1/2
C(11)	-0.05316(17)	0.09002(16)	0.9268(3)	3.58(11)	
C(12)	-0.09121(17)	0.08868(17)	1.0240(3)	3.83(11)	
C(13)	-0.0922(2)	0.05012(18)	1.1096(4)	5.97(14)	
C(14)	-0.1335(3)	0.0598(3)	1.1901(4)	7.44(17)	
C(15)	-0.1713(2)	0.1065(3)	1.1842(4)	7.18(16)	
C(16)	-0.17026(18)	0.14567(18)	1.0988(4)	5.32(12)	
C(17)	-0.12914(16)	0.13570(17)	1.0187(3)	3.41(10)	
C(18)	-0.11617(15)	0.16910(16)	0.9191(3)	2.82(10)	
H(1)	0.0156	0.2197	1.0422	4.3949	
H(2)	0.0402	0.2088	0.7523	3.4360	
H(3)	-0.0628	0.1919	0.7430	2.8528	
H(4)	-0.1342	0.0532	0.7329	3.9380	
H(5)	-0.1370	0.1206	0.7151	3.9380	
H(6)	-0.1644	0.1086	0.5411	5.6899	
H(7)	-0.2061	0.0702	0.6109	5.6899	
H(8)	-0.0825	-0.0015	0.4421	5.8523	
H(9)	-0.0905	0.0662	0.4427	5.8523	
H(10)	-0.0117	0.0440	0.5476	4.6763	
H(11)	-0.0490	0.0004	0.6153	4.6763	
H(12)	0.0347	0.1499	0.9531	3.7857	1/2

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy (continued)

atom	x	y	z	B_{eq}	occ
H(13)	0.0719	0.1277	0.8561	3.7857	1/2
H(14)	0.0891	0.1855	0.9149	3.7857	1/2
H(15)	-0.0657	0.0178	1.1133	7.1266	
H(16)	-0.1355	0.0339	1.2505	8.9207	
H(17)	-0.1993	0.1120	1.2405	8.6381	
H(18)	-0.1967	0.1781	1.0953	6.3811	

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.0343(15)	0.0493(16)	0.0543(17)	-0.0019(12)	0.0114(14)	-0.0098(13)
O(2)	0.0366(16)	0.081(2)	0.095(2)	0.0008(14)	-0.0029(16)	-0.0544(18)
O(3)	0.107(2)	0.0546(18)	0.056(2)	0.0453(18)	0.0091(17)	0.0126(15)
O(4)	0.0386(15)	0.0451(16)	0.0501(18)	0.0085(13)	0.0015(13)	0.0004(14)
N(1)	0.0316(17)	0.0253(17)	0.0310(18)	0.0045(14)	0.0017(15)	0.0036(15)
N(2)	0.0285(17)	0.0322(17)	0.042(2)	0.0011(14)	0.0056(15)	-0.0103(14)
C(1)	0.108(5)	0.102(5)	0.029(4)	-0.057(4)	0.0000	0.0000
C(2)	0.038(3)	0.039(3)	0.027(4)	-0.018(3)	0.0000	0.0000
C(3)	0.031(2)	0.034(2)	0.044(2)	-0.0098(17)	0.000(2)	0.002(2)
C(4)	0.034(2)	0.022(2)	0.034(2)	0.0042(16)	0.0027(18)	0.0049(18)
C(5)	0.035(2)	0.032(2)	0.037(3)	0.002(2)	0.004(2)	0.0019(18)
C(6)	0.035(2)	0.041(2)	0.048(3)	-0.0015(18)	0.002(2)	-0.011(2)
C(7)	0.041(3)	0.067(3)	0.073(3)	0.006(2)	-0.004(2)	-0.032(3)
C(8)	0.051(3)	0.068(3)	0.066(3)	0.005(2)	0.002(3)	-0.032(2)
C(9)	0.045(2)	0.042(2)	0.061(3)	0.005(2)	0.003(2)	-0.017(2)
C(11)	0.061(3)	0.035(3)	0.039(3)	0.006(2)	-0.005(2)	0.002(2)
C(12)	0.076(3)	0.040(3)	0.029(3)	-0.003(2)	0.000(2)	0.007(2)
C(13)	0.114(4)	0.065(3)	0.048(3)	0.006(3)	0.002(3)	0.014(3)
C(14)	0.138(5)	0.096(4)	0.049(4)	-0.012(4)	0.017(4)	0.025(3)
C(15)	0.101(4)	0.114(5)	0.058(4)	-0.004(4)	0.032(3)	0.018(4)
C(16)	0.072(3)	0.080(3)	0.050(3)	0.000(3)	0.013(3)	0.007(3)
C(17)	0.049(3)	0.053(3)	0.027(3)	-0.005(2)	0.004(2)	0.000(2)
C(18)	0.033(2)	0.034(2)	0.041(3)	-0.003(2)	-0.007(2)	-0.005(2)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O1	C5	1.232(3)	O2	C7	1.427(4)
O2	C8	1.424(4)	O3	C11	1.215(4)
O4	C18	1.208(3)	N1	C4	1.456(4)
N1	C11	1.387(4)	N1	C18	1.403(4)
N2	C5	1.345(4)	N2	C6	1.459(4)
N2	C9	1.462(4)	C1	C2	1.301(6)
C2	C3	1.506(4)	C2	C3	1.506(4)
C3	C4	1.540(4)	C3	C10	1.546(7)
C4	C5	1.530(4)	C6	C7	1.494(5)
C8	C9	1.490(5)	C11	C12	1.481(5)
C12	C13	1.373(5)	C12	C17	1.376(4)
C13	C14	1.386(6)	C14	C15	1.369(6)
C15	C16	1.381(6)	C16	C17	1.380(5)
C17	C18	1.475(5)			

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C1	H1	1.06	C1	H1	1.06
C3	H2	0.95	C4	H3	0.95
C6	H4	0.95	C6	H5	0.95
C7	H6	0.95	C7	H7	0.95
C8	H8	0.95	C8	H9	0.95
C9	H10	0.95	C9	H11	0.95
C10	H12	0.95	C10	H13	0.95
C10	H14	0.95	C13	H15	0.95
C14	H16	0.95	C15	H17	0.95
C16	H18	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C7	O2	C8	108.8(3)	C4	N1	C11	125.5(3)
C4	N1	C18	122.9(3)	C11	N1	C18	111.1(3)
C5	N2	C6	127.1(3)	C5	N2	C9	117.7(3)
C6	N2	C9	114.6(3)	C1	C2	C3	122.1(2)
C1	C2	C3	122.1(2)	C3	C2	C3	115.7(4)
C2	C3	C4	109.3(2)	C2	C3	C10	104.0(3)
C4	C3	C10	114.1(3)	N1	C4	C3	110.6(3)
N1	C4	C5	113.3(2)	C3	C4	C5	111.2(3)
O1	C5	N2	121.5(3)	O1	C5	C4	119.3(3)
N2	C5	C4	119.1(3)	N2	C6	C7	110.7(3)
O2	C7	C6	112.9(3)	O2	C8	C9	111.7(3)
N2	C9	C8	110.8(3)	O3	C11	N1	124.2(4)
O3	C11	C12	129.5(4)	N1	C11	C12	106.3(3)
C11	C12	C13	130.3(4)	C11	C12	C17	108.1(4)
C13	C12	C17	121.5(4)	C12	C13	C14	117.5(4)
C13	C14	C15	120.7(4)	C14	C15	C16	122.1(5)
C15	C16	C17	116.9(4)	C12	C17	C16	121.2(4)
C12	C17	C18	108.4(3)	C16	C17	C18	130.4(4)
O4	C18	N1	124.1(3)	O4	C18	C17	129.9(4)
N1	C18	C17	106.0(3)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C2	C1	H1	132.9	C2	C1	H1	132.9
H1	C1	H1	94.3	C2	C3	H2	109.7
C4	C3	H2	109.8	C10	C3	H2	109.7
N1	C4	H3	107.2	C3	C4	H3	107.2
C5	C4	H3	107.1	N2	C6	H4	109.2
N2	C6	H5	109.1	C7	C6	H4	109.3
C7	C6	H5	109.2	H4	C6	H5	109.3
O2	C7	H6	108.6	O2	C7	H7	108.5
C6	C7	H6	108.7	C6	C7	H7	108.7
H6	C7	H7	109.4	O2	C8	H8	108.9
O2	C8	H9	108.9	C9	C8	H8	109.0
C9	C8	H9	109.0	H8	C8	H9	109.3
N2	C9	H10	109.1	N2	C9	H11	109.1
C8	C9	H10	109.2	C8	C9	H11	109.1
H10	C9	H11	109.5	C3	C10	H12	109.1
C3	C10	H13	109.3	C3	C10	H14	109.2
H12	C10	H13	109.8	H12	C10	H14	109.6
H13	C10	H14	109.8	C12	C13	H15	121.3
C14	C13	H15	121.2	C13	C14	H16	119.8
C15	C14	H16	119.6	C14	C15	H17	119.0
C16	C15	H17	118.9	C15	C16	H18	121.6
C17	C16	H18	121.5				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O1	C5	N2	C6	179.8(3)	O1	C5	N2	C9	9.2(5)
O1	C5	C4	N1	-129.2(3)	O1	C5	C4	C3	-4.0(4)
O2	C7	C6	N2	52.5(4)	O2	C8	C9	N2	-55.3(4)
O3	C11	N1	C4	-9.8(5)	O3	C11	N1	C18	177.5(4)
O3	C11	C12	C13	2.5(7)	O3	C11	C12	C17	-178.0(4)
O4	C18	N1	C4	10.0(5)	O4	C18	N1	C11	-177.1(3)
O4	C18	C17	C12	178.4(3)	O4	C18	C17	C16	-2.2(6)
N1	C4	C3	C2	-65.5(3)	N1	C4	C3	C10	50.4(4)
N1	C4	C5	N2	53.9(4)	N1	C11	C12	C13	-177.5(4)
N1	C11	C12	C17	2.1(4)	N1	C18	C17	C12	-0.7(4)
N1	C18	C17	C16	178.7(4)	N2	C5	C4	C3	179.1(3)
C1	C2	C3	C4	98.9(2)	C1	C2	C3	C10	-23.3(3)
C1	C2	C3	C4	98.9(2)	C1	C2	C3	C10	-23.3(3)
C2	C3	C4	C5	167.7(3)	C3	C2	C3	C4	-81.1(2)
C3	C2	C3	C10	156.7(3)	C3	C4	N1	C11	-76.8(4)
C3	C4	N1	C18	95.1(3)	C4	N1	C11	C12	170.1(3)
C4	N1	C18	C17	-170.8(3)	C4	C5	N2	C6	-3.4(5)
C4	C5	N2	C9	-174.0(3)	C5	N2	C6	C7	143.1(3)
C5	N2	C9	C8	-140.5(3)	C5	C4	N1	C11	48.8(4)
C5	C4	N1	C18	-139.3(3)	C5	C4	C3	C10	-76.4(4)
C6	N2	C9	C8	47.8(4)	C6	C7	O2	C8	-60.3(4)
C7	O2	C8	C9	61.4(4)	C7	C6	N2	C9	-46.1(4)
C11	N1	C18	C17	2.1(3)	C11	C12	C13	C14	-179.7(4)
C11	C12	C17	C16	179.7(3)	C11	C12	C17	C18	-0.8(4)
C12	C11	N1	C18	-2.6(4)	C12	C13	C14	C15	-0.6(8)
C12	C17	C16	C15	0.2(6)	C13	C12	C17	C16	-0.7(6)
C13	C12	C17	C18	178.8(3)	C13	C14	C15	C16	0.1(8)
C14	C13	C12	C17	0.9(6)	C14	C15	C16	C17	0.1(7)
C15	C16	C17	C18	-179.1(4)					

Table 8. Non-bonded Contacts out to 3.60 $\AA$

atom	atom	distance	ADC	atom	atom	distance	ADC
O1	C6	3.331(4)	55608	O1	C7	3.415(4)	55608
O1	C4	3.451(4)	55608	O1	O4	3.584(3)	55608
O1	N2	3.588(3)	55608	O2	C7	3.416(4)	44412
O2	C6	3.539(4)	44412	O3	C13	3.431(5)	55705
O4	C9	3.419(4)	45503	C1	C1	3.484(12)	45707
C9	C9	3.374(7)	55605	C10	C15	3.463(8)	55708

(2*R,3*R**,6*R**)-3-Cyano-2,6-dimethyl-4-methylene-1,7-di-morpholin-4-yl -heptane-1,7-dione (Table 2, entry 6)**

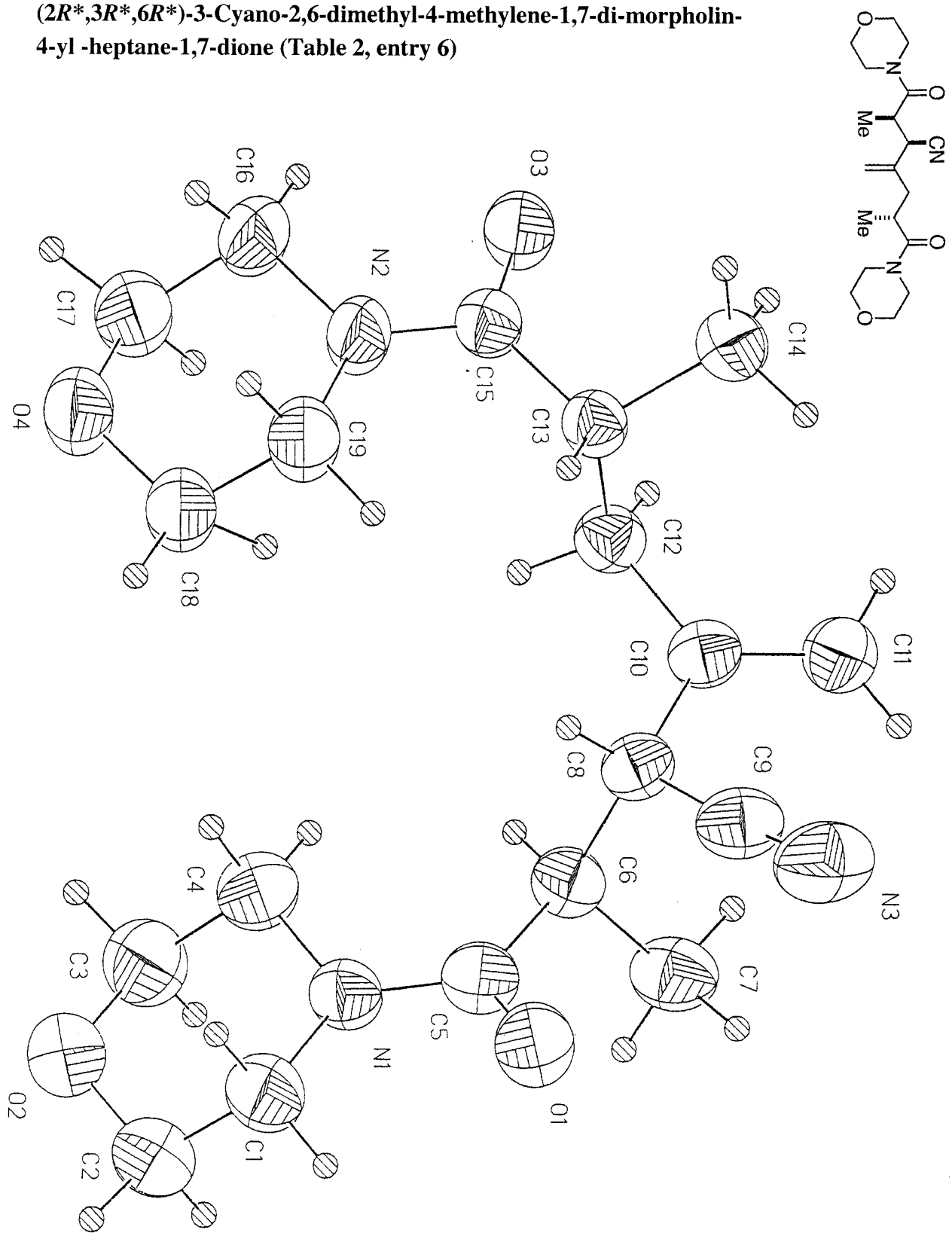


Table 1. Crystal data and structure refinement for VMD02.

Empirical formula	$C_{19}H_{29}N_3O_4$
Formula weight	363.45
Crystallization Solvent	Toluene/hexanes
Crystal Habit	Irregular chunk
Crystal size	0.15 x 0.12 x 0.11 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	CCD area detector
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 5738 reflections used in lattice determination	2.17 to 27.24°
Unit cell dimensions	a = 9.588(9) Å b = 20.254(19) Å β= 103.733(15)° c = 9.872(9) Å
Volume	1862(3) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	P2(1)/c
Density (calculated)	1.296 Mg/m^3
F(000)	784
Data collection program	Bruker SMART
θ range for data collection	2.01 to 28.56°
Completeness to θ = 28.56°	94.0 %
Index ranges	$-12 \le h \le 12, -26 \le k \le 27, -13 \le l \le 12$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.1
Reflections collected	27254
Independent reflections	4454 [R_{int}= 0.1213]
Absorption coefficient	0.091 mm^{-1}
Absorption correction	None
Max. and min. transmission (theory)	0.9899 and 0.9866

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Direct methods
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4454 / 0 / 351
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.372
Final R indices [$I>2\sigma(I)$, 2527 reflections]	R1 = 0.0616, *w*R2 = 0.1037
R indices (all data)	R1 = 0.1057, *w*R2 = 0.1129
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/[\sigma^2(Fo^2)$
Max shift/error	0.007
Average shift/error	0.000
Largest diff. peak and hole	0.405 and -0.242 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for VMD02. U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	5527(2)	4953(1)	12585(2)	66(1)
O(2)	951(2)	4398(1)	13624(2)	75(1)
O(3)	2733(2)	2515(1)	5974(2)	57(1)
O(4)	-1020(2)	3618(1)	7426(2)	73(1)
N(1)	3498(2)	4430(1)	12672(2)	53(1)
N(2)	1482(2)	3355(1)	6560(2)	61(1)
N(3)	7754(3)	4848(1)	10454(2)	79(1)
C(1)	3017(3)	5005(1)	13330(3)	64(1)
C(2)	2135(3)	4788(2)	14301(3)	72(1)
C(3)	1431(4)	3835(2)	13025(3)	74(1)
C(4)	2297(3)	4002(1)	12017(3)	64(1)
C(5)	4773(3)	4460(1)	12336(2)	52(1)
C(6)	5345(3)	3863(1)	11725(2)	49(1)
C(7)	6681(3)	3632(1)	12773(3)	60(1)
C(8)	5651(2)	4026(1)	10297(2)	46(1)
C(9)	6818(3)	4498(1)	10411(2)	57(1)
C(10)	5935(2)	3412(1)	9534(2)	45(1)
C(11)	7243(3)	3198(1)	9588(3)	57(1)
C(12)	4644(3)	3075(1)	8688(2)	47(1)
C(13)	4110(2)	3379(1)	7233(2)	43(1)
C(14)	5187(3)	3292(1)	6339(3)	53(1)
C(15)	2730(2)	3049(1)	6548(2)	47(1)
C(16)	127(3)	3050(2)	5868(3)	73(1)
C(17)	-801(3)	2995(2)	6856(4)	78(1)
C(18)	301(3)	3888(2)	8151(3)	82(1)
C(19)	1269(3)	3983(1)	7199(3)	72(1)

Table 3. Bond lengths [Å] and angles [°] for VMD02.

O(1)-C(5)	1.224(3)	C(18)-C(19)	1.482(4)
O(2)-C(2)	1.414(3)	C(18)-H(18A)	1.18(3)
O(2)-C(3)	1.411(3)	C(18)-H(18B)	0.98(2)
O(3)-C(15)	1.222(2)	C(19)-H(19A)	1.16(4)
O(4)-C(18)	1.410(3)	C(19)-H(19B)	0.99(2)
O(4)-C(17)	1.417(3)		
N(1)-C(5)	1.342(3)	C(2)-O(2)-C(3)	110.2(2)
N(1)-C(4)	1.463(3)	C(18)-O(4)-C(17)	110.3(2)
N(1)-C(1)	1.460(3)	C(5)-N(1)-C(4)	125.8(2)
N(2)-C(15)	1.350(3)	C(5)-N(1)-C(1)	118.43(19)
N(2)-C(16)	1.455(3)	C(4)-N(1)-C(1)	111.7(2)
N(2)-C(19)	1.456(3)	C(15)-N(2)-C(16)	119.7(2)
N(3)-C(9)	1.137(3)	C(15)-N(2)-C(19)	128.3(2)
C(1)-C(2)	1.488(4)	C(16)-N(2)-C(19)	111.9(2)
C(1)-H(1A)	1.06(3)	N(1)-C(1)-C(2)	109.9(2)
C(1)-H(1B)	0.95(2)	N(1)-C(1)-H(1A)	107.2(16)
C(2)-H(2A)	1.05(3)	C(2)-C(1)-H(1A)	107.6(17)
C(2)-H(2B)	1.01(3)	N(1)-C(1)-H(1B)	107.7(14)
C(3)-C(4)	1.479(4)	C(2)-C(1)-H(1B)	108.1(15)
C(3)-H(3A)	1.00(3)	H(1A)-C(1)-H(1B)	116(2)
C(3)-H(3B)	1.03(3)	O(2)-C(2)-C(1)	112.0(2)
C(4)-H(4A)	0.97(2)	O(2)-C(2)-H(2A)	109.3(16)
C(4)-H(4B)	1.04(3)	C(1)-C(2)-H(2A)	106.4(15)
C(5)-C(6)	1.511(3)	O(2)-C(2)-H(2B)	106.5(15)
C(6)-C(7)	1.517(3)	C(1)-C(2)-H(2B)	109.8(14)
C(6)-C(8)	1.543(3)	H(2A)-C(2)-H(2B)	113(2)
C(6)-H(6)	0.97(2)	O(2)-C(3)-C(4)	112.9(2)
C(7)-H(7A)	1.01(3)	O(2)-C(3)-H(3A)	104.1(14)
C(7)-H(7B)	1.02(2)	C(4)-C(3)-H(3A)	110.1(15)
C(7)-H(7C)	1.02(3)	O(2)-C(3)-H(3B)	112.3(16)
C(8)-C(9)	1.454(3)	C(4)-C(3)-H(3B)	105.2(17)
C(8)-C(10)	1.511(3)	H(3A)-C(3)-H(3B)	113(2)
C(8)-H(8)	0.95(2)	N(1)-C(4)-C(3)	110.3(2)
C(10)-C(11)	1.316(3)	N(1)-C(4)-H(4A)	112.1(15)
C(10)-C(12)	1.486(3)	C(3)-C(4)-H(4A)	107.8(14)
C(11)-H(11A)	1.01(2)	N(1)-C(4)-H(4B)	109.5(14)
C(11)-H(11B)	0.94(2)	C(3)-C(4)-H(4B)	107.7(14)
C(12)-C(13)	1.535(3)	H(4A)-C(4)-H(4B)	109(2)
C(12)-H(12A)	0.98(2)	O(1)-C(5)-N(1)	121.1(2)
C(12)-H(12B)	1.014(19)	O(1)-C(5)-C(6)	118.8(2)
C(13)-C(15)	1.494(3)	N(1)-C(5)-C(6)	119.99(19)
C(13)-C(14)	1.520(3)	C(5)-C(6)-C(7)	107.5(2)
C(13)-H(13)	0.968(19)	C(5)-C(6)-C(8)	110.99(17)
C(14)-H(14A)	0.99(2)	C(7)-C(6)-C(8)	112.1(2)
C(14)-H(14B)	1.01(2)	C(5)-C(6)-H(6)	112.0(12)
C(14)-H(14C)	1.03(2)	C(7)-C(6)-H(6)	109.2(12)
C(16)-C(17)	1.472(4)	C(8)-C(6)-H(6)	105.0(12)
C(16)-H(16A)	1.00(2)	C(6)-C(7)-H(7A)	114.0(14)
C(16)-H(16B)	1.02(3)	C(6)-C(7)-H(7B)	106.6(13)
C(17)-H(17A)	1.02(2)	H(7A)-C(7)-H(7B)	110.9(19)
C(17)-H(17B)	1.14(3)	C(6)-C(7)-H(7C)	110.1(14)

H(7A)-C(7)-H(7C)	104.2(18)	C(13)-C(14)-H(14C)	113.6(12)
H(7B)-C(7)-H(7C)	111.3(18)	H(14A)-C(14)-H(14C)	107.8(18)
C(9)-C(8)-C(10)	110.62(19)	H(14B)-C(14)-H(14C)	107.5(17)
C(9)-C(8)-C(6)	112.34(19)	O(3)-C(15)-N(2)	120.68(19)
C(10)-C(8)-C(6)	111.97(17)	O(3)-C(15)-C(13)	120.45(19)
C(9)-C(8)-H(8)	103.9(13)	N(2)-C(15)-C(13)	118.87(18)
C(10)-C(8)-H(8)	110.1(12)	N(2)-C(16)-C(17)	109.5(2)
C(6)-C(8)-H(8)	107.6(13)	N(2)-C(16)-H(16A)	106.7(14)
N(3)-C(9)-C(8)	176.7(2)	C(17)-C(16)-H(16A)	110.2(14)
C(11)-C(10)-C(12)	122.0(2)	N(2)-C(16)-H(16B)	114.8(16)
C(11)-C(10)-C(8)	122.3(2)	C(17)-C(16)-H(16B)	93.0(16)
C(12)-C(10)-C(8)	115.73(19)	H(16A)-C(16)-H(16B)	122(2)
C(10)-C(11)-H(11A)	121.7(13)	O(4)-C(17)-C(16)	111.5(2)
C(10)-C(11)-H(11B)	120.7(13)	O(4)-C(17)-H(17A)	105.7(13)
H(11A)-C(11)-H(11B)	117.6(18)	C(16)-C(17)-H(17A)	112.3(14)
C(10)-C(12)-C(13)	112.90(18)	O(4)-C(17)-H(17B)	115.4(15)
C(10)-C(12)-H(12A)	113.1(13)	C(16)-C(17)-H(17B)	94.6(16)
C(13)-C(12)-H(12A)	108.5(13)	H(17A)-C(17)-H(17B)	117(2)
C(10)-C(12)-H(12B)	110.1(12)	O(4)-C(18)-C(19)	110.6(2)
C(13)-C(12)-H(12B)	107.9(11)	O(4)-C(18)-H(18A)	120.4(14)
H(12A)-C(12)-H(12B)	103.8(17)	C(19)-C(18)-H(18A)	82.6(15)
C(15)-C(13)-C(14)	109.65(18)	O(4)-C(18)-H(18B)	105.8(14)
C(15)-C(13)-C(12)	107.85(17)	C(19)-C(18)-H(18B)	113.0(14)
C(14)-C(13)-C(12)	112.1(2)	H(18A)-C(18)-H(18B)	122(2)
C(15)-C(13)-H(13)	112.2(12)	N(2)-C(19)-C(18)	109.5(2)
C(14)-C(13)-H(13)	106.9(11)	N(2)-C(19)-H(19A)	110.1(17)
C(12)-C(13)-H(13)	108.2(11)	C(18)-C(19)-H(19A)	98.6(17)
C(13)-C(14)-H(14A)	110.7(13)	N(2)-C(19)-H(19B)	109.3(13)
C(13)-C(14)-H(14B)	108.6(12)	C(18)-C(19)-H(19B)	106.0(13)
H(14A)-C(14)-H(14B)	108.5(18)	H(19A)-C(19)-H(19B)	122(2)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for VMD02. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	656(11)	513(9)	842(12)	-149(8)	224(9)	-100(8)
O(2)	623(11)	904(12)	732(12)	-114(10)	190(10)	-13(10)
O(3)	515(9)	471(8)	724(10)	-150(7)	157(8)	-28(7)
O(4)	482(10)	748(11)	996(14)	-331(10)	251(9)	-95(8)
N(1)	547(12)	479(10)	565(11)	-106(8)	153(10)	-35(8)
N(2)	408(11)	610(11)	806(14)	-273(10)	148(10)	-46(9)
N(3)	923(17)	768(14)	666(14)	-37(11)	189(12)	-327(13)
C(1)	640(17)	594(15)	696(17)	-140(13)	178(14)	24(13)
C(2)	715(19)	777(18)	679(19)	-165(15)	187(16)	35(15)
C(3)	720(20)	762(19)	790(20)	-90(16)	241(17)	-136(16)
C(4)	629(17)	616(15)	676(17)	-113(13)	132(14)	-87(13)
C(5)	600(15)	453(12)	510(13)	-8(10)	123(11)	-10(11)
C(6)	554(14)	431(11)	495(13)	-14(10)	138(11)	-18(10)
C(7)	753(19)	564(15)	471(14)	52(12)	110(13)	75(13)
C(8)	488(13)	417(11)	461(12)	-3(9)	66(10)	-18(10)
C(9)	688(16)	514(13)	475(13)	14(10)	97(12)	-53(12)
C(10)	491(13)	434(11)	419(11)	37(9)	74(10)	11(9)
C(11)	548(16)	608(15)	540(14)	-4(12)	94(12)	74(12)
C(12)	503(14)	443(12)	470(13)	-31(9)	128(11)	-35(10)
C(13)	436(12)	410(11)	460(12)	-28(9)	124(10)	2(9)
C(14)	503(15)	635(15)	486(14)	-28(12)	169(12)	-48(12)
C(15)	457(13)	478(12)	486(12)	-51(10)	128(10)	-19(10)
C(16)	452(16)	850(20)	870(20)	-360(17)	122(15)	-109(14)
C(17)	617(19)	802(19)	970(20)	-367(17)	262(18)	-169(15)
C(18)	514(17)	920(20)	1050(20)	-519(19)	232(16)	-111(15)
C(19)	529(16)	680(16)	970(20)	-342(16)	216(16)	-82(13)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for VMD02.

	x	y	z	U_{iso}
H(1A)	2340(30)	5287(14)	12520(30)	120(11)
H(1B)	3840(30)	5221(11)	13860(20)	75(8)
H(2A)	2820(30)	4506(14)	15080(30)	109(10)
H(2B)	1720(30)	5188(12)	14690(30)	90(8)
H(3A)	530(30)	3607(11)	12540(30)	79(8)
H(3B)	2090(30)	3539(13)	13760(30)	101(10)
H(4A)	2620(30)	3590(11)	11680(20)	78(8)
H(4B)	1630(30)	4250(12)	11180(30)	87(8)
H(6)	4650(20)	3504(9)	11540(20)	51(6)
H(7A)	7460(30)	3976(11)	13010(20)	76(8)
H(7B)	7030(20)	3223(11)	12360(20)	72(7)
H(7C)	6440(20)	3530(11)	13710(30)	76(7)
H(8)	4840(20)	4254(10)	9760(20)	61(6)
H(11A)	7420(20)	2778(10)	9110(20)	59(6)
H(11B)	8050(20)	3433(10)	10090(20)	59(7)
H(12A)	3850(20)	3062(10)	9140(20)	62(7)
H(12B)	4860(20)	2592(10)	8560(20)	52(6)
H(13)	3990(20)	3849(9)	7343(19)	47(5)
H(14A)	5380(20)	2817(12)	6220(20)	71(7)
H(14B)	6120(30)	3512(10)	6820(20)	62(7)
H(14C)	4860(20)	3500(9)	5360(20)	57(6)
H(16A)	360(30)	2600(12)	5560(30)	77(8)
H(16B)	-570(30)	3355(14)	5220(30)	107(11)
H(17A)	-1800(30)	2823(10)	6390(30)	73(7)
H(17B)	-50(30)	2646(14)	7590(30)	118(11)
H(18A)	1240(30)	3540(14)	8740(30)	121(11)
H(18B)	60(30)	4302(12)	8560(20)	79(8)
H(19A)	540(40)	4323(17)	6390(40)	155(14)
H(19B)	2200(30)	4136(10)	7790(20)	71(7)

(2*S,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-4-methylene-7-morpholin-4-yl-heptanoic acid (21)**