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Review of alternative macrocyclization methods for the synthesis of macrolides

Revisió de mètodes alternatius de macrociclació per a la síntesi de macròlids

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Les ciències tenen les arrels amargues, però molt dolços els fruits.

Aristòtil

Primerament, vull agrair tot el suport rebut per part de la meva tutora, la Dra. Anna Maria Costa Arnau. Sense la teva ajuda aquest treball no hauria arribat a bon port. Gràcies per tots els consells, les indicacions i les hores dedicades a aquest petit projecte.

També vull donar les gràcies a l'Araceli i al Sergi. Els vostres ànims m'han permès seguir treballant com el primer dia. Gràcies per escoltar les meves inquietuds i oferir la vostra mà sempre que l'he necessitada.

REPORT

CONTENTS

1. SUMMARY

Macrolides, macrocyclic lactones containing at least a ring of twelve members, present many interesting features, such as antibiotic, antifungal or anticancer activities, among others. Isolation from natural sources often provides limited quantities of these compounds. Therefore there is great interest in the consecution of their total syntheses. A key step in their preparation is cyclization, since it is often a challenging step. The most common method to form the ring is macrolactonization, although, in recent years, ring-closing metathesis has also been used by many research groups. However, these methods are not always appropriate for all macrolides, depending on their size and structure. In this report, an exhaustive bibliographic search has been undertaken to analyze which alternative methods are being used most often to cyclize these compounds. SciFinder and Reaxys are the databases that have been chosen for this search during the period 2012 to 2017. Several methods have been identified. Apart from macrolatonizations and ring-closing metathesis, the most popular are cross-coupling methods and olefinations. The use of the most common alternatives for the total synthesis of natural product macrolides in the period 2012–2017 has been reviewed.

Keywords: Macrolide, Total Synthesis, Macrocyclization

2. RESUM

Els macròlids, lactones macrocícliques que contenen un mínim de dotze baules, presenten moltes propietats interessants, com activitats antibiòtiques, antifúngiques i anticancerígenes, entre d'altres. L'aïllament d'aquestes molècules de fonts naturals ens proporciona quantitats molt petites d'aquests compostos. Per això hi ha molt interès en les seves síntesis totals. Un pas clau en la seva preparació és la ciclació, ja que sovint és un pas complicat.. El mètode més comú per formar l'anell és la macrolactonització, tot i que, en aquests darrers anys, el tancament d'anell per metàtesi també ha estat usat per molts grups de recerca. Tot i això, aquests mètodes no són sempre adequats per molts macròlids, depenent de la seva mida i estructura. En aquest treball, s'ha realitzat una recerca bibliogràfica exhaustiva per trobar quins mètodes alternatius a la macrolactonització i la metàtesi s'empren més sovint per a la ciclació d'aquests compostos. Les bases de dades escollides per fer la cerca han estat SciFinder i Reaxys, en el període que va del 2012 al 2017. Diversos mètodes han estat identificats. A part de la macrolactonització i la metàtesi de tancament d'anell, els més populars són els acoblaments creuats i les olefinacions. S'ha revisat l'ús de cinc d'aquests mètodes per a la síntesi total de macròlids naturals en el període 2012–2017.

Paraules clau: Macròlids, Síntesi Total, Macrociclació

3. INTRODUCTION

Macrolides, macrocyclic lactones with a ring of twelve members or more,[1] present a number of interesting properties that make them especially useful in many areas.[2] For example, we can find macrolides with antibiotic, cytotoxic and antiangiogenesis properties, or having pheromone and insecticide activities. Since the first isolation of a macrolide in the 1950s, their properties have been investigated by many research groups, and many applications for this class of compounds have been found, particularly in drug discovery. For instance, Erythromycin A and its semi-synthetic analogs are used to treat bacterial respiratory infections, and Amphotericin B is a polyene antifungal drug. Other examples are Spinosyn A and D that are used against a wide variety of insects, and Epothilone A, an analogs of which has already been approved for the treatment of breast cancer (**Figure 1**).

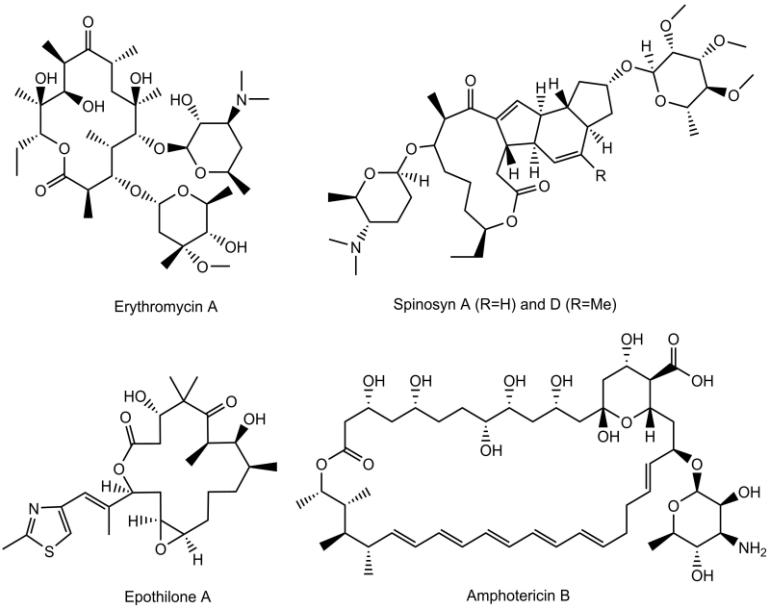
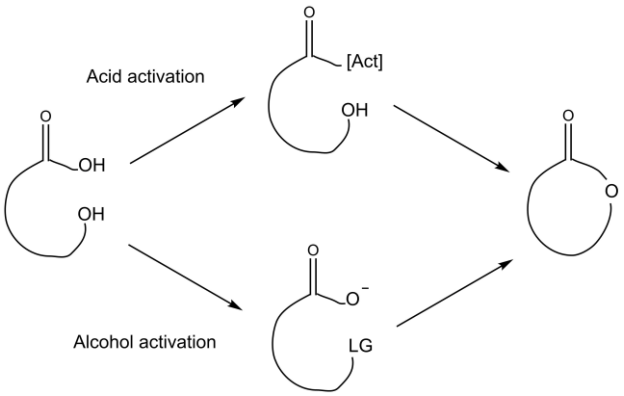


Figure 1. Examples of Macrolides.

Because of the minute amount of these compounds available by isolation from the natural sources, the total synthesis of macrolides is crucial to access enough quantities to study them further. Total synthesis of such complex molecules involves many steps and the order of these steps is important for the success of the synthesis. One of the most important steps is the formation of the ring, not always an easy task, although nowadays there are a wide range of methods available for macrocyclization, such as macrolactonization, the method traditionally used to construct the ring.

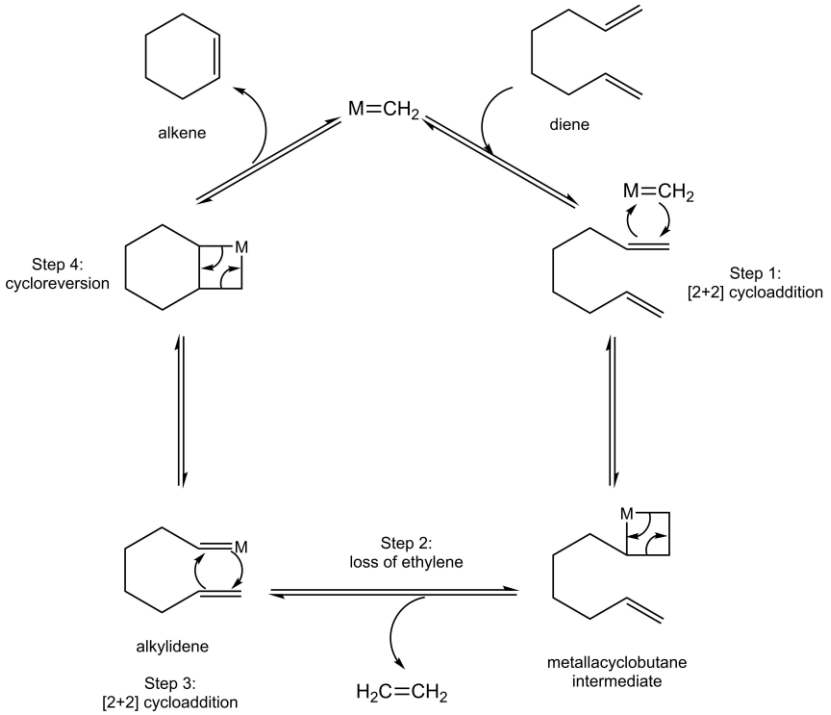
Macrolactonization[2] involves the reaction of a hydroxyl and a carboxylic acid group from a seco-acid. The activation of either the alcohol or the carboxylic acid terminal group is usually required to achieve the reaction (**Scheme 1**). Depending on the group activation, we can have different macrolactonization methods. Nowadays, some of the most commonly used methods in the synthesis of macrolides are the Yamaguchi, Shiina or Kita–Trost procedures, if the activated group is the acid, and the Mitsunobu protocol, if the activated group is the hydroxyl. The main problem that macrolactonization reactions present is the competition between intramolecular and intermolecular reactions. To solve this, the reaction is performed under high dilution conditions: the substrate is slowly added over many hours to a large volume of solvent. Another alternative method to avoid this situation is to immobilize the seco-acid, or an activated intermediate, on a solid support.



Scheme 1. Cyclization by macrolactonization.

Although macrolactonization is the typical method for the construction of a macrolide ring, in the last decade ring-closing metathesis[3] has been used more and more.

Ring-closing metathesis (RCM) is a cyclization method via carbon-carbon bond formation. It involves the reaction of two terminal alkenes (**Scheme 2**). The main advantage of RCM is the compatibility with most functional groups. In addition, it generates a double bond in the molecule that can be transformed into another functional group. However, controlling the stereochemistry of this double bond and finding appropriate reaction conditions is not an easy task. The reaction needs a catalyst to guarantee its success. Although the most common catalysts are ruthenium complexes, highly reactive molybdenum Schrock catalysts are also used.



Scheme 2. Cyclization by ring-closing metathesis.

Although macrolactonization reactions and ring-closing metathesis are commonly applied to form the ring of complex macrolides, their implementation is not always straightforward and application to a particular substrate can be problematic and low-yielding. Taking into account that formation of the ring is usually one of the last steps of a total synthesis, this can severely affect its global yield. Due to our involvement in the total synthesis of several macrolides,[4–8] our group has a long-standing interest in macrocyclization reactions in general and

macrolactonizations[9] in particular, a reaction which we have used regularly to form the lactone ring of naturally-occurring macrolides synthesized in our labs. Apart from the two methods described previously, other macrocyclization reactions are employed in the total synthesis of macrolides, although to a lesser extent. Knowing which methods are available to form the ring of complex macrolides and their advantages and disadvantages compared to the most standard methodologies will help us choose the best macrocyclization strategy for a particular substrate and streamline its total synthesis.

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4. OBJECTIVES

Considering the interest of our research group in the total synthesis of macrolides, our main objective is the analysis and review of alternatives to macrolactonization and RCM for the formation of the ring of a macrolide. To achieve this, the following steps were taken:

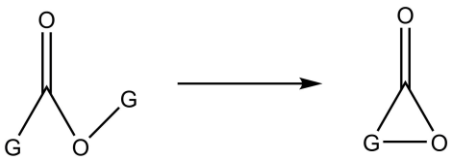
- Exhaustive review of the literature (2012–2017) using the Reaxys and SciFinder databases.
- Analysis of the results and organization of the references into tables.
- Review of the literature found for five selected methods.

5. METHODS

To fulfill our objective, we first searched the literature for reports on the total synthesis of macrolides that meet specific structural characteristics. We considered only natural-product macrolides and excluded cyclodepsipeptides, macrodiolides and ansa-macrolides. In addition, macrolides with a fused benzene ring were not taken into account. The search was made in the recent literature (2012–2017) and using two chemical databases: SciFinder and Reaxys.

First, we searched using the keywords “total synthesis macrolide” on both databases. This search was filtered by year, journal name and type of document. Moreover, we searched by reaction using **Scheme 3** as template on Reaxys. In that case, the filters that were applied are by year, type of document and number of steps.

To follow up, the results were analyzed visually one by one to ascertain whether the macrolide fulfilled the desired characteristics. Because of the fact that the search was made twice using different strategies, some results were duplicated and it was necessary to reject those. Finally, a table was generated to organize the data.



Scheme 3. Template used to search by reaction.

6. RESULTS AND DISCUSSION

After searching (for the period 2012–2017) for the total synthesis of macrolides published in the literature (as discussed in the Methods Section), the data was organized into tables (**Tables 1-3**). Tables 1 and 2 show the results of macrolactonization and RCM respectively, whereas Table 3 shows all the results of the alternative methods of cyclization. As observed in **Figure 2**, once the results are analyzed, we can confirm that the most used methods to cyclize the macrolide ring are macrolactonization, RCM and an alternative RCM method: ring-closing alkyne metathesis (RCAM). However, we can also conclude that coupling methods, such as the Stille, Heck or Suzuki couplings, are also frequently used, while methods that involve the formation of a double bond to close the ring, such as the Horner–Wadsworth–Emmons (HWE) or Wittig reactions, are less used. Finally, cyclizations using other methods are scarce.

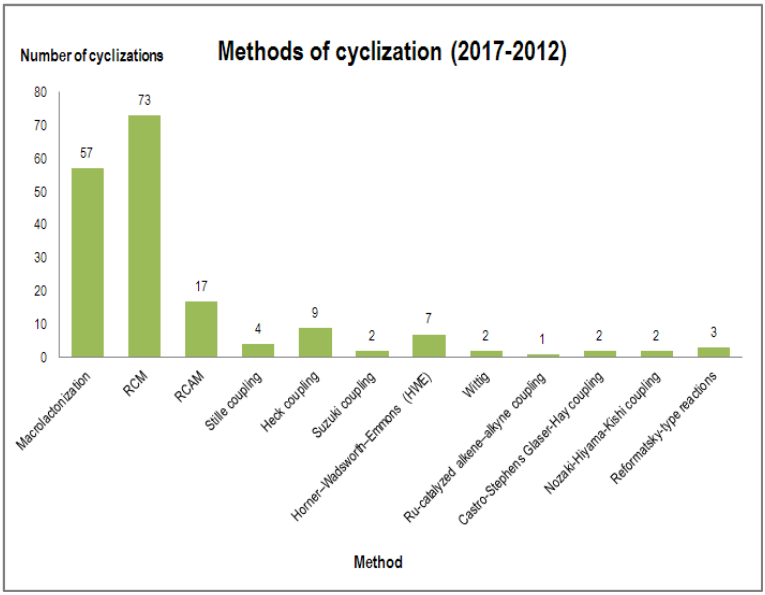


Figure 2. Methods of macrolide ring formation (2017–2012).

Figure 3 shows the number and type of cyclizations per year. As can be seen, the use of alternative methods has increased in the last years. However, macrolactonization and RCM remain the preferred methods to construct the ring of macrolides.

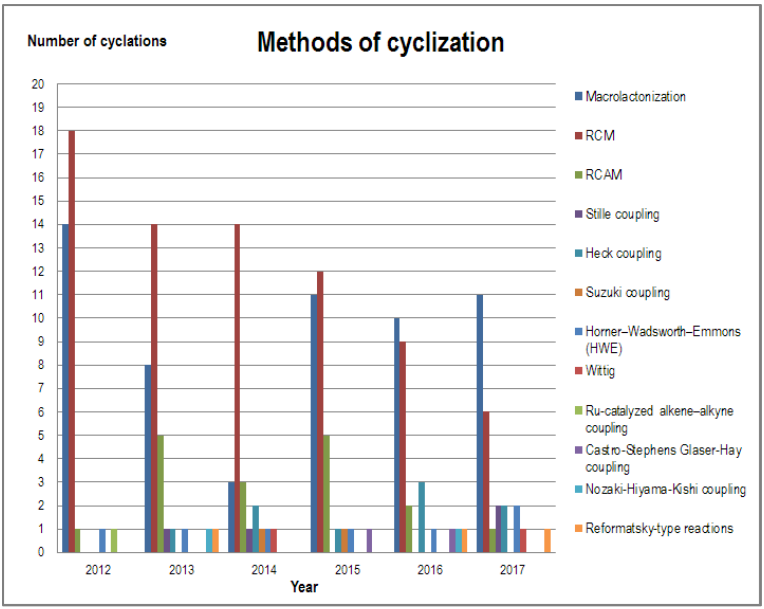


Figure 3. Methods of macrolide ring formation.

Particularly, a peak in the use of RCAM between the years 2013 and 2015 is observed. This can be attributed to the studies performed by Alois Fürstner, who has developed this method for the total synthesis of natural products. In addition, the use of cross couplings (Stille, Heck and Suzuki) and methods that form double bonds (Wittig and HWE) has increased in the last years. However, no Negishi cross coupling was found for the ring formation of macrolides, probably because of the difficulty of the preparation of the required organozinc compound. Another reaction that was not found is the Julia–Kocienski reaction, despite the fact that it is commonly used to form alkenes.

Moreover, only two of the alternative methods found forms a new stereocenter: the Nozaki–Hiyama–Kishi coupling and reactions that involve attack of an organometal to an aldehyde.

In the next pages, we will review the most used alternative methods for macrolide ring formation in the period 2012–2017. In addition, whenever possible, a comparison of the different

methods of ring formation (including macrolactonization and RCM) for a given compound is made.

2017	2016	2015	2014	2013	2012
Yamaguchi: Leptolyngbyolide C[10] Benzylbryostatin 10[a,11] Biselide A[12] Dendrodolide L[13] **Shiina:** Sacrolide A[14] Pestalotioprolide C[15] Halichondrins A-C[16] Aspergillide D[17] **Kita-Trost:** Amphidinolide E[4] **Keck:** Polycavernosides A and B[18] **Others:** Tylactone[19]	**Yamaguchi:** Sch-725674[20] Amphidinolide Q[21] (+)-Brefeldin A[22] Mandelalide A and Isomandelalide A[23] **Shiina:** Mandelalide A[24] (+)-Cladospolide D[25] Thuggacin A[26] Koshikalide[27] δ^{12}-Prostaglandin J_3[a,28] **Boeckman**: Several macrolide antibiotics[29]	**Yamaguchi:** (-)-A26771B[30] Recifeiolide[31] Enigmazole A[32] **Shiina:** Amphidinolide K[8] Paleo-soraphens[33] Dictyostatin[34] **Boeckman:** Lyngbouilloside[35] (-)-Lyngbyaloside B[36] **MNBA:** (-)-Eushearilide[a,37] **Others:** Musky macrolactones[38] Amphidinolide P[39]	**Yamaguchi:** (-)-Leiodermatolide[39] Spinosyn A[40] **Shiina:** Thuggacin B[41]	**Yamaguchi:** (+)-Neopeltolide[42] (+)-Aspicilin[43] Spirastrellolide A[44] Amphidinolides T1, T3, T4[45] Lactidomycin [46] **Shiina:** Dictyostatin[47] **Mitsunobu:** (+)-18-epi-Latrunculol A[48 49] **Others:** Amphidinolide P[50]	**Yamaguchi:** Spirastrellolide A methyl ester[51] Palmerolide C[52] Bafilomycin A1[53] Epothilones B and D[54] Ivorenolide A[55] Amphidinolide F[56 57] FD-891[58] (+)-Neopeltolide[59] (+)-Aspicilin[60] Aspergillides A and B[61] (-)-Exiguolide[62] **Shiina:** (-)-Hybridalactone[63] Halichondrin C[64 65] **Kita:** Amphidinolide W[66]

(a) Analog or derivative synthesis

Table 1. Macrolides prepared by macrolactonization in the period 2012–2017.

2017	2016	2015	2014	2013	2012
(+)-Methynolide[67]	Leiodolide A[73]	Desmethylerythromycin[a,81]	FD-891[96]	Epothilone D[111]	Balticolid[124]
Salinomycin[a,68]	Dendrodolide-L[74]	Tiacumicin B[82]	Ivorenolide B[97]	6-Deoxyerythronolide B[112]	Pikromycin[125]
Carolacton[a,69]	(-)-Lyngbyaloside B[75]	Mycalolides A and B[83]	Iriomoteolide 3a[98]	13-Demethyllyngbyaloside B[113]	6-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione[126]
Dodecanolides[70]	C-4-epi-Sch725674[76]	Pestalotioprolide A[84]	Sekothrixide[99]	(-)-Amphidinolide O[114]	(-)-Zampanolide[127]
Epothilones[a,71]	Gliomasolide C[20]	Lyngbyaloside C[85]	Amphidinolide Y[a,7]	(-)-amphidinolide P[114]	Palmerolide A[128]
Bryostatins[72]	Sch725674[76,77]	Ipomoeassin F[86–89]	Sch725674[100,101]	(+)-Neopeltolide and 8,9-Dehydroneopeltolide[115]	Dihydrocineromycine B[129]
	Tetradecen-13-olide[a,78]	Paleo-soraphens[33]	aspergillide B[a,102]	Yuzu lactone, Ambrettolide and Epothilone C[116]	Ripostatin B[130–133]
	Sporiolide B[79]	(-)-Exiguolide[90,91]	Carbohydrate-fused macrocycles[103]	Aspergillides A, B and C[117]	Ripostatin A[134]
	2,11-Cembranoid[80]	(+)-Neopeltolide[92]	Aspicillin[104]	Pladienolide B[118]	Iriomoteolide 1a[135]
		Migrastatin and Isomigrastatin [93]	Pectenotoxin-2[105]	Bafilomycin[119]	FD-895[136]
		Cytochalasin B[94]	Ripostatin[a,106]	Lyngbyaloside B[120]	Amphidinolactone A[137]
		Amphidinolide P[95]	Carolacton[107]	Carolacton[121]	Amphidinolides B, G, and H[138]
			Dendrodolide A[108 109]	Tulearin C[122]	Gephyromantolide A[139]
			Dihydroecklonialactone B[110]	Soraphen A[a,123]	(+)-Neopeltolide core[140]
					(+)-Aspicilin[141]
					Isomigrastatin[142]
					Aspergillide A[61]
					4,8-Didesmethyl telithromycin[143]

(a) Analog or derivative synthesis

Table 2. Macrolides prepared by RCM in the period 2012–2017.

	2017	2016	2015	2014	2013	2012
RCAM	(+)-Aspicilin[144]	Enigmazole A[145] Ivorenolide A[146]	Tulearin A and C[147] Dihydrocineromycin B[148,149] Brefeldin A[150] Ivorenolide B[151] Brefeldin A[150]	Mandelalide A[152,153] Leiodermatolide[154] Cucujolide V[155,156]	Lactimidomycin and Isomigrastatin[157] Amphidinolide F[158,159] WF-1360F[160] Polycavernoside A[161] A26771B[162]	Leiodermatolide[163]
Stille coupling	Biselyngbyaside[164] Chivosazole F[165]			Biselyngbyolide[166,167]	Truncated superstolide A[168]	
Heck coupling	Pestalotioprolide G[169] Mandelalides A-D[170]	Maltepolide C[171] Biselyngbyolide B[172] (-)-Mandelalide A[173]	Palmerolide A[174]	Kulkenon[175] Mandelalide A[176]	Palmerolide A[177]	
Suzuki coupling			Tiacumicin B[178]	Ripostatin [a,106]		
HWE	Gliomasolide E[a,179] Neomaclafungin A[180]	Brefeldin A[181]	(-)-Marinisporolide C[182,183]	Mandelalide A[184]	Lactimidomycin[a,185,186]	(-)-Zampanolide and (+)-Dactylolide[187]
Ru-catalyzed alkene–alkyne coupling						Laulimalide[188]
Wittig	Aspicillin[189]			(+)-Chloriolide[190]		
Castro–Stephens Glaser–Hay coupling		Ivorenolide A[191]	Lactimidomycin[192]			
Nozaki–Hiyama–Kishi coupling		Sacrolide A[193]			Cethromycin[a,194]	
Organometal addition to an aldehyde	Aplyronine A[195]	Borrelidin [a,196]			Epothilone D[197]	

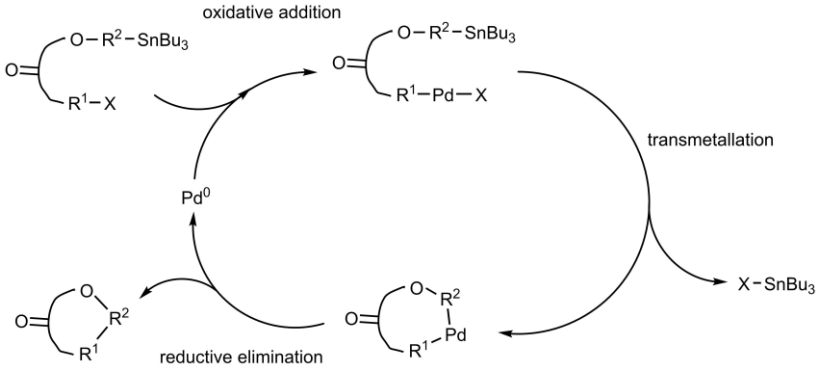
(a) Analog or derivative synthesis

Table 3. Macrolides prepared by other methods (2012–2017).

6.1. MACROCYCLIZATION VIA STILLE COUPLING

The Stille coupling[198] is a palladium-catalysed cross-coupling reaction that involves the reaction of organostannanes and aryl or vinyl halides to form a new C–C bond. In 1976, the first report of the reaction was made by Eaborn and Kosugi. However, Stille and his co-workers transformed it into a standard method in organic synthesis. The use of the Stille coupling has increased in the last few years and is used more and more to construct a variety of ring systems.[199–202] Its tolerance towards most functional groups made the Stille coupling an effective reaction, displaying high selectivity.

A scheme of Stille coupling is shown in **Scheme 4**. An oxidative addition between Pd^0 and the vinyl halide part in the molecule forms an intermediate species that transmetallates with the organostanne. Transmetallation is believed to be the slow step of the reaction, as the only observable species is the vinylpalladium intermediate. Later, a reductive elimination forms the macrolide ring.



Scheme 4. The Stille coupling to form a macrolide.

The total synthesis of natural products using a Stille reaction as the macrocyclization step has been reviewed, although the recent literature is not covered.[199–202]

Truncated Superstolide A (**Figure 4**) was successfully synthesized using Stille coupling as the macrocyclization step in 2013 by Jin and his co-workers.[168] Superstolides A and B were isolated in minute amounts from the deep-water marine sponge *Neosiphonia superstes* and exhibit a potent antiproliferative effect against several tumor cell lines. Several years ago, Jin initiated research towards the total synthesis of Superstolides A and B. Because of the structural complexity of the target molecules, it would be extremely challenging to develop a

practical synthesis that provides adequate amounts. Therefore they decided to develop first a practical total synthesis of an analog.

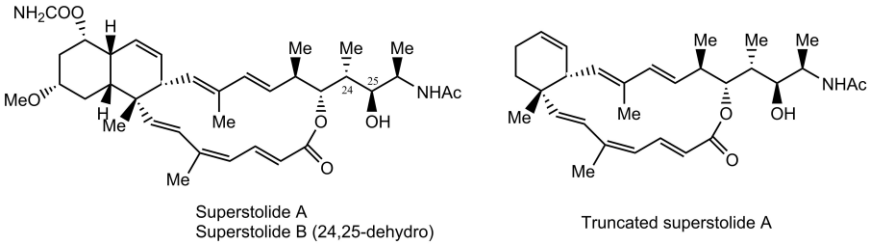
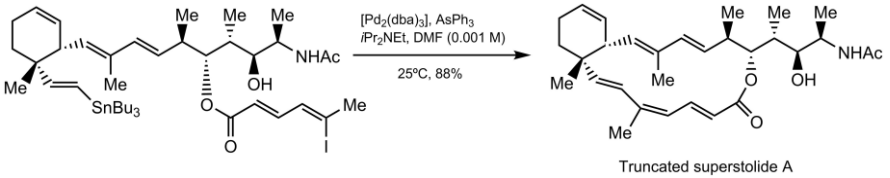


Figure 4. Superstolide A, Superstolide B and truncated Superstolide A.

Considering the drawbacks of macrolactonization in the previous studies, they used the Stille coupling to form the ring. The Stille macrocyclization of truncated Superstolide A was achieved in excellent yield (88%), using the conditions developed by Farina in 1991[203] (**Sheme 5**).



Scheme 5. Cyclization step to form truncated superstolide A.

In 2014, the research group of Suenaga achieved the first total synthesis of Biselyngbyolide A,[166] an 18-membered marine macrolide with significant biological activities. Using a similar approach, they published the total synthesis of Biselyngbyolide B[167] in 2016 and of Biselyngbyaside in 2017[164] (**Figure 5**).

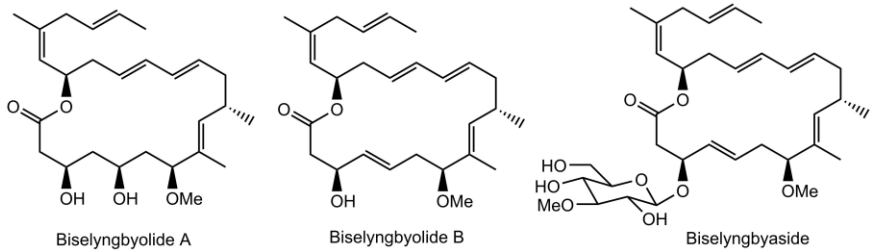
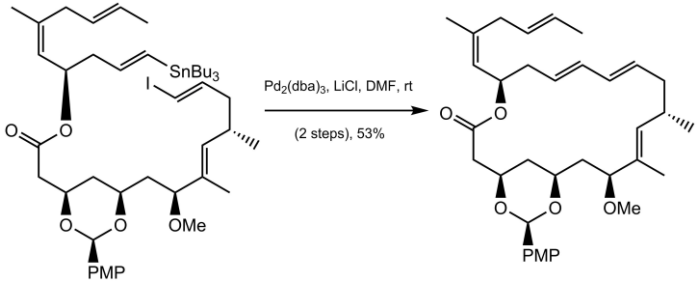


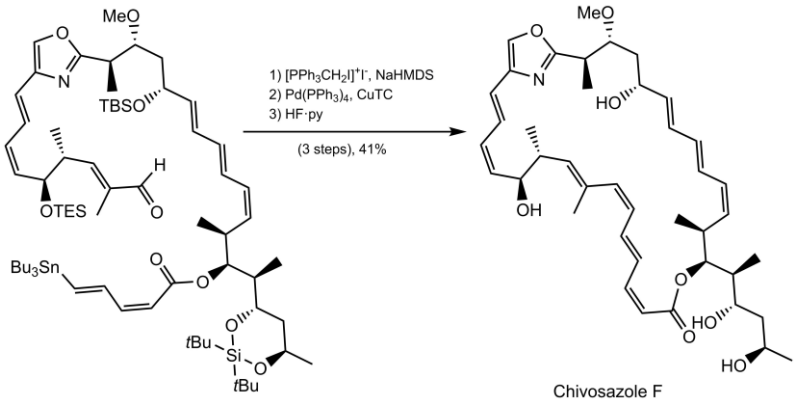
Figure 5. Biselyngbyolide A, Biselyngbyolide B and Biselyngbyaside.

In all of these syntheses, they build the ring using the Stille coupling (**Scheme 6**). The first intention was to form the ring using macrolactonization, but they could not obtain the hydroxyacid precursor because the conjugated diene was unstable under the oxidation reaction conditions. In the three cases, the yield achieved was 53%, 94% and 81% respectively.



Scheme 6. Cyclization step to obtain protected Biselyngbyolide A.

Chivosazole F was synthesised by the Paterson research group in 2017.[165] They first wanted to use a Horner–Wadsworth–Emmons reaction to form the C2–C3 bond of the macrolide. This would avoid manipulating a vulnerable (*Z*,*E*,*Z*,*E*)-tetraenoate motif. However, the required aldehyde could not be prepared because of the instability of the precursor. The researchers chose a Stille coupling as an alternative. Finally, the cyclization of Chivosazole F was achieved in 41% of yield (three steps) (**Scheme 7**).

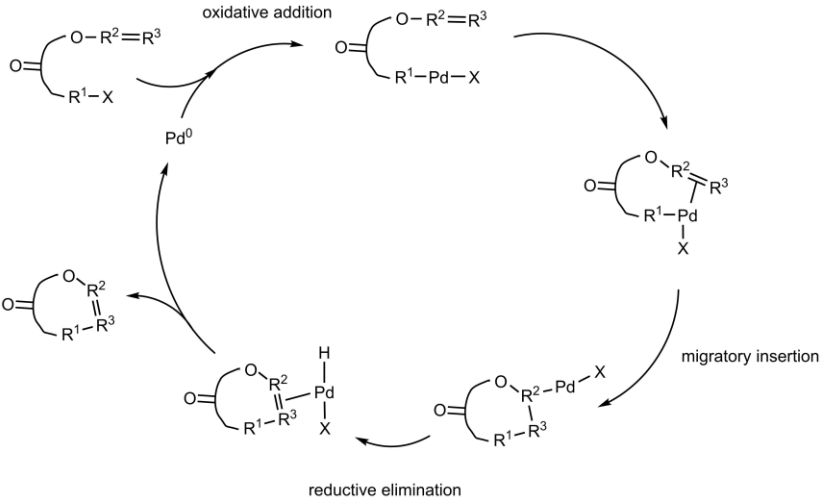


Scheme 7. Cyclization step to form Chivosazole F.

6.2. MACROCYCLIZATION VIA HECK COUPLING

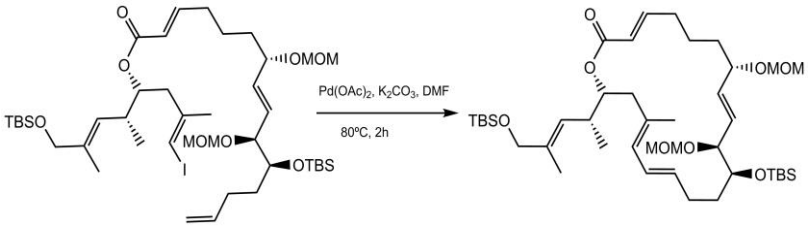
The Heck coupling[204] is a palladium-catalyzed cross-coupling reaction between an aryl or vinyl halide with an alkene in the presence of a base which results in the formation of a C–C bond. The Heck coupling is also called Mizoroki–Heck reaction as the result of the investigations that Mizoroki and Heck made independently. However, Heck developed the general method that is used nowadays. Although small variations of substrates or ligands can change dramatically the results of the reaction, the Heck reaction is one of the most versatile reactions in the synthesis of natural products.

In **Scheme 8** we can see the construction of a macrolide using the Heck coupling. In most cases, Pd^0 is prepared from palladium complexes by reduction. An oxidative addition is required to insert palladium in the aryl or vinyl halide bond. In the following step, the alkene coordinates with Pd and a migratory insertion follows. Finally, a reductive elimination forms the ring of the macrolide. The first Heck coupling used in the total synthesis of a macrolide was reported by Zeigler and co-workers in 1981 in their total synthesis of carbomycin B.[205] Since then many research groups have used the Heck coupling as the macrocyclization step, and the recent literature has been reviewed.[199]

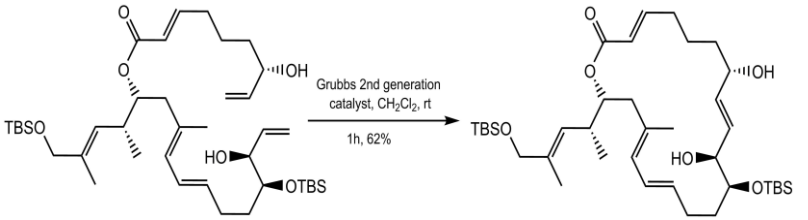


Scheme 8. The Heck coupling to form a macrolide.

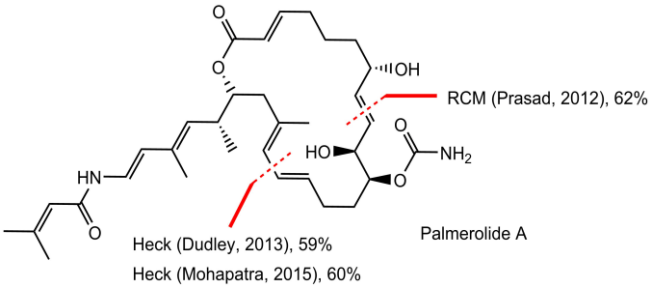
Palmerolide A was prepared by the research groups of Dudley[177] and Mohapatra,[174] using a similar Heck macrocyclization (**Scheme 9**). Furthermore, Palmerolide A has also been synthesized using RCM by Prasad in 2012.[128] The cyclization yield was 62% and Grubbs second generation catalyst was used (**Scheme 10**). **Scheme 11** shows the structure of Palmerolide A and a comparative between the different macrocyclization methods used.



Scheme 9. Cyclization step using the Heck coupling to form protected Palmerolide A.[174]

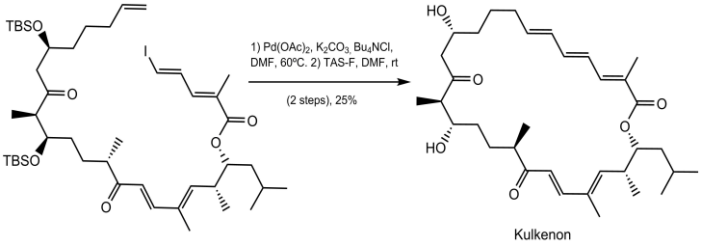


Scheme 10. Cyclization step using RCM to form protected Palmerolide A.[128]



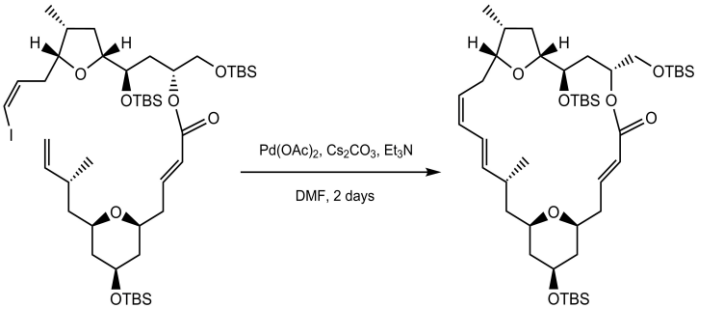
Scheme 11. Palmerolide A: comparison of methods used for formation of the ring.

In 2014, Kulkenon was prepared by Kalesse.[175] A Heck macrocylization, followed by deprotection, permitted the synthesis of Kulkenon in 25% yield for the two steps (**Scheme 12**). The Heck reaction afforded an inseparable mixture of isomers that could only be separated after deprotection of the two TBS groups. The authors offer no explanation as to the identity of the isomers formed during the cyclization. This represents the first total synthesis of Kulkenon and permitted the assignment of the correct configuration of this interesting natural product.



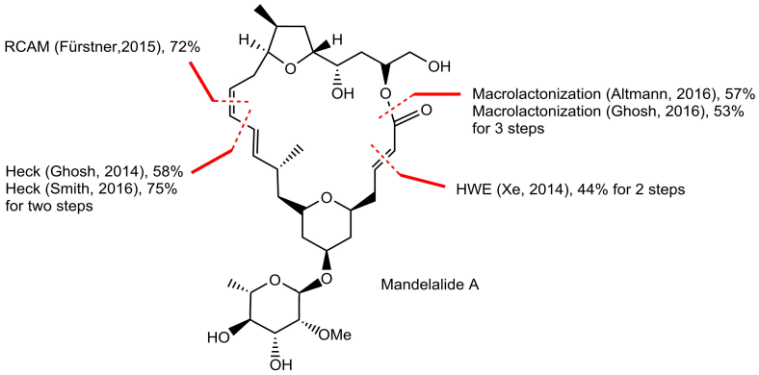
Scheme 12. Last steps in the total synthesis of Kulkenon.

Mandelalide A was also prepared using an intramolecular Heck reaction by two different research groups in 2014 and 2016 (**Scheme 13**). Gosh and co-workers achieved a 58% yield in the Heck macrocyclization step.[176] This allowed them to complete the total synthesis of Mandelalide A aglycone. The research group of Smith prepared the natural product macrolide using similar conditions achieving a 75% yield in this step.[173] They applied the same approach to the synthesis of Mandelalide L, an analog of Mandelalide A.



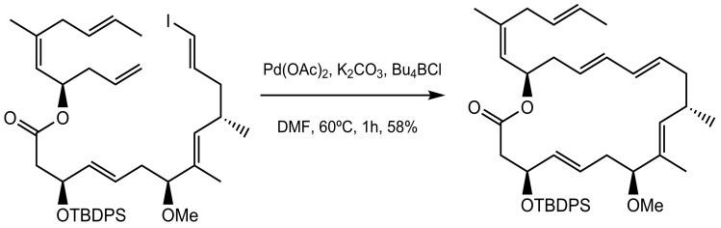
Scheme 13. Cyclization step to form the proposed structure of Mandelalide A aglycone.[176]

In addition, Mandelalide A was also synthesised using a macrolactonization in 2016 by two research groups. Ghosh and his co-workers used a Yamaguchi macrolactonization to achieve the protected macrolide in 56% yield.[23] Altmann's research group tried to employ Yamaguchi, Keck and Corey–Nicolaou macrolactonization protocols but they only obtained traces of Mandelalide A. Fortunately, the Shiina conditions allowed them to obtain a 57% yield in the cyclization step using high-dilution conditions with 4-fold excess of MNBA and 10-fold excess of DMAP.[24] However, the double bond conjugated to the carboxylic acid group partially migrated to the β,γ position and an isomerization step was needed. Moreover, Mandelalide A was also cyclized using a HWE reaction,[184] as explained in section 6.5 and a RCAM[152,153] (**Scheme 14**).



Scheme 14. Mandelalide A: comparison of methods used for formation of the ring.

Biselyngbyolide B was also macrocyclized using a Heck reaction in 2016 by Goswami.[172] They studied the optimum reagents needed for this transformation and discovered that a combination of $Pd(OAc)_2/K_2CO_3/Bu_4NCl$ in DMF afforded the desired macrocycle in 58% yield (**Scheme 15**).



Scheme 15. Cyclization step to form protected Biselyngbyolide B.

The same year Ghosh prepared Maltepolide C, a macrolide that was first isolated from the fermentation broth of the Myxobacterium *Sorangium Cellulosum* (**Figure 6**).[171] The macrocyclization was achieved in 55% yield over two steps (**Scheme 16**).

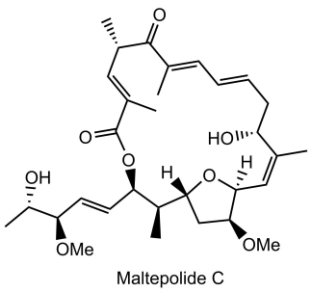
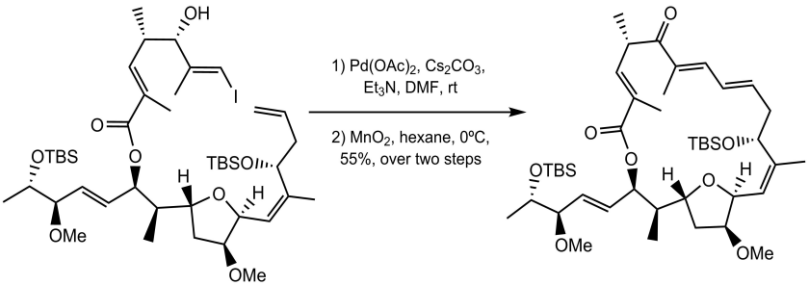
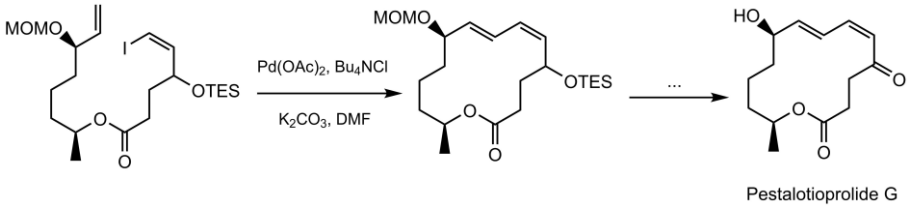


Figure 6. Structure of Maltepolide C.



Scheme 16. Cyclization step to form protected Maltepolide C.

Pestalotioprolide G was synthesized in 2017 by Goswami.[169] The authors chose a Heck macrocyclization, instead of the more common macrolactonization approaches for two reasons. First, the synthetic route would be more convergent, and second, it would avoid the difficult synthesis of the acid functionality at C1 from its corresponding alcohol in presence of a sensitive diene moiety. After screening a number of reaction conditions, they only achieved a 25% yield in the cyclization. They attributed this low yield to the ring strain which was expected to develop during the installation of the diene moiety. This is the first report of the construction of such a 14-membered ring system using a Heck macrocyclization (**Scheme 17**).

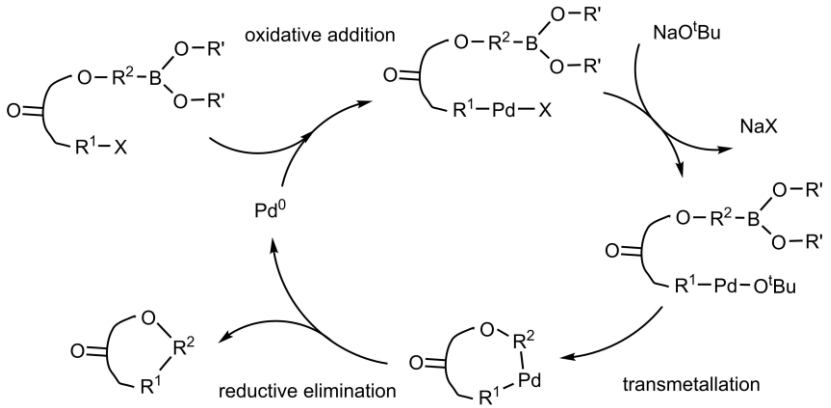


Scheme 17. Cyclization step to form Pestalotioprolide G.

6.3. MACROCYCLIZATION VIA SUZUKI COUPLING

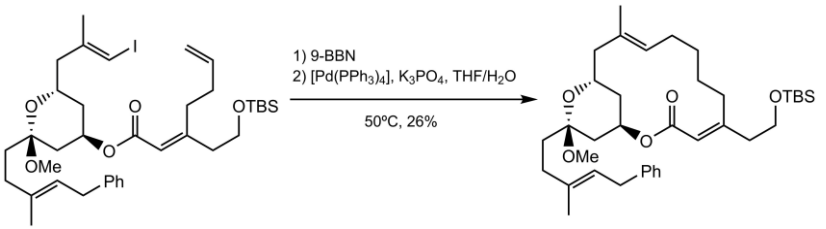
The Suzuki coupling[206] is a palladium-catalyzed cross-coupling reaction where an organoborane and a vinyl or aryl halide react to give the coupled product under basic conditions. This reaction is also called Suzuki–Miyaura coupling, recognizing the efforts of both Miyaura and Suzuki in developing the method. However, the reaction is well-known as Suzuki coupling. The method provides a good versatile solution to construct a new C–C bond with a high tolerance of many functional groups. In addition, the stability to air and moisture of the organoboranes involved has turned the reaction into one of the most used cross-couplings in organic chemistry.

The catalytic cycle of the Suzuki coupling is shown in **Scheme 18**. To begin with, an oxidative addition between the vinyl or aryl halide and palladium takes place. The presence of a base gives an intermediate that allows the transmetallation to occur, obtaining a species that is transformed into the macrolide by reductive elimination. The first Suzuki macrocyclization used in the total synthesis of a macrolide was White's total synthesis of rutamycin in 1998.[207] Since then many examples have appeared in the literature,[199] although only two in the period examined.

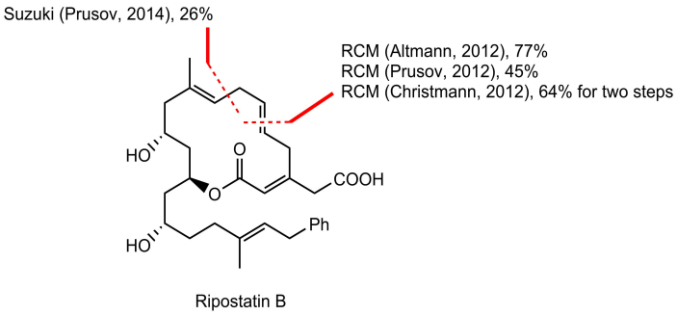


Scheme 18. Proposed catalytic cycle of the Suzuki coupling to form a macrolide.

In 2014, Prusov and co-workers synthesized 5,6-dihydroripostatin A, a Ripostatin analog, in 26% yield using an intramolecular Suzuki reaction (**Scheme 19**).[106] In view of the poor yield obtained, they tried to use a macrolactonization but were not able to prepare the required seco-acid. An alternative Suzuki macrocyclization also failed. Fluorinated analogues were then prepared using RCM, as in a previous total syntheses,[130–133] obtaining, in this case, good yields (**Scheme 20**).

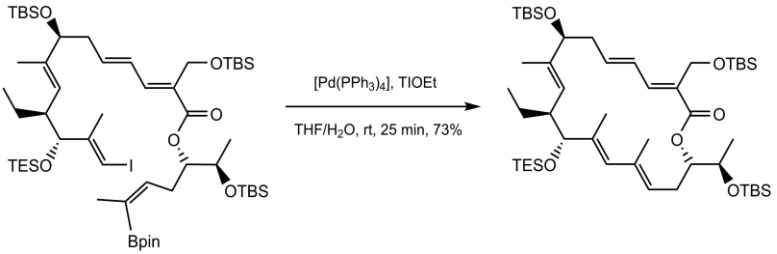


Scheme 19. Cyclization step to form protected 5,6-dihydroripostatin A.

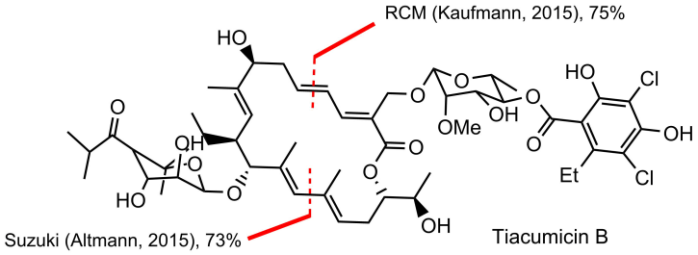


Scheme 20. Ripostatin B: comparison of methods used for formation of the ring.

The aglycone of Tiacumicin B, also called lipiarmycin A3 or fidaxomicin, is an atypical macrolide antibiotic used in the treatment of *Clostridium difficile* infections. Its total synthesis was reported by Glaus and Altmann in 2015 for the first time.[178] The ring closure was effected using [$Pd(PPh_3)_4$], TlOEt and was complete in less than 30 minutes at room temperature obtaining a 73% yield (**Scheme 21**). In addition, Tiacuminicin B was also synthesised the same year using RCM in the macrocylization step by Elias Kaufmann and his co-workers.[82] Using the second generation Grubbs catalyst (20 mol %) a 75% yield was obtained, although as a 2:1 *E*:*Z* mixture. The *Z* alkene could be isomerized to the desired *E* compound. As a result the overall yield for the E alkene increased to 63% (**Scheme 22**).



Scheme 21. Cyclization step to form protected Tiacumicin B.

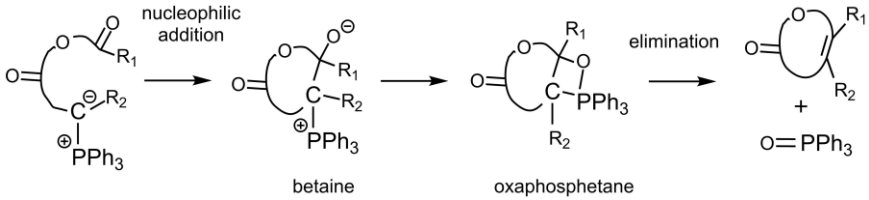


Scheme 22. Tiacumicin B: comparison of methods used for formation of the ring.

6.4. MACROCYCLIZATION VIA WITTIG REACTION

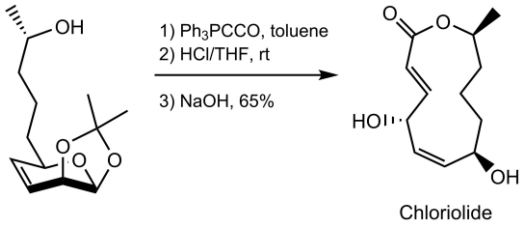
The Wittig reaction[208] involves the formation of a double bond between an aldehyde or a ketone with a triphenyl phosphonium ylide, also called a Wittig reagent. In 1954, George Wittig discovered this reaction and became a popular way to synthesize alkenes. Nowadays, it is also used to form the ring in organic macrocycles. The Wittig reaction is compatible with most of the functional groups but if the aldehyde or ketone is sterically hindered, the reaction may be slow and give poor yields.

In **Scheme 23**, the Wittig reaction in its intramolecular version to form a macrolide is shown. First, nucleophilic addition of the Wittig reagent to the carbonyl gives an intermediate betaine. A carbon-carbon bond rotation of this betaine forms an oxaphosphetane that eliminates triphenylphosphine oxide to form the macrolide ring.



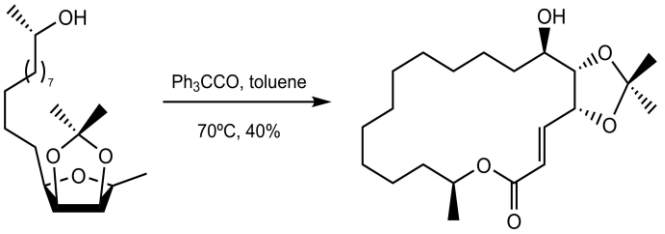
Scheme 23. Wittig reaction to form a macrolide.

During the period examined only two total syntheses of macrolides using a Wittig macrocyclization have appeared in the literature, both by the group of Schobert. In 2014, they prepared Chloriolide[190] as shown in **Scheme 24**. The air- and moisture-stable ylide is prepared by reaction of an alcohol with Ph_3PCCO. Then, they unmask the hemiacetal by acid treatment, a process that converts the ylide into the corresponding phosphonium salt. The ylide is then regenerated with NaOH and reacts in situ with the aldehyde in equilibrium with the hemiketal, forming the desired *E*-alkene in 65% yield.

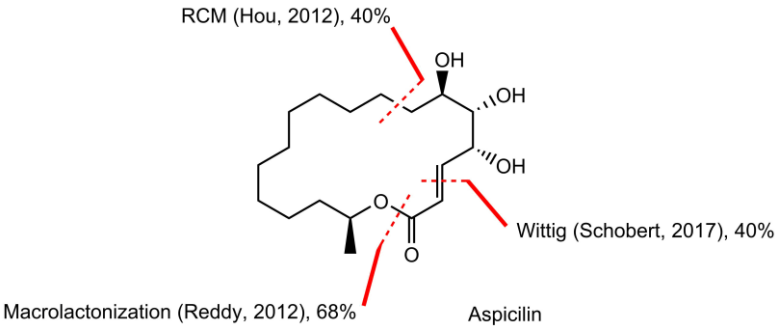


Scheme 24. Cyclization step to form Chloriolide.

The same group prepared also Aspicilin in 2017 using a similar strategy (**Scheme 25**).[189] The reaction temperature had to be controlled to avoid a competitive intramolecular conjugate addition between to the α,β-unsaturated ester formed in the intramolecular Wittig reaction, forming a tetrahydrofuran ring. Running the Wittig reaction at 70 ºC, suppressed the undesired conjugate addition and provided aspicillin in 40% yield. Moreover, Aspicilin was also prepared in 2012 by Hou using RCM conditions with the second generation Grubbs catalyst in 40% yield.[141] Furthermore, this macrolide has also been synthesized using a macrolatonization.[60] In 2012, Reddy used a Yamaguchi reaction to provide the protected macrolide in 68% yield (over 2 steps) (**Scheme 26**).



Scheme 25. Cyclization step to form protected Aspicilin.



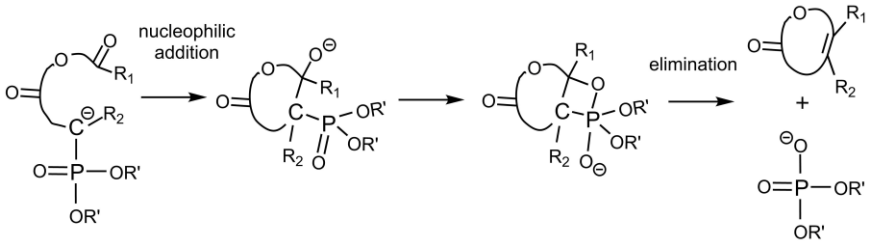
Scheme 26. Aspicilin: comparison of methods used for formation of the ring.

6.5. MACROCYCLIZATION VIA HORNER-WADSWORTH-EMMONS REACTION

The Horner–Wadsworth–Emmons olefination (HWE) is the reaction between an aldehyde or a ketone with a stabilized phosphonate carboanion that involves the formation of a double bond. The HWE reaction shares some characteristics of the Wittig reaction, but as result of the more

nucleophilic and less basic properties of phosphonate-stabilized carboanions, the reaction is milder and more likely to occur.

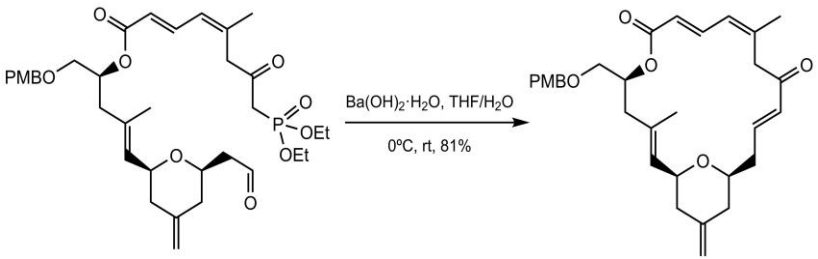
Scheme 27 shows a representation of the HWE reaction for the formation of macrocycles. At the beginning, a nucleophilic addition of the carbanion to the aldehyde or ketone produces an intermediate that converts into an oxaphosphetane. Finally, elimination of a phosphate generates the macrocyclic alkene.



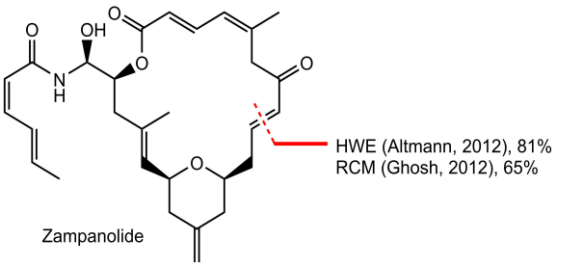
Scheme 27. HWE reaction to form a macrolide.

The intramolecular Horner-Wadsworth-Emmons reaction has been a reliable procedure for the formation of macrolides since the pioneering studies, in 1979, of Stork and Nakamura[209] and Nicolaou.[210] During the period examined several product macrolides have been cyclized using this method.

For example, the macrocycle of Zampanolide and Dactylolide was successfully synthesized using the HWE reaction in 2012 by Altmann in excellent yield (**Scheme 28**).[187] The synthesis of side chain-modified zampanolide analogs using the same approach is also described in the paper. In addition, Zampanolide was also synthesised in 2012 using RCM by the Ghosh research group using the Grubbs II catalyst in 65% yield[127] (**Scheme 29**).

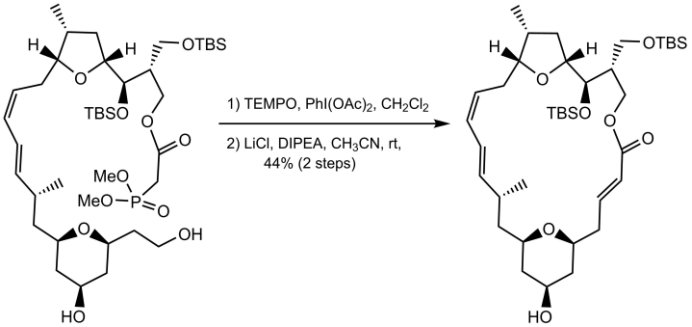


Scheme 28. Cyclization step to form the core macrocycle of Zampanolide and Dactylolide.



Scheme 29. Zampanolide: comparison of methods used for formation of the ring.

An intramolecular HWE reaction was also used to prepare Mandelalide A in 2014 by the research group of Xu and Ye.[184] The macrocyle was obtained in 44% yield for two steps (**Scheme 30**).



Scheme 30. Cyclization step to form protected Mandelalide A.

In 2013, Nagorny published the total synthesis of Lactimidomycin using a HWE cyclization.[186] The high ring-strain of this 12-membered unsaturated macrolide complicates the preparation of the cycle (**Figure 7**). The authors chose a HWE reaction to form at the same time the α,β-unsatured lactone and the ring, thus minimizing manipulation of this sensitive moiety. After optimization, a Zn(II)-mediated HWE reaction furnished the desired macrocycle in 93% yield. Finally, deprotection and installation of the side chain afforded the final compound (**Scheme 31**).

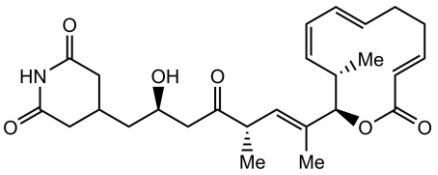
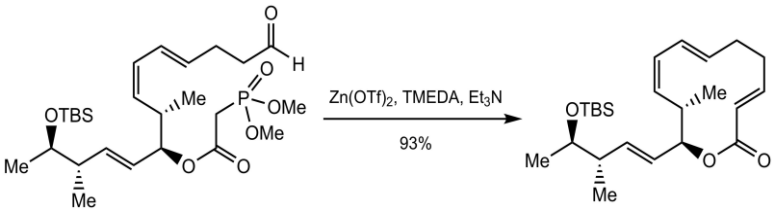


Figure 7. Structure of Lactimidomycin.



Scheme 31. Cyclization step to form protected Lactimidomycin macrocycle.

Dias and de Lucca published in 2015 the first total synthesis of Marinisporolide C, a 34-membered oxopolyene macrolide using an intramolecular HWE reaction.[182] The authors initially planned to synthesise Marinispolide A, which is a geometrical isomer of Marinispolide C (**Figure 8**). Surprisingly, after HWE macrocyclization and global deprotection, they isolated, in 15% yield, Marisnispolide C (**Scheme 32**). When Marinispolide A is exposed to ambient light, an equilibrium mixture favoring Marisnispolide C is obtained after 2 h. This seems to indicate that Marinispolide C is the thermodynamically most stable isomer. As the authors conducted their reactions in the dark, they believe that Marinispolide C was formed due to acid-catalyzed isomerization. Two years later, in 2017, a full report of this total synthesis was published.[183] In this second article, the authors describe that attempts at the total synthesis of the Marinispolides using several macrolactonization protocols were unsuccessful, probably due to the presence of an α-substituent in the α,β-unsaturated seco-acid.

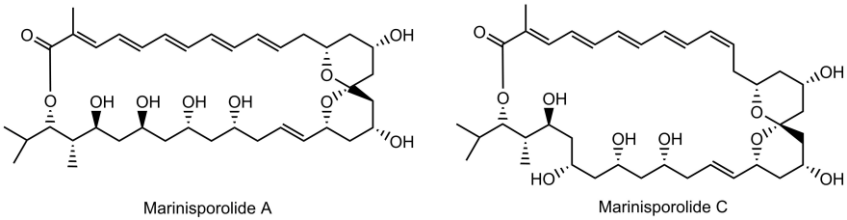
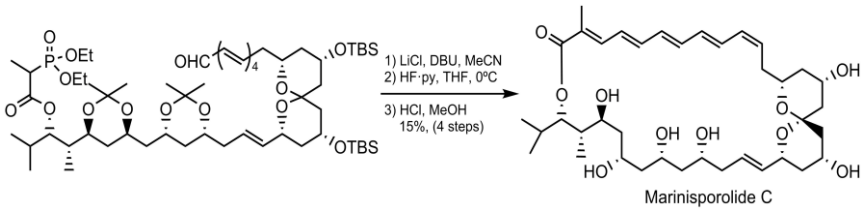
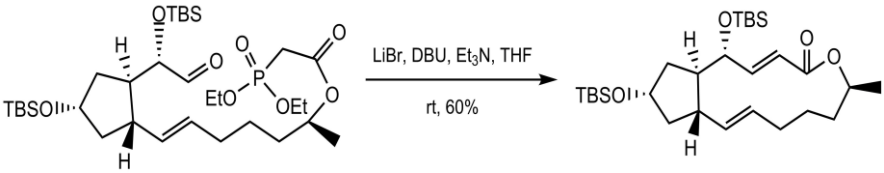


Figure 8. Structures of Marinisporolide A and C.

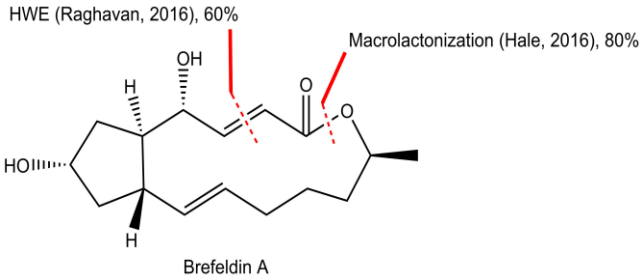


Scheme 32. Cyclization step to form protected Marinisporolide C.

Brefeldin A was synthesized in 2016 by Raghavan and Yelleni.[181] They used the Roush–Masamune conditions (LiBr, DBU and Et_3N) to form the ring in 60% yield (**Scheme 33**). Finally, deprotection of the silyl ethers under acid conditions furnished the final compound. An alternative synthesis of Brefeldin A using a Yamaguchi macrolactonization was also described in 2016 by Hale in 80% yield[22] (**Scheme 34**).

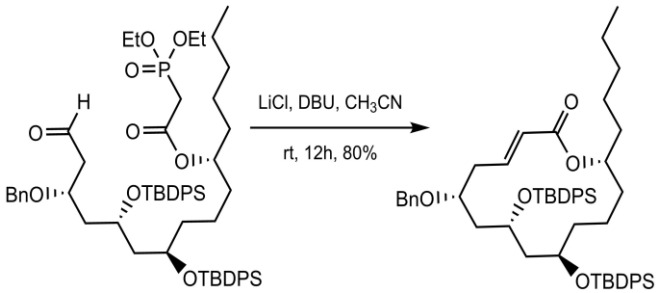


Scheme 33. Cyclization step to form protected Brefeldin A.



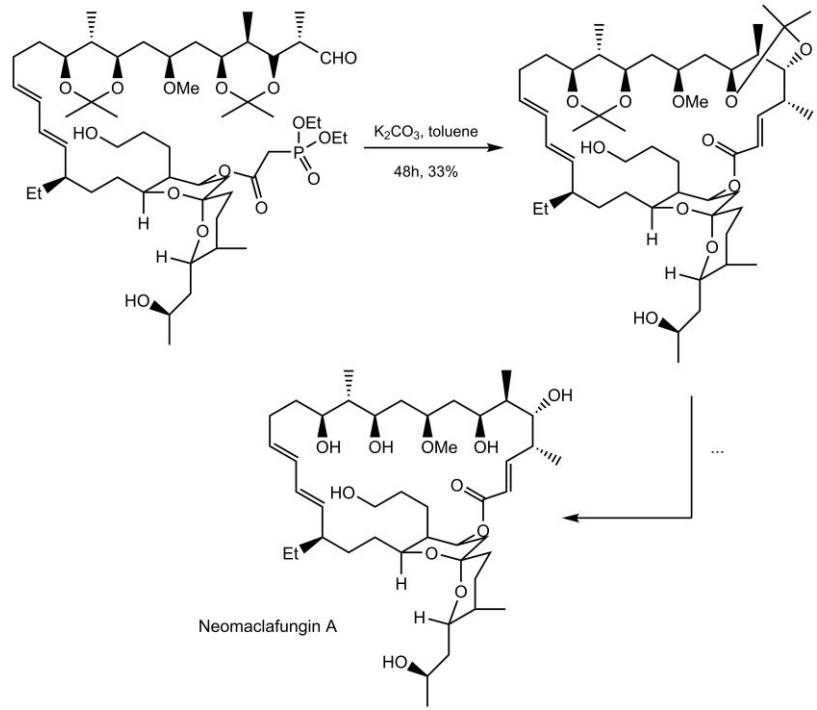
Scheme 34. Brefeldin A: comparison of methods used for formation of the ring.

Two diasteromers of Gliomasolide E were prepared in 2017 by the group of Mohapatra.[179] They also used the Roush–Masamune conditions obtaining a 80% yield in the HWE cyclization (**Scheme 35**). By comparison of the NMR data of the two Gliomasolide E diasteromers with that of the natural product, they could assign the absolute stereochemistry of the natural product.



Scheme 35. Cyclization step to form two protected diasteromers of Gliomasolide E.

In 2017, the total synthesis of Neomaclafungin A was published by Wu.[180] The formation of the ring of this complex molecule worked in only 33% yield (**Scheme 36**). Nevertheless, after a difficult final global deprotection, they could complete the synthesis of the macrolide and establish its relative and absolute configuration.



Scheme 36. Structure and cyclization step to form Neomaclafungin A.

7. CONCLUSIONS

In this work, a bibliographic search has been undertaken to find which macrocyclization methods, apart from macrolactonization and ring-closing metathesis, are used nowadays for the synthesis of macrolides. Many methods have been identified and five of them have been reviewed. Three of these methods were cross-coupling methods and the other two were based on the formation of a double bond.

Analysis of the number of articles per method, we can conclude, as expected, that macrolactonization and RCM are still preferred to cyclize macrolides. However, a growth in the use of alternative methods is observed, especially for RCAM. Cross-coupling methods are also gaining popularity for macrocyclization. Ring-closure of the cycle by formation of a double bond (Wittig and HWE) is less used.

The literature review reveals that it is not straightforward to predict the best approach to cyclize a particular structure. Without doubt, macrolactonization is the most general strategy but, even though there are many different conditions for this reaction, sometimes a particular substrate will not macrolactonize successfully (because of ring strain, instability of the substrate...). In these instances, RCM approaches are probably the best alternative if the macrolide has a suitable structure. For macrolides with 1,3-dienes, Heck, Suzuki or Stille cross-couplings can also be used with some confidence. Despite all the benefits that macrolactonization and RCM have, alternative methods can be beneficial in some cases, as the literature review attests, and afford, in some cases, the same or better yields than classical macrolactonization or RCM approaches.

8. REFERENCES AND NOTES

1. https://goldbook.iupac.org/html/M/M03663.html. .
2. Parenty A, Moreau X, Niel G, Campagne J-M. *Chem Rev*. 2012; 113: PR1-PR40.
3. Gradillas A, Perez-Castells J. *Angew Chem, Int Ed*. 2006; 45: 6086–6101.
4. Bosch L, Mola L, Petit E, Saladrigas M, Esteban J, Costa AM, Vilarrasa J. *J Org Chem*. 2017; 82: 11021–11034.
5. Rodríguez-Escrich C, Urpí F, Vilarrasa J. *Org Lett*. 2008; 10: 5191–5194.
6. Chiara T, Benet P, Marion B, Janine C, Christophe M, Oriol P, Carles R, Fèlix U, Jaume V, Fernando DJ, Isabel B. *ChemBioChem*. 2011; 12: 1293.
7. Mola L, Olivella A, Urpi F, Vilarrasa J. *Tetrahedron Lett*. 2014; 55: 900–902.
8. Sanchez D, Andreou T, Costa AM, Meyer KG, Williams DR, Barasoain I, D?az JF, Lucena-Agell D, Vilarrasa J. *J Org Chem*. 2015; 80: 8511–8519.
9. Bartra, M.; Urpí, F.; Vilarrasa J. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products . Lukacs, G.* 1993; p vol 2, 1–65.
10. Cui J, Morita M, Ohno O, Kimura T, Teruya T, Watanabe T, Suenaga K, Shibasaki M. *Chem Eur J*. 2017; 23: 8500–8509.
11. Green AP, Hardy S, Lee ATL, Thomas EJ. *Org Biomol Chem*. 2017; 15: 9497–9526.
12. Hayakawa I, Okamura M, Suzuki K, Shimanuki M, Kimura K, Yamada T, Ohyoshi T, Kigoshi H. *Synthesis*. 2017; 49: 2958–2970.
13. Regalla VR, Addada RR, Puli VS, Saxena AS, Chatterjee A. *Tetrahedron Lett*. 2017; 58: 2344–2346.
14. Mohri T, Ogura Y, Towada R, Kuwahara S. *Tetrahedron Lett*. 2017; 58: 4011–4013.
15. Reddy SN, Sabitha G. *Tetrahedron Lett*. 2017; 58: 1198–1201.
16. Yahata K, Ye N, Iso K, Naini SR, Yamashita S, Ai Y, Kishi Y. *J Org Chem*. 2017; 82: 8792–8807.
17. Jena BK, Reddy GS, Mohapatra DK. *Org Biomol Chem*. 2017; 15: 1863–1871.
18. Iwasaki K, Sasaki S, Kasai Y, Kawashima Y, Sasaki S, Ito T, Yotsu-Yamashita M, Sasaki M. *J Org Chem*. 2017; 82: 13204–13219.
19. Lowell AN, Demars MD, Slocum ST, Yu F, Anand K, Chemler JA, Korakavi N, Priessnitz JK, Park SR, Koch AA, Schultz PJ, Sherman DH. *J Am Chem Soc*. 2017; 139: 7913–7920.
20. Seetharamsingh, Khairnar P V, Reddy DS. *J Org Chem*. 2016; 81: 290–296.
21. Mishra VK, Ravikumar PC, Maier ME. *J Org Chem*. 2016; 81: 9728–9737.
22. Xiong Z, Hale KJ. *Org Lett*. 2016; 18: 4254–4257.
23. Veerasamy N, Ghosh A, Li J, Watanabe K, Serrill JD, Ishmael JE, McPhail KL, Carter RG. *J Am Chem Soc*. 2016; 138: 770–773.
24. Bruetsch TM, Bucher P, Altmann K-H. *Chem Eur J*. 2016; 22: 1292–1300.
25. Reddy CR, Dilipkumar U, Mallesh K, Latha B, Shravya R. *Tetrahedron: Asymmetry*. 2016; 27: 222–225.
26. Yadav JS, Dutta P. *J Org Chem*. 2016; 81: 1786–1797.
27. Kunifuda K, Iwasaki A, Nagamoto M, Suenaga K. *Tetrahedron Lett*. 2016; 57: 3121–3123.
28. Nicolaou, Pulukuri KK, Rigol S, Heretsch P, Yu R, Grove CI, Hale CRH, ElMarrouni A, Fetz V, Brönstrup M, Aujay M, Sandoval J, Gavrilyuk J. *J Am Chem Soc*. 2016; 138: 6550–6560.

29. Seiple IB, Zhang Z, Jakubec P, Langlois-Mercier A, Wright PM, Hog DT, Yabu K, Allu SR, Fukuzaki T, Carlsen PN, Kitamura Y, Zhou X, Condakes ML, Szczypiski FT, Green WD, Myers AG. *Nature*. 2016; 533: 338–345.
30. Saidhareddy P, Shaw AK. *RSC Adv*. 2015; 5: 29114–29120.
31. Di Franco T, Epenoy A, Hu X. *Org Lett*. 2015; 17: 4910–4913.
32. Ai Y, Kozytska M V, Zou Y, Khartulyari AS, Smith AB. *J Am Chem Soc*. 2015; 137: 15426–15429.
33. Lu H-H, Hinkelmann B, Tautz T, Li J, Sasse F, Franke R, Kalesse M. *Org Biomol Chem*. 2015; 13: 8029–8036.
34. Wuensch S, Breit B. *Chem Eur J*. 2015; 21: 2358–2363.
35. Chegondi R, Hanson PR. *Tetrahedron Lett*. 2015; 56: 3330–3333.
36. Fuwa H, Okuaki Y, Yamagata N, Sasaki M. *Angew Chem Int Ed*. 2015; 54: 868–873.
37. Tonoi T, Kawahara R, Yoshinaga Y, Inohana T, Fujimori K, Shiina I. *Tetrahedron Lett*. 2015; 56: 1356–1359.
38. Fortunati T, D'Acunto M, Caruso T, Spinella A. *Tetrahedron*. 2015; 71: 2357–2362.
39. Paterson I, Ng KK-H, Williams S, Millican DC, Dalby SM. *Angew Chem Int Ed*. 2014; 53: 2692–2695.
40. Kim HJ, Choi S-H, Jeon B-S, Kim N, Pongdee R, Wu Q, Liu H-W. *Angew Chemie - Int Ed*. 2014; 53: 13553–13557.
41. Matsuzawa A, Opie CR, Kumagai N, Shibasaki M. *Chem Eur J*. 2014; 20: 68–71.
42. Ghosh AK, Shurrush KA, Dawson ZL. *Org Biomol Chem*. 2013; 11: 7768–7777.
43. Gandi VR. *Tetrahedron*. 2013; 69: 6507–6511.
44. Arlt A, Benson S, Schulthoff S, Gabor B, Fürstner A. *Chem Eur J*. 2013; 19: 3596–3608.
45. Clark JS, Romiti F. *Angew Chem Int Ed*. 2013; 52: 10072–10075.
46. Nagasawa T, Kuwahara S. *Org Lett*. 2013; 15: 3002–3005.
47. Ho S, Bucher C, Leighton JL. *Angew Chem Int Ed*. 2013; 52: 6757–6761.
48. Williams BD, Smith AB. *Org Lett*. 2013; 15: 4584–4587.
49. Williams BD, Smith AB. *J Org Chem*. 2014; 79: 9284–9296.
50. Williams DR, Myers BJ, Mi L, Binder RJ. *J Org Chem*. 2013; 78: 4762–4778.
51. Paterson I, Anderson EA, Dalby SM, Lim JH, Maltas P. *Org Biomol Chem*. 2012; 10: 5873–5886.
52. Florence GJ, Wlochal J. *Chem Eur J*. 2012; 18: 14250–14254.
53. Kleinbeck F, Fettes GJ, Fader LD, Carreira EM. *Chem Eur J*. 2012; 18: 3598–3610.
54. Martin N, Thomas EJ. *Org Biomol Chem*. 2012; 10: 7952–7964.
55. Zhang B, Wang Y, Yang S-P, Zhou Y, Wu W-B, Tang W, Zuo J-P, Li Y, Yue J-M. *J Am Chem Soc*. 2012; 134: 20605–20608.
56. Mahapatra S, Carter RG. *Angew Chem Int Ed*. 2012; 51: 7948–7951.
57. Mahapatra S, Carter RG. *J Am Chem Soc*. 2013; 135: 10792–10803.
58. Yadav, Das SK, Sabitha. *J Org Chem*. 2012; 77: 11109–11118.
59. Athe S, Chandrasekhar B, Roy S, Pradhan TK, Ghosh S. *J Org Chem*. 2012; 77: 9840–9845.
60. Raji Reddy C, Rao NN, Sujitha P, Kumar CG. *European J Org Chem*. 2012: 1819–1824.
61. Sharma GVM, Manohar V. *Tetrahedron Asymmetry*. 2012; 23: 252–263.
62. Cook C, Liron F, Guinchard X, Roulland E. *J Org Chem*. 2012; 77: 6728–6742.
63. Ota K, Sugata N, Ohshiro Y, Kawashima E, Miyaoka H. *Chem Eur J*. 2012; 18: 7,13531-13537.
64. Yamamoto A, Ueda A, Bremond P, Tiseni PS, Kishi Y. *J Am Chem Soc*. 2012; 134: 893–896.
65. Ueda A, Yamamoto A, Kato D, Kishi Y. *J Am Chem Soc*. 2014; 136: 5171–5176.
66. Chatterjee B, Mondal D, Bera S. *Tetrahedron: Asymmetry*. 2012; 23: 16,1170-1185.
67. Suzuki T, Fujimura M, Fujita K, Kobayashi S. *Tetrahedron*. 2017; 73: 3652–3659.
68. Zhang W, Wu J, Li B, Lian X, Xia J, Zhou Q, Wu S. *Eur J Med Chem*. 2017; 138: 353–356.
69. Solinski AE, Koval AB, Brzozowski RS, Morrison KR, Fraboni AJ, Carson CE, Eshraghi AR, Zhou G, Quivey RG, Voelz VA, Buttaro BA, Wuest WM. *J Am Chem Soc*. 2017; 139: 7188–7191.
70. Peram PS, Vences M, Schulz S. *Org Biomol Chem*. 2017; 15: 6967–6977.

71. Foley CN, Chen L-A, Sackett DL, Leighton JL. *ACS Med Chem Lett*. 2017; 8: 701–704.
72. Dumeunier R, Gregson T, MacCormick S, Omori H, Thomas EJ. *Org Biomol Chem*. 2017; 15: 2768–2783.
73. Wullschleger CW, Li J, Edenharter A, Altmann K-H. *Synlett*. 2016; 27: 2726–2730.
74. Bujaranipalli S, Das S. *Tetrahedron Asymmetry*. 2016; 27: 254–260.
75. Fuwa H, Yamagata N, Okuaki Y, Ogata Y, Saito A, Sasaki M. *Chem Eur J*. 2016; 22: 6815–6829.
76. Sharma BM, Gontala A, Kumar P. *Eur J Org Chem*. 2016; 2016: 1215–1226.
77. Bodugam M, Javed S, Ganguly A, Torres J, Hanson PR. *Org Lett*. 2016; 18: 516–519.
78. Menke M, Peram PS, Starnberger I, H?dl W, Jongsma GFM, Blackburn DC, R?del M-O, Vences M, Schulz S. *Beilstein J Org Chem*. 2016; 12: 2731–2738.
79. Sridhar G, Sharma GVM. *Synth Commun*. 2016; 46: 314–321.
80. Welford AJ, Caldwell JJ, Liu M, Richards M, Brown N, Lomas C, Tizzard GJ, Pitak MB, Coles SJ, Eccles SA, Raynaud FI, Collins I. *Chem Eur J*. 2016; 22: 5657–5664.
81. Andrade RB. *Synlett*. 2015; 26: 2199–2215.
82. Kaufmann E, Hattori H, Miyatake-Ondozabal H, Gademann K. *Org Lett*. 2015; 17: 3514–3517.
83. Kita M, Oka H, Usui A, Ishitsuka T, Mogi Y, Watanabe H, Tsunoda M, Kigoshi H. *Angew Chem Int Ed*. 2015; 54: 14174–14178.
84. Tadpetch K, Jeanmard L, Rukachaisirikul V. *Tetrahedron Asymmetry*. 2015; 26: 918–923.
85. Chang C-F, Stefan E, Taylor RE. *Chem Eur J*. 2015; 21: 10681–10686.
86. Zong G, Barber E, Aljewari H, Zhou J, Hu Z, Du Y, Shi WQ. *J Org Chem*. 2015; 80: 9279–9291.
87. Zong G, Hirsch M, Mondrik C, Hu Z, Shi WQ. *Bioorganic Med Chem Lett*. 2017; 27: 2752–2756.
88. Zong G, Whisenhunt L, Hu Z, Shi WQ. *J Org Chem*. 2017; 82: 4977–4985.
89. Zong G, Aljewari H, Hu Z, Shi WQ. *Org Lett*. 2016; 18: 1674–1677.
90. Li H, Xie H, Zhang Z, Xu Y, Lu J, Gao L, Song Z. *Chem Commun*. 2015; 51: 8484–8487.
91. Zhang Z, Xie H, Li H, Gao L, Song Z. *Org Lett*. 2015; 17: 4706–4709.
92. Yu M, Schrock RR, Hoveyda AH. *Angew Chem Int Ed*. 2015; 54: 215–220.
93. LoRe D, Zhou Y, Mucha J, Jones LF, Leahy L, Santocanale C, Krol M, Murphy P V. *Chem Eur J*. 2015; 21: 18109–18121.
94. Sellstedt M, Schwalfenberg M, Ziegler S, Antonchick AP, Waldmann H. *Org Biomol Chem*. 2015; 14: 50–54.
95. Jecs E, Diver ST. *Org Lett*. 2015; 17: 3510–3513.
96. Kanoh N, Kawamata A, Itagaki T, Miyazaki Y, Yahata K, Kwon E, Iwabuchi Y. *Org Lett*. 2014; 16: 5216–5219.
97. Wang Y, Liu Q-F, Xue J-J, Zhou Y, Yu H-C, Yang S-P, Zhang B, Zuo J-P, Li Y, Yue J-M. *Org Lett*. 2014; 16: 2062–2065.
98. Kumar SM, Prasad KR. *Chem Asian J*. 2014; 9: 3431–3439.
99. Terayama N, Yasui E, Mizukami M, Miyashita M, Nagumo S. *Org Lett*. 2014; 16: 2794–2797.
100. Sunnam SK, Prasad KR. *Tetrahedron*. 2014; 70: 2096–2101.
101. Bali AK, Sunnam SK, Prasad KR. *Org Lett*. 2014; 16: 4001–4003.
102. Pradhan TR, Das PP, Mohapatra DK. *Synthesis*. 2014; 46: 1177–1184.
103. Desmond RT, Magpusao AN, Lorenc C, Alverson JB, Priestley N, Peczuh MW. *Beilstein J Org Chem*. 2014; 10: 2215–2221.
104. Zhang H, Yu EC, Torker S, Schrock RR, Hoveyda AH. *J Am Chem Soc*. 2014; 136: 16493–16496.
105. Fujiwara K, Suzuki Y, Koseki N, Aki Y-I, Kikuchi Y, Murata S-I, Yamamoto F, Kawamura M, Norikura T, Matsue H, Murai A, Katoono R, Kawai H, Suzuki T. *Angew Chem Int Ed*. 2014; 53: 780–784.
106. Tang W, Liu S, Degen D, Ebright RH, Prusov E V. *Chem Eur J*. 2014; 20: 12310–12319.
107. Hallside MS, Brzozowski RS, Wuest WM, Phillips AJ. *Org Lett*. 2014; 16: 1148–1151.

108. Venkanna, Siva, Poornima, Babu KS, Rao JM. *Tetrahedron Lett*. 2014; 55: 403–406.
109. Poornima, Venkanna, Swetha, Kamireddy K reddy, Siva B, Babu P, Ummanni R, Babu KS. *Tetrahedron*. 2016; 72: 4789–4797.
110. Becker J, Butt L, Von Kiedrowski V, Mischler E, Quentin F, Hiersemann M. *J Org Chem*. 2014; 79: 3040–3051.
111. Sang F, Feng P, Chen J, Ding Y, Duan X, Zhai J, Ma X, Zhang B, Zhang Q, Lin J, Chen Y. *Eur J Med Chem*. 2013; 68: 321–332.
112. Gao X, Woo SK, Krische MJ. *J Am Chem Soc*. 2013; 135: 4223–4226.
113. Fuwa H, Yamagata N, Saito A, Sasaki M. *Org Lett*. 2013; 15: 1630–1633.
114. Hwang M-H, Han S-J, Lee D-H. *Org Lett*. 2013; 15: 3318–3321.
115. Fuwa H, Kawakami M, Noto K, Muto T, Suga Y, Konoki K, Yotsu-Yamashita M, Sasaki M. *Chem Eur J*. 2013; 19: 8100–8110.
116. Wang C, Yu M, Kyle AF, Jakubec P, Dixon DJ, Schrock RR, Hoveyda AH. *Chem Eur J*. 2013; 19: 2726–2740.
117. Lambu MR, Kumar S, Yousuf SK, Sharma DK, Hussain A, Kumar A, Malik F, Mukherjee D. *J Med Chem*. 2013; 56: 6122–6135.
118. Kumar VP, Chandrasekhar S. *Org Lett*. 2013; 15: 3610–3613.
119. Chevalley A, Prunet J, Mauduit M, Ferezou J-P. *European J Org Chem*. 2013: 8265–8278.
120. Yadav JS, Haldar A, Maity T. *European J Org Chem*. 2013: 3076–3085.
121. Sharma GVM, Reddy SV. *RSC Adv*. 2013; 3: 21759–21762.
122. Yadav, Venkatesh, Swapnil, Prasad. *Tetrahedron Lett*. 2013; 54: 2336–2339.
123. Canterbury DP, Scott KEN, Kubo O, Jansen R, Cleveland JL, Micalizio GC. *ACS Med Chem Lett*. 2013; 4: 1244–1248.
124. Radha Krishna P, Prabhakar S, Ramana V. *Tetrahedron Lett*. 2012; 53: 6843–6845.
125. Oh H-S, Kang H-Y. *J Org Chem*. 2012; 77: 1125–1130.
126. Radhakrishna P, Kumar PVA. *Helv Chim Acta*. 2012; 95: 1623–1629.
127. Ghosh AK, Cheng X, Bai R, Hamel E. *European J Org Chem*. 2012: 4130–4139.
128. Pawar AB, Prasad KR. *Chem Eur J*. 2012; 18: 15202–15206.
129. Reddy GV, Kumar RSC, Siva, Babu KS, Rao JM. *Synlett*. 2012; 23: 2677–2681.
130. Winter P, Hiller W, Christmann M. *Angew Chem Int Ed*. 2012; 51: 3396–3400.
131. Tang W, Prusov E V. *Angew Chemie - Int Ed*. 2012; 51: 3401–3404.
132. Glaus F, Altmann K-H. *Angew Chemie - Int Ed*. 2012; 51: 3405–3409.
133. Glaus F, Altmann K-H. *Chimia (Aarau)*. 2013; 67: 227–230.
134. Tang W, Prusov E V. *Org Lett*. 2012; 14: 4690–4693.
135. Huang J, Yang J. *Synlett*. 2012; 23: 737–740.
136. Villa R, Mandel AL, Jones BD, La Clair JJ, Burkart MD. *Org Lett*. 2012; 14: 5396–5399.
137. Pradhan TR, Mohapatra DK. *Tetrahedron Asymmetry*. 2012; 23: 709–715.
138. Hara A, Morimoto R, Iwasaki Y, Saitoh T, Ishikawa Y, Nishiyama S. *Angew Chem Int Ed*. 2012; 51: 9877–9880.
139. Poth D, Wollenberg KC, Vences M, Schulz S. *Angew Chemie - Int Ed*. 2012; 51: 2187–2190.
140. Sharma GVM, Reddy SV, Ramakrishna KVS. *Org Biomol Chem*. 2012; 10: 3689–3695.
141. Wang C-Y, Hou D-R. *J Chinese Chem Soc*. 2012; 59: 389–393.
142. Dias LC, Monteiro GC, Amarante GW, Conegero LS, Finelli FG. *Tetrahedron Lett*. 2012; 53: 707–709.
143. Velvadapu V, Glassford I, Lee M, Paul T, Debrosse C, Klepacki D, Small MC, MacKerell AD, Andrade RB. *ACS Med Chem Lett*. 2012; 3: 211–215.
144. Schaubach S, Michigami K, Fürstner A. *Synthesis*. 2017; 49: 202–208.
145. Ahlers A, De Haro T, Gabor B, Fürstner A. *Angew Chem Int Ed*. 2016; 55: 1406–1411.
146. Schaubach S, Gebauer K, Ungeheuer F, Hoffmeister L, Ilg MK, Wirtz C, Fürstner A. *Chem - A Eur J*. 2016; 22: 8494–8507.
147. Lehr K, Schulthoff S, Ueda Y, Mariz R, Leseurre L, Gabor B, Fuerstner A. *Chem Eur J*. 2015; 21:

219–227.
148. Rummelt SM, Preindl J, Sommer H, Fuerstner A. *Angew Chem Int Ed*. 2015; 54: 6241–6245.
149. Sommer H, Fuerstner A. *Chem Eur J*. 2017; 23: 558–562.
150. Fuchs M, Fürstner A. *Angew Chem Int Ed*. 2015; 54: 3978–3982.
151. Ungeheuer F, Fürstner A. *Chem Eur J*. 2015; 21: 11387–11392.
152. Willwacher J, Fuerstner A. *Angew Chem Int Ed*. 2014; 53: 4217–4221.
153. Willwacher J, Heggen B, Wirtz C, Thiel W, Fürstner A. *Chem Eur J*. 2015; 21: 10416–10430.
154. Mailhol D, Willwacher J, Kausch-Busies N, Rubitski EE, Sobol Z, Schuler M, Lam M-H, Musto S, Loganzo F, Maderna A, Fürstner A. *J Am Chem Soc*. 2014; 136: 15719–15729.
155. Hoetling S, Haberlag B, Tamm M, Collatz J, Mack P, Steidle JLM, Vences M, Schulz S. *Chem Eur J*. 2014; 20: 3183–3191.
156. Hötling S, Bittner C, Tamm M, D?hn S, Collatz J, Steidle JLM, Schulz S. *Org Lett*. 2015; 17: 5004–5007.
157. Micoine K, Persich P, Llaveria J, Lam M-H, Maderna A, Loganzo F, Fürstner A. *Chem Eur J*. 2013; 19: 7370–7383.
158. Valot G, Regens CS, O'Malley DP, Godineau E, Takikawa H, Fürstner A. *Angew Chem Int Ed*. 2013; 52: 9534–9538.
159. Valot G, Mailhol D, Regens CS, O'Malley DP, Godineau E, Takikawa H, Philipps P, Fürstner A. *Chem Eur J*. 2015; 21: 2398–2408.
160. Neuhaus CM, Liniger M, Stieger M, Altmann K-H. *Angew Chem Int Ed*. 2013; 52: 5866–5870.
161. Brewitz L, Llaveria J, Yada A, Fürstner A. *Chem - A Eur J*. 2013; 19: 4532–4537.
162. Persich P, Llaveria J, Lhermet R, de Haro T, Stade R, Kondoh A, Fürstner A. *Chem Eur J*. 2013; 19: 13047–13058.
163. Willwacher J, Kausch-Busies N, Fürstner A. *Angew Chemie - Int Ed*. 2012; 51: 12041–12046.
164. Sato E, Sato M, Tanabe Y, Nakajima N, Ohkubo A, Suenaga K. *J Org Chem*. 2017; 82: 6770–6777.
165. Williams S, Jin J, Kan SBJ, Li M, Gibson LJ, Paterson I. *Angew Chem Int Ed*. 2017; 56: 645–649.
166. Tanabe Y, Sato E, Nakajima N, Ohkubo A, Ohno O, Suenaga K. *Org Lett*. 2014; 16: 2858–2861.
167. Sato E, Tanabe Y, Nakajima N, Ohkubo A, Suenaga K. *Org Lett*. 2016; 18: 2047–2049.
168. Chen L, Riaz Ahmed KB, Huang P, Jin Z. *Angew Chem Int Ed*. 2013; 52: 3446–3449.
169. Paul D, Das S, Goswami RK. *J Org Chem*. 2017; 82: 7437–7445.
170. Nazari M, Serrill JD, Wan X, Nguyen MH, Anklin C, Gallegos DA, Smith AB, Ishmael JE, McPhail KL. *J Med Chem*. 2017; 60: 7850–7862.
171. Rao KN, Kanakaraju, Kunwar, Ghosh S. *Org Lett*. 2016; 18: 4092–4095.
172. Das S, Paul D, Goswami RK. *Org Lett*. 2016; 18: 1908–1911.
173. Nguyen MH, Imanishi M, Kurogi T, Smith AB. *J Am Chem Soc*. 2016; 138: 3675–3678.
174. Jena BK, Mohapatra DK. *Tetrahedron*. 2015; 71: 5678–5692.
175. Symkenberg G, Kalesse M. *Angew Chem Int Ed*. 2014; 53: 1795–1798.
176. Reddy KM, Yamini V, Singarapu KK, Ghosh S. *Org Lett*. 2014; 16: 2658–2660.
177. Lisboa MP, Jones DM, Dudley GB. *Org Lett*. 2013; 15: 886–889.
178. Glaus F, Altmann K-H. *Angew Chem Int Ed*. 2015; 54: 1937–1940.
179. Reddy RG, Venkateshwarlu R, Ramakrishna KVS, Yadav JS, Mohapatra DK. *J Org Chem*. 2017; 82: 1053–1063.
180. Zhu S, Wu Y. *Chem Asian J*. 2017; 12: 2211–2215.
181. Raghavan S, Yelleni MKR. *J Org Chem*. 2016; 81: 10912–10921.
182. Dias LC, De Lucca EC. *Org Lett*. 2015; 17: 6278–6281.
183. Dias LC, De Lucca EC. *J Org Chem*. 2017; 82: 3019–3045.
184. Lei H, Yan J, Yu J, Liu Y, Wang Z, Xu Z, Ye T. *Angew Chem Int Ed*. 2014; 53: 6533–6537.
185. Larsen BJ, Sun Z, Lachacz E, Khomutnyk Y, Soellner MB, Nagorny P. *Chem - A Eur J*. 2015; 21:

19159–19167.
186. Larsen BJ, Sun Z, Nagorny P. *Org Lett*. 2013; 15: 2998–3001.
187. Zurwerra D, Glaus F, Betschart L, Schuster J, Gertsch J, Ganci W, Altmann K-H. *Chem Eur J*. 2012; 18: 16868–16883.
188. Trost BM, Amans D, Seganish WM, Chung CK. *Chem Eur J*. 2012; 18: 2961–2971, S2961/1–S2961/41.
189. Schmidt R, Ostermeier M, Schobert R. *J Org Chem*. 2017; 82: 9126–9132.
190. Ostermeier M, Schobert R. *J Org Chem*. 2014; 79: 4038–4042.
191. de Leseleuc M, Godin E, Parisien-Collette S, Levesque A, Collins SK. *J Org Chem*. 2016; 81: 6750–6756.
192. Li W, Georg GI. *Chem Commun*. 2015; 51: 8634–8636.
193. Jena BK, Reddy AV V, Mohapatra DK. *Asian J Org Chem*. 2016; 5: 340–342.
194. Wagh B, Paul T, Debrosse C, Klepacki D, Small MC, Mackerell AD, Andrade RB. *ACS Med Chem Lett*. 2013; 4: 1114–1118.
195. Hayakawa I, Saito K, Matsumoto S, Kobayashi S, Taniguchi A, Kobayashi K, Fujii Y, Kaneko T, Kigoshi H. *Org Biomol Chem*. 2017; 15: 124–131.
196. Gündemir-Durmaz T, Schmid F, El Baz Y, Husser A, Schneider C, Bilitewski U, Rauhut G, Garnier D, Baro A, Laschat S. *Org Biomol Chem*. 2016; 14: 8261–8269.
197. Wessjohann LA, Scheid GO, Eichelberger U, Umbreen S. *J Org Chem*. 2013; 78: 10588–10595.
198. Espinet P, Echavarren AM. *Angew Chem Int Ed*. 2004; 43: 4704–4734.
199. Ronson TO, Taylor RJK, Fairlamb IJS. *Tetrahedron*. 2015; 71: 989–1009.
200. Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem Int Ed*. 2005; 44: 4442–4489.
201. Pattenden G, Sinclair DJ. *J Organomet Chem*. 2002; 653: 261–268.
202. Duncton MAJ, Pattenden G. *J Chem Soc Perkin Trans 1 Org Bio-Organic Chem*. 1999: 1235–1246.
203. Farina V, Krishnan B. *J Am Chem Soc*. 1991; 113: 9585–9595.
204. Beletskaya IP, Cheprakov A V. *Chem Rev*. 2000; 100: 3009–3066.
205. Ziegler FE, Chakraborty UR, Weisenfeld RB. *Tetrahedron*. 1981; 37: 4035–4040.
206. Miyaura N, Suzuki A. *Chem Rev*. 1995; 95: 2457–2483.
207. White JD, Tiller T, Ohba Y, Porter WJ, Jackson RW, Wang S, Hanselmann R. *Chem Commun*. 1998: 79–80.
208. Maryanoff BE, Reitz AB. *Chem Rev*. 1989; 89: 863–927.
209. Stork G, Nakamura E. *J Org Chem*. 1979; 44: 4010–4011.
210. Nicolaou KC, Seitz SP, Pavia MR, Petasis NA. *J Org Chem*. 1979; 44: 4011–4013.

9. ACRONYMS

Ac	Acetyl
Bpin	"Boron pinacolate"
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
HMDS	Hexamethyldisilazane
HWE	Horner-Wadsworth-Emmons
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	Methoxymethyl
NMR	Nuclear Magnetic Resonance
OAc	Acetoxy
OTf	Triflate
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
py	Pyridine
RCAM	Ring-closing alkyne metathesis
RCM	Ring-closing metathesis
TAS-F	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
TES	Triethylsilane
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine