Chapter 3

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

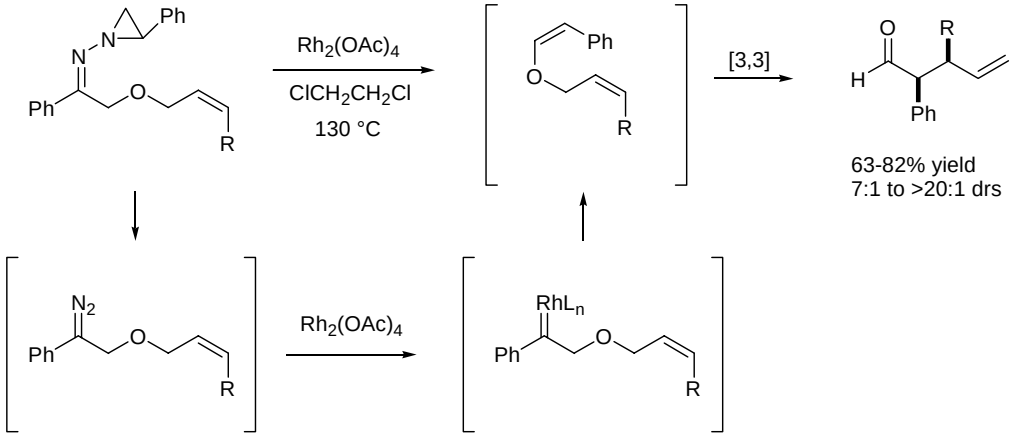
Introduction

Synthetic chemists typically form the individual bonds of a target molecule in a stepwise fashion. Chemical tools which enable the construction of *several* bonds in one sequence, importantly, bypass the need to isolate intermediates and change the reaction conditions. Consequently, these tandem[1] or domino methods reduce the amount of waste generated (e.g., solvents, reagents, adsorbents), and the amount of labor required to make complex molecules.[2] Tandem transformations have been well established for the synthesis of cyclic or polycyclic systems.[2] However, few tandem strategies have been developed for the synthesis of structurally complex acyclic motifs. The Claisen rearrangement is a remarkable method for constructing stereocenters in acyclic architectures.[3] As such, developing tandem methods based on the Claisen transformation will result in powerful chemical tools for addressing stereochemistry on acyclic frameworks.

Representative tandem reactions involving the Claisen rearrangement. The majority of tandem strategies based on the Claisen rearrangement fall into one of two categories: those that involve the *in situ* generation of allyl vinyl ethers followed by subsequent Claisen rearrangement,[4] or those that involve Claisen rearrangement combined in sequence with other carbon-carbon bond forming reactions. The former

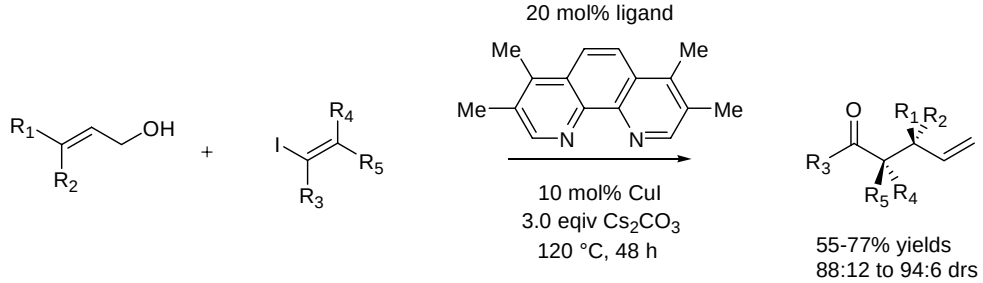
class has been quite useful considering that allyl vinyl ethers are often acid sensitive and difficult to isolate. In particular, the classical aliphatic Claisen reaction has found only limited application in synthesis, compared to other Claisen variants, due to a lack of general methods for the stereoselective synthesis of these sensitive precursors. An advance in this area was recently made by Stoltz through his development of a tandem Bamford-Stevens/thermal aliphatic Claisen rearrangement sequence (Scheme 1).[5]

Scheme 1. Tandem rhodium-catalyzed Bamford-Stevens/thermal aliphatic Claisen rearrangement sequence



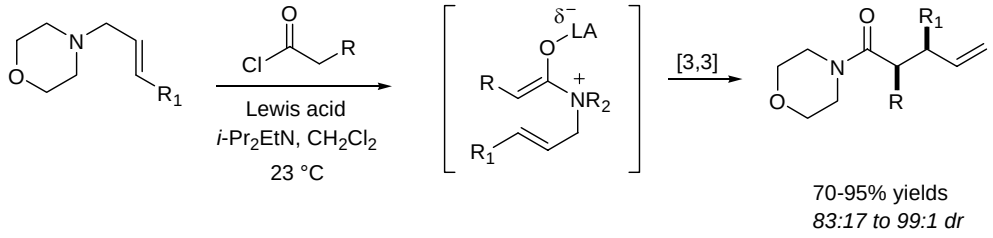
In addition, Buchwald recently reported the copper-catalyzed C-O coupling/Claisen rearrangement, a cascade process which also addresses the stereoselective synthesis of simple allyl vinyl ethers (Scheme 2).[6]

Scheme 2. Domino copper-catalyzed C-O Coupling-Claisen rearrangement



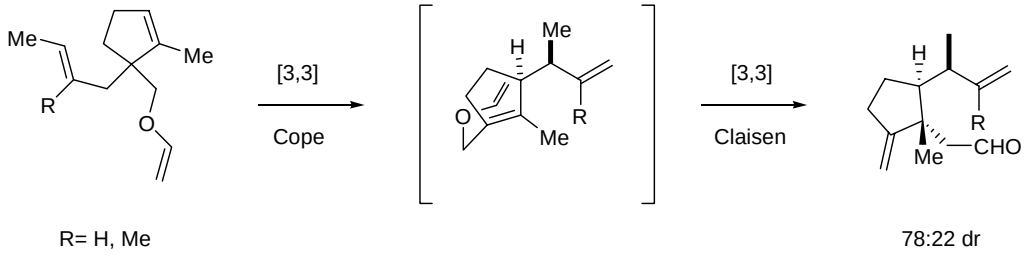
Notably, our acyl-Claisen methodology (Chapter 2) is also considered a tandem transformations; a transient zwitterionic intermediates is generated *in situ* which then undergoes [3,3]-bond reorganization (Scheme 3).[7]

Scheme 3. Acyl-Claisen rearrangement



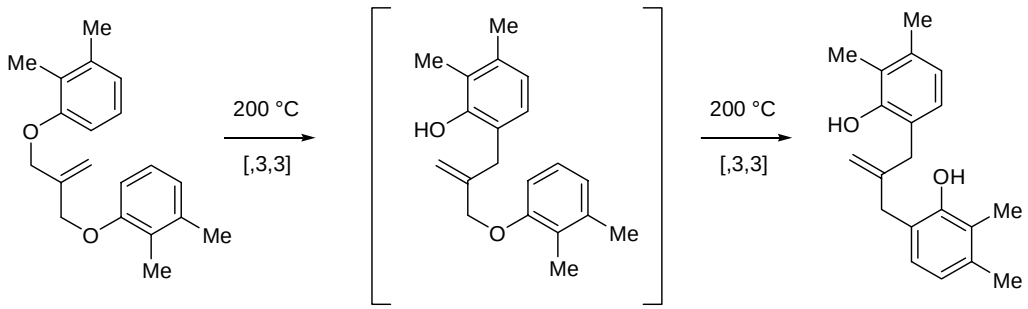
The combination of Claisen rearrangements with other carbon-carbon bond forming methods have resulted in powerful methods for synthesizing complex cyclic or polycyclic systems. For example, tandem Cope-Claisen sequences have been shown to build molecules with three contiguous stereocenters on a carbocycle (Scheme 4).[4] Other noteworthy tandem methods of this sort involve merging the Claisen rearrangement with ring closing methods, such as the intramolecular ene,[8] Diels Alder,[9] Bergman cyclization,[10] and exo-dig cyclization.[11]

Scheme 4. Example of a tandem Cope/Claisen rearrangement



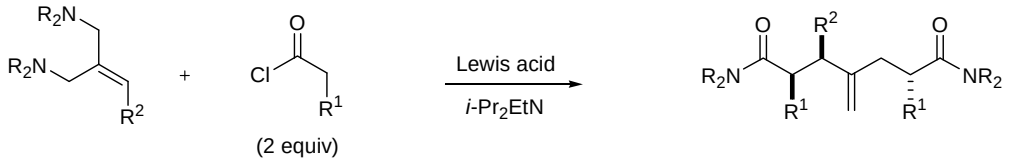
Of particular note, the tandem reaction based upon two successive aromatic Claisen rearrangements was developed by Hiratani et al. (Scheme 5).[12] By heating bisallylic ether to approximately 200 °C, the "double Claisen" rearrangement occurs to provide an aromatic product containing two new carbon-carbon bonds. This methodology has been used by Hiratani and coworkers for the synthesis of novel materials including calixarenes,[13] rotaxanes[14] and polymers.[15] However, this methodology has not been applied for stereoselective synthesis.

Scheme 5. Double-Claisen rearrangement



Herein we describe a novel cascade process based on our acyl-Claisen rearrangement. Our proposed tandem acyl-Claisen rearrangement combines the convenience of generating allyl vinyl ethers *in situ*, with the power of performing two carbon-carbon bond forming reactions in sequence (Scheme 6). Importantly, this proposed three component coupling enables the construction of complex *acyclic* systems in the context of the 2,3,6-trisubstituted-1,7-dioxo-heptane architecture. In addition, this cascade Claisen sequence uses simple allyl diamines and acid chloride precursors—chemicals that are readily available in a diverse range of structural formats. As such, we expect our tandem process to be broadly useful for both the fields of natural product synthesis and medicinal chemistry.

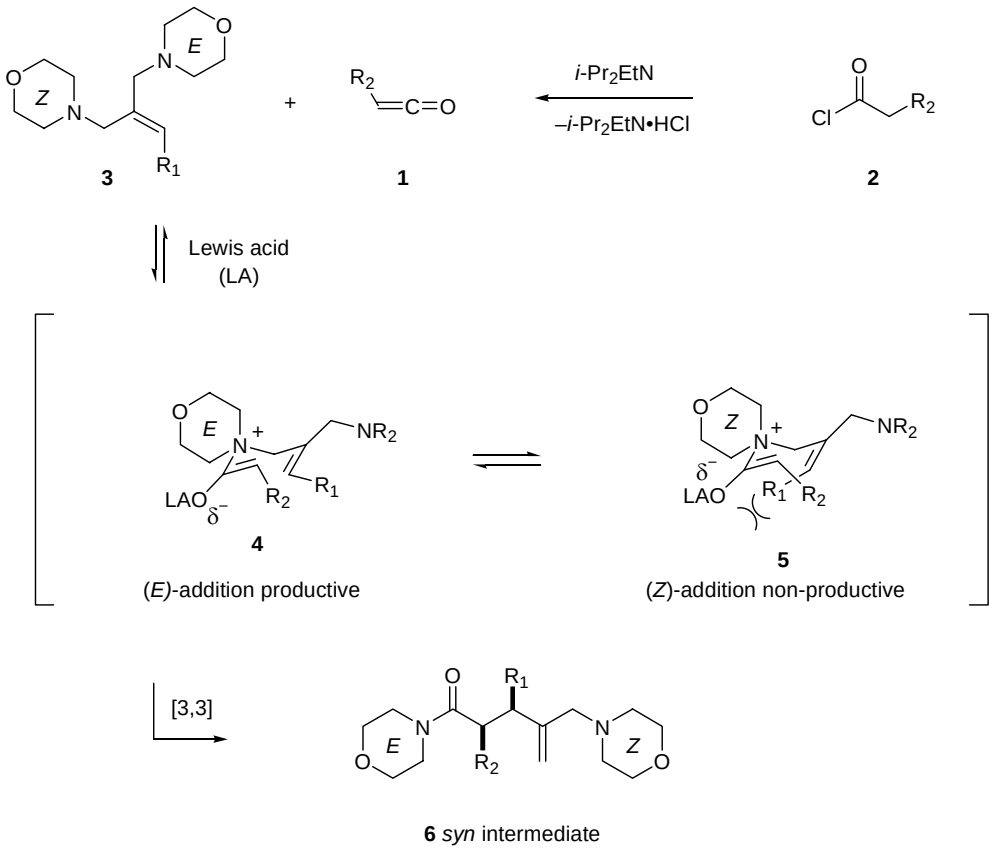
Scheme 6. Proposed tandem-acyl Claisen rearrangement for the rapid construction of stereochemically complex acyclic frameworks



Reaction Design

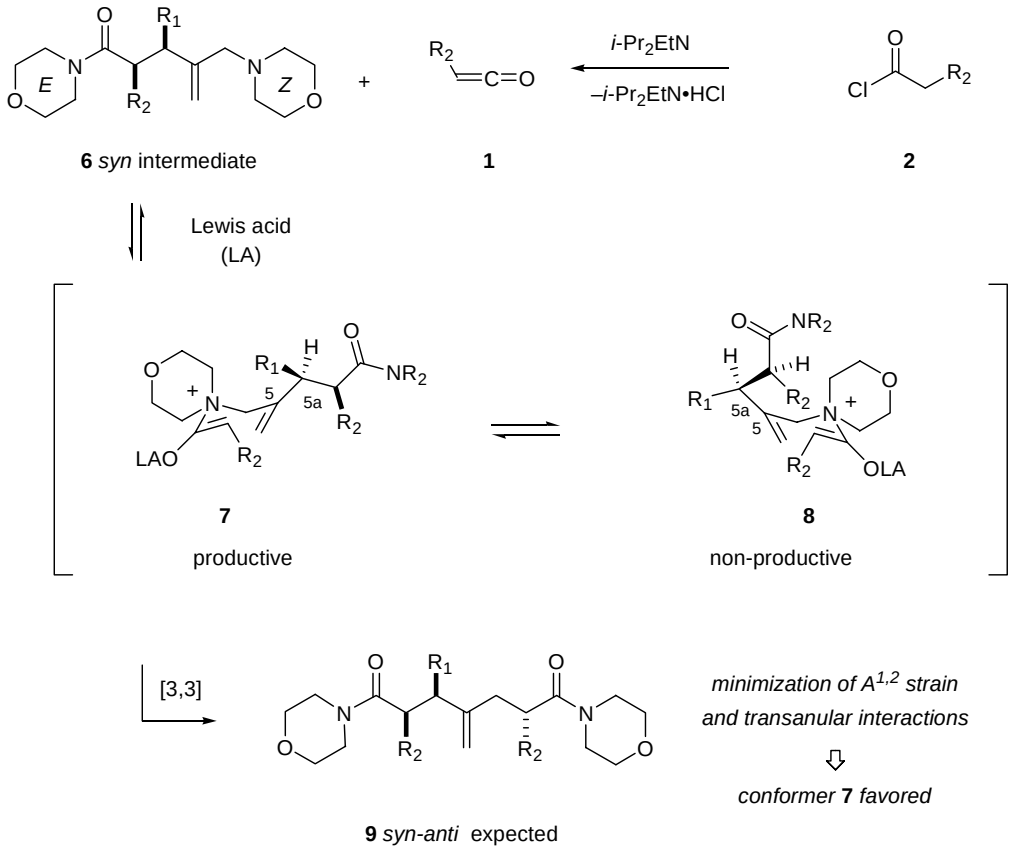
Based on our acyl-Claisen studies,[16] we envisioned that a variety of ketenes **1**, generated *in situ* from acid chloride **2**, would participate in a tandem acyl-Claisen rearrangement with allyl diamines **3** (Scheme 7 and Scheme 8). Addition of the (*Z*)- or (*E)*-amine component of diamine **3** to ketene **1** would provide the regioisomeric allyl vinyl ammonium complexes **4** and **5,** respectively (Scheme 7). Given that the (*Z*)-amine derived conformation **5** should be destabilized on the basis of 1,3 diaxial interactions, *and* that the ketene-addition step is likely reversible,[17] the first Claisen rearrangement was expected to proceed selectively via (*E*)-ammonium complex **4**. As a central design element, this regioselective addition-rearrangement would provide the 2,3-disubstituted intermediate **6** with high levels of *syn* selectivity while revealing an allyl amine component that can participate in a second acyl-Claisen transformation.

Scheme 7. Mechanistic rationale for predicted stereochemistry in the first Claisen event



In this context, the addition of a second equivalent of ketene **1** to intermediate **6** would result in an ammonium enolate that can adopt two chair rearrangement topographies **7** and **8**. Minimization of $A^{1,2}$ strain[18] about the C(5)–C(5a) bond of conformer **8** was expected to enforce transannular interactions between the C(5a)-amide moiety and the axial methylene group. In contrast, the same torsional constraints in topography **7** positions the bulky C(5a)-amide chain away from the [3,3]-isomerization event. As such, the second Claisen step was anticipated to proceed *via* conformer **7** to furnish the structurally complex 2,3,6-trisubstituted-1,7-diamido-heptane **9** with 2,3-*syn*-3,6-*anti* diastereocontrol.

Scheme 8. Mechanistic rationale for predicted stereochemistry in the second Claisen event

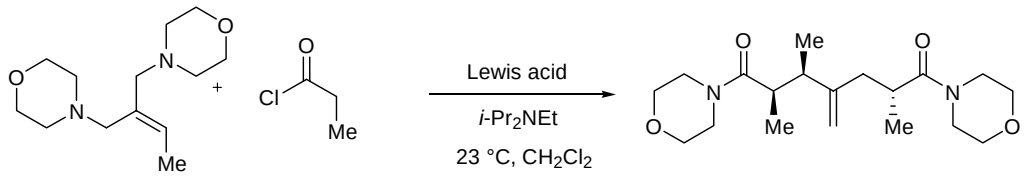


Results and Discussion

Our tandem acyl-Claisen strategy was first evaluated using allyl dimorpholine **10** with propionyl chloride in the presence of *i*-Pr_2EtN and a series of metal salts. As revealed in Table 1, this tandem sequence was successful with a variety of Lewis acids including $Yb(OTf)_3$, $TiCl_4(THF)_2$, MgI_2 and $AlCl_3$. In all cases, the major constituent **12** was determined to be the 2,3-*syn*-3,6-*anti* isomer,[19] as predicted in our design plan. The superior levels of diastereocontrol (98:2 dr) and reaction efficiency (97% yield) exhibited

by $Yb(OTf)_3$ (entry 1) defined this Lewis acid as the optimal catalyst for further exploration.

Table 1. Lewis Acid Promoted Tandem Acyl-Claisen Rearrangement between Propionyl Chloride and Allyl Dimorpholine **12**[a]



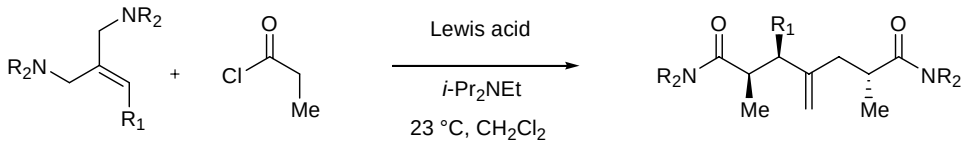
10 **11** **12** *syn-anti isomer*

entry	Lewis acid	equiv of LA	% yield of **12**	*synanti/ anti-anti*[b,c]
1	$Yb(OTf)_3$	2.0	97	98:2
2	$TiCl_4(THF)_2$	2.0	93	98:2[d]
3	MgI_2	4.0	70	98:2
4	$AlCl_3$	2.0	93	64:36

[a] Reactions performed in CH_2Cl_2 at 23 °C. [b] Ratios determined by GLC. [c] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [d] Reaction performed at –20 °C.

Allyl dimorpholine component. Experiments that examine the scope of the allyl dimorpholine substrate are summarized in Table 2. The reaction appears quite general with respect to the nature of the tertiary amine component (entries 1–3, 82–93% yield, ≥95:5 dr). Considerable variation in the olefin substituent can also be tolerated to afford acyclic arrays that incorporate alkyl, halo, cyano, alkoxy and sulfanyl substituents in excellent yield and diastereoselectivity (entries 4–7, 74–93% yield, 90:10 to 99:1 *syn-anti:anti-syn*). As revealed with the cyano- and phenylthio-substituted amines (cf. entries 6 and 7), the reaction exhibits broad latitude with respect to the electronic contribution of the olefin substituent (≥70% yield, ≥93:7 dr).

Table 2. Tandem Acyl-Claisen Rearrangement between Propionyl Chloride and Representative Allyl Dimorpholines



	allyl diamine			
entry	NR_2	olefin–R_1	% yield	*syn–anti/ syn–syn*[a,b]
1	morpholine	Me (**10**)	97	98:2[c]
2	pyrrolidine	Me (**13**)	90	95:5
3	piperidine	Me (**14**)	99	96:4
4	morpholine	Cl (**15**)	98	99:1
5	morpholine	OBz (**16**)	86	91:9[c]
6	morpholine	CN (**17**)	78	97:3[c,d]
7	morpholine	SPh (**18**)	70	93:7[d]
8	morpholine	H (**19**)	92	55:45
9	morpholine	Ph (**20**)	70	55:45

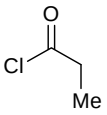
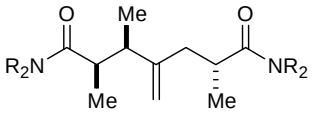
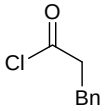
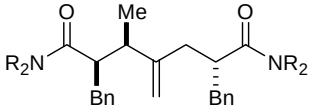
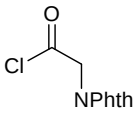
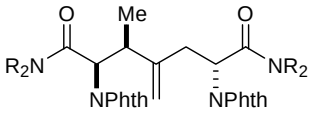
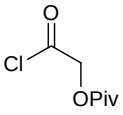
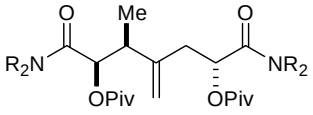
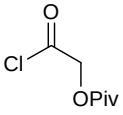
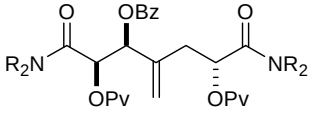
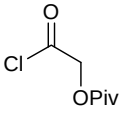
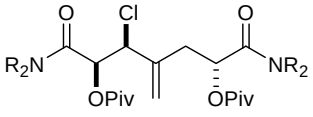
[a] Ratios determined by GLC or HPLC. [b] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [c] Relative configurations assigned by X-ray analysis. [d] Using $TiCl_4(THF)_2$.

Use of the unsubsituted allyl diamine **20** (R_1 = H) with propionyl chloride, however, afforded the tandem adduct without any diastereocontrol (92% yield, 55:45 dr, entry 6). In this case, the Claisen event occurs without stereochemical bias because a β stereocenter is *not* evolved from the first Claisen transformation. As a result, rearrangement through both conformers **4** and **5** should be equally favorable (see Scheme 7). When R_1 = Ph, poor diastereocontrol was also observed presumably for a different reason (70% yield, 55:45 dr, entry 7).[20] Here, we speculate that the phenyl substituent must be as sterically demanding as the β-substituted amide side chain. Consequently, diastereocontrol is impaired as chair transition states **7** and **8** become energetically similar (see Scheme 8).

Acid chloride component. The effect of the acid chloride component on the tandem acyl-Claisen rearrangement has also been examined (Table 3). Significant

structural variation in the ketene surrogate (R_2 = Me, Bn, NPhth, or OPiv) is possible without loss in yield or diastereoselectivity (74–99% yield, 83:17 to 97:3 *syn-anti:anti-syn*, entries 1–6). A powerful feature of this cascade reaction is the capacity to build functional and stereochemical arrays that are not readily available using conventional chemical methods. As demonstrated in entry 3, implementation of α-phthalylglycyl chloride allows the rapid construction of carbon tethered α-amino carbonyls. This tandem strategy also provides an attractive alternative to iterative aldol processes. Indeed, the synthesis of a variety of divergently substituted polyol systems can be achieved using α-pivaloxy chloride with alkyl, halo, or alkoxy-substituted diamines (entries 4–6, 74–95% yield, ≥95:5 dr).[21]

Table 3. Tandem Acyl-Claisen Rearrangement between Representative Allyl Dimorpholines and Acid Chlorides.[a]

entry	amine	acid-Cl	product[b]	% yield	*syn–anti/ syn–syn*[c,d]
1	**10**			97	98:2[e]
2	**10**			99	92:8
3	**10**			98	95:5[e]
4	**10**			97	97:3[f]
5	**16**			71	92:8[f,g]
6	**15**			84	95:5[f]

[a] With 2 equiv. of $Yb(OTf)_3$ and *i*-Pr_2NEt at 23 °C in CH_2Cl_2. [b] NR_2 = *N*-morpholine. [c] Ratios determined by GLC. [d] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [e] Relative configurations assigned by X-ray analysis. [f] Ratios determined by ^1H NMR. [g] Using $TiCl_4(THF)_2$.

Applications for macrolide synthesis

A stereochemical pattern commonly found in polyketide natural products (e.g., methynolide, erythronolide, tylonolide) is the 2,3-*syn*-3,6-*anti*-2,6-dimethyl-1,7-diox-heptane (Figure 1).[22] Notably, this stereochemical array can be accessed in *one* step from diamine **16** and propionyl chloride by our tandem acyl-Claisen rearrangement. Moreover, the C(4) olefin functionality renders these Claisen adducts versatile substrates

for subsequent transformations (e.g., oxidative or reductive elaboration). Consequently, our tandem acyl-Claisen technology should enable the design of flexible and convergent synthetic routes, easily adaptable to a variety of macrolide antibiotics, and their analogues.

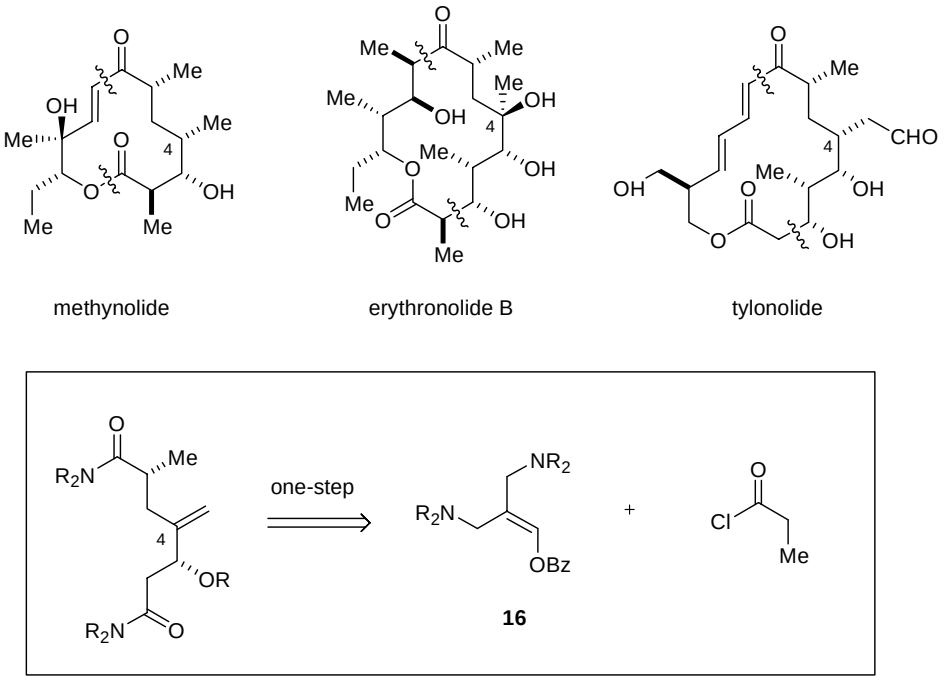
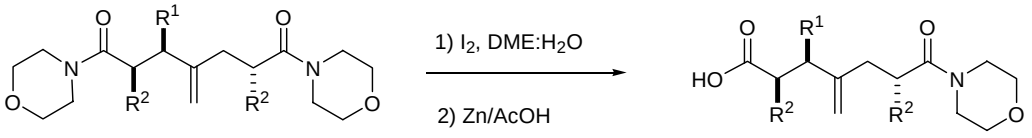


Figure 1. Applications of the tandem acyl-Claisen rearrangement for macrolide synthesis

Regioselective hydrolysis

Finally, it is important to note that the regioselective hydrolysis of the α,β-disubstituted amide of these dicarbonyl Claisen adducts is possible with the use of an iodolactonization-ring opening sequence[23] (Table 4). The regioselectivity of this hydrolysis generally increases with the increasing steric demands of the β-substituent (cf. entries 1–5).

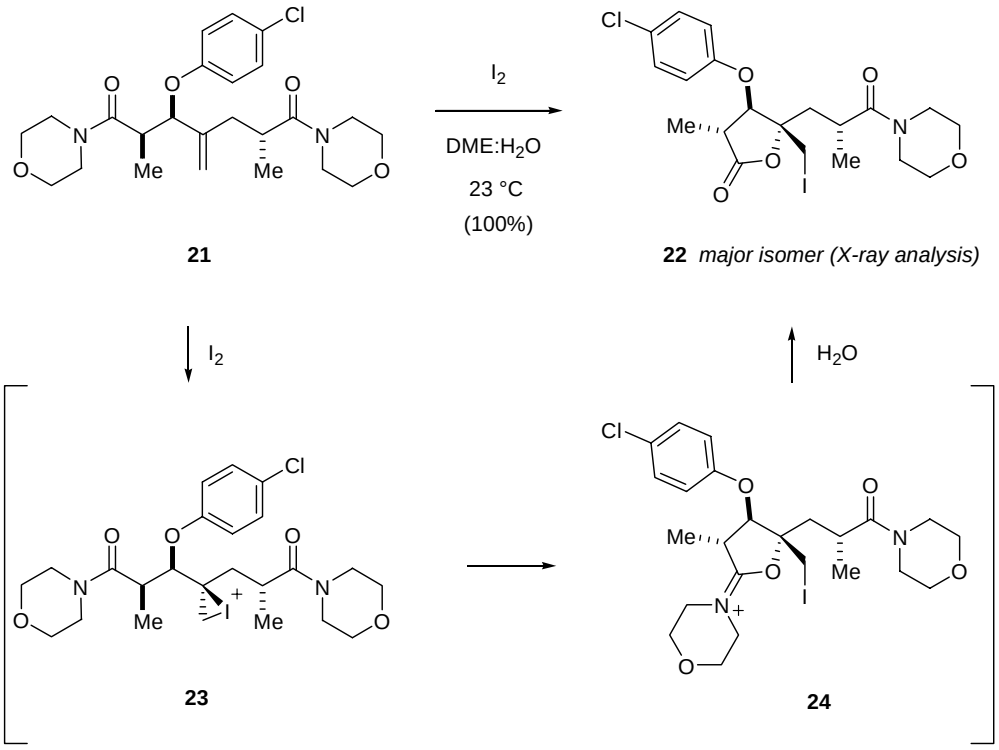
Table 4. Regioselective hydrolyisis of the tandem Claisen bisamides



	bis-amide			
entry	R^1	R^2	% yield	regioselectivity
1	Me	Me	83	92:8
2	Me	Bn	82	92:8
3	*p*-ClPh	Me	80	90:10
4	BzO	Me	88	83:17
5	CN	Me	89	1:1

Mechanistic considerations. In initial experiments, we observed that treatment of **21** with I_2, provided lactone **22** as the major isomer in (90:10 dr, 100% yield) (Scheme 9). Single crystal X-ray analysis of this product revealed its three dimensional structure, and thus, the regio- and stereochemical bias of the iodolactonization. Based on these observations, we propose that minimization of $A^{1,2}$ strain[24] about the alkene results in stereoselective iodine addition to the sterically less hindered face of the alkene (the *re* face as shown in Figure 1). The α,β-amide group must be conformationally pre-organized,[25] and as such kinetically favored, to attack the resulting iodonium **23**, producing iminium ion **24**, which is then hydrolyzed to the observed lactone **22**. Reductive opening of lactone **22** by zinc affords the corresponding acid.

Scheme 9. Rationale for regioselectivity in the iodolactonization



Concluding Remarks

We have designed and studied a new tandem acyl-Claisen rearrangement that tolerates a range of alkyl-, aryl-, and heteroatom-substituted acid chloride and allyl dimorpholine reaction partners. The reaction efficiently furnishes the complex 2,3,6-trisubstituted-1,7-diamido-heptane structures with excellent 2,3-*syn*-3,6-*anti* diastereocontrol. In the next chapter, work aimed at demonstrating the applicability of this new tandem acyl-Claisen rearrangement for natural product synthesis is presented.

Experimental Methods

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[26] 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.[27] 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. ^{1}H 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 ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (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.

Morpholin-4-yl-acetic acid ethyl ester (25). 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 concentrated to provide **25** (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 calcd 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 (26). Following a modified version of the procedure described by McElvain,[28] a round bottom flask charged with **25** (10.0 g, 58.0 mmol) and NaOEt (2.0 g, 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 **26** 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 calcd for $(C_{11}H_{20}N_2O_3H)^+$ requires m/z 229.1552, found *m/z* 229.1555.

General Procedure A: Preparation of the allylic diamines (unoptimized reaction conditions)**.** According to a modified procedure of Werner,[29] to a solution of the triphenylphosphonium halide salt in THF was added *t*-BuOK portionwise. After 1 h, a solution of the ketone **26** 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.

1,3-Dimorpholin-4-yl-2-ethylidene-propane (10). 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 **26** (1.40 g, 6.00 mmol) in THF (30 mL) to provide **10** 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 calcd 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 (15). 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 **26** (1.00 g, 4.38 mmol) in THF (30 mL) to provide **15** 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}; ^{1}H 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 calcd 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 (18). 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 **26** (1.00 g, 4.38 mmol) in THF (20 mL) to provide **18** 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}; ^{1}H 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 calcd 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 (17). Prepared according to general procedure A from cyanomethyltriphenylphosphonium chloride (3.30 g, 11.0 mmol) and ketone **26** (500 mg, 2.19 mmol) in THF (22 mL) to provide **17** 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 calcd 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 (16). Based upon a modified procedure of Boeckman[30], a solution of benzoic acid 2-methyl-propenyl ester[31] (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, 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

16 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 calcd 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 (14). 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 (**27**) (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 **27**. 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 **14** 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 (13). To a solution of pyrrolidine (7.75 mL, 93.0 mmol) in THF (40.0 mL) at 23 °C was added **27** (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 carefully 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 **13** 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 calcd 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 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 (12).** Prepared according to the general procedure C from **10** (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 compound **12** 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 calcd 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 **14** (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 calcd 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 **13** (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}; ^{1}H 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 calcd 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 **15** (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 calcd 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 **18** (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 calcd 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 **17** (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 calcd for $(C_{19}H_{29}N_3O_4)^+$ requires m/z 363.2158, found *m/z* 363.2162. See X-ray data.

(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 **16** (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}; ^1H 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 $O(CH_2CH_2,)_2N$), 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 calcd 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 **10** (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 calcd 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 **10** (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 calcd 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 **16** (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,)$_2$N), 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 calcd 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 **10** (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,)$_2$N), 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 calcd 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 **15** (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}; ^{1}H 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 calcd 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,[23] 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.

(2*R,3*R**,6*R**)-4-Methylene-7-morpholin-4-yl-2,3,6-trimethyl-heptanoic acid (Table 4, entry 1).** Prepared according to the general procedure D from **12** (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 calcd 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 (Table 4, entry 2).** 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 the title compound as a white solid (35.8 mg, 0.095 mmol) in 82% yield: 92:8 regioselectivity by ^{1}H NMR analysis. Major isomer (α,β-disubstituted acid): IR (film) 3028, 2943, 2866, 2248, 1730, 1599, 1452, 1112, 911, 726 cm^{-1}; ^{1}H 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 calcd 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 (Table 4, entry 3).** 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 calcd 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).*

X-ray Crystal Data

(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)**

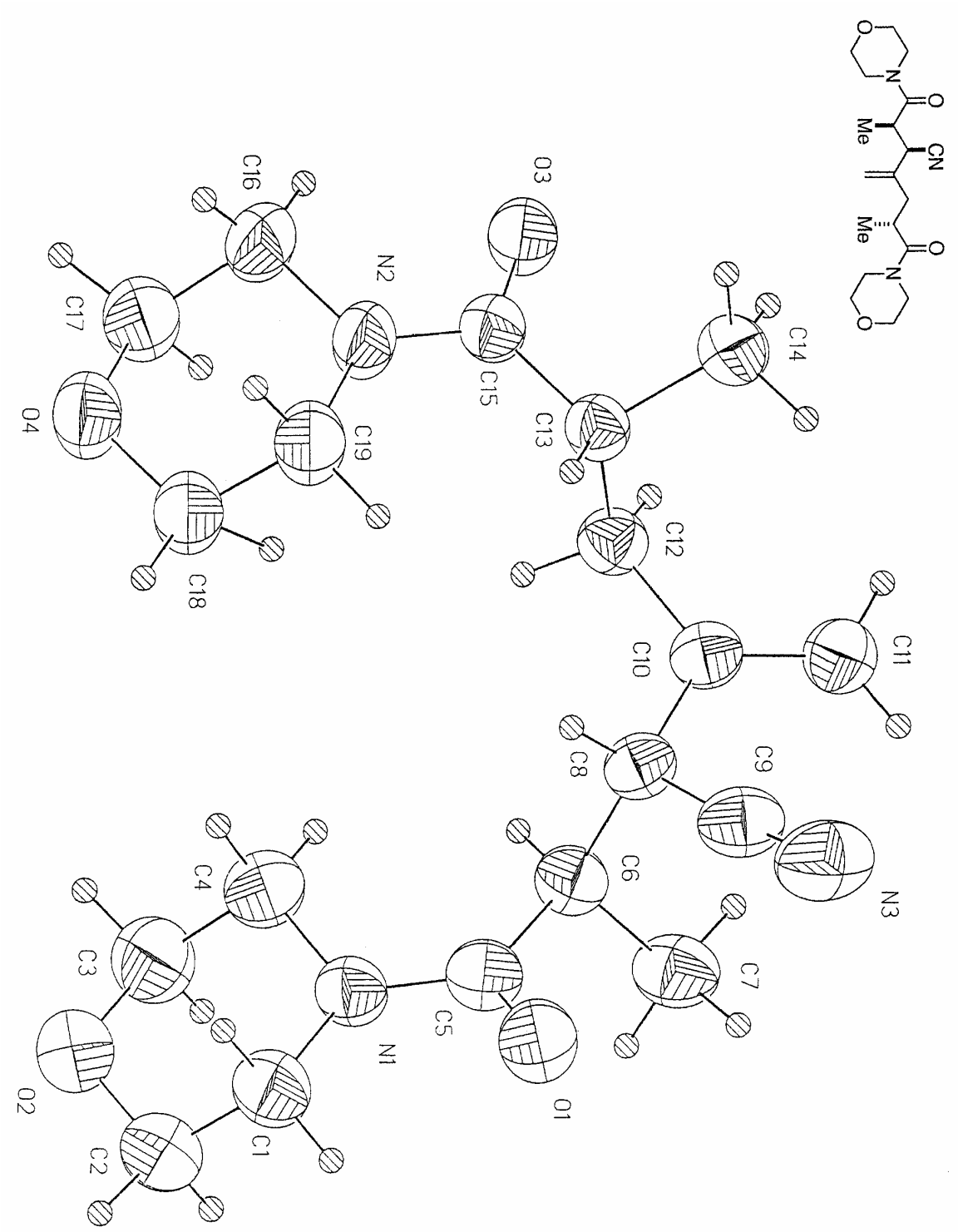


Table 1. Crystal data and structure refinement for VMD02.

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)

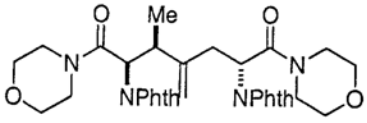
Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for VMD02. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	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*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)**



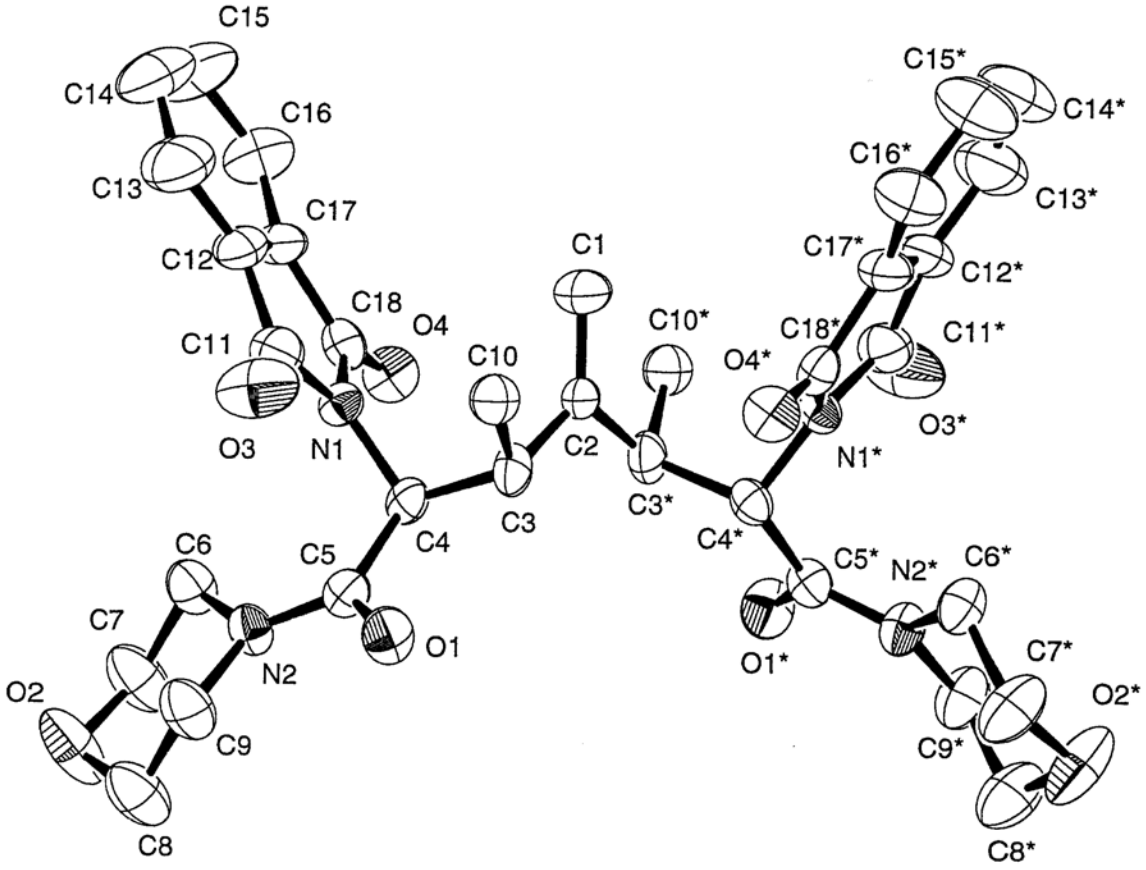


Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy

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 Å

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**)-4-Methylene-7-morpholin-4-yl-2,3,6-trimethyl-heptanoic acid (Table 4, entry 1)**

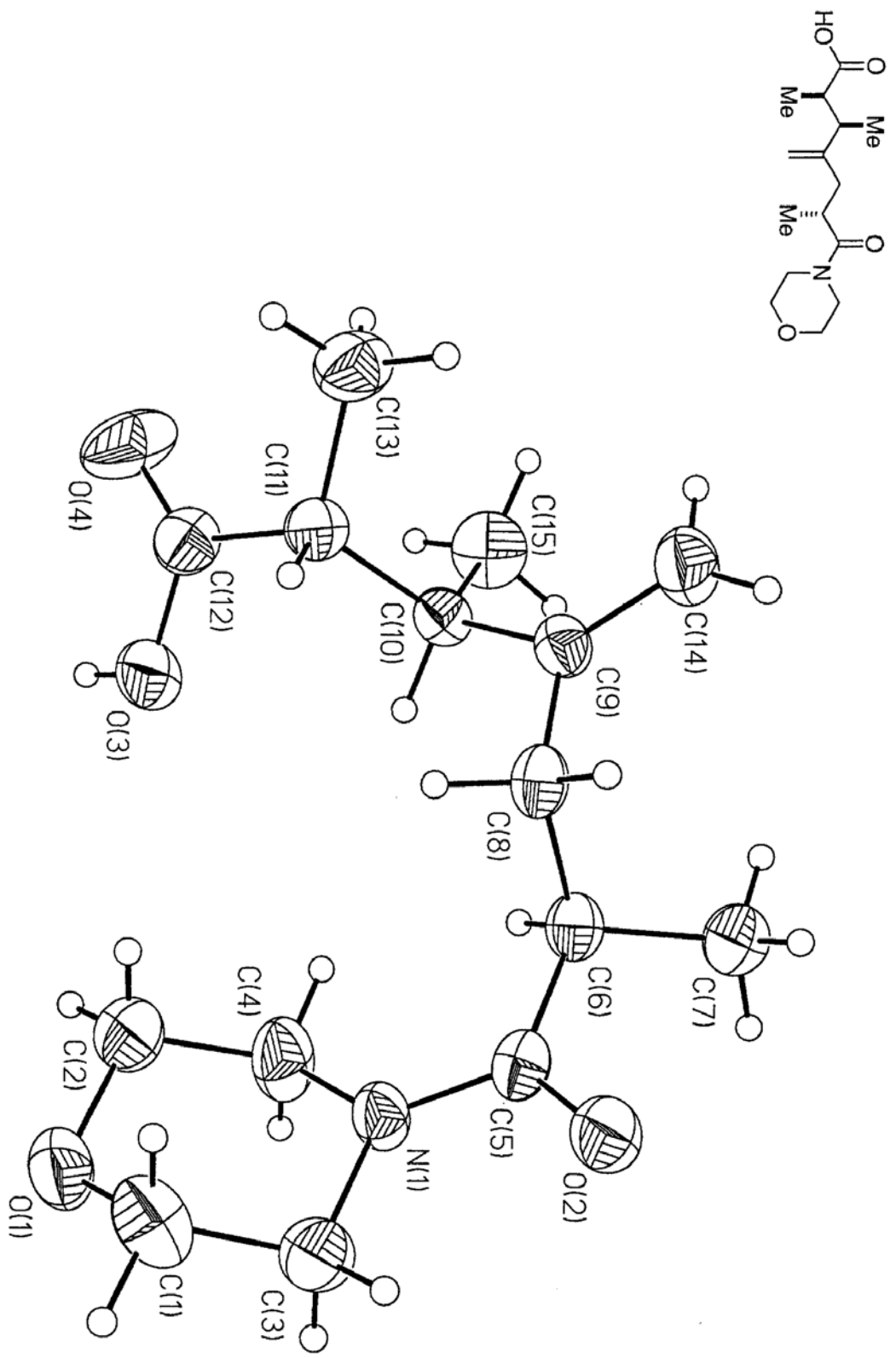


Table S-1. Crystal data and structure refinement for 1.

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.

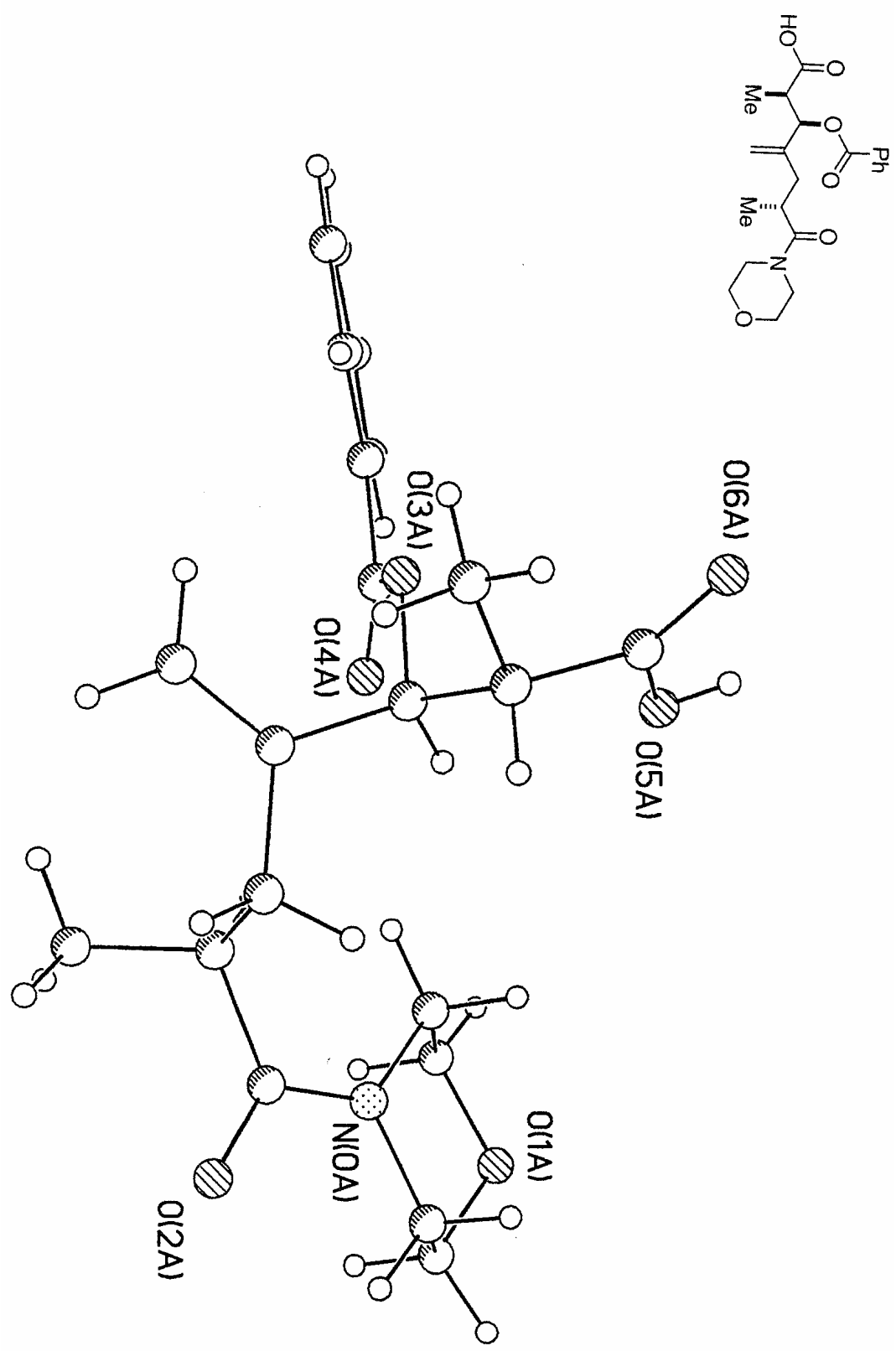
O(1)-C(1)	1.418(3)	O(1)-C(2)	1.427(3)
O(2)-C(5)	1.238(2)	O(3)-C(12)	1.333(3)
O(4)-C(12)	1.193(3)	N(1)-C(5)	1.350(3)
N(1)-C(3)	1.459(3)	N(1)-C(4)	1.462(3)
C(1)-C(3)	1.492(3)	C(2)-C(4)	1.494(3)
C(5)-C(6)	1.510(3)	C(6)-C(7)	1.523(3)
C(6)-C(8)	1.545(3)	C(8)-C(9)	1.502(3)
C(9)-C(14)	1.322(3)	C(9)-C(10)	1.513(3)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

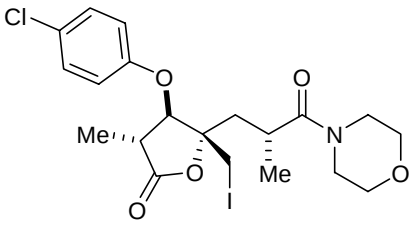
Table S-4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

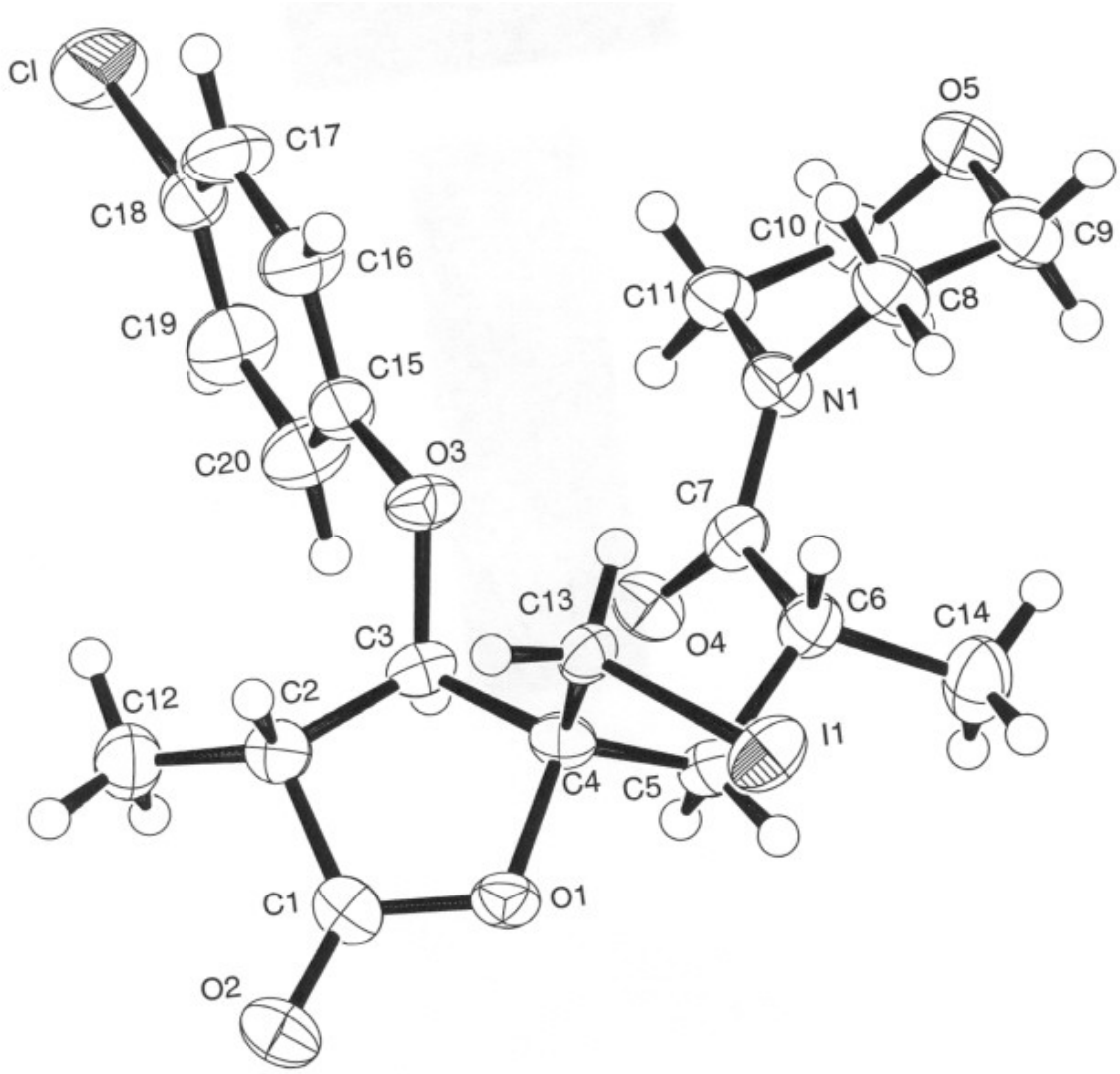
	U11	U22	U33	U23	U13	U12
O(1)	42(1)	49(1)	60(1)	13(1)	-1(1)	11(1)
O(2)	27(1)	65(1)	55(1)	18(1)	-3(1)	-2(1)
O(3)	26(1)	70(1)	48(1)	14(1)	-5(1)	3(1)
O(4)	28(1)	134(2)	48(1)	-15(1)	5(1)	-2(1)
N(1)	26(1)	36(1)	45(1)	9(1)	-2(1)	0(1)
C(1)	60(2)	43(2)	58(2)	9(1)	-9(1)	-2(2)
C(2)	35(2)	63(2)	61(2)	16(2)	9(1)	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*S,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-4-methylene-7-morpholin-4-yl-heptanoic acid (Table 4, entry 3)**



4-(4-Chloro-phenoxy)-5-iodomethyl-3-methyl-5-(2-methyl-3-morpholin-4-yl-3-oxo-propyl)-dihydro-furan-2-one (22)





EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$IClO_5NC_{20}H_{25}$
Formula Weight	521.78
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.40 X 0.08 X 0.03 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.7866(3)Å b = 18.5666(2) Å c = 11.3212(3) Å β = 106.400(1)° V = 2175.05(9) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.593 g/cm^3
F_{000}	1048.00
μ(MoKα)	66.41 cm^{-1}

B. Intensity Measurements

Diffractometer	SMART CCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{max}$	49.4°

No. of Reflections Measured	Total: 10108 Unique: 3934 (R_{int} = 0.047)
Corrections	Lorentz-polarization Absorption (Tmax = 0.96 Tmin = 0.57)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2177
No. Variables	253
Reflection/Parameter Ratio	8.60
Residuals: R; Rw; Rall	0.030 ; 0.029; 0.071
Goodness of Fit Indicator	1.03
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.46 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.40 $e^-/\AA^3$

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

atom	x	y	z	B_{eq}
I(1)	0.61458(3)	0.07747(2)	0.46885(3)	3.371(8)
Cl	1.3528(1)	0.28931(9)	1.2178(1)	5.17(4)
O(1)	0.8798(3)	-0.0158(2)	0.6339(3)	2.51(8)
O(2)	1.0510(3)	-0.0688(2)	0.6022(3)	3.13(9)
O(3)	0.9820(3)	0.1470(2)	0.8012(3)	2.55(8)
O(4)	0.8761(3)	0.0559(2)	1.0065(3)	2.68(8)
O(5)	0.6653(3)	0.2415(2)	1.1681(3)	3.16(9)
N(1)	0.7661(3)	0.1594(2)	1.0060(3)	2.5(1)
C(1)	1.0059(5)	-0.0186(3)	0.6418(4)	2.4(1)
C(2)	1.0748(4)	0.0478(2)	0.7068(4)	2.4(1)
C(3)	0.9832(4)	0.0709(3)	0.7795(4)	2.3(1)
C(4)	0.8479(4)	0.0486(3)	0.6959(4)	2.2(1)
C(5)	0.7542(4)	0.0202(3)	0.7631(4)	2.4(1)
C(6)	0.6933(4)	0.0744(3)	0.8308(4)	2.5(1)
C(7)	0.7874(5)	0.0962(3)	0.9547(4)	2.3(1)
C(8)	0.6591(4)	0.2097(3)	0.9588(4)	2.9(1)
C(9)	0.5836(5)	0.2180(3)	1.0521(4)	3.2(1)
C(10)	0.7662(5)	0.1906(3)	1.2148(4)	3.2(1)
C(11)	0.8468(4)	0.1803(3)	1.1270(4)	2.7(1)
C(12)	1.2147(5)	0.0343(3)	0.7753(4)	3.2(1)
C(13)	0.7935(4)	0.1060(3)	0.5997(4)	2.4(1)
C(14)	0.5741(5)	0.0397(3)	0.8575(5)	3.9(1)
C(15)	1.0741(4)	0.1762(3)	0.9017(4)	2.4(1)
C(16)	1.0976(5)	0.2481(3)	0.8948(5)	3.6(1)
C(17)	1.1825(5)	0.2843(3)	0.9916(5)	4.0(1)
C(18)	1.2443(4)	0.2458(3)	1.0951(5)	3.2(1)
C(19)	1.2224(5)	0.1737(3)	1.1024(4)	3.8(1)
C(20)	1.1378(5)	0.1379(3)	1.0048(4)	3.5(1)
H(1)	1.0724	0.0835	0.6461	2.8249
H(2)	1.0022	0.0455	0.8555	2.7412
H(3)	0.6859	-0.0033	0.7038	2.8628
H(4)	0.7996	-0.0140	0.8219	2.8628
H(5)	0.6675	0.1161	0.7810	3.0188
H(6)	0.6924	0.2552	0.9443	3.4801
H(7)	0.6037	0.1916	0.8839	3.4801
H(8)	0.5461	0.1731	1.0625	3.7873

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

atom	x	y	z	B_{eq}
H(9)	0.5171	0.2527	1.0227	3.7873
H(10)	0.8201	0.2074	1.2913	3.7638
H(11)	0.7292	0.1457	1.2265	3.7638
H(12)	0.9090	0.1437	1.1579	3.1903
H(13)	0.8897	0.2241	1.1205	3.1903
H(14)	1.2196	-0.0020	0.8355	3.8218
H(15)	1.2598	0.0189	0.7188	3.8218
H(16)	1.2522	0.0775	0.8143	3.8218
H(17)	0.8554	0.1152	0.5562	2.8355
H(18)	0.7801	0.1486	0.6411	2.8355
H(19)	0.5350	0.0735	0.8988	4.6475
H(20)	0.5140	0.0260	0.7820	4.6475
H(21)	0.6004	-0.0015	0.9078	4.6475
H(22)	1.0548	0.2739	0.8222	4.2673
H(23)	1.1977	0.3345	0.9864	4.7746
H(24)	1.2655	0.1478	1.1749	4.4980
H(25)	1.1244	0.0874	1.0092	4.1910

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

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I(1)	0.0410(2)	0.0452(2)	0.0360(2)	-0.0108(2)	0.0013(1)	-0.0029(2)
Cl	0.0523(9)	0.067(1)	0.062(1)	-0.0069(8)	-0.0088(8)	-0.0335(8)
O(1)	0.038(2)	0.030(2)	0.029(2)	-0.002(2)	0.011(2)	-0.008(1)
O(2)	0.050(2)	0.039(2)	0.033(2)	0.009(2)	0.016(2)	-0.002(2)
O(3)	0.036(2)	0.025(2)	0.029(2)	-0.002(1)	-0.001(2)	-0.004(2)
O(4)	0.036(2)	0.035(2)	0.029(2)	0.009(2)	0.007(2)	0.003(1)
O(5)	0.049(2)	0.040(2)	0.033(2)	0.005(2)	0.016(2)	-0.003(2)
N(1)	0.031(2)	0.037(3)	0.024(2)	0.004(2)	0.002(2)	-0.008(2)
C(1)	0.039(3)	0.036(3)	0.019(3)	0.005(3)	0.012(2)	0.004(2)
C(2)	0.037(3)	0.029(3)	0.026(3)	-0.001(2)	0.013(2)	0.003(2)
C(3)	0.034(3)	0.024(3)	0.026(2)	-0.004(2)	0.004(2)	-0.001(2)
C(4)	0.035(3)	0.028(3)	0.020(3)	0.000(2)	0.009(2)	-0.006(2)
C(5)	0.034(3)	0.027(3)	0.030(3)	-0.004(2)	0.008(2)	-0.004(2)
C(6)	0.032(3)	0.034(3)	0.030(2)	-0.005(3)	0.010(2)	-0.001(3)
C(7)	0.035(3)	0.035(4)	0.022(3)	-0.007(2)	0.014(2)	0.000(2)
C(8)	0.040(3)	0.041(4)	0.028(3)	0.010(2)	0.007(2)	-0.002(2)
C(9)	0.040(3)	0.040(4)	0.037(3)	0.008(2)	0.006(3)	-0.002(3)
C(10)	0.044(3)	0.042(4)	0.031(3)	0.006(3)	0.006(3)	-0.002(3)
C(11)	0.034(3)	0.034(3)	0.029(3)	0.002(2)	0.002(2)	-0.005(2)
C(12)	0.035(3)	0.046(4)	0.041(3)	-0.002(3)	0.013(3)	-0.004(3)
C(13)	0.027(3)	0.031(3)	0.031(3)	-0.006(2)	0.007(2)	-0.006(2)
C(14)	0.039(3)	0.070(4)	0.042(3)	-0.011(3)	0.017(3)	-0.017(3)
C(15)	0.030(3)	0.035(3)	0.027(3)	-0.001(2)	0.005(2)	-0.006(2)
C(16)	0.042(3)	0.035(4)	0.047(3)	0.000(3)	-0.005(3)	0.002(3)
C(17)	0.049(4)	0.030(4)	0.058(4)	-0.003(3)	-0.008(3)	-0.010(3)
C(18)	0.030(3)	0.043(4)	0.046(3)	-0.004(3)	0.004(3)	-0.018(3)
C(19)	0.052(4)	0.051(4)	0.031(3)	-0.004(3)	-0.004(3)	-0.002(3)
C(20)	0.052(4)	0.041(4)	0.033(3)	-0.009(3)	0.002(3)	-0.004(3)

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(Å)

atom	atom	distance	atom	atom	distance
I1	C13	2.141(4)	CL	C18	1.742(5)
O1	C1	1.338(5)	O1	C4	1.475(5)
O2	C1	1.196(5)	O3	C3	1.435(5)
O3	C15	1.392(5)	O4	C7	1.224(5)
O5	C9	1.428(5)	O5	C10	1.425(5)
N1	C7	1.358(5)	N1	C8	1.464(6)
N1	C11	1.453(5)	C1	C2	1.517(6)
C2	C3	1.515(6)	C2	C12	1.510(6)
C3	C4	1.555(6)	C4	C5	1.522(6)
C4	C13	1.518(6)	C5	C6	1.522(6)
C6	C7	1.536(6)	C6	C14	1.542(6)
C8	C9	1.513(7)	C10	C11	1.505(6)
C15	C16	1.365(7)	C15	C20	1.375(7)
C16	C17	1.387(7)	C17	C18	1.373(7)
C18	C19	1.367(7)	C19	C20	1.388(6)

Table 4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
C2	H1	0.95	C3	H2	0.95
C5	H3	0.95	C5	H4	0.95
C6	H5	0.95	C8	H6	0.95
C8	H7	0.95	C9	H8	0.95
C9	H9	0.95	C10	H10	0.95
C10	H11	0.95	C11	H12	0.95
C11	H13	0.95	C12	H14	0.95
C12	H15	0.95	C12	H16	0.95
C13	H17	0.95	C13	H18	0.95
C14	H19	0.95	C14	H20	0.95
C14	H21	0.95	C16	H22	0.95
C17	H23	0.95	C19	H24	0.95
C20	H25	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C1	O1	C4	111.6(3)	C3	O3	C15	119.0(3)
C9	O5	C10	110.3(4)	C7	N1	C8	127.4(4)
C7	N1	C11	120.4(4)	C8	N1	C11	112.0(4)
O1	C1	O2	121.2(4)	O1	C1	C2	110.5(4)
O2	C1	C2	128.3(5)	C1	C2	C3	100.9(4)
C1	C2	C12	113.3(4)	C3	C2	C12	118.6(4)
O3	C3	C2	114.2(4)	O3	C3	C4	108.3(3)
C2	C3	C4	103.7(3)	O1	C4	C3	101.6(3)
O1	C4	C5	103.5(4)	O1	C4	C13	108.9(3)
C3	C4	C5	115.4(3)	C3	C4	C13	110.8(4)
C5	C4	C13	115.2(4)	C4	C5	C6	117.7(4)
C5	C6	C7	111.5(4)	C5	C6	C14	108.9(4)
C7	C6	C14	107.7(4)	O4	C7	N1	121.8(4)
O4	C7	C6	120.1(4)	N1	C7	C6	118.0(4)
N1	C8	C9	109.6(4)	O5	C9	C8	111.1(4)
O5	C10	C11	111.2(4)	N1	C11	C10	110.6(4)
I1	C13	C4	114.4(3)	O3	C15	C16	115.8(4)
O3	C15	C20	124.3(4)	C16	C15	C20	119.9(5)
C15	C16	C17	121.4(5)	C16	C17	C18	118.4(5)
CL	C18	C17	119.6(4)	CL	C18	C19	119.6(4)
C17	C18	C19	120.7(5)	C18	C19	C20	120.4(5)
C15	C20	C19	119.2(5)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C1	C2	H1	107.8	C3	C2	H1	107.8
C12	C2	H1	107.8	O3	C3	H2	110.0
C2	C3	H2	110.1	C4	C3	H2	110.2
C4	C5	H3	107.3	C4	C5	H4	107.3
C6	C5	H3	107.5	C6	C5	H4	107.4
H3	C5	H4	109.5	C5	C6	H5	109.7
C7	C6	H5	109.5	C14	C6	H5	109.6
N1	C8	H6	109.4	N1	C8	H7	109.4
C9	C8	H6	109.5	C9	C8	H7	109.4
H6	C8	H7	109.4	O5	C9	H8	109.1
O5	C9	H9	109.0	C8	C9	H8	109.2
C8	C9	H9	109.0	H8	C9	H9	109.4
O5	C10	H10	109.1	O5	C10	H11	109.0
C11	C10	H10	109.0	C11	C10	H11	109.0
H10	C10	H11	109.5	N1	C11	H12	109.2
N1	C11	H13	109.3	C10	C11	H12	109.1
C10	C11	H13	109.1	H12	C11	H13	109.5
C2	C12	H14	109.3	C2	C12	H15	109.4
C2	C12	H16	109.3	H14	C12	H15	109.6
H14	C12	H16	109.6	H15	C12	H16	109.5
I1	C13	H17	108.3	I1	C13	H18	108.3
C4	C13	H17	108.2	C4	C13	H18	108.2
H17	C13	H18	109.4	C6	C14	H19	109.4
C6	C14	H20	109.3	C6	C14	H21	109.3
H19	C14	H20	109.6	H19	C14	H21	109.7
H20	C14	H21	109.6	C15	C16	H22	119.3
C17	C16	H22	119.3	C16	C17	H23	120.8
C18	C17	H23	120.8	C18	C19	H24	119.7
C20	C19	H24	119.8	C15	C20	H25	120.5
C19	C20	H25	120.4				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
I1	C13	C4	O1	64.1(4)	I1	C13	C4	C3	175.0(3)
I1	C13	C4	C5	-51.6(4)	CL	C18	C17	C16	179.3(4)
CL	C18	C19	C20	-179.0(4)	O1	C1	C2	C3	23.0(4)
O1	C1	C2	C12	150.8(4)	O1	C4	C3	O3	153.3(3)
O1	C4	C3	C2	31.6(4)	O1	C4	C5	C6	-175.8(3)
O2	C1	O1	C4	176.2(4)	O2	C1	C2	C3	-155.9(5)
O2	C1	C2	C12	-28.0(7)	O3	C3	C2	C1	-150.3(3)
O3	C3	C2	C12	85.3(5)	O3	C3	C4	C5	-95.5(4)
O3	C3	C4	C13	37.8(5)	O3	C15	C16	C17	176.8(5)
O3	C15	C20	C19	-176.4(5)	O4	C7	N1	C8	-175.2(4)
O4	C7	N1	C11	-1.8(7)	O4	C7	C6	C5	-23.8(6)
O4	C7	C6	C14	95.6(5)	O5	C9	C8	N1	56.9(5)
O5	C10	C11	N1	-55.7(5)	N1	C7	C6	C5	158.6(4)
N1	C7	C6	C14	-82.0(5)	C1	O1	C4	C3	-18.2(4)
C1	O1	C4	C5	-138.2(3)	C1	O1	C4	C13	98.8(4)
C1	C2	C3	C4	-32.6(4)	C2	C1	O1	C4	-2.8(5)
C2	C3	O3	C15	-85.0(5)	C2	C3	C4	C5	142.8(4)
C2	C3	C4	C13	-83.9(4)	C3	O3	C15	C16	158.2(4)
C3	O3	C15	C20	-23.3(6)	C3	C4	C5	C6	74.2(5)
C4	C3	O3	C15	159.9(3)	C4	C3	C2	C12	-156.9(4)
C4	C5	C6	C7	-78.4(5)	C4	C5	C6	C14	162.9(4)
C6	C5	C4	C13	-57.1(5)	C6	C7	N1	C8	2.4(7)
C6	C7	N1	C11	175.8(4)	C7	N1	C8	C9	119.9(5)
C7	N1	C11	C10	-120.7(5)	C8	N1	C11	C10	53.6(5)
C8	C9	O5	C10	-59.9(5)	C9	O5	C10	C11	59.0(5)
C9	C8	N1	C11	-54.0(5)	C15	C16	C17	C18	0.8(8)
C15	C20	C19	C18	-1.4(8)	C16	C15	C20	C19	2.1(8)
C16	C17	C18	C19	-0.1(8)	C17	C16	C15	C20	-1.8(8)
C17	C18	C19	C20	0.4(8)					

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O1	O2	3.362(4)	75603	O2	C1	3.112(5)	75603
O2	C13	3.268(5)	75603	O2	C10	3.314(6)	75703
O2	C2	3.399(5)	75603	O2	O2	3.415(6)	75603
O4	C12	3.352(6)	75703	O4	C3	3.412(5)	75703
O4	O4	3.421(6)	75703	O5	C13	3.338(6)	4
O5	C8	3.432(5)	4	C1	C1	3.250(9)	75603

References

(1) We use the term ‘tandem’ or ‘domino’ as defined by Ho to mean “two or more reactions whose occurrence is in a specific order, see: Ho, T. L. *Tandem Organic Reactions;* Wiley-Interscience: New York, 1992.

(2) For comprehensive reviews on tandem transformations, see: (a) Ho, T. L. *Tandem Organic Reactions;* Wiley-Interscience: New York, 1992. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(3) See Chapter 1 for a discussion of the Claisen rearrangement and references therein.

(4) For a review of tandem reactions involving the Claisen rearrangement, see: Ho, T. L. *Tandem Organic Reactions;* pp 346–351; Wiley-Interscience: New York, 1992.

(5) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426–12427.

(6) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979.

(7) See Chapters 1 and 2 for discussion of the ketene-Claisen and acyl-Claisen rearrangement, respectively.

(8) Kaden, S.; Hiersemann, M. *Synlett* **2002**, 1999–2002.

(9) Magriotis, P. A.; Kim, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2972–2973.

(10) Frank, S. A.; Works, A. B.; Roush, W. R. *Can. J. Chem. Rev. Can. Chim.* **2000**, *78*, 757–771.

(11) Ovaska, T. V.; Roses, J. B. *Org. Lett.* **2000**, *2*, 2361–2364.

(12) Hiratani, K.; Takahashi, T.; Kasuga, K.; Sugihara, H.; Fujiwara, K.; Ohashi, K. *Tetrahedron Lett.* **1995**, *36*, 5567–5570.

(13) Hiratani, K.; Kasuga, K.; Goto, M.; Uzawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 12677–12678.

(14) Hiratani, K.; Suga, J.; Nagawa, Y.; Houjou, H.; Tokuhisa, H.; Numata, M.; Watanabe, K. *Tetrahedron Lett.* **2002**, *43*, 5747–5750.

(15) Yang, G.; Matsuzono, S.; Koyama, E.; Tokuhisa, H.; Hiratani, K. *Macromolecules* **2001**, *34*, 6545–6547.

(16) See Chapter 2.

(17) Tidwell, T. T. *Ketenes* Wiley; New York, 1995.

(18) For examples of A(1,2) strain directed reactions, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(19) Determined by single crystal X-ray analysis of an acid derivative, see experimental methods for more details.

(20) This reaction was also conducted at – 40 °C. The major product observed at this temperature was the results of a single, rather than tandem, Claisen rearrangement.

(21) Reaction of benzolyoxy acid chloride affords the respective tandem adduct in good yields, but modest selectivity (75%, 4:1 dr). Other acid chlorides (R_2 = OTBDPS, OAc) demonstrated good diastereoselectivity (>95:5) albeit in modest conversion to the desired product (less than 50%).

(22) Macrolide Antibiotics. Chemistry, Biology, and Practice; Omura, S., Ed,; Academic Press: Orlando FL, 1984.

(23) Metz, P. *Tetrahedron* **1993,** *49,* 6367.

(24) For examples of A(1,2) strain directed reactions, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(25) Low level molecular mechanic modeling (MM2) calculations reveal that the carbonyl of the α,β-substituted amide is closer in proximity to the alkene (than the other amide carbonyl) by 0.87 angstroms.

(26) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

(27) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

(28) Thomas, W.B.; McElvain, S.M. *J. Am. Chem. Soc.* **1934,** *56,* 1806.

(29) Werner, D. S.; Stephenson, G. *Liebigs Ann.* **1996**, 1705.

(30) Boeckman, R. K.; Ko S.S. *J. Am. Chem. Soc.* **1982,** *104,* 1033.

(31) Olofson R. A.; Dang, V. A. *J. Org. Chem.* **1990,** *58,* 1.