Pergamon

Tetrahedron 58 (2002) 2905–2928

TETRAHEDRON

Tetrahedron report number 604

New aspects of the Ireland and related Claisen rearrangements

Yonghai Chai, Sang-phyo Hong, Harriet A. Lindsay, Chris McFarland and Matthias C. McIntosh*

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR 72701, USA

Received 14 September 2001

Contents

Keywords: Ireland–Claisen rearrangement; allylation; diastereoselection.

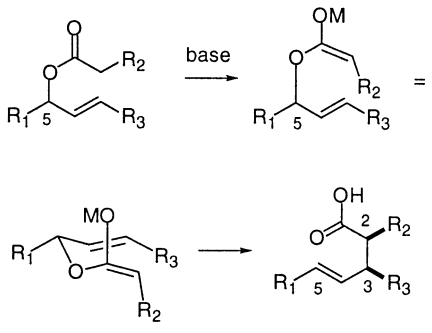
Abbreviations: BOC=*t*-butoxycarbonyl; BPS=*t*-butyldiphenylsilyl; BuLi=*n*-butyllithium; Cy=cyclohexyl; DBU=diazabicycloundecane; DMF=*N*,*N*-dimethylformamide; DMPU=dimethylpropylene urea; Ds=Diastereoselectivity; HMPA=Hexamethylphosphoramide; ICL=iodine monochloride; IPC=Isopinylcampheyl; *i*PrI=isopropyl iodide; KHMDS=potassium hexamethyldisilylamide; LDA=lithium diisopropylamide; LHMDS=lithium hexamethyldisilylamide; LICA=lithium isopropylcyclohexylamide; MEM=Methoxyethoxymethyl; MS=molecular sieves; MsCl=methanesulfonyl chloride; NaH=sodium hydride; NMI=N-methylimidazole; NMO=*N*-methylmorpholine-*N*-oxide; PCy_3=Tricyclohexylphosphine; PhH=Benzene; PhMe=Toluene; Piv=Pivaloyl; PMB=*p*-methoxybenzyl; RCM=ring closing metathesis; Rs=Regioselectivity; rt=room temperature; TBAF=tetrabutylammonium fluoride; TBSCl=*t*-butyldimethylsilyl chloride; TBSOTf=*t*-butyldimethylsilyl trifluoromethanesulfonate; TDS=Thexyldimethylsilyl; TESCl=triethylsilyl chloride; THF=Tetrahydrofuran; TIPSOTf=triisopropylsilyl trifluoromethanesulfonate; TMG=Tetramethylguanidine; TMSCl=trimethylsilyl chloride; TMSI=trimethylsilyl iodide; TMSOTf=trimethylsilyl trifluoromethanesulfonate; TPP=Tetraphenylporphyrin.

* Corresponding author. Tel.: +1-501-575-4692; fax: +1-501-575-4049; e-mail: mcintosh@uark.edu

PII: S0040-4020(02)00164-3

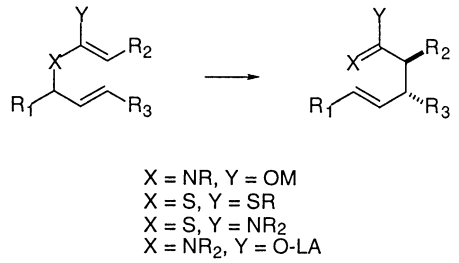
1. Introduction

Since its introduction in 1972, the Ireland–Claisen rearrangement has become widely used in the synthesis of a diverse range of natural products and other targets (Scheme 1).[1–3] The popularity of the reaction is due to several factors: (i) the ease of preparation of the allylic ester reactants; (ii) the ability to control the *E*/*Z* geometry of the ester enolate and hence the relative stereochemistry between C-2 and C-3 of the pentenoic acid product; (iii) the frequently high chirality transfer between the allylic stereocenter of the allyl ketene acetal (C-5, pentenoic acid numbering) and the newly formed stereocenter(s) at C-2 and/or C-3 of the pentenoic acid; (iv) the generally high level of alkene stereocontrol. By comparison to other Claisen rearrangement methods, the Ireland protocol also has the advantages that (v) the reaction is typically performed at or below room temperature; (vi) the reaction is performed under basic rather than acidic conditions; (vii) generally only a 1:1 stoichiometry is needed between the allylic alcohol and the carbonyl components.



Scheme 1.

More recently, several variations of the Claisen rearrangement have been reported which also possess some of the features of the Ireland variant, including the amide Claisen, *S*,*S*- and *N*,*S*-ketene acetal Claisen and the zwitterionic Claisen rearrangements (Scheme 2).[2,3] This review will focus only on those variants of the Claisen rearrangement for which the methods of formation of the ester enolate or ketene acetal are generally stereoselective. The parent Claisen and the Johnson- and Eschenmoser–Claisen rearrangements, in which the geometry of the ketene acetals is often difficult to control, will not be covered.



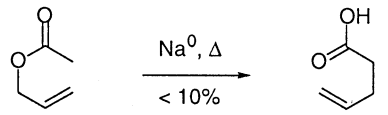
Scheme 2.

The purpose of this Report is to review the recent Ireland and related Claisen rearrangement literature. The focus will be principally on the literature since the last extensive review of the Claisen rearrangement by Frauenrath in 1995.[2h] However, some earlier reports are included if they did not appear in previous reviews or if they help to emphasize a particular aspect of the Claisen rearrangement that the authors wish to highlight. This report is not intended as an exhaustive review of the Ireland–Claisen literature, so many meritorious examples are not included. The authors have collected those examples that they consider to possess some novel aspect that has either not previously been reviewed or that has been under-utilized in synthesis. The examples that are included of course reflect the authors' own prejudices and they are wholly responsible for any oversights or misjudgements in this regard. The asymmetric Claisen rearrangement has recently been reviewed[3] and is therefore not a major focus of this report as such, although some examples are included in other contexts.

The outline of the review given above is somewhat arbitrary, and indeed several examples could well have been placed under more than one sub-heading. The review is broadly organized into the classical Ireland variant of Claisen rearrangement in which esters were employed as rearrangement precursors and more recent variants that employed non-esters. Within the Ireland–Claisen rearrangement section, the topics are further sub-divided by novel methods of ketene acetal formation, novel allylic ester substrates, post-rearrangement transformations and applications to natural and unnatural product synthesis. The natural products applications section includes several uses of the Ireland–Claisen rearrangement that have not been broadly utilized and therefore merit special attention. Natural product syntheses that employed more commonly used variations of the Ireland–Claisen rearrangement are not included.

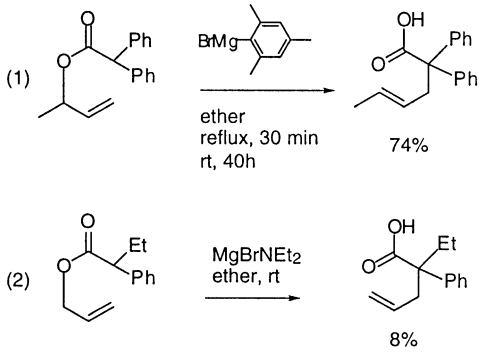
2. History

Since the history of the ester enolate Claisen rearrangement has not been described in detail in previous reviews,[4] all of the examples prior to and including Ireland's first publication are presented here. The first report of an ester enolate Claisen rearrangement appeared in 1937. Tseou and Wang reported the formation of pent-4-enoic acid upon attempted acetoacetic ester condensation of allyl acetate (Scheme 3).[5] Sodium metal was added to neat allyl acetate and the mixture heated for 3 h to ca. 100°C to afford the pentenoic acid in low yield.[5b]



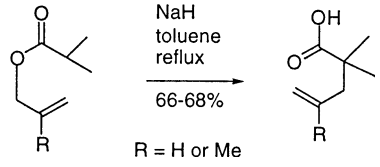
Scheme 3.

In 1949 Arnold and Searles reported that treatment of several allyl diphenyl acetates with mesitylMgBr or NaH afforded 2,2-diphenylpentenoic acids (Eq. (1), Scheme 4).[6] They also found that $MgBrNEt_2$ could effect the rearrangement of phenylethyl allyl acetate, albeit in very low yield (Eq. (2)). In some cases the reaction mixtures were heated under reflux in ether or toluene, but others underwent rearrangement at or near room temperature. High reaction temperatures were necessary when NaH was used as base, and almost certainly reflects inefficient enolization rather than a need for high temperature to effect the rearrangement.



Scheme 4.

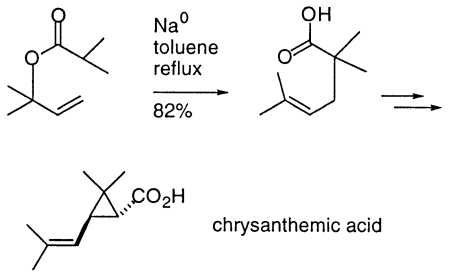
In 1960 Brannock et al. reported the rearrangement of allyl and methallyl isobutyrates upon treatment with NaH in toluene under reflux (Scheme 5).[7] These results demonstrated that phenyl substitution on the ester was not necessary to obtain good yields of rearrangement products.



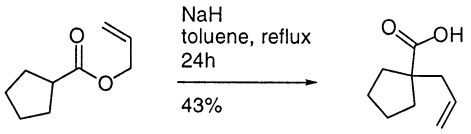
Scheme 5.

In 1964, Julia et al. used the ester enolate Claisen rearrangement for the first time in natural product synthesis in the preparation of (±)-chrysanthemic acid (Scheme 6).[8] This was also the first ester enolate rearrangement of a 3° allylic ester (vide infra).

In 1972 Arnold and Hoffman described the ester enolate rearrangements of several allyl cycloalkane carboxylic esters (Scheme 7).[9] These examples showed that the rearrangement could be used to install quaternary centers within a cycloalkane ring. As with most previous examples, the reaction conditions were harsh, and would not be of use for more sensitive substrates.

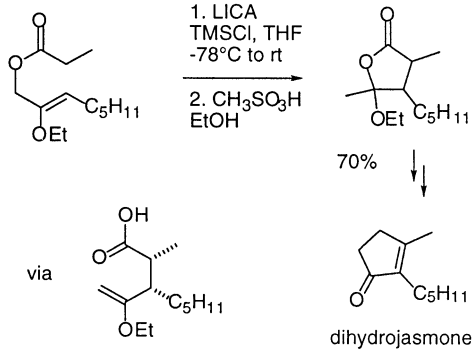


Scheme 6.



Scheme 7.

Also in 1972, Ireland and Mueller reported the transformation that has come to be known as the Ireland–Claisen rearrangement (Scheme 8).[1a] Use of a lithium dialkylamide base allowed for efficient low temperature enolization of the allylic ester. They found that silylation of the ester enolate suppressed side reactions such as decomposition via the ketene pathway and aldol-type condensations. Although the rearrangement was presumably diastereoselective, the stereochemistry of the alkyl groups was not an issue in its application to the synthesis of dihydrojasmone.

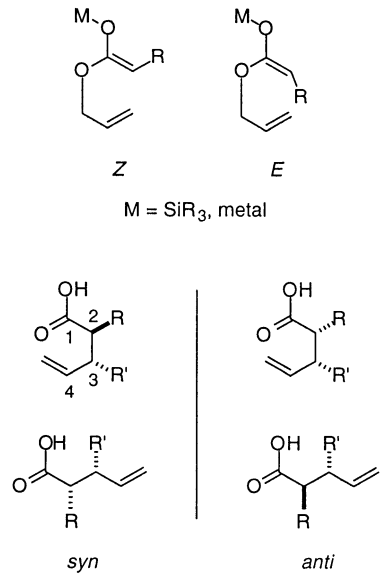


Scheme 8.

3. Nomenclature

For the sake of simplicity, *E*- and *Z*- will refer to the geometries of ester enolates and silyl ketene acetals with the carbonyl oxygen given highest priority irrespective of priority by CIP rules (Scheme 9). For non-esters the *E*/*Z* designation will follow CIP rules.

The *syn* and *anti* stereochemical designations of the pentenoic acid products are given based on the extended chain conformation in which the C-1/C-2/C-3/C-4 dihedral angle is 180° (Scheme 9). However, the closed conformation in which the C-1/C-2/C-3/C-4 dihedral angle is 0° is often more useful in showing how the product stereochemistry derives from the transition state of the rearrangement.



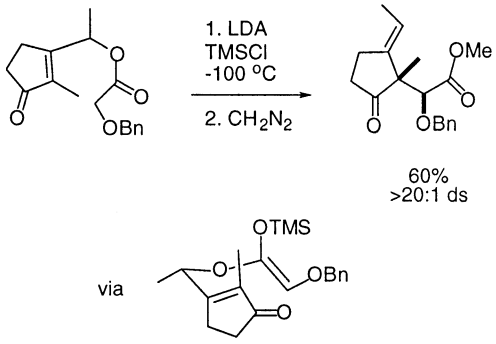
Scheme 9.

4. Allylic ester precursors

4.1. New methods of ketene acetal formation

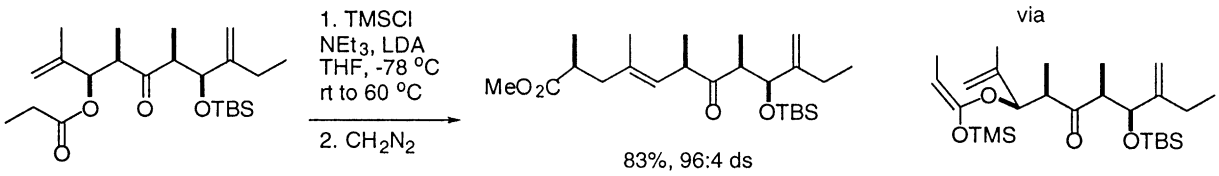
4.1.1. Chemoselective deprotonations. Since the Ireland–Claisen rearrangement typically begins with deprotonation of an allylic ester, the scope of the reaction is potentially limited by the presence of other acidic protons in the molecule. Several examples of selective deprotonation of esters in the presence of other carbon acids have been reported.

4.1.1.1. Ester vs ketone. In 1983, Burke et al. reported the enolization of an allylic glycolate in the presence of the unprotected cyclopentenone (Scheme 10).[10] Only slightly over one equivalent of base was necessary to effect the rearrangement, indicating that concomitant enolization of the enone was not competitive. The stereochemical outcome of the rearrangement of the *Z*-silylketene acetal is consistent with the expected chair-like transition state.



Scheme 10.

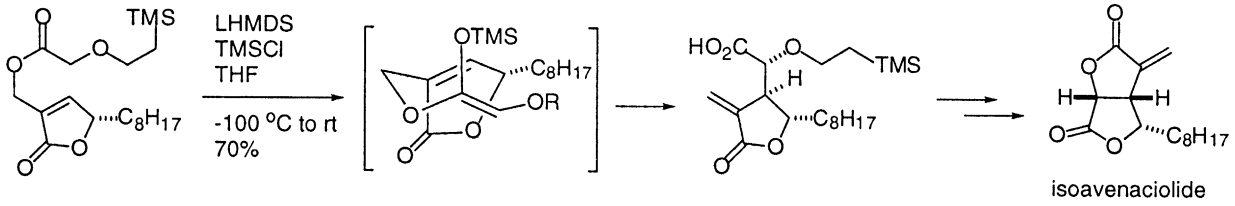
Paterson et al. reported several examples of enolizations of propionate esters in the presence of ketones bearing two different enolizable hydrogens using an internal quench protocol (Scheme 11).[11] The conformation of the ketone



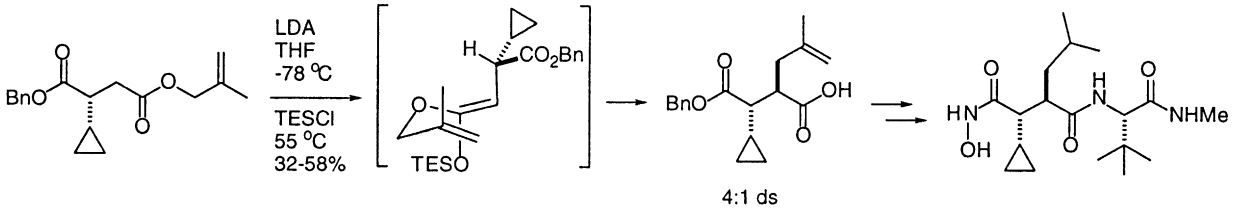
Scheme 11.

presumably inhibited abstraction of the α-keto protons. However, concentrations of LDA greater than 15 mM resulted in 10–20% of elimination products resulting from ketone enolization. The transformation was used in the total synthesis of (−)-ebelactone A and B. The Ireland–Claisen rearrangement of similar unprotected ketones was also employed in two-directional chain synthesis.[11b]

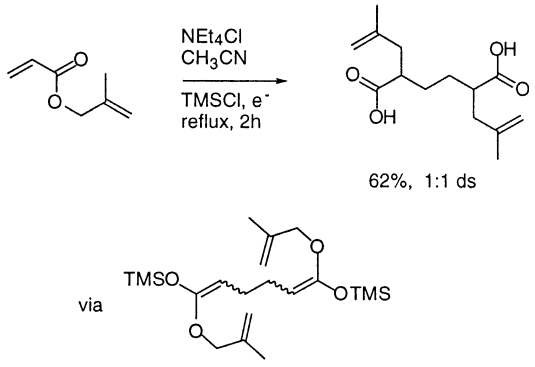
4.1.1.2. Ester vs butenolide. In 1992 Burke et al. reported the selective enolization of a glycolate in the presence of a butenolide (Scheme 12).[12] The rearrangement of the *Z*-silyl ketene acetal occurred via a chair-like transition state to afford the *exo* methylene butyrolactone. The pentenoic acid products were transformed into isoavenaciolide and related targets.



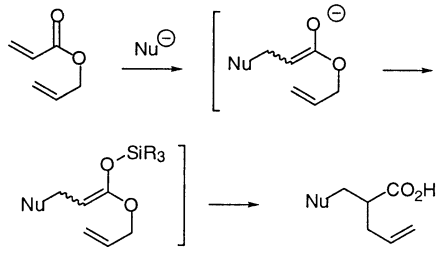
Scheme 12.



Scheme 13.



Scheme 14.



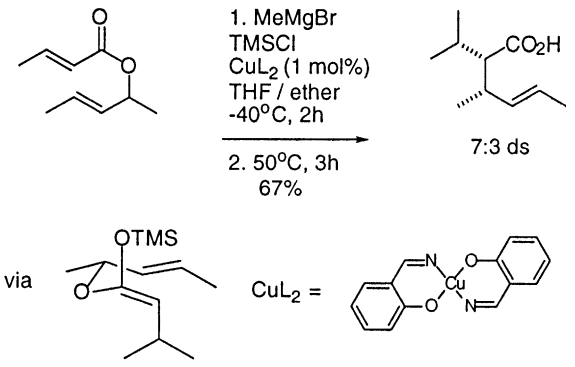
Scheme 15.

4.1.1.3. Ester vs branched ester. Martin et al. have reported several examples of selective enolization of an allyl ester in the presence of a vicinal branched ester (Scheme 13).[13] The facial selectivity of the rearrangements was dictated by allylic strain. The lowest energy allylic conformer of the *E*-silyl ketene acetal would be expected to adopt an eclipsed geometry between the ether oxygen and the allylic proton.[14] The allylic alkene would preferentially approach the silyl ketene acetal from the face *syn* to the smaller carboxybenzyl substituent. The pentenoic acid products were transformed into a series of matrix metalloproteinase (MMP) inhibitors.

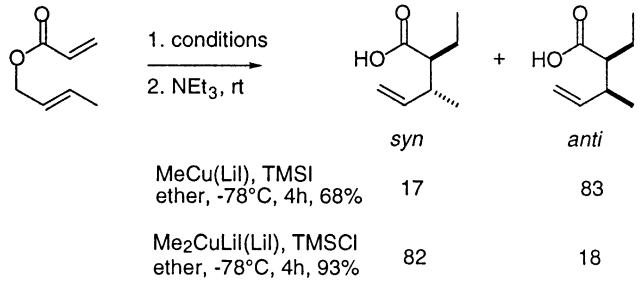
4.1.2. Electrochemical reduction. Troll and Wiedemann dimerized allyl acrylates to the dimeric silyl ketene acetals via electrochemical reduction (Scheme 14).[15] The diallyl adipic diacids were isolated as 1:1 mixtures of diastereomers.

4.1.3. Conjugate additions. Several groups have employed conjugate additions of nucleophiles to allyl acrylates to generate intermediate enolates. The enolates were trapped as silyl ketene acetals (Scheme 15).

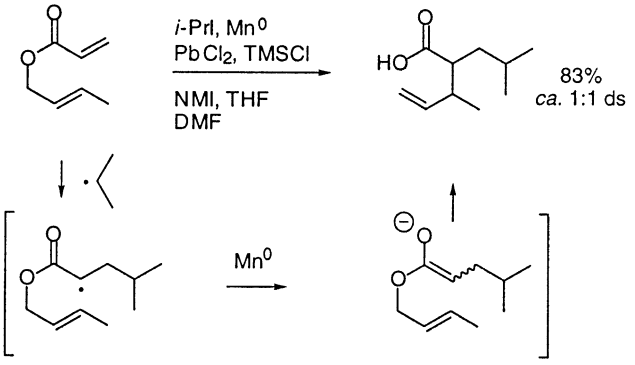
4.1.3.1. Alkyl Cu reagents. Kuwajima and Aoki first reported a conjugate addition/Ireland–Claisen rearrangement sequence (Scheme 16).[16] Cu-catalyzed



Scheme 16.



Scheme 17.



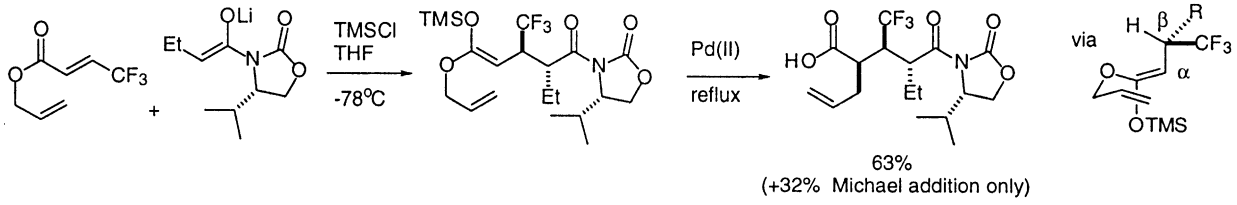
Scheme 18.

addition of MeMgBr to a series of allyl acrylates yielded the desired pentenoic acids, albeit in modest diastereoselectivity. The low diastereoselectivity reflected a lack of control of enolate geometry.

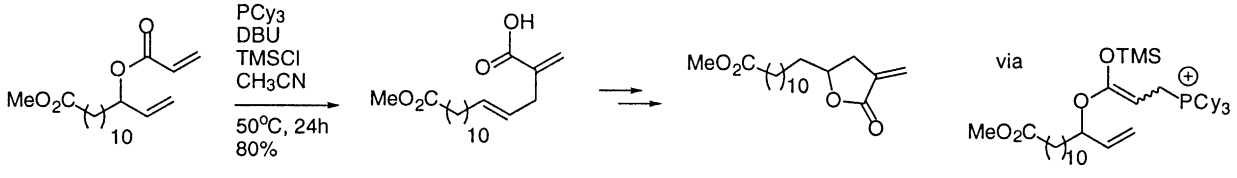
Olsson et al. found that the stereochemistry of the pentenoic acid products could be controlled by the nature of the Cu nucleophile (Scheme 17).[17] Use of MeCu(LiI) and TMSI yielded principally the *anti*-pentenoic acid, whereas addition of $Me_2CuLiI(LiI)$ and TMSCl yielded the *syn*-pentenoic acid as the major diastereomer.

4.1.3.2. Alkyl radicals. Takai et al. reported that the $PbCl_2$-catalyzed addition of alkyl radicals to allyl acrylates yielded pentenoic acids in good yields although essentially no diastereoselectivity was observed (Scheme 18).[18] As with the examples cited above, the low diastereoselectivity reflected a lack of control of enolate geometry. The conjugate addition was thought to occur via Mn-mediated reduction of the alkyl iodide to the alkyl radical. The radical underwent conjugate addition to the allyl acrylate to afford the α-carboxyl radical. Further reduction of the carboxyl radical was followed by in situ trapping as the silyl ketene acetal.

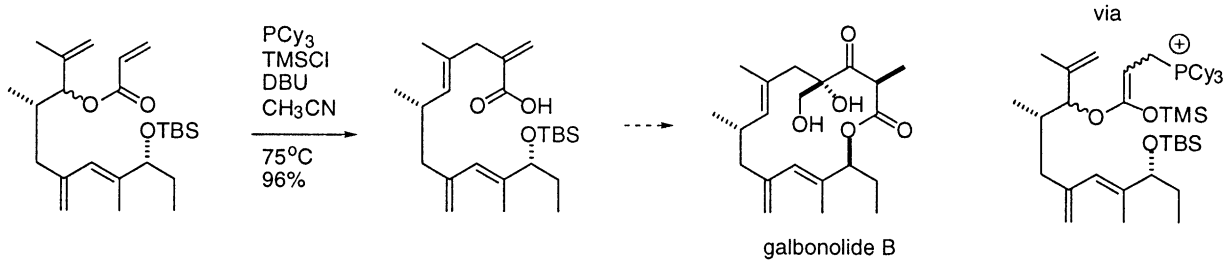
4.1.3.3. Enolates. Yamazaki et al. employed the Evans oxazolidinone enolate in diastereoselective Michael additions to β-CF_3 acrylates to afford intermediate allyl silyl ketene acetals.[19a] The products were isolated as ca. 2:1 mixtures of pentenoic acids and Michael addition adducts (Scheme 19). The rearrangement of the silyl ketene acetal was catalyzed by $PdCl_2(CH_3CN)_2$. Pd(II) catalysis of the Ireland–Claisen rearrangement is rarely used, since the reaction often occurs at or below room temperature.[20] The rearrangement apparently occurred via the *Z*-silyl ketene acetal and exhibited high 1,2-asymmetric induction. The lowest energy conformation about the C_α–C_β bond should have the geometry shown, with the allylic (C_β) hydrogen eclipsed with the *cis* oxygen (cf. Scheme 13).[14] Preferential attack of the allyl group *syn* to the CF_3 group would afford the observed stereoisomer. The authors suggested that the facial selectivity of the rearrangement was due to the Cieplak effect,[19b] with the new bond being formed *anti* to the more electron rich C–C σ* bond.



Scheme 19.



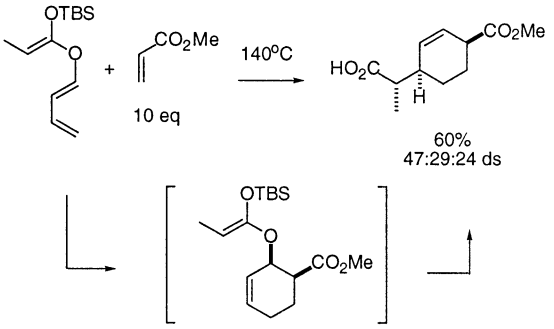
Scheme 20.



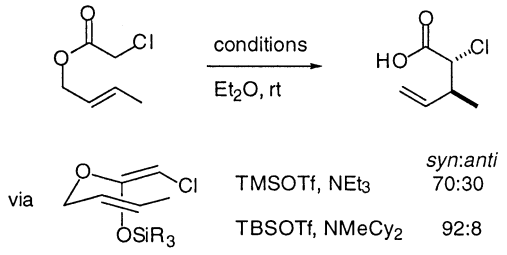
Scheme 21.

4.1.3.4. Phosphines. Inanaga et al. reported the first example of a nucleophile catalyzed Ireland–Claisen rearrangement (Scheme 20).[21] Conjugate addition of tricyclohexylphosphine to allyl acrylates generated intermediate phosphonium allyl silyl ketene acetals which underwent rearrangement to yield α-substituted acrylates after elimination of the phosphine. Subsequent transformations yielded the *exo*-methylene butyrolactone.

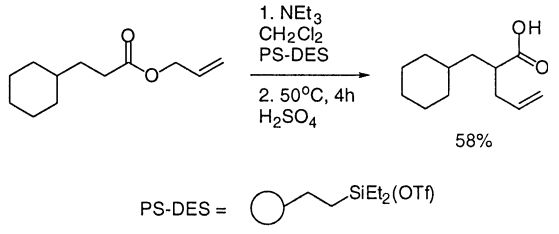
Thomas and Smith adapted the Inanaga procedure in an approach to galbonolide B (Scheme 21).[22] Tricyclohexylphosphine catalysis afforded the desired acrylate in almost quantitative yield.



Scheme 22.



Scheme 23.



Scheme 24.

4.1.4. Via Diels–Alder cycloaddition. Neier et al. made use of the Diels–Alder reaction to generate an allyl silyl ketene acetal in situ (Scheme 22).[23] Diels–Alder cycloaddition of a silyl ketene acetal derived from a dienol propionate yielded an intermediate allyl silyl ketene acetal which underwent in situ Ireland–Claisen rearrangement. The pentenoic acid products were formed in 60% yield as a 47:29:24 mixture of diastereomers, from which the major diastereomer shown below was isolated.

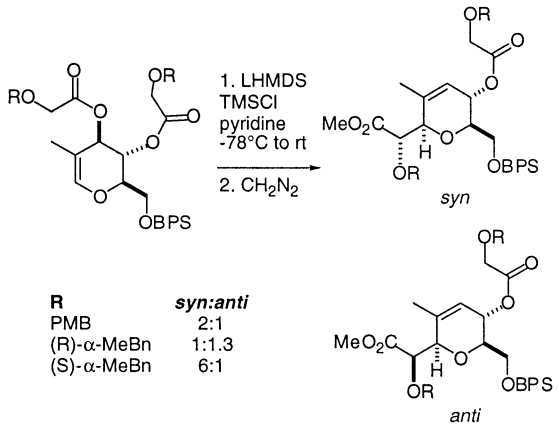
4.1.5. Silyl triflates and tertiary amine bases. Nakai et al. reported a study of the effect of the size of the trialkylsilyl triflate and the tertiary amine base on the diastereoselectivity of the Ireland–Claisen rearrangement (Scheme 23).[24] The best diastereoselectivity (92:8 *syn*/*anti*) was obtained when a bulky amine (Cy_2NMe) and a bulky silylating agent (TBSOTf) were used. Under these conditions the rearrangements occurred principally via the *Z*-silyl ketene acetal.

4.1.6. Solid supported silyl triflate. Porco and Hu recently described the first solid phase Ireland–Claisen rearrangement on a polystyrene resin (Scheme 24).[25] Treatment of allylic esters with a polymer supported silyl triflate yielded the desired pentenoic acids after cleavage from the support.

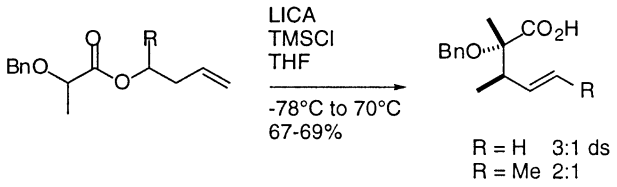
4.2. Novel Claisen rearrangement substrates

4.2.1. α-Oxygenated allylic esters

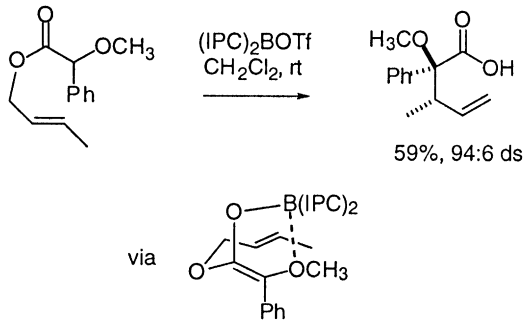
4.2.1.1. Glycolates. Allylic glycolates have been employed extensively in the Ireland–Claisen rearrangement and their rearrangement chemistry has been previously reviewed.[2,3] However, a novel means of improving stereocontrol in a glycolate Claisen rearrangement deserves



Scheme 25.



Scheme 26.



Scheme 27.

mentioning. In studies directed toward spongistatin I, Heathcock et al. noted a low diastereoselectivity in the Ireland–Claisen rearrangement of PMB-protected glycal-based allylic glycolates (Scheme 25).[26] Based on earlier studies by Kallmerten and Gould on an asymmetric Ireland–Claisen rearrangement,[27] Heathcock was able to improve the diastereoselectivity by using enantiomerically pure α-methylbenzyl glycolates. While the achiral PMB ester yielded only a 2:1 ratio of *syn* and *anti* acids, the matched (*S*)-α-methylbenzyl-protected glycolate increased the selectivity to 6:1.

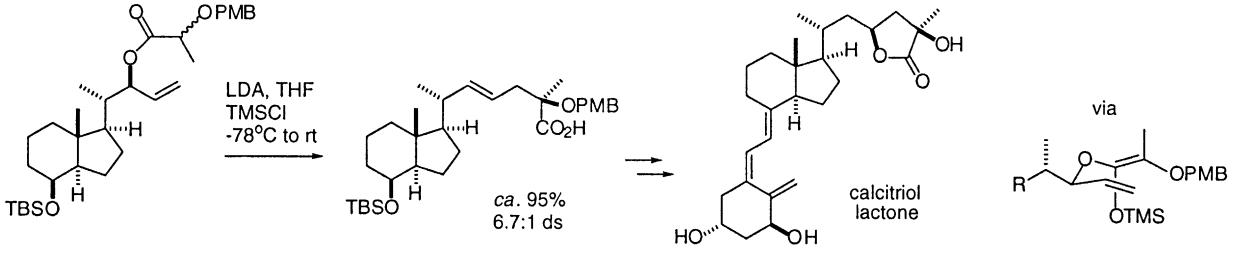
4.2.1.2. Lactates, mandelates and other higher esters. In contrast to the extensive use of glycolate esters, lactate, mandelate and other higher α-oxygenated esters have been used much less frequently. Early work by Bartlett et al. showed that the Ireland–Claisen rearrangement could be used to prepare allylated lactic acids in good yield, but the diastereoselectivity was disappointingly low (Scheme 26).[28]

Oh et al. obtained high diastereoselectivity in the Ireland–Claisen rearrangement of allyl mandelates by using $(IPC)_2BOTf$ to give a 94:6 diastereoselectivity favoring the *syn* diastereomer, presumably via the chelated boron ketene acetal (Scheme 27).[29] Interestingly, although the boron was substituted with chiral non-racemic substituents, the enantioselectivity of the rearrangement was very low (<10%). The mandelate boron ketene acetals underwent rearrangement at considerably lower temperatures than the silyl ketene acetals derived from lactates. In contrast to the extensive use of boron enolates in aldol reactions,[30] boron ketene acetals have been used infrequently in the Ireland–Claisen rearrangement (cf. Scheme 60).

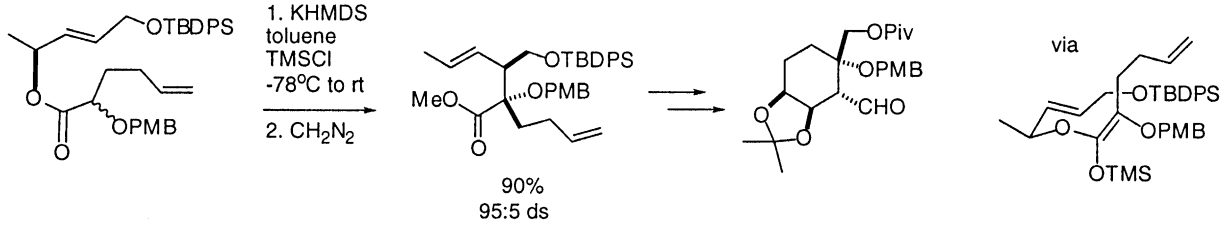
Takano et al. used the Ireland–Claisen rearrangement of an allyl lactate in the total synthesis of calcitriol lactone (Scheme 28).[31] The rearrangement proceeded in 85% de (6.7:1 ds) via *O*-silylation of the intermediate Li-chelated *Z*-enolate. Takano noted that the corresponding benzyl ether gave significantly lower de (70%) than the PMB ether. This is presumably due to the PMB ether's greater Lewis basicity and hence its greater propensity to coordinate to lithium.

Recently Langlois et al. showed that high (95:5) diastereoselectivity could be achieved in the Ireland–Claisen rearrangement of an allyl 2-OPMB-hexenoate ester by using KHMDS and TMSCl in toluene at −78°C (Scheme 29).[32] The diastereoselectivity was substantially lower when LDA was used as the base. The pentenoic ester product was further elaborated to the aldehyde shown using a ring closing metathesis (RCM) reaction to close the carbocyclic ring (vide infra). The aldehyde was projected to serve as an intermediate in the synthesis of fumagillin and ovalicin.

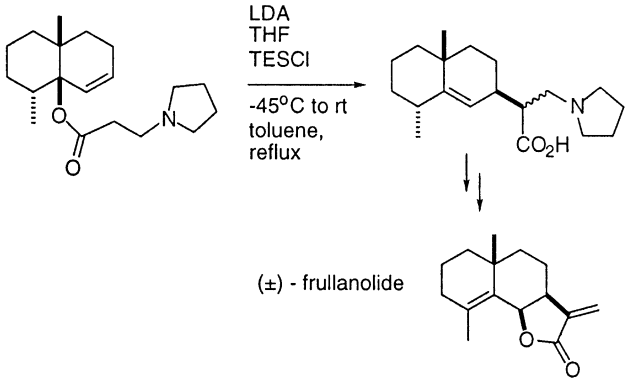
4.2.2. Tertiary alcohol-derived allylic esters. Compared to 1 and 2° alcohols, 3° alcohol derived allylic esters have received comparatively little attention as substrates in the Ireland–Claisen rearrangement. This may reflect difficulty in the synthesis of the requisite 3° ester. In addition, stereocontrol in the formation of the resultant alkene may be problematic. The difference in size of the two allylic substituents is in general large for 2° allylic stereocenters since



Scheme 28.



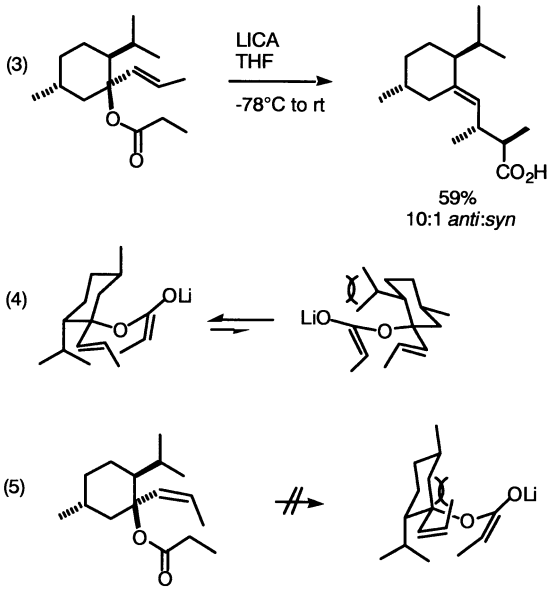
Scheme 29.



Scheme 30.

one substituent is always H (cf. Scheme 1). However, for 3° stereocenters, a smaller size difference will lead to lower alkene stereoselectivity.

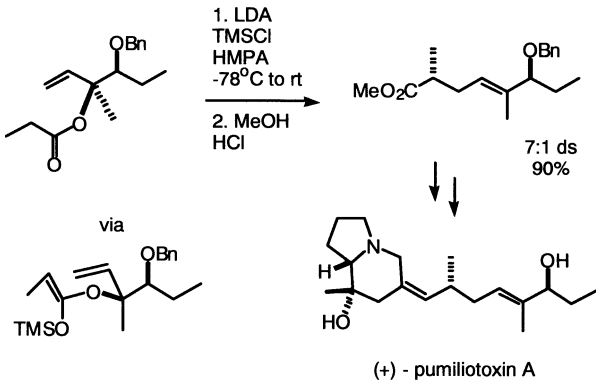
The first use of a 3° allylic ester in a Claisen rearrangement was that of Julia et al. (Scheme 6).[8] In 1977 Still and Schneider used an Ireland–Claisen rearrangement of a 3°



Scheme 31.

allylic ester in the synthesis of (±)-frullanolide (Scheme 30).[33] Rearrangement to the β-pyrrolidinomethyl ester was followed by Cope elimination to the *exo*-methylene lactone. Stereocontrol of the alkene was of course not an issue in this case since the alkene was confined within a ring.

In 1981 Hart et al. used menthone as a regenerable chiral auxiliary in an early example of an asymmetric Ireland–Claisen rearrangement (Scheme 31).[34,35] Rearrangement of the ester enolate gave ca. 10:1 diastereoselectivity of *anti* and *syn* pentenoic acids and as a single alkene stereoisomer (Eq. (3)). The pentenoic acid side chain was ozonolytically cleaved to afford an enantiomerically pure protected aldehyde. The cleavage also served to regenerate the chiral auxiliary. This is also one of the few examples of an exocyclic Claisen rearrangement.[36]

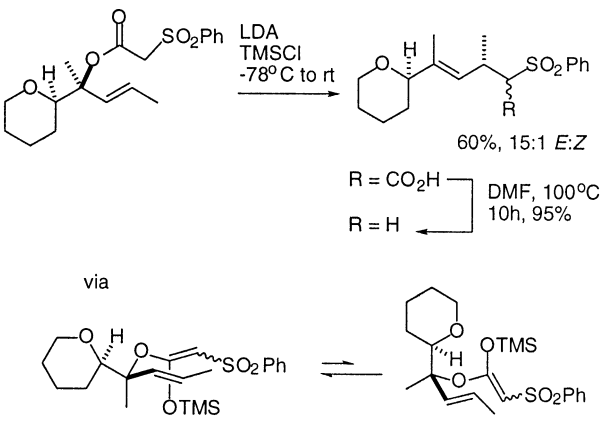


Scheme 32.

The high alkene stereocontrol was attributed to the severe 1,3-diaxial strain induced by the isopropyl group in the transition state leading to the *Z*-alkene (Eq. (4)). It is noteworthy that the attempted Ireland–Claisen rearrangement of the corresponding *cis* alkene failed, presumably due to allylic strain between the *cis*-methyl group of the alkene and the cyclohexane ring (Eq. (5)).[14]

Overman et al. used the Ireland–Claisen rearrangement of a 3° allylic ester in the synthesis of (+)-pumiliotoxin A (Scheme 32).[37] Rearrangement of the *Z*-silyl ketene acetal gave the *E*-alkene as the sole alkene stereoisomer and with 7:1 diastereoselectivity. The stereochemical outcome is consistent with the larger benzyloxypropyl substituent occupying the pseudo-equatorial position of the chair-like rearrangement transition state.

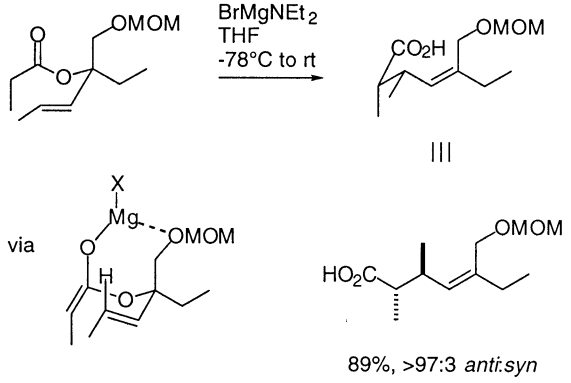
Interestingly, in model studies directed toward ambruticin, Davidson et al. found that the stereoselectivity of the Ireland–Claisen rearrangement depended on which diastereomer of the ester was used (Scheme 33).[38] While the (R^*,S^*) diastereomer shown afforded 15:1 stereoselectivity with respect to the alkene, the (R^*,R^*) stereoisomer gave only a 3:1 selectivity, although in both cases the larger pyranyl substituent preferentially occupied the pseudo-equatorial position of the Ireland–Claisen rearrangement transition state. It is noteworthy that the structurally analogous acyclic (*S*,*S*) diastereomer that Overman employed gave high alkene stereoselectivity (Scheme 32). The resulting sulfonyl pentenoic acids underwent thermal



Scheme 33.

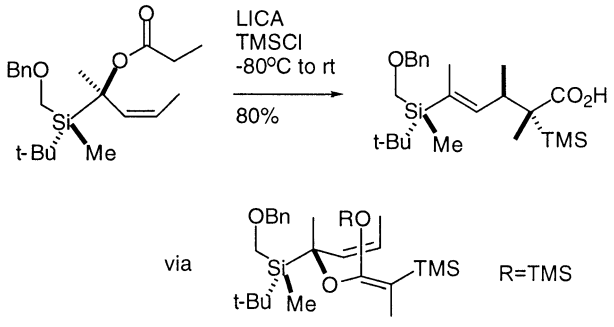
decarboxylation at 100°C to yield the sulfone partner for a subsequent Julia coupling.

Krafft et al. developed a clever solution to the alkene stereocontrol problem by employing chelation between the enolate and one of the 3° alcohol substituents (Scheme 34).[39] Chelation of the Mg enolate with the MOM protected hydroxymethyl substituent enforced its axial disposition to selectively yield the *Z*-alkene isomer in high yield and with high diastereoselectivity.



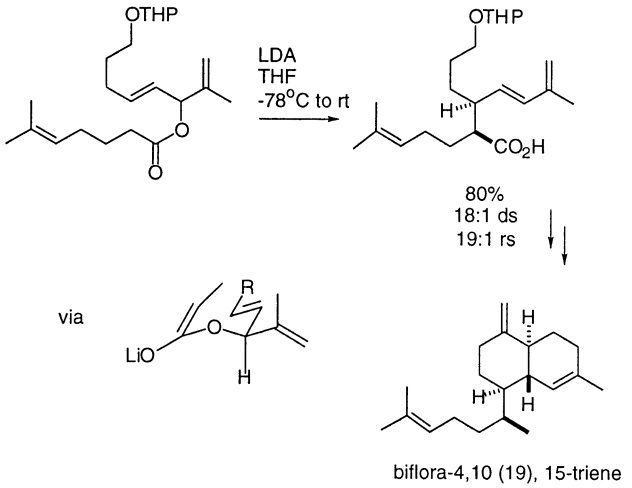
Scheme 34.

Bienz et al. have reported the Ireland–Claisen rearrangement of 3° allylic esters in which one of the allylic substituents is silicon (Scheme 35).[40] The larger silicon substituent occupies the pseudo-equatorial position of the chair to yield the *E*-vinylsilane product. Interestingly, the products apparently result from initial *C*-silylation of the propionate ester followed by a second *Z*-selective enolization of the resulting silyl propionate. The structure of the pentenoic acid product was verified by X-ray crystallographic analysis.



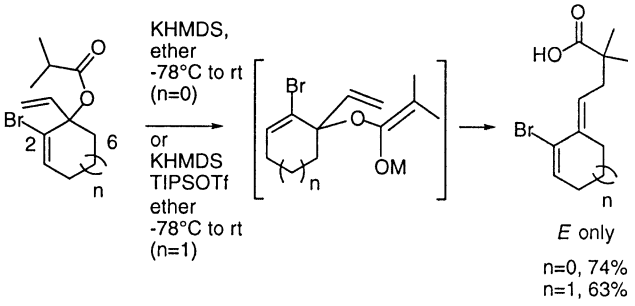
Scheme 35.

4.2.3. Bis-allylic esters. The Claisen rearrangement of bis-allyl vinyl ethers and related systems has been studied by several groups.[41] Modest to high levels of regioselectivity were obtained in the parent Claisen as well as Johnson, Eschenmoser and Ireland variants of the reaction. Parker and Farmar applied the Ireland–Claisen rearrangement of a bis-allylic ester to the synthesis of biflora-4,10(19),15-triene, using the rearrangement to install the 1,3-diene component for a subsequent intramolecular Diels–Alder reaction (Scheme 36).[42] The rearrangement proceeded with both high regio- and diastereoselectivity.

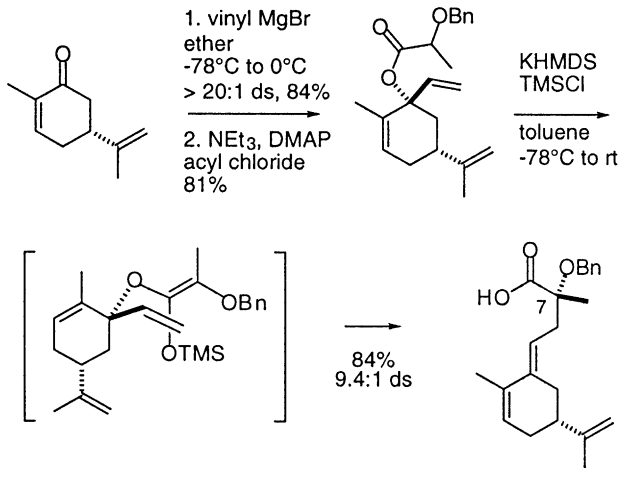


Scheme 36.

McIntosh et al. have reported a regioselective Ireland–Claisen rearrangement of bis-allylic esters derived from cycloalkenones, in which the carbinol carbon is 3° and contained within the cycloalkene ring.[43] All previous examples of Claisen rearrangements of bis-allylic systems employed substrates in which the carbinol carbon was acyclic. The rearrangement proceeded with very high alkene stereoselectivity for substrates bearing substituents at either C-2 or C-6 (Scheme 37). The rearrangements presumably occurred via chair-like transition states with the larger 3° allylic substituent disposed in a pseudo-equatorial position.



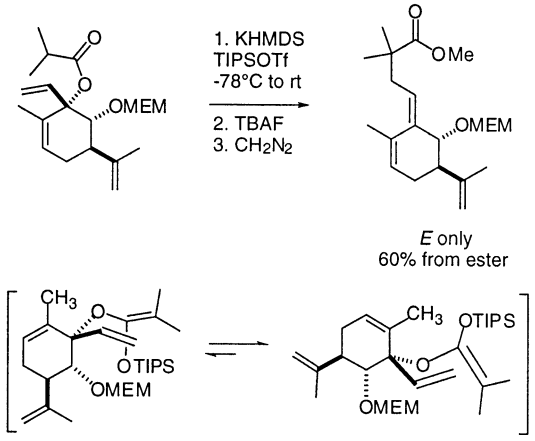
Scheme 37.



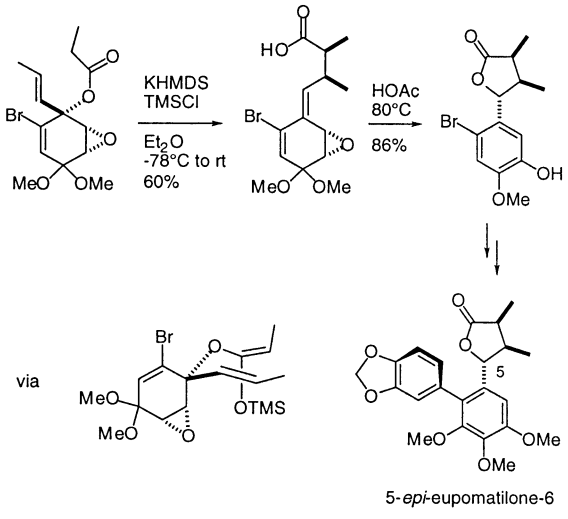
Scheme 38.

One advantage of using cycloalkenones as precursors to the *bis*-allylic esters is that the 3° allylic stereocenter may be formed with high 1,2- 1,3- and 1,4-stereocontrol in the addition of a vinyl or alkynyl nucleophile.[34,43] Thus, a net 1,*n*-asymmetric induction (n=4–7) could be obtained in the vinyl addition/Ireland–Claisen rearrangement sequence. For example, in preliminary studies directed toward the synthesis of the eunicellin diterpenes, a highly selective vinylMgBr addition to (*R*)-carvone was followed by Ireland–Claisen rearrangement using the Langlois conditions[32] to yield the key protected C-7 tertiary alcohol (eunicellin numbering) with good 1,6-stereocontrol (Scheme 38).[43]

The authors also reported that the Ireland–Claisen rearrangement of a carvone-derived 6-OMEM bis-allylic ester yielded only the *E*-diene (Scheme 39).[43] The *E*-diene could be quantitatively isomerized to the *Z*-diene, demonstrating that the *E*-isomer was the kinetic product. The reason for the observed stereoselectivity was not obvious, especially since the ostensibly larger CH_3 substituent must occupy a pseudo-axial position with respect to the Ireland–Claisen rearrangement transition state to yield the observed product.



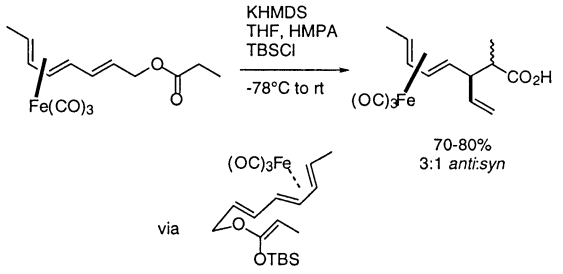
Scheme 39.



Scheme 40.

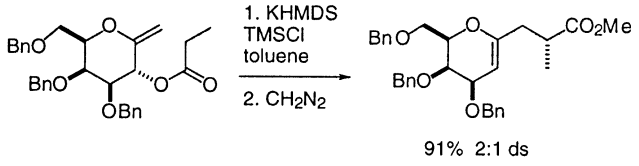
McIntosh and Hong have applied the Ireland–Claisen rearrangement of bis-allyl silyl ketene acetals in studies directed toward the synthesis of the eupomatilones (Scheme 40).[44] The 1,2-transposition of the alkene which occurred in the rearrangement afforded a reactive vinyl epoxide (cf. Scheme 52). Stereoselective cyclization of the carboxylic acid onto the vinyl epoxide generated the 5-aryl lactone, which was further manipulated to 5-*epi*-eupomatilone-6.

4.2.4. Fe–diene complexes. Roush and Works reported a novel diastereofacially selective Ireland–Claisen rearrangement of Fe-complexed trienic allylic esters (Scheme 41).[45] Although the rearrangement proceeded with excellent facial selectivity, only modest *syn/anti* selectivity was obtained.



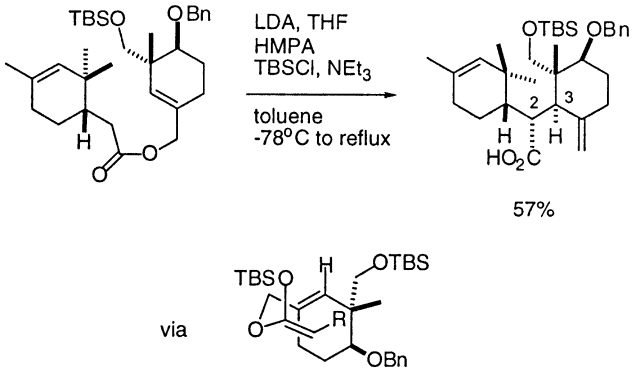
Scheme 41.

4.2.5. Methylidene enol ethers. Langlois et al. reported the Ireland–Claisen rearrangement of methylidene enol ethers derived from sugars to yield novel *C*-glycosides (Scheme 42).[46] Although the yields were high, the diastereoselectivities were generally very modest.



Scheme 42.

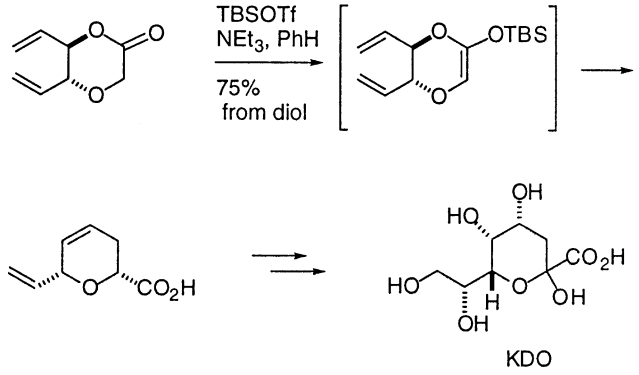
4.2.6. Hindered esters. Magnus and Westwood have reported an Ireland–Claisen rearrangement approach to the taxol skeleton (Scheme 43).[47] The rearrangement presumably occurred via the highly congested *Z*-silyl ketene acetal to install the C-2 and (neopentyl) C-3 stereocenters



Scheme 43.

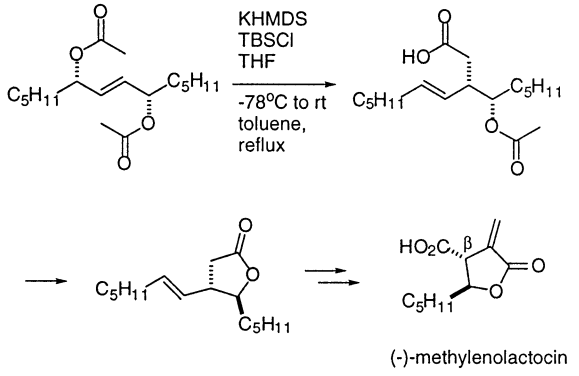
with high diastereoselectivity. The unusually high temperature of the rearrangement was presumably necessary to overcome steric hindrance in the transition state.

4.2.7. Symmetrical and pseudo-symmetrial substrates. Burke and Sametz have used an Ireland–Claisen rearrangement to desymmetrize a C_2 symmetric mannitol-derived divinyl diol to yield an enantiopure 2,6-disubstituted pyran (Scheme 44).[48] The pyran was an intermediate in the total synthesis of KDO.



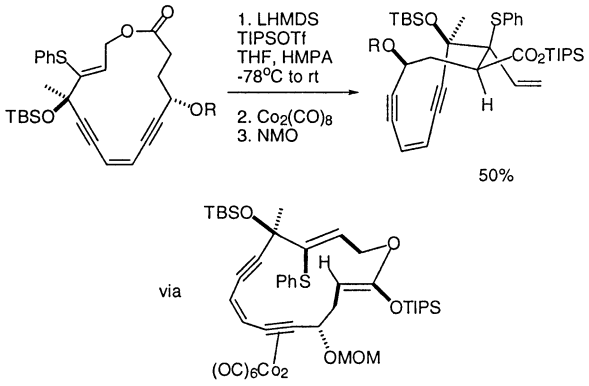
Scheme 44.

Garcia et al. used a related strategy in the total synthesis of methylenolactocin (Scheme 45).[49] The C_2 symmetric bis-silyl ketene acetal underwent Ireland–Claisen rearrangement to the corresponding pentenoic acid. The superfluous pentyl side chain was oxidatively cleaved to install the β-carboxylic acid group.



Scheme 45.

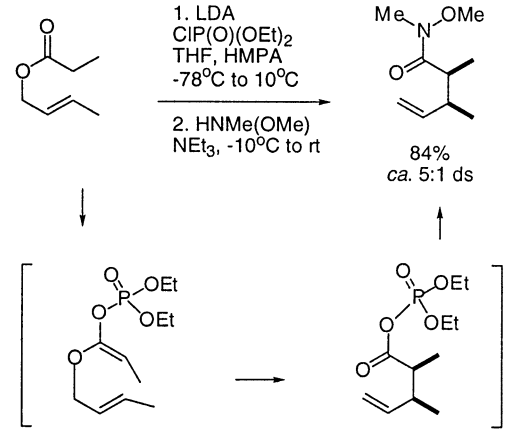
4.2.8. Complex induced rearrangements. Magriotis et al. reported an interesting ring contraction variant of the Ireland–Claisen rearrangement in studies directed toward the enediyne antibiotics.[50] They found that the bending of the alkyne that is induced upon its complexation with $Co_2(CO)_6$ resulted in a facile rearrangement of an otherwise unreactive allyl silyl ketene acetal (Scheme 46). In situ decomplexation of the metal gave the desired carbocycle. The high diastereoselectivity of the rearrangement was argued to be due to transannular interactions and the anti-periplanar effect,[51] in which the 3° allylic oxygen substituent was disposed *anti* to the forming C–C bond. Several diastereoselective Ireland–Claisen rearrangements of allyl ketene acetals bearing allylic oxygen or nitrogen substituents have been reported (vide infra).[51b]



Scheme 46.

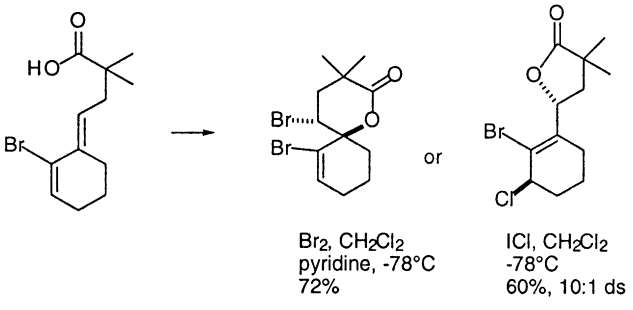
4.3. Post-rearrangement transformations

4.3.1. Acylation. Funk et al. reported an efficient means of in situ esterification and amidation of the pentenoic acid products of the Ireland–Claisen rearrangement (Scheme 47).[52] Use of diethyl chlorophosphate instead of a silylating reagent resulted in formation of an intermediate enol phosphate. Rearrangement yielded an acyl phosphate that could be treated in situ with a nucleophile to directly afford the substituted product.

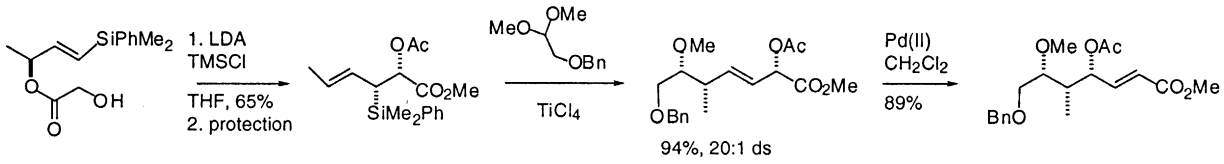


Scheme 47.

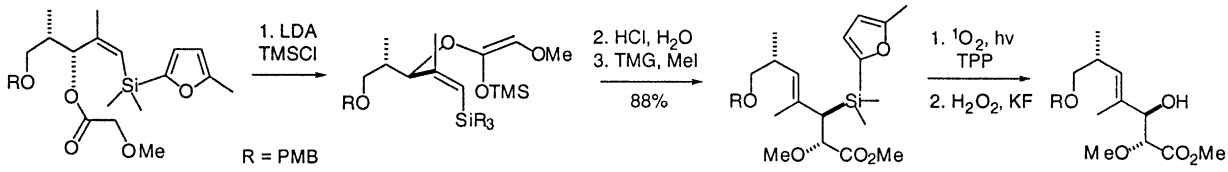
4.3.2. Diene oxidation. The pentenoic acid products of the Ireland–Claisen rearrangement of bis-allylic esters derived from cycloalkenones possess a diene that extends both inside and outside of the cycloalkene ring. McIntosh et al. demonstrated that addition of electrophilic reagents such as Br_2 and ICl to the dienes could generate novel lactones with



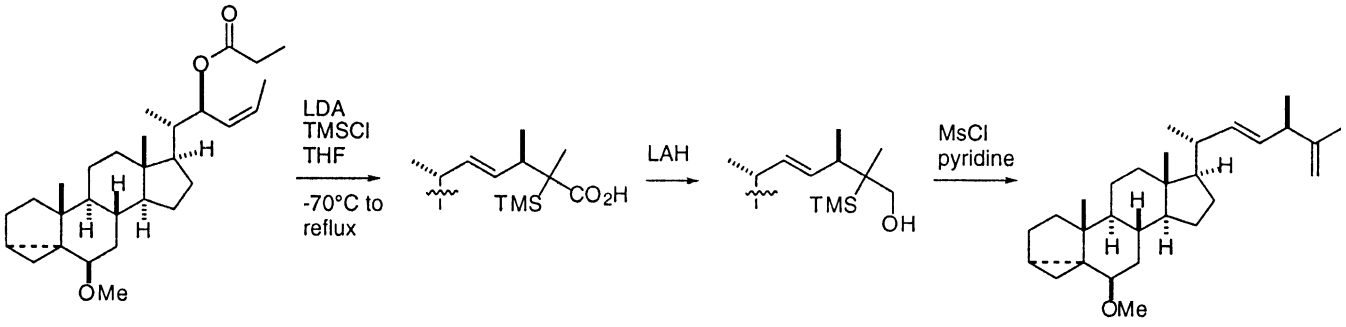
Scheme 48.



Scheme 49.



Scheme 50.



Scheme 51.

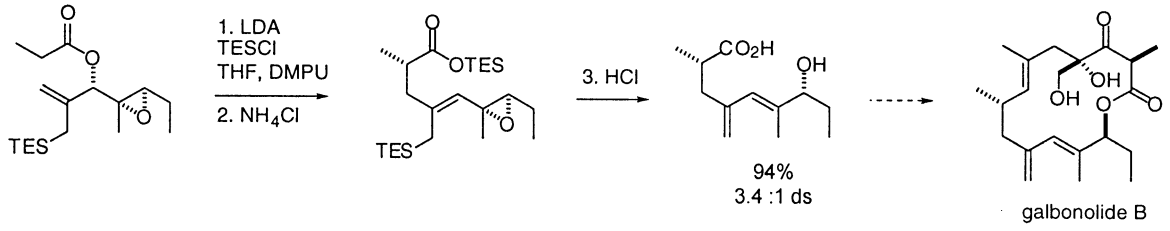
high regio- and stereoselectivity (Scheme 48).[53] Treatment of an *E*-bromodienic acid with Br_2 afforded solely the spirocyclic pentanolide, whereas treatment of the same acid with ICl yielded the attached ring chlorobutanolide via an intermediate chloroiodide.

4.3.3. Allyl silane additions. The Ireland–Claisen rearrangement of vinylsilanes yields allylsilanes, which may be used as nucleophiles in subsequent reactions. Panek et al. have demonstrated the utility of such chiral allyl silanes in synthesis.[54] Rearrangement of the vinyl silane glycolates yielded the *syn* pentenoic acids (Scheme 49). Lewis acid mediated addition of the allyl silane to an aldehyde or aldehyde equivalent generated the *syn*-5,6 methyl/alkoxy adduct. Pd catalyzed [3,3]-rearrangement of the resulting allylic ester gave the conjugated ester with the all *syn* stereochemical triad. The ester was transformed in three steps into a protected pyranoside. An interesting feature of the synthesis is that neither of the stereocenters generated in the Ireland–Claisen rearrangement reside in the final product.

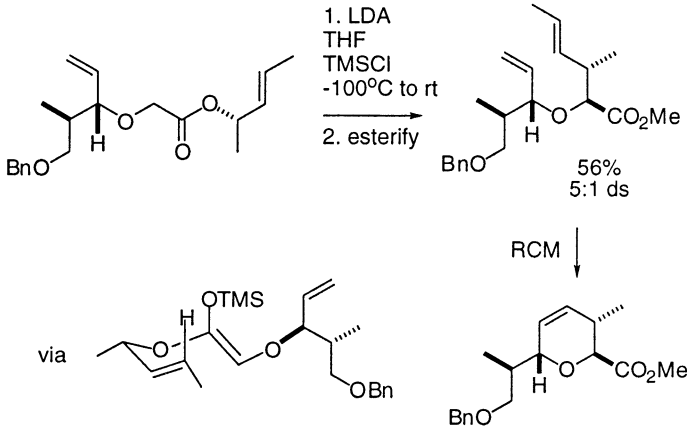
4.3.4. Tamao oxidation. Kocienski et al. have used a vinylsilane as a masked vinyl alcohol in the synthesis of the C-26 to C-32 fragment of rapamycin (Scheme 50).[55] Ireland–Claisen rearrangement of the vinylsilane glycolate ester via the *Z*-silyl ketene acetal yielded the corresponding *anti* pentenoic acid with high diastereoselectivity. Oxidative cleavage of the furyl substituent and Tamao oxidation then afforded the allylic alcohol.

4.3.5. Peterson olefination. Zhabinskii et al. have used the Ireland–Claisen rearrangement to append a 1,4-diene side chain onto a steroid D-ring (Scheme 51).[56] After rearrangement of the *Z*-crotyl propionate, the pentenoic acid product was again enolized and C-silylated in situ. Peterson olefination via reduction of the carboxylic acid and mesylation yielded the 1,4-diene product.

4.3.6. Vinyl epoxide fragmentation. As mentioned above, the 1,2-transposition of the alkene that occurs by virtue of the rearrangement can result in a new functional group array. Parsons et al. have employed the Ireland–Claisen



Scheme 52.

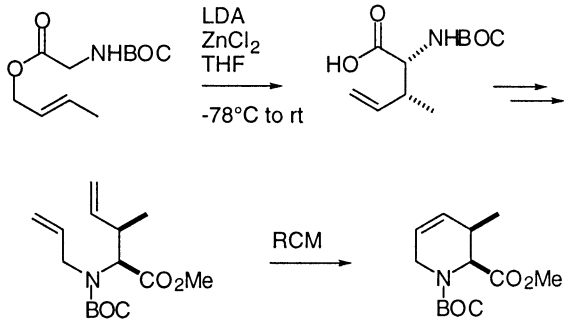


Scheme 53.

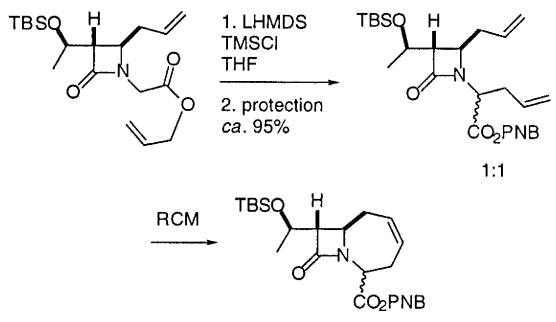
rearrangement of epoxy allylic esters to generate reactive vinyl epoxides. The vinyl epoxides underwent fragmentation upon in situ treatment with acid to yield allylic dienols (Scheme 52).[57] The protocol was used in studies directed toward the synthesis of galbonolide B (cf. Scheme 21).

4.3.7. Alkene metathesis. Several groups have employed ring closing metathesis (RCM) of Ireland–Claisen rearrangement-derived pentenoic acids in the synthesis of both carbocyclic and heterocyclic ring systems.[32,58] Burke et al. prepared a number of *O*-allyl pentenoates by rearrangement of *O*-allyl allylic glycolates. RCM yielded substituted pyrans (Scheme 53).[59]

Piscopio et al. prepared a range of heterocycles and carbocycles by RCM of alkenyl pentenoic acids.[60] For example, Ireland–Claisen rearrangement of an allyl glycinate using



Scheme 54.



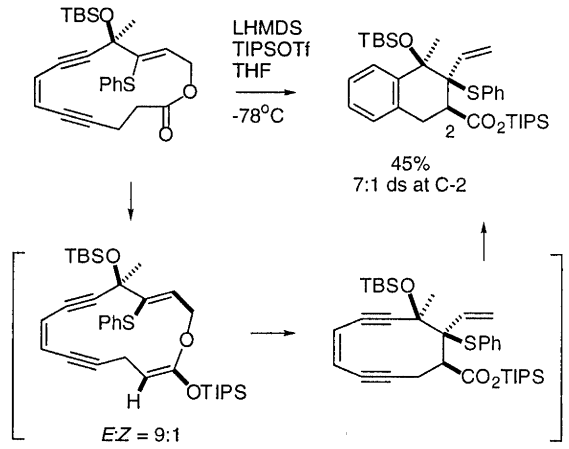
Scheme 55.

the procedure of Kazmaier[61] yielded the corresponding 2-amino pentenoic acid (Scheme 54). *N*-Allylation and RCM yielded the pipecolic acid.

Barrett et al. have used the Ireland–Claisen rearrangement/RCM sequence to prepare novel beta lactams (Scheme 55).[62] Although the rearrangement gave no diastereoselectivity, the RCM proceeded in essentially quantitative yield to give the bicyclic lactams.

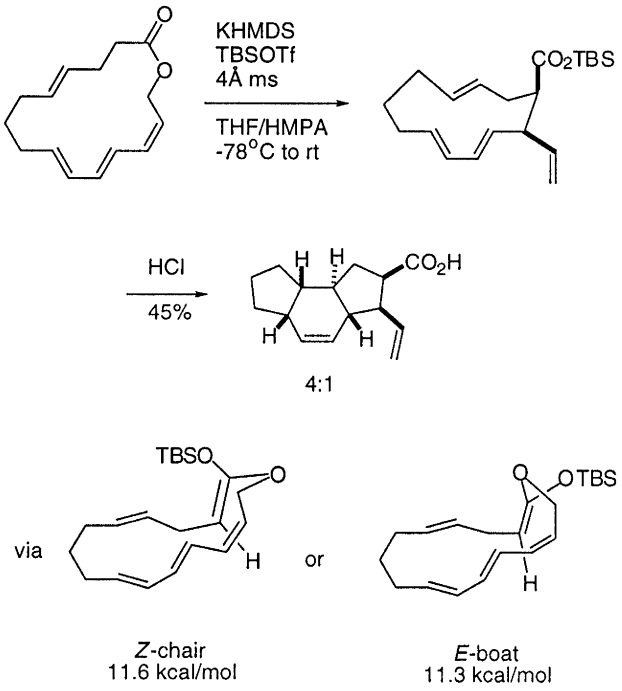
4.3.8. Tandem reactions

4.3.8.1. Claisen rearrangement/Bergman cyclization. Magriotis and Kim used the Ireland–Claisen rearrangement to contract a 14-membered enediyne lactone to a strained 10-membered carbocyclic enediyne (Scheme 56).[63] The carbocycle underwent spontaneous Bergman cyclization[64] to afford the tetrahydronaphthalene as a 7:1 mixture of diastereomers at C-2. The diastereoselectivity of the rearrangement was attributed to the antiperiplanar effect[51] in which the 3° allylic C–O bond was disposed *anti* to the forming C–C bond.



Scheme 56.

4.3.8.2. Claisen rearrangement/Diels–Alder cycloaddition. Roush et al. used the Ireland–Claisen rearrangement to contract a 16-membered lactone to a 12-membered carbocycle that possessed both a diene and

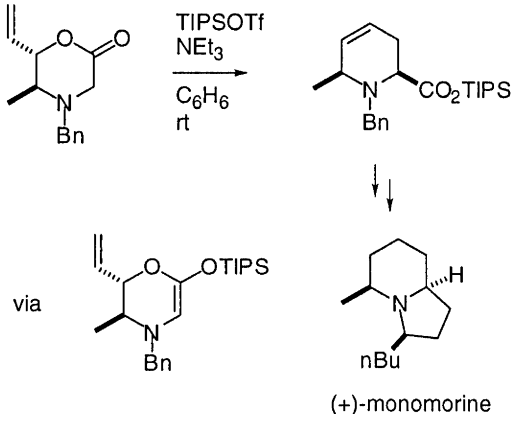


Scheme 57.

a dienophile (Scheme 57).[65] The resulting intramolecular Diels–Alder reaction afforded a tricycle as a 4:1 mixture of diastereomers. The *E*-ketene acetal boat and the *Z*-ketene acetal chair transition states for the rearrangement were calculated to be of approximately equal energy.

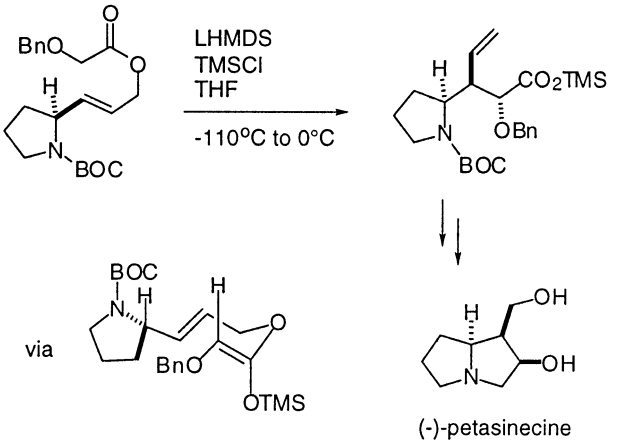
4.4. Natural and unnatural products

4.4.1. (+)-Monomorine. Angle and Breitenbucher reported the total synthesis of (+)-monomorine using the Ireland–Claisen rearrangement of a vinyl morpholinone to generate the requisite *cis*-2,6-disubstituted pipecolic ester intermediate (Scheme 58).[66] The silyl ester was homologated and cyclized to generate the indolizidine bicycle.



Scheme 58.

4.4.2. (−)-Petasinecine. Mulzer and Shanyoor prepared (−)-petasinecine using the Ireland–Claisen rearrangement to install the vicinal stereocenters of the B-ring of the alkaloid (Scheme 59).[67] Rearrangement of the *Z*-silyl ketene

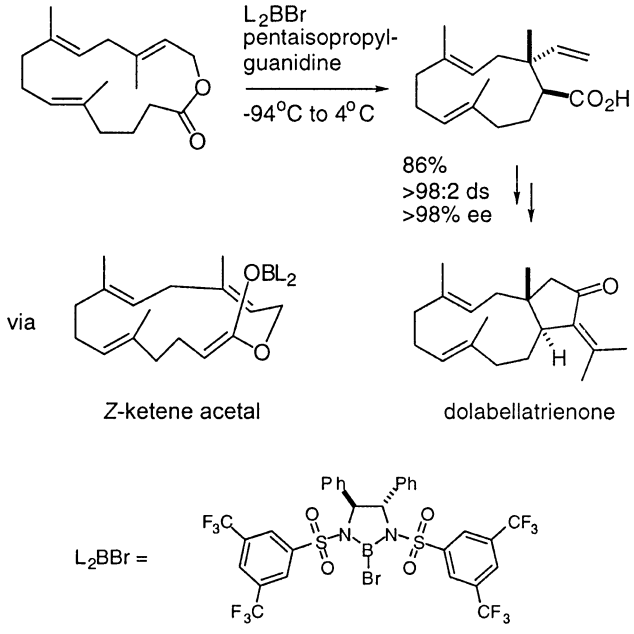


Scheme 59.

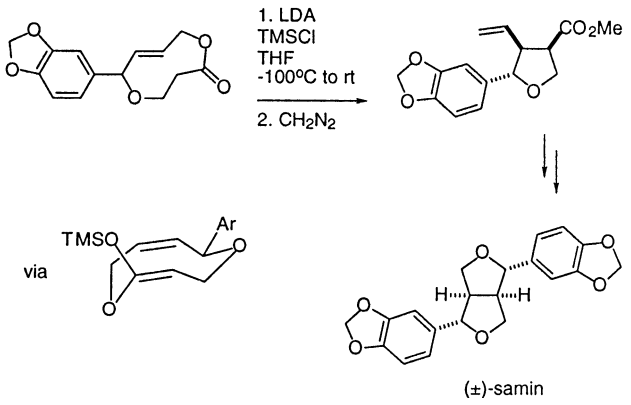
acetal of the glycolate ester occurred with complete relative and 1,2-stereocontrol to afford the desired pentenoic acid. The transition state of the rearrangement presumably adopted the conformation shown with the nitrogen oriented antiperiplanar to the forming C–C bond.[51]

4.4.3. (+)-Dolabellatrienone. Corey and Kania have prepared the bicyclic marine diterpenoid (+)-dolabellatrienone via the Ireland–Claisen rearrangement using Corey's previously reported chiral borane reagent (Scheme 60).[68] Ring contraction of the 15-membered ring lactone occurred with both high diastereo- and enantioselectivity via the *Z*-boron ketene acetal. The alkene and carboxylic acid group were manipulated in several steps to form the isopropylidene cyclopentanone ring of the natural product. As noted previously, boron ketene acetals have been used very infrequently in Ireland–Claisen rearrangements, although the work of Corey[68] and Oh[29] demonstrate their synthetic utility.

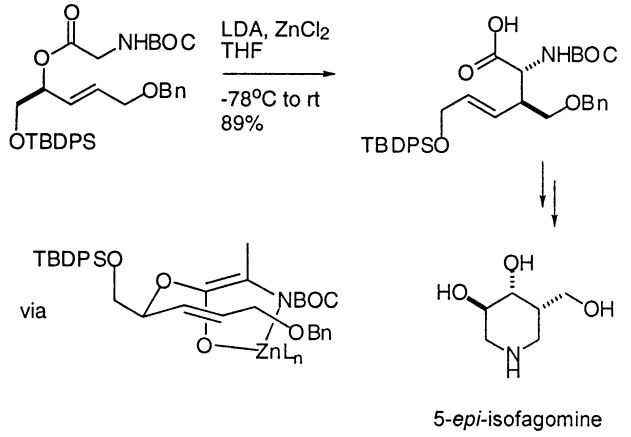
4.4.4. (±)-Samin. Knight et al. have employed a ring



Scheme 60.



Scheme 61.

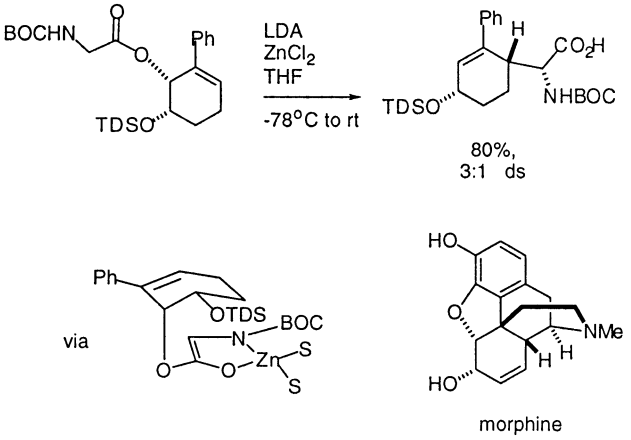


Scheme 62.

contraction via the Ireland–Claisen rearrangement of an aryl lactone to generate a 2,3,4-trisubstituted tetrahydrofuran intermediate in the synthesis of (±)-samin (Scheme 61).[69] The rearrangement proceeded via a boat transition state of the cyclic *E*-silyl ketene acetal.

4.4.5. 5-*epi*-Isofagomine. Kazmaier et al. have reported extensive studies of the Ireland–Claisen rearrangement of allyl glycinates as well as higher homologs. Much of this chemistry has been reviewed.[70] Kazmaier and Schneider employed the rearrangement of an *O*-allyl glycine as a key step in an asymmetric synthesis of 5-*epi*-isofagomine (Scheme 62).[71] The rearrangement occurred via a chair-like transition state of the Zn-chelated *Z*-enolate.

4.4.6. Morphine. Hudlicky et al. have also used Kazmaier's procedure in studies directed toward the synthesis of morphine (Scheme 63).[72] The rearrangement of the *cis*-arene diol-derived allylic ester gave only modest diastereoselectivity, apparently as a result of competitive chair and boat transition states.

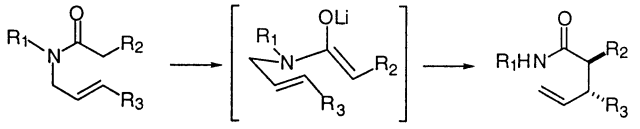


Scheme 63.

5. Non-ester precursors

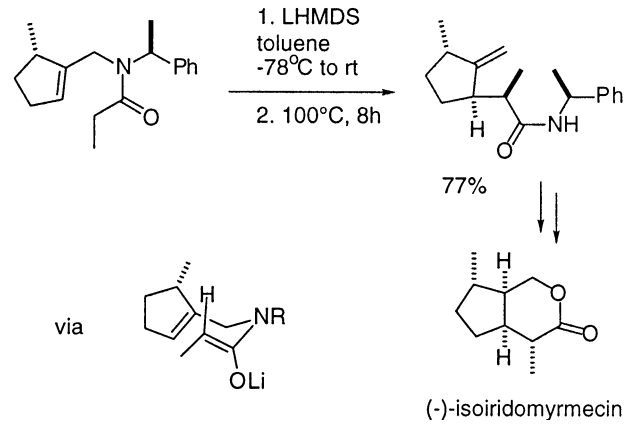
5.1. Amide Claisen rearrangements

The Claisen rearrangement of allylic amides was first reported by Tsunoda et al. in 1990.[73] Allylic amides have been invariably rearranged as their lithium enolates and generally require elevated temperatures (>100°C) (Scheme 64). Since decomposition of the amide enolate via the ketene is not a competitive side reaction as it is with ester enolates, there is no need to prepare the analogous silyl amide acetal. Another important feature of amides is that the *Z*-amide enolate is easily prepared with high stereoselectivity, since the transition state leading to the *E*-enolate suffers from substantial allylic strain. This is both an advantage and a disadvantage, since it means that the diastereomers which would derive from an *E*-enolate are not directly accessible. Since much of the work has been previously reviewed,[2] only recent efforts in this area are included.



Scheme 64.

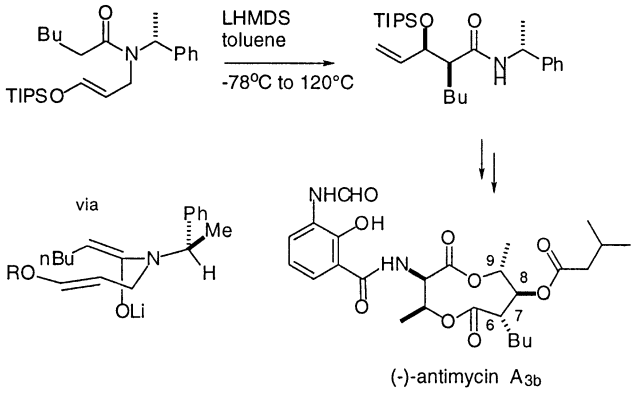
5.1.1. (−)-Isoiridomyrmecin. Tsunoda et al. have reported that the Claisen rearrangement of allylic amides occurs with good to excellent diastereoselectivity and with moderate levels of 1,4-asymmetric induction when α-chiral amine-derived amides are employed (e.g. α-methylbenzylamine).[74] They have used the asymmetric Claisen rearrangement of an allylic amide in the synthesis of (−)-isoiridomyrmecin (Scheme 65).[75] Rearrangement of



Scheme 65.

the *Z*-amide enolate via a chair-like transition state installed the vicinal stereocenters α and β to the carbonyl group of the natural product with very high diastereoselectivity.

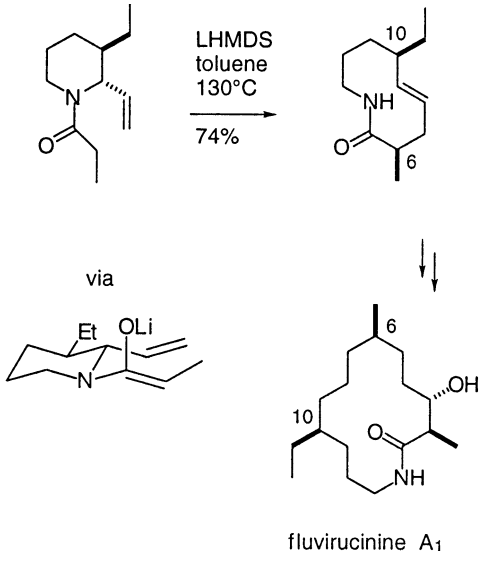
5.1.2. (−)-Antimycin A_{3b}. More recently Tsunoda et al. have used the Claisen rearrangement of an amide enolate in an asymmetric synthesis of (−)-antimycin A_{3b} (Scheme 66).[76] The requisite enantiopure allylic amide was efficiently prepared in two operations by addition of *N*-silylated (*R*)-α-methylbenzylamine to acrolein and acylation of the resultant allylic amine. The rearrangement yielded an inseparable 82:18 mixture of diastereomeric *syn* pentenoic amides. The product was ultimately used to assemble the C-6 to C-9 fragment of antimycin A_{3b}.



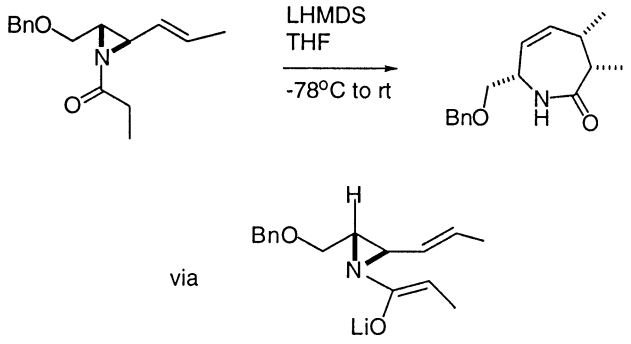
Scheme 66.

5.1.3. Fluvirucinine A_1. Suh et al. have used the amide Claisen rearrangement in an asymmetric synthesis of the macrolactam fluvirucinine A_1 (Scheme 67).[77] The rearrangement of the 2-vinylpiperidine resulted in ring expansion to the 10-membered lactam. The rearrangement occurred via a chair-like transition state of the *Z*-amide enolate to yield the *E*-alkene and install the desired *cis* stereochemistry at C-6 and C-10.

5.1.4. Aziridinyl amides. Somfai et al. have used the amide Claisen rearrangement to ring expand allylic aziridine



Scheme 67.

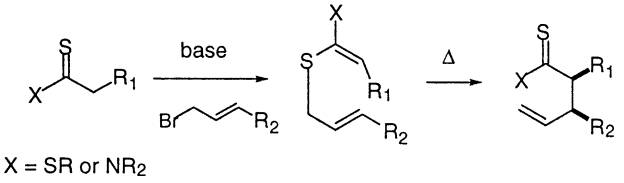


Scheme 68.

amides to form substituted caprolactams (Scheme 68).[78] The rearrangements took place via a boat-like transition state of the *Z*-amide enolate. By contrast with other amide Claisen rearrangements, the ring strain of the aziridine allowed the rearrangement to occur at or below room temperature.

5.2. *S,S*- and *N,S*-Ketene Claisen rearrangements

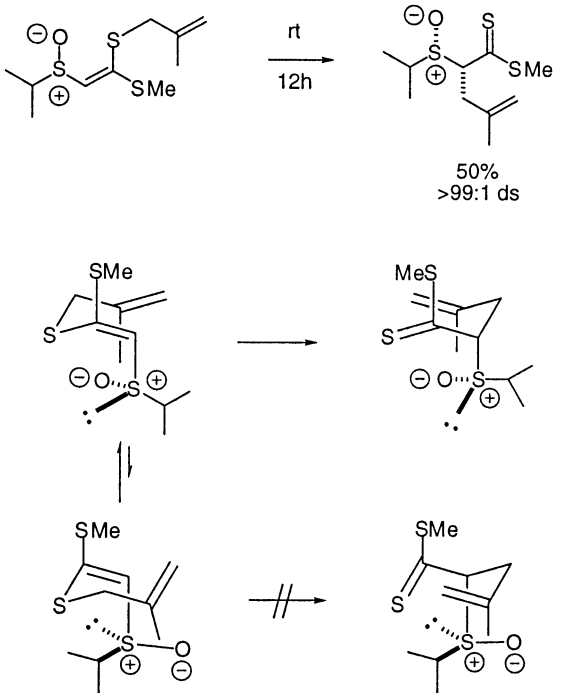
S,S- and *N,S*-Ketene acetals are prepared differently than ketene acetals derived from esters. Instead of deprotonating the parent carbon acid, the *S,S*- and *N,S*-ketene acetals are prepared by S-allylation of the dithioester or thioamide anions (Scheme 69). Under these conditions the *Z*-ketene acetal is formed selectively (for the priority order S>X). Since earlier work by Beslin et al.[79] in the area of dithioester-derived Claisen rearrangements and Yoshida et al.[80] in thioamide-derived Claisen rearrangements has been reviewed,[2] only recent efforts will be described.



Scheme 69.

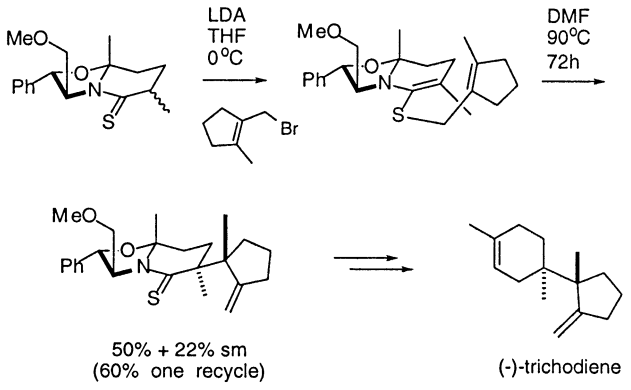
5.2.1. *S,S*-Ketene acetals. Metzner et al. have recently reported a Claisen rearrangement of an *S,S*-ketene acetal which proceeded with very high levels of 1,2-asymmetric induction directed by an adjacent sulfoxide stereocenter (Scheme 70).[81] The rearrangement was thought to proceed via a chair-like transition state with the sulfoxide disposed such that both the sulfoxide oxygen and the isopropyl group are oriented away from the allylic sulfur atom. These results are analogous to those obtained by Beslin et al. in the rearrangement of *S,S*- and *N,S*-ketene acetals bearing an adjacent stereogenic carbinol center.[79]

5.2.2. *N,S*-Ketene acetals. Meyers[82,83] and Rawal[84] have recently reported the diastereoselective Claisen rearrangements of *N,S*-ketene acetals using chiral amine-based auxiliaries. As with the *S,S*-ketene acetals, the *N,S*-acetals were prepared by *S*-allylation of the thioamide anions.



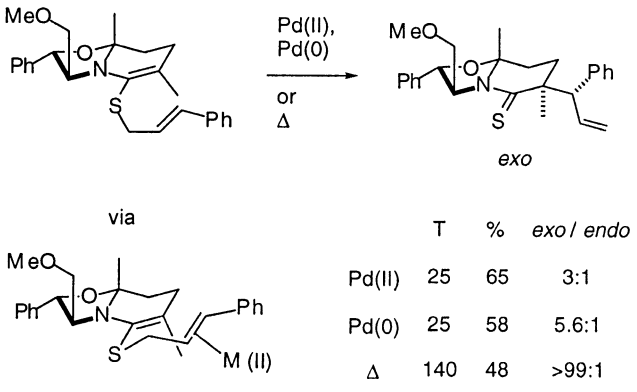
Scheme 70.

5.2.2.1. Bicyclic *N,S*-acetals. Meyers and Lemieux have used a chiral non-racemic bicyclic thiolactam as a scaffold for generating vicinal 4° stereocenters with high remote asymmetric induction (Scheme 71).[82] Interestingly, in contrast to allylic oxygen- and nitrogen-based Claisen rearrangements, the *N,S*-ketene acetal was in equilibrium with the rearranged pentenoic thioamide. Optimal rearrangement conditions afforded the rearranged product in 50% yield accompanied by 22% recovered starting material. The overall yield could be increased to 60% with one recycle. The rearrangement product was used in the first asymmetric synthesis of (−)-trichodiene.



Scheme 71.

Subsequent studies by Meyers et al. showed that the temperature of the Claisen rearrangement could be dramatically decreased by use of Pd or Ni catalysis (Scheme 72).[83] Whereas thermal rearrangement required 140°C to afford a 48% yield of product, both Pd(0) and Pd(II) catalysis resulted in room temperature rearrangement in higher

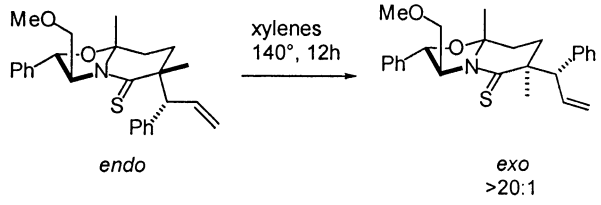


	T	%	*exo* / *endo*
Pd(II)	25	65	3:1
Pd(0)	25	58	5.6:1
Δ	140	48	>99:1

Scheme 72.

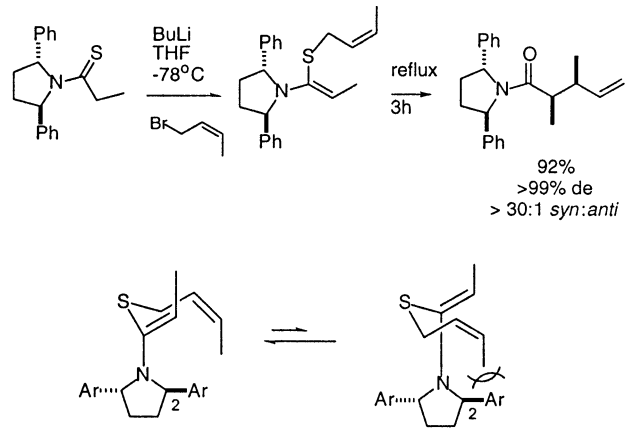
yield, albeit with considerably lower diastereoselectivity. The Pd(II) and Ni(II) catalyzed rearrangements presumably occurred via the metal–olefin π-complex. As noted previously, catalysis of the Ireland–Claisen rearrangement by Pd(II) or other transition metal complexes is relatively rare, since the thermal rearrangements often proceed at or below room temperature.

The reversibility of the Claisen rearrangement was illustrated by the thermal conversion of the *endo* Claisen rearrangement product to the *exo* product in high diastereoselectivity upon heating (Scheme 73).



Scheme 73.

5.2.2.2. Acyclic *N,S*-acetals. Rawal et al. have reported the diastereoselective Claisen rearrangement of *N,S*-ketene acetals using a 2,5-trans-diphenylpyrrolidine chiral auxiliary (Scheme 74).[84] *S*-Allylation occurred with high *Z*-selectivity to give the *N,S*-ketene acetals. Claisen rearrangement via a chair-like transition state occurred so



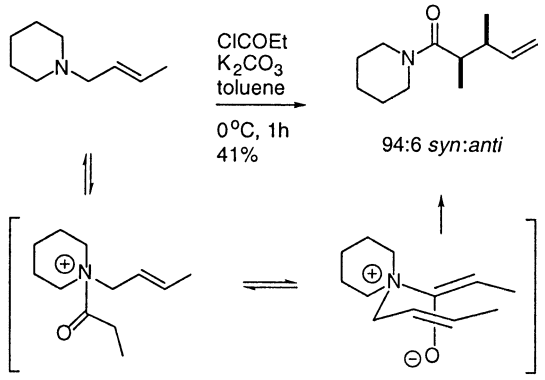
Scheme 74.

as to place the allylic alkene *anti* to the pyrrolidine C-2 aryl substituent.

5.3. Zwitterionic Claisen rearrangements

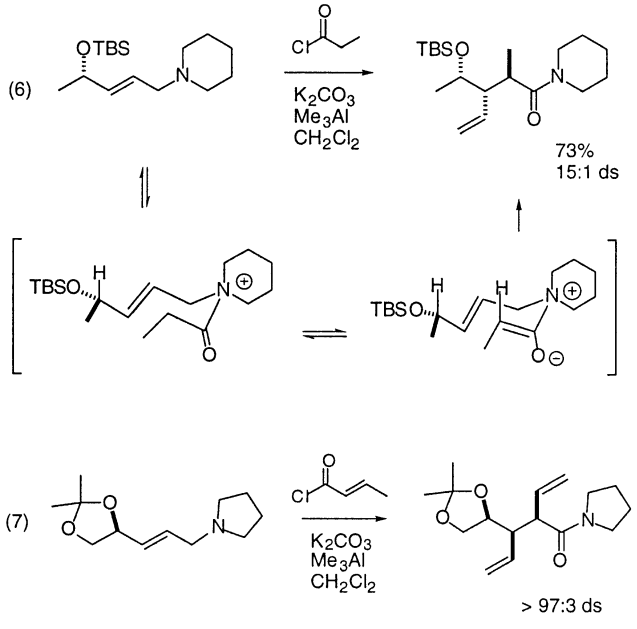
In contrast to the Claisen rearrangements of amide enolates, zwitterionic Claisen rearrangements proceed at or below room temperature. As with the neutral amide enolates, enolization of the acyl ammonium ions is highly *Z*-selective.

5.3.1. Relative stereocontrol. Yu et al. showed that the rearrangements of simple acylated allyl amines proceeded with high *syn* diastereoselectivity to give pentenamides in moderate yields (Scheme 75).[85] The rearrangement of the *Z*-amide enolate presumably occurred via a chair-like transition state to selectively afford the *syn* diastereomer.



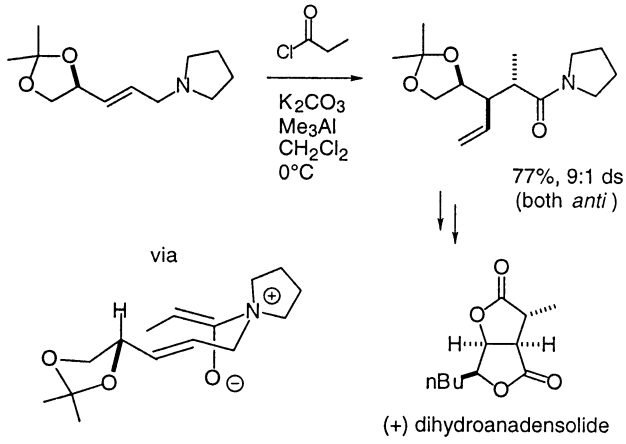
Scheme 75.

5.3.2. 1,2-Asymmetric induction. In the first publication on zwitterionic Claisen rearrangements derived from allylic amines, Nubbemeyer reported in 1995 that amines possessing an allylic stereocenter underwent rearrangement with high *anti* selectivity and high 1,2-asymmetric induction (Eq. (6), Scheme 76).[86] As with other Claisen rearrangements bearing allylic heteroatom substituents, the transition state likely adopted the orientation shown with the allylic heteroatom substituent disposed antiperiplanar to the forming C–C bond.[51] Interestingly, when acrylic acyl chlorides were used in the reactions, the 2,3-*syn* diastereomers were produced with >97:3 diastereoselectivity (Eq. (7)).[87]



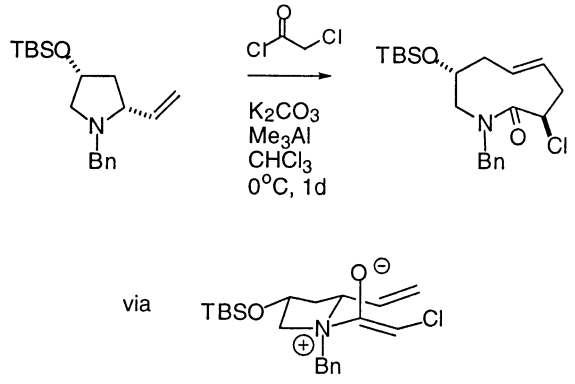
Scheme 76.

The rearrangement was employed by Nubbemeyer as a key step in the synthesis of (+)-dihydroanadensolide (Scheme 77).[87] The vinyl group of the pentenoic amide served as a precursor to a carboxylate group.



Scheme 77.

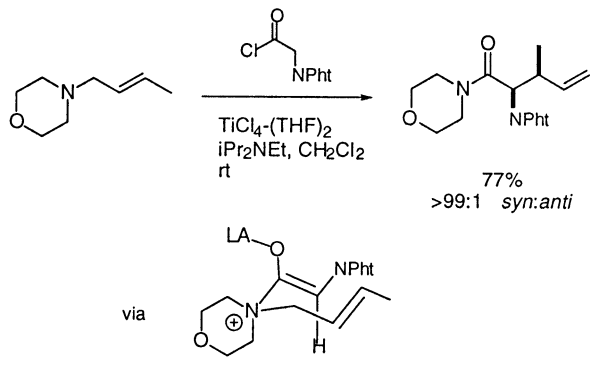
Nubbemeyer and Sudau also used the zwitterionic Claisen rearrangement to ring expand substituted pyrrolidines to form 9-membered lactams (Scheme 78).[88] Rearrangement via the expected *Z*-enolate resulted in formation of the *trans* chloro TBS ether.



Scheme 78.

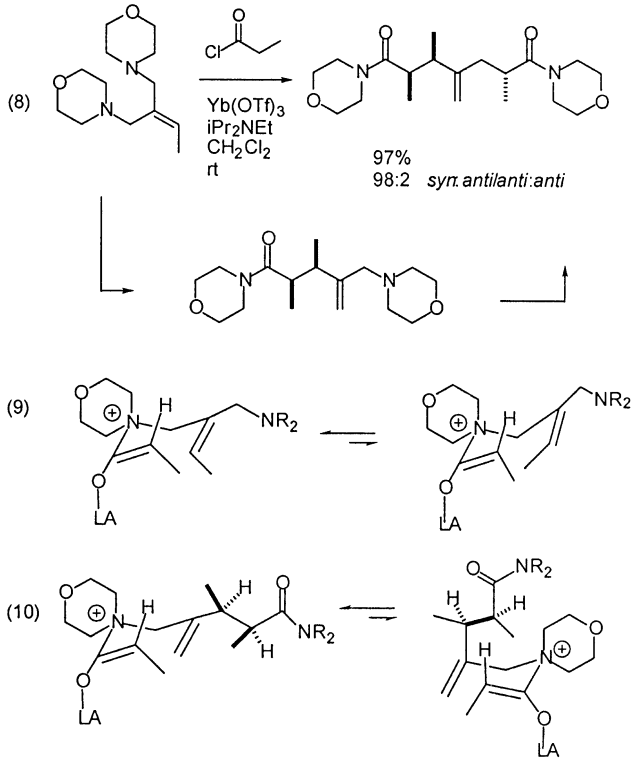
5.3.3. Catalyzed zwitterionic rearrangements

5.3.3.1. Relative stereocontrol. MacMillan et al. have recently reported a Lewis acid catalyzed ketene Claisen rearrangement.[89] The reaction is presumed to occur by addition of the allylic morpholines to in situ generated ketenes to afford Lewis acid coordinated zwitterionic intermediates (Scheme 79). The rearrangements do not proceed in the absence of Lewis acid. The reactions afford pentenoic amides in good to excellent yield and with high diastereoselectivity.



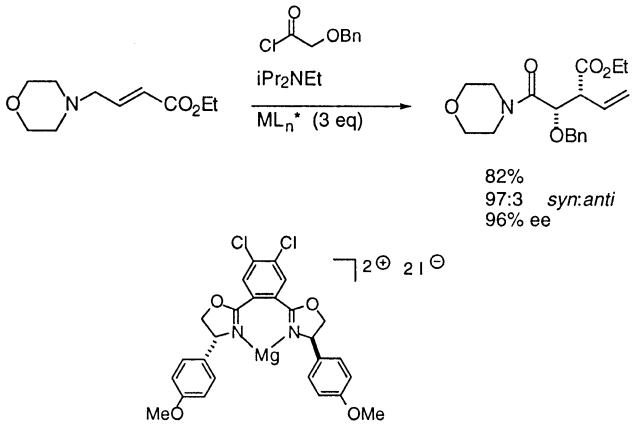
Scheme 79.

5.3.3.2. Iterative rearrangements. MacMillan and Dong were also able to effect iterative Claisen rearrangements using allylic bis-amines (Scheme 80).[90] Treatment of the bis-amine under $Yb(OTf)_3$ catalysis gave high yields and high diastereoselectivities of the doubly rearranged products (Eq. (8)). The initial rearrangement occurred through the less hindered trans amine to afford the *syn* pentenamide via the usual *Z*-enolate (Eq. (9)). The transition state through which the second rearrangement proceeded was dictated by minimization of $A^{1,2}$ strain (Eq. (10)).[14]



Scheme 80.

5.3.3.3. Asymmetric rearrangements. One of the attractive features of the MacMillan chemistry is that chiral Lewis acids could be employed to effect an enantioselective Claisen rearrangement.[91] Treatment of allylic morpholines as before but in the presence of 3 equiv. of a chiral oxazoline-based Mg reagent gave the pentenoic acids in good to excellent yields, diastereoselectivities and enantioselectivities (Scheme 81). Although the reported rearrangements were not catalytic in Lewis acid, it seems likely that with appropriate choice of metal and ligand the rearrangement will become a truly catalytic process.



Scheme 81.

6. Conclusions

As the above examples illustrate, the Ireland–Claisen rearrangement and variants thereof continue to offer an efficient and flexible means of preparing a wide variety of pentenoic acid derivatives with regio-, diastereo- and enantiocontrol. The examples also illustrate the imaginative uses to which the pentenoic acids have been put in the assembly of natural products and other targets.

Acknowledgements

We would like to thank Kay Brummond, University of Pittsburgh, and Timo Ovaska, Connecticut College, for proofreading the manuscript, and Tom Hoye, University of Minnesota, for directing our attention to the early ester enolate Claisen rearrangement chemistry. We also thank Todd Phipps and Tripura Yaramasu for assistance in copying references.

References

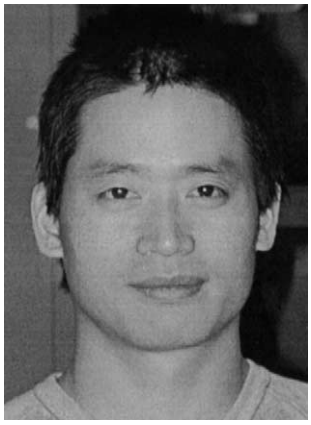
1. (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650–657. Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572–3582.
2. For reviews which include the Ireland–Claisen rearrangement, see: (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 1423–1452. (b) Bennett, G. B. *Synthesis* **1977**, 589–606. (c) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 503–572. (d) Blechert, S. *Synthesis* **1989**, 71–82. (e) Wipf, P. *Compre-*

hensive Organic Synthesis; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 827–873. (f). Tadano, K. *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1992; pp 405–455. (g) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17–29. (h) Frauenrath, H. *Stereoselective Synthesis*; Helchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E21d, pp 3301–3756.

3. For reviews of the asymmetric Claisen rearrangement, see: Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50.
4. The Ziegler review lists all of the references to the pre-Ireland ester enolate Clasien rearrangement (Ref. 2a).
5. (a) Tseou, H.-F.; Wang, Y.-T. *J. Chin. Chem. Soc.* **1937**, *5*, 224–229. (b) The report is ambiguous about the reaction temperature.
6. Arnold, R. T.; Searles, S. *J. Am. Chem. Soc.* **1949**, *71*, 1150–1151. Arnold, R. T.; Parham, W. E.; Dodson, R. M. *J. Am. Chem. Soc.* **1949**, *71*, 2489.
7. Brannock, K. C.; Pridgen, H. S.; Thompson, B. *J. Org. Chem.* **1960**, *25*, 1815–1816.
8. Julia, S.; Julia, M.; Linstrumelle, G. *Bull. Soc. Chim. Fr.* **1964**, *25*, 2693–2694.
9. Arnold, R. T.; Hoffman, C. *Synth. Commun.* **1972**, *2*, 27–33.
10. Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228.
11. (a) Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513–7516. Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288–3300. (b) Paterson, I.; Hulme, A. N.; Wallace, D. J. *Tetrahedron Lett.* **1991**, *32*, 7601–7604.
12. Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228–2235.
13. Pratt, L. M.; Beckett, R. P.; Bellamy, C. L.; Corkill, D. J.; Cossins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.; Drummond, A. H.; Helfrich, K.; Lewis, C. N.; Mangan, M.; Martin, F. M.; Miller, K.; Nayee, P.; Ricketts, M. L.; Thomas, W.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1359–1364. Pratt, L. M.; Bowles, S. A.; Courtney, S. F.; Hidden, C.; Lewis, C. N.; Martin, F. M.; Todd, R. S. *Synlett* **1998**, 531–533.
14. For reviews of allylic strain directed reactions, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
15. Troll, T.; Wiedemann, J. *Tetrahedron Lett.* **1992**, *33*, 3847–3850.
16. Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 7457–7460.
17. Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631–12644. Eriksson, M.; Nilsson, M.; Olsson, T. *Synlett* **1994**, *1994*, 271–272.
18. Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728–8729.
19. (a) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140–8141. See also, Yamazaki, T.; Ichige, T.; Takei, S.; Kawashita, S.; Kitazume, T.; Kubota, T. *Org. Lett.* **2001**, *3*, 2915–2918. (b) For a recent review of the Cieplak hypothesis, see: Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265–1336.
20. For a review of catalysis of the Claisen rearrangement, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 206–247.
21. Hanamoto, T.; Baba, Y.; Inanaga, J. *J. Org. Chem.* **1993**, *58*, 299–300.
22. Smith, P. M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3541–3556.
23. Soldermann, N.; Velker, J.; Vallat, O.; Stoeckli-Evans, H.; Neier, R. *Helv. Chim. Acta* **2000**, *83*, 2266–2276.
24. Kobayashi, M.; Masumoto, K.; Nakai, E. i; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 3005–3008.
25. Hu, Y.; Porco, Jr., J. A. *Tetrahedron Lett.* **1999**, *40*, 3289–3292.
26. Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145–4152.
27. Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152–1156.
28. Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941–3945.
29. Oh, T.; Wrobel, Z.; Devine, P. N. *Synlett* **1992**, 81–83.
30. For a review, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.
31. Hatakeyama, S.; Sugawara, M.; Kawamura, M.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1229–1231.
32. Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797–4800.
33. Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 948–950.
34. Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418–5420.
35. For other transformations using the same strategy for regeneration of the chiral auxiliary, see: Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283–5287. Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185–1191.
36. Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2618–2628. Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2629–2635. Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 2095–2100. Crandall, J. K.; Tindell, G. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1411–1412. Kachinsky, J. L. C.; Salomon, R. G. *J. Org. Chem.* **1986**, *43*, 44. See also Refs. 43,44.
37. Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669–3670.
38. Davidson, A. H.; Eggleton, N.; Wallace, I. H. *J. Chem. Soc., Chem. Commun.* **1991**, 378–380.
39. Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093–5101.
40. Enev, V.; Stojanova, D.; Bienz, S. *Helv. Chim. Acta* **1996**, *79*, 391–404.
41. Reed, Jr., S. F. *J. Org. Chem.* **1965**, *30*, 1663–1665. Cresson, P.; Lacour, L. *Compt. Rend. Acad. Sci. Série C* **1966**, *262*, 1157–1160. Cresson, P.; Bancel, S. *Compt. Rend. Acad. Sci. Série C* **1968**, *266*, 409–412. Bancel, S.; Cresson, P. *Compt. Rend. Acad. Sci. Série C* **1969**, *268*, 1535–1537. Parker, K. A.; Farmar, J. G. *Tetrahedron Lett.* **1985**, *26*, 3655–3658. Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316–322. Tanis, S. P.; McMills, M. C.; Scahill, T. A.; Kloosterman, D. A. *Tetrahedron Lett.* **1990**, *31*, 1977–1980. Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, 716–727. Mulzer, J.; Bock, H.; Eck, W.; Buschmann, J.; Luger, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 414–416.
42. Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023–4028.
43. Zhang, X.; McIntosh, M. C. *Tetrahedron Lett.* **1998**, *39*, 7043–7046. McIntosh, M. C.; Hong, S.-p.; Lindsay, H. A.; Yaramasu, T.; Zhang, X. *J. Org. Chem.* accepted for publication.

44. Hong, S.-p.; McIntosh, M. C. *Tetrahedron* **2001**, *57*, 5055–5060. Hong, S.-p.; McIntosh, M. D. *Org. Lett.* **2002**, *4*, 19–21.
45. Roush, W. R.; Works, A. B. *Tetrahedron Lett.* **1997**, *38*, 351–354.
46. Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677–5680.
47. Magnus, P.; Westwood, N. *Tetrahedron Lett.* **1999**, *40*, 4659–4662.
48. Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71–74.
49. Ariza, X.; Garcia, J.; Lopez, M.; Montserrat, L. *Synlett* **2001**, 120–122.
50. Vourloumis, D.; Kim, K. D.; Petersen, J. L.; Magriotis, P. A. *J. Org. Chem.* **1996**, *61*, 4848–4852.
51. (a) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438–2440. Diastereoselectivities of Ireland–Claisen rearrangements of substrates possessing allylic oxygen stereocenters are not uniformly high: (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263–5266.
52. Funk, R. L.; Stallman, J. B.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8847–8848.
53. Hong, S.-p.; McIntosh, M. C.; Barclay, T.; Cordes, W. *Tetrahedron Lett.* **2000**, *41*, 155–159.
54. Panek, J. S.; Yang, M.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003–1010 and references cited therein.
55. Norley, M. C.; Kocienski, P. J.; Faller, A. *Synlett* **1994**, 77–78. Norley, M. C.; Kocienski, P. J.; Faller, A. *Synlett* **1996**, 900–901.
56. Khripach, V. A.; Zhabinskii, V. N.; Konstantinova, O. V.; Khripach, N. B. *Tetrahedron Lett.* **2000**, *41*, 5765–5767.
57. Eshelby, J. J.; Parsons, P. J.; Sillars, N. C.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1497–1498.
58. For a review of RCM, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
59. Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160–3161.
60. Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158–3159.
61. Kazmaier, U. *Tetrahedron* **1994**, *50*, 12895–12902.
62. Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716–3721.
63. Magriotis, P. A.; Kim, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2972–2973.
64. Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25–31.
65. Frank, S. A.; Works, A. B.; Roush, W. R. *Can. J. Chem.* **2000**, *78*, 757–771.
66. Angle, S. R.; Breitenbucher, J. G. *Tetrahedron Lett.* **1993**, *34*, 3985–3988.
67. Mulzer, J.; Shanyoor, M. *Tetrahedron Lett.* **1993**, *34*, 6545–6548. See also, Hauske, J. R.; Julin, S. M. *Tetrahedron Lett.* **1993** (1993), 4909–4912.
68. Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229–12230.
69. Hull, H. M.; Jones, E. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1779–1788.
70. Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523–1535. Kazmaier, U. *Bioorg. Chem.* **1999**, 201–206. Kazmaier, U. *Liebigs Ann./Recl.* **1997**, 285–295. Kazmaier, U. *Amino Acids* **1996**, *11*, 283–299.
71. Schneider, C.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, 1155–1159.
72. Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T.; Abboud, K. *J. Org. Chem.* **1997**, *62*, 1194–1195. Hudlicky, T.; Oppong, K.; Duan, C.; Stanton, C.; Laufersweiler, M. J.; Natchus, M. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 627–629.
73. Tsunoda, T.; Sasaki, O.; Ito, S. *Tetrahedron Lett.* **1990**, *31*, 727–730.
74. Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S. *Tetrahedron Lett.* **1992**, *33*, 1651–1654.
75. Tsunoda, T.; Tatsuki, S.; Kataoka, K.; Ito, S. *Chem. Lett.* **1994**, 543–546.
76. Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S. *Tetrahedron Lett.* **2000**, *41*, 7667–7671.
77. (a) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3545–3547. For an earlier related zwitterion variant, see: (b) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690–6692.
78. Lindström, U. M.; Somfai, P. *Chem.-Eur. J.* **2001**, *7*, 94–98. Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385–8386.
79. Beslin, P.; Perrio, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95,96*, 383–384. Beslin, P.; Perrio, S. *Tetrahedron* **1991**, *47*, 6275–6286. Beslin, P.; Perrio, S. *Tetrahedron* **1992**, *48*, 4135–4146. Beslin, P.; Perrio, S. *Tetrahedron* **1993**, *49*, 3131–3142. See also, Beslin, P.; Lelong, B. *Tetrahedron* **1997**, *53*, 17253–17264.
80. Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yohsida, Z. *J. Org. Chem.* **1983**, *48*, 3631–3639.
81. Alayrac, C.; Fromont, C.; Metzner, P.; Anh, N. T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 371–374.
82. Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453–5457.
83. Watson, D. J.; Devine, P. N.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 1363–1367.
84. He, S.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 190–191.
85. Yu, C.-M.; Choi, H.-S.; Lee, J.; Jung, W.-H.; Kim, H.-J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 115–116.
86. Nubbemeyer, U. *J. Org. Chem.* **1995**, *60*, 3773–3780.
87. Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677–3686.
88. Sudau, A.; Nubbemeyer, U. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1140–1143.
89. Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726–9727.
90. Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2448–2449.
91. Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911–2912.

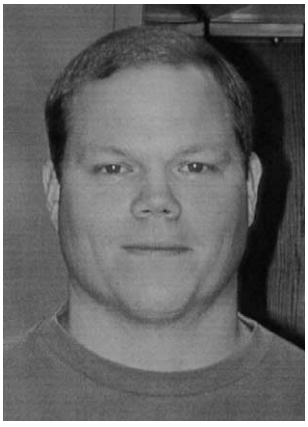
Biographical sketch



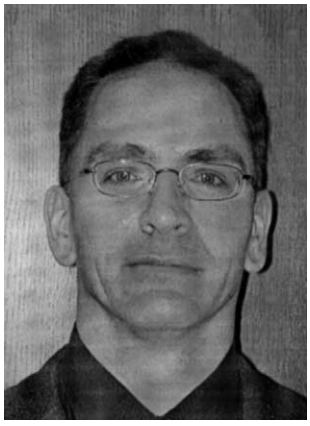
Yonghai Chai received his B.Sc. degree from Beijing Medical University in applied chemistry in 1993. From 1993 to 1995, he worked at the Institute of Materia Medica, Chinese Academy of Medical Science. He then moved to Peking Union Medical College, where he received his M.S. degree in synthetic medicinal chemistry in 1998. After gaining industrial experience at Qihuang Pharmaceutical Company and Pfizer Inc., he moved to the University of Arkansas, where he is currently working toward his Ph.D. in chemistry.

Harriet Lindsay received a B.A. in Chemistry from Hendrix College in 1992. She then continued her studies at the University of Arkansas at Little Rock, where she received an M.S. in Chemistry in 1995. In 1997, she moved to the University of Arkansas, where she completed an Ed.D. in higher education and is currently working toward a Ph.D. in organic chemistry under the direction of Matt McIntosh. Her research interests include synthetic methodology and natural products synthesis. She will join the faculty of Eastern Michigan University in the fall of 2002.

Sang-phyo Hong was born in Taegu, South Korea in 1962 and received his M.E. in 1990 from Kyungpook National University. From 1994 to 1997, he held a R&D assistant manager position at the ISU Electronics in Taegu. He joined the McIntosh group at the University of Arkansas in 1997 where he developed applications of the Ireland Claisen rearrangement in natural product synthesis. After receiving his Ph.D. in 2001 he moved to the University of Pittsburgh as a postdoctoral fellow with Professor Kay Brummond.



Chris McFarland was born in 1975 in San Antonio, TX. He studied chemistry at Texas A&M University where he received his B.S. in 1993. He is currently pursuing his Ph.D. under the direction of Matt McIntosh at the University of Arkansas.



Matt McIntosh received his bachelor's degree in chemistry in 1987 from Virginia Tech where he worked under the direction of James F. Wolfe. He moved to Penn State for his Ph.D. in 1987 and joined the research group of Steven M. Weinreb. After receiving his Ph.D. in 1993 he moved to Stanford University to begin an American Cancer Society post-doctoral fellowship with Barry M. Trost. In 1996 he joined the faculty of the Department of Chemistry and Biochemistry at the University of Arkansas. In 1999 he received the Cottrell Scholar award from Research Corporation. His research interests include new applications of the Claisen rearrangement in natural products synthesis and transition metals in synthesis.