Novel Variants of the Zwitterionic Claisen Rearrangement and the Total Synthesis of Erythronolide B

Thesis by
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Abstract

This dissertation describes the development of three novel variants of the zwitterionic Claisen rearrangement. Initial studies demonstrate an efficient and diastereoselective ketene-Claisen rearrangement catalyzed by metal salts. This process involves the condensation of ketenes and allylic amines to form zwitterionic enolates which undergo [3,3]-sigmatropic rearrangements to afford α,β-disubstituted-γ,δ-unsaturated amides. The scope of this chemistry is further expanded through the development of a Lewis acid–catalyzed acyl-Claisen rearrangement which employs acid chlorides as ketene surrogates. Based on these studies, a new tandem acyl-Claisen rearrangement for the construction of structurally complex 1,7-dioxo-acyclic architectures is achieved. The versatility of this tandem transformation for macrolide antibiotic synthesis is demonstrated through a concise total synthesis of erythronolide B, in 24 linear steps.

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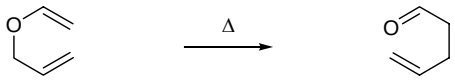
Chapter 1

The Lewis Acid–Catalyzed Ketene-Claisen Rearrangement

Introduction

In 1912, Claisen discovered that, at elevated temperatures, allyl vinyl ethers undergo a [3,3]-sigmatropic rearrangement to form γ,δ-unsaturated carbonyl compounds (equation 1).[1] Many elegant versions of this rearrangement have since been developed by Caroll, Eschenmoser, Johnson, Ireland, Bellus and others.[2] Consequently, the Claisen rearrangement now represents one of the most well-characterized and efficient methods available for the diastereoselective synthesis of structurally complex organic molecules. However, the development of enantioselective catalytic Claisen variants remains a valuable and challenging goal in synthetic chemistry.[3]



(eq. 1)

Asymmetric induction in the Claisen rearrangement has been achieved by the use of remote stereocontrol in chiral precursors or chiral auxillaries attached at various positions on the allyl vinyl ether.[2] In recent years, noteworthy enantioselective variants of the Claisen process involving external sources of chirality have also been achieved, by exploiting charge accelerated Claisen rearrangements.[3] While the thermal sigmatropic rearrangement of ally vinyl ethers require high temperatures (150 to 200 °C), charge accelerated rearrangements occur at temperatures as low as –78 °C. Incorporation of

either negative charge (at position 2a) or positive charge (at position 3) has been shown to facilitate this pericylic process (Figure 1).[2]

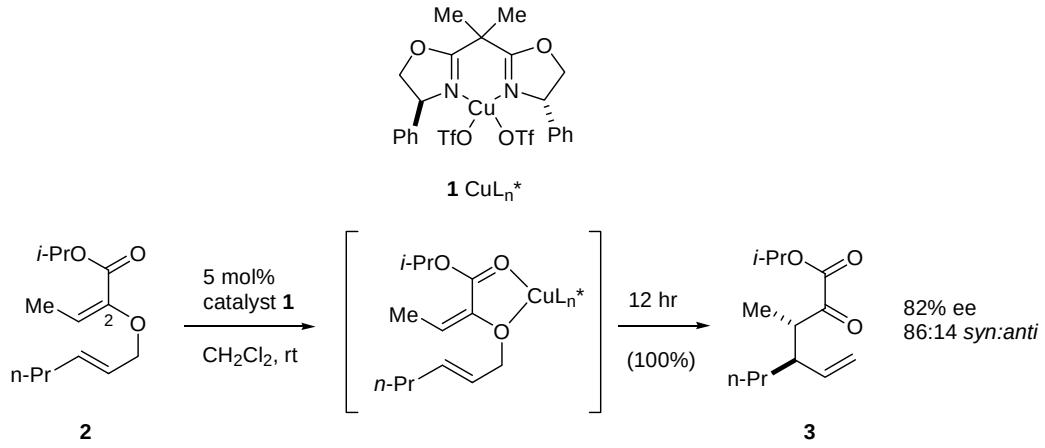
anion-accelerated
Ireland Claisen

cation accelerated
oxonia-Claisen

Figure 1. Charge-acceleration in the Claisen rearrangement

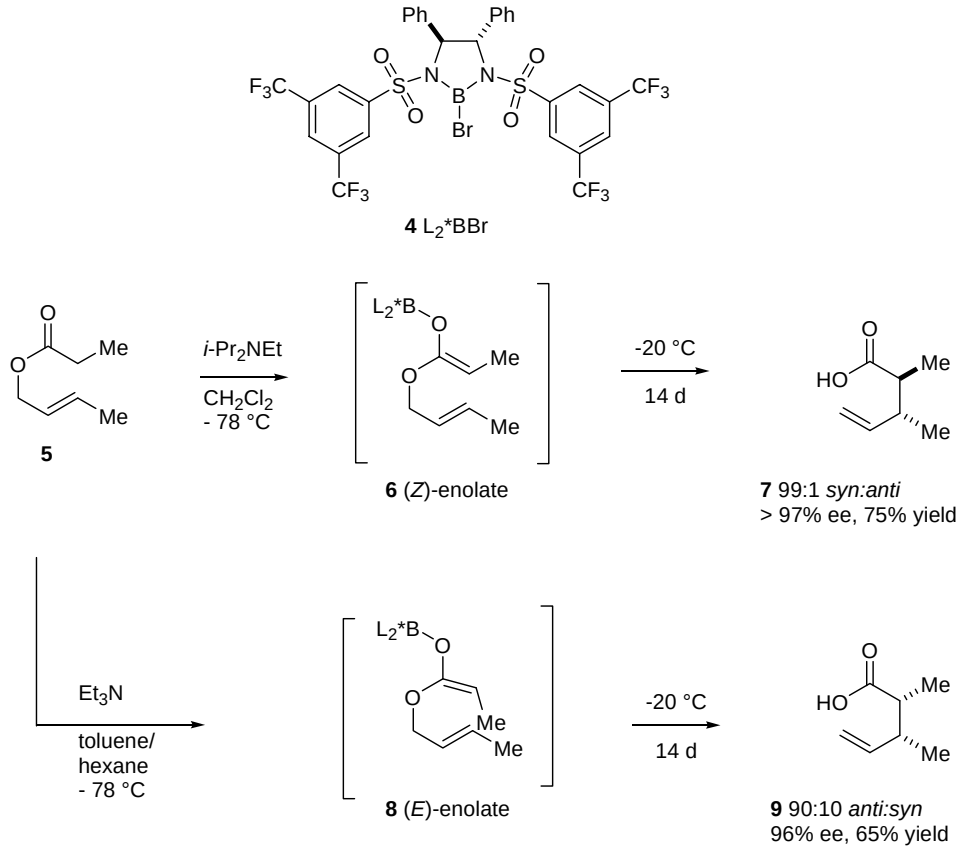
Despite the efforts of many research groups, only one asymmetric catalytic variant of the Claisen rearrangement has been demonstrated to date. In 2002, Hiersemann achieved the first enantioselective cation-accelerated Claisen rearrangement of allyl vinyl ethers (**1**) catalyzed by the copper bisoxazaline (**2**) to provide esters (**3**) (Scheme 1).[4] For acceptable levels of enantioselectivity to be obtained (72 to 88% e.e.), a chelating ester at the 2-position in the allyl vinyl ether substrates (**1**) is required. Although a breakthrough achievement, the inherent substrate limitation and the non-trivial synthesis of these precursors hinder the generality and synthetic utility of this method.

Scheme 1. First enantioselective catalytic Claisen rearrangement (Hiersemann, 2002)



Notably, a highly enantioselective and diastereoselective version of the Ireland-Claisen rearrangement of achiral esters has been developed by Corey (Scheme 2).[5] In the presence of the stillbenediamine derived bis(sulfonamide)boron Lewis acid **4**, crotyl propionate **5** is deprotonated by *i*-Pr_2NEt at –78 °C to furnish the (*Z*)-enolate **6** which upon warming rearranges to the *syn*-2,3-dimethyl-5-hexenoic acid **7** (97% e.e. and 99:1 dr). By simply changing the solvent system and the tertiary amine used for enolate formation, the (*E*)-enolate **8** can be accessed which subsequently rearranges to afford the *anti* isomer **9** in excellent enantio- and diastereoselectivity.

Scheme 2. Corey's enantioselective Ireland-Claisen promoted by boron complex **4**



Corey successfully applied this transformation in the total syntheses of natural products (+) fuscol[6] and dolabellatrienone.[7] Unfortunately, in addition to extended reaction times required (14 days), this methodology requires stoichiometric amounts of the chiral complex **4**. Turnover of the complex in this process is most likely inhibited by the formation of a stable boron-carboxylate complex **10** as the immediate product of the rearrangement (Figure 2).

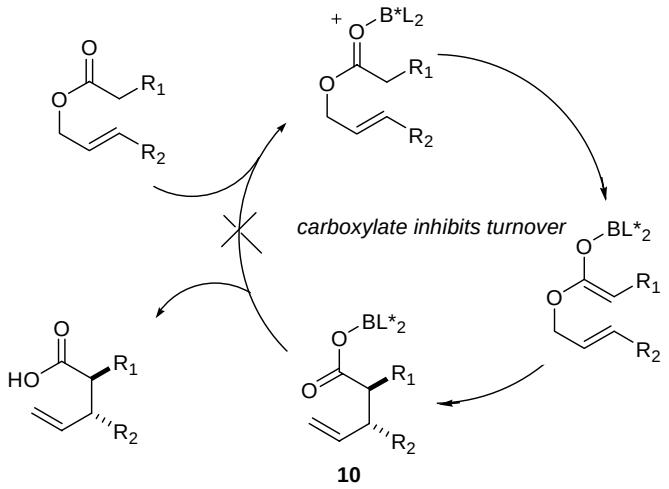


Figure 2. Carboxylate **10** inhibits catalytic turnover

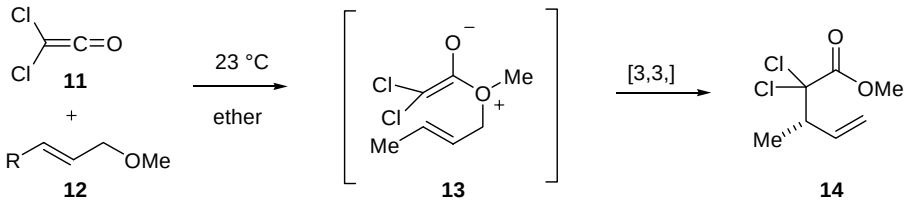
The development of enantioselective catalytic Claisen rearrangements with general synthetic versatility remains a valuable, yet unrealized goal. Our approach to this challenge begins with the design of a novel Claisen rearrangement that is amenable to Lewis acid catalysis (in contrast to the Ireland-Claisen reaction), and has greater substrate scope and a more facile starting material synthesis than the metal-catalyzed oxonia-Claisen methodology.

Reaction Design

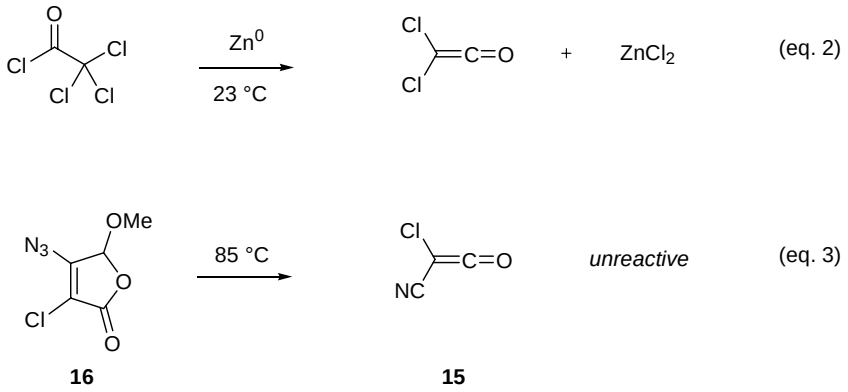
This research program was inspired by the conceptually novel ketene-Claisen rearrangement reported by Bellus in 1978 (Scheme 3).[8] Although expecting dichloroketene (**11**) and allyl ether (**12**) to participate in a [2+2] cycloaddition, the authors found instead that these reagents condense to form a zwitterionic enolate (**13**) which subsequently undergoes [3,3]-sigmatropic rearrangement to form γ,δ-unsaturated esters (**14**). The range of ketenes that could be used was reported to be limited to only

highly electron deficient ketenes, such as dichloroketene and chloro(trichloroethyl)ketene.

Scheme 3. Ketene-Claisen rearrangement by Bellus (1978)



However, detailed inspection of these reports revealed that the desired Claisen process occurred only when ketenes were generated *in situ* by the zinc-promoted dehalogenation of α-chloro acid chlorides, forming zinc(II) chloride as a byproduct (equation 2). For example, the highly electron deficient chlorocyanoketene **(15**) generated by thermolysis of lactone **16**, fails to participate in the ketene-Claisen rearrangement, even at elevated temperatures (equation 3).

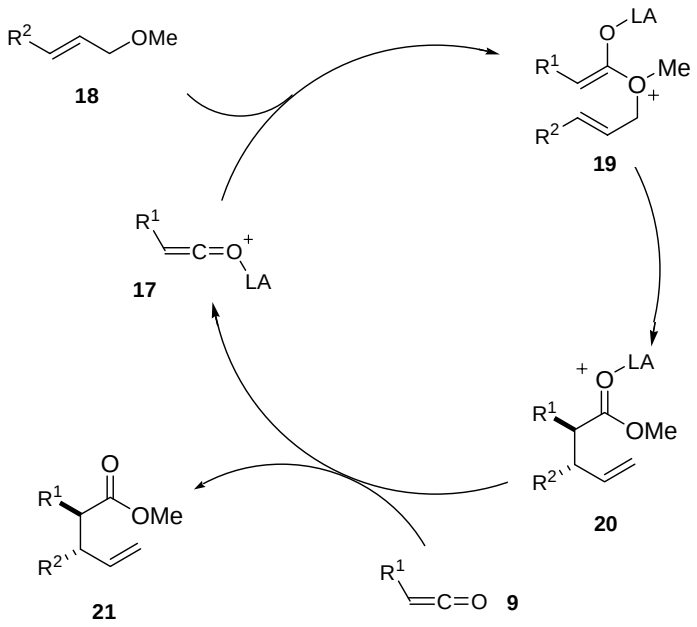


Based on these observations, we speculated that zinc chloride was a key component in this process, possibly activating the ketene towards nucleophilic attack. As such, we recognized the potential to use chiral Lewis acids as an attractive platform to induce asymmetry in the ketene-Claisen rearrangement. In contrast to Corey's boron-

mediated ester enolate Claisen reaction, where the anionic carboxylate product binds irreversibly to the boron Lewis acid, the product of the ketene-Claisen reaction is a neutral ester species which should therefore readily dissociate from a variety of Lewis acidic metals

As shown in Scheme 4, we envisioned that a range of ketenes **9** could undergo Lewis-acid activation (see **17**) and condense with allyl vinyl ethers **18** to produce zwitterionic allyl–vinyl oxonium complexes **19** which would subsequently undergo [3,3]-sigmatropic rearrangement to afford the metal-bound ester **20**. Dissociation of the neutral ester product **21** would regenerate the catalytically active Lewis acid species.

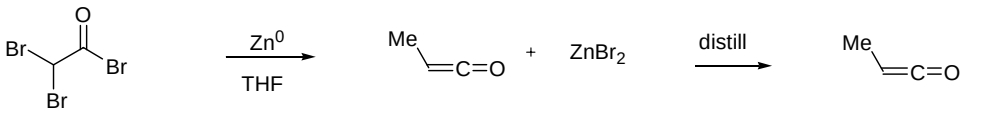
Scheme 4. Proposed Lewis acid–catalyzed ketene-Claisen rearrangement



Results and Discussion

In order to test whether or not the Lewis acid plays a catalytic role in the ketene-Claisen rearrangement, the ketene component needed to be isolated free from any salt byproducts prior to use. This was accomplished by Ward's procedure;[9] treatment of bromoacetyl bromide (**22**) with zinc produces methylketene (**23**) which can be co-distilled to provide a methylketene solution in THF (Scheme 5).

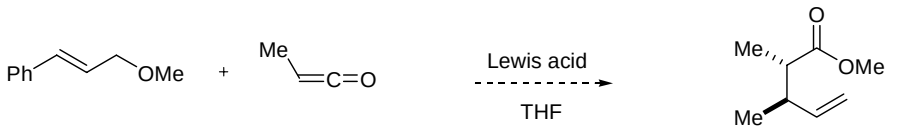
Scheme 5. Ward procedure for synthesizing methyl ketene



22 **23** *(**23** in THF)*

Our proposed ketene-Claisen rearrangement was first examined using cinnamyl methyl ether **24** and methylketene **23** (Scheme 6). In the presence of a variety of Lewis acids, the ether **24** failed to react with methylketene to produce the desired Claisen product **25** (Scheme 6).[10]

Scheme 6. Attempted Lewis acid–catalyzed ketene-Claisen rearrangement of **24**



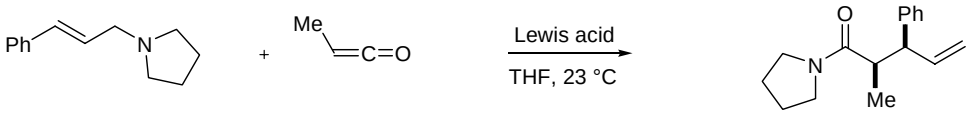
24 **23** **25** *not observed*

We reasoned that the allyl ether was not nucleophilic enough to condense with methyl ketene—a less electrophilic ketene than the halogenated ketenes used by Bellus. As a result, we considered using a more reactive nucleophile, such as an allylic amine.

The ability of allylic tertiary amines to participate in the ketene-Claisen has been previously studied by several groups.[11]

To our delight, we observed that cinammyl pyrrolidine **26** and methylketene **23** undergo an efficient ketene-Claisen rearrangement at room temperature under the influence of Lewis acids to provide Claisen adducts **27** (Table 1). A variety of oxophilic metal salts efficiently promote this transformation when used in stoichiometric amounts, including $ZnBr_2$, $AlMeCl_2$, $MgBr_2$, and $Yb(OTf)_2$ (entries 6–9). Moreover, this procedure can indeed be performed using catalytic quantities of Lewis acid with $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$, $TiCl_4$, and $ZnBr_2$ (entries 2-5).

Table 1. Lewis acid–promoted ketene-Claisen rearrangement between cinnamyl pyrrolidine and methyl ketene



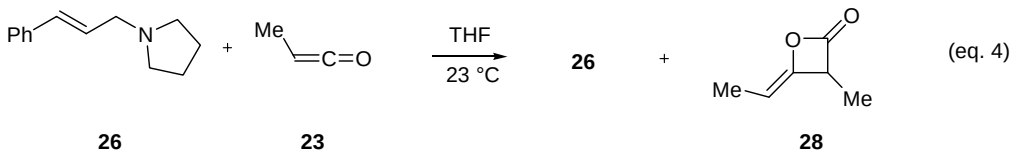
26 **23** **27**

entry	Lewis acid	equiv	% conv[a]	*syn:anti*[b]
1	--	--	NR	--
2	$AlCl_3$	0.20	90	>99:1
3	$TiCl_2(O\textit{i}\text{-}Pr)_2$	0.20	88	>99:1
4	$TiCl_4$	0.10	80[c]	>99:1
5	$ZnBr_2$	0.20	60	>99:1
6	$ZnBr_2$	1.0	89	>99:1
7	$AlMeCl_2$	1.0	80	>99:1
8	$MgBr_2$	1.0	80	>99:1
9	$Yb(OTf)_2$	1.0	90	>99:1

[a] Conversion based on ^{1}H NMR analysis of the unpurified reaction mixture. [b] Product ratios determined by GLC using a Bodman CC1701 column.

Role of the Lewis acid. The success of the ketene-Claisen rearrangement is contingent on the use of Lewis acids. In experiments conducted without metal salts, Claisen product **27** was not observed (Table 1, entry 1). Instead, these experiments

resulted in the recovery of the starting amine **26** and isolation of a β-lactone product **28** (equation 4).



26 **23** **28**

Product **28** presumably arises from the dimerization of methylketene, by a pathway known to be catalyzed by tertiary amines.[12] As shown in Figure 3, in the absence of Lewis acids, allyl amine **26** condenses with ketene **23** to form a zwitterionic enolate **29** which adds to a second equivalent of ketene **23**. The resulting zwitterionic intermediate **30** eventually undergoes intramolecular cyclization via **31** to form the observed ketene dimer **28**.

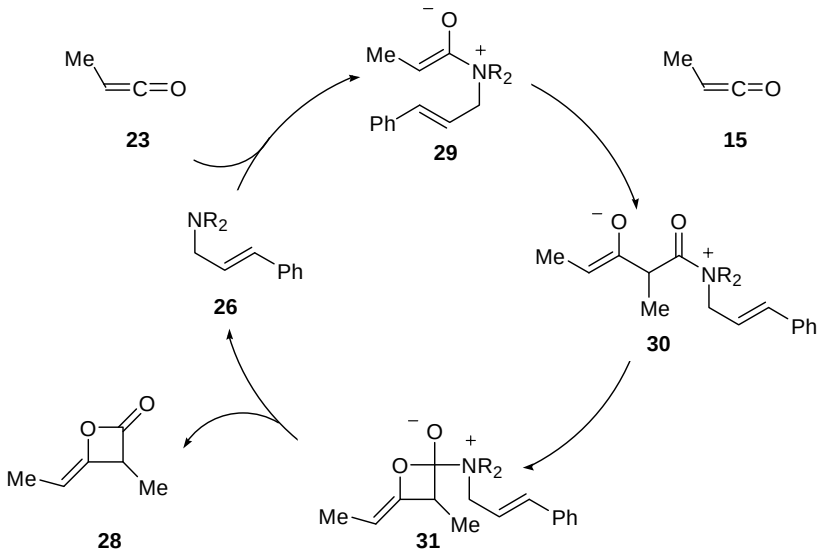
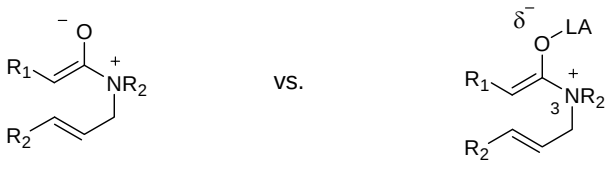


Figure 3. Amine catalyzed ketene dimerization pathway

As such, contrary to what we had previously speculated, the Lewis acid does not appear necessary for activation of ketene towards nucleophilic addition by allyl pyrrolidine. *What role then does the Lewis acid play in catalyzing the ketene-Claisen*

rearrangement? We proposed that binding of the Lewis acid to the resulting allyl-vinyl ammonium complex **29** helps deter ketene dimerization by attenuating the nucleophilicity of this zwiterrionic enolate (Figure 4). In addition, the Lewis acid bound zwitterion **32** is presumably more activated towards [3,3]-sigmatropic rearrangement than zwitterions **29** because **32** posses greater cationic character at the 3 position. This increased positive charge should accelerate rearrangement, as in the cation-accelerated oxonia Claisen (see Figure 1).



29 favors ketene dimerization

32 favors [3,3] rearrangement

Figure 4. Role of the Lewis acid (LA) in catalyzing the ketene-Claisen rearrangement

Origins of stereoselectivity. This new Lewis acid–catalyzed ketene-Claisen rearrangement was found to be highly stereoselective (Table 1, entries 2–9). Based on GC and ^{1}H NMR analysis, the *syn* diastereomer was observed to be favored over the *anti* isomer with >99:1 diastereoselectivity in the presence of every Lewis acids that was successful in this rearrangement. The high levels of stereoselectivity observed result from two sequential and highly selective steps.

First, addition of nucleophiles to monosubstituted ketenes usually results in exclusive formation of the (*Z*)-enolate (Figure 5).[13] As the lowest unoccupied molecular orbital (LUMO) is the C=O π^* orbital that lies in the plane defined by the ketene,[14] nucleophiles encounter a destabilizing steric interaction with the bulky R substituent on

the terminal carbon. Consequently, approach of the nucleophile occurs preferentially from the opposite side to the bulkier substituents, resulting in selective formation of the (*Z*)-enolate.

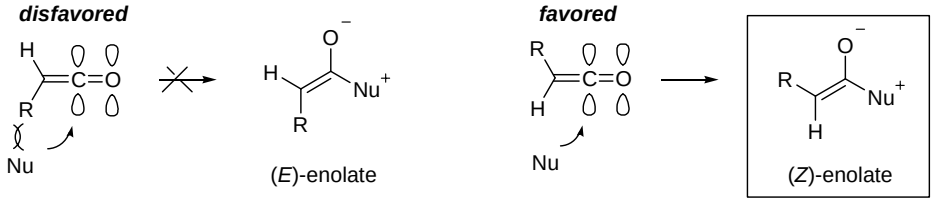


Figure 5. Origins of (*Z*)-enolate geometry control in additions to monosubstituted ketenes

Second, based on previous Claisen studies,[2] we predict that the zwitterionic enolate undergoes rearrangement through a highly ordered chair-like transition state to form the carbon-carbon σ bond in a diastereoselective fashion (Figure 6). The sense of diastereoselectivity is consistent with the model depicted. Notably, as the ketene-Claisen rearrangement proceeds at lower temperatures (room temperature) than a typical thermal aliphatic Claisen rearrangement (150 to 200 °C), higher levels of stereocontrol are achieved (>99:1 *syn:anti*).

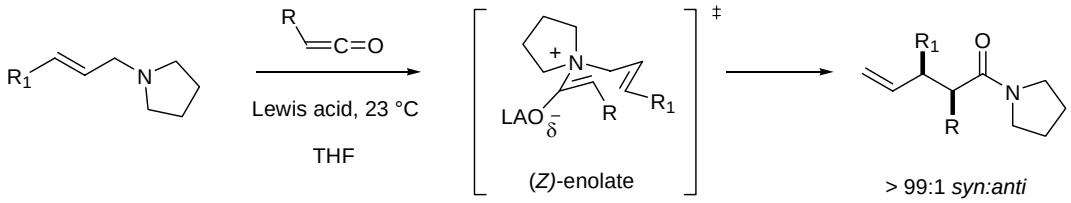
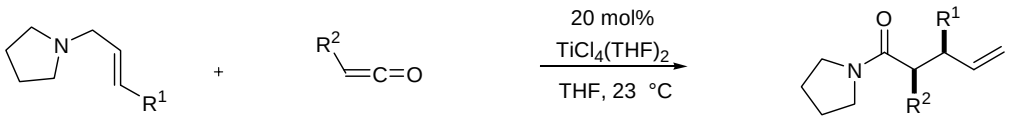


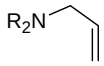
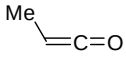
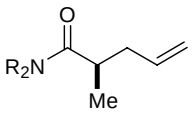
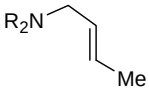
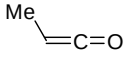
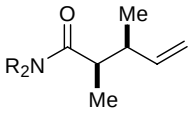
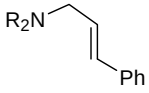
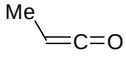
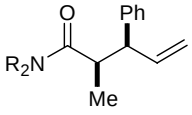
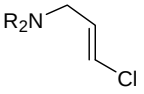
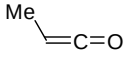
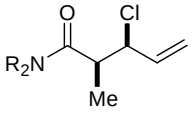
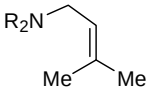
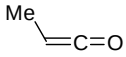
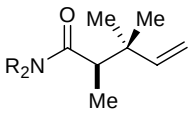
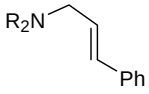
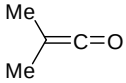
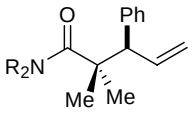
Figure 6. Origins of diastereoselectivity in the ketene-Claisen rearrangement

Scope of the ketene-Claisen rearrangement. Experiments that probe the scope of the ketene-Claisen rearrangement are outlined in Table 2. Variation in the allyl substituent (R = hydrogen, alkyl, aryl or halogen) was possible without loss in yield or diastereoselectivity (> 75% yield, > 99:1 *syn*:*anti*). Notably, access to quaternary carbons

at both the α and β positions to the amide moiety in the Claisen adduct are possible (entry 6 and 5, respectively).

Table 2. Ketene-Claisen rearrangement of representative allyl pyrrolidines

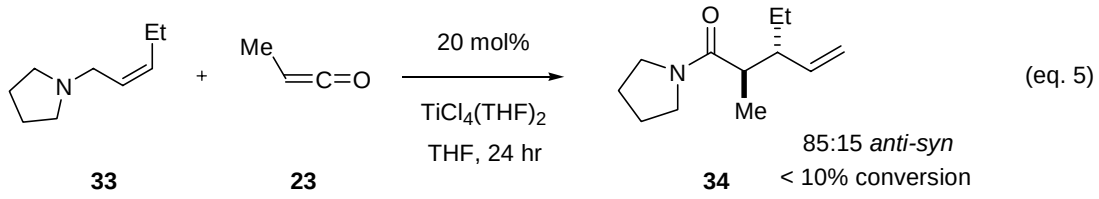


entry	amine[a]	ketene	product[a]	yield	*syn:anti*[b,c]
1				84	--
2				84	>99:1
3				85	>99:1
4				77	>99:1
5				68	--
6				86	--

[a] NR_2 = *N*-pyrrolidine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by chemical correlation to known compounds (See experimental methods).

While excellent levels of *syn* stereoselection and reaction efficiency were observed with *trans*-allyl pyrrolidines (Table 2, entries 2–4, and 6), the *cis*-allylic pyrrolidines react less efficiently. For example, subjecting the (Z)-*N*-2-pentenyl-

pyrrolidine **33** to the standard reaction conditions resulted in only trace amounts of rearrangement product **34** as detected by ^{1}H NMR (equation 5).



These results can be understood by examining the transition states involved in the rearrangement of the *trans*- versus *cis*- allylic pyrrolidines (Figure 7). In the case of the *trans*-crotyl pyrrolidine **35**, a low-energy chair-like transition state **36** is accessible that places all substituents in pseudo-equatorial orientations. However, for the *cis* isomer **37,** the corresponding chair-like transition state **38** positions the R substituent in a pseudoaxial orientation, resulting in destabilization from the resulting 1,3-diaxial interaction of this substituent with the metal-bound enolate oxygen. As such, the rate of rearrangement for **37** to product **39** would be expected to be slower than the rate of rearrangement for the **35** to product **40**. As a consequence, ketene dimerization can compete with the desired rearrangement process, resulting in diminished yields of the desired **39**.

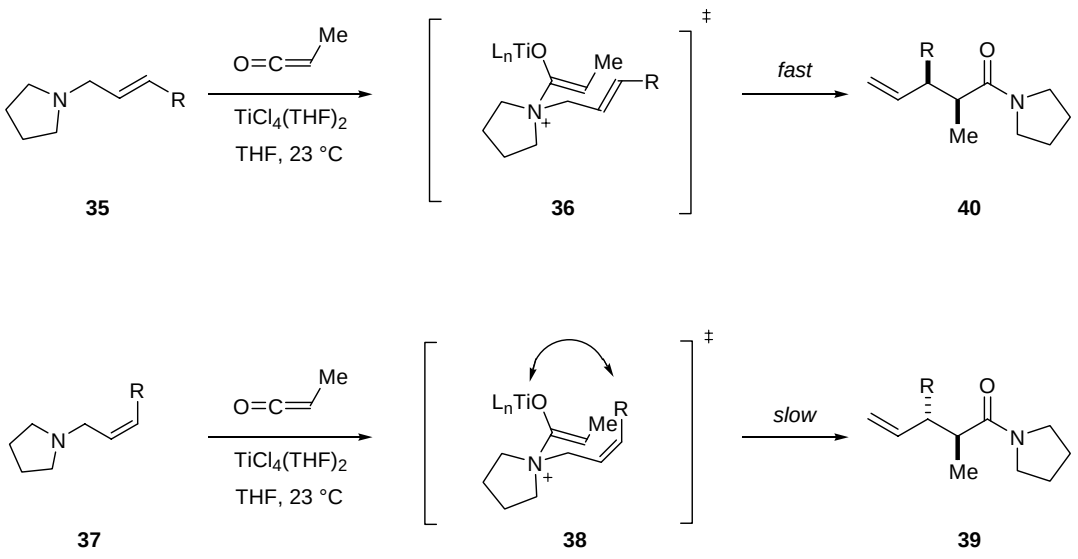


Figure 7. Rationale for relative rates of rearrangement for the *trans* vs. *cis* allyl amines

Concluding Remarks

A novel Lewis acid–catalyzed ketene Claisen rearrangement has been accomplished. A variety of allylic pyrrolidines can be tolerated by this methodology. However, demonstrating diversity in the ketene component was difficult to achieve. In the Ward procedure for generating ketenes, ketenes are isolated by codistillation with ethereal solvents. As such, only ketenes of low molecular weight, such as methylketene or dimethylketene can be accessed by this protocol. This limitation prompted us to explore a new strategy that generates ketenes *in situ* from readily available and bench-stable precursors (Chapter 2).

Experimental Methods

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[15] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N*,*N*-diisopropylethylamine and dichloromethane were distilled from calcium hydride prior to use. Air sensitive solids were dispensed in an inert atmosphere glovebox. 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.[16] 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), AMX-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H 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 are reported in terms of chemical shift. 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 Berkeley Mass Spectral facility. Gas chromatography was performed on Hewlett-Packard 5890A and

6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm).

Methyl ketene (23): Methyl ketene was freshly prepared for each use according to the procedure of Ward.[9] Zinc powder was activated by washing with aqueous 1 *N* HCl, water, methanol and ether, followed by drying *in vacuo*. The activated zinc powder (1.00 g, 15.3 mmol) was suspended in THF in a 100 mL receiving flask and attached to a short path distillation apparatus with a 50 mL Schlenk flask connected to the receiving end. The pressure within the apparatus was reduced to 110 torr. A solution of freshly distilled 2-bromopropionyl bromide (0.52 mL, 5.0 mmol) in THF (3.5 mL) was added dropwise via a 22 gauge Teflon cannula tightened with a metal clamp. The ketene formed immediately and codistilled with the THF. The distillate was collected in the N_2 (l) cooled Schlenk flask. After addition of acid bromide was complete (8–10 minutes), the distillation was continued for another 5 minutes. The distillate was then warmed to –78 ^oC in a CO_2/acetone bath under N_2 (g) resulting in a bright yellow solution which was used without further purification. The IR spectrum of the solution displays an intense ketene band at 2130 cm^{-1}.

General Procedure: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with THF and the allyl pyrrolidine. The solution was stirred for 10 min before the ketene was added in portions of approximately 30 drops every 15 min via a 22 gauge Teflon cannula. Addition of ketene (5–7 mL) was continued (1.5–2 h) until the allyl pyrrolidine was

completely consumed (1.5–2 h) as determined by TLC (5 % Et_3N:EtOAc). The resulting dark red solution was then diluted with ether and aqueous 1 N NaOH. The aqueous layer was then extracted with ether, and the combined organic layers were washed with brine, dried and concentrated. The resulting residue was purified by flash chromatography with 50% Et_2O/hexanes to provide the title compounds.

***N*-(2-Methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 1).** Prepared according to the general procedure from (*E*)-*N*-2-Propenyl pyrrolidine (76 mg, 0.68 mmol), $TiCl_4(THF)_2$, (44 mg, 130 μmol), and methyl ketene to provide the pure product as a yellow oil in 84 % yield (96 mg, 0.57 mmol); IR 2980, 2880, 1629, 1463, 1440, 919 cm^{-1}; ^{1}HNMR (500 MHz) δ 5.76 (m, 1H, C**H**CH_2), 5.05 (dd, *J* = 1.5, 3.4 Hz, 1H, CHC**H**$_2$), 5.01 (dd, J = 1.5, 3.4 Hz, 1H, CHC**H**$_2$), 3.40–3.49 (m, 4H, (C**H**$_2$)$_2$N), 2.57 (m, 1H, C**H**C=O), 2.43 (m, 1H, C**H**$_2$CH=CH_2), 2.11 (m, 1H, C**H**$_2$CH=CH_2), 1.93 (m, 2H, C**H**$_2$$CH_2$N), 1.83 (m, 2H, C**H**$_2$$CH_2$N), 1.10 (d, *J* = 6.8 Hz, 3H, C**H**$_3$CH=O); ^{13}C NMR (125 MHz) δ 174.49, 136.27, 116.30, 46.38, 45.62, 38.02, 37.88, 26.08, 24.26, 16.86; LRMS (FAB) *m/z* 168 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{17}NO)^+$ requires m/z 167.1310, found *m/z* 167.1308.

***N*-(2,3 Dimethyl-4-pentenoyl)-pyrrolidine (Table 2, entry 2).** Prepared according to the general procedure from (*E*)-*N*-2-butenyl pyrrolidine (94.4 mg, 0.753 mmol), $TiCl_4(THF)_2$, (50 mg, 150 μmol), and methyl ketene to provide the pure product as a yellow oil in 84 % yield (114 mg, 0.628 mmol). All spectral data were in complete agreement with those previously reported.[17]

(2R*, 3R*)-*N*-(3-Phenyl-2-methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 3). Prepared according to the general procedure from (*E*)-*N*-3-Phenyl-2-propenyl pyrrolidine (107 mg, 0.571 mmol), $TiCl_4(THF)_2$, (19 mg, 57 μmol), and methyl ketene to provide 80% yield of the pure product (111 mg, 0.46 mmol) as a white solid: mp 85–86 ^oC; IR 2980, 2880, 1629, 1459, 1440, 923 cm^{-1}; ^1H NMR (400 MHz) δ 7.16–7.30 (m, 5H, Ph), 5.95–6.04 (ddd, *J* = 8.05, 10.9, 16.5 Hz, 1H, C**H**CH_2), 4.97 (d, *J* = 0.8 Hz, 1H, CHC**H**$_2$), 4.93–4.94 (m, 1H, CHC**H**$_2$), 3.56 (t, *J* = 9.0 Hz, 1H, C**H**$CH=CH_2$), 3.40–3.47 (m, 4H, (C**H**$_2$)O), 2.87 (m, 1H, C**H**C=O), 1.78–1.91 (m, 4H, C**H**$_2$$CH_2$N), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 173.79, 141.90, 139.76, 128.45, 128.30, 126.44, 115.43, 53.46, 46.59, 45.60, 42.99, 26.01, 24.28, 16.14; LRMS (FAB) *m/z* 244 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}NOH)^+$ requires *m/z* 244.1702, found *m/z* 244.1702; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found C, 79.02; H, 8.41; N, 5.71.

***N*-3-Chloro-2-propenylpyrrolidine (Table 2, entry 4).** Prepared according to the procedure of Butler.[18] (*E*)-1,3 dichloropropene was added dropwise to a refluxing mixture of pyrrolidine (6.3 mL, 110 mmol), $NaHCO_3$ (6.4 g, 76 mmol) and water (6 mL). After stirring the reaction at reflux for 3 h, the organic layer was separated from the aqueous layer and distilled to provide pure product as a colorless oil in 20 % yield (2.2 g, 15 mmol): bp (72 ^oC, 10 torr); IR 2814, 1637, 1455, 1297, 116, 907 cm^{-1}; ^1HNMR (400 MHz) δ 6.15 (dt, *J* = 13.2, 1.2 Hz, 1H, ClC**H**), 6.03 (m, 1H, ClCH=C**H**), 3.10 (d, *J* = 7.0 Hz, 1H, C**H**$_2$CH=CH), 2.50 (m, 4H, $(CH_2)_2N$), 1.80 (m, 4H, (C**H**$_2$$CH_2$)N); ^{13}C NMR

(100 MHz) 131.20, 119.86, 55.71, 53.85, 23.46; δ Anal. Calcd for $C_7H_{12}ClN$: C, 57.73; H, 8.31; N, 9.62. Found C, 57.41; H, 8.66; N, 9.85.

(2*R, 3*R**)-*N*-(3-Chloro-2-methy-4-pentenoyl)-pyrrolidine (Table 2, entry 4).** Prepared according to the general procedure from (*E*)-*N*-3-chloro-2-propenyl pyrrolidine (81.1 mg, 0.557 mmol), $TiCl_4(THF)_2$, (36 mg, 11 μmol), and methyl ketene to provide 77% yield of the pure product (86.4 mg, 0.431 mmol) as a yellow oil; IR 2980, 2880, 1633, 1459, 1440, 934 cm^{-1}; ^1H NMR (500 MHz) δ 5.90 (ddd, *J* = 8.4, 10.2, 16.9 Hz, 1H, C**H**=CH_2), 5.29 (dt, *J* = 16.9, 0.9 Hz, 1H, CH=C**H**$_2$), 5.14 (dd, *J* = 10.3, 19.7 Hz, 1H, CH=C**H**$_2$), 4.50 (t, *J* = 8.8 Hz, 1H, CHCCl), 3.38–3.59 (m, 4H, (C**H**$_2$)$_2$N), 2.83 (m, 1H, CHC=O), 1.79–1.98 (m, 4H, (C**H**$_2$$CH_2$) N, 1.29 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (125 MHz) δ 171.47, 136.37, 117.83, 65.29, 46.74, 45.68, 45.53, 25.97, 24.25, 15.95; LRMS (FAB) *m/z* 201 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{16}ClNO)^+$ requires m/z 201.0920, found *m/z* 201.0917.

(2-Methyl-3,3-dimethyl-4-pentenoyl)-pyrrolidine (Table 2, entry 5). Prepared according to the general procedure from (*E*)-*N*-3-methyl-2-butenyl pyrrolidine (87 mg, 0.62 mmol), $TiCl_4(THF)_2$, (42.0 mg, 126 μmol), and methyl ketene to provide 68% yield of the pure product (81 mg, 0.42 mmol) as a yellow oil; IR 2976, 2880, 1725, 1629, 1455, 1436, 1193, 919 cm^{-1}; ^1H NMR (500 MHz) δ 5.93 (dd, *J* = 10.3, 17.9 Hz, 1H, C**H**=CH_2), 4.95 (dd, *J* = 1.4, 6.2 Hz, 1H, CH=C**H**$_2$), 4.92 (s, 1H, CH=C**H$_2$**), 3.38–3.52 (m, 4H, $(CH_2)_2N$), 2.44 (q, *J* = 7.0 Hz, 1H, (C**H**)C=O), 2.26 (m, 2H, C**H$_2$**CH_2N), 1.86 (m, 2H, C**H$_2$**CH_2N),), 1.07 (s, 3H, $(CH_3)_2C$), 1.03 (d, *J* = 5.6 Hz, 6H, $(CH_3)_2CH$=O); ^{13}C

NMR (100 MHz) δ 174.04, 146.77, 111.25, 47.25, 45.91, 45.52, 39.35, 26.21, 24.71, 24.38, 23.80, 13.06; LRMS (FAB) *m/z* 195 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{12}H_{21}NO)^+$ requires m/z 195.1623, found *m/z* 195.1626.

(2,2 Dimethyl-3-phenyl-4-pentenoyl)-pyrrolidine (Table 2, entry 6). Prepared according to the general procedure from (*E*)-*N*-3-phenyl-2-propenyl pyrrolidine (68 mg, 0.36 mmol), $TiCl_4(THF)_2$, (22 mg, 66 μmol), and dimethyl ketene to provide 86% yield of the pure product (110 mg, 0.46 mmol) as a colorless oil; IR 3057, 2980, 2883, 1602, 1471, 1409 cm^{-1}; ^1H NMR (500 MHz) δ 7.18–7.27 (m, 5H, Ph), 6.30 (m, 1 H, C**H**CH_2), 5.13 (d, *J* = 10.1 Hz, 1H, CH=C**H**$_2$), 5.09 (d, *J* = 16.9 Hz, 1H, CH=C**H**$_2$), 3.64 (d, *J* = 9.6 Hz, 1H, C**H**CH=CH_2), 3.07–3.48 (m, 4H, (C**H**$_2)_2$O), 1.65 (m, 4H, (C**H**$_2$$CH_2)_2$N), 1.27 (s, 3H, $(CH_3)_2$CC=O), 1.22 (s, 3H, $(CH_3)_2$CC=O); ^{13}C NMR (125 MHz) δ 174.86, 141.08, 137.16, 129.09, 127.89, 126.56, 117.09, 57.17, 48.56, 47.36, 27.18, 25.22, 23.61, 22.87; LRMS (FAB) *m/z* 257 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{17}H_{23}NO)^+$ requires m/z 257.1780, found *m/z* 258.1775; Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found C, 79.01; H, 9.28; N, 5.40.

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Chapter 2

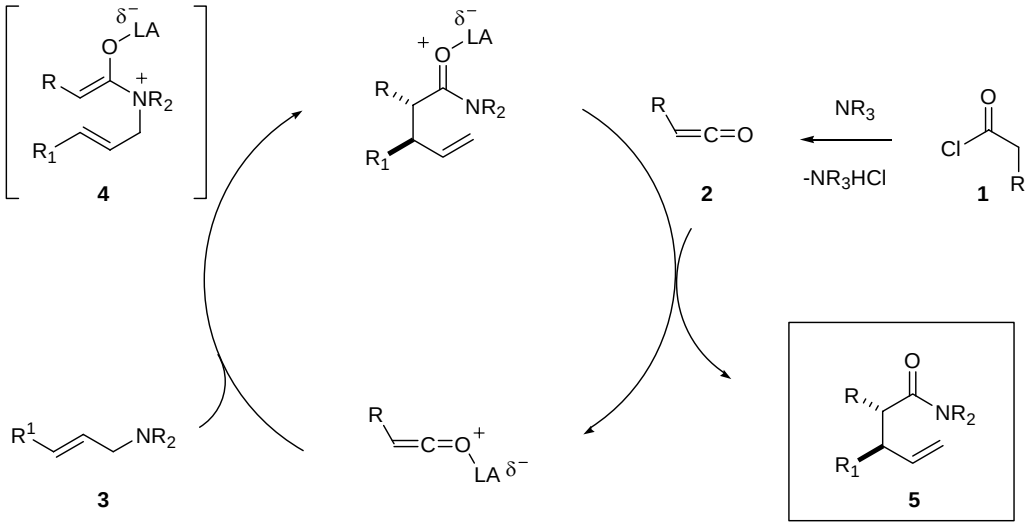
The Lewis acid–Catalyzed Acyl-Claisen Rearrangement[1]

Reaction Design

In the previous chapter, we developed a ketene-Claisen rearrangement that was susceptible to Lewis acid catalysis, and effective with a range of allylic pyrrolidines. The synthetic utility of this method, however, was hampered by difficulties associated with preparing, storing and isolating the inherently unstable ketene. Therefore, we decided to investigate an alternative strategy by generating the ketenes *in situ*. In 1911, Staudinger demonstrated the amine-promoted dehydrohalogenation of acid chlorides to form ketenes.[2,3] We reasoned that acid chlorides could be advantageous as ketene surrogates as they are more readily available and bench-stable precursors.[4] Furthermore, the Ward procedure (Chapter 1) resulted in ethereal ketene solutions, while the Staudinger method would permit the use of non-coordinating solvents less likely to buffer the Lewis acidity of catalytic metal salts.

As illustrated in Scheme 1, we envisioned that a range of acid chlorides (**1**) would undergo amine-promoted dehydrohalogenation to form ketenes (**2**) *in situ*. In the presence of Lewis acids, ketenes (**2**) would undergo addition by tertiary allyl amines (**3**), forming the metal-bound zwitterionic intermediates (**4**). Complex **4** would subsequently undergo [3,3]-sigmatropic rearrangement to afford Claisen products (**5**).

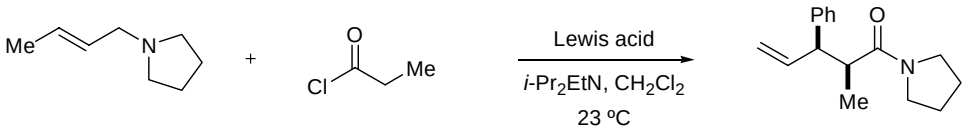
Scheme 1. Proposed Lewis–acid catalyzed acyl-Claisen rearrangement



Results and Discussion

Initial investigations of our proposed Lewis acid–catalyzed acyl-Claisen rearrangement was conducted using crotyl pyrrolidine **6** and propionyl chloride **7** in the presence of Hünig's base and a variety of metal salts (Table 1). This process produces rearrangement product **8** efficiently using one equivalent of Me_2AlCl. Unfortunately, poor efficiency was observed using catalytic amounts of various Lewis acids, with $Yb(OTf)_3$ being the only exception (87% yield, entry 7).[5]

Table 1. Effect of Lewis acid on the acyl–Claisen rearrangement of cinnamyl pyrrolidine



6 **7** **8**

entry	Lewis acid	equivalents	% conversion[a]	*syn:anti*[b]
1	--	--	--	--
2	$AlMe_2Cl$	1.0	94	>991:
3	$AlMe_2Cl$	0.1	34	>99:1
4	$MgBr_2$	0.1	20	>99:1
5	$Zn(OTf)_2$	0.1	<5	>90:1
6	$TiCl_4(THF)_2$	0.1	13	>99:1
7	$Yb(OTf)_3$	0.1	84	>99:1

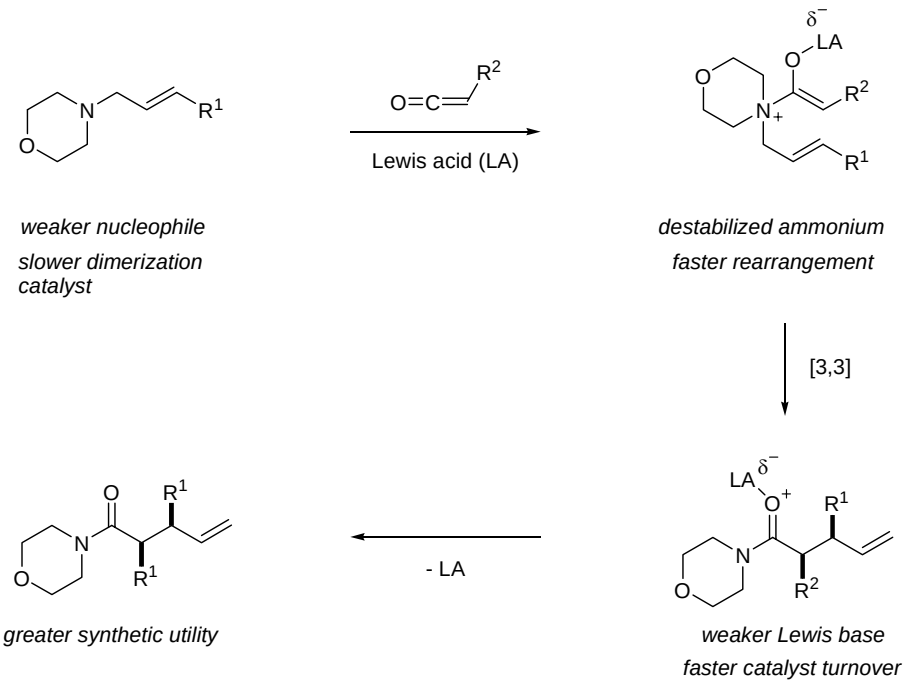
[a] Conversion based on ^1H NMR analysis of the unpurified reaction mixture. [b] Product ratios determined by GLC using a Bodman CC1701 column.

With these initial reaction parameters, competitive consumption of ketene occurs by the pyrrolidine-catalyzed dimerization pathway, resulting in poor conversion to the desired products (see Chapter 1). In the Lewis acid–catalyzed ketene-Claisen rearrangement, the ketene component was used in large excess. As such, ketene dimerization was not detrimental to the efficiency of the reaction with respect to the limiting pyrrolidine reagent. Concerns over the ability of pyrrolidines to dimerize ketenes prompted us to investigate allyl morpholines which might better participate in the acyl-Claisen rearrangement without significantly promoting the nonproductive ketene dimerization process.

N-allyl morpholines appeared to be attractive substrates for further investigation based on many reasons (Scheme 2). First, in comparison to pyrrolidine, the morpholine nitrogen has reduced basicity and nucleophilicity.[6] Consequently, allyl morpholines should be less efficient nucleophilic catalysts for ketene dimerization. Second, the electron-withdrawing effect of the oxygen in the morpholine ring should destabilize the

cationic charge on the nitrogen in the zwitterionic intermediate, and thereby increase the rate of sigmatropic rearrangement. Third, because the resulting morpholine amide products are less Lewis basic than pyrrolidine amides, dissociation of the product from the metal center should be more facile, thus improving catalyst turnover. Finally, morpholine amides own greater synthetic utility than their pyrrolidine counterparts. Similar to Weinreb amides,[7] morpholine-derived amides can be converted to ketones by treatment with alkylmetal nucleophiles,[8] and to aldehydes by reduction with LAH.[9]

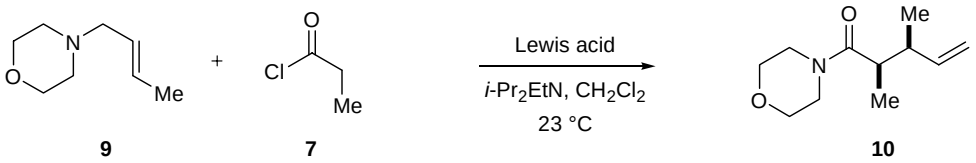
Scheme 2. *N*-allyl morpholines for the acyl-Claisen rearrangement



In contrast to our results with allyl pyrrolidines, the acyl-Claisen strategy was successful using propionyl chloride (**7**) and (*E*)-crotyl morpholine (**9**) in the presence of *i*-Pr_2EtN and *catalytic* amounts of Lewis acids, including $Yb(OTf)_3$, $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ and $TiCl_4(THF)_2$ (cf. Table 1 and Table 2). In all cases the 1,2-disubstituted Claisen

adduct **10** was formed in high yield (>75%, entries 2–5) and with excellent levels of stereocontrol (>99:1 *syn*:*anti*). The excellent levels of diastereoselectivity and catalyst efficiency displayed by $TiCl_4(THF)_2$ defined this metal salt as the optimal catalyst for exploration of this new acyl-Claisen rearrangement.

Table 2. Catalyzed acyl-Claisen rearrangement between crotyl morpholine and propionyl chloride



9 **7** **10**

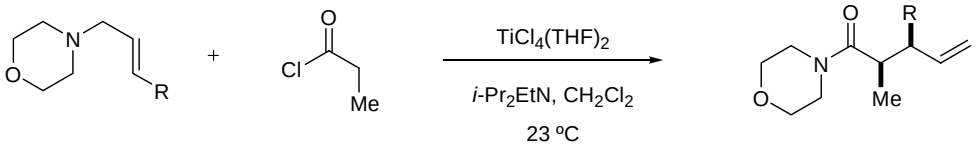
entry	Lewis acid	mol% cat	% yield	*syn*:*anti*[a]
1	--	10	NR	--
2	$Yb(OTf)_3$	10	80	>99:1
3	$AlCl_3$	10	90	>99:1
4	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	10	76	>99:1
5	$TiCl_4(THF)_2$	5	92	>99:1

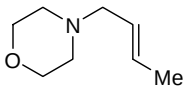
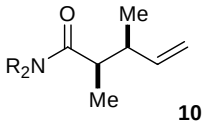
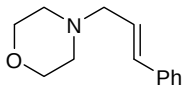
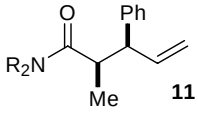
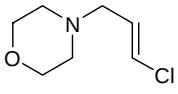
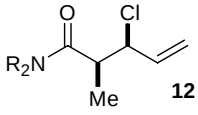
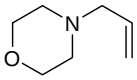
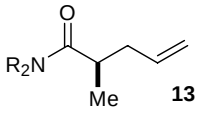
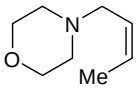
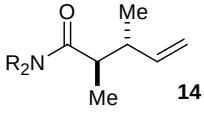
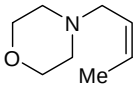
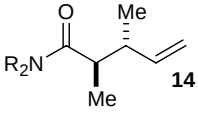
[a] Conversion based on ^{1}H NMR analysis of the unpurified reaction mixture.

Scope of the Acyl-Claisen Rearrangement

Allyl morpholine components. Experiments that probe the scope of the allyl morpholine reaction component are summarized in Table 3. Significant structural variation in the allyl substituent (R_1 = H, alkyl, aryl or halogen, entries 1–4) is possible without loss in yield or diastereoselectivity (>76% yield, >99:1 *syn*:*anti*).

Table 3. Catalyzed acyl–Claisen rearrangement between representative allyl morpholines and propionyl chloride



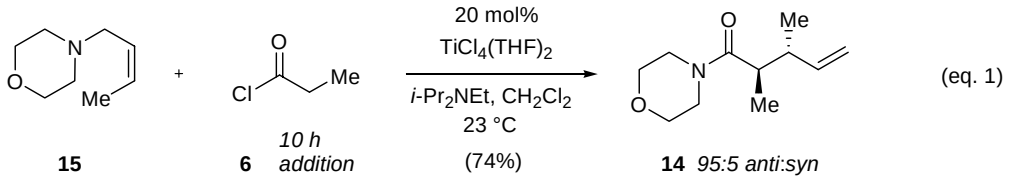
entry	amine	mol% cat	product[a]	yield	*syn:anti* [b,c]
1		5	 **10**	92	>99:1
2		10	 **11**	76	>99:1
3		10	 **12**	95	>99:1
4		10	 **13**	95	>99:1
5	 **15**	10	 **14**	NR	--
6	 **15**	100	 **14**	>95[d]	<5:95[d]

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single crystal X-ray analysis or chemical correlation to a known compound (See Experimental Methods). [d] Conversion and diastereoselectivity determined by 1H NMR analysis of unpurified reaction mixture.

While *trans*-disubstituted allylic morpholines reacted efficiently with propionyl chloride under catalysis of $TiCl_4(THF)_2$, our initial experiment with the corresponding *cis* isomer was unsuccessful (cf. entry 1 and entry 5). However, the desired *anti*-1,2-

dimethyl- substituted Claisen product **14** could be formed when stoichiometric amounts of $TiCl_4(THF)_2$ was used to promote the reaction (entry 6).

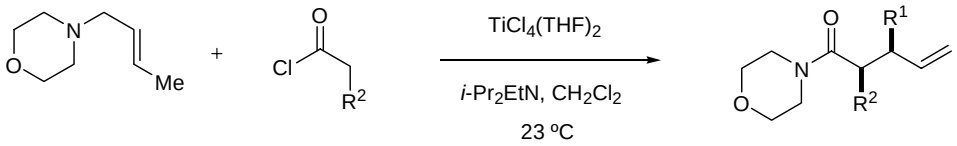
The underlying reason for the failure of the Lewis acid–catalyzed rearrangement of *cis*-crotyl morpholine substrates is non-productive ketene dimerization. We speculated that the ketene-Claisen rearrangement for *cis*-crotyl morpholine could be rendered catalytic in $TiCl_4(THF)_2$, if the rate of ketene dimerization was significantly decelerated. Because ketene dimerization is presumably second-order with respect to ketene, we expected that maintaining a lower concentration of ketene in the reaction solution would inhibit dimerization. Furthermore, we reasoned this could be achieved by slower addition of the acid chloride (i.e., ketene precursor) to the reaction mixture. Indeed, when propionyl chloride is added by syringe pump over the course of 10 h, the reaction of **15** proceeds to give the desired **14** in 74% yield (95:5 *anti:syn*) using 20 mol% $TiCl_4(THF)_2$ (equation 1).

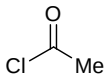
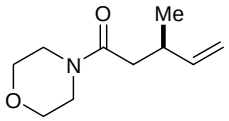
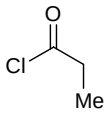
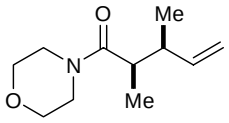
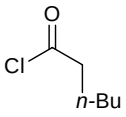
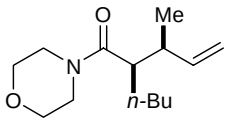
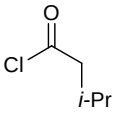
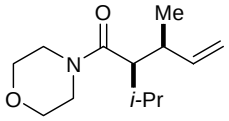
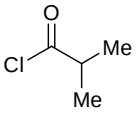
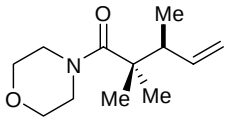


(eq. 1)

Acid chloride components. As shown in Table 4, a variety of sterically unhindered alkyl substituted acid chlorides, such as acetyl chloride, propionyl chloride, and hexenoyl chloride, reacted successfully (entries 1–3). Acid chlorides which are sterically more encumbered were not well tolerated by this process. Isovaleroyl chloride reacts more sluggishly (entry 4), and the α-disubstituted isobutyroyl chloride produced no observable Claisen products (entry 5).

Table 4. Acyl-Claisen rearrangement of allyl morpholines and representative acid chlorides



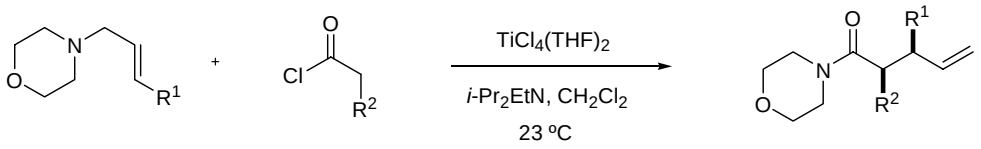
entry	acid-Cl	product	yield	*syn*:*anti*[a,b]
1			81	--
2[c]			92	>99:1
3			93	>99:1
4			28[d]	>99:1
5			NR	--

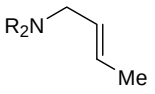
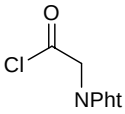
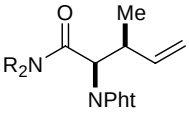
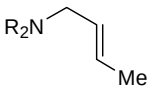
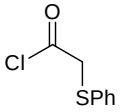
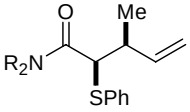
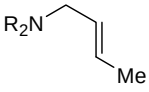
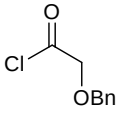
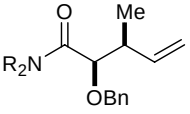
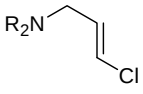
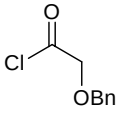
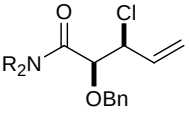
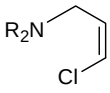
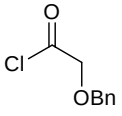
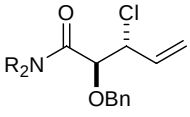
[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Relative configurations assigned by analogy to results summarized in Table 4. [c] Reaction conducted with 5 mol% $TiCl_4(THF)_2$. [d] Conversion determined by ^1H NMR analysis of unpurified reaction mixture.

Heteroatom-substituted acid chlorides were also examined and were found to participate in the acyl-Claisen rearrangement (Table 5). This process provides a new Lewis acid–catalyzed strategy for the production of unnatural β-substituted α-amino acids using α-phthalylglycyl chloride (77% yield, 99:1 *syn*:*anti*, entry 1). This reaction is also tolerant of oxygen[10] and sulfur substituents on the acyl chloride component (>81% yield, >86:14 *syn*:*anti*, entries 2–3). A powerful feature of this new Claisen

rearrangement is the capacity to build diverse functional and stereochemical arrays that are not readily available using conventional catalytic methods. For example, both the *syn* and *anti*-α-oxy-β-chloro Claisen isomers and can be accessed in high yield and stereoselectivity from chloro-substituted allyl morpholines and α-benzyloxyacetyl chloride (entries 4–5).[11]

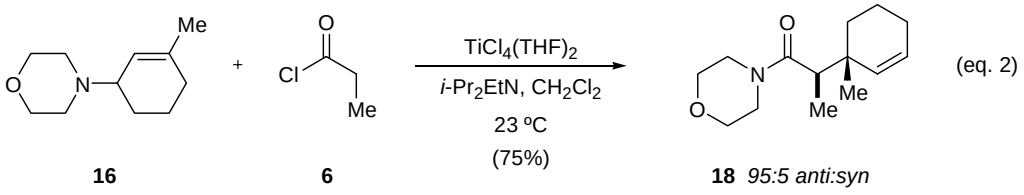
Table 5. Catalyzed Acyl–Claisen rearrangement between allyl morpholines and representative acid chlorides



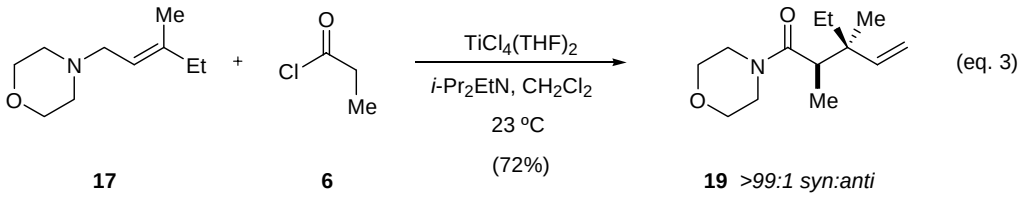
entry	amine[a]	acid-Cl	product[a]	yield	*syn:anti*[b,c]
1				77	>99:1
2				81	92:8
3				91	86:14
4				83	90:10
5				70	10:90

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single crystal X-ray analysis or chemical correlation to a known compound (see Experimental Methods).

A further illustration of the ability of this methodology to access elusive structural motifs is presented in the rearrangement of 3,3-disubstituted allyl morpholines **16** and **17** (equations 2 and 3). The key issue in these reactions is π-facial discrimination in the transition state to selectively build quaternary carbon stereocenters on both cyclic and acyclic architecture. The reaction of propionyl chloride with 1-methyl-3-*N*-morpholino-cyclohexene **16** provides excellent levels of diastereocontrol in the formation of the quaternary carbon bearing cyclic adduct **18** (equation 2). As illustrated in equation 3, the methyl versus ethyl substitution pattern on morpholine **17** can be distinguished in the reaction to furnish the acyclic product **19** with complete diastereselectivity (>99:1 *syn*:*anti*).



16 **6** **18** *95:5 anti:syn* (eq. 2)



17 **6** **19** *>99:1 syn:anti* (eq. 3)

Concluding Remarks

A new Lewis acid–catalyzed acyl-Claisen rearrangement that tolerates a range of alky, aryl and heteroatom-substituted acid chloride and allylic morpholine reaction partners has been achieved. Based on these studies, we have subsequently accomplished

two novel enantioselective variants of the zwitterionic-Claisen rearrangement: (1) a chiral magnesium (II)-bis(oxazoline) Lewis acid promoted enantioselective acyl-Claisen rearrangement with chelating acid chlorides, and (2) a chiral boron Lewis acid promoted enantioselective acyl-Claisen rearrangement (for details, see Tehshik Yoon's Ph.D. thesis).[12] Furthermore, these fundamental studies established a foundation for the design of a novel tandem acyl-Claisen rearrangement presented in the following chapter.

Experimental Method

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[13] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N*,*N*-diisopropylethylamine and dichloromethane were distilled from calcium hydride prior to use. Air sensitive solids were dispensed in an inert atmosphere glovebox. 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.[14] 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), AMX-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H 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 are reported in terms of chemical shift. 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 Berkeley Mass Spectral facility. Gas chromatography was performed on Hewlett-Packard 5890A and

6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm).

General Procedure A: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added dropwise over 1 min. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

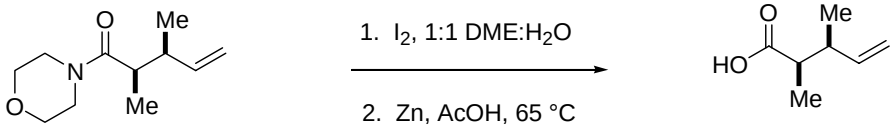
General Procedure B: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added slowly by syringe pump over 4–10 h. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and

concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

(2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (10).** Prepared according to general procedure A from (*E*)-*N*-but-2-enyl morpholine (**9**) (115 mg, 0.81 mmol), $TiCl_4(THF)_2$ (27 mg, 81 µmol), *i*-Pr_2NEt (213 µL, 1.22 mmol), and propionyl chloride (980 µL, 1 M solution in CH_2Cl_2, 0.98 mmol) in CH_2Cl_2 (8.1 mL) to provide the purified product as a colorless oil in 92% yield (148 mg, 0.75 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 2926, 2860, 1633, 1459, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 7.3, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 4.87–4.96 (m, 2H, CH=C**H**$_2$), 3.34–3.60 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.52 (dq, *J* = 7.1, 7.1 Hz, 1H, C**H**CH_3), 2.37 (q, *J* = 7.1 Hz, 1H, C**H**CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 142.3, 114.3, 67.3, 67.0, 46.5, 42.3, 40.5, 40.3, 16.3, 14.8; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{11}H_{19}NO_2)^+$ requires *m/z* 197.1416, found *m/z* 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.

Determination of the Relative Configuration of (2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (5) by Correlation with (2*R**,3*S**)-2,3-Dimethyl-4-pentenoic acid.** A solution of (2*R**,3*S**)-*N*-(2,3-dimethyl-4-pentenoyl)-morpholine (**10**) (22 mg, 0.11 mmol) in 1,2-DME (0.25 mL) and H_2O (0.25 mL) was placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine

(61 mg, 0.24 mmol) and was stirred in the absence of light. After 30 min, the reaction was diluted with Et_2O (1 mL) and washed sequentially with 10% aqueous $Na_2S_2O_3$ (1 mL) and brine (1 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated to give (2*S**,3*S**,4*R**)-4-iodomethyl-2,3-dimethyl-γ-butyrolactone as a yellow oil. This crude residue was dissolved in glacial AcOH (1 mL) and placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with zinc dust (65 mg, 1.0 mmol) and stirred at 65 °C for 3 h. After allowing the reaction to cool to rt, 1 *N* HCl (aq) (1 mL) was added, and the mixture was extracted with ether (3 x 1 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to give a light pink oil that exhibited spectral data identical in all respects to those reported for (2*R**,3*S**)-2,3-dimethyl-4-pentenoic acid.[15]



(2*S,3*S**)-*N*-(2-Methyl-3-phenyl-4-pentenoyl)-morpholine (11).** Prepared according to general procedure A from (*E*)-*N*-(3-phenyl-2-propenyl)-morpholine (201 mg, 0.99 mmol), $TiCl_4(THF)_2$ (33 mg, 99 μmol), *i*-Pr_2NEt (258 μL, 1.43 mmol), and propionyl chloride (1.48 mL, 1 M solution in CH_2Cl_2, 1.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C to provide the pure product as white needles in 74% yield (194 mg, 0.75 mmol); >99:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3057, 2988, 2968, 2930, 1637, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H, Ph), 5.99 (ddd, *J* = 7.8, 10.4, 17.9 Hz, 1H, C**H**=CH_2), 4.95–5.02 (m, 2H, CH=C**H**$_2$), 3.48–3.66 (m, 9H, N(C**H**$_2$C**H**$_2$)$_2$, C**H**Ph), 3.04 (dq, *J* = 6.8, 9.9 Hz, 1H, C**H**CH_3), 0.90 (d, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ

174.0, 141.7, 139.8, 128.6, 128.3, 126.7, 115.7, 67.0, 66.7, 53.4, 46.2, 42.1, 39.7, 16.7; LRMS (FAB) m/z 259; HRMS (FAB) exact mass calcd for ($C_{16}H_{21}NO_2$) requires *m/z* 259.1572, found *m/z* 259.1569. Diastereomer ratio was determined by GLC with a CC-1701 column (70 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 31.3 min, *anti* adduct t_r = 30.2 min.

(2*R,3*S**)-*N*-(3-Chloro-2-methyl-4-pentenoyl)-morpholine (12).** Prepared according to general procedure A from (*E*)-*N*-(3-chloro-2-propenyl) morpholine (112 mg, 0.69 mmol), $TiCl_4(THF)_2$ (23 mg, 69 µmol), *i*-Pr_2NEt (181 µL, 1.04 mmol), and propionyl chloride (1.04 mL, 1 M solution in CH_2Cl_2, 1.04 mmol) in CH_2Cl_2 (7 mL) to provide the pure product as a pale yellow oil in 95% yield (143 mg, 0.66 mmol); >99:1 *syn*:*anti* . *Syn* isomer: IR (CH_2Cl_2) 3057, 2976, 2864, 1640, 1463, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.12–5.31 (m, 2H, CH=C**H**$_2$), 4.51 (t, *J* = 8.4 Hz, 1H, C**H**Cl), 3.50–3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.98 (dq, *J* = 6.8, 8.8 Hz, 1H, C**H**CH_3), 1.27 (d, *J* = 6.8, 3H, CH_3); ^{13}C NMR (75 MHz) δ 172.0, 136.6, 118.4, 67.2, 67.0, 65.4, 46.7, 42.7, 42.5, 16.7; LRMS (FAB) *m/z* 217 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{16}ClNO_2$) requires *m/z* 217.0870, found *m/z* 217.0868. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 7 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 18.7 min and 19.2 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 19.6 min and 19.8 min. Relative configuration assigned by analogy.

***N*-(2-Methyl-4-pentenoyl)-morpholine (13).** Prepared according to general procedure A from *N*-allyl morpholine (161 mg, 1.3 mmol), $TiCl_4(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (336 μL, 0.94 mmol), and propionyl chloride (1.5 mL, 1 M solution in CH_2Cl_2, 1.5 mmol) in CH_2Cl_2 (13 mL) to provide the pure product as a clear oil in 95% yield (221 mg, 1.2 mmol); IR (CH_2Cl_2) 2976, 2864, 1640, 1467, 1436 cm^{-1}; ^1H NMR (400 MHz) δ 5.66–5.77 (m, 1H, C**H**=CH_2), 4.96–5.05 (m, 2H, CH=C**H**$_2$), 3.47–3.64 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.64–2.72 (m, 1H, C**H**CH_3), 2.35–2.42 (m, 1H, C**H**$_2$CH=CH_2), 2.06–2.13 (m, 1H, C**H**$_2$CH=CH_2), 1.08 (d, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.5, 136.0, 116.7, 67.0, 66.8, 46.0, 42.1, 38.1, 35.1, 17.3; LRMS (FAB) *m/z* 183 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{17}NO_2$) requires *m/z* 183.1259, found *m/z* 183.1253.

(2*R,3*R**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (14)**. Prepared according to general procedure B from (*Z*)-*N*-but-2-enyl morpholine (**15**) (88 mg, 0.62 mmol), $TiCl_4(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (163 μL, 0.94 mmol), and propionyl chloride (750 μL, 1 M solution in CH_2Cl_2, 0.75 mmol), added over 8h, in CH_2Cl_2 (4.2 mL) to provide the pure product as a clear oil in 74% yield (91 mg, 0.46 mmol); 95:5 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 2976, 2864, 1637, 1463, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, *J* = 8.2, 10.2, 18.3 Hz, 1H, C**H**=CH_2), 4.96–5.12 (m, 2H, CH=C**H**$_2$), 3.44–3.66 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.36–2.49 (m, 2H, C**H**CH3), 1.02 (d, *J* = 6.5 Hz, 3H, CH_3), 0.94 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 141.6. 115.4, 67.4, 67.1, 46.5, 42.4, 41.8, 40.4, 19.3; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass for ($C_{11}H_{19}NO_2$) requires *m/z* 197.1416, found 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn*

adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.

(2*R,3*S**)-*N*-(Methyl-2-phthalimido-4-pentenoyl)-morpholine (Table 5, entry 1).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (75 mg, 0.53 mmol), $TiCl_4(THF)_2$ (17.7 mg, 53 μmol), *i*-Pr_2NEt (139 μL, 0.80 mmol), and phthalylglycyl chloride (1.3 mL, 0.5 M solution in CH_2Cl_2, 0.64 mmol), added over 3h, in CH_2Cl_2 (10.6 mL) to provide the pure product as white crystals in 77% yield (134 mg, 0.41 mmol); 98:2 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3065, 2976, 2864, 1776, 1718, 1660, 1459, 1436, 1382, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.81 (m, 4H, Ph**H**), 5.79 (ddd, *J* = 7.6, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 5.04–5.18 (m, 2H, CH=C**H**$_2$), 4.76 (d, *J* = 10.2 Hz, 1H, C**H**NR_2), 3.63–3.71 (m, 1H, C**H**CH_3), 3.39–3.56 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.5, 139.6, 134.4, 131.3, 123.6, 116.6, 66.8, 66.5, 54.5, 46.3, 42.5, 36.5, 16.5; LRMS (FAB) *m/z* 329 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{18}H_{21}N_2O_4)^+$ requires *m/z* 329.1501, found *m/z* 329.1504. Diastereomer ratio was determined by GLC with a CC-1701 column (50 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 51.8 min, *anti* adduct t_r = 49.2 min.

(2*R,3*S**)-*N*-(3-Methyl-2-phenylthio-4-pentenoyl)-morpholine (Table 5, entry 2).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (67 mg, 0.48 mmol), $TiCl_4(THF)_2$ (15.9 mg, 47.5 μmol), *i*-Pr_2NEt (124 μL, 0.71 mmol), and phenylthioacetyl chloride (569 μL, 1 M solution in CH_2Cl_2, 0.57 mmol), added over 4 h,

in CH_2Cl_2 (9.5 mL) to provide the pure product as a light orange oil in 81% yield (107 mg, 0.39 mmol); *syn*:*anti* 92:8. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2864, 1640, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.49 (m, 2H, Ph), 7.28–7.30 (m, 3H, Ph), 5.75 (ddd, *J* = 7.5, 8.8, 16.3 Hz, 1H, C**H**=CH_2), 4.99–5.10 (m, 2H, CH=C**H**$_2$), 3.73 (d, *J* = 9.7 Hz, 1H, C**H**SPh), 3.11–3.58 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.76–2.82 (m, 1H, C**H**CH_3), 1.28 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 140.3, 134.0, 129.1, 128.4, 115.6, 78.3, 66.9, 66.4, 53.9, 46.4, 42.3, 39.7, 17.9; LRMS (FAB) *m/z* 292 $(MH)^+$; HRMS (FAB) exact mass calcd for ($C_{16}H_{22}NO_2S$) requires *m/z* 292.1371, found *m/z* 292.1373. Diastereomer ratios were determined by ^1H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-methyl-4-pentenoyl)-morpholine (Table 5, entry 3).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (**9**) (60 mg, 0.43 mmol), $TiCl_4(THF)_2$ (14 mg, 43 μmol), *i*-Pr_2NEt (111 μL, 0.64 mmol), and benzyloxyacetyl chloride (0.51 mL, 1 M solution in CH_2Cl_2, 0.51 mmol), added over 2h, in CH_2Cl_2 (8.5 mL) to provide the pure product as a pale yellow oil in 91% yield (112 mg, 0.39 mmol); 86:15 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3068, 2746, 2864, 1640, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.36 (m, 5H, Ph), 5.68 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.00–5.08 (m, 2H, CH=C**H**$_2$), 4.62 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 4.43 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 3.92 (d, *J* = 8.9, 1H, C**H**OCH_2Ph), 3.55–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.55–2.62 (m, 1H, C**H**CH_3), 1.15 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.9, 137.3, 128.5, 128.0, 115.8, 84.2, 72.2, 67.1, 66.8, 45.7, 42.5, 41.5, 17.0; LRMS (FAB) *m/z* 290 $(MH)^+$; HRMS (FAB) exact mass calcd for

($C_{17}H_{24}NO_3$) requires *m/z* 289.1756, found *m/z* 290.1755. Diastereomer ratios were determined by ^{1}H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 4).** Prepared according to the general procedure A from (*E*)-*N*-(3-chloro-2-propenyl)-morpholine (100 mg, 0.62 mmol), $TiCl_4(THF)_2$, (21 mg, 62 μmol), *i*-Pr_2NEt (151 μL, 86.7 mmol), and propionyl chloride (0.74 mL, 1 M solution in CH_2Cl_2, 0.74 mmol) in CH_2Cl_2 (12 mL) to provide the pure product as a yellow oil in 84% yield (160 mg, 0.52 mmol); 90:10 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2907, 2864, 1648, 1444, 1274, 1247, 1116 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30–7.40 (m, 5H, Ph), 5.92 (ddd, *J* = 8.5 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2) 5.39 (d, *J* = 16.9 Hz, 1 H, CH=C**H**$_2$), 5.26 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.72–4.73 (m, 1H, C**H**Cl), 4.71 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 7.4 Hz, 1H, C**H**OCH_2Ph), 3.50–3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.0, 136.5, 134.4, 128.5, 128.3, 128.1, 119.5, 82.4, 72.5, 66.9, 66.7, 62.4, 45.8, 42.8; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10 °C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

(2*R,3*R**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 5).** Prepared according to the general procedure A from (*Z*)-*N*-(3-chloro-2-propenyl)-morpholine (82 mg, 0.51 mmol), $TiCl_4(THF)_2$, (17 mg, 51 μmol), *i*-Pr_2NEt (290 μL, 1.66

mmol), and propionyl chloride (1.52 mL, 1 M solution in CH_2Cl_2, 1.52 mmol) in CH_2Cl_2 (10 mL) to provide the pure product as a yellow oil in 71% yield (110 mg, 0.36 mmol); 90:10 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 3057, 2976, 2907, 1652, 1444, 1239, cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.38 (m, 5H, Ph), 6.00 (ddd, *J* = 8.4 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2), 5.48 (dd *J* = 0.9 Hz, *J* = 16.0 Hz, 1 H, CH=C**H**$_2$), 5.35 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.75 (t, *J* = 8.3 Hz, 1H, C**H**Cl), 4.63 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.51 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 8.3 Hz, 1H, C**H**OCH_2Ph), 3.50–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.3, 136.7, 134.5, 128.6, 128.3, 128.1, 119.8, 78.5, 71.9, 66.9, 66.6, 60.5, 46.0, 42.7; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10`°C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

(*E*)-*N*-(3-Ethyl-3-methyl-2-propenyl)-morpholine (17). 2-Methyl-3-penten-1-ol was prepared using a modification of the procedure outlined by Corey and coworkers:[16] To a solution of 2-pentyn-1-ol (2.5 mL, 27 mmol) in THF (100 mL) was added Red-Al (8.1 mL of a 3.5 M solution in toluene, 28 mmol). The resulting solution was warmed to reflux for 3.5 h and then cooled to –78 ^oC, before a solution of iodine (20.5 g, 81.0 mmol) in THF (50 mL) was added dropwise by syringe. The resulting solution was then allowed to warm to rt before Et_2O (200 mL) was added, and the reaction mixture washed with 5% Na_2SO_4 (3 x 200 mL), dried (Na_2SO_4), and

concentrated to afford 3-iodo-2-penten-1-ol as a crude product that was used without further purification.

To a solution of copper (I) iodide (20.1 g, 0.11 mol) and methyl lithium (162 mL of a 1.3 M solution in Et_2O, 0.21 mol) in Et_2O (60 mL) at 0 °C was added a solution of the crude 3-iodo-2-penten-1-ol. The reaction mixture was stirred at 0 ^oC for 62 h and then washed with sat. aq. NH_4Cl (3 x 200 mL), dried (Na_2SO_4), and concentrated to provide 2-methyl-3-penten-1-ol in 91% yield (2.1 g, 21 mmol) as a pure oil by ^1H NMR analysis. Spectroscopic data of this material were in complete agreement with reported literature values.[17]

Morpholine **17** was prepared using a modification of the procedure outlined by Froyen and coworkers:[18] To a solution of 2-methyl-3-peten-1-ol (1.3 g, 13 mmol) and triphenylphosphine (3.6 g, 14 mmol) in THF (10 mL) was added *N*-bromosuccinimide (2.5 g, 14 mmol). After 15 min, morpholine (2.7 mL, 31 mmol) was added dropwise and the resulting brown solution was heated to 70 °C for 2.5 h. Upon cooling to rt, the reaction mixture was diluted with Et_2O (25 mL) and filtered through a pad of Celite©. The filtrate was then extracted with aqueous 1*N* HCl (100 mL). The product containing aqueous layer was then washed with Et_2O (3 x 100 mL), and then made alkaline by the addition of NaOH (4 g). The aqueous solution was then extracted with Et_2O (3 x 100 mL), the combined organic layers dried (Na_2SO_4), and then concentrated by rotary evaporation at 0 ^oC under reduced pressure. The resulting residue was then distilled (110 °C, 20 mm) to afford (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (**17**) as a colorless oil in 49% yield (1.0 g, 6.0 mmol); IR 2968, 1455, 1293, 1116, 1004, 907 cm^{-1}; ^1H NMR (400 MHz) δ 5.21–5.25 (m, 1H, C**H**=CCH_3), 3.65–3.77 (m, 4H, O(C**H**$_2$)$_2$), 2.96 (d, *J* =

7.0 Hz, 2H, C**H**$_2$C=CH), 2.44 (m, 4H, N(C**H**$_2$)$_2$), 2.01 (q, *J* = 7.3 Hz, 2H, CH$_3$C**H**$_2$), 1.63 (s, 3H, C**H**$_3$C=CH), 0.97–1.04 (m, 3H, CH$_3$C**H**$_2$); ^{13}C NMR (100 MHz) δ 141.1, 118.7, 67.0, 56.0, 53.5, 32.4, 16.4, 12.5; LRMS (FAB) *m/z* 169 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{19}NO)^+$ requires *m/z* 169.1467, found *m/z* 169.1464.

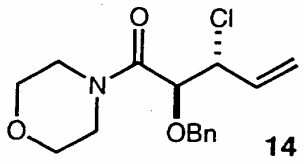
(1´*S,2*R*)-*N*-(2-(1´-Methylcyclohex-2´-enyl)-propanoyl)-morpholine (18).** Prepared according to general procedure A from 1-methyl-3-*N*-morpholino-cycohexene[19] (**16**) (50 mg, 0.28), $TiCl_4(THF)_2$, (9 mg, 27 μmol), *i*-Pr$_2$NEt (71 μL, 0.41 mmol), and propionyl chloride (0.41 mL, 1M solution in CH_2Cl_2, 0.41 mmol) in CH_2Cl_2 (3 mL) to provide the product as a yellow oil in 72% yield (45 mg, 0.36 mmol); 95:5 dr. Major isomer: IR (CH_2Cl_2) 2968, 2934, 2864, 1633, 1459, 1432, 1239, 1116 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.72 (d, *J* = 10.2 Hz, 1H, CH$_2$CH=C**H**), 5.64 (m, 1H, CH$_2$C**H**=CH), 3.54–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.62 (q, *J* = 6.9 Hz, 1H CHC=O), 1.92 (m, 2H, C**H**$_2$CH=CH), 1.68–1.73 (m, 1H, CH$_2$), 1.53–1.67 (m, 2H, CH$_2$), 1.34–1.39 (m, 1H, CH$_2$), 1.09 (d, *J* = 6.9Hz, 3H, C**H**$_3$CHC=O), 1.06 (s, 3H, C**H**$_3$CCH=CH); ^{13}C NMR (100 MHz) δ 174.5, 134.1, 126.4, 67.1, 66.8, 50.1, 46.9, 42.1, 37.4, 33.2, 25.0, 24.7, 19.2, 13.3; LRMS (FAB) *m/z* 237 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{14}H_{23}NO_2)$ requires *m/z* 237.1729, found *m/z* 237.1731. Diastereomer ratios were determined by ^{1}H NMR analysis.

(2*R,3*R**)-*N*-(2,3-Dimethyl-3-ethyl-4-pentenoyl)-morpholine (19).** Prepared according to general procedure B from (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (135 mg, 0.80 mmol), $TiCl_4(THF)_2$, (27 mg, 81 μmol), *i*-Pr$_2$NEt (0.56 mL, 3.2 mmol),

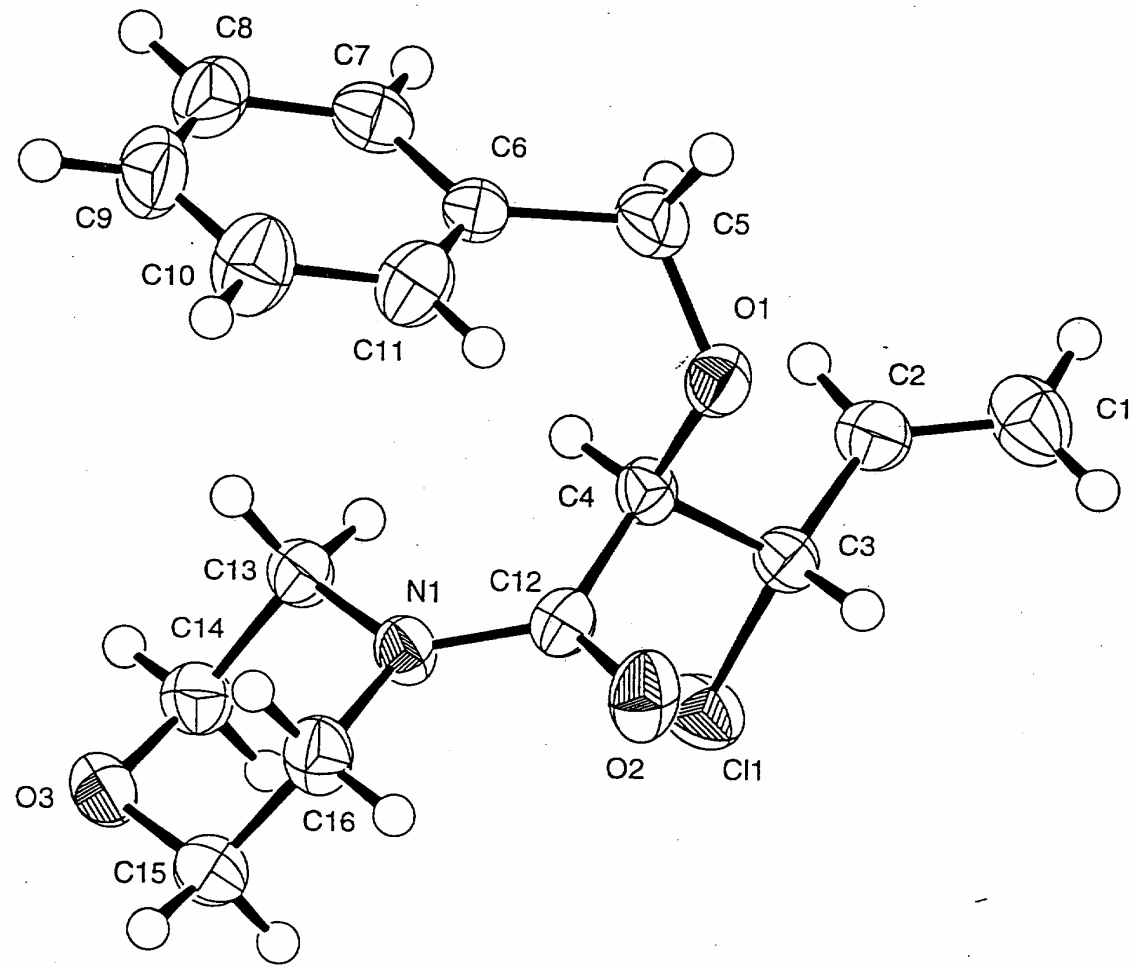
and propionyl chloride (2.4 mL, 1 M solution in CH_2Cl_2, 2.4 mmol) in CH_2Cl_2 (2.7 mL) to provide the pure product as a yellow oil in 72% yield (130 mg, 0.58 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 1633, 1459, 1432, 1235 cm^{-1}; ^1H NMR (400 MHz) δ 5.88 (dd, *J* = 10.9 Hz, 17.6 Hz, 1H, CH=C**H**$_2$), 5.03 (dd, *J* = 1.5, 10.9 Hz, 1H, CH=C**H**$_2$), 4.88 (dd, *J* = 1.4, 17.6 Hz, 1H, CH=C**H**$_2$), 3.49–3.64 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.63 (q, *J* = 6.9 Hz, 1H, C**H**C=O), 1.32–1.49 (m, 2H, C**H**$_2$CH$_3$), 1.02 (d, *J* = 6.9 Hz, 3H, C**H**$_3$CHC=O), 0.99 (s, 3H, C**H**$_3$C), 0.73 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz) δ 174.1, 143.8, 67.0, 66.7, 66.6, 46.8, 42.7, 42.2, 41.8, 30.9, 18.7, 13.3, 8.3; LRMS (FAB) *m/z* 225 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{13}H_{23}NO_2)^+$ requires *m/z* 225.1710, found *m/z* 225.1727.

X-ray Crystal Data

(2*R,3*R**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 5)**



14



EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}ClNO_3H_{20}$
Formula Weight	309.79
Crystal Color, Habit	colorless, blades
Crystal Dimensions	0.45 X 0.21 X 0.15 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 19.9407(11)Å b = 15.6857(9) Å c = 10.1045(5) Å V = 3160.5(3) Å^3
Space Group	Pbcn (#60)
Z value	8
D_{calc}	1.302 g/cm^3
F_{000}	1312.00
μ(MoKα)	19.12 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)
$2\theta_{max}$	52.1°

No. of Reflections Measured	Total: 15231 Unique: 3290 (R_{int} = 0.041)
Corrections	Lorentz-polarization Absorption (Tmax = 0.96 Tmin = 0.56)

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))	1777
No. Variables	190
Reflection/Parameter Ratio	9.35
Residuals: R; Rw; Rall	0.031 ; 0.035; 0.065
Goodness of Fit Indicator	1.38
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.17 $e^-/Å^3$

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

atom	x	y	z	B_{eq}
Cl(1)	0.83240(3)	0.11510(3)	0.02084(6)	3.579(14)
O(1)	0.75978(7)	0.33195(9)	0.16424(13)	2.90(3)
O(2)	0.71559(7)	0.18075(9)	0.27638(14)	3.59(4)
O(3)	0.57402(7)	0.04944(10)	-0.05896(14)	3.40(4)
N(1)	0.65927(8)	0.16133(10)	0.08421(15)	2.56(4)
C(1)	0.93863(11)	0.29648(16)	0.0967(2)	4.11(6)
C(2)	0.88327(11)	0.27408(13)	0.0392(2)	2.97(5)
C(3)	0.83158(10)	0.21842(12)	0.10154(18)	2.47(5)
C(4)	0.76076(10)	0.25370(12)	0.09084(18)	2.36(5)
C(5)	0.73829(11)	0.40391(13)	0.0879(2)	3.56(6)
C(6)	0.66668(11)	0.39854(12)	0.0404(2)	2.68(5)
C(7)	0.65122(12)	0.41985(14)	-0.0891(2)	3.24(6)
C(8)	0.58538(13)	0.42017(15)	-0.1329(2)	3.81(6)
C(9)	0.53508(13)	0.39724(16)	-0.0480(3)	4.26(7)
C(10)	0.54949(13)	0.37448(18)	0.0792(3)	4.62(7)
C(11)	0.61497(12)	0.37572(15)	0.1243(2)	3.74(6)
C(12)	0.70977(10)	0.19433(13)	0.1567(2)	2.46(5)
C(13)	0.64871(11)	0.17191(13)	-0.0577(2)	2.73(5)
C(14)	0.63127(11)	0.08704(14)	-0.1191(2)	3.15(5)
C(15)	0.58707(11)	0.03529(15)	0.0781(2)	3.33(6)
C(16)	0.60405(11)	0.11653(14)	0.1495(2)	3.12(5)
H(1)	0.9482	0.2772	0.1838	4.9264
H(2)	0.9697	0.3322	0.0517	4.9264
H(3)	0.8751	0.2943	-0.0480	3.5670
H(4)	0.8424	0.2110	0.1924	2.9675
H(5)	0.7492	0.2635	0.0009	2.8288
H(6)	0.7667	0.4086	0.0128	4.2751
H(7)	0.7427	0.4535	0.1411	4.2751
H(8)	0.6862	0.4345	-0.1486	3.8833
H(9)	0.5752	0.4362	-0.2213	4.5746
H(10)	0.4899	0.3972	-0.0777	5.1143
H(11)	0.5144	0.3577	0.1371	5.5463
H(12)	0.6245	0.3608	0.2135	4.4851
H(13)	0.6885	0.1934	-0.0972	3.2782
H(14)	0.6130	0.2109	-0.0722	3.2782
H(15)	0.6224	0.0953	-0.2106	3.7837

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

atom	x	y	z	B_{eq}
H(16)	0.6683	0.0496	-0.1090	3.7837
H(17)	0.5483	0.0109	0.1176	3.9984
H(18)	0.6237	-0.0031	0.0862	3.9984
H(19)	0.5657	0.1524	0.1507	3.7446
H(20)	0.6168	0.1034	0.2378	3.7446

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

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	0.0470(4)	0.0319(3)	0.0571(4)	0.0003(3)	0.0037(3)	-0.0104(3)
O(1)	0.0386(9)	0.0325(9)	0.0392(8)	0.0064(7)	-0.0102(7)	-0.0091(7)
O(2)	0.0427(10)	0.0692(12)	0.0244(8)	-0.0075(9)	-0.0030(8)	0.0041(7)
O(3)	0.0420(10)	0.0422(10)	0.0448(9)	-0.0137(8)	-0.0089(8)	0.0040(7)
N(1)	0.0343(11)	0.0381(11)	0.0247(10)	-0.0083(9)	-0.0022(8)	0.0023(8)
C(1)	0.0364(15)	0.0516(17)	0.0680(17)	-0.0040(12)	0.0069(13)	-0.0093(13)
C(2)	0.0327(13)	0.0347(13)	0.0455(13)	0.0018(11)	0.0038(11)	0.0008(11)
C(3)	0.0348(12)	0.0277(12)	0.0314(12)	-0.0004(10)	-0.0026(11)	-0.0050(9)
C(4)	0.0324(12)	0.0312(12)	0.0260(11)	-0.0007(10)	-0.0039(10)	-0.0047(9)
C(5)	0.0410(14)	0.0320(14)	0.0624(16)	-0.0002(11)	-0.0080(13)	-0.0062(11)
C(6)	0.0360(13)	0.0243(12)	0.0415(14)	0.0036(10)	-0.0064(12)	-0.0061(9)
C(7)	0.0504(15)	0.0291(13)	0.0434(15)	-0.0010(11)	0.0036(12)	-0.0073(10)
C(8)	0.0587(18)	0.0443(15)	0.0418(14)	0.0059(13)	-0.0165(13)	-0.0043(12)
C(9)	0.0385(15)	0.0575(18)	0.0660(18)	0.0077(13)	-0.0143(14)	-0.0075(14)
C(10)	0.0393(16)	0.080(2)	0.0566(17)	0.0045(14)	0.0042(14)	0.0025(14)
C(11)	0.0478(16)	0.0558(17)	0.0385(13)	0.0060(13)	-0.0021(13)	0.0000(12)
C(12)	0.0298(13)	0.0349(13)	0.0288(13)	0.0035(11)	0.0003(11)	-0.0006(10)
C(13)	0.0394(13)	0.0355(13)	0.0289(12)	-0.0059(10)	-0.0044(10)	0.0029(9)
C(14)	0.0465(15)	0.0382(14)	0.0351(13)	-0.0047(11)	-0.0064(11)	-0.0007(11)
C(15)	0.0372(13)	0.0427(15)	0.0467(14)	-0.0073(11)	-0.0008(11)	0.0096(11)
C(16)	0.0338(13)	0.0507(15)	0.0340(12)	-0.0061(11)	0.0010(11)	0.0039(11)

The general temperature factor expression:

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

References

(1) The research described in this chapter was conducted in collaboration with Tehshik Yoon and has been previously reported, see Yoon, T. P.; Dong, V. M.; MacMillan, D.W.C. *J. Am. Chem.* **1999**, *121*, 9726 and Yoon, T.P., Ph.D. Thesis, California Institute of Technology, 2002, chapter 3.

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(4) As the ketene was prepared as a solution in THF, the exact amounts of ketene added to the reaction were not determined.

(5) Use of triethyl amine, pyridine, DMAP, and DBU all resulted in diminished yields of the desired product in comparison to the use of Hünig's base.

(6) The p*K*a of protonated *N*-methylpyrrolidine is 10.3, while the protonated *N*-methylmorpholine has a p*K*a of 7.4. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution;* Butterworths: London, 1965.

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(10) Experiments were conducted which demonstrate that benzyloxyacetyl chloride reacts with *trans*-crotyl morpholine over 24 hr to provide the corresponding Claisen product in the absence of Lewis acid, in poor efficiency and diastereoselectivity (24% conversion, 26:74 *syn:anti*). This non-Lewis acid–activated background process was diminished by slow addition of the acid chloride.

(11) An enantioselective proline-catalyzed α-chlorination of aldehydes has recently been discovered in our research group (Brochu, M. P.; Brown, P. S; MacMillan, D.W.C.M., unpublished results). For a review of chiral auxiliary–based methods for construction of halogenated stereocenters, see: Duhamael, P. *Ind. Chem. Libr.* **1996**, 8, 176.

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Chapter 3

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

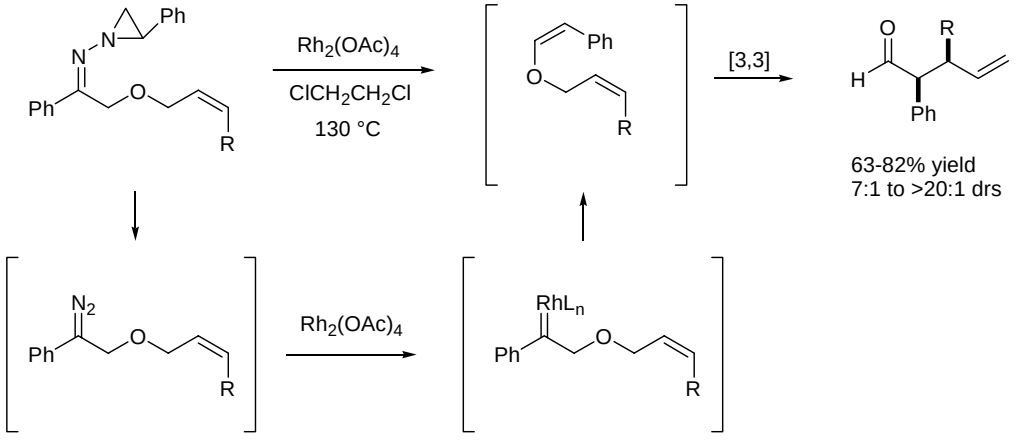
Introduction

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

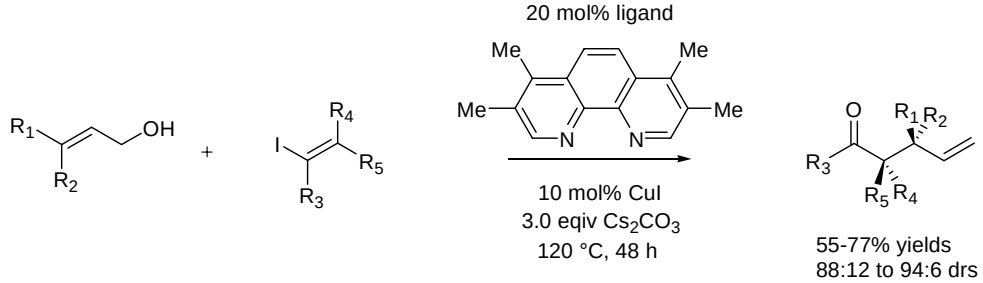
class has been quite useful considering that allyl vinyl ethers are often acid sensitive and difficult to isolate. In particular, the classical aliphatic Claisen reaction has found only limited application in synthesis, compared to other Claisen variants, due to a lack of general methods for the stereoselective 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



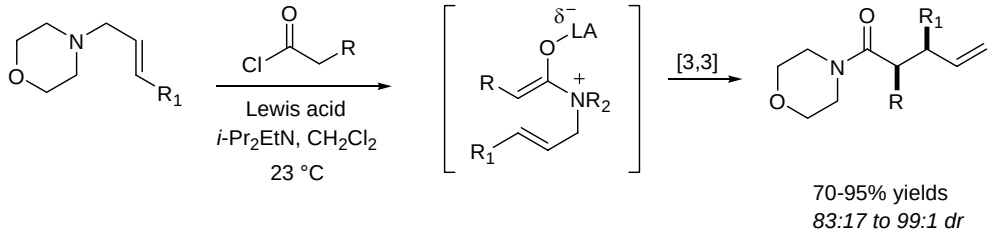
In addition, Buchwald recently reported the copper-catalyzed C-O coupling/Claisen rearrangement, a cascade process which also addresses the stereoselective synthesis of simple allyl vinyl ethers (Scheme 2).[6]

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



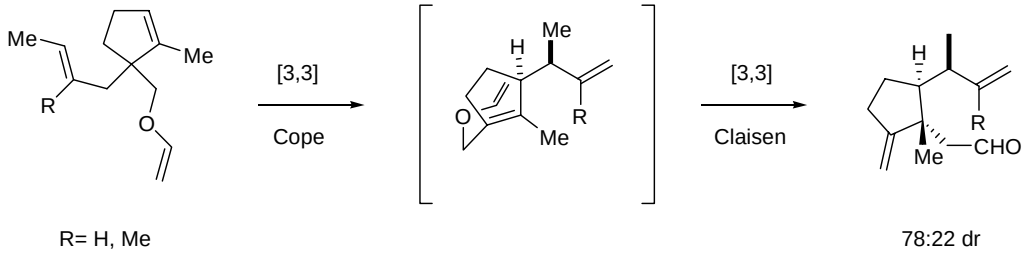
Notably, our acyl-Claisen methodology (Chapter 2) is also considered a tandem transformations; a transient zwitterionic intermediates is generated *in situ* which then undergoes [3,3]-bond reorganization (Scheme 3).[7]

Scheme 3. Acyl-Claisen rearrangement



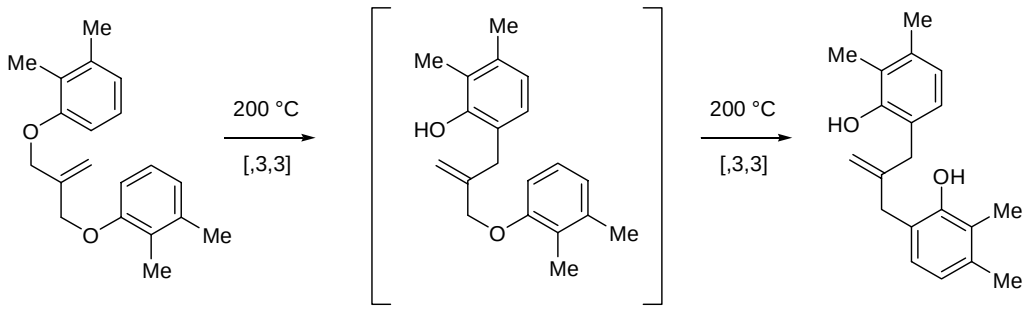
The combination of Claisen rearrangements with other carbon-carbon bond forming methods have resulted in powerful methods for synthesizing complex cyclic or polycyclic systems. For example, tandem Cope-Claisen sequences have been shown to build molecules with three contiguous stereocenters on a carbocycle (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



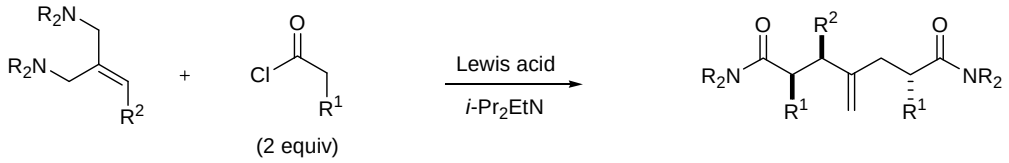
Of particular note, the tandem reaction based upon two successive aromatic Claisen rearrangements was developed by Hiratani et al. (Scheme 5).[12] By heating bisallylic ether to approximately 200 °C, the "double Claisen" rearrangement occurs to provide an aromatic product containing two new carbon-carbon 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.

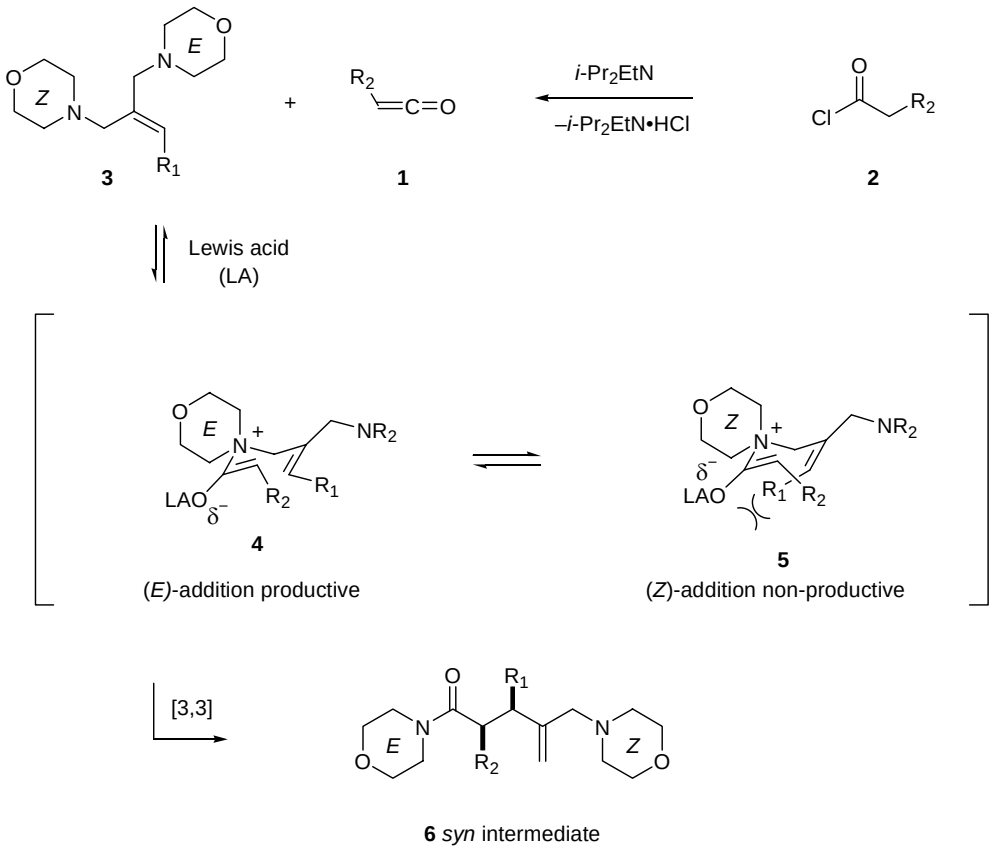
Scheme 6. Proposed tandem-acyl Claisen rearrangement for the rapid construction of stereochemically complex acyclic frameworks



Reaction Design

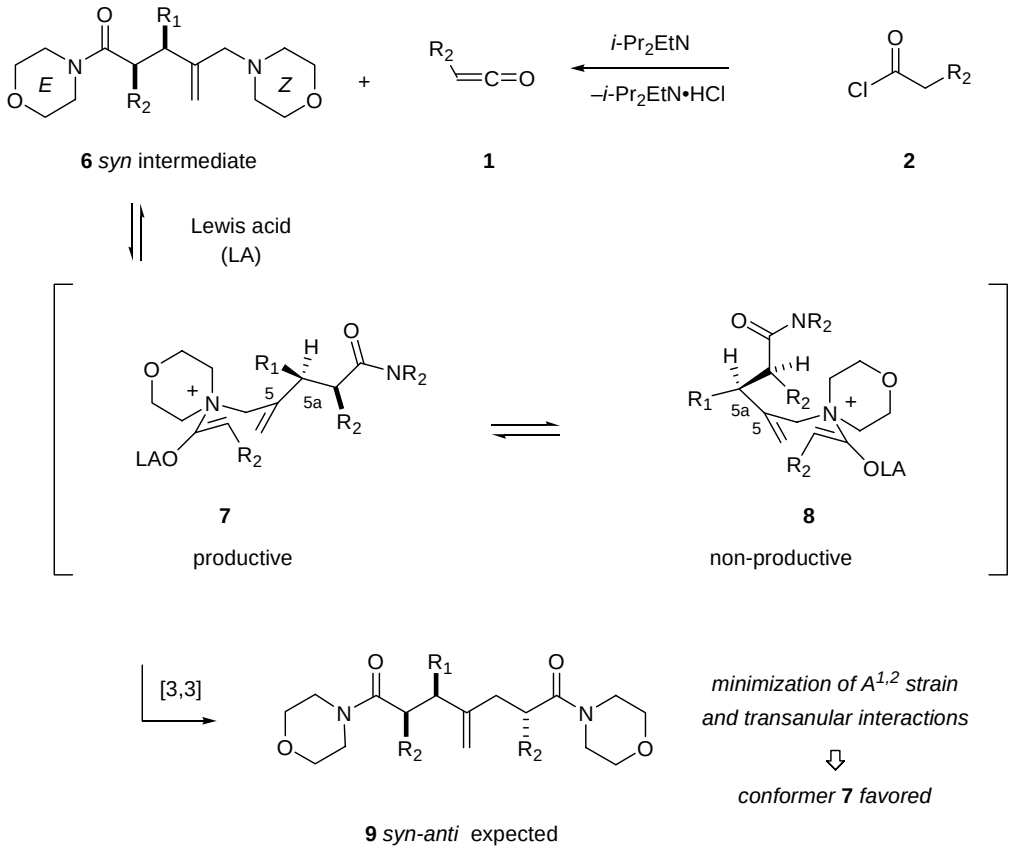
Based on our acyl-Claisen studies,[16] we envisioned that a variety of ketenes **1**, generated *in situ* from acid chloride **2**, would participate in a tandem acyl-Claisen rearrangement with allyl diamines **3** (Scheme 7 and Scheme 8). Addition of the (*Z*)- or (*E)*-amine component of diamine **3** 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

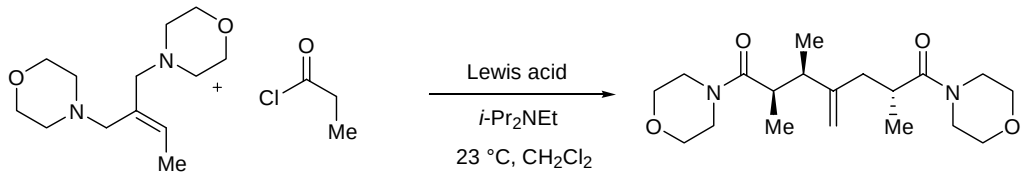


Results and Discussion

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]



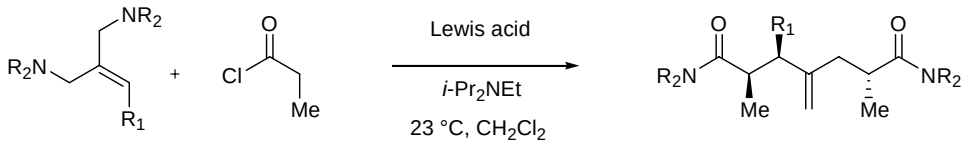
10 **11** **12** *syn-anti isomer*

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

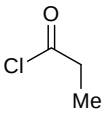
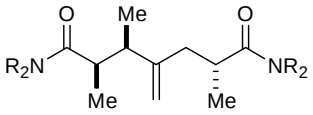
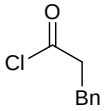
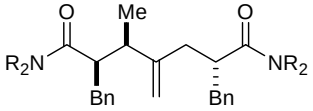
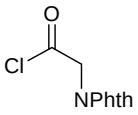
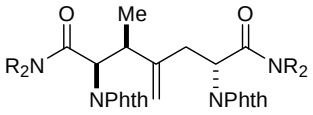
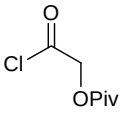
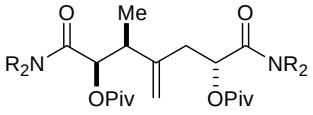
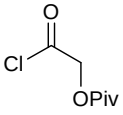
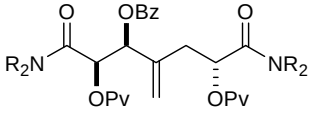
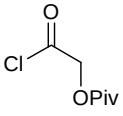
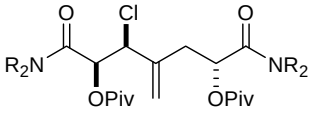
[a] Ratios determined by GLC or HPLC. [b] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [c] Relative configurations assigned by X-ray analysis. [d] Using $TiCl_4(THF)_2$.

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.

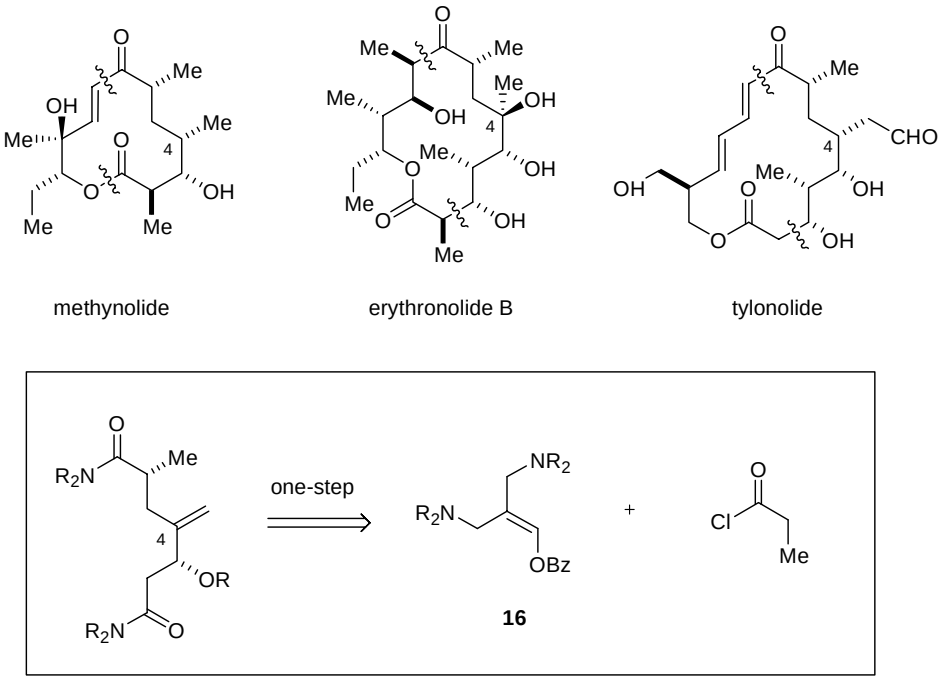
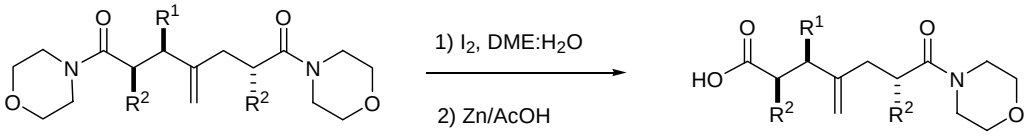


Figure 1. Applications of the tandem acyl-Claisen rearrangement for macrolide synthesis

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).

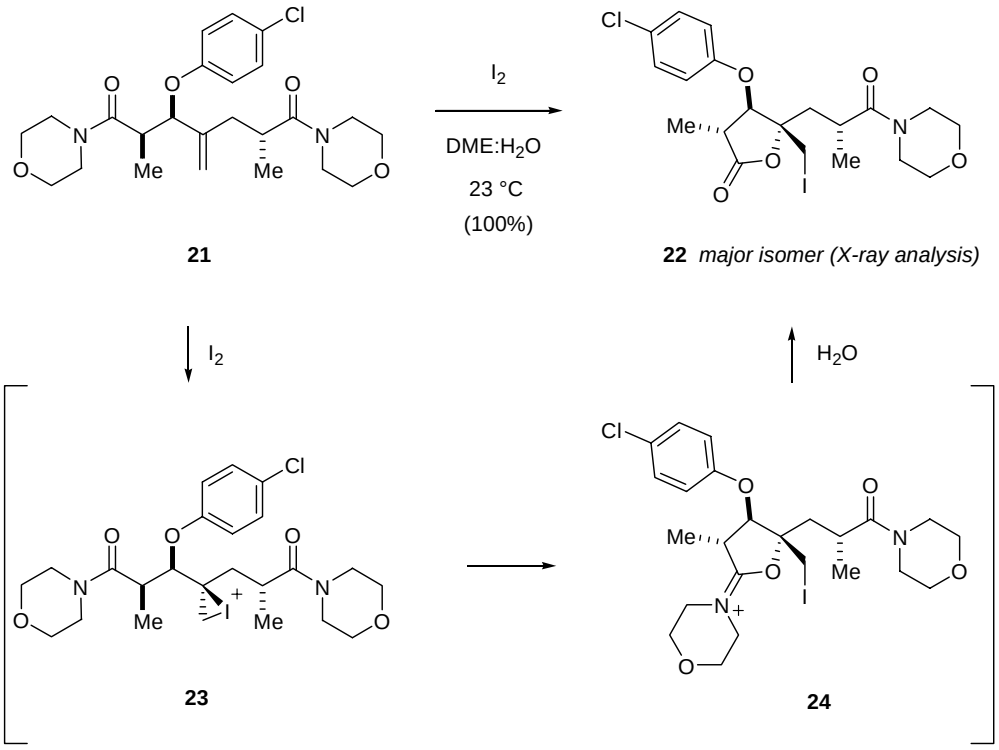
Table 4. Regioselective hydrolyisis of the tandem Claisen bisamides



	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)**

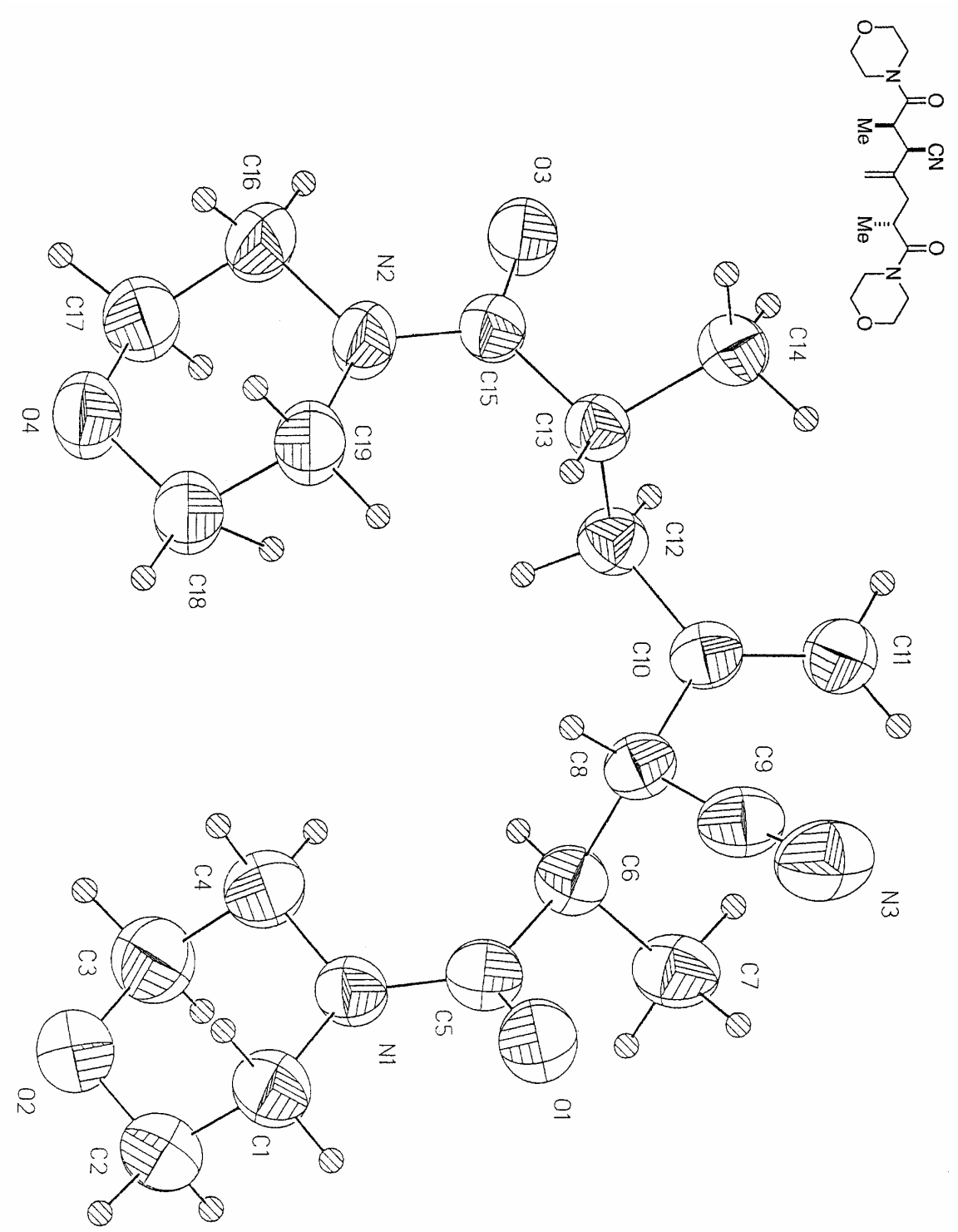


Table 1. Crystal data and structure refinement for VMD02.

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)

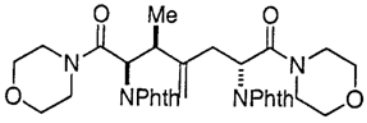
Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for VMD02. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	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)**



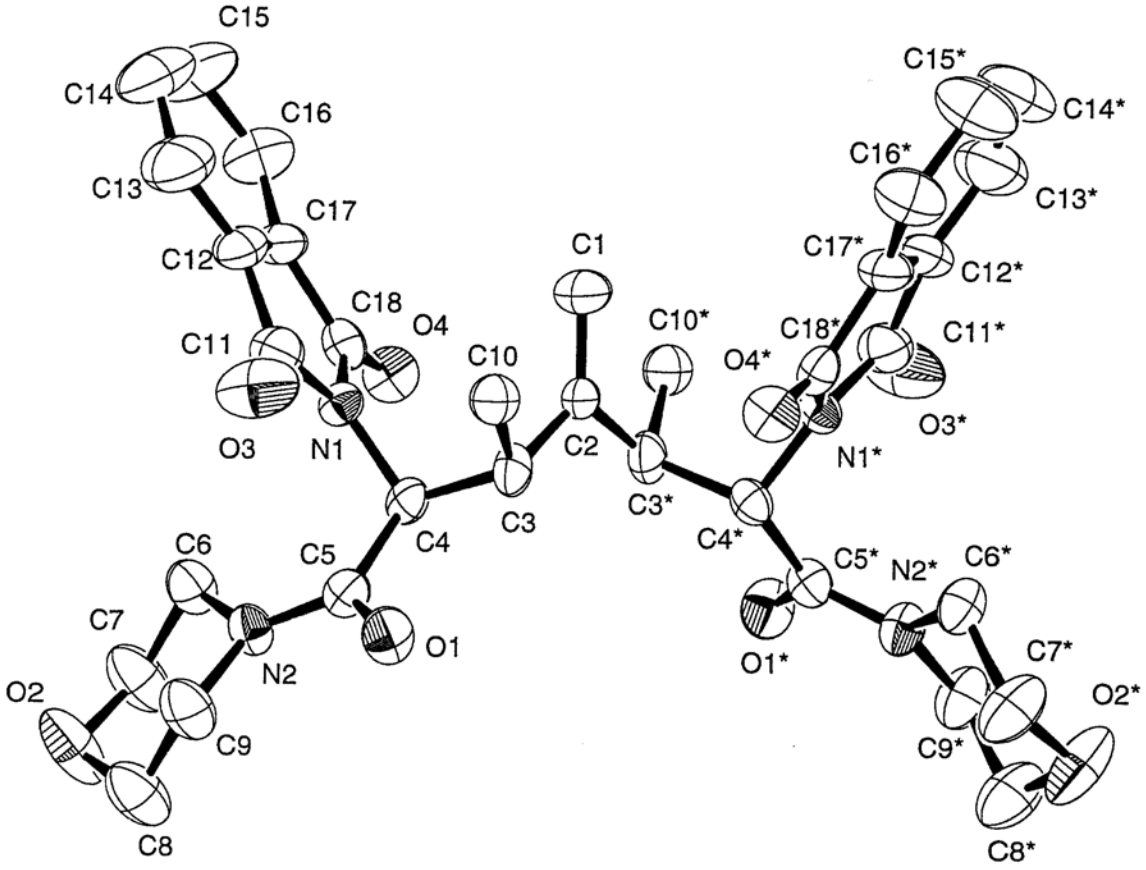


Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy

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)**

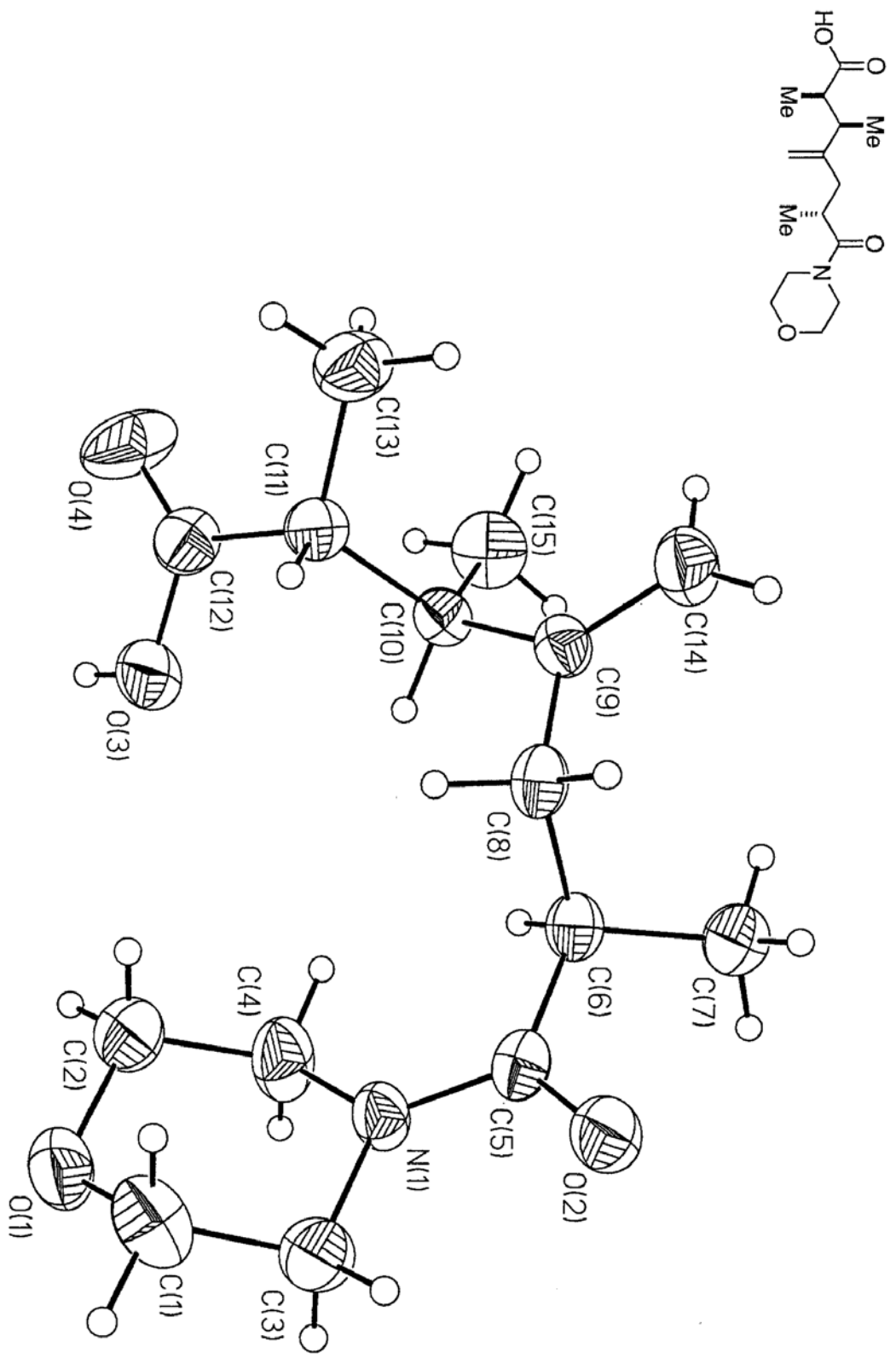


Table S-1. Crystal data and structure refinement for 1.

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.

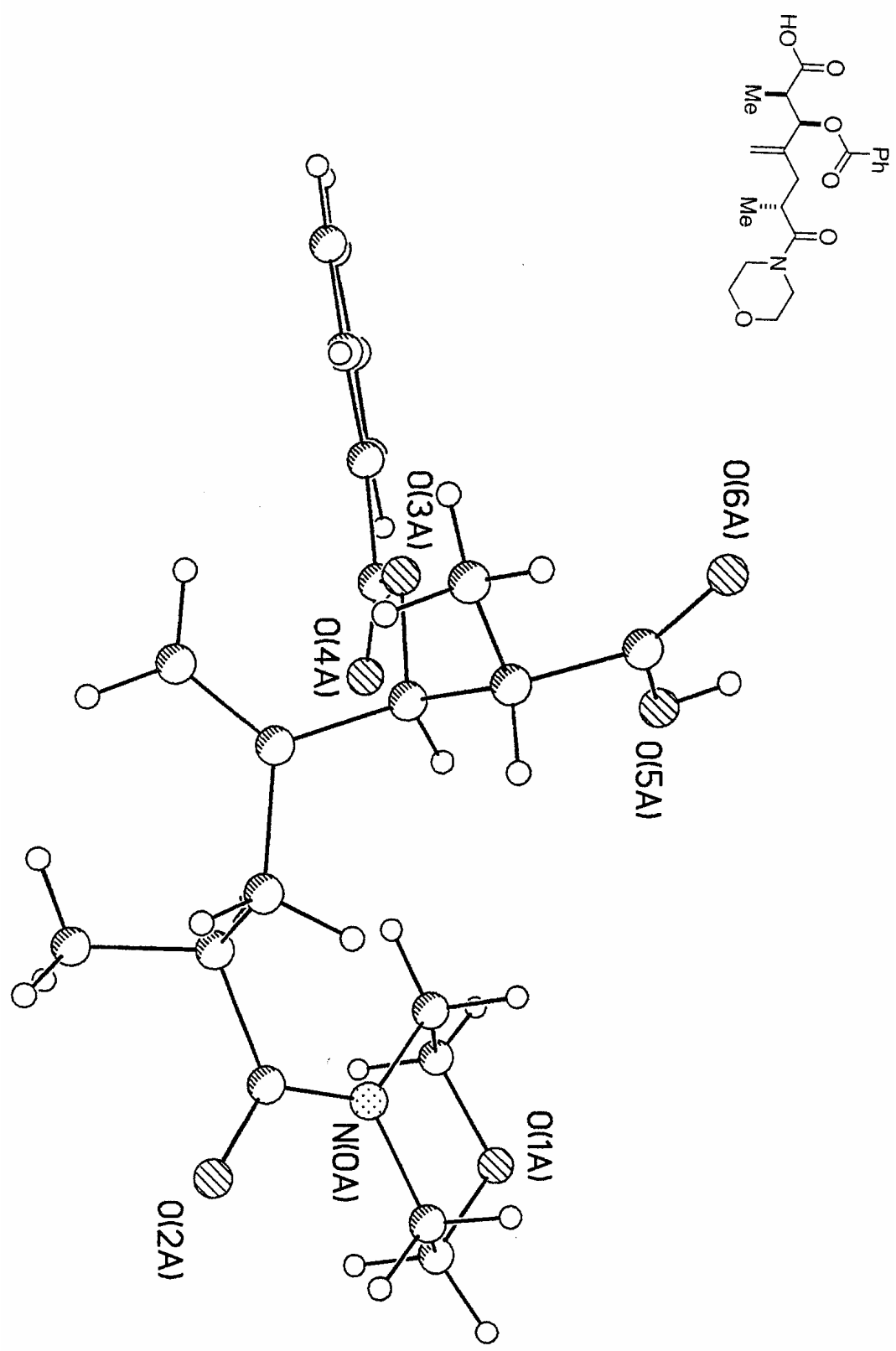
O(1)-C(1)	1.418(3)	O(1)-C(2)	1.427(3)
O(2)-C(5)	1.238(2)	O(3)-C(12)	1.333(3)
O(4)-C(12)	1.193(3)	N(1)-C(5)	1.350(3)
N(1)-C(3)	1.459(3)	N(1)-C(4)	1.462(3)
C(1)-C(3)	1.492(3)	C(2)-C(4)	1.494(3)
C(5)-C(6)	1.510(3)	C(6)-C(7)	1.523(3)
C(6)-C(8)	1.545(3)	C(8)-C(9)	1.502(3)
C(9)-C(14)	1.322(3)	C(9)-C(10)	1.513(3)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

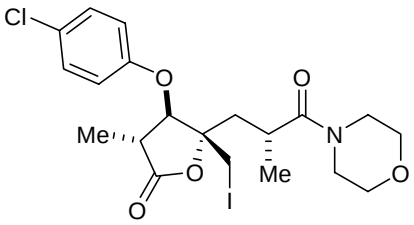
Table S-4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

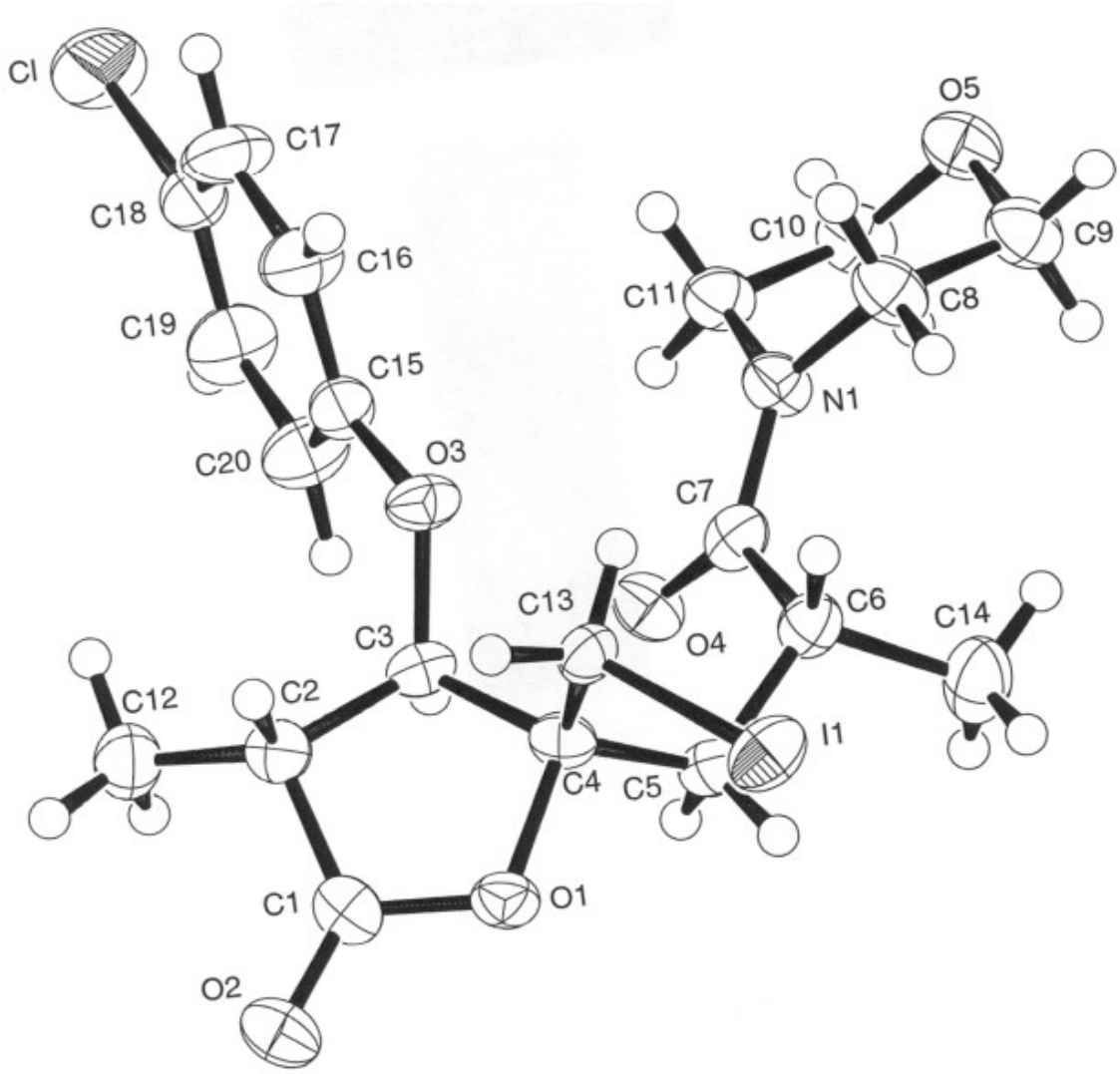
	U11	U22	U33	U23	U13	U12
O(1)	42(1)	49(1)	60(1)	13(1)	-1(1)	11(1)
O(2)	27(1)	65(1)	55(1)	18(1)	-3(1)	-2(1)
O(3)	26(1)	70(1)	48(1)	14(1)	-5(1)	3(1)
O(4)	28(1)	134(2)	48(1)	-15(1)	5(1)	-2(1)
N(1)	26(1)	36(1)	45(1)	9(1)	-2(1)	0(1)
C(1)	60(2)	43(2)	58(2)	9(1)	-9(1)	-2(2)
C(2)	35(2)	63(2)	61(2)	16(2)	9(1)	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

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(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%).

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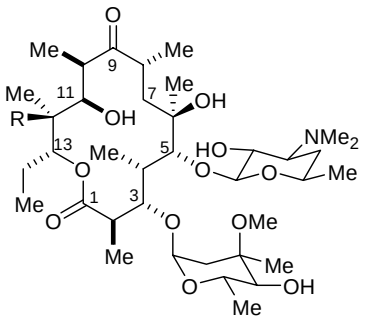
Chapter 4

Erythronolide B and the Erythromycins

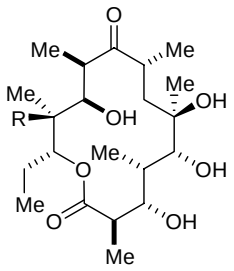
Isolation and Structure

Isolated in 1952 from the soil bacteria *actinomycetes*,[1] the erythromycins are a distinguished family of natural products by virtue of their clinically useful antibacterial properties and complex structures. Soon after their discovery, scientists elucidated the structure of erythromycin A (**1**),[2] and then erythromycin B (**2**),[3,4] through extensive degradation studies (Figure 1).[5] X-ray crystallography studies have established the three dimensional structure of these natural products.[6] The erythromycins are characterized by 14-membered macrolactones with glycosidic linkages at C(3) and C(5) to 6-deoxysugars, L-cladinose and D-desosamine, respectively. The name "erythronolide" refers to the polyketide derived-aglycone (e.g., **3** and **4**, Figure 1), while the letter codes (i.e., A, B, etc.) reflect each isomer and its order of discovery. In contrast to erythronolide A (**3**), erythronolide B (**4)** is a natural product and more importantly, the biogenic precursor of all the erythromycin isomers.



1 R = OH erythromycin A

2 R = H erythromycin B



3 R = OH erythronolide A

4 R = H erythronolide B

Figure 1. Representative members of the erythromycin macrolide family of antibiotics

Biosynthesis of Erythronolide B

Our understanding on the biosynthesis of polyketides derives mainly from extensive studies conducted on the biosynthetic mechanism of the erythromycins.[7] The first polyketide synthase genome sequenced was that of 6-deoxyerythronolide B synthase (DEBS).[8] Many *Streptomyces* polyketide synthases sequenced thereafter proved similar in structure and function to DEBS. The genes directing the synthesis of erythronolide B encode for three large multifunctional proteins: DEBS1, DEBS 2, and DEBS 3. Through a stepwise process, polyketide synthase (PKS) builds erythronolide B from simple carbon building blocks, as illustrated in Figure 2. The enzyme KS (ketosynthase) anchors the growing polyketide chain via a disulfide linkage to a cysteine residue. In one cycle of the biosynthesis, AT (acyltransferase) transfers an α-carboxylated nucleophile from the acyl-CoA to the ACP (acyl carrier protein), and acyl-KS and acyl-ACP catalyze the adol bond formation. This process can then repeat itself until the enzyme TE (thioesterase) terminates chain elongation and forms the macrocycle. Cytochrome *P*-450 uses

molecular oxygen to oxidize the C(6) position of the macrolactone (6-deoxyerythronolide B) to form erythronolide B. Subsequent steps involve attachment of the sugars to make the erythromycins. Fundamental mechanistic studies of these enzymes are ongoing, with recent efforts in this area aimed at eventually exploiting the biosynthesis of polyketides to make new macrolides because of their potential for fighting infectious diseases.[9]

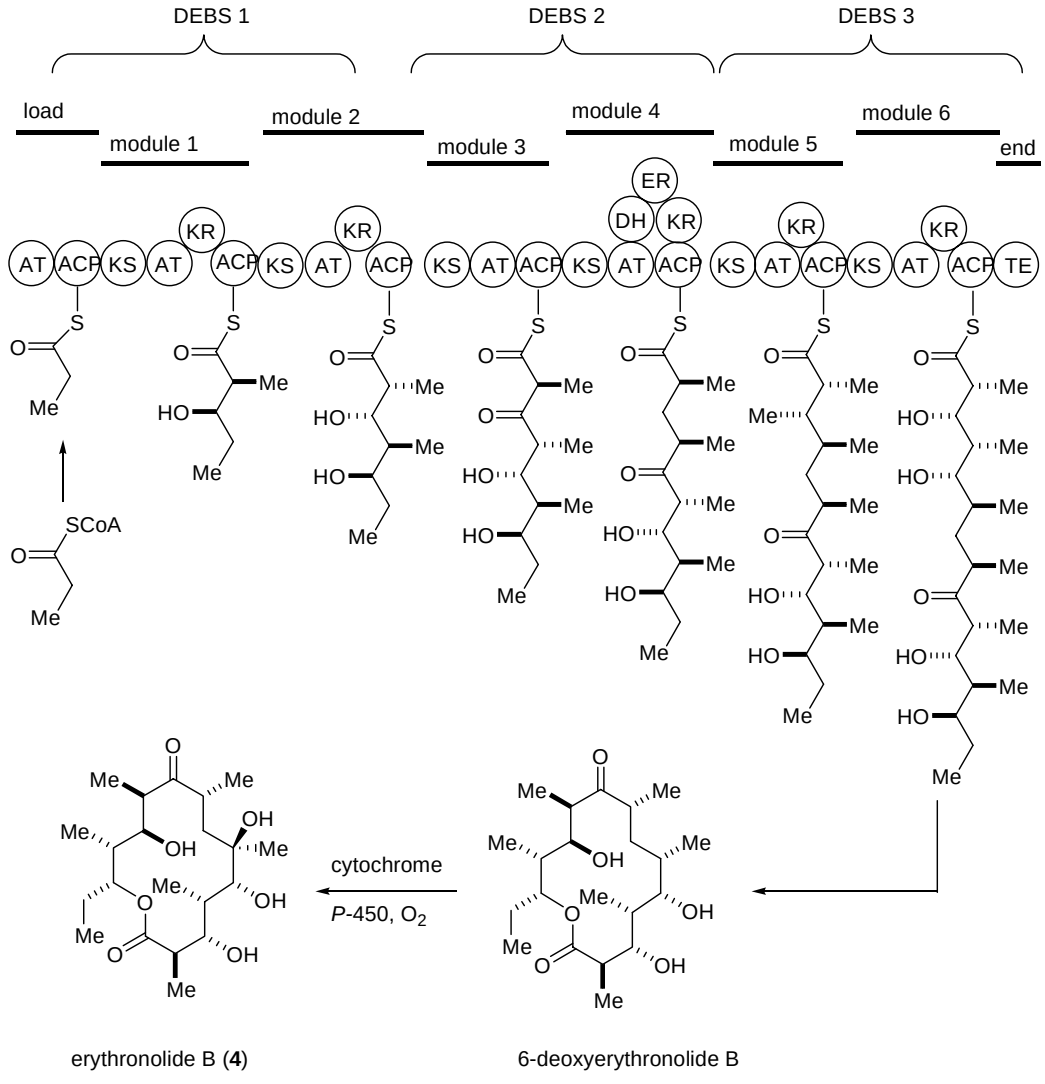


Figure 2. Predicted domain organization and biosynthetic intermediates of the erythromycin synthase. Each circle represents an enzymatic domain as follows: ACP, acyl carrier protein; AT, acyltransferase; DH, dehydratase; ER, β-ketoacyl-ACP enoyl reductase; KR, β-ketoacyl-ACP reductase; KS, β-ketoacyl-ACP synthase; TE, thioesterase

Comparison to fatty acid synthesis. Notably, the biosynthesis of polyketides bears mechanistic similarities to vertebrate fatty acid synthesis.[7] Both pathways are triggered by the Claisen condensation reaction between a starter carboxylic acid and a dicarboxylic acid (e.g., malonic or methylmalonic acid). In addition, both pathways involve the multifunctional polypetide-enzymes, KS (ketosynthases) and ACP (acyl carrier protein). Furthermore, both pathways are inhibited by a fungal product called cerulenin.[7]

Polyketide architectures, however, far exceed fatty acid structures in complexity as a result of two distinctions in their biosynthesis. First, in fatty acid synthesis three enzymatic, three steps operate in sequence to eventually form the saturated carbon chain: ketoreduction by KR (ketoacylACP reductase), dehydration by DH (dehydratase) and enoyl reduction by ER (enoyl reductase) (Figure 3). In contrast, these enzymatic steps function at various points in polyketides synthesis, resulting in greater functional group variety. Second, fatty acid synthesis uses only malonly pieces, whereas polyketide synthases incorporate more varied materials: malonly, methylmalonyl and ethylmalony extender units.

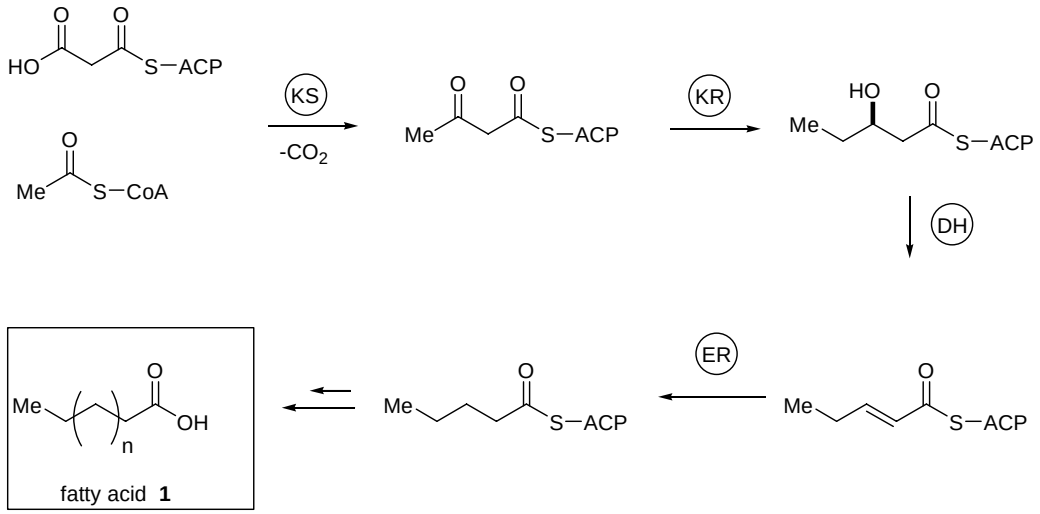


Figure 3. Biosynthesis of fatty acids involves the three enzymatic steps by KR (ketoacylACP reductase), DH (dehydratase) and ER (enoyl reductase)

Clinical Usage

Over the past forty years, erythromycin A, commonly referred to as erythromycin, has been used to fight a variety of infections including pneumonia, diphtheria, pertussis, chlamydia, trachomatis, and conjunctivitis.[10] As one of the oldest and safest antibiotics, erythromycin continues to be a useful alternative to penicillin. This antibiotic acts by reversibly binding the 50S ribosomal subunit of a susceptible microorganism.[11] Because ribosomes are responsible for protein synthesis in a cell, binding to the 50S ribosome inhibits the microorganism's growth. Recently, the structural basis for this binding event was reported; an X-ray crystal structure of eythromycin bound to the ribosome reveals that the antibiotic participates in hydrogen bonding to six adjacent nitrogenous bases of the nucleotides in the 23S RNA ribozyme (a subunit of the 50S ribosome).[12]

Although erythromycin has been widely used over the past four decades, improvement in its biological and chemical properties is still needed and pursued. The

current drawbacks of erythromycin include acid sensitivity, poor intestinal absorption, low tissue and cellular penetration, poor digestive tolerance, and undesirable interactions with other drugs. Under acidic conditions (e.g. in the stomach), erythromycin decomposes to two weaker antibiotics. As such, absorption of the drug is variable and difficult to predict. Because of its acid sensitivity and complex structure, modification of erythromycin has been difficult.

Concluding Remarks

Antibiotic-resistant strains of bacteria are still a major concern to public health. Unfortunately, the erythromycin structures are complex and difficult to modify. As such, chemical tools that facilitate the production of erythromycin-like antibiotics will increase our ability to treat resistant bacterial strains.

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Chapter 5

Synthetic Strategies towards Erythronolide B and Erythromycin B

Introduction

Due to their fascinating structures and important biological activity, macrolide natural products, especially the erythromycins, have been popular targets for total synthesis and thus, an inspiration for discovering new synthetic methods with wide applications.[1] As synthetic targets, macrolides pose various challenges, such as installing the numerous chiral stereocenters, closing a macrocycle and selectively attaching sugars to the macrolactone. In 1956, R. B. Woodward acknowledged these challenges, stating "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."[2] Woodward and coworkers eventually addressed the stereochemical issues, identified elements crucial for forming macrocycles, and solved the glycosylation problem in elegant studies culminating in the total synthesis of erythromycin A, published after Woodward's death in 1981.[3]

For more than two decades since Woodward's achievement, synthesizing members of the erythromycin family has been the focus of at least twenty research groups worldwide and thus, hailed as the "most extensive single project in the history of synthetic organic chemistry."[1c] To date, there are three total syntheses of the digylcosides (one of erythromycin A (**1**)[3] and two of erythromycin B (**2**)[4]), and several syntheses of the aglycones, erythronolide A (**3**),[5] erythronolide B (**4**),[6] 6-

deoxyerythronolide B (**5**),[7] and 9-(*S*)-dihydroerythronolide A (**6**)[8] (Figure 1). In addition, researchers have also reported various seco-acids syntheses.[1b]

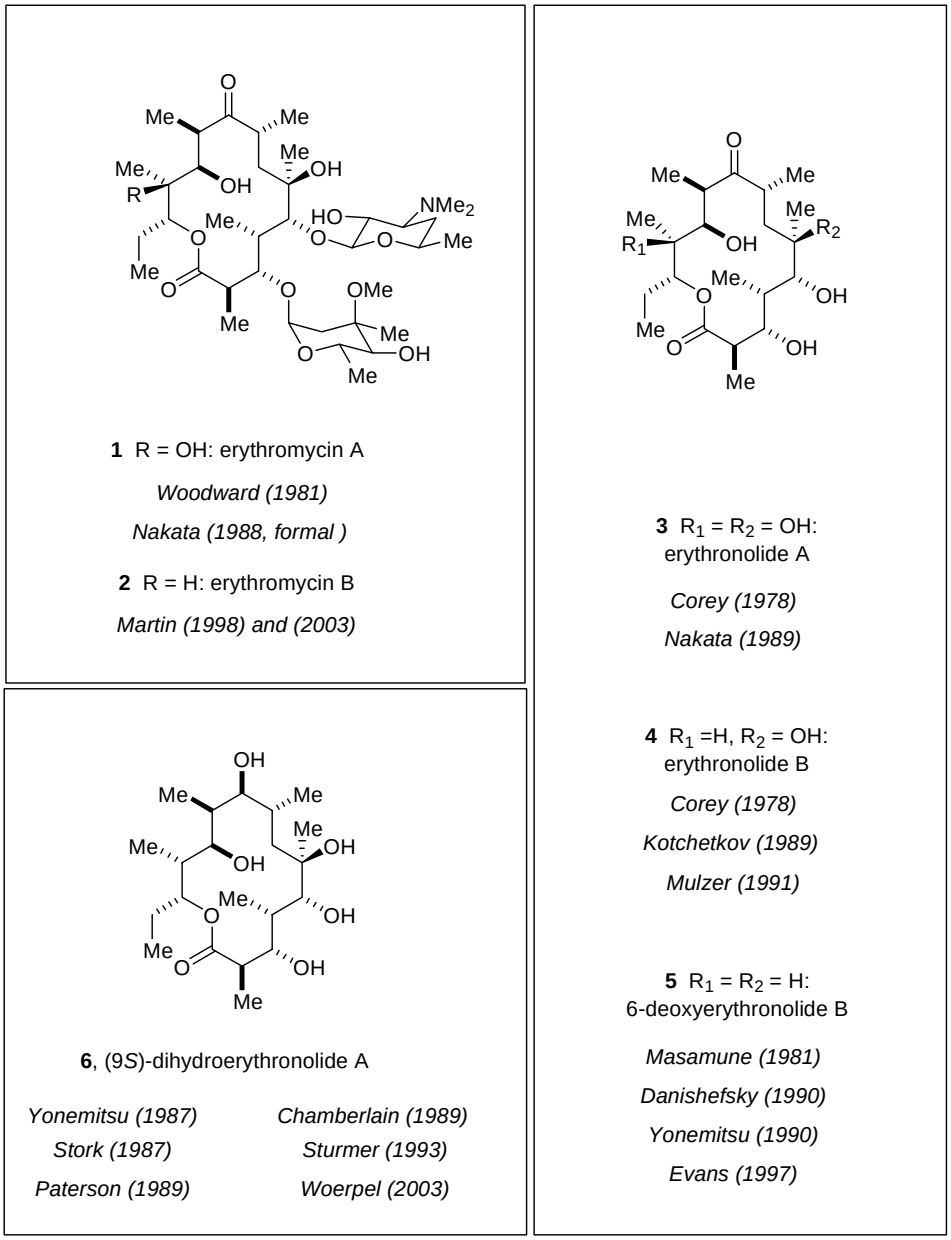


Figure 1. Erythromycin family: popular targets in total synthesis for more than two decades

All these strategies, however, can be classified into three main approaches (defined below) for addressing the polyketide's stereochemical challenges.[1b]

(1) *ring cleavage approach:* involves exploiting a medium ring's conformational bias to stereoselectively form chiral centers on the ring, followed by cleavage of the ring to achieve the desired acyclic architecture;

(2) *carbohydrate approach:* involves manipulating existing stereocenters and functionality from the chiral pool, namely sugars, to form the desired acyclic frameworks;

(3) *acylic approach*: involves using stereoselective methods to form new asymmetric centers in acyclic systems.

Approaches to Erythronolide B and Erythromycin B

Erythronolide B (**4**) holds a central position in the erythromycin family as a biosynthetic precursor to the other members of this antibiotic clan.[9] Notably, this natural product has been previously synthesized by all three of the main strategies defined above, by three different research groups (Corey,[6a] Kotchetkov,[6b] and Mulzer[6c]). In addition, Martin and coworkers have recently reported a new approach to closely related erythromycin B (**2**).[4] The following discussion aims to summarize key aspects of these four syntheses. In particular, the strategy used to address the stereogenic centers on the C(1) to C(9) fragment of erythronolide B will be stressed to establish appropriate context for our work in this field.

Corey's synthesis

In 1978, E. J. Corey achieved the landmark first total synthesis of erythronolide B (Figure 2).[6a] Corey's plan involves a ring closing lactonization of seco-acid **7** using a general method developed in his lab for forming macrolactones. Treatment of **7** with disulfide **8**, forms an activated ester **9** which cyclizes in refluxing toluene to **10** in 50% yield (Scheme 1). The success of this ring-closing strategy has had a tremendous impact; all subsequent erythromycin syntheses contain the same C-O lactone bond disconnection.[1]

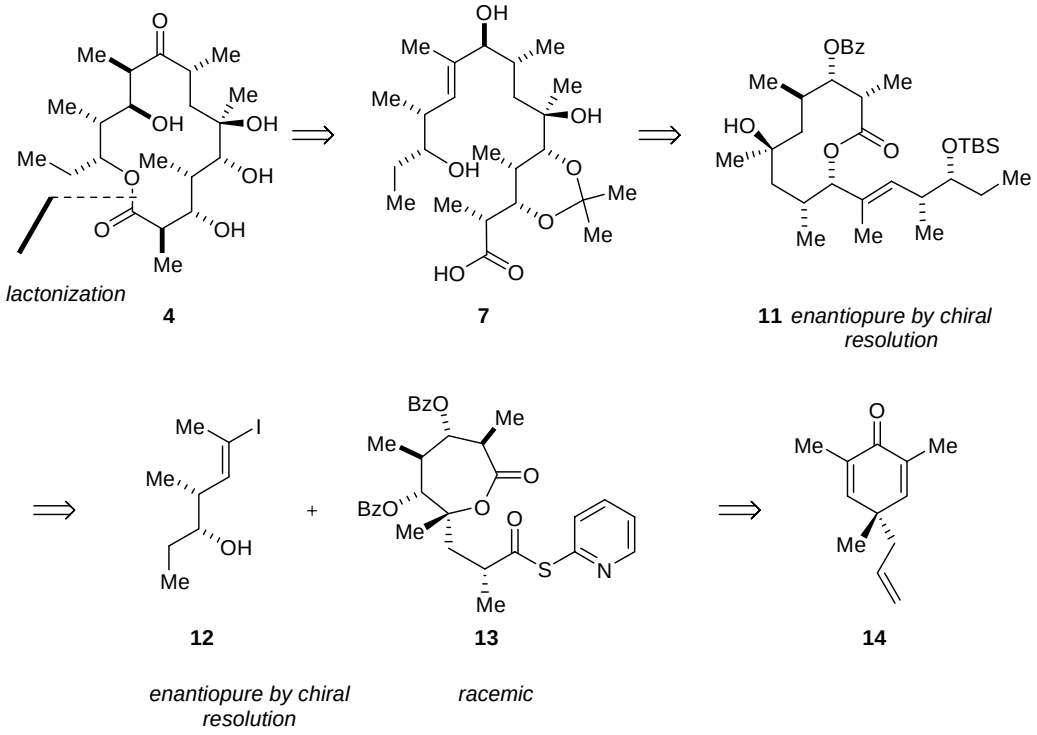
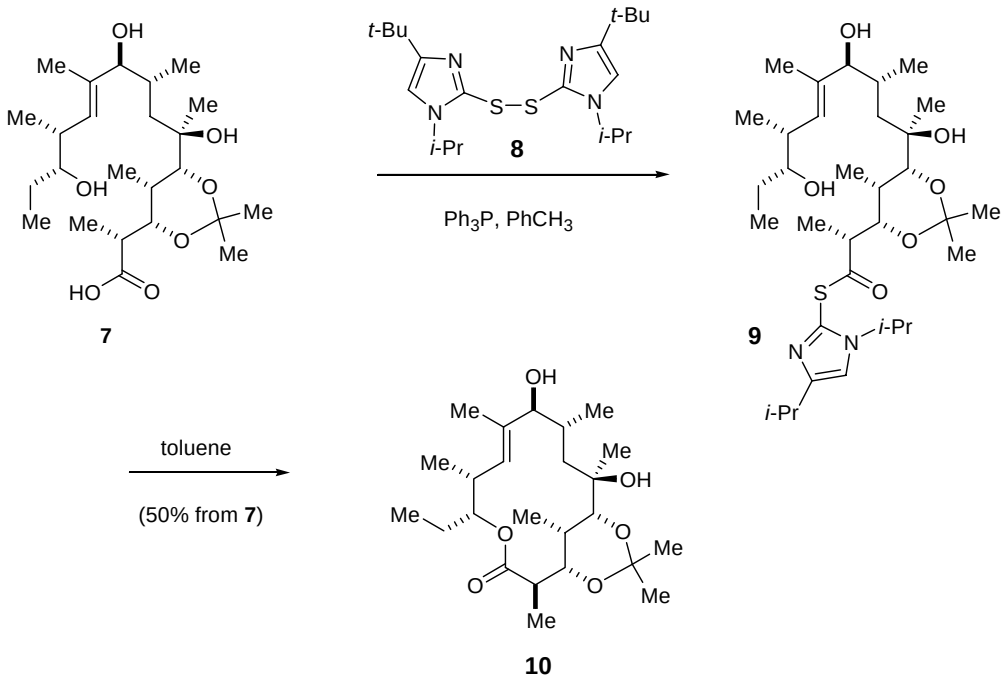


Figure 2. Corey's synthesis (thirty steps from **14**, < 0.5% yield)

Scheme 1. Corey's general macrolactonization method

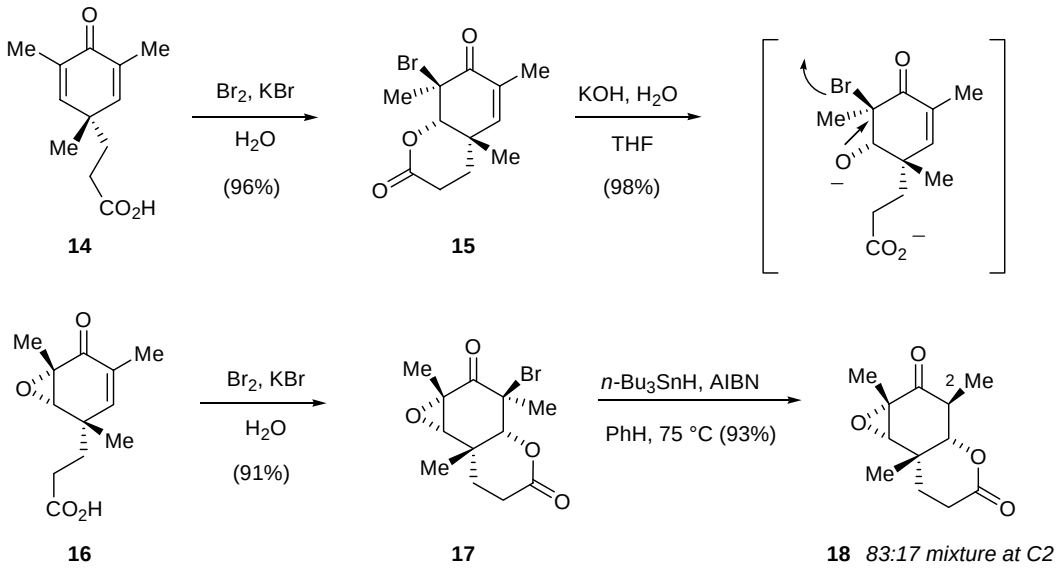


One current drawback of Corey's route involves the chiral resolution of advanced intermediate **11**, by the coupling of enantiopure **12** (which was also obtained by chiral resolution) to a racemic mixture of **13** (Figure 2). As a result of these resolution steps, Corey's synthesis suffers a significant loss in efficiency (> 25%). This historic synthesis of erythronolide B requires thirty transformations from **14**, and has an approximate overall yield of less than 0.5%.

Ring cleavage approach. Corey successfully installs the six chiral centers on the C(1) to C(9) fragment **13** of erythronolide B by a ring cleavage approach (see Schemes 2 and 3). Essential to his strategy is the bromolactonization of symmetrical intermediate **14** to create three stereocenters in a diastereoselective fashion, yielding lactone **15**. Upon saponification to epoxide **16**, a second bromolactonization gives intermediate **17**, creating

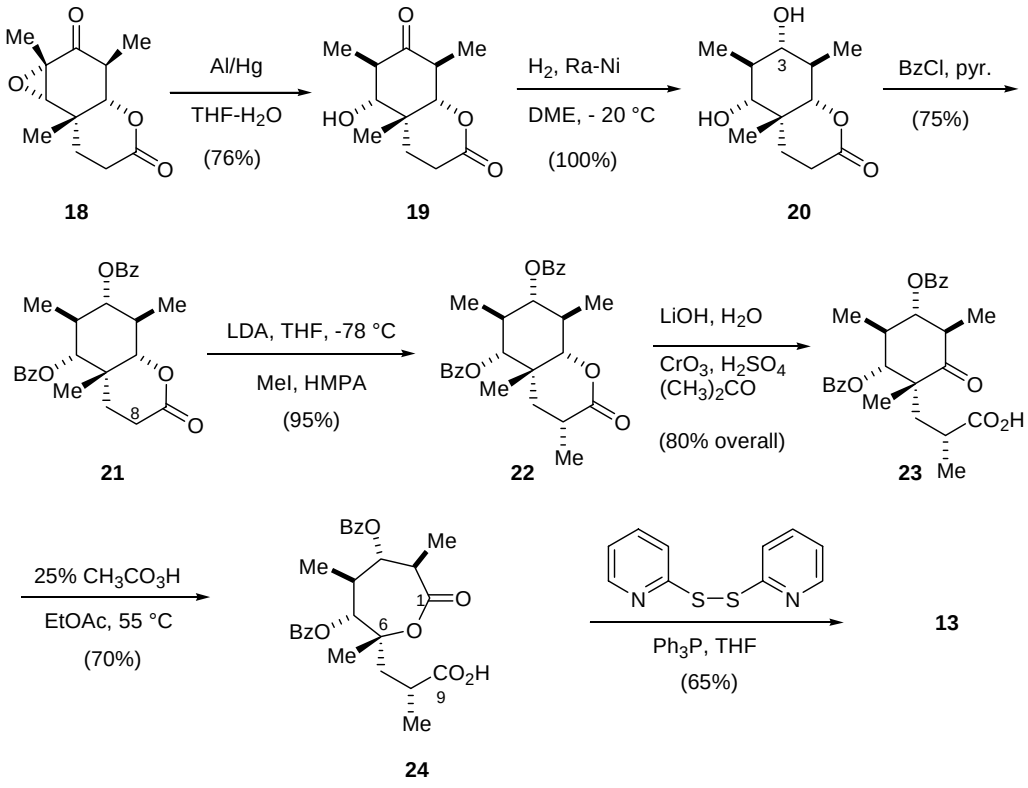
two additional stereocenters in the process. The carbon-bromide bond can then be reduced by radical cleavage providing **18** as a 83:17 mixture.

Scheme 2. Corey's ring-cleavage approach to C(1)–C(9) segment of erythronolide B



The epoxide **18** is reductively opened by aluminum amalgam to form a hydroxyl ketone **19** (Scheme 3). Importantly, the diastereoselective hydrogenation of ketone **19** installs the requisite C(3) hydroxyl stereocenter. After protection of **20** with benzoyl chloride, critical introduction of the C(8)-methyl stereocenter was achieved by alkylation of **21** with methyl iodide to provide **22**. Jones oxidation of **22** provides ketone **23**—properly functionalized to undergo ring cleavage. A Bayer-villager oxidation of the carobocyclic ring or **23** enables *ring cleavage* to lactone **24**, installing the key C(6) tertiary alcohol stereocenter. Esterification of **24** provides **13** which contains the key stereocenters in the C(1)–C(9) segment, and is activated for coupling to iodide **12** (see Figure 2).

Scheme 3. Corey's ring-cleavage to install the C(6) stereocenter



Kotchetkov's synthesis

In 1974, Miljkovic *et al.* proposed using sugars as the basic building blocks for the synthesis of polyketides.[10] Five years later, Hannessian realized this idea by synthesizing a seco-acid of erythronolide A from glucose.[11] Aside from a different protecting group plan, Kotchetkov essentially mimics Hannesian's scheme to make erythronolide B (Figure 3). Based on Woodward's seco-acid cyclization precedence,[3] Kotchetkov prepared the seco-acid **25** containing the presumably critical 3,5;9,11-bis(cyclo)acetal protecting groups. (Indeed, with the Corey-Nicolaou double activation method, **25** lactonizes to form the corresponding macrolactone in 50% yield.) The key

fragments in Kotchetkov's synthesis, sulfoxide **26** and ketone **27** were both derived from levoglucosan **28**.

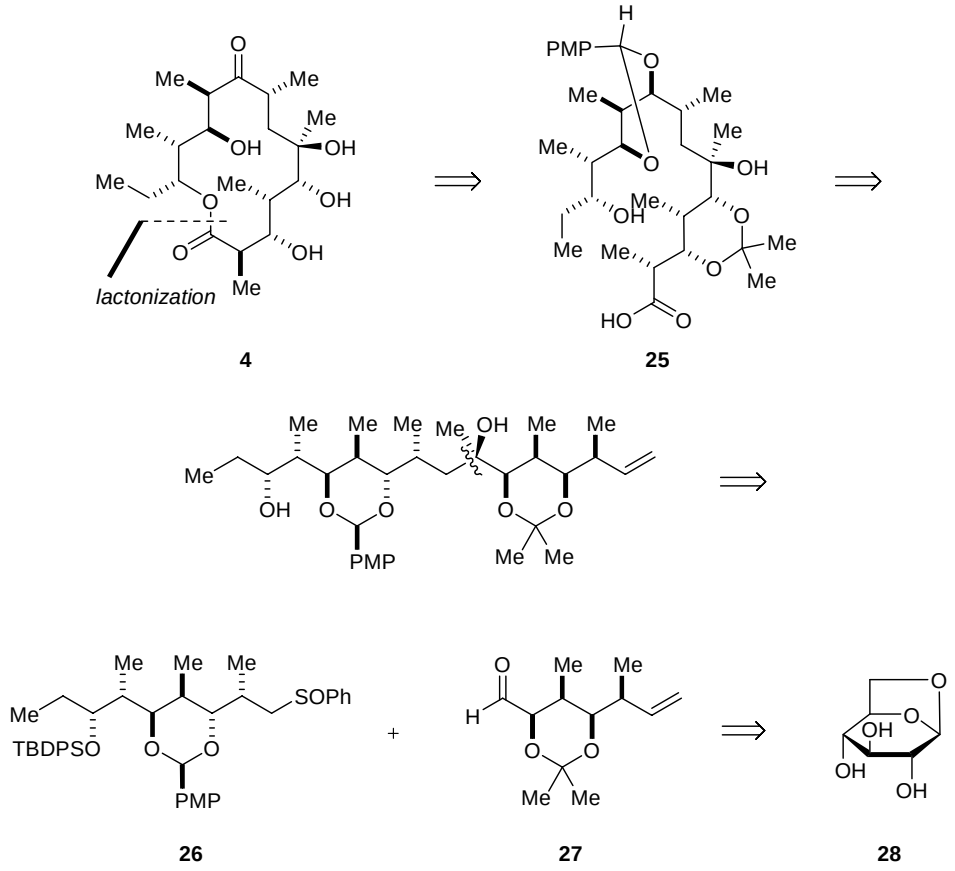
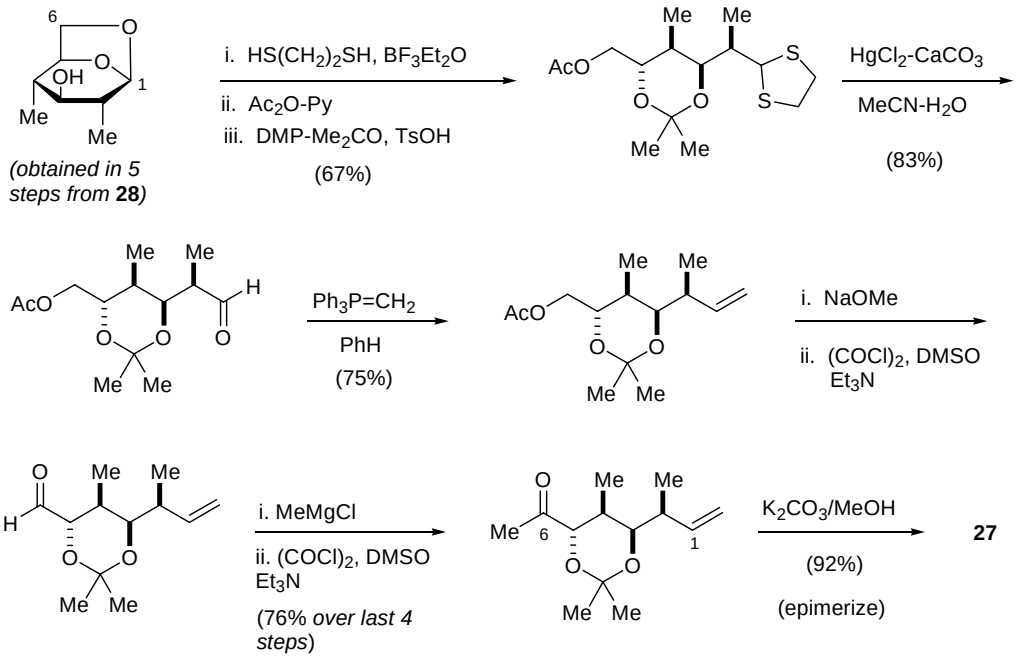


Figure 3. Kotchetkov's synthesis (thirty-six steps from **28**)

Sugar approach. Unfortunately, using levoglucosan as the chiral source necessitates many protecting group and functional group manipulations which diminishes the efficiency of this route. For example, Scheme 4 outlines the sixteen functional group and protecting group interchanges required for elaborating the sugar **28** to the C(1)–C(6) segment **27** of erythronolide B. In spite of starting with chiral building blocks which already contain most of the required asymmetric centers, Kotchetkov's

synthesis requires thirty-six transformations from **28**. Furthermore, a sugar approach hampers the design of flexible syntheses, and as such limits access to clinical analogues.

Scheme 4. Kotchetkov's derivitization of levoglucason to C(1) to C(6) fragment **27**



Mulzer's Synthesis

In 1991, Mulzer and coworkers completed the total synthesis of erythronolide B in twenty-five linear steps from *(R)*-2,3-*O*-isopropylideneglyceraldehyde **29**, in an approximate overall yield of 0.8% (Figure 4).[6c] Mulzer speculated that reducing the number of tetrahedral centers on the seco-acid, especially in the region surrounding C(9), could aid cyclization. Indeed, the 8,9 anhydro seco acid **30** smoothly formed macrolactone **31**, under Yamaguchi's conditions (> 85% yield). The key coupling in this route involves the Cram-chelate[12] selective addition of the allyl sulfide anion **32** to ketone **33** installing the requisite C(6) tertiary alcohol center (96% yield, 88:12 dr). Fragments **32** and **33** were both derived from **29**.

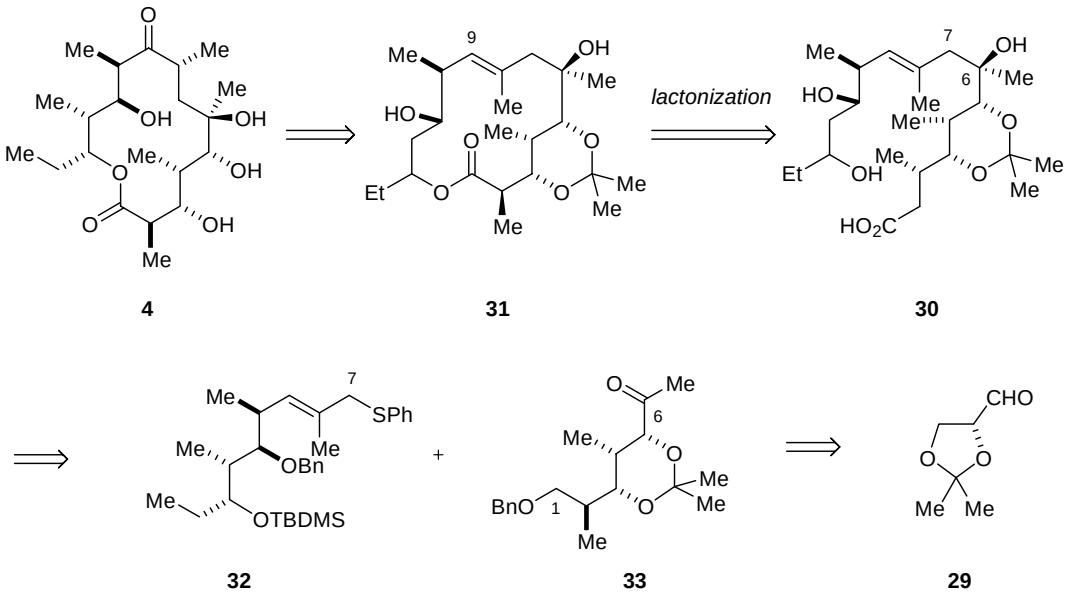
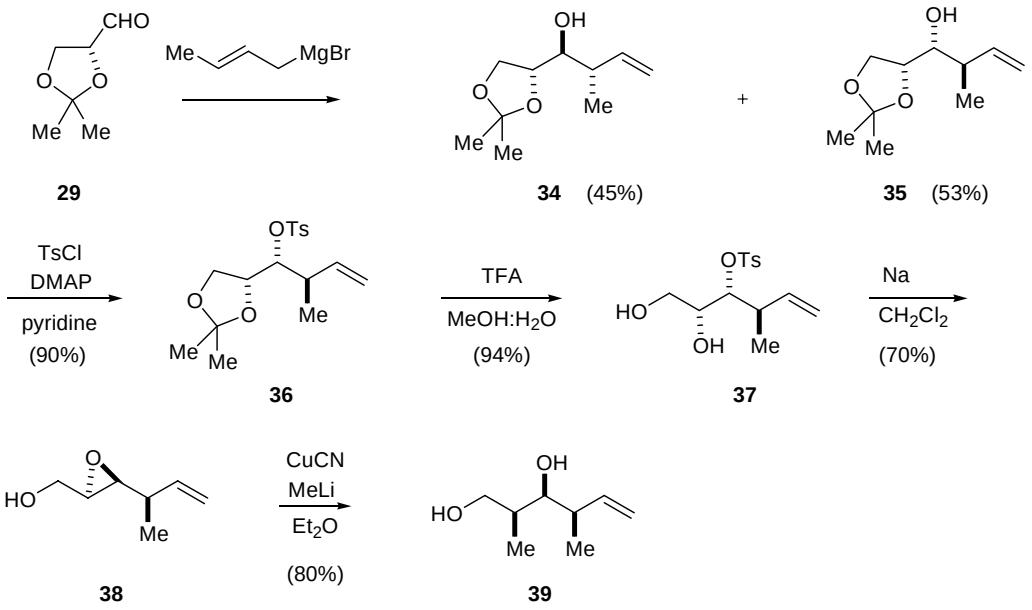


Figure 4. Mulzer synthesis (twenty-five steps from **29**, 0.8% yield)

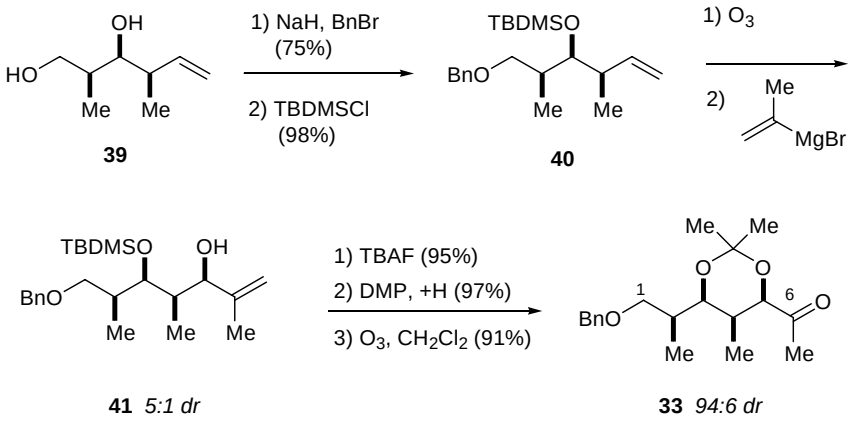
Acyclic approach. As shown in Scheme 5, Mulzer's synthesis of the C(1)–C(6) fragment **33** involves allylation of aldehyde **29** to produce a mixture of **34** and **35** in 45% and 55% yield, respectively.[13] The alcohol **34** was then transformed via intermediates **36**, and **37** to epoxy alcohol **38**, which upon treatment with Lipshutz' methylcuprate regiospecifically furnished the 1,3-diol **39** in about 40% yield overall.[14] (Notably, alcohol **35** also obtained from the allyation of aldehyde **29** was transformed to sulfoxide **32**).

Scheme 5. Mulzer's acyclic approach to C(1)–C(6) fragment of erythronolide B



As shown in Scheme 6, compound **39** was then monbenzylated at the primary position, and silylated to give **40**, which was subjected to ozonolysis to form an aldehyde that was treated with isopropenylmagnesium bromide. The silyl group suppresses a 1,3-chelate mechanism, enabling a Felkin-Anh pathway to occur and form **41** as a 5:1 mixture of diastereomers. Subsequent deprotection, acetonide protection and ozonolysis yields **33,** which can be epimerized at C(6) to enrich the diasteromeric ratio to 94:6.

Scheme 6. Felkin selective allylation to install the C(5) hydroxyl stereocenter



39 **40** **41** *5:1 dr* **33** *94:6 dr*

Martin's synthesis of erythromycin B

In 2003, Martin and coworkers reported their second-generation approach to erythromycin B which involves twenty-seven transformations and an approximate overall yield of 0.8% from furan-aldehyde **42** (Figure 5). For the first time in a macrolide synthesis, the sugar residue is appended *prior* to the macrolactonization step. Under Yamaguchi's protocol, **43** cyclizes to form the corresponding macrocycle in excellent yield (85%). Two key disconnections, a crotyllation and an aldol transformation, reveal alehdyde **44**, **45**, and the C(3) to C(9) fragment **46**.

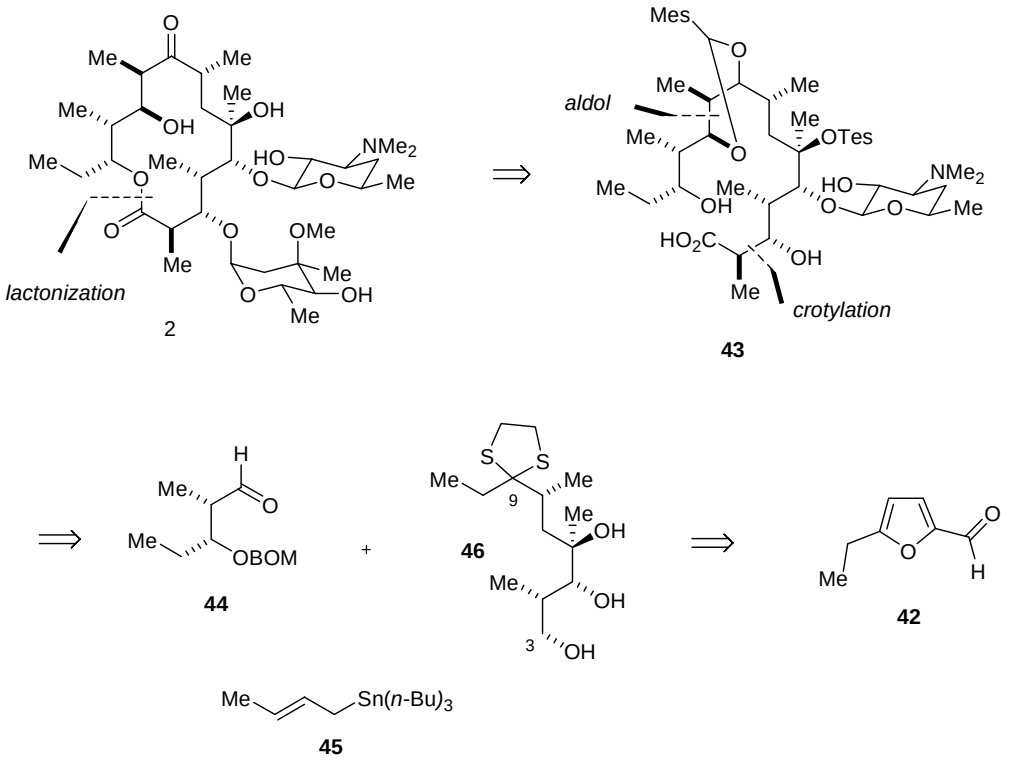
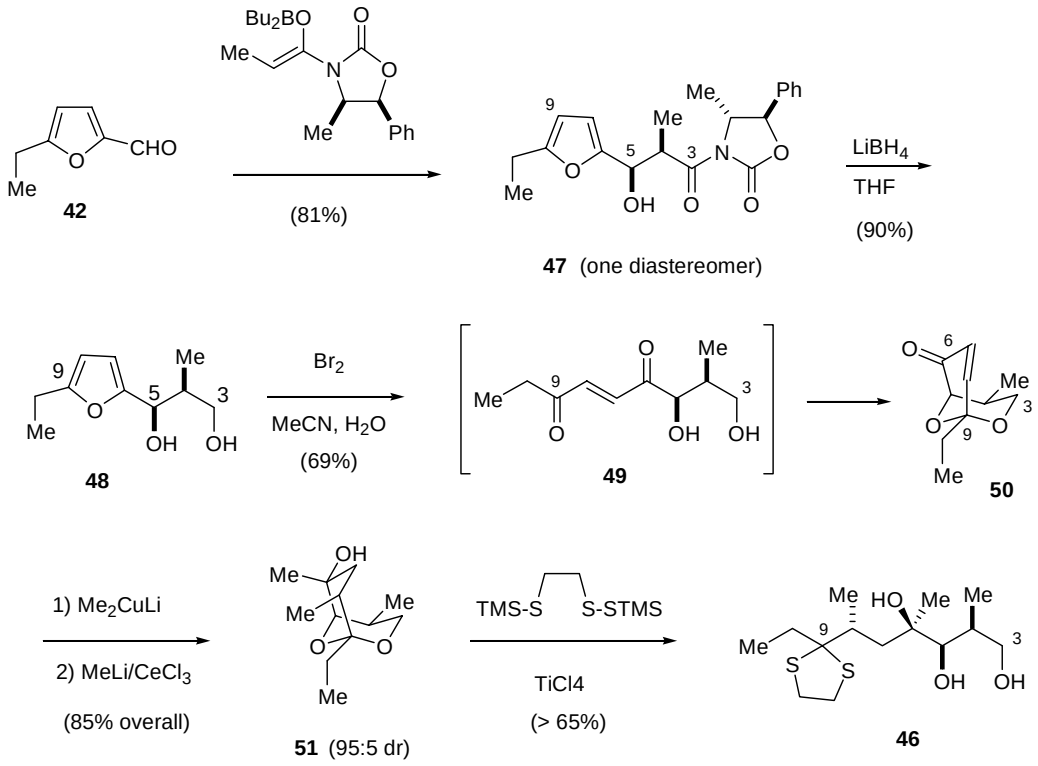


Figure 5. Martin's synthesis (twenty-seven steps from **42**, 0.8% yield)

Synthesis of the C(3)–C(9) fragment. Martin developed an elegant six-step synthesis of the C(3) to C(9) fragment **46**, starting from the known aldehyde **42**, which was prepared by a Vilsmeier-Haack formylation of 2-ethylfuran.[15] As shown in Scheme 7, aldehyde **42** was subjected to a diastereoselective Evan's aldol protocol to provide **47** in 81% yield as one diastereomer. Reductive removal of the auxiliary with lithium borohydride affords **48** in 90% yield. Oxidation of diol **48** with bromine, forms an intermediate dihydroxy enedione **49** which *in situ* undergoes acid-catalyzed bicycloketalization to provide **50** in 69% yield. Importantly, the conformation of this bicycle enables highly stereoselective 1,4-addition of lithium dimethylcuprate, followed by stereoselective 1,2-addition of methyl lithium to furnish **51** in 85% overall yield.

Treatment of **51** with an ethanedithiol protecting group opens the bicycle, affording the acyclic C(3)–C(9) backbone **46**.

Scheme 7. Martin's approach to the C(3)–C(9) segment of erythromycin



Concluding Remarks

Arguably, the most effective strategy for addressing stereochemistry in the erythromycins rely on the *acyclic* approach, applying, namely, aldol or allylation reactions *iteratively*.[16] In contrast to the *sugar* or *ring-cleavage* strategies, applying stereoselective bond forming methods also enable the development of more convergent and flexible synthetic routes. Remarkably, the Claisen rearrangement,[17] has not been exploited in the synthesis of the erythromycin family, *despite* its efficacy for constructing

stereocenters on acyclic architectures. The next chapter presents our contributions to the field of macrolide antibiotic synthesis through a novel synthesis of erythronolide B based on our tandem acyl-Claisen rearrangement.[18]

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(16) For an excellent use of aldol chemistry in macrolide synthesis, see Evan's synthesis of oleandymycin and 6-deoxyerythronolide b (18 linear steps), reference 7c.

(17) See Chapter 1 for discussion of the Claisen rearrangement, and reference therein.

(18) See Chapter 3 for discussion of the tandem acyl-Claisen rearrangement.

Chapter 6

Applications of the Tandem Acyl-Claisen Rearrangement in Macrolide Synthesis: ATotal Synthesis of Erythronolide B

Synthesis Plan

Our retrosynthesis for erythronolide B (**1**) involves three key disconnections leading to known aldehyde **2**,[1] propionate fragment **3,** and ketone **4** (Figure 1). This route relies on a macrolactonization to form the 14-membered ring, and standard aldol technology to establish the requisite links between fragments **4** and **2**, and fragments **4** and **3**. The structurally complex C(3)–C(9) backbone (**4**) will be accessed by an asymmetric tandem acyl-Claisen rearrangement[2] between diamine **5** and propionyl chloride (**6**).

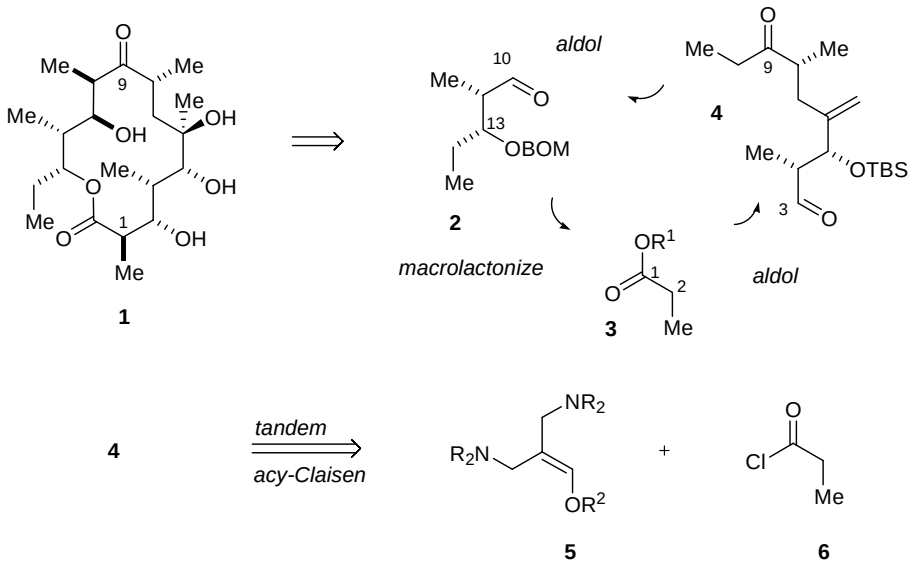
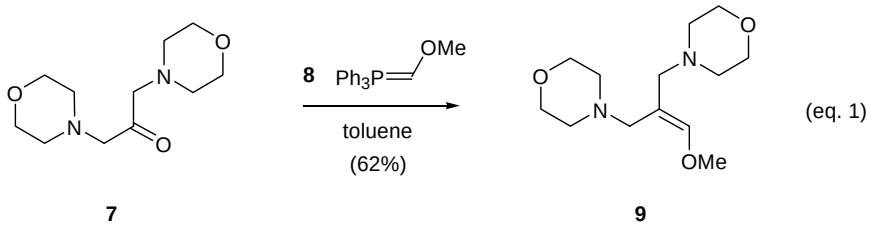


Figure 1. A novel synthesis of erythronolide B

Tandem Acyl-Claisen Rearrangement

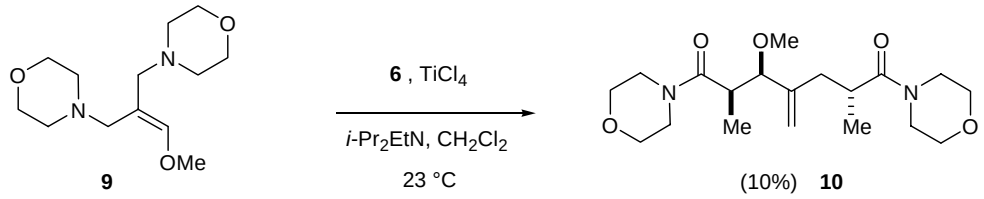
Our studies began with the Wittig olefination of bismorpholino-ketone **7**[3] with ylide **8** to prepare the methoxy substituted diamine **9** (62% yield, equation 1).



7 **9**

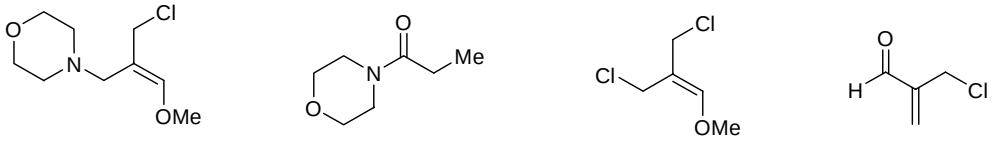
Subjecting diamine **9** and propionyl chloride (**6**) to representative conditions for the tandem acyl-Claisen rearrangement[2] yielded the desired product **10** with poor efficiency (<10% yield), in conjunction with an elaborate mix of byproducts **11**, **12**, **13**, and **14** (Scheme 1).

Scheme 1. Tandem acyl-Claisen rearrangement with diamine **9**



9 (10%) **10**

mainly decomposition of diamine **9** *observed*

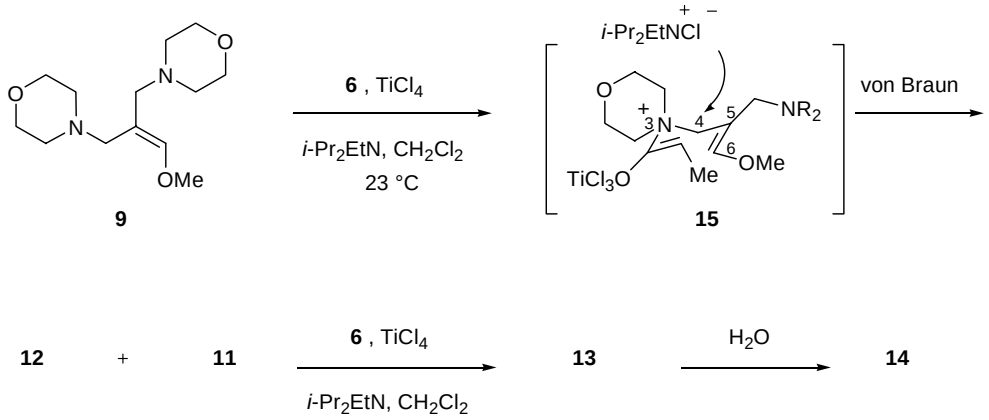


11 **12** **13** **14**

These results indicated diamine **9** was decomposing via von Braun cleavage.[4] As illustrated in Scheme 2, diamine **9** condenses with ketene to form an ammonium intermediate **15**, which was expected to smoothly undergo rearrangement to Claisen

product **10**. However, the competing nucleophilic attack of chloride ion on C(4) cleaves the C(4)–N(3) σ bond, and expels by-products **12** and **11**. An analogous degradation of amine **11** can be envisioned to from the dichloride **13**, which subsequently hydrolyzes to the observed aldehyde **14**.

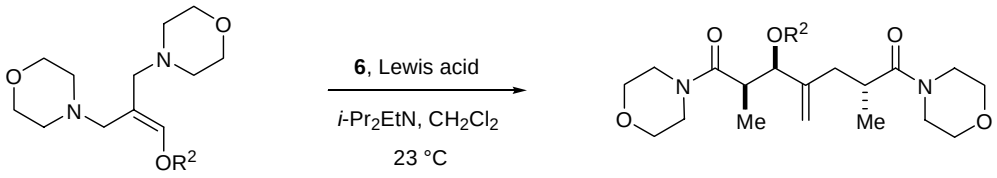
Scheme 2. Von Braun cleavage of diamine **9**

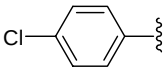
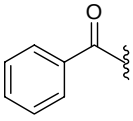
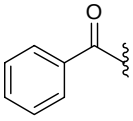


Electronic considerations for the protecting group in diamine 5. The methoxy substituent of diamine **9** supplies significant electron density to the C(5)–C(6) π system. This electron donation stabilizes the partial positive charge that develops on C(4) as this carbon center undergoes S_N2 attack by chloride ion (Scheme 2). As a result, electron donating substituents accelerate von Braun cleavage. We reasoned that the Claisen rearrangement could thus be favored by using protecting groups on the oxygen atom which are relatively electron-withdrawing (e.g., R^2 = *p*-ClPh or Bz) (Table 1). Indeed, diamine **16**, undergoes Claisen rearrangement over von Braun cleavage to a greater extent than **9**, affording the corresponding tandem Claisen product in moderate yield and excellent selectivity (55% yield, 94:6 dr, Table 1, entry 2). However, as the *p*-chlorophenyl ether linkage is not readily cleavable,[5] we decided to test diamine **17**. This

substrate (**17**) efficiently undergoes Claisen rearrangement with acceptable levels of diastereocontrol (75% yield, 83:17 dr, entry 3). To our delight, by changing the Lewis acid from $TiCl_4$ to $Yb(OTf)_2$, further improvements in the both efficiency and selectivity were observed (86%, 91:9 dr entry 4). Importantly, the benzoate group is readily removable under basic conditions.[6]

Table 1. Effects of representative protecting groups (R^2) on the tandem-Claisen rearrangement



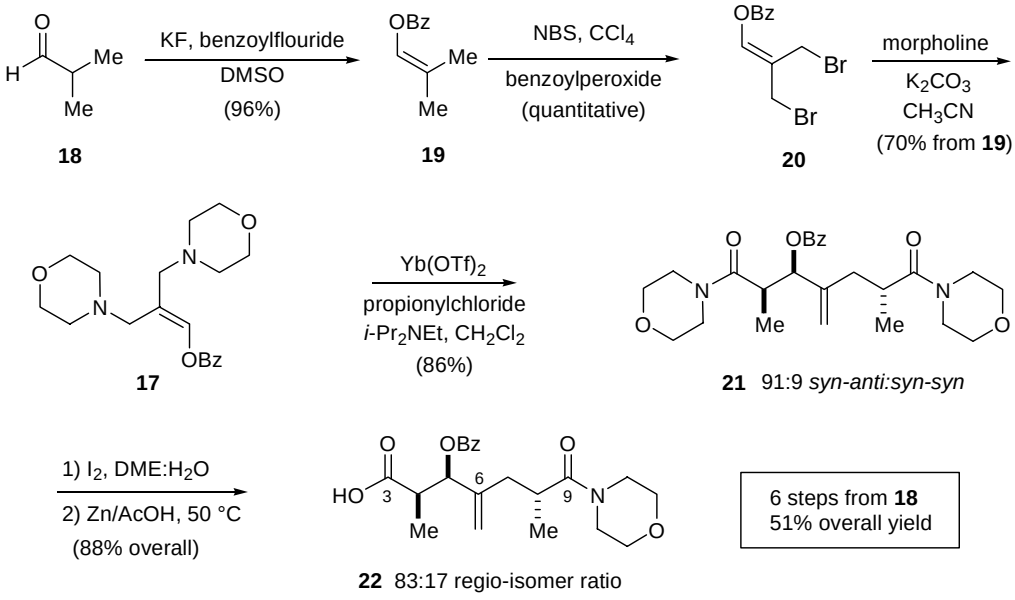
entry	allyl diamine	R^2	Lewis acid	% yield	*syn-anti/ syn-syn*[a]
1	**9**	Me	$TiCl_4$	10	70:30
2	**16**		$TiCl_4$	55	94:6[b]
3	**17**		$TiCl_4$	75	83:17
4	**17**		$Yb(OTf)_3$	86	91:9

[a] Diastereomeric ratio determined by ^1H NMR analysis.

We developed an efficient route to access diamine **17** on preparative scale (ca >50 grams) from readily available isobuterylaldehyde **18** (Scheme 3). Treatment of **18** with KF, and benzoyl fluoride in DMSO furnishes known **19**[7] in 96% yield. Bis-allylic bromination of **19** followed by treatment of the resulting dibromide **20** with morpholine

affords diamine **17** in 70% yield.[8] As summarized in Scheme 3, subjection of diamine **17** with propionyl chloride under optimal rearrangement conditions provides the C(3)–C(9) segment **21** of erythronolide B in excellent yield and selectivity (86% yield, 91:9 *syn-anti*:*syn-syn*). Regioselective hydrolysis of bisamide **21** was achieved by iodolactonization with I_2, followed by reductive opening of the lactone with zinc to provide acid **22** in 88% yield with good regioselectivity (88:17).[9]

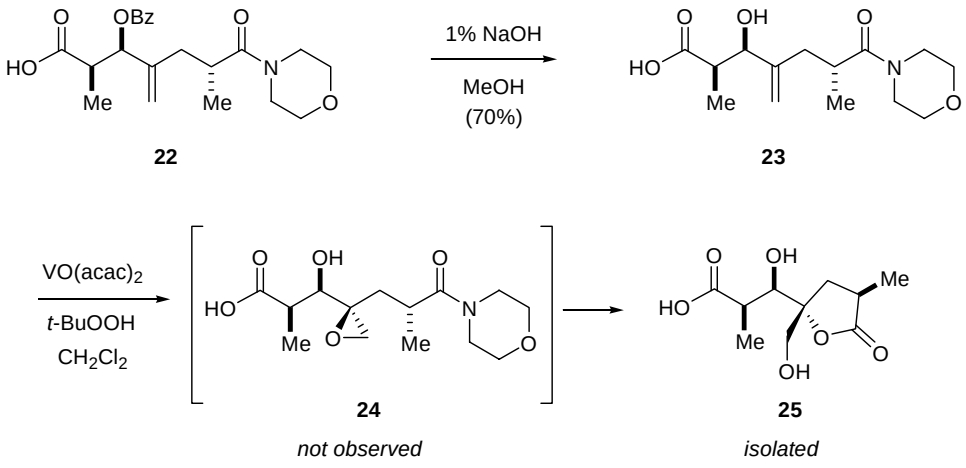
Scheme 3. Synthesis of the C(3)–C(9) fragment **22**



Initial Attempts to Stereoselectively Oxidize C(6)

With **22** in hand, we proceed to install the final stereocenter on this C(3) to C(9) fragment. However, stereoselectively oxidization of the C(6) position proved more difficult than anticipated. Our efforts began with deprotection of **22** to alcohol **23** (Scheme 4). Directed epoxidation with $VO(acac)_2$[10] on **23** was expected to provide oxirane **24**, however, lactone **25** was isolated instead. Presumably, the intramolecular addition of the amide carbonyl to the oxirane ring of **24** produces an imminium intermediate which affords **25** upon aqueous treatment. Unfortunately, this epoxide opening could not be suppressed in the presence of $VO(acac)_2$.

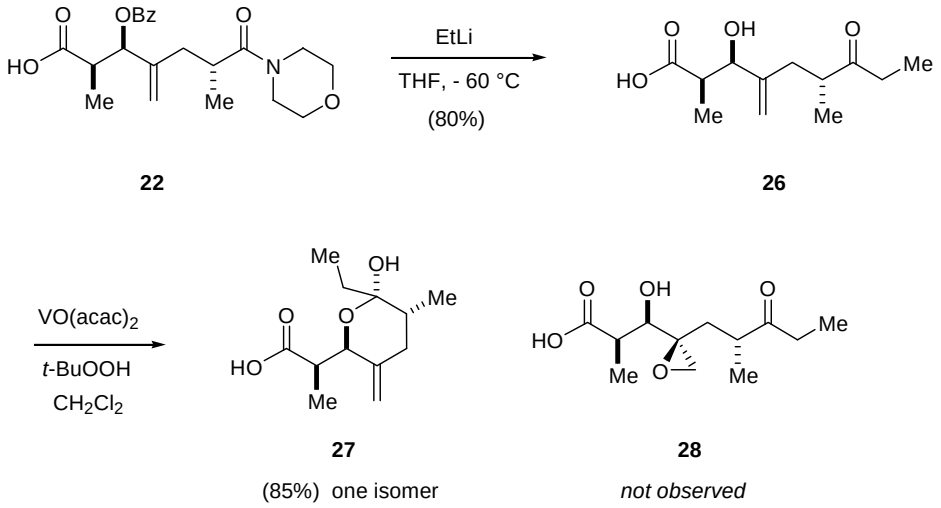
Scheme 4. Directed epoxidation of amide **23** with VO $(acac)_2$



As the amide functionality appeared problematic, we decided to delay epoxidation of the double bond until after the conversion of the morpholine-amide **22** to ethyl ketone **26** (Scheme 5). Treatment of **22** with freshly prepared EtLi, cleaves the benzoate ester and functionalizes the amide ester to afford **26** (80% yield).[11] Unfortunately, exposure of

26 to $VO(acac)_2$ resulted in facile intramolecular cyclization to ketal **27**,[12] and not the desired epoxide **28**.

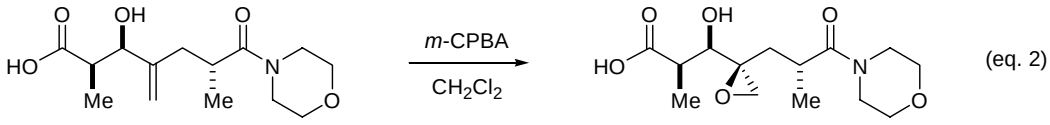
Scheme 5. Directed epoxidation of ketone **26** with $VO(acac)_2$



22 **26**

27 (85%) one isomer **28** *not observed*

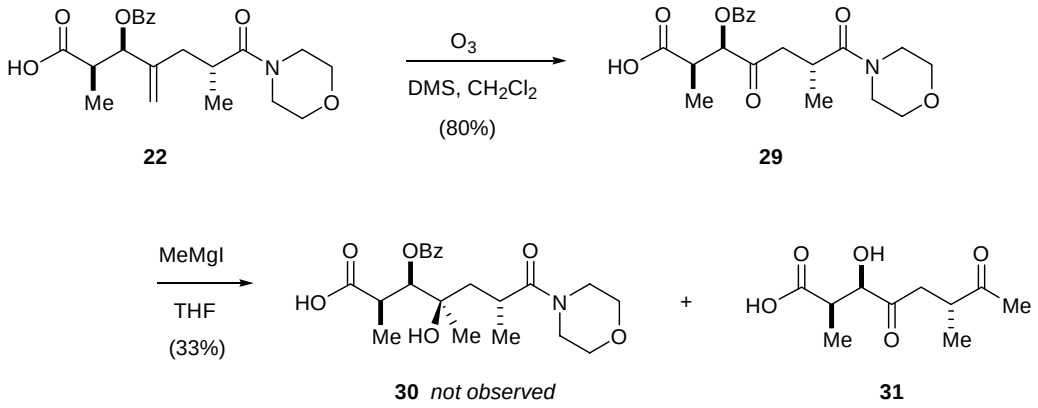
In contrast to the $VO(acac)_2$ epoxidation, we found that the *m*-CPBA epoxidation of **23** resulted in quantitative oxidation to desired product **24**. However, this oxidation was non-diastereoselective (1:1 dr) (equation 2).



23 **24** (quantitative) 1:1 dr (eq. 2)

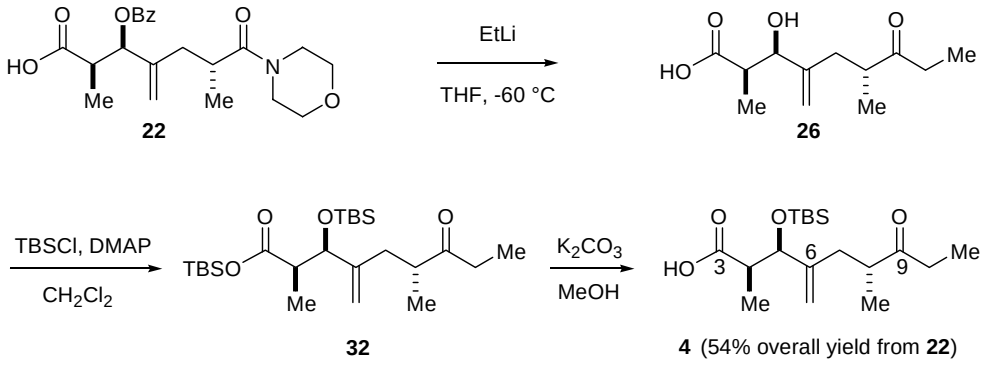
As an alternative to epoxidation, we explored the Felkin-selective[13] grignard addition. Transformation of alkene **22** to ketone **29** by ozonolysis, followed by addition of methylmagnesium bromide to provide **30** was also unsuccessful (Scheme 6). In this case, the grignard reagent reacts with the morpholine-amide in preference to the ketone functionality to produce methyl ketone **31**.

Scheme 6. Ozonolysis/grignard strategy on **22**



As stereoselective oxidation of the C(6) position proved difficult in the presence of the both the amide and ketone carbonyls, we decided to delay installing this stereocenter to a later stage of the synthesis. To prepare fragment **4** which was properly elaborated for the key aldol coupling (Figure 1), we treated amide **22** with EtLi to form ketone **26** (Scheme 7). As **26** proved acid labile and prone to intramolecular hemi-ketal formation, it was immediately treated with TBSCl to produce silylester **27**. This ester was treated with aqueous base to provide the desired ketone **4** in 54% overall yield from **22**.

Scheme 7. Elaboration of racemic bisamide **22** to racemic ketone **4**

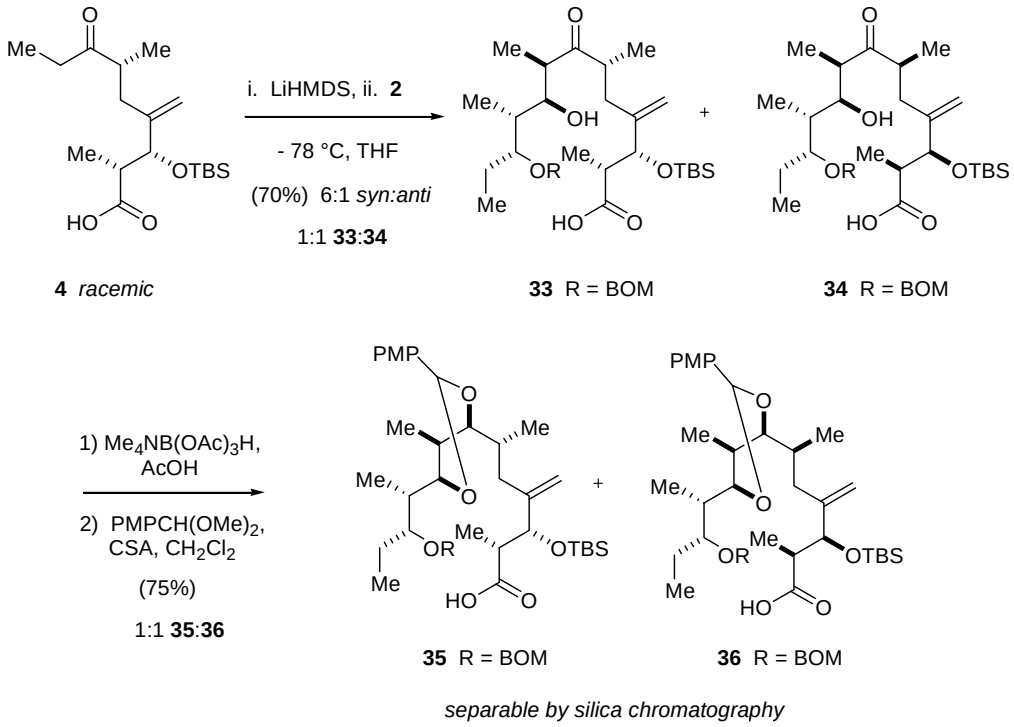


Chiral Resolution of Ketone 4 by Aldol Coupling to Aldehyde 2

We sought to explore the final stages of our synthesis plan prior to investing efforts on developing an asymmetric route to **4**. As such, ketone **4** was optically resolved by coupling to **2** based on Martin's reported aldol coupling of an analogous substrate.[14] As shown in Scheme 8, treatment of the racemic mixture of ketone **4** with lithium hexamethyldisilazide**,** followed by addition of aldehyde **2** affords products **33** and **34** as an inseparable equimolar mixture in 70% yield (6:1 *syn:anti*). The stereochemical relationship between the newly formed centers was assigned by analogy to Martin's system.[14]

Next, we installed the critical C(9), C(11) cyclic protecting group to ensure efficient ring-closing.[16] Although, the C(9) hydroxyl stereocenter would ultimately be lost through oxidation, the 9-(*S*) configuration at this center has proven instrumental in previous seco acid marcocylizations.[21] Treatment of **33** and **34** with $Me_4NB(OAc)_3H$ affords an *anti*-selective reduction to provide the desired 9-(*S*) diastereomer which was converted to the *para*-methoxybenzilydene acetals **35** and **36** in 75% overall yield.[14] These diastereomers were separated by chromatography and individually characterized. With the identity of the desired diastereomer **35** secured by Mosher ester analysis,[15] we proceeded to elaborate this material to the seco-acid of erythronolide B through the Evan's aldol transformation.

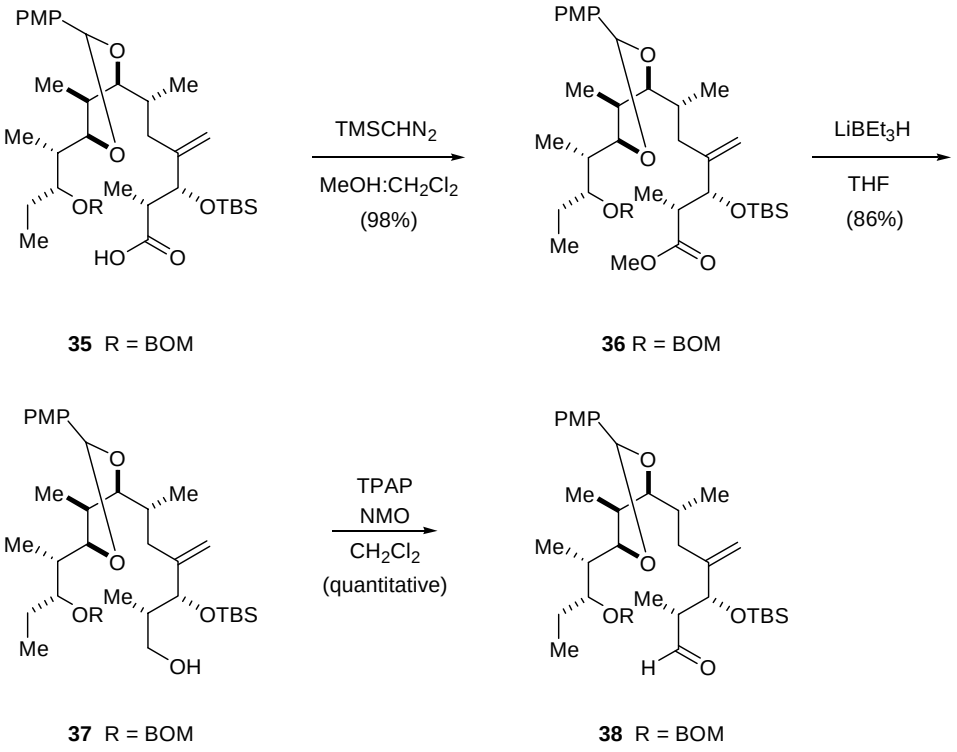
Scheme 8. Synthesis of the C(3)–C(15) fragment **35** and **36**



Synthesis of Seco Acid 42

As outlined in Scheme 9, esterification of **35** with trimethylsilyl diazomethane provides **36**, which undergoes $LiBEt_3H$ reduction to afford alcohol **37** in 83% yield. Subjecting **37** to TPAP oxidation quantitatively furnishes aldehyde **38**.

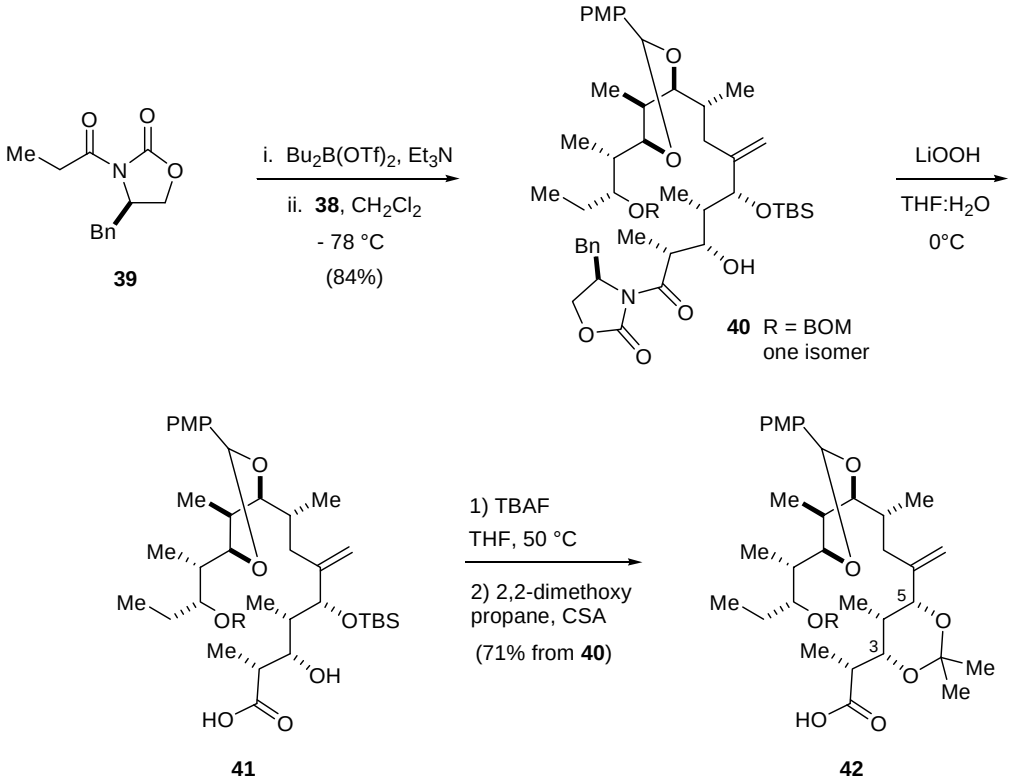
Scheme 9. Transformation of the acid **35** to aldehyde **38**



To establish the final carbon atoms and install the critical C(2) and C(3) asymmetric centers, we pursued the aldol reaction between (*R*)-(-)-4-benzyl-3-propionyl-2-oxazolidinone (**39**) and freshly prepared aldehyde **38** (Scheme 10). By Evan's protocol,[21] **40** was furnished in 85% yield as one diastereomer. Next, to ensure pre-organization of our seco acid for ring closing, we installed the critical C(3),C(5) cyclic protecting group.[16] Deprotection of the silyl moiety in **41** by TBAF at 50 ºC provided a

diol, which was transformed into acetonide **42** (71% overall yield from **40**). The desired stereochemistry obtained from the *syn*-Felkin selective aldol coupling was confirmed by two key NMR experiments: (1) observation of nOe coupling between H-3 and H-5, and (2) ^{13}C NMR analysis by the Rychnovsky acetonide method (experimental methods).[17]

Scheme 10. Elaboration of aldehyde **38** to the seco acid **42**

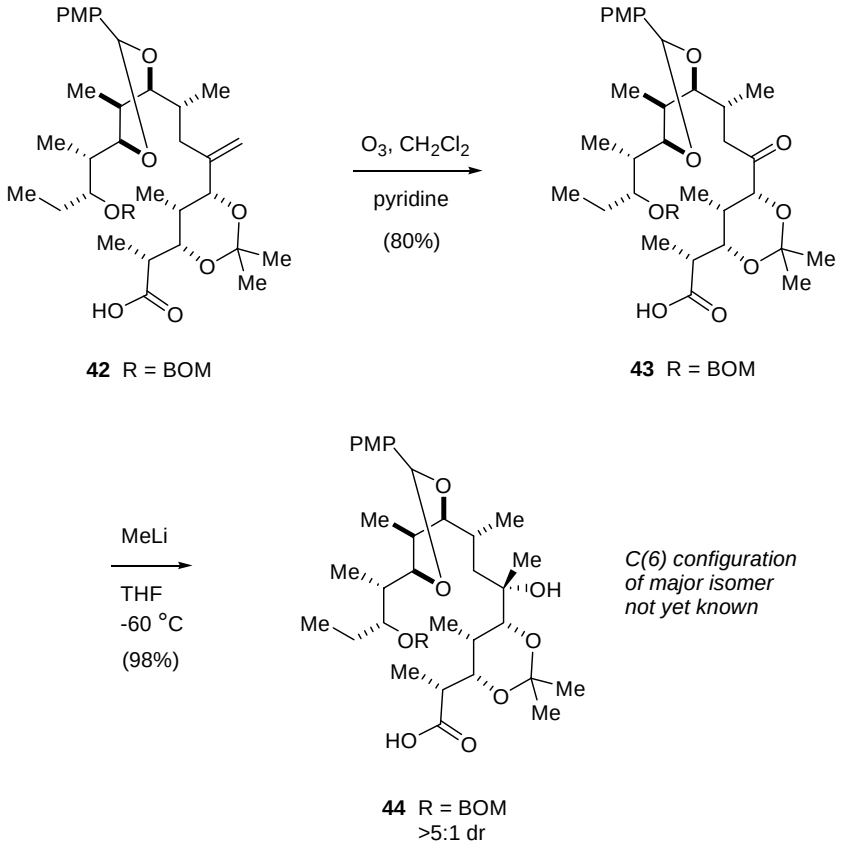


At this junction in our route, the two cyclic protecting groups critical for macrocyclization were in place. Furthermore, we had successfully installed nine of the ten requisite asymmetric stereocenters of the erythronolide B (**1**) skeleton. With **42** in hand, the final stereochemical challenge that remained was the tertiary alcohol stereocenter. As such, we returned to pursuing a stereoselective oxidation of C(6).

Late-Stage Attempts to Stereoselective Oxidize C(6)

Felkin-selective organolithium approach. Ozonolysis of alkene **42** to ketone **43** proceeded in good yield, contingent upon the presence of pyridine as a buffer in the oxidation (80% yield) (Scheme 11). The addition of methyllithium to ketone **43** at low temperature provided **44** with the tertiary alcohol stereocenter in >5:1 diastereoselectivity and 98% yield.

Scheme 11. Installing the C(**6**) stereocenter by an organolithium addition



42 R = BOM

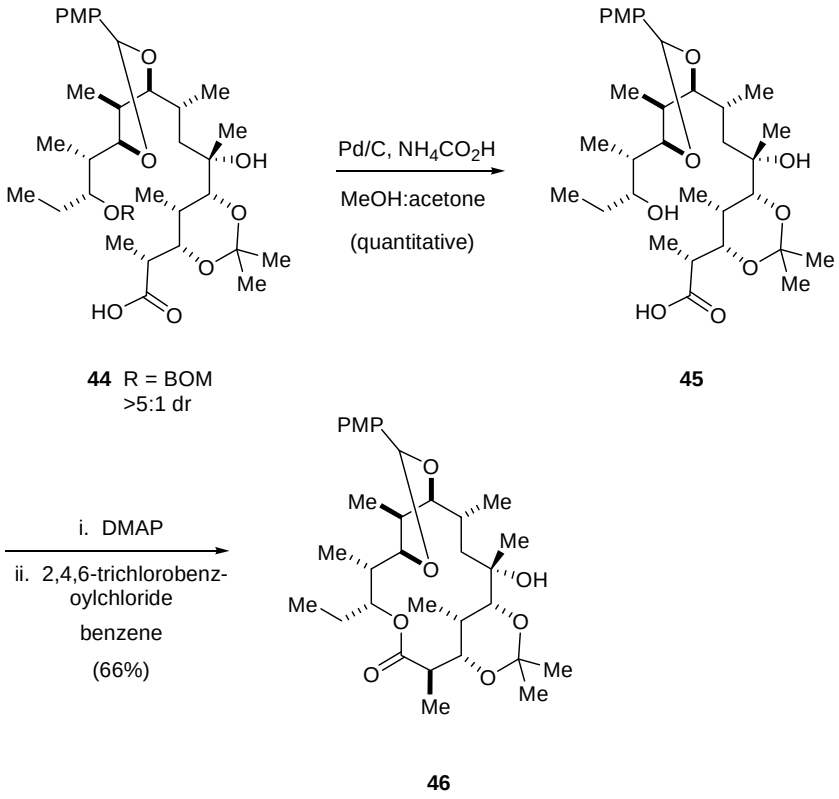
43 R = BOM

44 R = BOM
>5:1 dr

To establish the configuration of the C(6) stereogenic center, we needed to elaborate **44** for comparison to an intermediate in Kotchetkov's synthesis.[18] As shown in Scheme 12, hydrogenating **44** with Pd/C and ammonium formate yields **45**. Subjection

of seco acid **45** under Yamaguchi's macrolactonization conditions resulted in formation of the macrocycle **46** in 66 % yield. To our surprise, this material did *not* correlate to the published ^{1}H NMR data reported by Kotchetkov.[18] This result indicated that contrary to our predictions based on the Felkin-Anh model,[13] and contrary to precedence based on an analogous substrate,[19] the undesired epimer was obtained in this MeLi addition.[20]

Scheme 12. Synthesis of the C(**6**) epi-macrolactone **46**



44 R = BOM
>5:1 dr

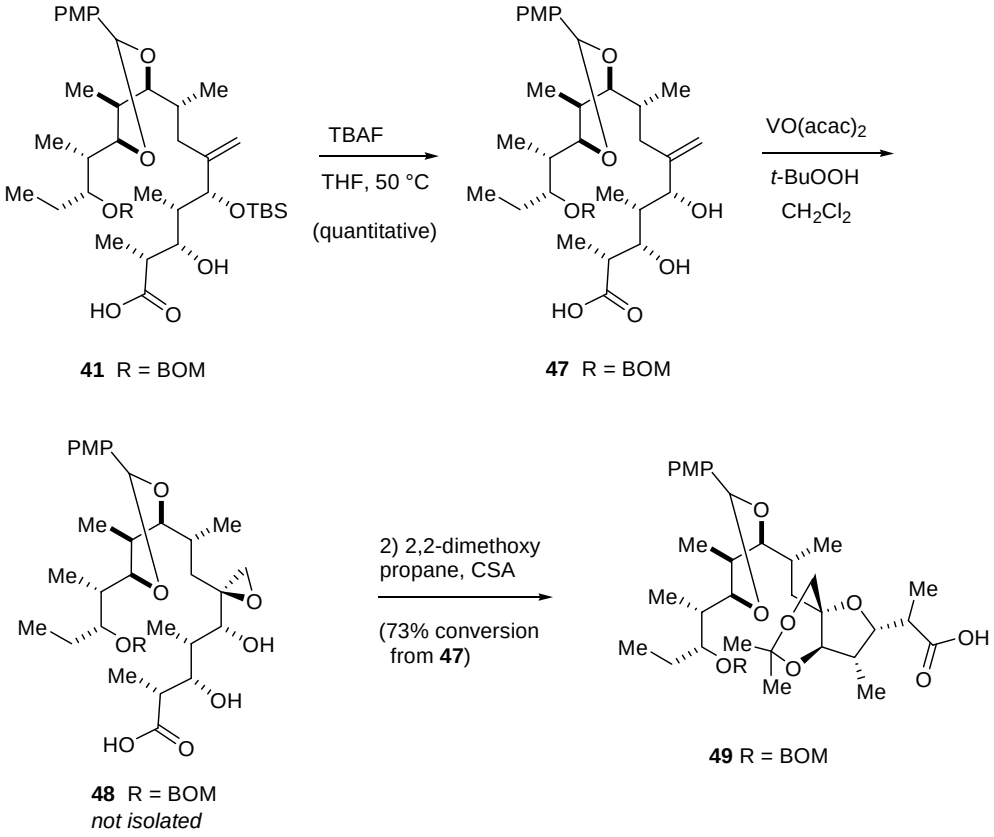
45

46

Directed epoxidation approach. As depicted in Scheme 13, TBAF deprotection of silylester **41** provides an allylic alcohol **47** which appeared to be an attractive substrate for directed epoxidation by $VO(acac)_2$ to provide **48**. Subjection of **47** to $VO(acac)_2$ results in a complex mixture of products as observed by ^{1}H NMR analysis. Previous reports indicate that diol-epoxide functionalities analogous to the desired oxirane **48** are

extremely labile.[21] As such, we treated **48** (without further purification) to 2,2 dimethoxy propane/CSA in an attempt to produce the corresponding acetonide. However, under these conditions, formation of the tetrahydrofuran protected acetonide **49** was observed (73% conversion by LC/MS).

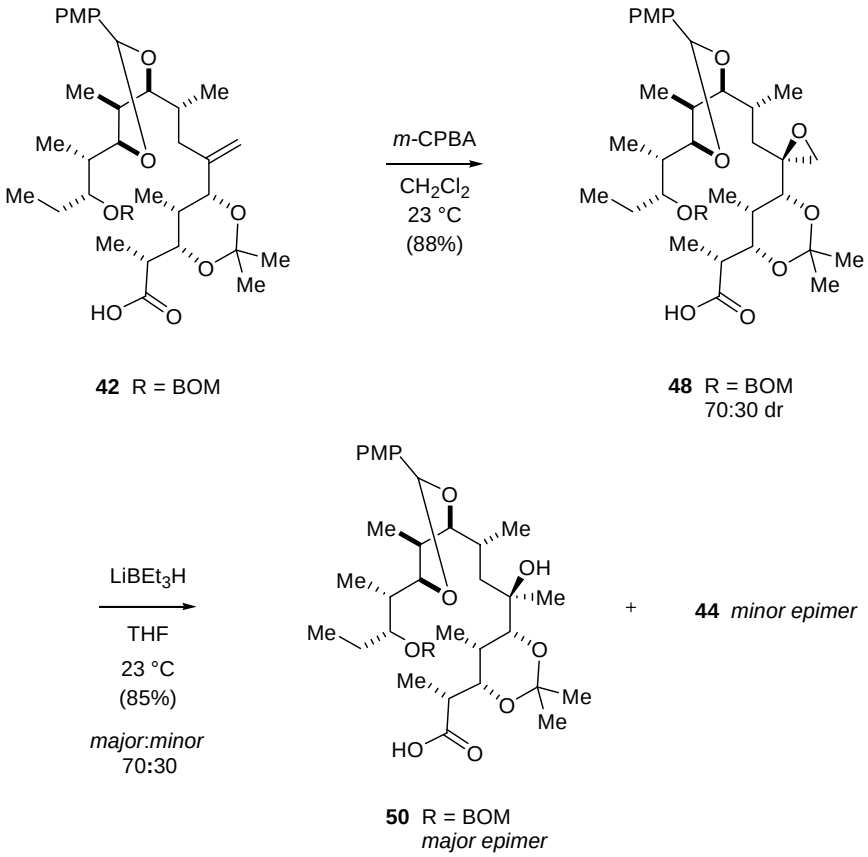
Scheme 13. Directed epoxidation of **47**



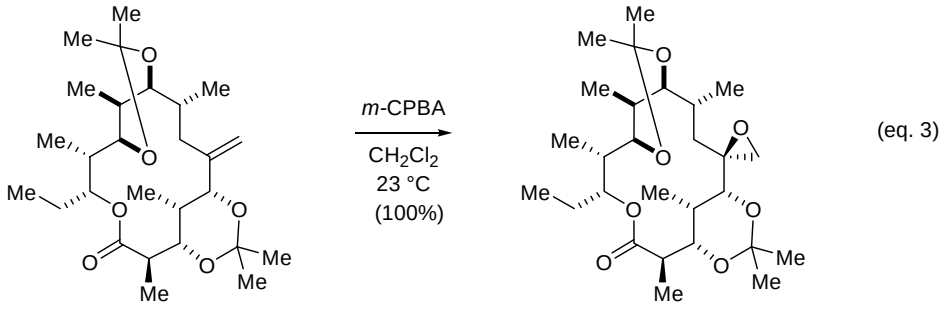
Epoxidation by m-CPBA. Bloch and coworkers reported that control of the diastereofacial selectivity in the epoxidation of rigid allylic ethers was possible using *m*-CPBA.[22] Inspired by this report, we took an alternative route to install the C(6) stereocenter (Scheme 14). Oxidation of **42** with *m*-CPBA provides **48** which was reduced with $LiBEt_3H$,[23] to provide **50** in 75% overall yield (70:30 dr). To our delight,

^{1}H NMR studies confirmed that the major product obtained from this sequence was indeed the desired epimer; the minor component proved identical to product **44** obtained from the ozonolysis-methyllithium sequence (Scheme 11). Preliminary efforts towards enhancing the facial selectivity in this oxidation by variation in solvent (e.g., THF, toluene, acetonitrile, dichloromethane) were not fruitful.

Scheme 14. Synthesis of seco acid **50**



In addition, we also examined the facial selectivity afforded by epoxidation on the macrocyclic ring of **51**.[24] Treatment of macrolactone **51** with *m*-CPBA occurs with no facial bias, affording macrolactone **52** as an equimolar mixture of diastereomers (equation 3).



(eq. 3)

51 **52** *1:1 dr*

As such, seco acid **50** containing the requisite C(6) stereocenter was elaborated to erythronolide B.

Completion of Erythronolide B

Macrolactonization. As shown in Scheme 15, hydrogenation of **50** with Pd/C and ammonium formate enabled the selective removal of the benzyloxymethylether (BOM) protecting group (in the presence of the benzylidine acetal) to provide **53**. Under Yamaguchi's conditions, **53** undergoes efficient ring closing to afford macrolactone **54** (65% yield). ^{1}H NMR and COSY experiments verified the structure of macrolactone **54**, as the data obtained from these experiments is consistent with the literature reported data for this compound (Table 2).[18] Consequently, a formal synthesis of erythronolide B was achieved by interception of Kotchetkov's intermediate.

Scheme 15. Synthesis of macrolactone **54**

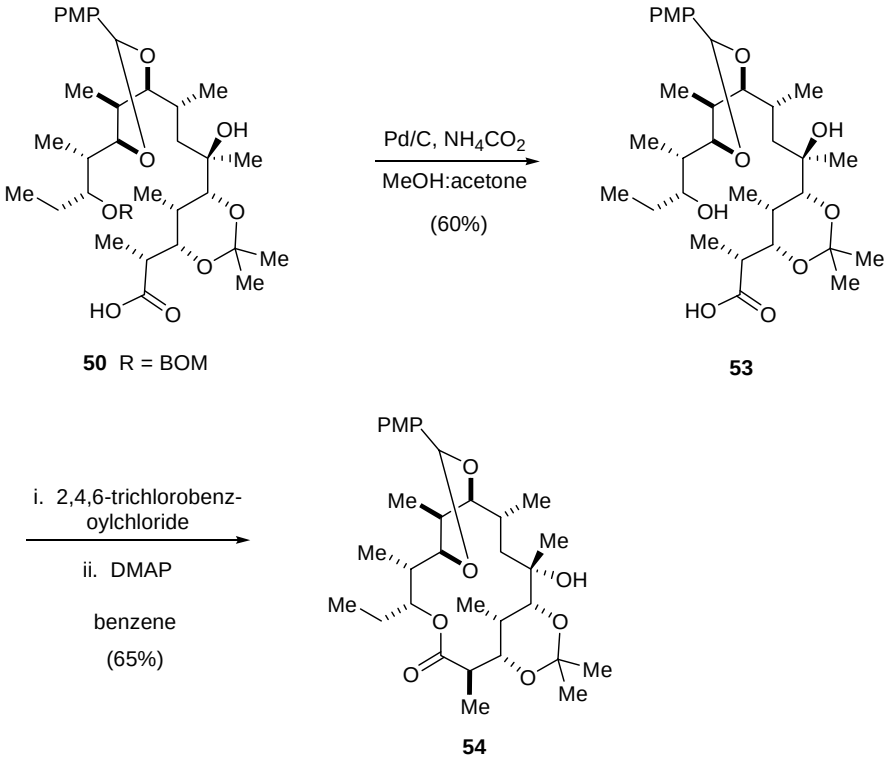


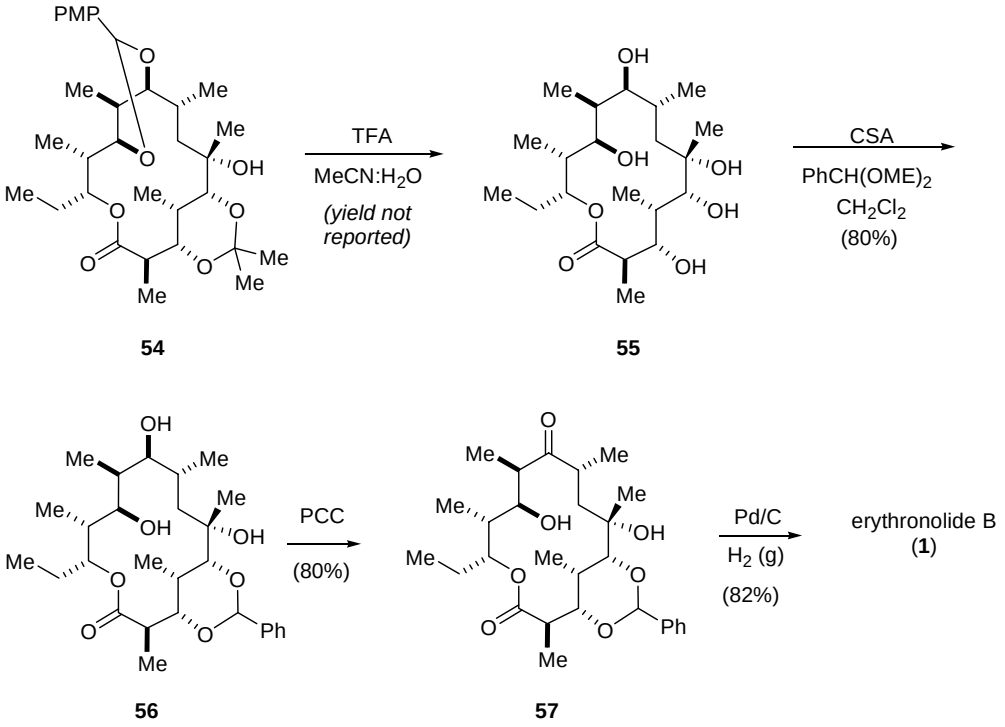
Table 2. Comparison of ^{1}H NMR Data for Macrolactone **54** and Kotchetkov's Macrolactone

	^{1}H δ (multiplicity, *J* (Hz), integration)	
COSY assignment	Macrolactone **54**[a]	Literature Report[b]
p-MeO**Ar**-	7.51 (d, *J* = 8.1 Hz , 2 H)	7.50 (m, 2H)
p-MeOArC**H**	5.69 (s, 1H,)	5.69 (s, 1H)
p-MeO**Ar**	6.90 (d, *J* = 8.7 Hz, 2 H)	6.89 (m, 2H)
H-13	5.45 (dd, *J* = 4.1 Hz, 10 Hz, 1H)	5.47 (ddd, *J* = 0.9, 4.5, 10 Hz, 1H)
H-5	4.06 (s, 1 H)	4.06 (d, *J* = 1.2 Hz, 1H)
p-**Me**OAr-	3.80 (s, 3H)	3.80 (s, 3H)
H-3	3.90 (d, *J* = 10.5 Hz, 1H)	3.90 (dd, *J* = 1.0, 10.5 Hz, 1H)
H-11	3.65 (d, *J* = 9.3 Hz, 1H)	3.66 (dd, *J* = 1.5, 9.1 Hz, 1H)
H-9	3.35 (d, *J* = 10.2 Hz, 1H)	3.35 (dd, *J* = 10.5 Hz)
H-2	2.77 (dq, *J* = 6.5, 10.5 Hz, 1H)	2.78 (dq *J* = 6.5, 10.5 Hz, 1H)
H-8	2.50 (m, 1H)	2.51 (dddq, *J* = 2, 6, 10.5 Hz, 1H)
OH-6	2.23 (br s, 1H)	2.23 (br s, 1H)
H-4, 10, 12, 14	1.60-1.80 (m, 4H)	1.60-1.80 (m, 4H)
H-14'	1.48 (m, 1 H)	1.46 (m, 1H)
H-7 and 7'	1.30 -1.50 (m, 2H)	1.30-1.50(m, 2H)
-OCMe_2O-	1.48 and 1.53 (2s, 6H)	1.48 and 1.53 (2s, 6H)
Me-6	1.25 (s, 3H)	1.25 (s, 3H)
Me-2, Me-4, and Me-8	1.21-1.27 (m, 9H)	1.21 (d, *J* = 6.5 Hz, 3H, Me-2) 1.23 (d, *J* = 6.5 Hz, 3H, Me-4) 1.26 (d, *J* =6.0 Hz, 3H, Me-8)
Me-10 or Me-12	1.02 (d, *J* = 6.0 Hz, 3H)	1.02 (d, 3H)
Me-10 or Me-12	0.88 (d, *J* = 6.9 Hz, 3H)	0.88 (d, 3H)
Me-14	0.87 (t, *J* = 6.9 Hz, 3H)	0.87 (t, *J* = 7.3Hz, 3H)

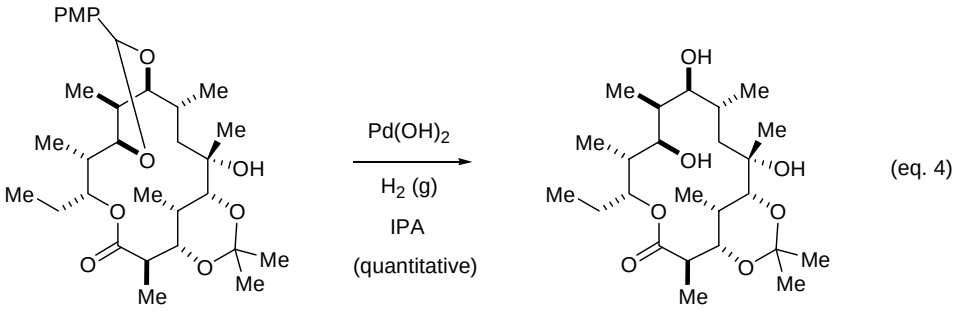
[a] Spectra for macrolactone **54** recorded on a Varian Mercury-300 in $CDCl_3$. [b] Spectra for Kotchetkov's macrolactone recorded on a Bruker WM-250 instrument in $CDCl_3$.[18]

From macrolactone **54**, Kotchetkov and coworkers accessed erythronolide B in four subsequent transformations (Scheme 16).[18] Global deprotection of **54** provided the tetraol **55**. Selective 3,5-O-benzylidenation results in **56**, which was then oxidized to **54**. Compound **54** was deprotected by hydrogenation to provide **1**.[18]

Scheme 16. Kotchetkov's closing sequence from macrolactone **54** to erythronolide B



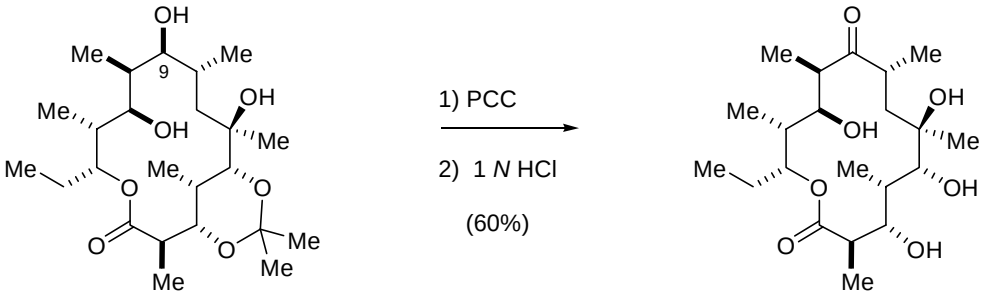
In contrast to the closing stages of Kotchetkov's synthesis, we accessed erythronolide B by achieving selective removal of the benzylidine acetal protecting group: submitting macrolactone **54** to hydrogenolysis with Pearlman's catalyst (20% $Pd(OH)_2/C$) in 2-propanol revealed triol **58** (equation 4).



54 **58**

As previously shown, PCC effected the regioselective oxidation of the C(9) carbinol,[25] prior to acetonide deprotection under acidic conditions,[26] to afford erythronolide B (**1**) in 60% yield from **58** (Scheme 17). Our synthetic material is identical to a natural sample of erythronolide B,[27] by ^{1}H NMR analysis (see Table 3), TLC, and FAB MS.[28]

Scheme 17. Final oxidation/deprotection to erythronolide B (**1**)



58 **1**

Table 3. ^{1}H NMR Data for erythronolide B (**1**)[28]

	^{1}H δ (multiplicity, *J* (Hz), integration)		
proton	Literature Report[a]	Synthetic Sample[b]	Natural Sample[b]
H-13	5.22, (dq, *3.8, 9.5*, 1H)	5.22 (ddd, *2.0, 7.5, 16.5*, 1H)	5.22 (ddd, *2.0, 7.1, 15.9*, 1H)
OH-3	3.92 (s, 1H)	3.94 (s, 1H)	3.94 (s, 1H)
H-3	3.88 (d, *9.5*, 1H)	3.91 (s, 1H)	3.91 (s, 1H)
OH	3.72 (s, 2H)	3.72 (s, 2H)	3.73 (s, 2H)
H-11	3.68 (m, 1H)	3.68 (m, 1H)	3.68 (m, 1H)
OH	3.07 (s, 1H)	3.06 (s, 1H)	3.03 (s, 1H)
H-2, H-8, H-10	2.72-2.86 (m)	2.72-2.86 (m)	2.72-2.86 (m)
OH	2.67 (s, 1H)	2.67 (s, 1H)	2.67 (s, 1H)
Me-4	1.07 (d, *7.1*, 3H)	1.07 (d, *6.6*, 3H)	1.07 (d, *6.6*, 3H)
Me-10	1.02 (d, *7.0*, 3H)	1.02 (d, *6.6*, 3H)	1.02 (d, *7.2*, 3H)
MeCH_2-13	0.93 (t, *7.3*, 3H)	0.94 (t, *7.2*, 3H)	0.93 (t, *7.3*, 3H)
Me-12	0.88 (d, *7.0*, 3H)	0.88 (d, *6.0*, 3H)	0.88 (d, *7.0*, 3H)

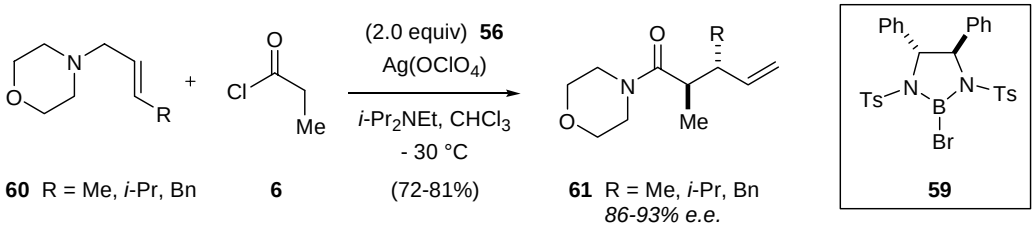
[a] Data reported by Mulzer and recorded on in $CDCl_3$ at 270 MHz.[29] [b] Data recorded on a Varian Mercury-300 in $CDCl_3$.

With the final stages of our synthesis plan explored, we began investigations on developing an enantioselective route to ketone **4**, which had previously been resolved by aldol coupling to aldehyde **2** (Scheme 8).

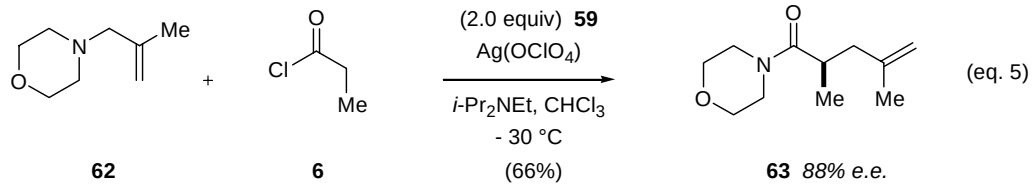
Asymmetric Tandem-Acyl Claisen Rearrangement

Background. Tehshik Yoon and Dr. Sung-gon Kim, a graduate student and postdoctoral fellow in our labs, developed an asymmetric variant of the acyl-Claisen rearrangement employing chiral boron Lewis acid complex **59** (Scheme 18).[30]. Importantly, propionyl chloride (**6**) efficiently participates in this process with several alkyl-substituted allyl morpholines (**60**) to provide Claisen adducts **61** (72–81% yields, 86–93% e.e.).

Scheme 18. Asymmetric acyl-Claisen rearrangement by Yoon and Kim



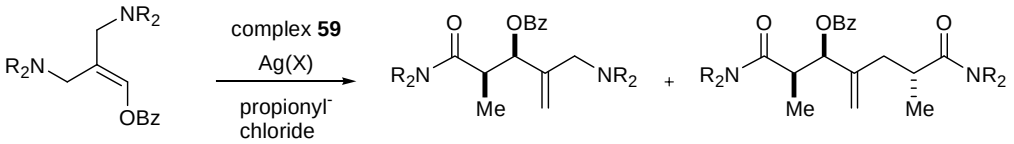
Additionally, the sterically hindered methallyl-amine **62** rearranges to **63** with good enantioselectivity, albeit in modest yield (equation 5).



Inspired by these findings, we decided to study the ability of boron complex **59** to promote the tandem acyl-Claisen rearrangement between diamine **17** and propionyl chloride (Table 4). Following Yoon and Kim's protocol, we observed that **17** undergoes acyl-Claisen rearrangement to form **64** in poor efficiency with moderate levels of enantiocontrol (25 % yield, 67 % e.e., entry 1). With triflate as the counter ion, slightly

higher efficiency and similar enantioselectivity were observed (35% yield, 67% e.e., entry 2). In both cases, the tandem Claisen product **21** was *not* observed. Our initial efforts to improve these results, however, were frustrated by an apparent variability in the quality of boron complex **59**.

Table 4. Preliminary results on the asymmetric acyl-Claisen rearrangement of diamine **17**



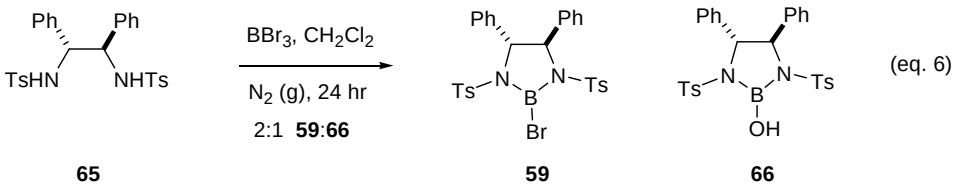
17 NR_2 = *N*-morpholine

64 NR_2 = *N*-morpholine

21 NR_2 = *N*-morpholine *(not observed)*

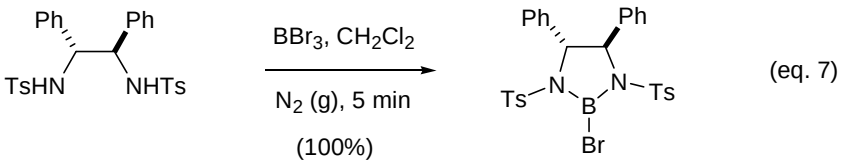
entry	(X)	temperature	solvent	% yield **64**	% e.e.
1	$OClO_4$	- 30 °C	$CHCl_3$	25%	67%
2	OTf	- 20 °C	CH_2Cl_2	35%	67%

***Improving the preparation of boron complex* 59.** Following the standard procedure,[31] complex **59** is formed by aging a solution of the diamine ligand (**65**) and BBr_3 in CH_2Cl_2 under N_2(g) for 24 hrs (refer to equation 6). Removal of the solvent *in vacuo*, produced a solid material which was successfully used without further purification *or* characterization by Yoon and Kim. In our hands, this protocol yielded inconsistent results. As such, we decided to characterize the complex obtained. Surprisingly, ^{1}H NMR analysis of the isolated solid revealed a mixture of species **59** and **66** in a ratio of two to one (equation 6).



65 **59** **66**

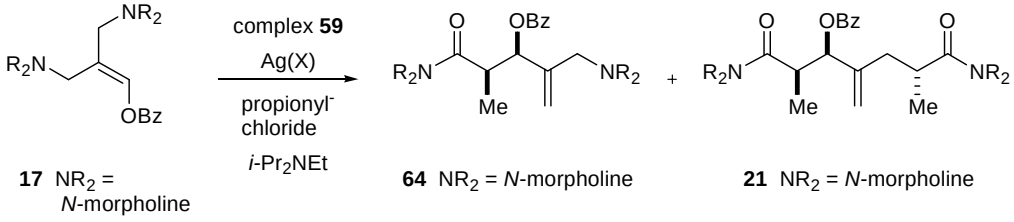
Monitoring complex formation by ^{1}H NMR revealed that the desired transformation was complete in less than 5 minutes, not 24 hours (equation 7). Moreover, the desired complex **59** was observed to degrade to the inactive complex **66** over the 24 hr aging period. As such, an improved protocol for formation of this moisture sensitive boron complex **59** *without* contamination of **66** was developed based on a shorter complex aging period (for more details, see experimental methods).



65 **59**

Consequently, we observed a significant enhancement in results for the acyl-Claisen rearrangement of diamine **17** (Table 5). As highlighted in entry 3, the mono-Claisen product **64** is formed in 57% yield with excellent diastereoselectivity and good enantioselectivity (>99:1 dr, 85% e.e.). To our delight, the enantioenriched tandem product **21** was also isolated from this process in 30% yield, with good diastereoselectivity and outstanding enantioselectivity (5:1 dr, >95% e.e., entry 3). With a reliable method for formation of complex **59**, current studies in this lab are underway to find optimal conditions for accessing tandem adduct **21** exclusively. Factors including solvent, tertiary amine, acid chloride-addition time and temperature should play significant roles in this transformation.

Table 5. Temperature and counter-ion effects on the asymmetric tandem Claisen rearrangement



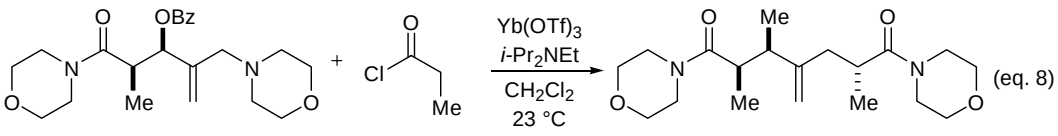
17 NR_2 = *N*-morpholine

64 NR_2 = *N*-morpholine

21 NR_2 = *N*-morpholine

			product **64**			tandem product **21**		
entry	(X)	temp	% yield	% e.e.	*syn/anti*	% yield	% e.e.	*syn-anti/ syn-syn*
1	OTf	- 20 °C	37%	71%	>99:1	<5%	--	--
2	OTf	-30 °C	57%	85%	>99:1	20%	>95%	5:1
3	$OClO_4$	-30 °C	57%	85%	>99:1	30%	>95%	5:1
4	$OClO_4$	-45 °C	72%	87%	>99:1	--	--	--

Remarkably, the mono-Claisen product **64** can be formed exclusively at lower temperatures (entry 4).[32] Under these conditions, **64** was isolated efficiently with high levels of enantio- and diastereo-control (75% yield, 87% e.e., >99:1 dr). Subjection of **64** to standard acyl-Claisen rearrangement conditions, in a separate step, affords efficient access to enantioenriched **21** with excellent diastereoselectivity (equation 8).[32] Importantly, tandem adduct **21** represents the C(3) to C(9) fragment in our synthesis of erythronolide B. Consequently, in lieu of a chiral resolution (Scheme 8), enantioselective synthesis of ketone **4** can now be achieved. Notably, using a different acid chlorides in the second Claisen rearrangement can be envisioned to further expand the applications of this methodology.



64 **6** **21** *87% e.e., 94:6 dr*

Concluding Remarks

A novel approach to erythronolide B has been realized (twenty four steps from known ester **19**, ca. 1.3% yield). This synthesis features a tandem acyl-Claisen rearrangement of diamine **17** and propionyl chloride to rapidly install three of the four requisite stereocenters in the C(3)–C(9) polyketide backbone. In addition, a novel Lewis acid promoted enantioselective variant of this key transformation was accomplished using chiral boron complex **59**. Subsequent installation of the essential C(6) stereocenter proved more challenging than anticipated. As a consequence, insights gained from facing these challenges will be valuable for further improving this route, as well as the future planning of macrolide syntheses based on our tandem Claisen technology.

The success of our first approach to erythronolide B relies on a conventional macrolactonization to form the 14-membered ring. Future studies in this lab will focus on developing a more aggressive ring closing strategy, with the aim of reducing the number of "non-productive" functional/protecting group manipulations required by a standard macrolactonization plan (Figure 2). Notably, carbon-carbon bond forming ring closures (e.g., olefin metathesis, Nozaki-Kishi) have yet to be exploited in the synthesis of the erythromycins.

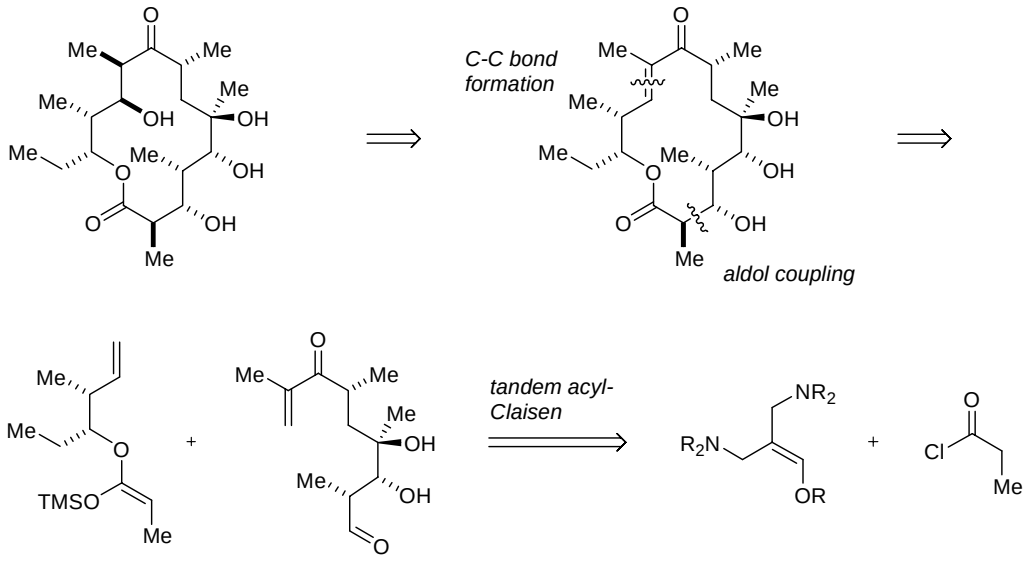


Figure 2. Future directions: Using the tandem acyl Claisen rearrangement to explore unconventional ring-closing strategies in erythromycin syntheses

Experimental Methods

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[33] 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.[34] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

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

Benzoic acid-2-(-*N*-methyl-morpholinyl)-3-(-N-morpholinyl)-propenyl ester (17). Based upon a modified procedure of Boeckman,[35] a solution of benzoic acid 2-methyl-propenyl ester[36] (**19**) (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 (**20**), which was used without further purification. A solution of the crude dibromide **20** 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 **17** 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.

(2*R,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-1,7-dimorpholin-4-yl-4-methylene-heptane-1,7-dione (21).** To a flask containing $Yb(OTf)_3$ (258 mg, 0.416 mmol) was added the allyl dimorpholine **17** (72.1 mg, 0.208 mmol) in 4.0 mL of CH_2Cl_2, followed by *i*-Pr_2NEt (0.15 mL, 0.83 mmol) at 23 °C. After 5 min a solution of the propionyl chloride (0.75 mL, 1 M solution in CH_2Cl_2, 0.75 mmol) was added dropwise over 1 min. The resulting solution was maintained at 23 °C until the allyl dimorpholine **17** 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 provide **21** 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*S,3*R**,6*R**)-3-Benzoate-2,6-dimethyl-4-methylene-7-morpholin-4-yl-heptanoic acid (22).** Following the Metz protocol,[37] to a solution of **21** in 1.2 mL of 1:1 DME/H_2O at 23 °C was added I_2 (60.0 mg, 0.254 mmol), and the resulting solution maintained in the absence of light for 3 h. The solution was then diluted with EtOAc (30 mL), and the resulting mixture was successively washed 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 1.0 mL of AcOH, treated with Zn dust (40 mg, 0.61 mmol) and then heated at 50 °C for 2 h. Subsequently, 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 afford **22** as a white solid (20.7 mg, 53.3 μmol) in 88% yield: 83:17 regioselectivity by ^{1}H NMR analysis. The resulting product mixture can be titruated with ether to remove the minor regioisomer component. 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.

(2*S,3*R**,6*R**)-3-(tert-Butyl-dimethyl-silanyloxy)-2,6-dimethyl-4-methylene-7-oxo-nonanoic acid (4).** To a solution of **22** (1.10 g, 2.82 mmol) in 25 mL of THF at –63 °C ($CHCl_3/CO_2$ bath) was added 25 mL of freshly prepared EtLi as a 0.70 M solution in THF over 30 min via syringe pump. After 1 hr, the reaction was quenched by the addition of 50 mL of saturated NH_4Cl and 50 of 1 N $KHSO_4$. After 5 min, the resulting solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The ketone **26** was used without further purification. A solution of TBSCl (1.70 g, 11.3 mmol) and imidazole (1.50 g, 22.0 mmol) in 5.6 mL of DMF was added via cannula to ketone **26** under Ar (g) at rt. After 16 hr, the mixture was diluted with 50 mL of 1 N $KHSO_4$ and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting bis-protected silyl ether **32** was dissolved in 55 mL of MeOH and cooled (0 °C) and 23 mL of an aqueous solution of 0.25 M K_2CO_3 was added. After 30 min, 50 mL of 1 N $KHSO_4$ was added. The resulting mixture was concentrated in vacuo to remove MeOH. The remaining aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 520 mg (1.52 mmol) of **4** as a colorless oil in 54% yield. ^1H

NMR (300 MHz, $CDCl_3$) δ 5.16 and 4.89 (2s, 2H, C=CH_2), 4.46 (d, *J* = 4.8 Hz, 1H, CHOTBS), 2.76–2.88 (m, 1H,) 2.60–2.70 (m,1H), 2.44–59 (m, 1H), 2.38 (dd, *J* = 7.2, 15.3 Hz, C**H**$_2$C=CH_2), 2.01 (dd, *J* = 7.4, 15.8 Hz, C**H**$_2$C=CH_2), 1.13 (d, *J* = 7.2 Hz, 3H, Me), 1.10 (d, *J* = 7.8 Hz, 3H, Me), 1.07 (t, *J* = 7.2 Hz, 3H, **CH$_3$**CH_2), 0.91 (s, 9H, -$C(Me)_3$), 0.06 and 0.00 (2s, 6H, $Si(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 214.5, 179.0, 146.5, 113.1, 76.3, 44.4, 44.0, 34.5, 34.5, 26.1, 18.4, 17.3, 10.6, 8.1, –4.1, –5.0; HRMS (FAB) exact mass calcd for ($C_{18}H_{34}O_4Si$ + H^+) requires *m/z* 343.2305, found *m/z* 343.2301.

(2*R*, 3*R*, 6*R*, 7*S*, 8*S*, 9*R*, 10*R*, 11*R*)-11-Benzyloxymethoxy-3-(tert-butyl-dimethyl-silanyloxy)-9-hydroxy-2,6,8,10-tetramethyl-4-methylene-7-oxo-tridecanoic acid and 11-Benzyloxymethoxy-3-(tert-butyl-dimethyl-silanyloxy)-9-hydroxy-2,6,8,10-tetramethyl-4-methylene-7-oxo-tridecanoic acid (33) and compound 34.

Based on a modification of Martin's procedure,[1] a solution of the racemic ketone **4** (676 mg, 1.97 mmol) in 6.6 mL of THF was added to a solution of freshly prepared lithium hexamethyldisilazide (5.91 mmol) in 7.7 mL of THF at – 78 °C. After 2 h, a solution of freshly prepared aldehyde **2**[1] (1.40 g, 5.92 mmol) in 6.4 mL of THF was added, and the mixture maintained at – 78 °C for 2 h. The reaction was quenched by the addition of saturated NH_4Cl (2 mL) and the resultant mixture was allowed to warm to ambient temperature. The solution was diluted with 0.2 N $KHSO_4$ (60 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (5% gradient to 10% EtOAc/hexanes) to afford (943

mg, 1.63 mmol) **33** and **34** as a colorless oil and inseparable 1:1 mixture of diastereomers in 83% yield. The resulting mixture was used without further purification.

(2S, 3R, 6R)-6-[(4S, 5S, 6S)-6-((1S, 2R)-2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-2-methyl-4-methylene-heptanoic acid (35) and diastereomer 36. Following a modification of Martin's procedure, anhydrous acetic acid was slowly added to a solution of $Me_4NBH(OAc)_3$ (2.90g, 11.08 mmol) in 11 mL of CH_3CN. After the solution was stirred at rt for 40 min, it was cooled to –45 °C, and the ketones **33** and **34** (943 mg, 1.63 mmol) in 11 mL of CH_3CN was added. The resulting frozen solution was maintained between –40 and –50 °C for 8 h, and then warmed to 10 °C over a period of 8 h. The reaction mixture was poured into saturated $NaHCO_3$ (200 mL) and the mixture was stirred at rt for 30 min. The resulting mixture was extracted with EtOAc (3 x 200 mL), and the combined extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (5% gradient to 10% EtOAc/hexanes) to afford (633 mg, 1.09 mmol) of the corresponding diol as a foam-like solid and 2:1 mixture of diastereomers in 67% yield.[38] This material was used without further purification. To a solution of the diol as a 2:1 mixture of isomers (377 mg, 0.650 mol) in 7 mL of CH_2Cl_2 was added (0.28 mL, 1.95 mmol) of *p*-methoxyanisaldehyde and (7.5 mg, 0.0325 mmol) of CSA under Ar(g) at ambient temperature. After 6 hr, the reaction mixture was quenched by the addition of Hünig's base (0.23 mL, 1.32 mmol) and concentrated in vacuo. The residue was purified by flash chromatography (10% gradient to 20% EtOAc/hexanes) to afford 214 mg of the major

isomer as a colorless oil (70% yield based on a theoretical yield of 0.43 mol), and 78.0 mg of the minor isomer as a colorless oil (50% yield based on a theoretical yield of 0.22 mol). Mosher ester analysis revealed the major isomer to be the desired product. *Major isomer* (**35**): IR (thin film) 3500–2600 (br, COOH), 1710, 1517, 1462, 1250, 1042, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.0–9.0 (br s, 1H, -COOH), 7.36 (d, *J* = 8.4 Hz , 2H, *p*-MeO**Ar**-), 7.23–7.29 (m, 5H, Ph), 6.85 (d, *J* = 8.1 Hz, 2H, *p*-MeO**Ar**), 5.54 (s, 1H, *p*-MeOArC**H**), 5.18 and 4.93 (2s, 2H, C=CH_2), 4.79 (dd, *J* = 6.6, 11.7 Hz, 2H, -OCH_2O-), 4.63(d, *J* = 2.1 Hz, 2H, $PhCH_2$-), 4.48 (d, *J* = 3.9 Hz, 1H, CHOTBS), 3.94–4.02 (m, 2H, CH(OPMB), 3.78 (s, 3H, *p*-**Me**OAr-), 3.37 (d, *J* = 10.5 Hz, 1H, CH(OBOM), 2.49–2.60 (m, 2H,) 2.07 (d, *J* = 14.7 Hz, 1H), 1.70–1.80 (m, 4H), 1.48 (dq, *J* = 7.3, 21.5 Hz, 1H), 1.19 (d, *J* = 7.2 Hz, 3H, Me-10), 1.09 (d, *J* = 7.2 Hz, 3H, Me–8), 1.08 (d, *J* = 6.6 Hz, 3H, Me-6), 0.87 (s, 9H, -$C(Me)_3$), 0.86–0.90 (m, 3H, C**H**$_3$$CH_2$-), 0.82 (d, *J* = 6.6 Hz, 3H,Me-5), 0.018 and –0.008 (2s, 6H, $Si(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 179.9, 159.7, 146.3, 138.1, 131.9, 128.5, 127.8, 127.6, 127.4, 127.3, 113.7, 95.4, 84.8, 78.5, 75.5, 75.4, 69.4, 55.5, 44.1, 37.2, 37.0, 29.9, 29.7, 29.6, 26.1, 25.9, 18.4, 16.2, 13.5, 10.9, 10.4, 7.6, –4.0, –4.8; HRMS (ES) exact mass calcd for ($C_{40}H_{62}O_8Si + Na^+$) requires *m/z* 721.4112, found *m/z* 721.4103; $[\alpha]_D^{23}$ = ─ 11.1 (c = 1.0, $CHCl_3$); TLC R_f = 0.14 (20% EtOAc/hexanes).

Diastereomer 36: IR (thin film) 3500–2600 (br, COOH), 1710, 1616, 1518, 1462, 1380, 1250, 1101, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz , 2H, *p*-MeO**Ar**-), 7.23–7.29 (m, 5H, Ph), 6.87 (d, *J* = 8.5 Hz, 2H, *p*-MeO**Ar**), 5.69 (s, 1H, *p*-MeOArC**H**), 5.19 and 4.94 (2s, 2H, C=CH_2), 4.81 (d, *J* = 6.5 Hz, 1H, -OC**H**$_2$O-), 4.76 (d,

J = 6.0 Hz, 1H, -OC**H**$_2$O-), 4.69 (d, *J* = 12.0 Hz, 1H, PhC**H**$_2$-), 4.60 (d, *J* = 12.5 Hz, 1H, PhC**H**$_2$-), 4.54 (d, *J* = 3.0 Hz, 1H, CHOTBS), 4.00 (ddd , *J* = 1.5, 10.0 Hz, 1H CH(OPMB), 3.91–3.94 (m, 1H, 3.94–4.02, 1H, CH(OPMB), 3.79 (s, 3H, *p*-**Me**OAr-), 3.44 (d, *J* = 10.5 Hz, 1H, CH(OBOM), 2.56–2.66 (m, 3H), 1.67–1.90 (m, 4H), 1.49 (dq, *J* = 7.3, 21.3 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H, Me), 1.03 (d, *J* = 6.5 Hz, 3H, Me), 1.08 (d, *J* = 6.6 Hz, 3H, Me-6), 0.89 (s, 9H, -C(Me)$_3$), 0.88–0.91 (m, 3H, C**H$_3$**CH$_2$-), 0.84 (d, *J* = 7.0 Hz, 3H), 0.0 and – 0.005 (2s, 6H, Si(Me)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 178.5, 159.9, 146.7, 138.0, 131.9, 128.5, 128.5, 127.9, 127.7, 127.4, 113.8, 113.4, 95.4, 85.3, 78.6, 75.3, 75.1, 69.8, 55.5, 43.6, 37.3, 36.0, 29.3, 29.0, 26.1, 26.0, 18.4, 16.4, 13.6, 10.9, 9.8, 7.7, –4.0, –4.9; HRMS (ES) exact mass calcd for ($C_{40}H_{62}O_8Si + Na^+$) requires *m/z* 721.4112, found *m/z* 721.4106; $[\alpha]_D^{23} = -7.04$ (c = 1.0, $CHCl_3$); TLC R_f = 0.19 (20% EtOAc/hexanes).

(2*S*, 3*R*, 6*R*)-6-[(4*S*, 5*S*, 6*S*)-6-((1*S*, 2*R*)- 2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-2-methyl-4-methylene-heptanoic acid methyl ester (36). To a solution of the acid **35** (50.0 mg, 0.0715 mmol) in 0.20 mL of MeOH and 2.0 mL of CH_2Cl_2 was added $TMSCHN_2$ (0.25 mL, 2.0 M solution in hexanes, 0.50 mmol) dropwise. After 30 min, the resulting yellow solution was cooled (0 °C) and quenched by addition of AcOH (0.20 mL). The resulting mixture was diluted with 10 mL of aqueous $NaHCO_3$ (sat) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/hexanes) to afford the product **36** as a colorless oil in 98% yield (45.0 mg): IR (thin film) 2931, 2361, 2339, 1735, 1616,

1518, 1457, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz , 2 H, *p*-MeO**Ar**-), 7.20 –7.27 (m, 5H, Ph), 6.85 (d, *J* = 8.7 Hz, 2 H, *p*-MeO**Ar**), 5.53 (s, 1H, *p*-MeOArC**H**), 5.14 and 4.90 (2s, 2H, C=CH_2), 4.79 (dd, *J* = 6.6, 18.6 Hz, 2H, -OCH_2O-), 4.62(dd, *J* = 11.9, 20.0 Hz, 2H, -CH_2Ph), 4.42 (d, *J* = 5.1 Hz, 1H, CHOTBS), 3.95–4.02 (m, 2H), 3.78 (s, 3H, *p*-**Me**OAr-), 3.62 (s, 3H, MeOC=O), 3.37 (d, *J* = 10.5 Hz, 1H), 2.43–2.51 (m, 2H,) 2.07 (d, *J* = 14.7 Hz, 1H), 1.67–1.85 (m, 4H), 1.49 (dq, *J* = 7.2, 21.8 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H, Me), 1.08 (d, *J* = 6.6 Hz, 3H, Me), 0.97 (d, *J* =6.6 Hz, 3H, Me), 0.92–0.86 (m, 3H, -CH_2C**H_3**), 0.87 (s, 9H, -$C(Me)_3$), 0.81 (d, *J* = 7.2 Hz, 3H, Me), –0.011 and – 0.022 (2s, 6H, $Si(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 174.7, 159.7, 146.6, 138.1, 131.9, 128.5, 127.7, 127.6, 127.3, 113.7, 113.5, 95.4, 95.3, 84.8, 78.6, 76.0, 75.4, 69.7, 55.5, 51.8, 44.4, 37.2, 36.8, 30.0, 29.6, 26.0, 25.9, 18.4, 16.0, 13.6, 10.9, 10.8, 7.5, –4.0, –4.9; HRMS (FAB) exact mass calcd for ($C_{41}H_{64}O_8Si$) requires *m/z* 712.4371, found *m/z* 712.4370; $[\alpha]_D^{23} = -7.2$ (c = 1.0, $CHCl_3$).

(2*S*, 3*R*, 6*R*)-6-[(4*S*, 5*S*, 6*S*)-6-((1*S*, 2*R*)-2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-2-methyl-4-methylene-heptan-1-ol (37). To a solution of the ester **36** (46.0 mg, 0.0645 mmol) in 1.30 mL of THF at 0 °C was added (0.26 mL, 0.26 mmol) of a 1.0 M solution of $LiBEt_3H$ in THF under Ar (g). After 1 hr, the reaction was quenched with 5 mL of H_2O and then diluted with 10 mL 0.5 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/hexanes) to afford the product **37** as a

colorless oil in 86% yield (38.0 mg): IR (thin film) 3507, 2960, 2881, 1616, 1517, 1456, 1250, 1103, 1046, 831, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.0 Hz , 2H, *p*-MeO**Ar**-), 7.25–7.29 (m, 5H, Ph), 6.84 (d, *J* = 8.7 Hz, 2H, *p*-MeO**Ar**), 5.54 (s, 1H, *p*-MeOArC**H**), 5.17 and 4.93 (2s, 2H, C=CH_2), 4.79 (dd, *J* = 6.6, 19.8 Hz, 2H, -OCH_2O-), 4.61 (s, 2H, $PhCH_2$-), 4.36 (app s, 1H, CHOTBS), 4.06 (d, *J* = 10.5 Hz, 1H), 3.97 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H, *p*-**Me**OAr-), 3.51 (d, *J* = 7.2 Hz, 2H, -C**H**$_2$OH), 3.36 (d, *J* = 11.1 Hz, 1H, CH(OBOM), 2.46–2.60 (m, 1H,) 2.13 (d, *J* = 14.1 Hz, 1H), 1.68–1.82 (m, 1H), 1.48 (dq, *J* = 7.2, 21.5 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H, Me), 0.98 (d, *J* = 6.0 Hz, 3H, Me), 0.87 (s, 9H, -$C(Me)_3$), 0.87 (m, 3H, C**H**$_3$$CH_2$-), 0.81 (d, *J* = 6.6 Hz, 3H, Me), 0.75 (d, *J* = 7.2 Hz, 3H, Me), 0.073 and 0.0090 (2s, 6H, $Si(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 159.8, 147.3, 137.9, 131.9, 128.5, 127.8, 127.7, 127.3, 113.7, 112.7, 95.3, 95.0, 84.9, 78.3, 75.0, 72.5, 70.0, 65.4, 55.6, 39.6, 38.6, 36.9, 29.3, 29.0, 26.3, 25.5, 18.6, 15.9, 13.3, 10.8, 9.8, 7.5, –4.0, –4.7; HRMS (FAB+) exact mass calcd for ($C_{40}H_{64}O_7Si$) requires *m/z* 684.4421, found *m/z* 684.4450; $[\alpha]_D^{23}$ = ─ 16.6 (c = 1.0, $CHCl_3$).

4-Benzyl-3-[8-[6-(2-benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-5-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-2,4-dimethyl-6-methylene-nonanoyl]-oxazolidin-2-one (40). To a solution of the alcohol **37** (46.8 mg, 0.0666 mmol) and NMO (30 mg, 0.26 mmol) in CH_2Cl_2 (2.5 mL) was added TPAP (2 mg, 5.7 mmol) at ambient temperature. After 15 min, the resulting heterogeneous black solution was flushed through a plug of silica gel (15 mL) with 20% EtOAc/hexanes (75 mL) as the eluent. After concentration in vacuo, the resulting aldehyde **38** was used immediately without further purification. According to Evan's protocol,[21] to a cooled (0

°C) solution of (*R*)-(-)-4-Benzyl-3-propionyl-2-oxazolidinone[39] in CH_2Cl_2 (1.0 mL) was added freshly prepared di-*n*-butylboron triflate (134.0 mg, 0.466 mmol) dropwise followed by Hünig's base (112.0 μL, 0.644 mmol). After 30 min, the resulting clear and colorless mixture was cooled to –78 °C and freshly prepared aldehyde **38** (45.5 mg, 0.0666 mmol) was added dropwise as a solution in CH_2Cl_2 (0.30 mL). After 30 min, the resultant solution was warmed to 0 °C and maintained at that temperature for 2 hr. The reaction mixture was quenched by the addition of 0.80 mL of an aqueous 0.25 N $NaHPO_4$ solution, 0.80 mL of MeOH, and 1.2 mL of 30% aqueous H_2O_2 in 0.60 mL of MeOH. The resultant solution was stirred at ambient temperature for 45 min. The mixture was than diluted with 15 mL of NH_4Cl (sat) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% gradient to 25% EtOAc/hexanes) to afford the product **40** (51.2 mg) as a colorless oil in 84% yield: IR (thin film) 3526, 2932, 1783, 1692, 1616, 1517, 1381, 1249, 1210, 1103, 1044, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz , 2 H, *p*-MeO**Ar**-), 7.17 –7.33 (m, 10H, Ph), 6.87 (d, *J* = 9.0 Hz, 2 H, *p*-MeO**Ar**), 5.547(s, 1H, *p*-MeOArC**H**), 5.12 and 4.91 (2s, 2H, C=CH_2), 4.82 (dd, *J* = 6.6, 27.0 Hz, 2H, -OCH_2O-), 4.65 (d, *J* = 9.6 Hz, 2H, $PhCH_2$-), 4.23–3.87 (m, 8H), 3.80 (s, 3H, *p*-**Me**OAr-), 3.44 (d, *J* = 10.2 Hz, CH(OBOM), 3.21 (dd, *J* = 3.2, 22.3 Hz, 1H), 2.74 (dd, *J* = 9.6, 22.5 Hz, 1H), 2.49–2.61 (m, 1H,) 2.12–1.63 (m, 6H), 1.59 (br s, 1H), 1.47 (dq, *J* = 1.50, 21.7 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 3H, Me), 1.26 (d, *J* = 6.6 Hz, 3H, Me), 1.0 (d, *J* = 6.6 Hz, 3H, Me), 0.90 (s, 9H, -$C(Me)_3$), 0.89–0.88 (m, 3H, C**H**$_3CH_2$-), 0.85 (d, *J* = 7.2 Hz, 3H, Me), 0.078 and 0.016 (2s, 6H, $Si(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 175.9, 159.7, 152.8, 147.7,

138.1, 135.1, 132.0, 129.5, 129.1, 128.5, 127.6, 127.3, 113.7, 111.7, 95.6, 95.5, 84.9, 80.0, 79.0, 75.7, 73.8, 69.8, 66.2, 55.6, 55.2, 41.6, 39.2, 37.9, 37.4, 35.2, 29.6, 29.4, 26.2, 26.0, 18.5, 16.5, 15.3, 13.8, 10.9, 8.5, 7.7, –3.7, –4.7; HRMS (ES) exact mass calcd for $(C_{53}H_{77}NO_{10}Si + Na^+)^+$ requires *m/z* 938.5214, found *m/z* 938.5217; $[\alpha]_D^{23} = -12.8$ (c = 1.0, $CHCl_3$).

(2*R*, 3*S*, 4*S*, 5*R*, 8*R*)-8-[(4*S*, 5*S*, 6*S*)-6-((2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-5-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-2,4-dimethyl-6-methylene-nonanoic acid (41). To a solution of 51.2 mg of imide **40** (0.0559 mmol) in 5.7 mL of THF and 2.13 mL of H_2O at 0 °C was added 0.569 mL of a 30% aqueous solution of H_2O_2 followed by 1.42 mL (1.70 mmol) of a 1.20 M LiOH (aq). After 2.5 hr, the resulting solution was quenched with 3.0 mL of 1.25 M $Na_2S_2O_3$ (aq) and stirred for another 30 min. The resulting solution was then allowed to warm to ambient temperature. After 15 min, the reaction was diluted with 10 mL of 0.3 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford the product **41** (30.0 mg) as a colorless oil in 71% yield: IR (thin film) 3287 (br COOH), 2960, 2928, 2856, 1751, 1616, 1517, 1456, 1405, 1250, 1028, 834, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz , 2 H, *p*-MeO**Ar**), 7.24–7.31 (m, 5H, Ph), 6.87 (d, *J* = 8.5 Hz, 2H, *p*-MeO**Ar**), 5.65 (s, 1H, *p*-MeOArC**H**), 5.13 and 4.98 (2s, 2H, $C{=}CH_2$), 5.06 (d, *J* = 7.5 Hz, 1H, C**H**$_2$Ph), 4.77 (d, *J* = 7.5 Hz, 1H, C**H**$_2$Ph), 4.67 (d, *J* = 12.0 Hz, -OC**H**$_2$O-) 4.47 (d, *J* = 12.5 Hz, 1H, -

OC**H**$_2$O-), 4.29 (d, *J* = 4.5 Hz, 1H, H-5), 4.10 (ddd, *J* = 2.9, 5.9, 9.0 Hz, 1H, H-13), 4.00 (dd, 1H, *J* = 1.5, 10.5 Hz, 1H, H-11), 3.82 (d, *J* = 10.0 Hz, 1H, H-3), 3.80 (s, 3H, *p*-**Me**OAr-), 3.32 (d, *J* = 10.5 Hz, 1H, H-9), 2.65 (dq, *J* =6.5, 10.0 Hz, 1H, H-2), 2.32–2.50 (m, 2H, OH and H-8), 2.27 (d, *J* = 14.0 Hz, 1H, H-7), 1.95–1.85 (m, 2H, H-14 and H-12), 1.84–1.76 (m, 1H, H-10), 1.77–1.71 (m, 1H, H-4), 1.66–1.55 (m, 2H, H-14' and H-7'), 1.32 (d, *J* =6.5 Hz, 3H, Me-2), 1.21 (d, *J* = 7.0 Hz, 3H, Me-10), 1.00 (d, *J* = 6.5 Hz, 3H, Me-8), 0.97 (s, 9H, -C(Me)$_3$), 0.90 (t, *J* =7.5 Hz, 3H, -CH$_2$C**H$_3$**), 0.89 (d, *J* = 7.5 Hz, 3H, Me-4), 0.82 (d, *J* = 6.5 Hz, 3H, Me-12), 0.188 and 0.069 (2s, 6H, Si(Me)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) 177.0, 169.0, 146.3, 137.5, 132.0, 128.6, 128.1, 128.0, 127.5, 114.8, 113.9, 95.7, 95.0, 86.5, 80.7, 79.0, 75.8, 75.0, 70.0, 55.5, 43.7, 39.2, 38.3, 36.1, 29.9, 29.0, 26.2, 25.7, 18.3, 16.0, 15.2, 13.6, 10.4, 7.3, 6.5, –3.9, –4.7; HRMS (FAB) exact mass calcd for $(C_{43}H_{68}O_9Si - H^+)^-$ requires *m/z* 755.4554, found *m/z* 755.4559; $[\alpha]_D^{23}$ = ─ 5.9 (c = 1.0, $CHCl_3$); TLF R_f value = 0.51 (50% EtOAc/hexanes).

(*R*)-2((4*S*, 5*S*, 6*R*)-(6-{(*R*)-3-[(4*S*, 5*S*,6*S*)-6-((1*S*,2*R*)-2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-1-methylene-butyl}-2,2,5-trimethyl-[1,3]dioxan-4-yl)-propionic acid (42). To a solution of 30.0 mg (0.0396 mmol) of silyl ether **41** in 1.10 mL of THF at ambient temperature was added 0.180 mL of 1.0 M TBAF solution in THF. The resultant clear yellow solution was warmed to 50 °C and maintained at that temperature for 8 hr before the reaction was quenched by the addition of 2.0 mL of 0.5 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting diol was used

without further purification. TLC R_f = 0.10 (50% EtOAc/hexanes). To a solution of this diol in 2,2-dimethoxypropane (1.80 mL) was added CSA (4.0 mg, 0.017 mmol) at ambient temperature. After 6 hr, 0.10 mL of Hünig's base was added and the resulting solution concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford the product (30.0 mg) as a colorless oil in 71% yield: IR (thin film) 3500–2500 (br COOH), 2932, 1734, 1517, 1454, 1381, 1250, 1102, 1039, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz , 2 H, *p*-MeO**Ar**-), 7.24 –7.31 (m, 5H, Ph), 6.86 (d, *J* = 8.5 Hz, 2H, *p*-MeO**Ar**), 5.57 (s, 1H, *p*-MeOArC**H**), 5.21 and 4.95 (2s, 2H, C=CH_2), 4.98 (d, *J* = 7.0 Hz, 1H, C**H**$_2$Ph), 4.79 (d, *J* = 7.0 Hz, 1H, C**H**$_2$Ph), 4.65 (d, *J* = 12.0 Hz, -OC**H**$_2$O-) 4.54 (d, *J* = 11.5 Hz, 1H, -OC**H**$_2$O-), 4.08 (ddd, *J* = 2.8, 5.8, 8.8 Hz, 1H, H-13), 3.99 (dd, 1H, *J* = 1.5, 10.5 Hz, 1H, H-11), 3.84 (dd, *J* = 2.2, 10.0 Hz, 1H, H-3), 3.80 (s, 3H, *p*-**Me**OAr-), 3.37 (d, *J* = 10.5 Hz, 1H, H-9), 2.63 (dq, *J* =6.7, 10.1 Hz, 1H, H-2), 2.40–2.50 (m, 1H), 2.22 (d, *J* = 13.5 Hz, 1H, H-7), 1.95–1.60 (m, 6H), 1.50 and 1.48 (2s, 6H, -CMe_2), 1.28 (d, *J* =7.0 Hz, 3H, Me-2), 1.22 (d, *J* = 7.5 Hz, 3H, Me-10), 0.96 (d, *J* = 6.5 Hz, 3H, Me-8), 0.89 (t, *J* =7.3 Hz, 3H, -CH_2C**H**$_3$), 0.85 (d, *J* = 7.0 Hz, 3H, Me-4), 0.84 (d, *J* = 7.5 Hz, 3H, Me-12); ^{13}C NMR (75 MHz, $CDCl_3$) 175.2, 160.0, 143.4, 137.6, 131.8, 128.6, 128.1, 128.0, 127.4, 113.9, 112.9, 99.9, 95.4, 94.7, 86.3, 80.3, 75.3, 75.1, 73.1, 70.0, 55.5, 42.7, 38.5, 36.1, 32.5, 30.1, 29.9, 28.8, 28.6, 25.5, 19.9, 15.6, 14.9, 13.6, 10.4, 7.4, 5.5; HRMS (FAB) exact mass calcd for ($C_{40}H_{58}O_9$) requires *m/z* 682.4081, found *m/z* 682.4067; $[\alpha]_D^{23}$ = ─ 16.2 (c = 1.0, $CHCl_3$); TLC R_f = 0.36 (50% EtOAc/hexanes).

(*R*)-2-[(4*S*,5*S*,6*R*)-6-((*S*)-2-{(2*R*)-2-[(4*S*,5*S*,6*S*)-6-((1*S*,1*R*)-2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-propyl}-oxiranyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl]-propionic acid (48). To a solution of the olefin **42** (10.0 mg, 14.7 μmol) in CH_2Cl_2 (1.0 mL) was added *m*-CPBA (40 mg, 70% maximum purity with the remainder as 3-chlorobenzoic acid and water) at 0 °C. After 1 hr, the solution was allowed to warm to rt and allowed to stir for another 2 hr. The resulting mixture was then quenched by the addition of 0.50 mL of a 1.0 M solution of Na_2SO_3. The resultant solution was stirred at ambient temperature for 10 min. The mixture was then diluted with 10 mL EtOAC and washed with 10 mL of 10% Na_2SO_3. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a pH 8.5 buffer solution (20 mL), washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 9.0 mg (88% yield) of a colorless oil; diastereomeric ratio: 2:1. *Major isomer* **48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz , 2 H, *p*-MeO**Ar**-), 7.24–7.31 (m, 5H, Ph), 6.87 (d, *J* = 8.7 Hz, 2H, *p*-MeO**Ar**), 5.56 (s, 1H, *p*-MeOArC**H**), 5.03 (d, *J* = 6.6 Hz, 1H, C**H**$_2$Ph), 4.80 (d, *J* = 6.6 Hz, 1H, C**H**$_2$Ph), 4.66 (d, *J* = 11.4 Hz, -OC**H**$_2$O-) 4.53 (d, *J* = 12.3 Hz, 1H, -OC**H**$_2$O-), 4.26 (d, *J* = 1.5Hz, 1H), 4.13–4.03 (m, 1H), 3.97 (dd, *J* = 1.3, 10.1 Hz, 1H), 3.85–3.80 (m, 1H), 3.80 (s, 3H, *p*-**Me**OAr-), 3.32 (d, *J* = 11.1 Hz, 1H, H-9), 3.07 (d, *J* = 5.4 Hz, 1H, C**H**$_2$OC-), 2.67–2.58 (m, 1H, H-2), 2.35 (d, *J* = 5.7 Hz, 1H, C**H**$_2$OC-), 2.22 (dd, *J* = 2.7, 15.0 Hz, 1H), 1.98 – 1.58 (m, 8H), 1.49 and 1.42 (2s, 6H, -CMe_2), 1.27 (d, *J* = 6.6 Hz, 3H, Me-2), 1.21 (d, *J* = 6.6 Hz, 3H, Me-10), 1.00 (d, *J* = 6.6 Hz, 3H, Me-8), 0.92–0.85 (m, 6H);

HRMS (FAB) exact mass calcd for $(C_{40}H_{58}O_{10} - H^+)^-$ requires *m/z* 697.3951, found *m/z* 697.3940.

(*R*)-2-((4S,5S,6R)-6-{(1R,3R)-3-[(4S,5S,6S)-6-((1S,2R)-2-Benzyloxymethoxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-1-hydroxy-1-methyl-butyl}-2,2,5-trimethyl-[1,3]dioxan-4-yl)-propionic acid (50). To a solution of the epoxide **48** (6.0 mg, 8.6 μmol) in THF (2.0 mL) was added dropwise $LiEt_3BH$ (0.40 mL, 0.40 mmol as a 1.0 M solution in THF) at 0 °C under Ar(g). After 5 min, the resulting solution was allowed to warm and stirred at ambient temperature for 5.5 hr. The reaction was quenched by the addition of 2.0 mL 0.5 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5:25:70 AcOH/EtOAc/hexanes) to afford **50** (5.1 mg) as a colorless oil in 85% yield as a 2:1 mixture of isomers. *Major isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.0 Hz , 2 H, *p*-MeO**Ar**-), 7.29 –7.31 (m, 5H, Ph), 6.88 (d, *J* = 9.0 Hz, 2H, *p*-MeO**Ar**), 5.52 (s, 1H, *p*-MeOArC**H**), 4.92 (d, *J* = 6.9 Hz, -OC**H**$_2$O-), 4.78 (d, *J* = 7.2 Hz, 1H, -OC**H**$_2$O-), 4.67 (d, *J* = 1.5 Hz, 1H), 4.26 (d, *J* = 1.5Hz, 1H), 4.04–3.61 (m, 3H), 3.80 (s, 3H, *p*-**Me**OAr-), 3.28 (d, *J* = 10.8 Hz, 1H, H-9), 2.69 (dq, *J* = 4.4, 14.3 Hz, 1H, H-2), 2.54–2.40 (m, 1H), 2.22 (dd, *J* = 2.7, 15.0 Hz, 1H), 1.90 – 1.50 (m, 8H), 1.46 and 1.45 (2s, 6H, -CMe_2), 1.27 (d, *J* = 6.6 Hz, 3H, Me-2), 1.19 (d, *J* = 4.5 Hz, 3H, Me-10), 1.04 (d, *J* = 7.2 Hz, 3H, Me-8), 0.90 (t, *J* = 7.4 Hz, 3H, **CH$_3$**CH_2-), 0.81 (d, *J* = 7.2 Hz, 3H, Me); HRMS (FAB) exact mass calcd for $(C_{40}H_{60}O_{10} + H^+)^-$ requires *m/z* 701.4262, found *m/z* 701.4286.

(*R*)-2-((4*S*,5*S*,6*R*)-(6-{(1*R*,3*R*)-1-Hydroxy-3-[(4*S*,5*S*,6*S*)-6-((1*S*,2*R*)-2-hydroxy-1-methyl-butyl)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-1-methyl-butyl}-2,2,5-trimethyl-[1,3]dioxan-4-yl)-propionic acid (53). To a solution the seco acid **50** (5.1 mg, 7.3 μmol), 46.0 mg of Pd/C, in 2.0 mL of MeOH and 0.50 mL of acetone was added 146.0 mg of ammonium formate at ambient temperature. The reaction vessel was sealed under a balloon to trap the H_2 (g) released. After 6 h, the mixture was filtered through a plug of Celite© with 20 mL of EtOAc and diluted with 20 mL of 0.5 N $KHSO_4$. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5:25:70 AcOH/EtOAc/hexanes) to afford 2.5 mg of **53** as colorless oil in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.0 Hz , 2 H, *p*-MeO**Ar**-), 7.29 –7.31 (m, 5H, Ph), 6.88 (d, *J* = 9.0 Hz, 2H, *p*-MeO**Ar**), 5.52 (s, 1H, *p*-MeOArC**H**), 4.92 (d, *J* = 6.9 Hz, -OC**H**$_2$O-), 4.78 (d, *J* = 7.2 Hz, 1H, -OC**H**$_2$O-), 4.67 (d, *J* = 1.5 Hz, 1H), 4.26 (d, *J* = 1.5Hz, 1H), 4.04–3.61 (m, 3H), 3.80 (s, 3H, *p*-**Me**OAr-), 3.28 (d, *J* = 10.8 Hz, 1H, H-9), 2.69 (dq, *J* = 4.4, 14.3 Hz, 1H, H-2), 2.54–2.40 (m, 1H), 2.22 (dd, *J* = 2.7, 15.0 Hz, 1H), 1.90 – 1.50 (m, 8H), 1.46 and 1.45 (2s, 6H, -CMe_2), 1.27 (d, *J* = 6.6 Hz, 3H, Me-2), 1.19 (d, *J* = 4.5 Hz, 3H, Me-10), 1.04 (d, *J* = 7.2 Hz, 3H, Me-8), 0.90 (t, *J* = 7.4 Hz, 3H, **CH$_3$**CH_2-), 0.81 (d, *J* = 7.2 Hz, 3H, Me); HRMS (FAB) exact mass calcd for $(C_{32}H_{52}O_9 - H^+)^-$ requires *m/z* 579.3533, found *m/z* 579.3520.

13-Ethyl-4-hydroxy-17-(4-methoxy-phenyl)-2,4,7,7,10,14,19,20-octamethyl-6,8,12,16,18-pentaoxa-tricyclo[13.3.1.15,9]icosan-11-one (54).[18] To a solution of the seco acid **53** (4.6 mg, 7.9 μmol) in 0.50 mL of benzene at ambient temperature were added 0.265 mL (1.48 mmol) of Hünig's base and 0.154 mL (0.987 mmol) 2,4,6,-trichlorobenzoyl chloride. The resultant solution was stirred at ambient temperature for 8 h after which it was diluted with 50 mL of benzene and treated with 240 mg (1.97 mmol) *N*,*N*-(dimethylamino)pyridine). After 24 h, the resultant white mixture was quenched by the addition of 30 mL of NH_4Cl (sat). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (10% gradient to 20% EtOAc/hexanes) to afford 3.0 mg of macrolactone **54** as a colorless oil in 65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz , 2 H, *p*-MeO**Ar**-), 6.90 (d, *J* = 8.7 Hz, 2 H, *p*-MeO**Ar**), 5.69 (s, 1H, *p*-MeOArC**H**), 5.45 (dd, *J* = 4.1 Hz, 10 Hz, 1H, H-13), 4.06 (s, 1 H, H-5), 3.80 (s, 3H, *p*-**Me**OAr-), 3.90 (d, *J* = 10.5 Hz, 1H, H-3), 3.65 (d, *J* = 9.3 Hz, 1H, H-11), 3.35 (d, *J* = 10.2 Hz, 1H, H-9), 2.77 (dq, *J* = 6.5, 10.5 Hz, 1H, H-2), 2.50 (m, 1H, H-8), 2.23 (br s, 1H, OH-6), 1.60–1.80 (m, 4H, H-4, 10, 12, 14), 1.48 (m, 1 H, H-14'), 1.30 –1.50 (m, 2H, H-7 and 7'), 1.53 and 1.48 (2s, 6H, -OCMe_2O-), 1.25 (s, 3H, Me-6), 1.21–1.27 (m, 9H, Me-2, Me-4, Me-8), 1.02 (d, *J* = 6.0 Hz, 3H, Me-10 or Me-12), 0.88 (d, *J* = 6.9 Hz , 3H, Me-10 or Me-12), 0.87 (t, *J* = 6.9 Hz, 3H, Me-14); HRMS (FAB) exact mass calcd for $(C_{32}H_{50}O_8 - H^+)^-$ requires *m/z* 561.3427, found *m/z* 561.3426; TLC R_f = 0.21 (20% EtOAc/hexanes).

13-Ethyl-4-hydroxy-17-(4-methoxy-phenyl)-2,4,7,7,10,14,19,20-octamethyl-6,8,12,16,18-pentaoxa-tricyclo[13.3.1.15,9]icosan-11-one (58). According to a modified Evans procedure,[21] to a solution of 2.0 mg (3.6 μmol) of macrolactone **54** in 1.0 mL of 2-propanol at ambient temperature was added 10 mg of $Pd(OH)_2$. The vial was subsequently purged for 5 min with H_2 (g) under balloon pressure and maintained under positive H_2 (g) pressure (balloon). After 14 h, the mixture was filtered through a plug of Celite© with 20 mL of EtOAc and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 1.6 mg of macrolactone **58** as a colorless oil in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (dd, *J* = 1.0 Hz, 4.6 Hz, 9.3 Hz, 1H, H-13), 3.90 (s, 1H), 3.71 (d, *J* = 10.2 Hz, 1H), 3.58 (d, *J* = 9.3 Hz, 1H), 3.54 (d, *J* = 3.3 Hz, 1H), 3.24 (d, *J* = 7.5 Hz, 1H), 3.00 (m, 1H), 2.70 (dq, *J* = 6.5, 10.5 Hz, 1H, H-2), 2.17 (d, *J* = 0.9 Hz, 1H), 1.60–1.90 (m, 6H), 1.41 (s, 3H, Me), 1.40 (s, 3H, Me), 1.26 (d, *J* = 6.0Hz, 3H, Me), 1.21–1.14 (m, 2H), 1.14(s, 3H, Me), 1.12 (d, *J* = 7.2 Hz, 3H, Me), 1.01 (d, *J* = 7.2 Hz, 3H, Me), 0.91 (d, *J* = 6.6 Hz, 3H, Me), 0.83 (t, *J* = 7.4 Hz, 3H, Me), 0.74 (d, *J* = 7.2 Hz, 3H, Me); HRMS (FAB) exact mass calcd for ($C_{24}H_{44}O_7$ – H^+) requires *m/z* 445.3165 found *m/z* 445.3148; TLC R_f = 0.24 (50% EtOAc/hexanes).

Erythronolide B (1). Following a modified procedure by Corey, macrolactone **58** (0.40 mg, 0.90 μmol) was oxidized by treatment with PCC (4.0 mg, 0.018 mmol) and activated 3 Å mol sieves in CH_2Cl_2 (0.20 mL) at 0°C. After the reaction was complete as determined by TLC analysis (30 min), IPA (ca 10 drops) was added until the solution turns dark orange/brown. The resulting solution was filtered with Et_2O through a column

of silca gel (0.50 mL), and concentrated *in vacuo*. The resulting C(9) ketone was used with out further purification by subjection to 0.30 mL of 1 *N* HCl: THF (1:1) at ambient temperature. After 30 min, 5 mL of a saturated solution of $NaHCO_3$ (aq) was added. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL), and the organic layers washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified (20:1 MeOD:CDCl3, 0.40 mL of silica gel) to provide erythronolide B (**1**) as a white solid in 60% yield (0.20 mg). This synthetic material was identical to the natural sample of erythronolide (B) by co-elution on TLC; TLC R_f = 0.33 (10:1 $CHCl_3$:MeOH). Due to the high dilution of our ^{1}H NMR sample for **1**, the region between 1.22 to 1.99 ppm is obscured by ubiquitous grease. The observed ^{1}H NMR shifts are in complete accord with data obtained from the natural sample,[27] and data reported in the literature.[29]

	^{1}H δ (multiplicity, *J* (Hz), integration)		
proton	Literature Report[a]	Synthetic Sample[b]	Natural Sample[b]
H-13	5.22, (dq, *3.8, 9.5*, 1H)	5.22 (ddd, *2.0, 7.5, 16.5*, 1H)	5.22 (ddd, *2.0, 7.1, 15.9*, 1H)
OH-3	3.92 (s, 1H)	3.94 (s, 1H)	3.94 (s, 1H)
H-3	3.88 (d, *9.5*, 1H)	3.91 (s, 1H)	3.91 (s, 1H)
OH	3.72 (s, 2H)	3.72 (s, 2H)	3.73 (s, 2H)
H-11	3.68 (m, 1H)	3.68 (m, 1H)	3.68 (m, 1H)
OH	3.07 (s, 1H)	3.06 (s, 1H)	3.03 (s, 1H)
H-2, H-8, H-10	2.72-2.86 (m)	2.72-2.86 (m)	2.72-2.86 (m)
OH	2.67 (s, 1H)	2.67 (s, 1H)	2.67 (s, 1H)
Me-4	1.07 (d, *7.1*, 3H)	1.07 (d, *6.6*, 3H)	1.07 (d, *6.6*, 3H)
Me-10	1.02 (d, *7.0*, 3H)	1.02 (d, *6.6*, 3H)	1.02 (d, *7.2*, 3H)
MeCH_2-13	0.93 (t, *7.3*, 3H)	0.94 (t, *7.2*, 3H)	0.93 (t, *7.3*, 3H)
Me-12	0.88 (d, *7.0*, 3H)	0.88 (d, *6.0*, 3H)	0.88 (d, *7.0*, 3H)

[a] Data reported by Mulzer and recorded on in CDCl3 at 270 MHz.[40] [b] Data recorded on a Varian Mercury-300 in $CDCl_3$.

HRMS (FAB) exact mass calcd for $(C_{21}H_{38}O_7 + Na^+)^-$ requires *m/z* 425.2515, found *m/z* 425.2497; Mass fragmentation pattern for synthetic erythronolide B (**1**) is identical to the

reported fragmentation for natural erythronolide B.[41] LRMS/MS (ES) m/z found 425.3, 407.1, 327.1, 309.0, 291.1, 247.1, 207.0.

(*R,R*)-2-Bromo-4,5-diphenyl-1,3-bis-(toluene-4-sulfonyl)-[1,3,2]diazaborolidine (**59**). Based on a modified procedure by Yoon,[31] in a flame-dried 250 mL round-bottomed Schlenck flask was placed (*R,R*)-bis(4-methylbenzene-sulfonyl)-1,2-diphenyl-1,2-diaminoethane[42] (**65**) (445 mg, 0.854 mmol). The flask was sealed with a glass stopper with teflon tape, and then evacuated and flushed three times with Ar (g). The flask was then charged with 17 mL of dry CH_2Cl_2.[43] A 1.0 M solution of boron tribromide[44] in CH_2Cl_2 (1.10 mL, 1.10 mmol) was added by syringe, and the resulting pale yellow reaction mixture was stirred for 20 min. The flask was immersed in a water bath, and the solvent and residual boron compounds carefully removed under reduced pressure (0.50 mmHg) through two traps cooled by liquid nitrogen. The resulting residue was dried under vacuum (0.03 mmHg) for 20 min to quantitatively provide a pale orange solid (520 mg).[45] Purity by ^{1}H NMR analysis was typically greater than 95%. Complex (**56**): ^{1}H NMR (300 Hz) δ 7.35–7.29 (m, 6H, Ar), δ 7.25–7.20 (m, 4H, Ar), 7.07–7.04 (m, 8H, Ar), δ 5.0 (s, 2H, CHAr), δ 2.34 (s, 6H, Me). This material was used in the tandem acyl-Claisen rearrangement without further purification.

(*R, R*)-4,5-Diphenyl-1,3-bis-(toluene-4-sulfonyl)-[1,3,2]diazaborolidin-2-ol (**66**): ^{1}H NMR (300 Hz) δ 7.29 (d, *J* = 8.1, 4H, Ar), δ 7.09 (d, *J* = 13.0, 2H, Ar), 7.01 (t, *J* = 7.5 Hz, 4H, Ar), δ 6.94 (d, *J* = 13.5, 4H, Ar), δ 6.87 (d, *J* = 13.0, 4H, Ar), δ 6.59 (s, 1H), δ 4.59 (s, 2H, CHAr), δ 2.27 (s, 6H, Me).

(*2R, 3S*)-Benzoic acid 1-(1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-2-morpholin-4-ylmethyl-allyl ester (64). Based on a modified procedure by Yoon,[31] a dry flask in an inert atmosphere glovebox was charged with **59** (169 mg, 0.300 mmol) and anhydrous $AgClO_4$ (62.2 mg, 0.300 mmol). The flask was sealed with a rubber septum and removed from the glovebox. CH_2Cl_2 (1.5 mL) was introduced by syringe, and the resulting yellow mixture stirred in the absence of light for 1 hr under Ar (g). The resulting mixture was taken up in a disposable 2.5 mL syringed, which was then fitted with an Acrodisc® PTFE syringe filter and an 18 gauge disposable needle. The filtered solution was added directly to a solution of the diamine **17** (34.6 mg, 0.100 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was cooled to –45 °C. The solution was stirred for 10 min before propionyl chloride (0.30 mL of a 1 M solution in CH_2Cl_2, 0.30 mmol) was added dropwise over 0.5 min. After 18 hr, the reaction mixture was poured onto a mixture of EtOAc (10 mL) and 1 *N* NaOH (10 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aq. NaCl (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by silica gel (EtOAc) to provide **64** in 72% yield (29.1 mg); *syn*:*anti* >99:1 by ^{13}C NMR analysis; *syn* 87% e.e. *Syn* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.7, 9.0 Hz, 2H, Ar), 7.50 (t, *J* = 7.5 Hz, 1H, Ar), 7.38 (t, *J* = 12.5 Hz, 2H, Ar), 5.83 (d, *J* = 6.5 Hz, 1H, CHOBz), 5.11 (s, 2H, C**H**$_2$=C), 3.47–3.93 (m, 8H, O(CH_2CH_2,)$_2$NCO), 3.17 (dq, *J* = 5.6, 18.9 Hz, 1H, C**H**CHOBz), 3.11 (d, *J* = 23.0 Hz, 1H, C**H**(H)C=CH_2), 2.89 (d, *J* = 23.0, 1H, C**H**(H)C=CH_2), 2.46–2.52 (m, 4H), 2.24–2.35 (m, 4H), 1.18 (d, *J* = 12.0 Hz, 3H, Me); ^{13}C NMR (75 MHz) δ 171.5, 165.8, 141.7, 133.3, 130.3, 130.0, 128.7, 115.6,

74.2, 67.2, 67.0, 63.3, 53.8, 46.3, 42.5, 37.4, 11.2; HRMS (FAB) exact mass calcd for $(C_{22}H_{30}N_2O_5 + H)^+$ requires m/z 403.2233, found *m/z* 403.2233; $[\alpha]_D^{23} = -7.9$ (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiracel AS column and AS guard column (2.5% EtOH:hexanes, 1 mL/min flow); t_r = 18.8 min and 22.2 min.

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