Ester Coupling Reactions– an Enduring Challenge in the Chemical Synthesis of Bioactive Natural Products

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Ester Coupling Reactions– an Enduring Challenge in the Chemical Synthesis of Bioactive Natural Products

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In this review we investigate the use of complex ester fragment couplings within natural product total synthesis campaigns. We first outline the different biosynthetic and chemical strategies for performing complex ester couplings and on this mechanistic background we then present and discuss a collection of successful examples from the literature.

1. Introduction

For many, the first encounter with organic chemistry is in the teaching laboratories in high school or junior years at university, where one of the favorite experiments involves the formation of low molecular weight carboxylate[‡] esters, compounds with a distinctive panel of smells. Albeit simple from a synthetic perspective, such experiments carry the potential for important molecular insights as concerns an understanding of how very small changes in structure can drastically impact the biology, i.e. our perception, of molecules. How do a few extra methyl groups change the smell of a compound from glue-like to strawberry or banana?

Ester bonds are present in biological molecules, but they are notably absent from information-storing (DNA/RNA) and functional (proteins) biopolymers. The evolutionary logic may have favored, above all, stability in these biomolecules and thus weeded out the presence of ester functionalities as a consequence of their potential hydrolytic lability.[1] The domain of biology dominated by ester bonds is the metabolites. In particular, esters are key linking groups in many primary lipid metabolites, but they also constitute a class-defining functionality in many secondary metabolites, notably macrocyclic lactones belonging to the cyclodepsipeptide and polyketide classes.

In spite of the apparent simplicity, the construction of ester bonds often constitutes the most challenging synthetic operation in efforts aimed at preparing such complex natural products. Nature has developed her own synthetic logic for constructing ester/lactone linkages mainly as the final transformation along complex enzymatic assembly lines and this strategy has been mimicked by organic chemists in the form of macrolactonization reactions. This area has recently been reviewed.[2] In the absence of Natures amazing small molecule factories, macrolactonization is unfortunately not a general synthetic solution. Nature also constructs ester bonds in complex settings through e.g. Bayer-Villiger type oxidations of ketone functionalities and despite the alternative retrosynthetic disconnections enabled by the synthetic

version of this type of reaction, the applications in complex molecule synthesis remains relatively rare, especially in the case of macrocyclic targets. Whether the impetus being strategic considerations or a lack of alternative options, intermolecular ester coupling reactions remain a recurrent transformation within natural product total synthesis campaigns, however in the crowded and functionality-rich molecular environment of complex natural products, such couplings can present formidable challenges. In this review we will refer to these reactions as "complex ester couplings" in order to differentiate them from e.g. acetylations or other simple ester formations.[3]

Our agenda is an analysis of the area of complex ester fragment coupling reactions. As most of the examples fall within the classes of macrocyclic lactones, a large part of the review is devoted to this class of molecules, but other examples will be included as appropriate. A key intention is to point out techniques and procedures (the small tricks) that allow for boosting reactivity within the classic modes of activation. Curiously, as the introduction of new synthetic methodology in many areas of organic chemistry has expanded dramatically, the methods employed for performing (complex) ester couplings have seen much less development. Considering the importance of this functionality, this testifies to a problem that is not easy to address. In the end of the review, we will present a number of new approaches to the synthesis of ester/lactone bonds that hold potential for further development into mechanistically novel and reliable methods for performing challenging ester fragment couplings.

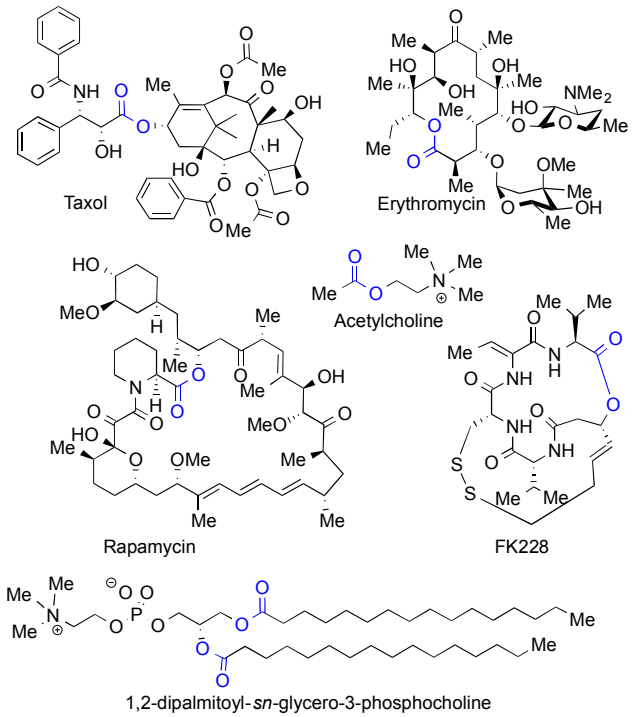


Figure 1 Examples of ester-containing natural products.

2. Biosynthesis of Esters

As mentioned in the introduction, many classes of metabolites contain ester functionalities. These range from the volatile ester odorants of the teaching laboratories, important neurotransmitters such as acetylcholine, lipids of all kinds, to complex terpenoids (Taxol), polyketides (Erythromycin) and cyclodepsipeptides (FK228 and Rapamycin, Fig. 1). In this section we will outline the enzymatic mechanisms employed during biosyntheses of ester-containing metabolites and discuss the different activation strategies that Nature has developed. Focus will remain on the complex secondary metabolites. This section will also include a short introduction to the logic of assembly-line biosynthesis.

2.1 Polyketide and non-Ribosomal Peptide Biosynthesis

The biosyntheses of macrocyclic lactones are performed by polyketide synthase (PKS), non-ribosomal peptide synthase (NRPS), or PKS-NRPS-hybrid assembly lines, where a cluster of enzymes catalyze the connection of simple building blocks in a linear fashion.[4] Recent authoritative reviews are available that cover this area in high detail.[4,5,6] In short, for PKS the building blocks consist of malonyl, methylmalonyl and acetyl, activated via a thioester linkage to coenzyme A. Units are iteratively incorporated via a Claisen condensation followed by optional reduction(s) and elimination to give rise to a variety of different two-carbon extensions of the chain, as is exemplified by the macrocyclic precursor, 6-deoxyerythronolide B, of the antibiotic Erythromycin (Scheme 1).

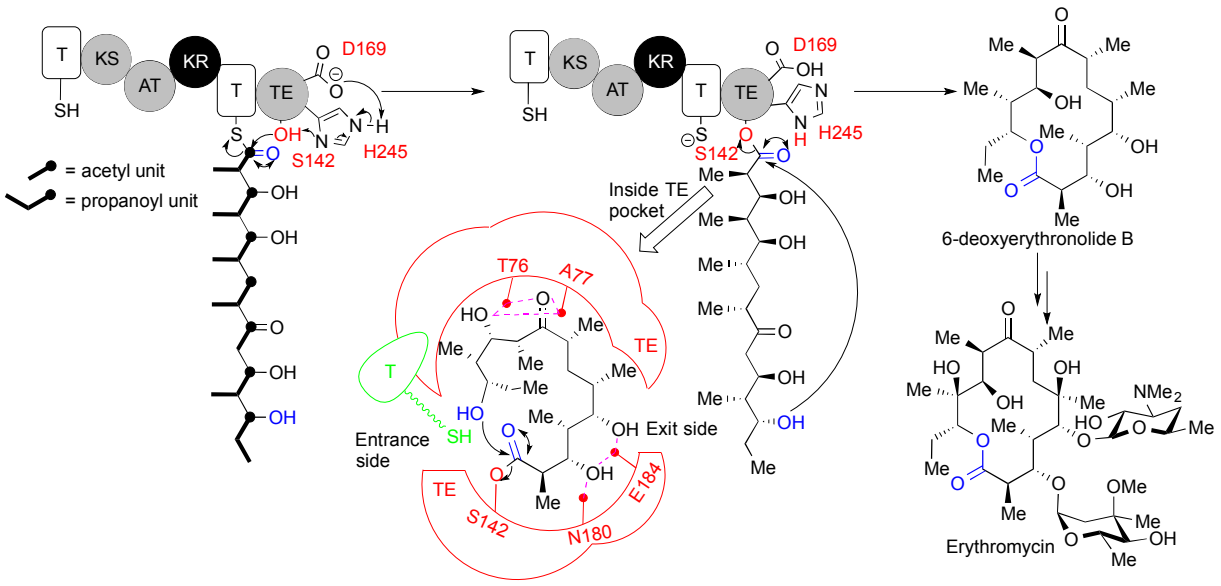
NRPS incorporate amino acids, both proteinogenic and non-proteinogenic, and to a lesser extent other small carboxylic acids. Amino acids are activated by adenylation followed by chain extension through amide bond formation. Several modifications can then occur to the amino acid unit, giving rise to an enormous structural diversity from the shuffling of relatively few different types of enzymes ordered in a specific assembly line. Many natural product macrocyclic lactones are synthesized by PKS-NRPS hybrid assembly lines (*e.g.* Rapamycin, Fig 1). Throughout the biosynthesis a thioester bond links the growing linear molecule to the assembly line until the last unit releases the chain (Scheme 1).

2.2 Chain Release

2.2.1 Condensation and Thioesterase Domains

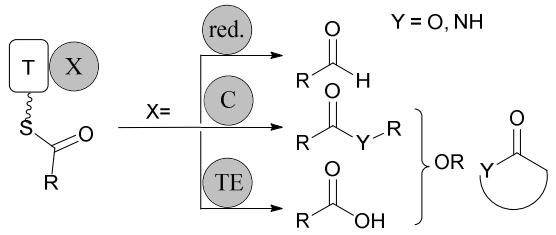
Three different termination strategies are known (Scheme 2).[7,8] Reductive cleavage through an NAD(P)H-coupled reaction results in formation of an aldehyde. The aldehyde will normally undergo further modification.[8] A condensation domain can use a nucleophile, intra- or intermolecularly, to cleave the thioester bond, releasing the assembly product. Condensation reactions are most common in chain elongation, but can also function as chain termination. One role of the condensation enzymes is to position the thioester and the nucleophile in close proximity. A histidine residue is situated close to the reaction site and is believed to function as a proton acceptor/donor to promote the coupling reaction.[9,10]

The most common releasing units are thioesterases (TEs) (Scheme 1-2), resulting in either macrocyclization or hydrolytic cleavage. The mechanism of hydrolysis and cyclization is the same, the essential deviation is the substrate binding pocket. A binding pocket that favors cyclization needs to be hydrophobic in order to exclude competing reactions from water. Simultaneously



Scheme 1 The release of 6-deoxyerythronolide B, the core of the aglycon of erythromycin. Thiolation unit (T) links the linear assembled chain. KS = ketosynthetase, AT = acyltransferase, KR = ketoreductase, TE = thioesterase. The TE cleaves the thioester via the activated serine in the catalytic triad.

it must stabilize the assembled chain in a cyclization-competent conformation that positions the two termini in close proximity (Scheme 1). This releases the macrocyclic lactone/lactam, which then may undergo further processing to yield the final natural product.[11] A thioesterase domain mediates the cyclization reaction forming 6-deoxyerythronolide B (Scheme 1).



Scheme 2 Three different types of enzymes can promote chain release from PKS and NRPS. The chain is connected via a thioester linkage to a thiolation unit (T), and can either be cleaved by a reductase (red.), a condensation (C), or a thioesterase (TE) unit.

2.2.2 Thioesterase Catalytic Mechanism

Thioesterases belong to the α/β hydrolase family, a large diverse group of enzymes.[12,13] The active site contains a serine, a histidine, and an aspartate unit, all shown to be key to the enzymatic activity forming a catalytic triad.[14,15] Stroud and co-workers reported the first crystal structure of the thioesterase from 6-deoxyerythronolide B synthetase (DEBS), the complex which forms 6-deoxyerythronolide B (Scheme 1).[14] Analysis of the crystal structure revealed that the catalytic triad was located within a channel passing through the entire TE and these observations led to a proposed structure for the bound substrate and the mechanism of cyclization (Scheme 1). Residues Asp-169, His-245, and Ser-142 form the catalytic triad that facilitates the cleavage of the thioester linkage between the thiolation unit of the assembly line and the linear polyketide product. In this process Serine-142 acts as a temporary carrier of the polyketide chain. Residues asparagine-180, glutamate-184, threonine-76, and alanine-77 are believed to be key in orchestrating the correct folding of the molecule within the cavity to favor cyclization. Transesterification to the terminal hydroxyl unit then results in the formation of the 14-membered lactone core of the erythromycin aglycon. In the crystal structure, the thioesterase exists as a dimer, leading to speculations that a dimer also constitutes the functional unit of the entire DEBS. A leucine-rich hydrophobic α-helix region connects the two monomers. A dimer moiety has also been observed in a recent structural study of the module responsible for assembling the macrocyclic precursor of Pikromycin, a polyketide closely related to Erythromycin.[16,17] The structure of the entire PKS module was analyzed via single-particle electron cryo-microscopy, revealing a dimeric complex.

2.3 Ester Fragment Couplings during Biosynthesis

Although our discussion so far could imply that Nature only constructs ester bonds in complex molecular settings as the final macrolactonization step during assembly line biosynthesis, this is not the case. Several macrocyclic natural products (e.g. Didemnin B and Hectochlorin, Fig. 2) contain two or more ester bonds within the central ring system, which necessitates that some bonds are constructed as fragment couplings. Studies of the assembly lines that construct these natural products have demonstrated that specialized condensation domains facilitate hindered coupling reactions between relatively small alcohol-containing fragments and the thioester-functionality terminating the growing chain. For instance, in the case of Didemnin B,[18] which contains two esters within the core ring system, ester 2 originates partly from 2-oxoisovalerate, the keto-acid precursor of valine. The keto-acid is first activated via adenylation, then incorporated into the growing chain and finally reduced to the α-hydroxy acid derivative. A condensation domain subsequently mediates the coupling reaction with the thioester terminus to form ester 2.[18] Ester 1 is formed in the last step of the biosynthesis as

part of the chain release through a canonical thioesterase-cleavage as outlined above (section 2.2). Hectochlorin contains three ester bonds in the core ring, 4 and 5 originate from 2-oxoisovalerate.[19] Reduction of the ketone of 2-oxoisovalerate to an alcohol followed by oxidation of the β-carbon leads to the unit destined for ester coupling. Fragment couplings of the very hindered secondary and tertiary alcohols with the thioester are promoted by condensation domains. Ester 3 is formed as a lactonization in the termination step.

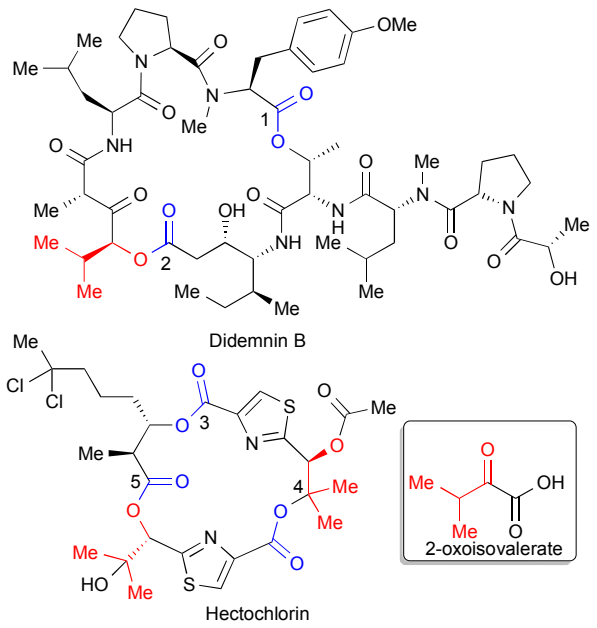
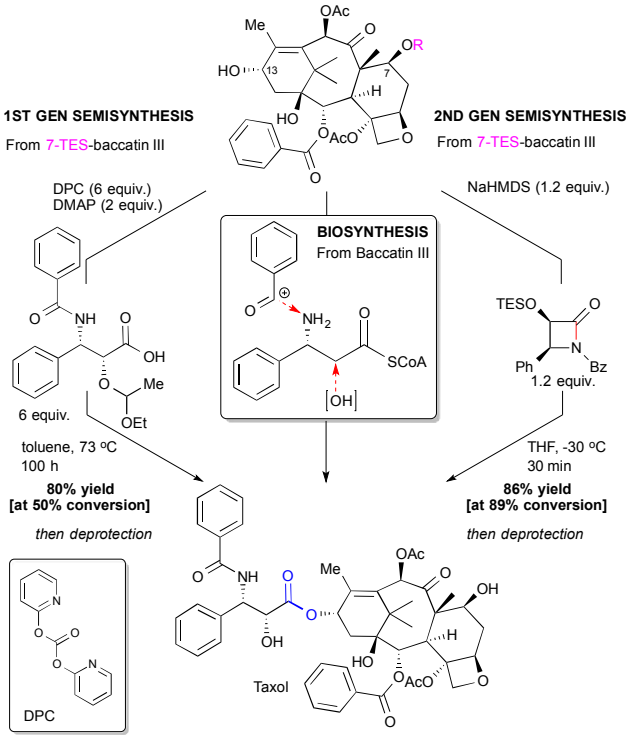


Figure 2 Macrocyclic natural products that contain multiple ester functionalities.

Examples of ester fragment couplings beyond assembly line biosynthesis are also known. A notable example is Taxol (Scheme 3) – a microtubule stabilizer originally isolated from the bark of the pacific yew tree and now approved for treatment of several malignancies – where attachment of the C13 side chain is biosynthetically installed as a fragment-type coupling as outlined in detail below. This example also precisely embodies the synthetic challenge that ester coupling reactions can turn out to be.[20]

During the ongoing clinical development of Taxol in the late 1980s, a difficult task turned out to be securing a sustainable supply route to the fully elaborated natural product.[20] The breakthrough came with the realization that an advanced precursor, 10-deacetylbaccatin III, could be isolated in large quantities from leaves of the yew tree. In order to realize a semi-synthesis of Taxol from Baccatin III (which can be readily accessed from 10-deacetylbaccatin III), an efficient method for constructing the ester functionality had to be developed. The steric bulk on both sides of the coupling junction combined with several additional functional groups constitutes a typical example of the type of ester bond that can prove very challenging as is analyzed in detail in the sections below. Indeed this turned out to be the case as was succinctly pointed out by Denis and co-workers in 1988: *"None of the various esterification procedures that are generally successful with hindered substrates was able to produce, even to a modest degree, the desired coupling"*[21]

Extensive experimentation resulted in the discovery that the key coupling reaction could be effected using a new reagent, di-2-pyridyl carbonate (DPC), developed a few years earlier by Kim and co-workers,[22] in combination with *N,N'*-dimethylaminopyridine (DMAP). Although uniquely successful for this challenging transformation, it is curious to note that virtually no additional comparable examples of the use of DPC, or related carbonate reagents, can be found in the literature. The seminal work by Denis and co-workers[21] that converged onto the detailed procedure depicted in Scheme 3 (left) was a milestone in the Taxol story, however viewed from a strictly synthetic perspective the method is in fact rather inefficient as well as quite wasteful. Key improvements to the semi-synthesis was subsequently made by Holton[23] and Ojima[24] who both reported that the chemical structure of the side chain (an α-hydroxy-β-amino acid derivative) could be uniquely exploited to facilitate the coupling, as it could be tied up into a reactive β-lactam functionality that could deliver the coupled product in high yield through reaction with the C13-alkoxide of protected Baccatin III (Scheme 3, right). Employing the β-lactam as a direct side chain precursor had another advantage as it allowed for an improved stereoselective synthesis compared to the acyclic precursor used by Greene and co-workers. The β-lactam strategy for introduction of the side chain also featured in the seminal syntheses of Taxol by the Nicolaou,[25] Holton,[23] and Danishefsky[26] groups.



Scheme 3 Semi-synthetic and biosynthetic strategies for attachment of the C13-ester side chain of Taxol.

Extensive studies of Taxol biosynthesis have revealed that the fully elaborated side chain is in fact not incorporated as a single entity (Scheme 3, middle).[27] Rather, a relatively unhindered β-phenylalanine side chain is introduced first onto Baccatin III followed by stereoselective P450-mediated hydroxylation of the α-carbon and final *N*-benzoylation (through the coupling of Bz-S-

CoA). So, at least in the case of Taxol, a maximally convergent, but also sterically congested, ester fragment coupling is not the preferred biosynthetic option.

2.4 Baeyer-Villiger Monooxygenases

In an unrelated mechanistic fashion Nature also makes esters/lactones via enzymes belonging to the Baeyer-Villiger monooxygenase (BVMO) family, which was first documented by Turfitt in 1948.[28] The BVMO family has since been divided into sub-classes but all share the following essential features; a flavin based prosthetic group (flavin mononucleotide – FMN; flavin adenine dinucleotide – FAD), O_2 as oxidant, and NAD(P)H as reducing agent.[29] BVMOs are involved in a variety of different processes, both in synthesis of secondary metabolites and in catabolism, allowing certain bacteria to utilize ketones as nutrients.[29,30] Often BVMOs catalyze oxidations other than ester formation (*e.g.* carbamate formation,[31] carbonate formation,[32] and sulphur oxidation[29]), and sometimes the ester formed is only present in precursor intermediates, but not in the final natural product.[33] Natural BVMOs and derived mutant enzymes have also been central in recent studies regarding the use of enzymes in organic synthesis to form esters with high stereo- and regioselectivity.[34,35,36,37] It remains difficult, however, to predict activity and selectivity for different substrates, and the method is not yet used regularly. Some examples of ester-containing natural products synthesized by BVMOs are shown in Figure 3.

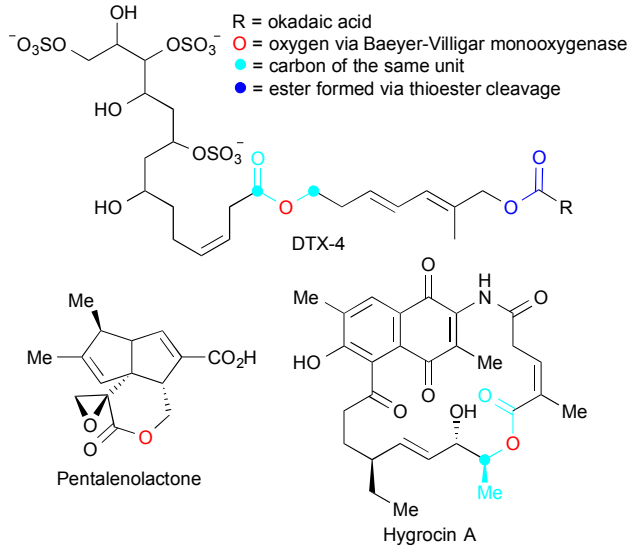
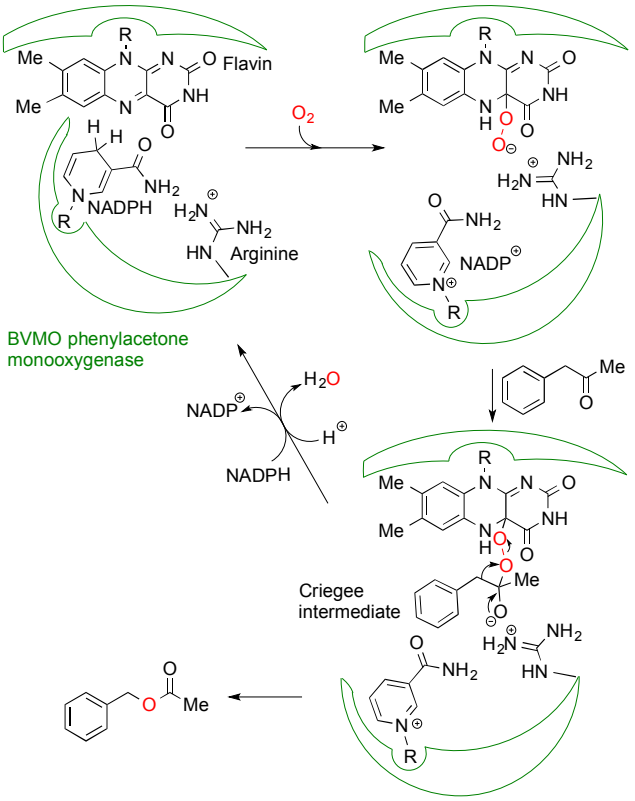


Figure 3 Natural product esters/lactones formed by BVMO.

DTX-4 is an okadaic acid derivative that originates from dinoflagellate cells.[38] It contains two esters, and by feeding experiments it has been shown that one ester derives from a ketone followed by oxidation by a BVMO. The other ester in DTX-4 is synthesized via the canonical thioester method. Also belonging to this family of natural products are DTX-5b and DTX-5c that both contain an ester synthesized by a BVMO.[39] The sesquiterpenoid antibiotic Pentalenolactone is a known electrophile, alkylating the active site cysteine of glyceraldehyde-3-phosphate dehydrogenase in bacteria.[40] The lactone moiety is installed from the ketone as part of a series of oxidation reactions late in the biosynthesis. Hygrocin A is a lactone polyketide which is formed by BVMO-mediated oxidation following macrolactamization.[41]

The BVMO catalytic mechanism has been studied in detail using simple substrates like cyclohexanone and phenylacetone (Scheme 4).[37,42,43] The flavin ring reacts with NADPH and O_2 to generate a peroxide-intermediate. An arginine residue close to the flavin binding site is believed to stabilize the negatively charged peroxide.[42]



Scheme 4 Proposed mechanism of BVMO phenylacetone monooxygenase.[42]

Nucleophilic attack on the ketone substrate leads to the intermediate originally suggested by Criegee during his studies on the Baeyer-Villiger reaction mechanism.[44] The arginine-residue in the active site is thought to maintain a key role in also stabilizing this intermediate. Last, the ester is formed via carbon migration followed by dehydration to reform the flavin. In total, a ketone, a molecule of O_2, a proton, and NADPH are transformed into an ester, a molecule of H_2O, and $NADP^+$.

3. Classic Activation Modes

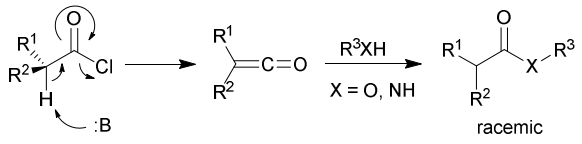
The enzymes involved in making Nature's ester bonds thus rely upon a few fundamental mechanisms, and in the vast majority of cases, save the BVMOs outlined above, the ester is constructed as a redox-neutral coupling reaction between an alcohol and the acid/ester functionality. Viewed from a strictly chemical perspective, the transformation happens either as a simple (and energy-neutral) O-O-transesterification or as an S-O transfer from the slightly more activated thioesters. In most cases it remains poorly understood how the activation is achieved at the level of individual functional groups, but most enzymes are likely to

utilize dual catalytic mechanisms to activate both substrates and collectively facilitate the transformation. Pre-organization of the linear chain, or substrate proximity in the intermolecular case, are critical elements in the catalysis.

In the absence of similar strong organizational principles, the chemical solution to the synthesis of complex ester bonds relies upon generation of species that are far more reactive. It should be noted that biomimetic strategies such as those reported by Corey, Nicolaou, Clark, Gerlach and others involving thioester intermediates has had significant success in (macro)lactonization chemistry,[45] but these methods are generally not employed for effecting ester fragment couplings. Fundamentally, all of the established chemical methods seek to generate the ester bond by the (in)direct dehydrative merger of a carboxylic acid and an alcohol, which on the practical level is achieved mainly through activation of the carboxylate functionality and to a lesser extent the alcohol functionality. In the end of the review, we will present a series of new methods that challenge this general dogma. In this section, we will briefly outline the fundamentals of the five chemical activation principles and reagents that currently comprise the core methodology for ester coupling reactions. We will keep focus on the known propensities for undesired reactivity that can complicate the application in complex molecules.

3.1 Acyl Halides

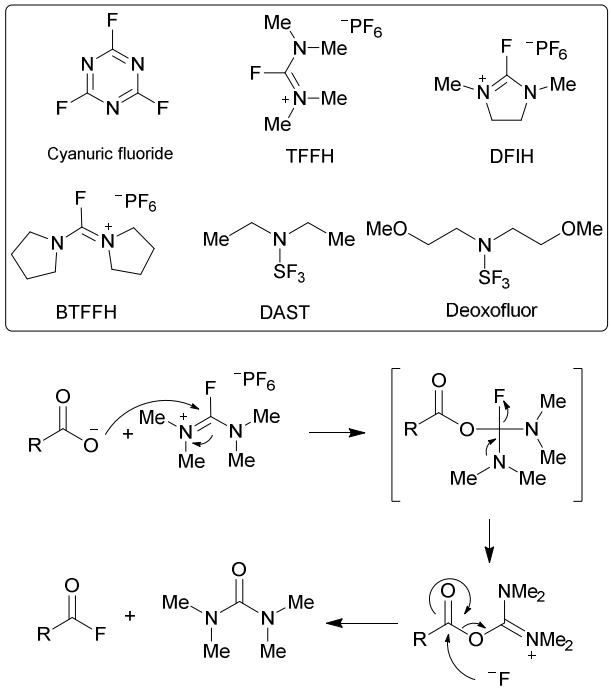
Due to the strong electrophilicity acyl chlorides would appear as appealing intermediates for constructing highly hindered ester bonds. This strategy, however, suffers from severe limitations.[46] Firstly, all the conventional methods for acid chloride formation[47] require the use of reagents like thionyl chloride, oxalyl chloride or phosphorus chlorides that generate hydrochloric acid as a byproduct, thus rendering these procedures irreconcilable with acid-labile substrates. Various protocols for the synthesis of acid chlorides under mild or acid-free conditions have been reported,[48] however, to the best of our knowledge, they have only seen scarce application in natural product synthesis.[49] Moreover, once formed, acid chlorides are prone to hydrolysis as well as racemization under basic conditions through the standard ketene intermediate (Scheme 5). Consequently, the use of acid chlorides in total synthesis has been confined either to the coupling of functionalized, orthogonally *N*-protected, single amino acids,[50,51] or to early stage coupling of small fragments that are stable under the acidic environment generated during the formation of the acyl chloride. [52]



Scheme 5 Racemization through the ketene intermediate is a common problem associated with the use of acyl chlorides as reagents in ester (and amide) coupling reactions.

An efficient way to circumvent the aforementioned problems is the activation of the carboxylic acid via acid fluoride formation.[53] These species can be generated *in situ* and are less sensitive towards moisture and, more importantly, compatible with acid-labile functional groups, like *t*-Bu esters or *N*-trityl side chain protection, as their formation requires mild conditions.

A broad spectrum of activating reagents such as cyanuric fluoride, fluoroformamidinium salts (TFFH, BTFFH, DFIH), diethylaminosulphur trifluoride (DAST) and deoxofluor (Scheme 6) are available. Mechanistically, the acyl fluoride is formed following an initial attack of the carboxylate group onto the fluoroformamidinium salt and then the fluoride ion released can re-attack the activated acyl group to afford the acyl fluoride and tetramethylurea (in the case of TFFH, Scheme 6). Racemization problems as well as other undesired reactivity are decreased with acyl fluorides which in many respects bear high resemblance to other types of *in situ* generated active esters.[54]



Scheme 6 Fluorinating agents and formation of an acyl fluoride using TFFH.

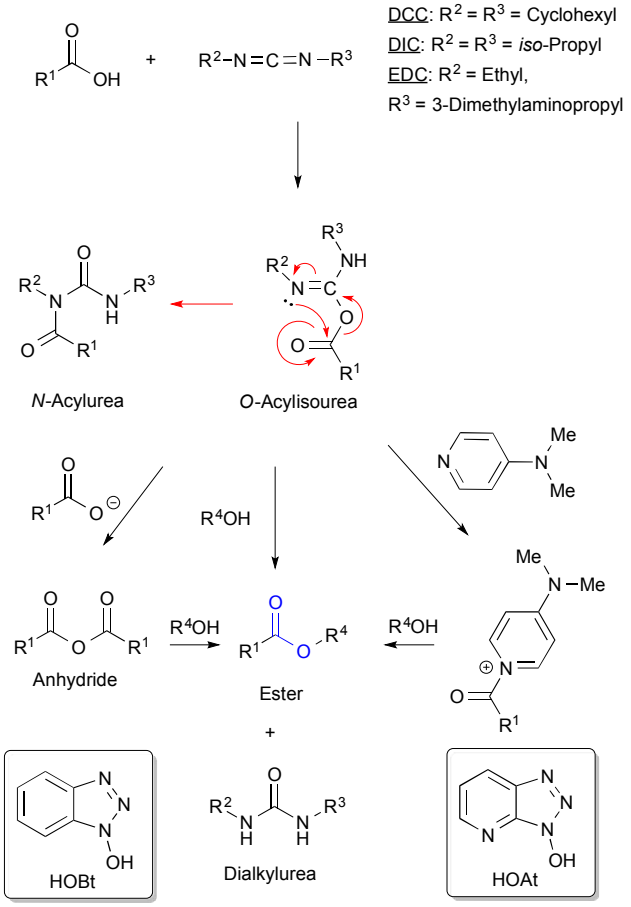
3.2 Carbodiimides

One of the most commonly used set of conditions for the formation of an ester bond was developed in 1978 by Neises and Steglich and employs *N,N'*-dicyclehexylcarbodiimide (DCC) and DMAP.[55] Before the development of the Steglich conditons, DCC was rarely used in the formation of ester bonds due to a high tendency to form the undesirable *N*-acylurea (Scheme 7).[55]

During a coupling reaction with DCC dicyclohexylurea (DCU) is formed as a byproduct (Scheme 7). DCU is insoluble in most organic solvents and can thus be filtered off after the reaction, however traces of DCU can persist which may complicate the subsequent chromatographic purification.[56] In such cases, the use of alternative carbodiimides, such as *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC) or *N,N'*-diisopropylcarbodimide (DIC), can be more advantageous. EDC and its urea byproduct are water-soluble and hence can be removed during aqueous workup.[57] DIC is more soluble in organic solvents, such as dichloromethane, than DCC.[58] This is

particularly useful in solid-phase synthesis, and DIC/DMAP has been used on several occasions for the solid-phase synthesis of depsipeptides.[59,60,61,62,63]

The initial step of the reaction mechanism is the reaction between the carboxylic acid and the carbodiimide, most likely via an ion pair, to form the *O*-acylisourea (Scheme 7).[64] This intermediate can now either react with another equivalent of the carboxylate to form the symmetric anhydride, with the alcohol to form the ester, or undergo intramolecular rearrangement to form the *N*-acylurea byproduct. The intramolecular rearrangement occurs via a four-centered transition state from the *E*-isomer of the imide, where the lone pair on the nitrogen atom and the carbonyl are on the same side of the double bond. Isomerization of the *Z*-isomer to the *E* isomer is acid catalyzed at pH 3-6, but can still occur slowly and uncatalyzed at pH above 7. At pH below 2 the rearrangement cannot occur due to the *O*-acylisourea existing primarily in its protonated form.[65] In the case of acids possessing strong electron-withdrawing groups at the α-position, formation of a ketene intermediate is also possible. Reaction of the ketene with the alcohol can also result in formation of the desired ester, although eventual stereochemistry in the acid component would be compromised.[66]



Scheme 7 Mechanism of carbodiimide/DMAP mediated ester coupling.

Reaction between the symmetrical anhydride and the alcohol will lead to the formation of the desired ester, while formation of the *N*-acylurea is, as already mentioned, undesirable since it leads to consumption of the carboxylate with no further formation of the desired ester. Alcohols are in general much poorer nucleophiles than amines, and hence the degree of *N*-acylurea formation is greater in carbodiimide mediated esterification reactions than in amide formations. Addition of DMAP in catalytic amounts can, however, compensate for this tendency by rapid reaction between DMAP and the *O*-acylisourea to form an acyl pyridinium species incapable of intramolecular byproduct formation, and which can react with the alcohol to form the ester. As we will see below, very subtle changes in reaction conditions can be critical for carrying out successful complex Steglich-type ester couplings.

In case of EDC the mechanism is more complex than depicted above, since this carbodiimide exists in a pH-dependent equilibrium of the open-chain carbodiimide and the ringclosed structural isomer.[67]

Other very commonly used *N*-acylurea suppressing additives for carbodiimide mediated couplings are the benzotriazole derivatives, including 1-hydroxybenzotriazole (HOBt, Scheme 7) and 1-hydroxy-7-azabenzotriazole (HOAt, Scheme 7). HOBt was described for the first time in 1970 by König and Geiger as an additive with the ability to decrease racemization and to hinder the formation of *N*-acylurea during peptide couplings with DCC.[68] Recently, Morales-Serna *et al*. have demonstrated the use of HOBt as an additive in EDC mediated ester formation with sterically hindered substrates.[69] HOAt was first described in 1993 by Carpino as an additive with enhanced reactivity in peptide couplings compared to HOBt. This is believed to be due to the neighboring group effect of the 7-aza derivative making proximity of the amine and the benzotriale coupled carboxylate possible. The amount of racemization in HOAt mediated couplings does not seem to decrease compared to HOBt mediated couplings.[70] Whether this neighboring group effect of HOAt is applicable to esterification reactions is not clear from the research literature. In fact, Xu and Miller report that ester formation, as a byproduct of an attempted amide formation with CbzSerOH and CbzThrOH, is diminished when DCC/HOAt is used instead of DCC/DMAP.[71]

3.3 Yamaguchi Anhydrides

The canonical Yamaguchi coupling, developed in 1979 by Yamaguchi and co-workers,[72] is the formation of an ester via alcoholysis of a mixed anhydride formed by reaction of 2,4,6-trichlorobenzoyl chloride (TCBC, Scheme 8) with the carboxylic acid of interest. In the original procedure the mixed anhydride is preformed using triethylamine (TEA) in THF, and isolated via filtration to remove the formed triethylamine hydrochloride salt, followed by simple concentration. The mixed anhydride can then be redissolved in benzene or toluene and subjected to the alcohol of interest in the presence of DMAP, to form the desired ester in high yields and short reaction times.[72] The original procedure has, however, been modified by Yonemitsu and co-workers to accomplish direct one-pot esterification without the need of isolation of the mixed anhydride.[73] Yamaguchi and co-workers report the method to be useful to form esters from both primary, secondary and tertiary alcohols, however the very sterically hindered *tert*-butyl pivalate ester could not be formed via this method.[72] The reaction can be run at room temperature, but is faster at higher temperatures, however higher temperatures also led to some extent of racemization in the case of chiral

compounds.[72] The Yamaguchi reaction has been extensively employed for performing macrolactonization reactions.[2]

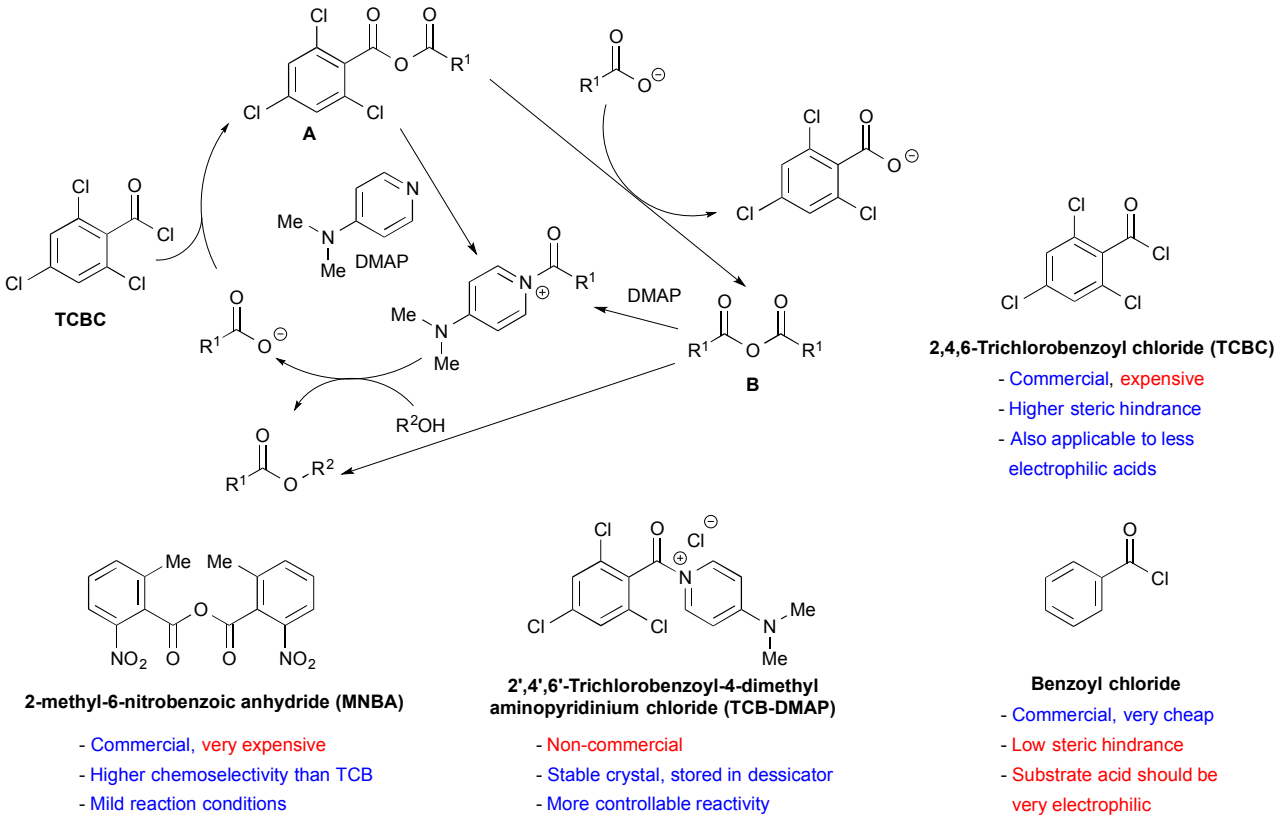
According to Yamaguchi and co-workers, the reaction is based on the formation and following alcoholysis of the mixed anhydride (**A**, Scheme 8), thus leading to the conclusion that the choice of aryl acid chloride should be focused on a compound that is sterically hindered so the alcoholysis of the mixed anhydride takes place selectively at the position of the carbonyl group of interest. Furthermore, the corresponding carboxylate formed from the alcoholysis should be a good leaving group.[72] However, a somewhat different mechanism was postulated by Dhimitruka and SantaLucia based on the observation that in the reaction between 2,4,6-trichlorobenzoyl chloride and propionic acid in the presence of triethylamine in THF, the symmetric aliphatic anhydride, and not the mixed anhydride, was isolated as the only product.[74] Similarly, Yonemitsu and co-workers also report in the key macrolactonization reaction in the synthesis of the macrolide Hygrolidin, that reaction with the Yamaguchi reagent in THF in the presence of triethylamine gives a 6:4 mixture of the mixed and symmetrical anhydride.[75]

The reaction mechanism proposed by Dhimitruka and SantaLucia[74] is initiated by nucleohilic attack of the carboxylate onto the aryl acid chloride to initially form the mixed anhydride (**A**, Scheme 8). The mixed anhydride then reacts with another equivalent of the carboxylate to form the symmetrical anhydride (**B**, Scheme 8) and the aryl carboxylate. Nucleophilic attack from the alcohol on the symmetrical anhydride forms the desired ester and reforms the carboxylate. The postulated mechanism is based on the assumption that the aliphatic carboxylate is a better nucleophile than both the alcohol and the aromatic carboxylate.

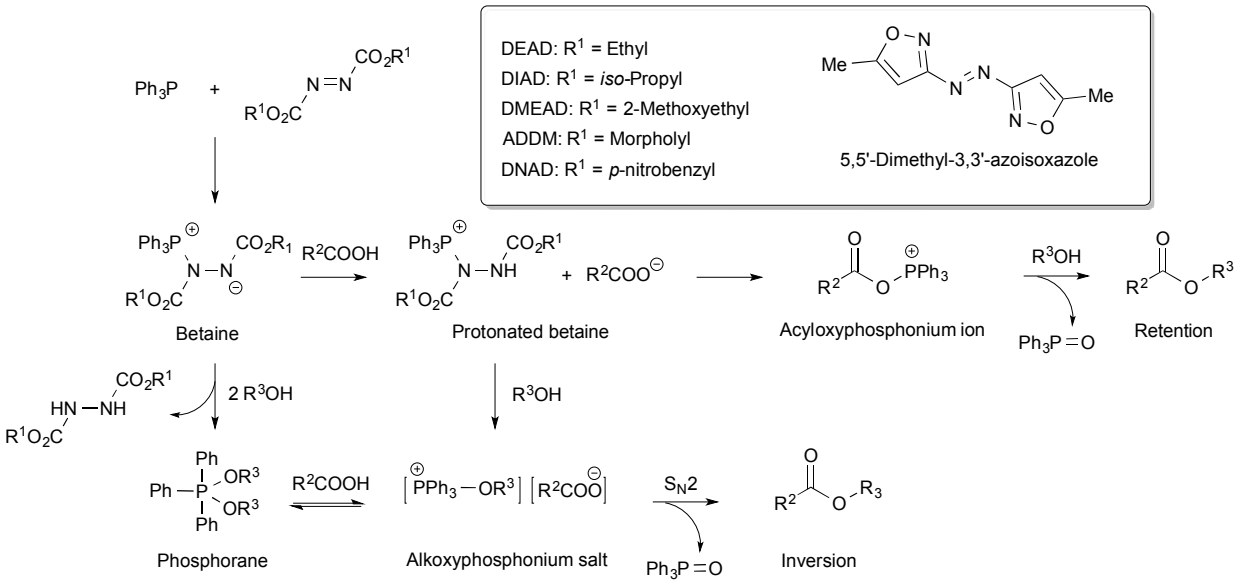
Furthermore, the selectivity of the reaction towards the aliphatic carbonyl would depend on this being a better electrophile than the aromatic carbonyl, rather than solely on steric effects.[74] Hence, depending on the substrate, the use of the unhindered benzoyl chloride (Scheme 8), instead of TCBC, is possible, which was also demonstrated recently by Hung *et al.* in the synthesis of Xnematide.[74,76] With the proposed mechanism, Dhimitruka and Santalucia also indicate that a two-step procedure and the use of excess DMAP is unnecessary.[74] DMAP acts as a nucleophilic catalyst accelerating the reaction by forming an acyl pyridinum salt prone to nucleophilic attack by the alcohol.

Recently, Okuno *et al.* have reported the synthesis and use of 2',4',6'-trichlorobenzoyl-4-dimethyaminopyridinium chloride (TCB-DMAP, Scheme 8) as a modified Yamaguchi reagent. TCB-DMAP is synthesized in one step from TCBC and has the apparent advantage of a lowered reactivity, giving a more controllable reaction.[77]

In 2002 and 2004 Shiina *et al.* reported the use of 2-methyl-6-nitro-benzoic anhydride (MNBA, Scheme 8) as a very effective reagent for ester formation and macrolactonization.[78] MNBA gave the desired ester in high yield at room temperature employing only slight excess of MNBA and carboxylic acid, in combination with 10 mol % of DMAP under basic conditions. In macrolactonization reactions DMAP was used in stoichiometric amounts and no additional base was added. In most of the esterification reactions examined, MNBA had a much higher



Scheme 8 Proposed mechanism of the Yamaguchi coupling along with structure and characteristics of alternative reagents.



Scheme 9 Mechanism of Mitsunobu esterification reaction and structures of activating agents.

chemoselectivity than TCBC, i.e. low formation of the byproduct formed from alcoholysis at the benzoic carbonyl of the mixed anhydride. Furthermore, MNBA was been reported to be both higher yielding and to give a higher ratio of monomer to dimer in macrolactonization reactions than TCBC under similar reaction conditions. The yield of the TCBC mediated reaction was improved when the reaction temperature was significantly increased, however this also lowered the monomer to dimer ratio.[78]

3.4 Mitsunobu Coupling

The Mitsunobu reaction, developed by Mitsunobu and Yamada in 1967,[79] allows for converting alcohol groups into a variety of functionalities, including esters. Contrary to the most widely used coupling reagents which activate the carboxylic acid for nucleophilic attack by the alcohol, in the Mitsunobu reaction the alcohol is activated towards nucleophilic attack from the carboxylic acid. This is achieved by reacting with a phosphine, typically triphenyl phosphine, and a dialkyl azodicarboxylate, usually diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD). A number of reports have focused on developing other azodicarboxylates such as DMEAD,[80] ADDM,[81] DNAD[82] and 5,5'-Dimethyl-3,3'-azoisoxazole[83] to solve the not uncommon problems with chromatographic purification. These reagents can be removed from the reaction mixture by alternative means, such as aqueous workup or filtration, and show similar reactivity and scope as DIAD and DEAD. However, 5,5'-Dimethyl-3,3'-azoisoxazole does show selectivity towards esterification of benzylic over aliphatic alcohols.[83]

The mechanism of the Mitsunobu reaction has been extensively studied, however, there are still aspects of the reaction that are not fully understood.[84,85,86,87,88] The first step of the reaction mechanism is the formation of the Morrison-Bruun-Huisgen intermediate betaine formed by nucleophilic attack of the phosphine on the azodicarboxylate (Scheme 9).[84,89] Abstraction of a proton from the carboxylic acid then gives the protonated betaine, which in turn can react with the alcohol to form the alkoxyphosphonium salt. The alcohol can also undergo nucleophilic attack onto the betaine to form the pentavalent phosphorane species, which is in equilibrium with the alkoxyphosphonium salt in presence of the acid.[84,87,90]

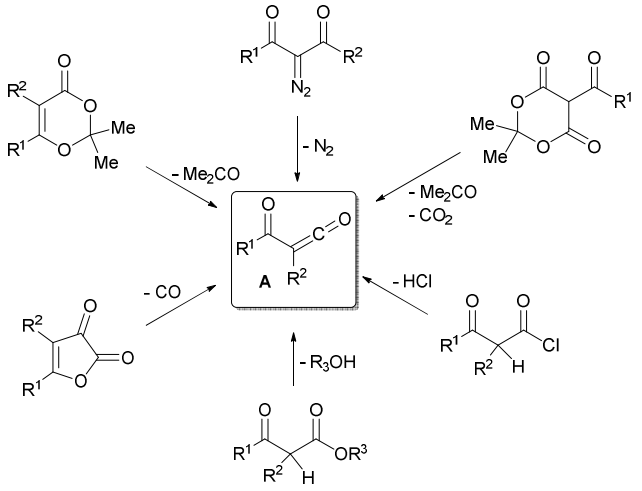
The equilibrium between the phosphorane and the alkoxyphosphonium salt depends on the polarity of the solvent, as well as the stoichiometry and pKa of the carboxylic acid.[87] Nucleophilic attack of the carboxylic acid onto the alkoxyphosphonium salt then leads to the formation of the ester and triarylphosphine oxide.[87,89] In case of chiral alcohols the reaction will proceed with inversion of the stereochemistry of the alcohol, unless very sterically hindered alcohols are employed.[90] Complete retention of stereochemistry of the alcohol was for instance observed in the total synthesis of (+)-Zampanolide.[91] The most likely explanation of this unusual observation was accounted to be failure of the Mitsunobu reagents to activate the alcohol due to sterics. Instead, formation of an acyloxyphosphonium ion and subsequent nucleophilic attack of the alcohol gave the ester with retention of configuration (Scheme 9).[91] Mechanistic studies of the Mitsunobu reaction by DeShong and co-workers also support this mechanism.[86]

3.5 Ketene intermediates

Ketenes are highly reactive intermediates that are usually generated *in situ* and get trapped immediately by a suitable trapping agent to provide a plethora of interesting compounds and important building blocks. Ketene chemistry traces back to the outset of the 20th century with the pioneering work by Staudinger[92] and Wilsmore[93]. The rich and diverse chemistry of ketene intermediates has been the subject of numerous comprehensive reviews over the years.[94] Therefore, for the purposes of this review we will focus solely on examples of ketene-mediated ester/lactone formation en route to the total synthesis of natural products.

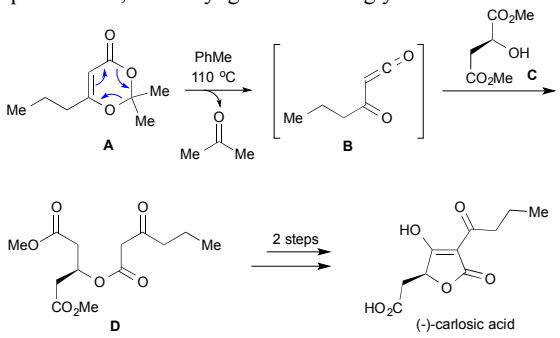
By far, the most commonly used ketene intermediate in total synthesis campaigns has been the acylketene species (or α-oxoketene), which gives rise to β-keto esters in the case of

intermolecular couplings, or *β*-keto lactones when the acylketene-trapping occurs intramolecularly by a pendant hydroxyl group.[94g] The transient acylketene intermediate (**A**) is generated *in situ* by thermolysis or photolysis of a variety of precursors (Scheme 10).



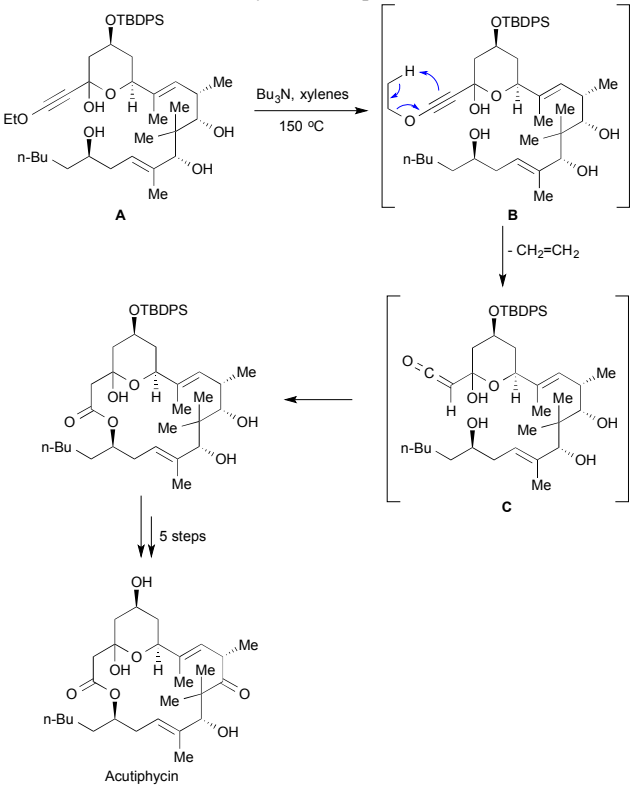
Scheme 10 Formation of the highly reactive acylketene intermediate from various precursors.

The first example of intermolecular capture of an acylketene intermediate was reported in 1990 by Sato *et al* in the total synthesis of the fungal metabolite (-)-carlosic acid (Scheme 11).[95] Thermolysis of 1,3-dioxin-4-one **A** in the presence of alcohol **C** as the nucleophile, initiates a retro-hetero-Diels-Alder reaction forming the acylketene species **B** which immediately gets trapped by alcohol **C** to produce the desired *β*-keto ester **D**. A recent example of a similar transformation can be found in the synthesis of the macrocyclic core of Lyngbyaloside B[96] (Table S1, entry 40, see Supplementary Information). The equivalent intramolecular version of this reaction has found many applications in the construction of complex medium- and large-ring macrolides, e.g. in the synthesis of Amphidinolide P,[97] Callipeltoside A,[98] and Lyngbouilloside aglycon[99].



Scheme 11 A facile synthesis of (-)-carlosic acid through an intermolecular trapping of acylketene.

In 1989, Funk and co-workers[100] reported a novel ketene mediated macrolactonization approach through a thermal retro-ene reaction of an alkyl alkynyl ether as the macrolactone precursor. The first application of this elegant protocol in total synthesis was reported by Jamison and co-workers in 2006 for the synthesis of Acutiphycin.[101] As depicted in Scheme 12, thermolysis of alkynyl ether **A** in the presence of a base effected a retro-ene reaction (**B**) to generate ethylene and ketene **C** that underwent a intramolecular coupling with the least hindered pendant hydroxyl group to form the macrocycle in an excellent yield of 90%. This method has been studied further as a mechanistic probe[102] however, to the best of our knowledge, an intermolecular variant has yet to be reported.



Scheme 12 Alkynyl ether as a ketene precursor in the total synthesis of Acutiphycin.

4. Representative Complex Ester Couplings in Total Synthesis of Natural Products

In this section we provide a number of examples of complex ester couplings from literature. The examples are selected from all of the canonical modes of activation and illustrate either very difficult couplings or alternative reagents/conditions in order to boost reactivity or suppress side reactions. In section 4.6 below and in Table S1 we provide, a more comprehensive collection of examples.

4.1 Steglich Variants

4.1.1 Ramoplanin A2

Ramoplanin is a lipoglycodepsipeptide antibiotic isolated from the fermentation broths of *Actinoplanes* sp. ATCC 33076 as a mixture of three closely related compounds, A1–A3, that differ only in the structure of the lipid side chain.[103] From this complex, Ramoplanin A2 (Fig. 4) is the most abundant and was therefore selected as the first target for total synthesis as the aglycon analogue. The Ramoplanin complex is 2–10 times more potent against Gram-positive bacteria than Vancomycin and is currently in Phase III clinical trials for the oral treatment of infections from Gram-positive pathogens.[104]

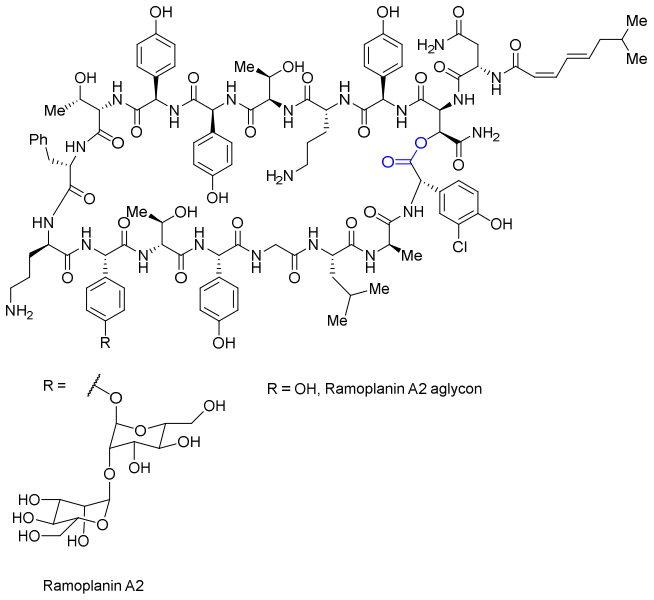
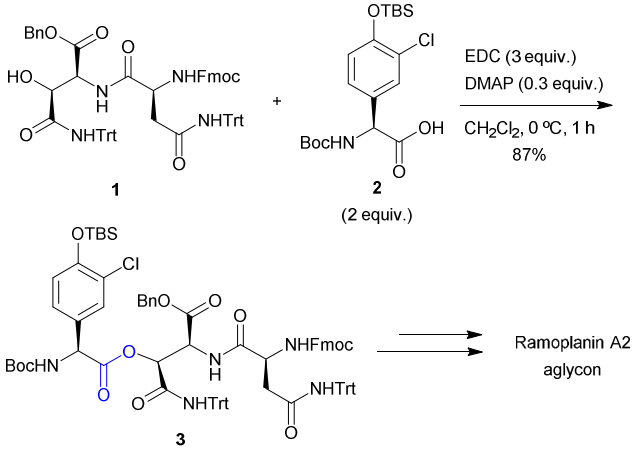


Figure 4 The chemical structure of Ramoplanin A2.

The chemical structure of Ramoplanin A2 was established in 1989 and was found to consist of a 49-membered ring containing 17 amino acid residues, 13 of which are non-proteinogenic and 7 bear the D-configuration. Boger and co-workers reported the first total synthesis of the Ramoplanin A2 aglycon in 2002,[105] followed by the total syntheses[106] of the two minor components of the Ramoplanin complex, A1 and A3, two years later.

Towards the synthesis of the Ramoplanin A2 aglycon, Boger and co-workers encountered one of the most recalcitrant ester bond formations ever reported (Scheme 13, Table S1, entry 7).[104] A wide range of esterification protocols, namely acyl fluoride activation, unhindered mixed anhydride activations, Mitsunobu esterification, Yamaguchi esterification, Corey-Nicolaou[45a] esterification, all failed to deliver the product in acceptable levels of conversion and diastereomeric ratios, or suffered from competitive β-elimination.

Benchmark protocols like DCC/DMAP or EDC/DMAP were able to facilitate the intended coupling but required extensive fine-tuning of the reaction conditions, with higher temperatures (23 vs 0 °C) or prolonged reaction time leading to unsatisfactory conversions. Also, the amount of DMAP used had a huge impact on the reaction's outcome with higher amounts (0.5-2 equiv. vs 0.15-0.3 equiv.) leading to epimerization products. Even though, at first sight, it may seem counterintuitive to lower the temperature or the equivalents of a catalyst in a reaction that is not working, it would appear that there is a delicate balance, when these highly reactive intermediates are generated in such complex settings, that can lead either to the formation of the desired product, or to intramolecular side-reactions causing racemization or degradation. Finally, the key esterification of **1** and **2** was accomplished via activation with EDC in the presence of a catalytic amount of DMAP (0.3 equiv.) at 0 °C, furnishing the desired ester **3** in excellent yield (87%) and diastereoselectivity (>10:1 dr).



Scheme 13 Ester bond formation conditions towards the synthesis of Ramoplanin A2 aglycon.

4.1.2 Pipecolidepsin A

Pipecolidepsin A is a "head-to-side-chain"[107] cyclodepsipeptide isolated from the marine sponge *Homophymia lamellosa* collected off the coast of Madagascar (Fig. 5).[108] It displays cytotoxicity against three human tumor cell lines, namely A549 (lung), HT-29 (colon) and MDA-MB-231 (breast) in the nanomolar range.[109] Pipecolidepsin A is characterized by a complex architecture containing a 25-membered macrolactone scaffold which incorporates several rare non-proteinogenic amino acid residues, with the D-*allo*-(2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethyl hexanoic acid and the L-*threo*-β-EtO-Asn residues being unprecedented in natural peptides.[110] The total synthesis and structural validation of this cyclodepsipeptide was reported by Pelay-Gimeno *et al.* in 2013.[109]

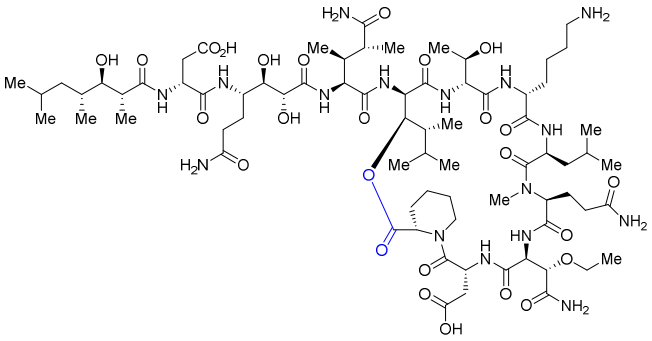
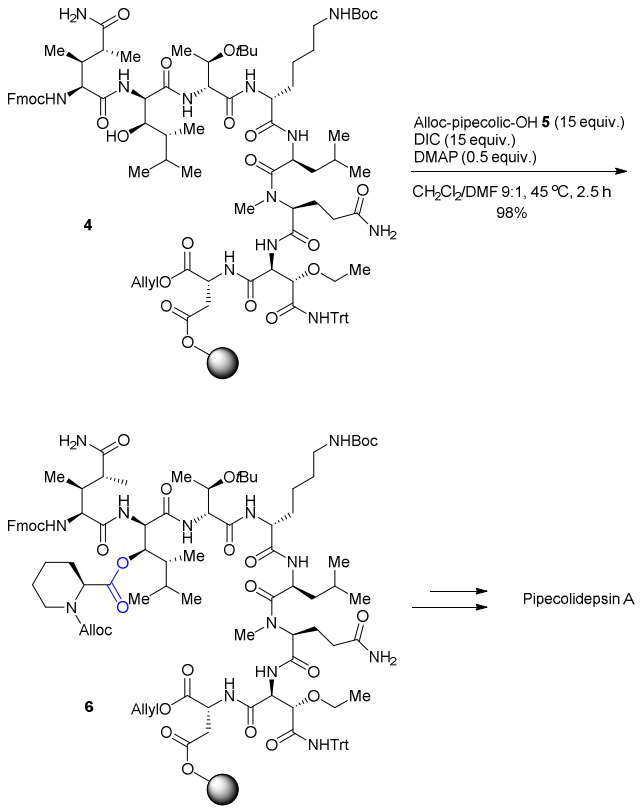


Figure 5 The chemical structure of Pipecolidepsin A.

The total synthesis of Pipecolidepsin A was performed on solid phase thus allowing rapid access to, potentially medicinally important, analogues. In regard to the formation of the key ester bond, the researchers had to overcome several pitfalls, mainly due to the significant steric hindrance of the secondary alcohol **4** (Scheme 14, Table S1, entry 10).



Scheme 14 Ester bond formation conditions towards the synthesis of Pipecolidepsin A.

Low conversions, loss of the Fmoc protecting group on the adjacent Fmoc-diMeGln residue, cleavage of the peptide from the resin at large scales and competitive epimerization were some of the synthetic challenges encountered during this esterification step. Various activation modes failed to deliver the product (Table 1, entries 1 and 2), while formation of the ester bond on a longer fragment could not be achieved even under extreme conditions, such as high temperatures or strong heating under microwave irradiation. Finally, only the modified Steglich esterification protocol using DIC/DMAP furnished the desired intermediate **6** (Table 1, entries 3–6) but, nonetheless, elevated temperature and huge excess of acid **5** and carbodiimide were necessary in order to achieve high yields with reasonable purity (Table 1, entries 5 and 6).

Table 1 Esterification optimization studies.

Entry	Coupling system	T (°C)	Time (h)	Yield (%)[a]
1[b]	**5** (5 equiv.), MSNT (5 equiv.), NMI (4 equiv.)	25	2	0
2[c]	Alloc-pipecolic-F (10 equiv.), DIPEA (25 equiv.)	25	4	0
3[b]	**5** (8 equiv.), DIC (8 equiv.), DMAP (1 equiv.)	25	20	27
4[b]	**5** (16 equiv.), DIC (10 equiv.), DMAP (1 equiv.)	25	4	15
5[b]	**5** (16 equiv.), DIC (10 equiv.), DMAP (0.5 equiv.)	45	30	84
6[b]	**5** (15 equiv.), DIC (15 equiv.), DMAP (0.5 equiv.)	45	2.5	98

[a] With respect to alcohol **4**. [b] dry CH_2Cl_2/dry DMF 9:1. [c] dry CH_2Cl_2. MSNT: 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole. NMI: *N*-methyl imidazole.

4.1.3 Iriomoteolide-3a

Iriomoteolide-3a is a 15-membered macrolide isolated from a marine benthic dinoflagellate *Amphidinium* strain, and is the first member of an unprecedented class of 15-membered macrolides, possessing four stereocentres in allylic positions, including an allyl epoxide moiety (Fig. 6).[111] Iriomoteloide-3a exhibits potent cytotoxicity against human B lymphocyte DG-75 and Raji cells in the low nanomolar range. The first total synthesis and structural validation of this macrolide was disclosed in 2009 by Nevado and co-workers.[112]

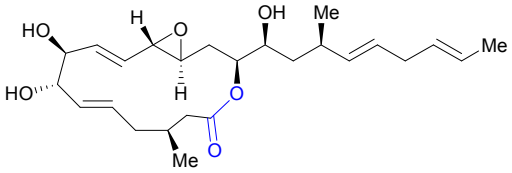
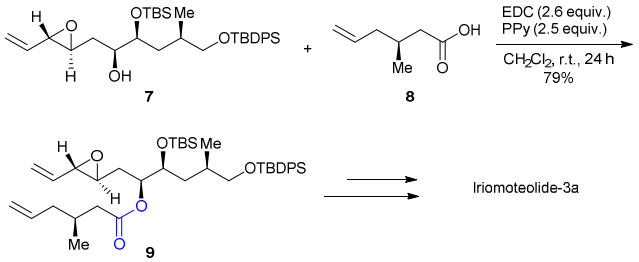


Figure 6 The chemical structure of Iriomoteolide-3a.

Towards the synthesis of Iriomoteolide-3a the key esterification reaction was accomplished through an intermolecular coupling of fragments **7** and **8** (Scheme 15, Table S1, entry 13), using EDC as the activating agent in the presence of an excess of 4-pyrrolidinopyridine (PPY, **C**, Fig. 7). Despite the presence of a fairly hindered secondary alcohol, the esterification reaction proceeded smoothly delivering ester **9** in high yield (79%) without any difficulties reported.



Scheme 15 Ester bond formation conditions towards the synthesis of Iriomoteolide-3a.

However, the use of PPY as the nucleophilic catalyst (in this case used in excess and not in a catalytic amount) in lieu of DMAP, was considered intriguing and prompted us to explore further the use of such nucleophilic catalysts in ester fragment couplings. Undoubtedly, the discovery by the groups of Litvinenko[113] and Steglich[114] almost half a century ago, that DMAP (**B**, Fig. 7) is a very efficient catalyst in acylation reactions enabling even the esterification of tertiary alcohols, sparked a revolution in the synthesis of ester bonds and has found various applications in terpene, nucleoside, steroid and carbohydrate chemistry.[115] Preceding this important discovery, pyridine (**A**, Fig. 7) was the only catalyst used in acylation reactions[116] and it represented a reliable, yet limiting, method for acylation of alcohols. In 1970, three years after the discovery of DMAP, Steglich and Höfle pushed the envelope further with their report of an even more effective acylation catalyst, PPY.[117] For many years, the notion that PPY had reached the limit of reactivity had been implicitly earning reputation,[118] and even Steglich himself in 1978 stated that *'it is unlikely that a better acyl transfer reagent than PPY will be found'*.[115] Nevertheless, almost three decades later, the

same scientist nullified his own sentence by demonstrating that conformational lock of the 4-amino group in a ring fused to the pyridine ring (**D**, Fig. 7) can enhance the catalytic activity of 4-(dialkylamino)pyridines.[119] At present, a plethora of nitrogen-based nucleophilic catalysts have been developed,[120] from the so called 'super-DMAP' analogues,[121,122] (**E**, Fig. 7) with increased reactivity in comparison to PPY, and 9-azajulolidine, to chiral DMAP derivatives[123] used as organocatalysts in enantioselective synthesis.

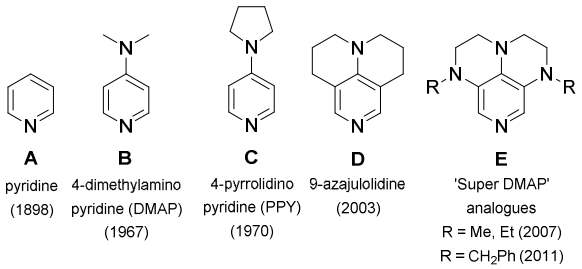


Figure 7 Nitrogen-based nucleophilic catalysts employed in acylation reactions.

However, in spite of the spectacular advances made in enhancing the reactivity of nucleophilic catalysts, these highly reactive species have yet to replace DMAP or PPY in esterification methodologies. Specifically within total synthesis projects, DMAP claims the lion share, as it is the first, and in most of the cases the only, activating agent examined for activation of the carboxylic acid. PPY has been applied to a much lesser extent, albeit in some cases it has been proven superior to DMAP, like in the total syntheses of Iriomoteolide-3a,[112] Iejimalide B (Table S1, entry 12)[124] and 506BD (Table S1, entry 14).[125]

Another interesting modification of the Steglich esterification protocol, with respect to the nucleophilic catalyst, is the Keck esterification. In 1985 Boden and Keck[126] reported that the usage of the hydrochloric salt of DMAP as an additive in combination with the coupling system DCC/DMAP plays a crucial role in preserving the active intermediates that are required for ester bond formation. According to the authors, DMAP•HCl acts as a proton source diminishing the formation of the undesired *N*-acylurea (Scheme 7). Camphorsulfonic acid (CSA) salts of DMAP have been employed in similar manner. Even though this methodology was originally designed for macrolactonization under high dilution conditions, it has found many applications in ester fragment couplings, like in the total syntheses of Lyngbyabellin A (Table S1, entry 5),[127] Aplyronine C[128] and Citrafungin A (Table S1, entry 4).[129]

4.2 Acyl Halide Approach

4.2.1 Halipeptin A

Halipeptin A is a cyclic lipodepsipeptide isolated from the marine sponge *Haliclona* collected in the waters off the Vanuatu Islands.[130,131] The initial, misassigned, structure was reported in 2001 by Gomez-Paloma and co-workers,[130] only to be revised by the same group one year later (Fig. 8).[131] Halipeptin A was found to possess very potent anti-inflammatory activity in vivo, a somewhat unexpected feature considering the peptidic nature of this molecule. In particular, preliminary pharmacological tests revealed a dose-dependent inhibition of mouse paw edema with a potency 40 and 130 times that of the classical anti-inflammatory drugs indomethacin and naproxen, respectively.[130] The first total synthesis of this natural product was reported in 2005 by Ma and co-workers.[132]

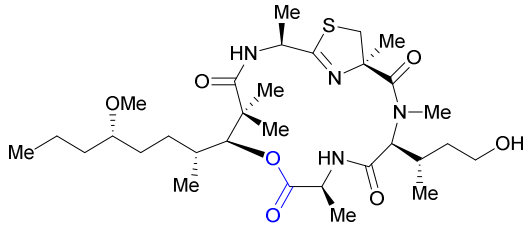
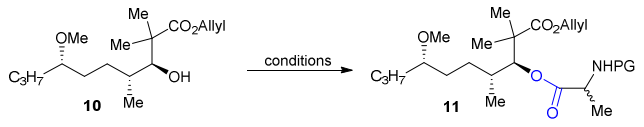


Figure 8 The chemical structure of Halipeptin A.

Towards the total synthesis of Halipeptin A, Ma and co-workers experienced significant difficulties constructing the depsipeptidic ester bond, mainly because of the steric hindrance arising from the extensive methylation around the secondary alcohol (**10,** Table 2).[132,133] The Yamaguchi method (Table 2, entry 1), the *p*-nitro-phenol activated ester procedure (Table 2, entry 2) and other activated esters, such as imidazolyl or succinimdyl (data not reported) were tried in vain. Moreover, under the classical EDC/DMAP activation mode the desired ester **11** was either not detected (Table 2, entries 3 and 4) or isolated with complete racemization at the alanine's chiral center (Table 2, entry 5). The latter was attributed to the slow rate of the reaction in the presence of a large excess of the coupling reagents.[133]

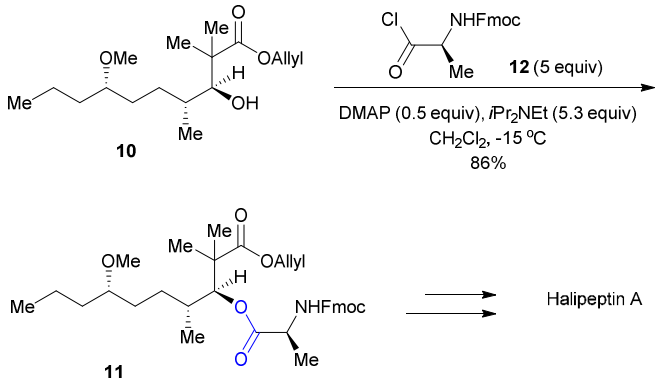
Table 2 Esterification optimization studies.



Entry	Conditions	Yield **11** (%)[a]
1	*N*-Boc-Ala (2 equiv.), 2,4,6-TCBC (2 equiv.), DMAP (2 equiv.), DIPEA (2.5 equiv.), PhMe, reflux	-
2	*N*-Boc-Ala-ONp (1.5 equiv.), HOBt (1.5 equiv.), NMM, DMF, r.t.	-
3	*N*-Boc-Ala (3 equiv.), EDC (3 equiv.), DMAP (1 equiv.), CH_2Cl_2, r.t.	-
4	*N*-Trt-Ala (3 equiv.), EDC (5 equiv.), DMAP (5 equiv.), CH_2Cl_2, r.t.	-
5	*N*-Boc-Ala (3 equiv.), EDC (5 equiv.), DMAP (5 equiv.), CH_2Cl_2, r.t., 24 hours	95[b]

[a] With respect to starting alcohol. [b] 1:1 mixture of **11** and its epimer. Trt: Trityl. Np: *p*-Nitrophenol.

Finally, the key esterification step was achieved by converting *N*-Fmoc-Ala-OH to the more reactive *N*-Fmoc-Ala-Cl counterpart (**12**) and coupling with alcohol **10** in the presence of DIPEA and DMAP catalyst at low temperature (Scheme 16, Table S1, entry 16).[132] Similar to the findings of Boger and co-workers for the synthesis of the Ramoplanin A2 aglycon, this reaction also required carefully controlled conditions with higher temperature (0 vs -15 °C) or higher amount of DMAP (1 equiv. vs 0.5 equiv.) leading to extensive epimerization at the α-carbon atom of the alanine residue. Under this optimized protocol, ester **11** was attained without racemization in excellent yield (86%).



Scheme 16 Ester bond formation conditions towards the synthesis of Halipeptin A.

4.2.2 Cruentaren A

Cruentaren A is a benzolactone-containing polyketide isolated from the fermentation broth of the myxobacterium *Byssovorax cruenta* (Fig. 9).[134] It exhibits antifungal activity and strong cytotoxicity against a panel of human cancer cell lines,[135,136] including the multi-drug resistant KB-V1 cell line (IC_{50} = 0.6 ng/mL) and the L929 cell line with an impressive IC_{50} value of 1.2 ng/mL. Moreover, Cruentaren A displays a, for this class of benzolactones, remarkable inhibitory activity against eukaryotic F-ATPases (IC_{50} = 15-30 nM), rendering it one of the most potent inhibitors of F_1-ATPase of yeast and mammals known to date.[135] The total synthesis of this biologically important benzolactone was reported independently by the groups of Maier[137] and Fürstner[138] in 2007 within just a few months.

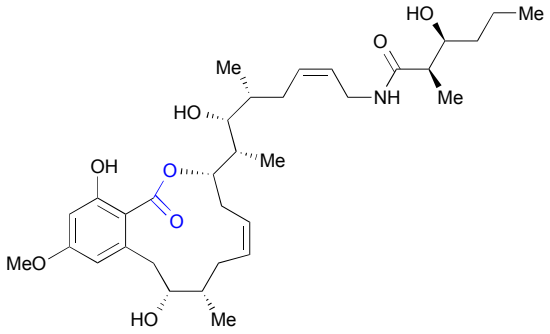
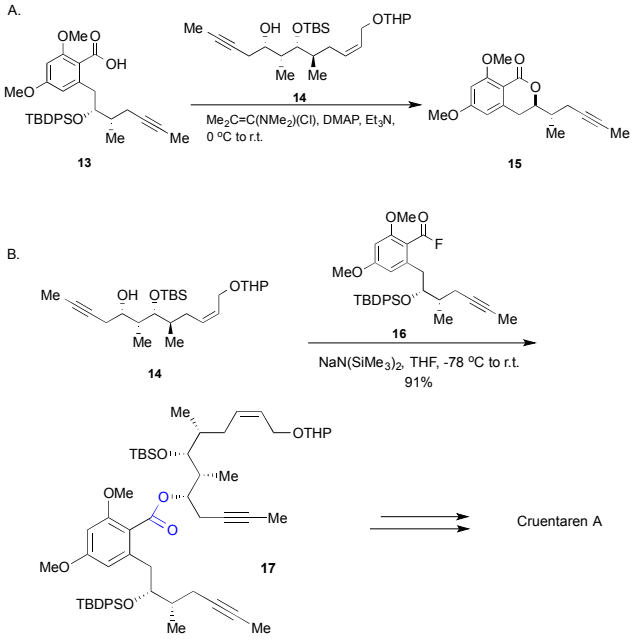


Figure 9 The chemical structure of Cruentaren A.

Towards the synthesis of Cruentaren A, both groups reported significant difficulties forming the ester bond.[138, 139] Fürstner and co-workers attempted to couple aromatic acid **13** with alcohol **14** (Scheme 17A). All the activating agents commonly employed in peptide synthesis, like carbodiimide-based reagents, Mukaiyama's[140] reagent, BOP[46] reagents, the formation of activated thioesters, but also benchmark protocols such as the Yamaguchi esterification, the Mitsunobu esterification and the Trost[141] esterification using Ru chemistry, led to unsatisfactory conversions or degradation of the starting materials. Moreover, functionalization of the acid via the acyl chloride intermediate under mild conditions[48f] and subsequent reaction with the alcohol, resulted in an intramolecular lactone formation (**15**) in quantitative yield (Scheme 17A).

Eventually, Fürstner and co-workers accomplished this difficult esterification reaction (Scheme 17B) by converting the acid to its acid fluoride counterpart (**16**) by treatment with cyanuric fluoride and pyridine, followed by addition of alcohol **14**. Under this protocol the desired ester (**17**) was formed in excellent yield (91%) in a straightforward and highly reproducible manner.



Scheme 17 A) Formation of the lactone byproduct. B) Ester bond formation conditions towards the synthesis of Cruentaren A, according to the method by Fürstner and co-workers.

4.3 Alternative Coupling Reagents

4.3.1 MA026

MA026 is a lipocyclodepsipeptide isolated from the fermentation broth of *Pseudomonas* sp. RtIB026 found in the digestive tract of the rainbow trout (Fig. 10).[142] It exhibits anti-hepatitis C virus (HCV) activity by means of suppressing HCV infection into host hepatocytes by inhibiting the entry process with an IC_{50} value of 4.68 μM.[143] The structure of MA026 was established in 2002 and was found to comprise a 25-membered cyclodepsipeptidic core, a chain peptide composed of six amino acid residues and the lipophilic terminating moiety (*R*)-3-hydroxydecanoic acid.[142] The total synthesis of MA026 was described by Sugawara and co-workers in 2013.[143]

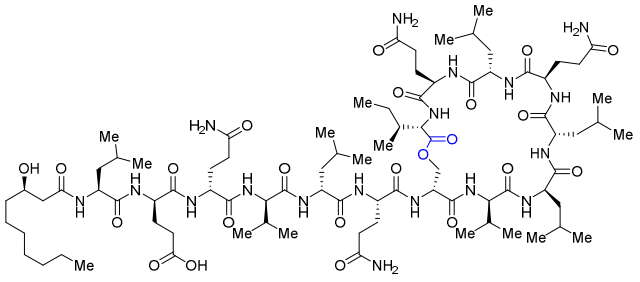
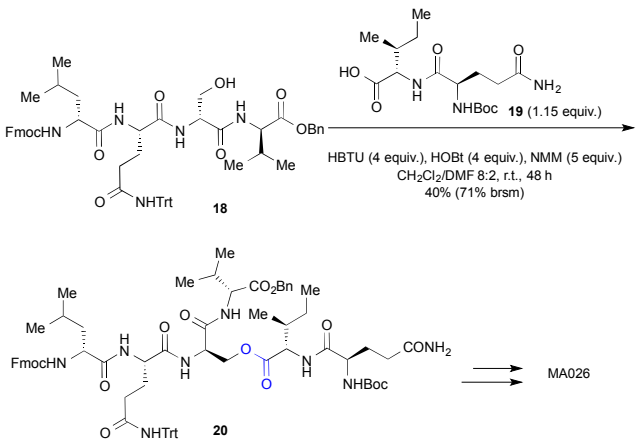


Figure 10 The chemical structure of MA026.

The esterification site for this difficult transformation was between the primary hydroxyl group of a serine residue (**18**) and the free carboxylic group of an isoleucine residue (**19**) (Scheme

18, Table S1, entry 20). The authors reported several failed attempts ascribed to the steric hindrance of both fragments.



Scheme 18 Ester bond formation conditions towards the synthesis of MA026.

Reactive mixed anhydride activations, EDC activation, the Mukaiyama reagent, the Shiina reagent, Yamaguchi esterification and the EDC/HOBt/NMM coupling system were proven unsuccessful.

Notably, the esterification step was achieved in the presence of HBTU, HOBt and NMM, which is a system usually applied to peptide bond formation rather than ester couplings. Nevertheless, with these conditions ester **20** was formed in reasonable yield (40%) with concomitant recovery of the starting alcohol and with minimal epimerization after prolonged reaction time.

4.3.2 Daptomycin

Daptomycin is a lipodepsipeptide antibiotic that belongs to the non-ribosomal peptide family and was isolated from the bacteria *Streptomyces roseoporus* obtained from a soil sample from Mount Ararat in Turkey (Fig. 11).[144] The chemical structure of Daptomycin was established in 1986 by Debono *et al.*,[145] and was found to contain a 10-amino acid ring, a 3-amino acid side chain and a decanoyl lipid side chain at the N-terminus.

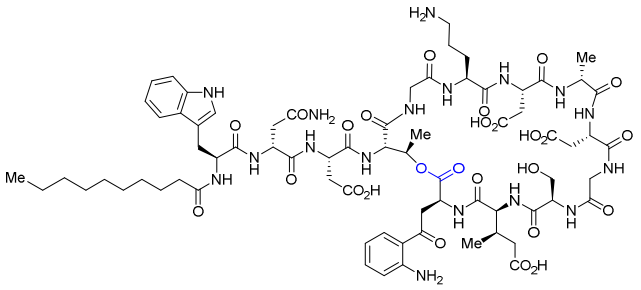
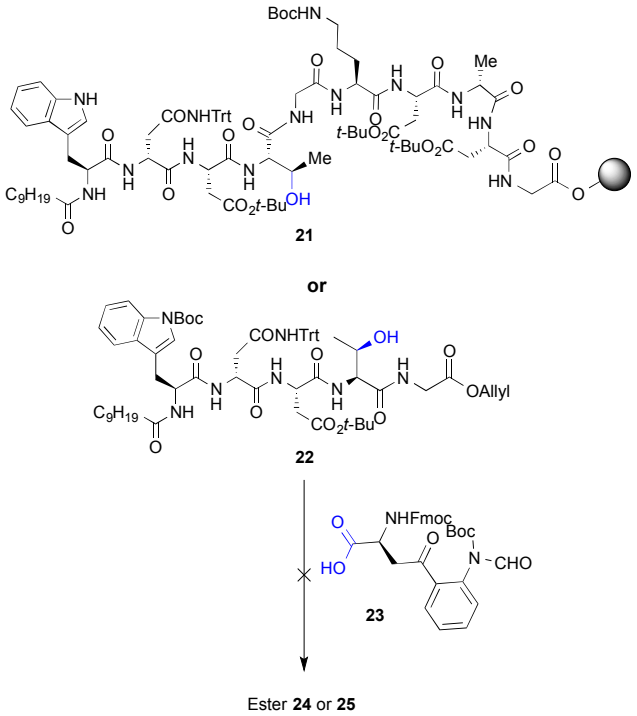


Figure 11 The chemical structure of Daptomycin.

Within the sequence there are two unnatural amino acid residues present, namely kynurenine (Kyn) and 3-methyl glutamic acid (3-mGlu), as well as three amino acid residues bearing the D-configuration. Daptomycin is approved by the FDA for treatment of skin and skin structure infections caused by Gram-positive pathogens and for treatment of bacteremia and right-sided endocarditis caused by *Staphylococcus aureus* including strains resistant to methicillin.[146] The first total synthesis of this cyclodepsipeptide was reported by Li and co-workers in 2013.[144] One of the highlights of the synthesis was undoubtedly the key macrocyclization step, which was achieved via a spectacular chemoselective serine ligation.



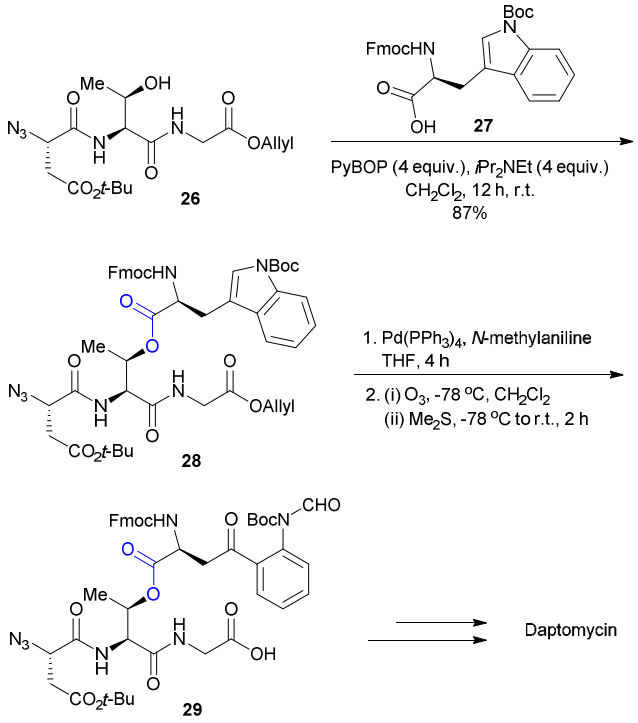
Scheme 19 Failed ester couplings towards Daptomycin

The formation of the depsipeptidic ester bond en route to Daptomycin proved to be the bottleneck of the synthesis, as the researchers had to revise their strategy twice before they finally achieved the key esterification reaction (Scheme 19-20, Table S1, entry 21).[144]

The first approach included the coupling of Fmoc-Kyn(Boc,CHO)-OH **23** with the free hydroxyl group of a resin-supported threonine residue **21** to form ester **24** (Scheme 19). The authors reported numerous fruitless attempts, including carbodiimide chemistry, Mukaiyama esterification and Yamaguchi esterification, which were attributed to the low reactivity of the Kyn residue in combination with the highly congested system induced by the large on-resin peptide fragment. To overcome this pitfall, a hybrid synthesis strategy was adopted, where the ester fragment coupling between alcohol **22** and acid **23** would be performed via solution-phase synthesis and then the generated ester **25** would be linked on a solid-phase pentapeptide. However, again, all efforts proved futile (Scheme 19). At that point, it became clear that the Kyn building block was not suitable for this difficult transformation and yet another strategy had to be designed where the threonine residue of a smaller peptide fragment (**26**) would be coupled with a tryptophan residue (**27**) using standard solution-phase conditions (Scheme 20).

After the esterification, Trp would be converted to Kyn in a single operation via ozonolysis of the indole moiety. Indeed, alcohol **26** was successfully coupled with Fmoc-Trp(Boc)-OH (**27**) in the presence of PyBOP and DIPEA, delivering the desired

ester **28** in excellent yield (87%) and without any epimerization. The choice of PyBOP as the coupling reagent is somewhat unexpected, as this type of phosphonium reagent is commonly used for peptide couplings rather than ester couplings. Subsequently, compound **28** was effectively transformed to the Kyn residue in two steps, via cleavage of the allyl-protecting group and ozonolysis of the generated acid, giving rise to intermediate **29** in excellent overall yield (81%).



Scheme 20 Ester bond formation conditions towards the synthesis of Daptomycin.

4.3.3 FK228

FK228, formerly known as FR-901228, (Fig. 12) is a bicyclic depsipeptide isolated in 1994 from the fermentation broth of *Chromobacterium violaceum*.[147] The structural complexity of FK228 and the remarkable antitumor activity against a range of solid tumor cells immediately established it as a "hot target" for total synthesis. FK228 showed potent inhibitory activity against histone deacetylase (HDAC1) and it was the first natural product HDAC inhibitor advanced to clinical trials as a potential anticancer therapy, before it was terminated at phase II due to adverse cardiotoxicity in patients with neuroendocrine tumors.[148,149] The first total synthesis and structural confirmation of this cyclodepsipeptide was disclosed in 1996 by Simon and co-workers.[150]

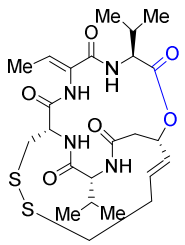
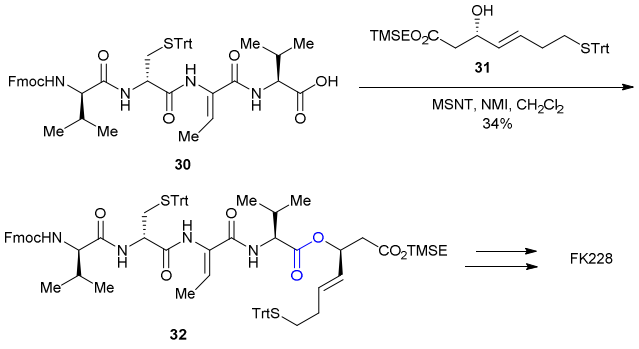


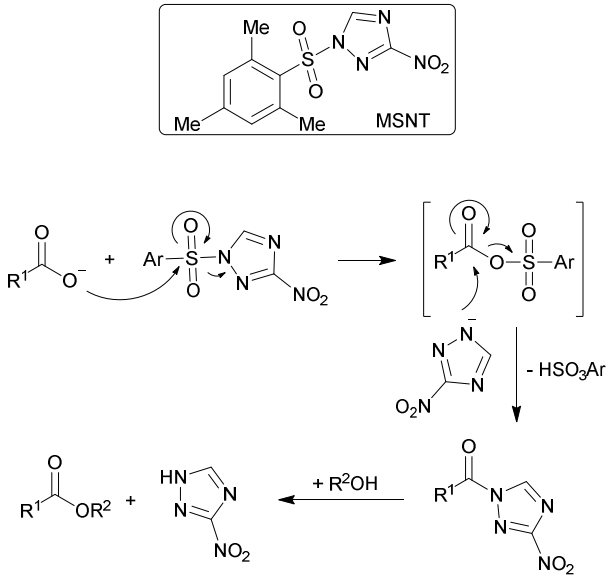
Figure 12 The chemical structure of FK228.

Towards the first total synthesis of FK228 Simon and co-workers employed the Mitsunobu macrolactonization conditions to construct the depsipeptidic ester bond, giving rise to the desired macrolactone in a reported 62% yield. However, when Williams and co-workers[151] adopted the same procedure in an effort to improve and scale up the synthesis, they were unable to reproduce the same result, isolating the same macrolactone in the much lower yield of 24%. Therefore, an alternative and more reliable cyclization protocol was imperative for a streamlined synthesis of the natural product or other unnatural synthetic analogues. Towards this end, Ganesan and co-workers[152] disclosed a strategically different approach in which the ester bond would be formed via an intermolecular fragment coupling and the key cyclization step would be achieved by means of macrolactamization. Nonetheless, the intermolecular coupling of acid **30** with alcohol **31** (Scheme 21, Table S1, entry 22) proved to be as challenging as the intramolecular macrolactonization. After several failed attempts, the authors reported epimerization problems when long reaction times were employed, the best result was obtained with MSNT in the presence of *N*-methylimidazole, which delivered ester **32** in mediocre yield (34%) and concomitant recovery of 42% of unreacted alcohol.



Scheme 21 Ester bond formation conditions towards the synthesis of FK228.

MSNT (Scheme 22) is a relatively uncommon reagent for activation of carboxylic acids and is still not frequently encountered in amide/ester bond formation reactions.



Scheme 22 Chemical structure of MSNT and proposed mechanism for the formation of the ester bond.

Originally, it was applied to phosphorylation reactions in the synthesis of oligonucleotides, in terms of activating the phosphoric acid of a phosphodiester intermediate to form a phosphotriester with the primary hydroxyl group of a nucleoside.[153]

Nevertheless, its full potential as a coupling reagent is starting to be acknowledged with its successful use in peptide bond formation,[154] as well as in esterification reactions.[155] The reagent has better activating properties than DCC or DIC in some cases, leading to high yields with lower levels of epimerization.[156] In the proposed mechanism for the MSNT mediated esterification reaction (Scheme 22), the generated 'active species' is the acyltriazole intermediate which undergoes nucleophilic attack by the hydroxyl group to yield the desired ester.

4.4 Yamaguchi Method

4.4.1 (+)-Migrastatin

(+)-Migrastatin (Fig. 13) is a 14-membered ring macrolide isolated from two different strains of *Streptomyces* sp., MK929-43F1[157] and NRRL 18993.[158] Migrastatin was found to inhibit anchorage-independent growth and migration of human tumor cells *in vitro*.[146,159]

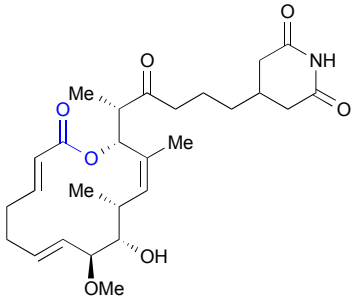
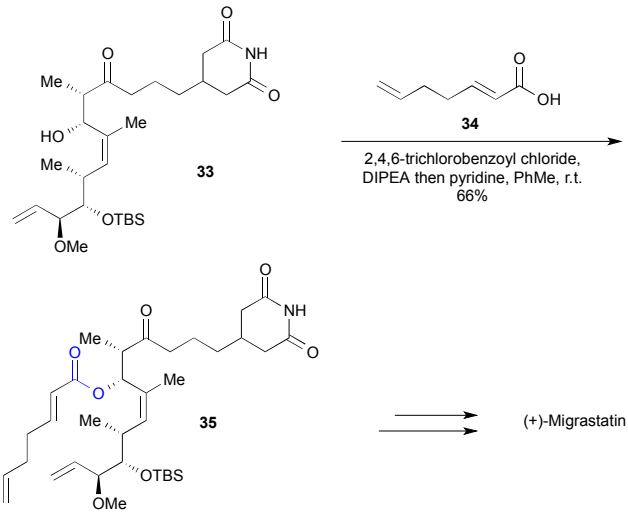


Figure 13 The chemical structure of (+)-Migrastatin.

The absolute stereochemistry of this macrolide was determined in 2002[160] and the first total synthesis was described in 2003 by Danishefsky and co-workers.[161]



Scheme 23 Ester bond formation conditions towards the synthesis of (+)-Migrastatin.

Towards the first total synthesis of (+)-Migrastatin, the condensation of *α*,*β*-unsaturated acid **34** with alcohol **33** turned out to be much more challenging than originally expected (Scheme 23, Table S1, entry 23).[161,162]

Numerous ester formation protocols, namely acid chloride functionalization, DCC or EDC activation, the Mukaiyama reagent and the Keck modification of the Steglich esterification, either led to decomposition of the starting materials or provided an inseparable mixture of the desired ester **35** with the corresponding *β*,*γ*-unsaturated ester.

To account for the latter, the authors invoked the formation of the vinylketene intermediate during acid activation, and following condensation with the secondary alcohol. Ultimately, the key ester bond was constructed via a modified Yamaguchi acylation protocol, using the less nucleophilic pyridine in lieu of DMAP to avoid the formation of the intermediate ketene. Under this optimized protocol, ester **35** was obtained in high yield (66%) without isomerization of the conjugated double bond.

4.4.2 (-)-Laulimalide

(-)-Laulimalide (Fig. 14) is a 20-membered marine macrolide isolated from two different marine sponges, the Indonesian *Hyattella* sp.[163] and the *Cacospongia mycofijiensis*[164] collected from Vanuatu. Initially, Laulimalide was found to exhibit potent cytotoxicity against a panel of drug-sensitive cancer cell lines[163,165] in the low nanomolar range. However, the interest of the synthetic chemistry community culminated when it was recognized as a microtubule-stabilizing antitumor agent, i.e. similar to the anticancer drugs Taxol and Taxotere.[166] The absolute configuration of this macrolide was confirmed through X-ray diffraction studies in 1996[167] and the first total synthesis was disclosed by Ghosh and Wang in 2000.[168] Subsequently, due to the unique structural architecture and the extraordinary biological activity of Laulimalide, several total syntheses of both the natural product and non-natural analogues have been reported.[169,170]

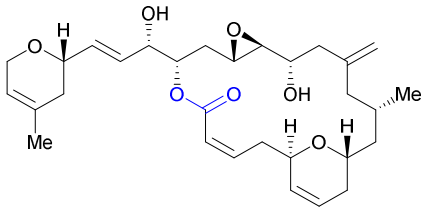
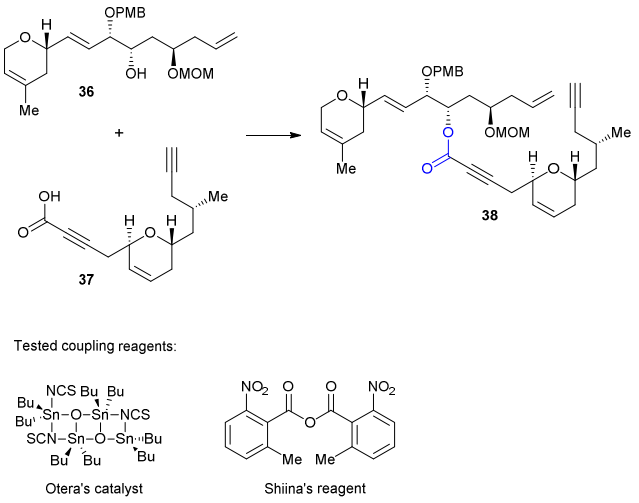


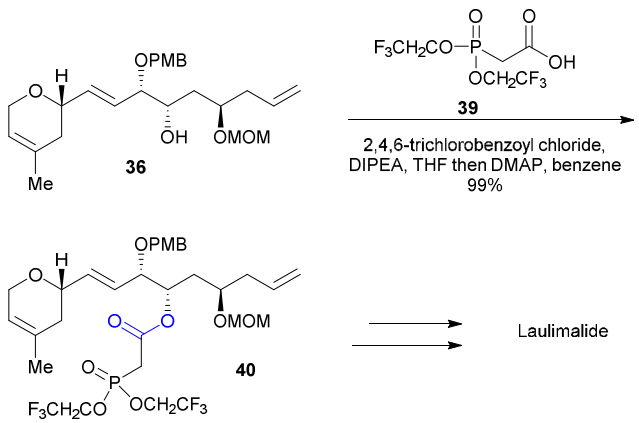
Figure 14 The chemical structure of (-)-Laulimalide.

In an effort to develop a new methodology for the synthesis of complex natural products, Trost and co-workers reported a route towards the total synthesis of Laulimalide wherein the key macrocyclization step was achieved through a novel ruthenium-catalyzed alkene-alkyne coupling.[170e,171] Prior to the cyclization step, a seemingly trivial, according to the authors, ester coupling between fragments **36** and **37** (Scheme 24, Table S1, entry 28) would set the stage to test the closing of the macrocycle. However, yet again, the esterification reaction posed formidable challenges. The Steglich and Kita[172] esterification protocols, conversion of the carboxylic acid to the corresponding acid chloride or fluoride, the use of Shiina's mixed anhydride procedure[78] or the transesterification of the methyl ester of **37** in the presence of the Otera's catalyst[173] failed to deliver the desired ester **38** in acceptable yields. Only the Yonemitsu modification[73] of the Yamaguchi protocol delivered the desired product, albeit in very low yield (18%).



Scheme 24 Unsatisfactory attempts on the esterification reaction

The disappointing results of the ester fragment coupling forced the authors to revise their strategy and attempt to couple alcohol **36** to acid **39** (Scheme 25, Table S1, entry 28). This coupling proceeded smoothly under the conventional Yamaguchi esterification protocol, delivering the desired *β*-ketophosphonate **40** in excellent yield. To account for this result, the authors proposed that the presence of the electron withdrawing substituents on the phosphonate group facilitates the *in situ* formation of the more reactive ketene intermediate that drives the reaction to completion.



Scheme 25 Ester bond formation conditions towards the synthesis of (-)-Laulimalide.

4.5 Mitsunobu Method

4.5.1 Leucascandrolide A

Leucascandrolide A (Fig. 15) is an 18-membered marine macrolide isolated in 1996 from the sponge *Leucascandra caveolata*.[174] The natural product possesses a unique structure comprising two trisubstituted tetrahydropyran rings, with one of them having an appending oxazole-containing side chain. Leucascandrolide A exhibits antifungal activity and potent cytotoxicity *in vitro* against KB carcinoma and P388 leukaemia cancer cell lines (IC_{50} values: 71 nM and 357 nM, respectively). The first total synthesis of this macrolide was reported in 2000 by Leighton[175] and co-workers, followed by several next generation syntheses.[176]

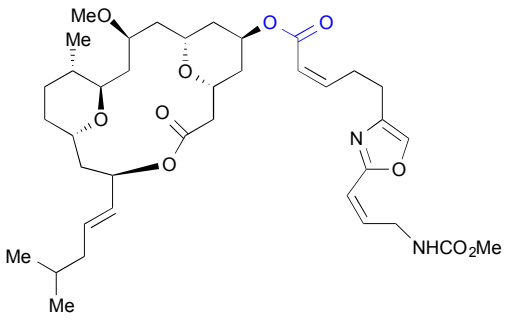
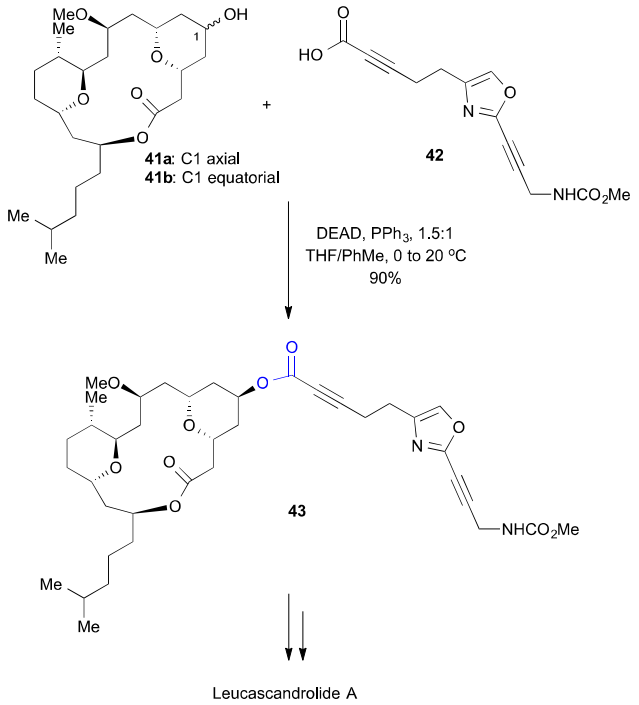


Figure 15 The chemical structure of Leucascandrolide A

In a second generation total synthesis of this complex macrolide, Paterson and Tudge[176c-d] attached the oxazole-containing side chain on the macrocycle via an intermolecular ester coupling between alcohol **41a** and acid **42** (Scheme 26, Table S1, entry 34).



Scheme 26 Ester bond formation conditions towards the synthesis of Leucascandrolide A.

Despite an ostensibly unproblematic coupling setup, the esterification reaction proved challenging from the onset. Numerous acid activation protocols, including acid chloride functionalization, failed to deliver any product and resulted in the complete recovery of the starting macrocyle **41a**. The authors attributed these fruitless attempts to the configuration of the secondary alcohol, being in the axial position of the tetrahydropyran ring. Therefore, an alternative pathway was designed, wherein the secondary alcohol was placed in the equatorial position (**41b**), by means of an oxidation/reduction sequence, and the coupling was achieved by employing the Mitsunobu esterification method, resulting in inversion of the stereochemistry of the ester to the desired axial position. This coupling proceeded without any difficulties, using an excess of DEAD and PPh_3, to afford ester **43** in excellent yield (90%).

4.5.2 Pochonin C

Pochonin C (Fig. 16) belongs to a family of closely related resorcyclic macrolides, Pochonins A-F, isolated in 2003 from the fermentation of *Pochonia chlamydosporia*.[177] From these natural products, Pochonin C stood out by exhibiting potent inhibitory activity in a cellular replication assay against the herpes simplex virus (HSV). Pochonin C is also closely related to another natural product named Radicicol (also known as Monorden) which is a potent HSP90 inhibitor.[178] The first total synthesis and structural elucidation of Pochonin C was disclosed in 2004 by Winssinger and co-workers.[179]

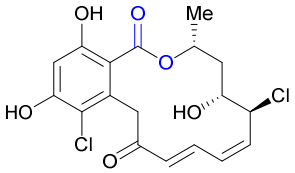
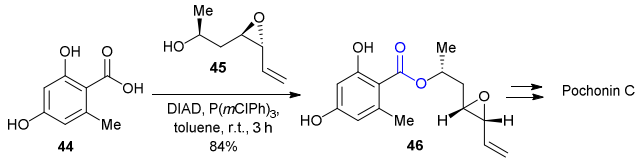


Figure 16 The chemical structure of Pochonin C.

Towards the total synthesis of Pochonin C, Winssinger and co-workers[179,180] chose to perform the esterification reaction between the commercially available unprotected dihydroxytoluic acid (**44**) and the secondary β-epoxy alcohol **45** (Scheme 27, Table S1, entry 32). Notably, the authors claimed that under carbodiimide or Mitsunobu conditions, the reaction worked best when the 2-OH group on the phenyl ring of compound **44** was unprotected. Thorough optimization of the Mitsunobu esterification reaction revealed that under the classical conditions (PPh_3, DIAD in a panel of different solvents, like CH_2Cl_2, THF or toluene) poor selectivity was obtained between the desired ester **46** and a *p*-phenol alkylated byproduct. However, the use of tris(3-chlorophenyl)phosphine[181] instead of the conventional triphenylphosphine gave rise to the desired ester **46** in high yield and with greater than 95:5 selectivity.



Scheme 27 Ester bond formation conditions towards the synthesis of Pochonin C.

4.6 Overview and Analysis

In Table S1, we have compiled a more comprehensive overview of representative complex ester coupling reactions in total synthesis[182-220] including those that have already been mentioned in the text. The table is organized after mode of activation and contains information about key reaction parameters, results, and reported unsuccessful strategies. In order to maintain a relatively concise layout, the list is intentionally not fully comprehensive, but we believe it contains sufficient examples to cover significant structure and reaction space. We of course apologize to those authors whose work has not been referenced in this table or elsewhere in the text. A birds-eye analysis of the couplings collected in Table S1 reveals that, not surprisingly, most of the difficulties reported could be related to sterical congestion and electronical factors, which result in poor reactivity of one or two reaction partners. Examples include couplings en route to the natural products Viequeamide A[187], Halipeptin A[132], Grassypeptolide[195] Rhizopodin[199,200,201,202,203], Filipin III[204], and Lyngbyaloside B[96] – to name only a few (Table S1, entries 8, 16, 17, 25, 26, and 40, respectively). Though the desired products could be isolated in good to excellent yields after optimization of the reaction conditions, it does not seem that there is one strategy that stands out as being superior when it comes to sterically or electronically unfavored fragment couplings.

Poor reactivity does not only result in low conversion of the reaction partners, but can also lead to further problems. A typical problem associated with prolonged reaction times is

epimerization, as e.g. observed in the key esterification step towards the synthesis of FK228[152] (Table S1, entry 22). Other examples for unwanted racemization at the α-carbon can, for example, be found in the synthesis of A83586C,[183] and in the synthetic route towards Ramoplanin A2[104] and Halipeptin A[132] (Table S1, entries 2, 7 and 16, respectively). By appropriate choice of the reaction conditions, the authors were able to optimize the diastereomeric ratio obtained, but the epimerization could not be suppressed completely. By contrast, Ye et al. succeeded in their total synthesis of LL15G256γ[196] in avoiding epimerization at the α-carbon of a serine-unit by a change in the protective group strategy (Table S1, entry 18).

While epimerization as mentioned above is a typical problem in the synthesis of depsipeptides, due to competing azlactone formation during coupling of carbamate protected amino acids, isomerizable double bonds constitute a structural feature that has caused problems in several macrolide syntheses. As mentioned, this was a significant obstacle in the synthesis of (+)-Migrastatin (Table S1, entry 23).[161,162] Likewise, extensive isomerization of the triene was observed in the coupling of the key fragments of Amphidinolide A. As this side reaction is base mediated, isomerization could effectively be suppressed by using Kita's 1-ethoxyvinyl ester conditions (Table S1, entry 36).[209,210,211,212] A change of the esterification protocol could, however, not prevent isomerization of the diene system in a fragment of the macrolide Amphidinolide E. Though the authors tested a plethora of different coupling conditions, protection of the diene moiety by complexation with $(CO)_3Fe$ was necessary to avoid isomerization of the diene to the fully conjugated species. Interestingly, the product isolated was later identified as the C2 inverted stereoisomer. As for the formation of the byproduct observed in the (+)-Migrastatin synthesis (*vide supra*), a ketene intermediate is discussed as being the cause for this epimerization (Table S1, entry 27).[205]

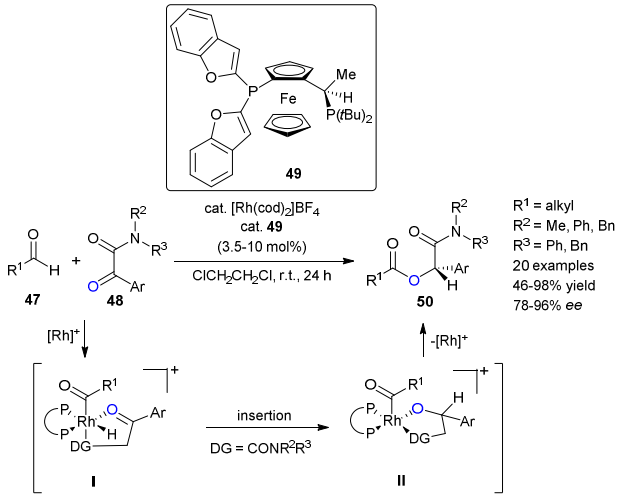
While it is, for example, often possible to anticipate problems arising from sterical or electronical factors, there are also quite a few reports of seemingly trivial ester couplings that turned out to be problematic. The fragment coupling in the synthesis of Cruentaren A, as outlined above, is a good example where good yields were only obtained after extensive experimentation (Table S1, entry 19).[138] Also the ester coupling in the synthesis of Aspercyclide C is described as being more difficult than expected (Table S1, entry 39).[217] It is notable that both these examples involve couplings of phenolic carboxylic acids.

A trend emerging from our literature survey is that the successful execution of complex ester couplings for two large fragments are quite rare; the typical conditions encountered involve the coupling of a relatively small acid fragment with a large alcohol fragment. Such a setup allows for tolerating the use of the acid fragment (and coupling reagent) in large excess in order to achieve sufficient reactivity, however as the acid fragment can typically not be recovered again, this is admittedly sub-optimal. The foundation of these short-comings is not entirely clear. It is, however, typical to observe that seemingly benign changes to the acid component, e.g. by peptide chain-extension from a monomer to a trimer, can drastically reduce reactivity under otherwise identical reaction conditions.

5 Emerging Methods

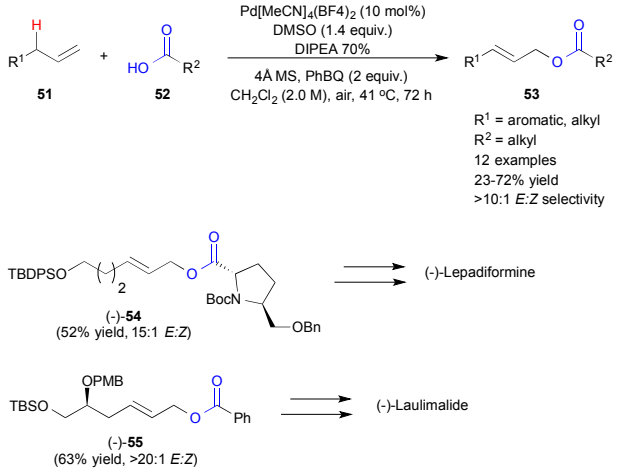
Despite of the application of metal-complexes as successful catalysts for numerous organic reactions, such reagents are only rarely used for esterification reactions. The ability of a metal center to organize two reactants, however, would appear as a promising strategy for effecting complex ester couplings. In this section we provide three recent examples demonstrating the use of metal complexes to facilitate the formation of ester bonds of a complexity relevant to natural product synthesis.

A recent report from Dong and co-workers on a new catalytic enantioselective method for performing intermolecular hydroacylations is noteworthy in the present context.[221] The authors developed a new class of Josiphos-ligands that in combination with rhodium(I) was able to catalyze the coupling between aldehydes (**47**) and aromatic α-ketoamides (**48**) (Scheme 28). The system reported effectively shut down competing aldehyde dimerization and remained effective even for highly congested substrate combinations. Mechanistically the reaction involves oxidative addition of the aldehyde to form an octahedral Rh(III)-complex (**I**, Scheme 28) followed by enantioselective insertion of the carbonyl group into the rhodium-hydride bond (**II**, Scheme 28). The ester (**50**) is then generated through a reductive elimination which also regenerates the Rh(I)-catalyst.



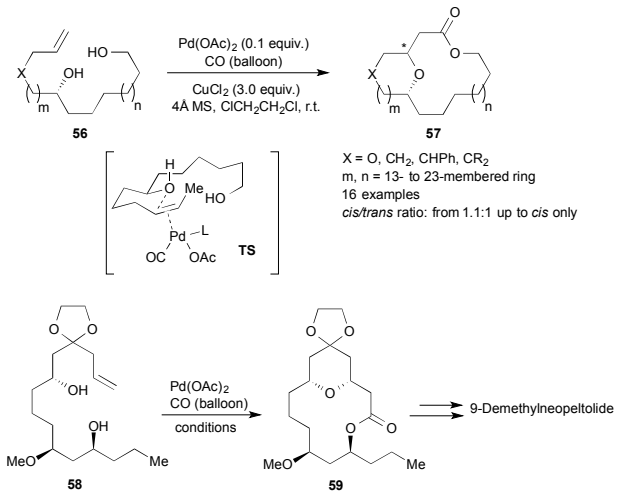
Scheme 28 Coupling of aldehydes with α-ketoamides and proposed transition states.

White and co-workers have reported an efficient catalytic system based on a Pd(II)-sulfoxide complex to perform allylic carboxylations using quinones as oxidants.[222] The method can effectively couple (stereochemically) complex carboxylic acids (**52**) with terminal olefins (**51**) under mild reaction conditions to give linear allylic esters such as **53** (Scheme 29). The internal double bond can be employed as a synthetic handle for further elaboration, allowing the efficient construction of complex structure surrounding the ester linkages. The importance of this methodology is highlighted by the efficient syntheses of compounds **54** and **55** which are intermediates in the total syntheses of the natural products Lepadiformine and Laulimalide, respectively. Within the structural constraints that are compatible with this method it constitutes a novel retrosynthetic option for certain ester-containing structures. The method has also been employed for macrolactonization.[223]



Scheme 29 Linear C-H allylic oxidation for the construction of allylic esters.

Recently, Dai and co-workers reported a palladium-catalyzed cascade alkoxycarbonylative macrolactonization to construct tetrahydropyran/tetrahydrofuran-containing macrolactones.[224] This structural motif has been found in many natural products with interesting biological activities. Starting from relatively easily synthesized alkenediols (**56**) and using $Pd(OAc)_2$ as catalyst and $CuCl_2$ as oxidant under a carbon monoxide atmosphere, a variety of THP/THF-containing macrolactones (**57**) with different ring sizes and substituents were synthesized in one step (Scheme 30).



Scheme 30 Pd-catalyzed cascade alkoxycarbonylative macrolactonization.

Mechanistically, the reaction proceeds through a Wacker-type oxypalladation and CO migratory insertion sequence, giving rise to a reactive acyl-palladium species, which subsequently gets trapped by the remote hydroxyl group to afford the bridged macrolactones. To account for the, in most of the cases, excellent *cis*-selectivity of the reaction, the authors proposed a *trans*-oxypalladation process via a chair-like transition state (**TS**, Scheme 30). With this protocol, diol **58** gave rise to *cis*-only THP-containing macrolactone **59**, which was converted in three steps to 9-Demethylneopeltolide,[225] a known macrolide inhibitor of P388 murine leukemia cells. A potential future extension of this or related methodologies to also perform intermolecular couplings would be a significant new tool for synthesis.

6 Conclusions

The inspiration for this review stems from our own endeavor to construct a depsipeptidic ester bond[226] en route to the total synthesis of a natural product.[227] Canvassing the literature in an effort to identify the best strategy for the formation of the ester bond, it became clear to us that an ester fragment coupling, in spite of the apparent synthetic challenges, would likely constitute a more reliable tool and bypass at least some of the inherent difficulties encountered in macrolactonization approaches, notably the presence of hard-to-predict conformational biases in the cyclization precursors. Moreover, for cyclodepsipeptides specifically, the notion that macrolactamization is preferred over macrolactonization has been documented.[228] We also noted that with regard to macrolides, the literature reports are divided fairly equally between macrolactonization and fragment coupling strategies.

As already mentioned, the successful coupling of large complex fragments through ester bonds remains challenging and in many cases it will be advisable to settle for a compromise with reduced convergency during synthetic planning. This may end up saving time and resources. It is clear that new reaction methodology that can address this challenge would be valuable.

As of current there is no general methodological solution to the "complex ester coupling problem" and therefore scouting reactivity space is likely to be part of any future efforts directed towards the synthesis of complex ester-containing natural products. In this review we have tried to provide an overview of this reactivity space that we missed going in to our own studies, as well as to provide some guidelines that may facilitate its successful navigation. It is our hope that other researchers may use this overview as a reference and inspiration when planning synthetic sequences involving the formation of complex ester bonds.

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Notes and References

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‡ In the context of this review the word ester is synonomous with carboxylate ester.

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