

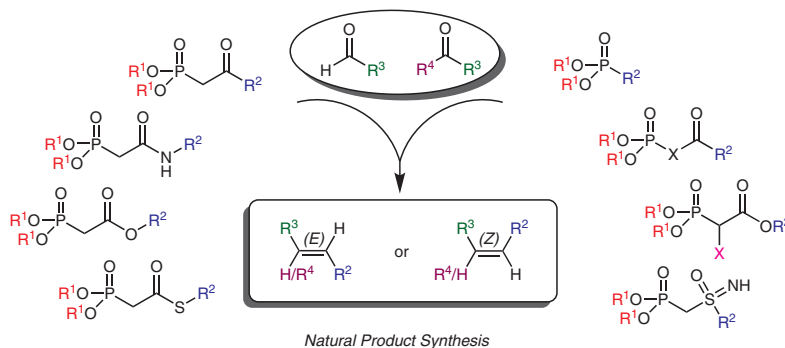
Applications of the Horner–Wadsworth–Emmons Olefination in Modern Natural Product Synthesis

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Abstract The Horner–Wadsworth–Emmons (HWE) reaction is one of the most reliable olefination reaction and can be broadly applied in organic chemistry and natural product synthesis with excellent selectivity. Within the last few years HWE reaction conditions have been optimized and new reagents developed to overcome challenges in the total syntheses of natural products. This review highlights the application of HWE olefinations in total syntheses of structurally different natural products covering 2015 to 2020. Applied HWE reagents and reactions conditions are highlighted to support future synthetic approaches and serve as guideline to find the best HWE conditions for the most complicated natural products.

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Key words HWE reaction, olefination, C=C bond formation, phosphonate, aldehyde, alkenes, natural products

1 Introduction and Historical Background

Carbon–carbon double bonds are ubiquitous in natural and biologically active products and common motifs in organic building blocks. The formation of a C=C bond, often

referred to as olefination, is a fundamental reaction in organic chemistry and allows further transformations, such as oxidation, metathesis, or polymerization. The challenge of selectively introducing double bond motifs into polyfunctional molecules motivated organic chemists early on, and gained an enormous momentum when Wittig published his discovery on carbonyl olefination in 1954 (Figure 1), later called the Wittig reaction. He treated carbonyl compounds with substituted quaternary phosphonium salts in the presence of certain condensing agents and discovered that the intermediate phosphonium ylides reacted with the carbonyl compound to form an unstable intermediate, which then broke down to phosphine oxide and an olefin.¹ This epochal discovery significantly changed the direction of olefination chemistry. Since then, the Wittig principle of double bond formation has been thoroughly studied and because of its effectiveness and applicability has led to the development of related transformations.² Most notably, in 1958 Horner showed that the acidity of a phosphonate correlates with its reactivity to form a stabilized phosphonate carbanion that reacts with carbonyl compounds to yield an olefin.³ To prove his theory, he reacted methyldiphenylphosphine oxide with benzophenone in the presence of sodium amide in benzene and obtained the predicted products diphenylphosphinic acid and 1,1-diphenylpropene. Wadsworth and Emmons discussed the reaction reported by Horner and defined its limitations in 1961.⁴ They found that both the Wittig and Horner reactions share same principles but with the major difference that phosphonate carbanions are stabilized by electron-withdrawing groups, which makes them more nucleophilic and less basic compared to phosphonium ylides (Figure 2). The systematic exploration of the now titled Horner–Wadsworth–Emmons (HWE) olefination opened a wide range of new possibilities and quickly became one of the most intensively studied and commonly applied reactions for selective double bond formation.

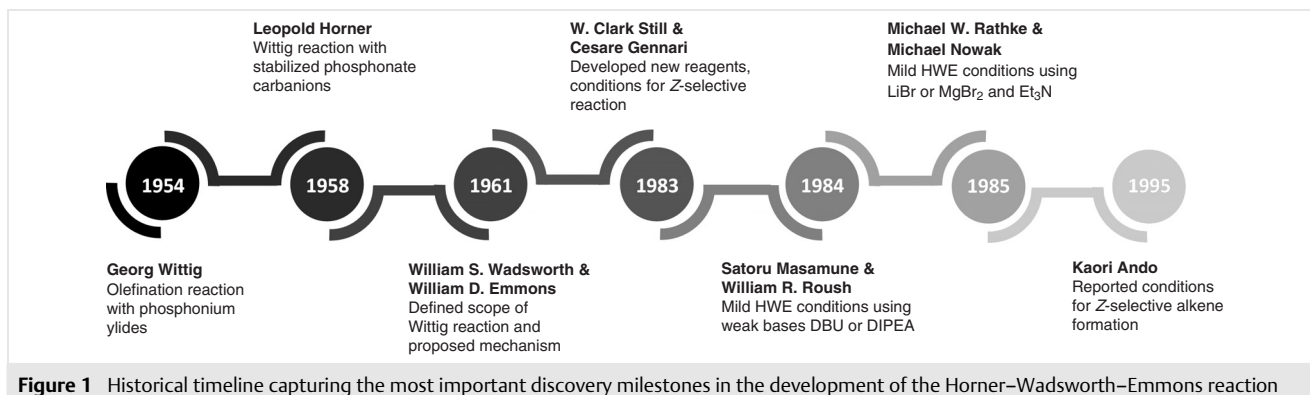


Figure 1 Historical timeline capturing the most important discovery milestones in the development of the Horner–Wadsworth–Emmons reaction

In 1983 Still and Gennari modified the HWE reaction to obtain almost exclusively Z-selective alkenes.^{5,6} This transformation was achieved by using electrophilic bis(trifluoroethyl)phosphonoacetate in combination with a strong dis-

sociating base, such as potassium hexamethyldisilazide (KHMDs) and 18-crown-6 in THF, which allowed highly stereoselective formation of Z-unsaturated esters. In 1995, Ando reported that the use of ethyl diphenylphosphono-

Biographical Sketches



Christine Beemelmans (1981) received her diploma in chemistry at the RWTH Aachen (Germany) in 2006. After a one-year research stay in Prof. Mikiko Sodeoka's group at RIKEN (Wako-Shi, Japan) she then performed her Ph.D. under the supervision of Prof. Hans-Ulrich Reissig with a fellowship from the Fonds der Chemischen In-

dustrie and the Studienstiftung des Deutschen Volkes. After postdoctoral stays in Prof. Keisuke Suzuki's group at the Tokyo Institute of Technology (Tokyo, Japan) and Prof. Jon Clardy's group at Harvard Medical School (USA), supported by fellowships from the German Exchange Service and German National Academy of Sciences

Leopoldina, she joined the Leibniz Institute for Natural Product Research and Infection Biology (Jena, Germany) as junior research group leader at the end of 2013. Her research focuses on the isolation, characterization, and total synthesis of microbial signaling molecules.



Dávid Roman received his B.Sc. degree in chemistry (2015) and M.Sc. degree in organic chemistry (2017) from University of Pavol Jozef Šafárik in Košice (Slovakia). After his graduation in 2017, he joined the lab of Dr Andreas Lerchner

in the DAX Global Discovery Chemistry (GDC) department of Novartis Institute for Biomedical research (NIBR) in Basel (Switzerland) for a research stay. Since 2018, he has been performing his doctoral studies in the group of Chemical Biology

of Microbe-Host Interactions led by Dr Christine Beemelmans at the Hans-Knoll Institute in Jena (Germany). His main research focuses on total synthesis and derivatization of natural products of microbial origin.



Maria Sauer received her B.Sc. and M.Sc. degrees in chemistry (2019) from Friedrich-Schiller-University in Jena (Germany). In

2019, she joined Dr. Christine Beemelmans' group where she is currently working on method development and applications

in total synthesis of biologically active natural products as part of her doctoral studies.

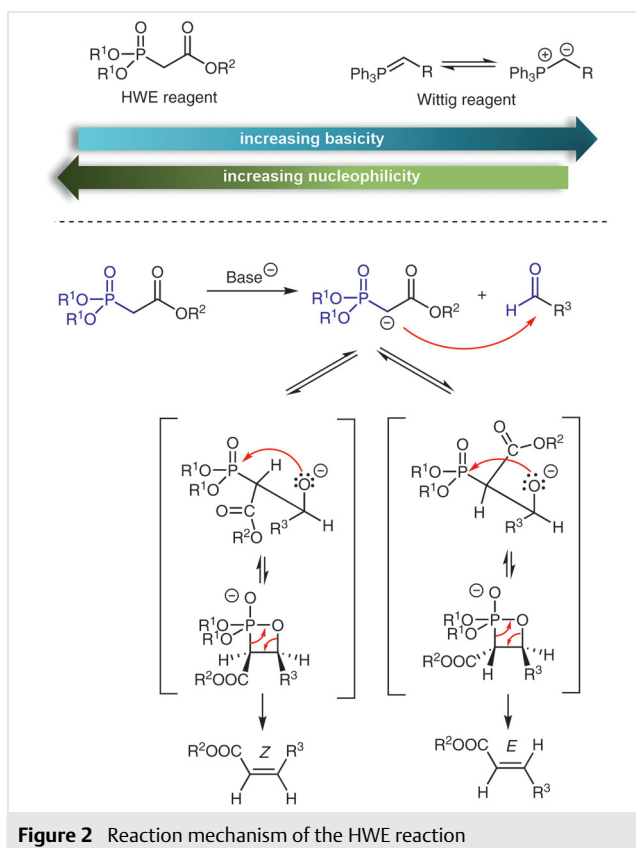


Figure 2 Reaction mechanism of the HWE reaction

acetate results in an almost exclusive formation of *Z*-alkenes by using Still's conditions [KHMDs/18-crown-6] and benzyltrimethylammonium hydroxide (Triton B) as a base.⁷

Shortly after the reports by Still and Gennari, Masamune and Roush reported in 1984 that the presence of lithium chloride leads to complexation of the phosphonate reagent, which results in increased acidity and reactivity; weaker bases like DBU or diisopropylethylamine (DIPEA) can be used for deprotonation.⁸ Rathke and Nowak extended these studies in 1985 and reported that the use of LiBr or MgBr₂ and triethylamine leads to a conversion of aldehydes and ketones with similar yields to those reactions reported with strong bases.⁹ These studies triggered a cascade of explorations to optimize the conditions for HWE reactions (phase transfer catalyst,¹⁰ microwave irradiation, metal-promoted HWEs),¹¹ selectivity (enantioselective or diastereoselective transformations),¹² and substrate scope. While these seminal findings unraveled the correlation of acidity, complexation, and reactivity in phosphonate-based olefination reactions, they also stimulated the usage of other heteroatom-

stabilized carbanions. This mainly includes the Julia-Kocienski olefination (methylated aryl alkyl sulfones)¹³ and Peterson olefination (α -silyl carbanion).¹⁴

The enormous numbers of HWE reaction possibilities in addition to its functional group compatibility and selectivity resulted in its wide synthetic use, in particular in natural product synthesis. Building up on preceding reviews that discuss the mechanisms and reaction scopes of Wittig² and HWE reactions,¹⁵ this review aims to highlight the diversity of employed HWE reagents and their applications in natural product total syntheses covering 2015 to 2020 (Scheme 1). Subsections are structured chronologically and according to the formation of macrocycles, such as small to medium rings, α,β -unsaturated carbonyls, and conjugated double bonds. The applied reagents and reaction conditions of the herein described syntheses are highlighted in Table 1 and allow the reader to navigate through the diversity of HWE reactions and support identifying suitable reagents and conditions for challenging natural product syntheses.

2 Applications of HWE

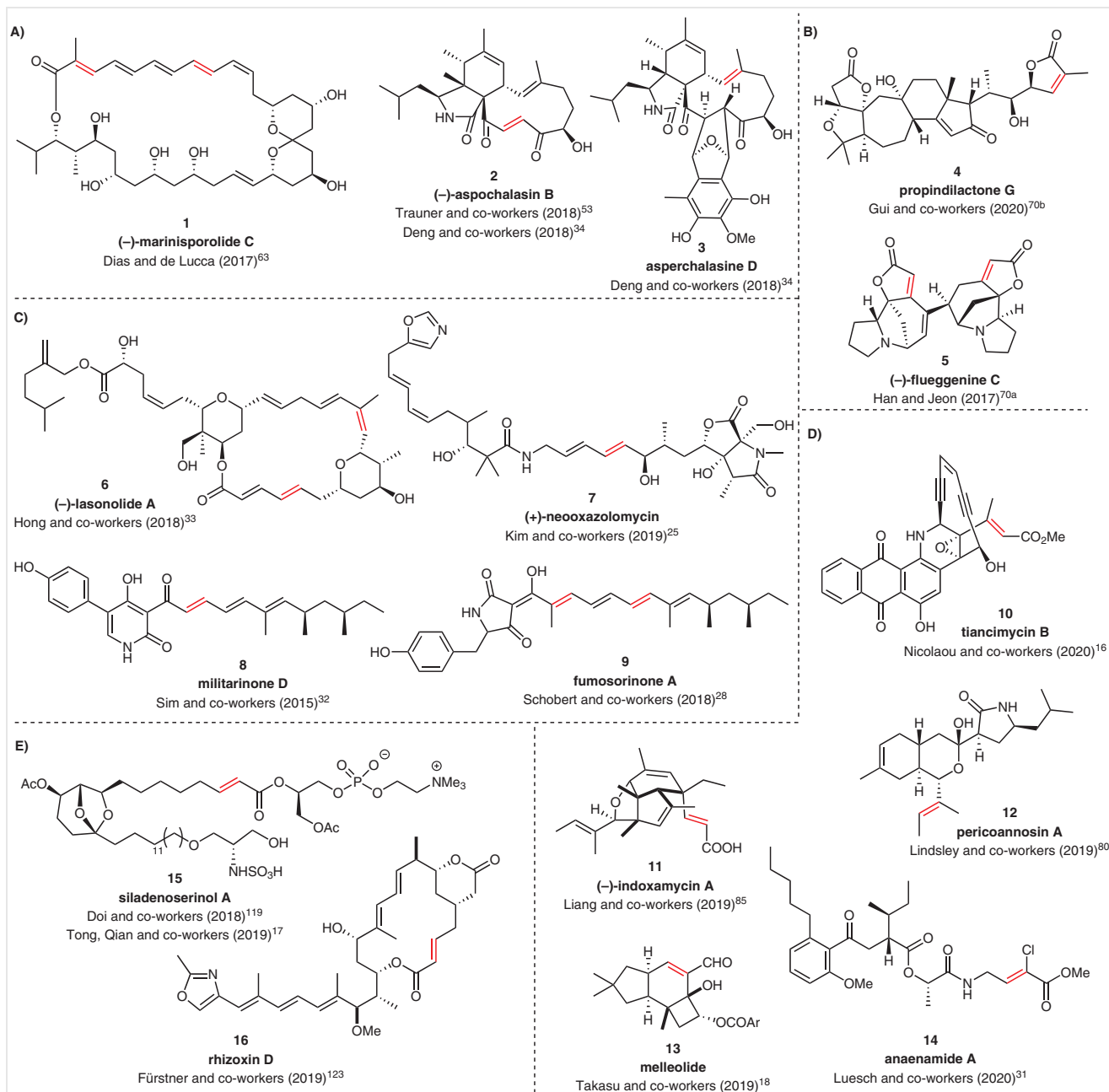
2.1 Cyclization by HWE Reactions

At the beginning of the 1970s the HWE reaction was examined a synthetic tool in the synthesis of lactones,³⁹ lactams,⁴⁰ macrocycles,⁴¹ and hetero-polycycles.⁴² Since then, intramolecular HWE-based cyclization reactions have become very popular in natural product total synthesis due to their functional group tolerance, high yields, and selectivity.⁴³

2.2.1 Formation of Medium- to Larger-Sized Rings

Polyfunctionalized macrocyclic natural products are ubiquitous in nature. Their stereochemical complexity and ring size most often confers high bioactivities, thus making them interesting targets for medicinal and organic chemists.⁴⁴ To showcase the application of HWE reaction, we selected four recent literature examples.

Cytochalasins are a diverse group of polyketide-derived macrocycles of fungal origin, which are known for their broad range of biological activities.⁴⁵ This includes cytotoxic, immunomodulatory, and nematocidal properties.⁴⁶ The cytochalasin family has been a popular synthetic target for decades⁴⁷ and numerous reports describe synthetic strategies towards cytochalasin B,⁴⁸ cytochalasin H,⁴⁹ cytochalasin O,⁵⁰ chaetochalasin A,⁵¹ aspochalasin B,⁵² and other related congeners of the cytochalasin family.



Scheme 1 Examples of some natural products synthesized using HWE reactions (highlighted red) presented herein incorporated in their total syntheses. Natural products are sorted according the outcome of the HWE reaction within their synthetic strategy for the formation of (A) macro- and medium-sized α,β -unsaturated rings, (B) small rings, (C) polyconjugated C=C bonds, (D) α,β -unsaturated esters and enones, and (E) coupling of larger building blocks.

Table 1 Summary of Some HWE Reagents and Conditions Sorted According to the General Formulas Presented

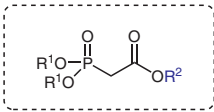
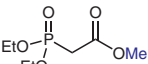
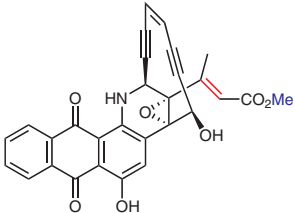
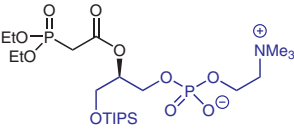
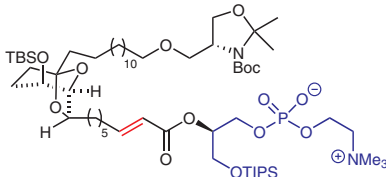
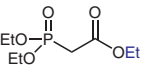
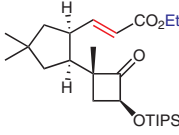
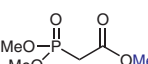
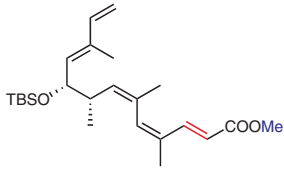
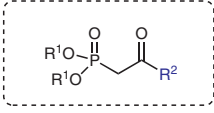
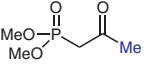
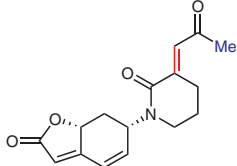
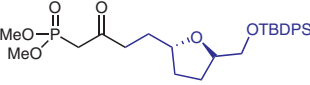
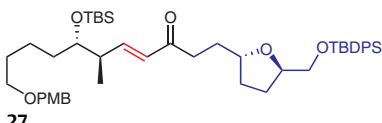
HWE phosphonate reagents	Conditions	Products of HWE reaction	Yield (%)	Ratio (<i>E/Z</i>)	Year (Section) ^a
					
 17	NaH, THF -78 to 0 °C, ca 5 h	 10	84	8:1	2020 ¹⁶ (2.5)
 18	DBU, LiCl, THF r.t., 2 h	 19	77	only <i>E</i>	2019 ¹⁷ (2.8)
 20	NaH, toluene 0 °C to r.t., 1.5 h	 21	78 (2 steps)	only <i>E</i>	2019 ¹⁸ (- ^b)
 22	<i>n</i> -BuLi, DMPU, THF 0 °C, 4.5 h	 23	98	20:1	2019 ¹⁹ (- ^b)
					
 24	NaH, <i>t</i> -BuOK, THF -78 °C to r.t., ca. 1 h	 25	20 (2 steps)	only <i>E</i>	2020 ²⁰ (- ^b)
 26	LiCl, DIPEA, MeCN 0 °C to r.t., 8 h	 27	91	only <i>E</i>	2020 ²¹ (2.8)

Table 1 (continued)

HWE phosphonate reagents	Conditions	Products of HWE reaction	Yield (%)	Ratio (E/Z)	Year (Section) ^a
 28	Ba(OH) ₂ ·8H ₂ O, THF r.t., 1 h	 29	85	only E	2018 ²² (-b)
 30	LiCl, Et ₃ N, THF 0 to 40 °C, 2.5 h	 31	90	only E	2016 ²³ (2.3)
 32	Ba(OH) ₂ ·8H ₂ O, THF r.t., 12.5 h	 33	73 (2 steps)	only E	2019 ²⁴ (-b)
 34	Ba(OH) ₂ , THF/H ₂ O -30 °C, 16 h	 35	75	only E	2019 ²⁵ (2.7)
 36	LiHMDS, HMPA, THF -78 °C to r.t., 2 h	 37	69	only E	2019 ²⁶ (-b)
 36	<i>n</i> -BuLi, THF -78 °C to r.t., ca 1 h	 38	96	5.6:1	2017 ²⁷ (-b)
 39	NaH, THF 0 °C to r.t.	 40	67	95% de	2018 ²⁸ (2.7)
 41	LDA, THF -78 to 0 °C, 2 h	 42	60 (2 steps)	5:1	2017 ²⁹ (2.7)
 43	<i>n</i> -BuLi, THF r.t., 17 h	 44	62	only E	2016 ³⁰ (2.7)

Table 1 (continued)

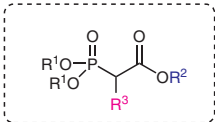
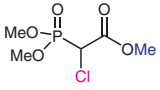
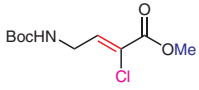
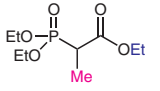
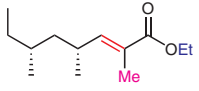
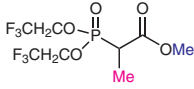
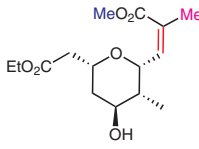
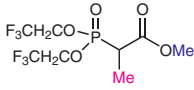
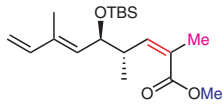
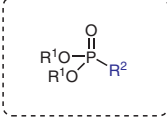
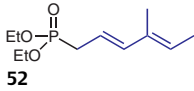
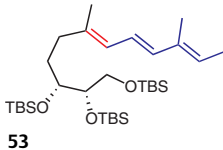
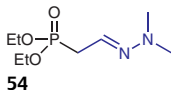
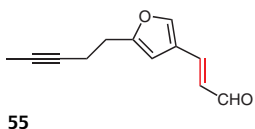
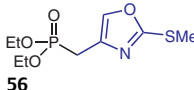
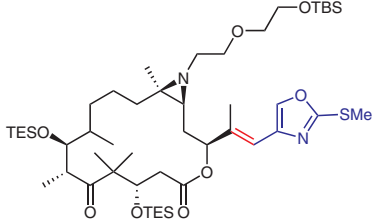
HWE phosphonate reagents	Conditions	Products of HWE reaction	Yield (%)	Ratio (E/Z)	Year (Section) ^a
					
 45	<i>n</i> -BuLi, THF −78 °C, 3 h	 46	50	6:1	2020 ³¹ (2.4)
 47	NaH, THF 0 °C to r.t., 1 h	 48	71 (2 steps)	1.2:3	2015 ³² (2.7)
 49	18-crown-6, KHMDS, THF −78 °C, 2 h	 50	74 (2 steps)	only Z	2018 ³³ (2.7)
 49	18-crown-6, KHMDS, THF −78 °C, 1.5 h	 51	90	1:20	2019 ¹⁹ (−b)
					
 52	KHMDS, THF 0 °C, 10 min	 53	82	7:1	2018 ³⁴ (2.2.1)
 54	LDA, THF r.t., 12 h	 55	86	only E	2016 ²³ (2.3)
 56	<i>n</i> -BuLi, THF −78 to 0 °C, 1.5 h	 57	55	only E	2020 ³⁵ (2.5)

Table 1 (continued)

HWE phosphonate reagents	Conditions	Products of HWE reaction	Yield (%)	Ratio (<i>E/Z</i>)	Year (Section) ^a
 58	LiCl, DIPEA, MeCN r.t., 24 h	 59	77	only <i>E</i>	2020 ³⁶ (2.4)
 60	NaH, toluene 0 °C, 11.5 h	 61	78 (2 steps)	only <i>E</i>	2019 ¹⁸ (2.3)
 62	<i>t</i> -BuOK, THF r.t., 5 h	 63	85	9.2:0.8	2016 ³⁷ (-b)
 64	<i>n</i> -BuLi, THF -78 °C, 2 h	 65	98	only <i>E</i>	2016 ³⁸ (-b)

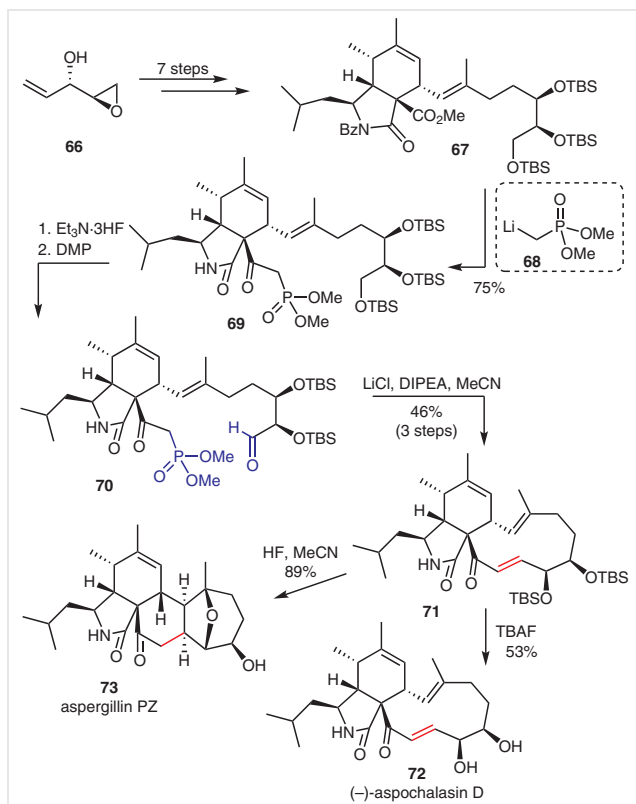
^a Section in which relevant material can be found for this synthesis.

^b Not discussed in following sections.

An excellent example of a ring-closing HWE reaction in the total synthesis of (–)-aspochalasin D (**72**) was described in 2018 by Trauner and co-workers (Scheme 2).⁵³ Their strategy started with epoxy alcohol **66** that was converted into isoindolone moiety **67** in 7 steps. Addition of dimethyl lithiomethylphosphonate (**68**) yielded *N*-debenzoylated phosphonate **69**. Aldehyde **70** was formed following selective TBS deprotection and oxidation with the Dess–Martin periodinane (DMP) of the primary alcohol. The HWE reaction using Masamune and Roush conditions (LiCl, DIPEA, MeCN) afforded macrocycle **71** without epimerization in 3 steps and 46% yield.⁸ The synthesis of (–)-aspochalasin D (**72**) was completed by TBS deprotection using tetrabutylammonium fluoride, while acidic TBS deprotection using HF in acetonitrile yielded aspergillin PZ (**73**) in 89% yield. (–)-Aspochalasin D (**72**) was treated in 45% yield.

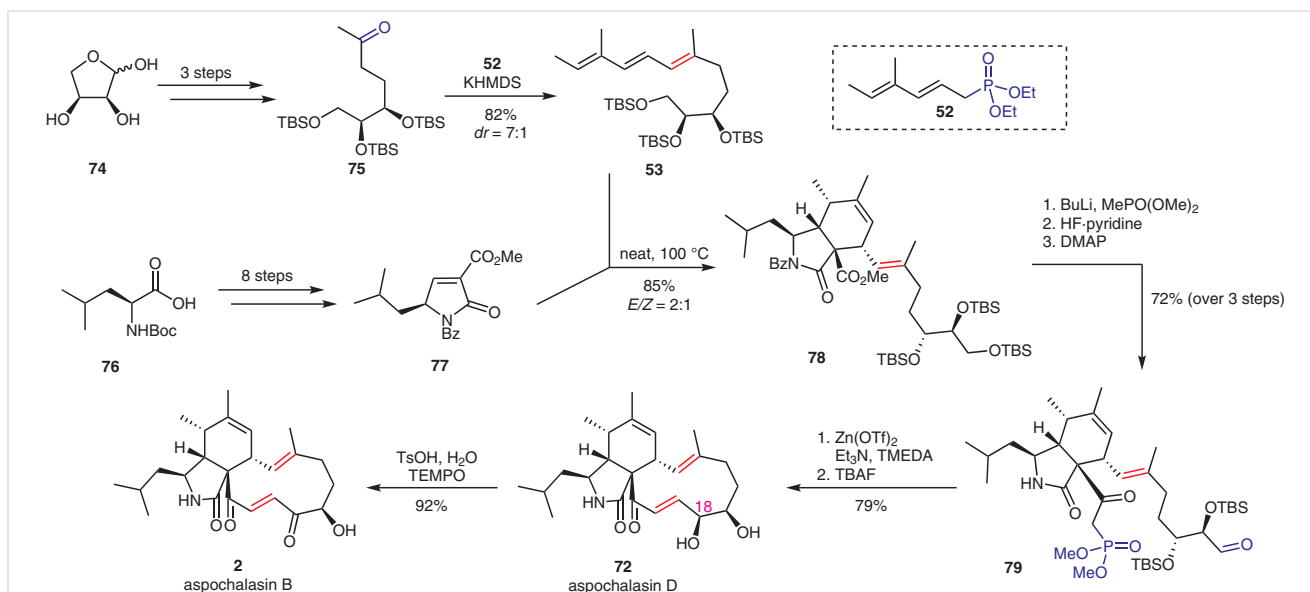
Deng and co-workers accomplished the first total syntheses of asperchhalasines A, D, E, and H in 2018, which included a highly diastereoselective intermolecular Diels–Alder reaction and an HWE macrocyclization step to yield the monomer aspochalasin B (**2**) (Scheme 3).³⁴ Their synthesis started with the stereospecific synthesis of triene

fragment **53**, starting from *L*-arabinose via a known 3-step sequence to obtain hemiacetal **74**.⁵⁴ This was followed by a Wittig reaction, TBS-protection, and the hydrogenation of the double bond to yield methyl ketone **75** in 69%. Methyl ketone **75** was directly subjected to an HWE reaction with dienyl phosphonate **52** under strongly basic conditions to give the conjugated triene **53** in 82% yield (*E/Z* ~7:1).⁵⁵ The synthesis of lactam **77** was achieved in 8 steps from *N*-Boc-*L*-leucine **76** via *C*-acylation with methyl chloroformate,⁵⁶ selenylation, and oxidative elimination. Heating a mixture of **53** and **77** (100 °C, neat) resulted in the formation of the Diels–Alder product **78** (*E/Z* 2:1). The phosphonate was installed by addition of dimethyl lithiomethylphosphonate to the methyl ester **78**. Deprotection and oxidation of the primary alcohol yielded aldehyde **79** as a substrate for HWE macrocyclization. The 11-membered enone **72** was not achieved after screening different reaction conditions (KHMSD, NaH, LiBr/Et₃N,⁹ K₂CO₃/18-crown-6⁵⁷ or NaOCH₂CF₃⁵⁸). Only a mild Lewis acid, Zn(OTf)₂, in combination with TMEDA and triethylamine was found to promote intramolecular HWE olefination. This was followed by TBS deprotection to obtain enone (–)-aspochalasin D (**72**) in 79% with minimal



Scheme 2 Synthesis of (-)-aspochalasin D and aspergillin PZ by Trauner and co-workers

epimerization at C18.⁵⁹ The synthesis of (-)-aspochalasin B (**2**) was completed after oxidation of the allylic alcohol in (-)-aspochalasin D (**72**) with TEMPO in 92% yield.

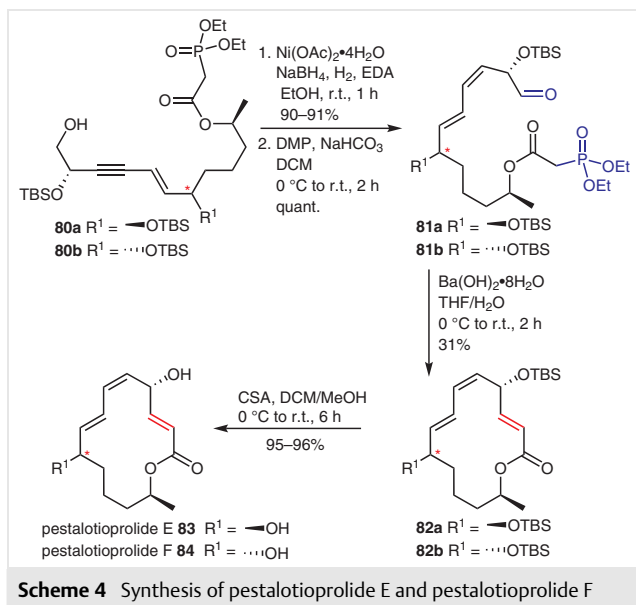


Scheme 3 Total synthesis of (-)-aspochalasin D and aspochalasin B by Deng and co-workers

Naturally occurring 12, 14, or 16-membered macrolides are most often of polyketide origin and have been shown to exhibit diverse pharmacological activities.⁶⁰ A series of new 14-membered macrolides, named pestalotioprolides B–H, were discovered from the mangrove-derived endophytic fungus *Pestalotiopsis microspora* by Liu, Proksch, and co-workers in 2016; the derivatives showed significant cytotoxicity against the murine lymphoma cell lines.⁶¹ The first total synthesis of derivatives pestalotioprolide E (**83**) and pestalotioprolide F (**84**), with revision of its proposed structure, was accomplished by Goswami and co-workers (Scheme 4).⁶² The key step of this synthesis was the HWE reaction of **81a** and **82b**, which were obtained by partial hydrogenation of Sonogashira products **80a** and **80b**. Oxidation of the primary alcohols yielded the corresponding aldehydes **81a** and **81b** that were necessary for the intramolecular HWE reaction.

After testing different macrocyclization conditions, the combination of LiCl/DIPEA or Ba(OH)₂·8H₂O were found to provide macrocycles **82a** and **82b** in optimized 30% yield. Subsequent desilylation of **82a** and **82b** resulted in pestalotioprolide E (**83**) and the revised structure of pestalotioprolide F (**84**), respectively.

Dias and de Lucca designed the first total synthesis of the 30-membered (-)-marinisporolide C (**1**) in 2017, which allowed the determination of the relative and absolute configuration of the natural product (Scheme 5).⁶³ Aldehyde **85** was prepared in 16 steps and elongated using Takai–Utimoto olefination with CHI₃ producing vinyl iodide **86** in 82% yield.⁶⁴ The free OH group in **86** was then subjected to Yamaguchi esterification with **87** to afford **88** in 92%.⁶⁵ Treatment with HF-pyridine led to global TBS deprotection and spiroketal formation. The remaining hydroxyl groups



Scheme 4 Synthesis of pestalotioprolide E and pestalotioprolide F

were again protected with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and afforded spiroketal **89**. Stille cross-coupling with **90** followed by oxidation of the primary alcohol with TEMPO and bis(acetoxy)iodobenzene (BAIB) provided the necessary aldehyde **91**. HWE olefination to the macrocycle was accomplished using Masamune–Roush conditions (LiCl, DBU) in acetonitrile. After global deprotection with HF-pyridine and HCl, (–)-marinisporolide C (**1**) was achieved in 25 steps (longest linear sequence) with 1.15% overall yield.

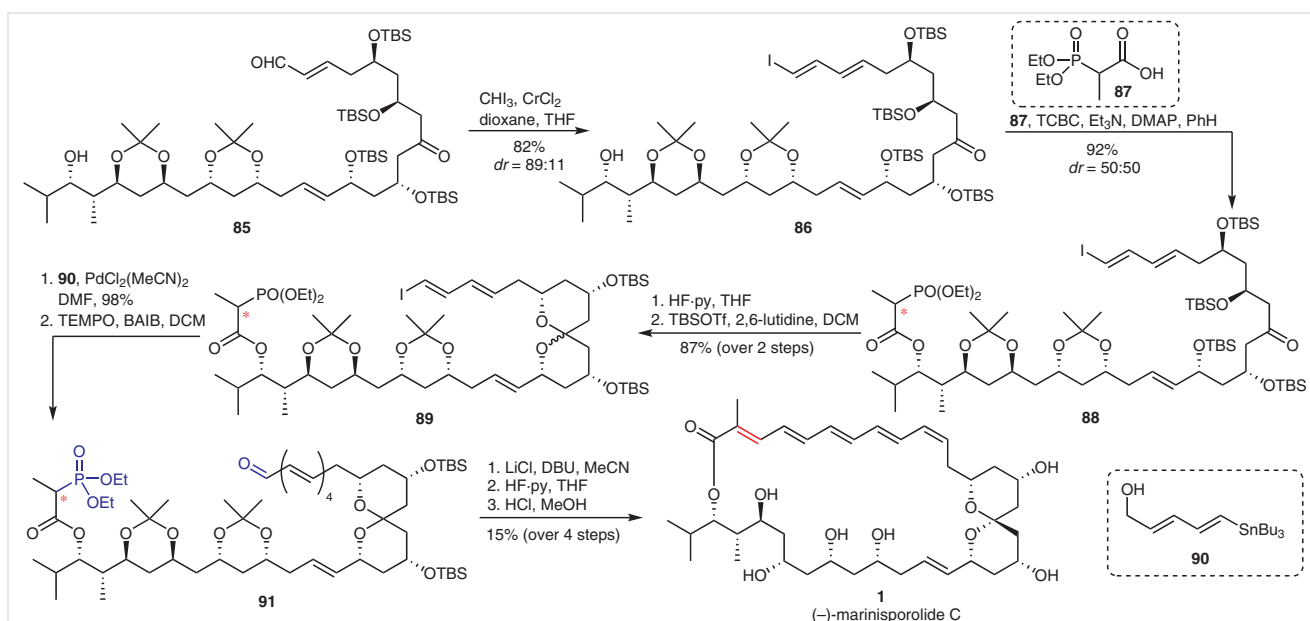
2.2.2 Formation of Small- to Medium-Sized Rings

The selective synthesis of small (3–5) and medium-sized (6–13) ring systems are still a challenge in total synthesis.⁶⁶ The HWE reaction has been applied in the formation of many five- and six-membered ring systems as shown in the following three examples.

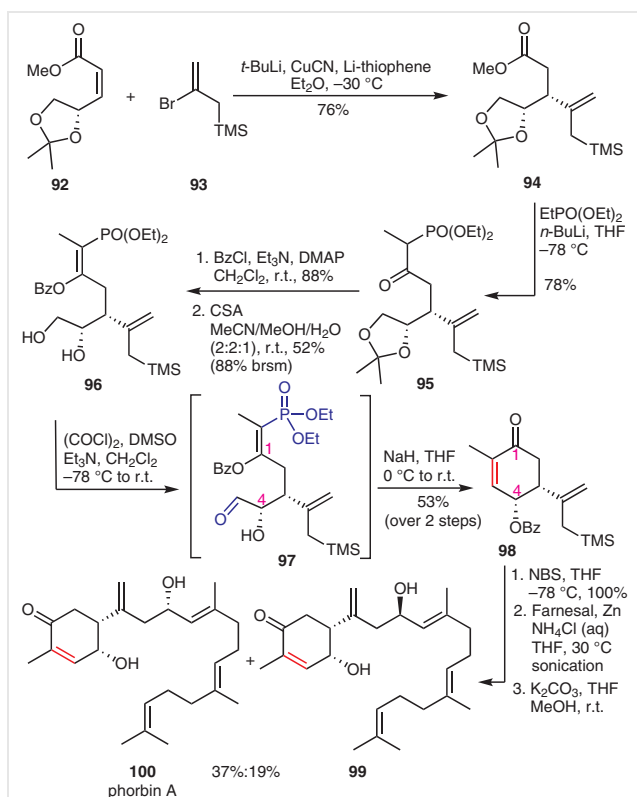
In 2015, Brimble and co-workers employed a one-pot benzoyl transfer-intramolecular HWE reaction as a key step in the construction of *cis*- γ -hydroxycarvone-based building blocks, which are important intermediates in the synthesis of sesterterpenoid natural products (Scheme 6).⁶⁷

The synthesis of the key starting material allylsilane **98** was accomplished in a 6-step synthesis from **92** and **93** via a sequence of diastereoselective conjugate addition, nucleophilic phosphonate addition, and the key benzoyl transfer-intramolecular HWE reaction to construct the cyclohexenone **98**. Subsequent transformation into an allyl bromide allowed Barbier coupling with farnesal and subsequent deprotection of the benzoyl group yielded phorbins A (**100**) and its C4'-epimer **99**. This synthetic approach showed that benzoyl enol ethers could serve as a masking group of β -ketophosphonates and allow a one-pot benzoyl transfer-intramolecular HWE reaction. The same protocol was also applied in the synthesis of sesterterpenoid natural products, such as phorbaketal A, which showed selective activity against a range of cancer cell lines.⁶⁸

In the same year, Hiemstra and co-workers described the total synthesis of sesquiterpene lactone aquatolide (**107**), which was isolated from *Asteriscus aquaticus*



Scheme 5 Final synthetic sequence within the total synthesis of (–)-marinisporolide C by Dias and de Lucca

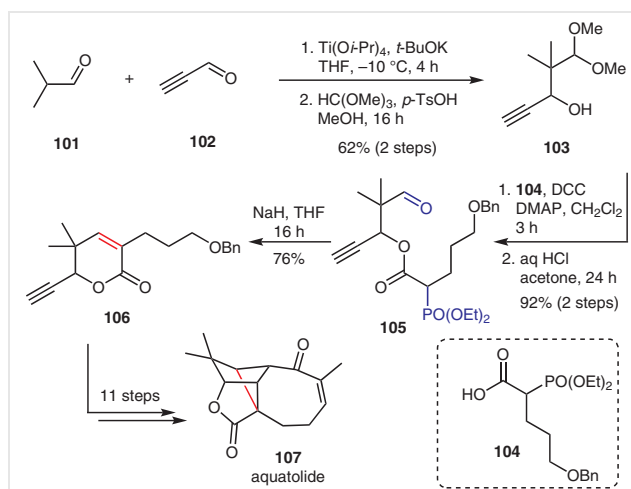


Scheme 6 Synthesis of phorbol A and its C-4' epimer by Brimble and co-workers

(Scheme 7).⁶⁹ The total synthesis started with a cross-aldol reaction of isobutyraldehyde (**101**) and propynal (**102**) followed by treatment with trimethyl orthoformate yielding acetal **103**. The intramolecular HWE-based cyclization was introduced after esterification with phosphonate **104** by treatment with an excess of NaH (1.5 equiv) under diluted conditions (0.02 M) to form pentenolide **106** in 76% yield. The synthesis required 11 more steps, including Crabbé homologation to an allene, photochemical [2+2]-cycloaddition, hydroboration, intramolecular Mukaiyama-type aldol reaction to cyclize the eight-membered ring, Dess–Martin oxidation, and Lewis acid catalyzed cyclization of silyl enol ether to yield racemic aquatolide (**107**) (16 steps, longest linear chain) with an overall yield of 2.2%.

Jeon and Han accomplished the first total synthesis of (–)-flueggeine C (**5**) (Scheme 8) in 2017,^{70a} which belongs to the plant-derived securinega alkaloids family.⁷¹

Their synthesis started with the conversion of Boc-protected D-proline **108** in 8 steps. This included diastereoselective Rauhut–Currier (RC) reaction to acetylated dimer **109**.⁷² The tertiary alcohols were both esterified by slow addition of diethylphosphonoacetic acid to **109** in the presence of DCC affording phosphonate **110** in 51% yield. The phosphonate **110** was then converted into olefin **111** via an intramolecular HWE using NaH as base that was followed

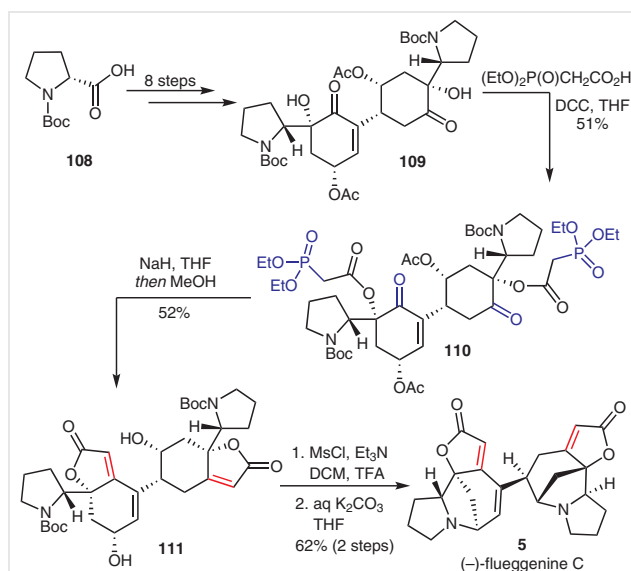


Scheme 7 Total synthesis of aquatolide by Hiemstra and co-workers

by methanolic deacetylation. Subsequent treatment of alcohol **111** with methanesulfonyl chloride and triethylamine followed by TFA-induced Boc-deprotection and final basic treatment (aq K₂CO₃ in THF) resulted in (–)-flueggeine C (**5**).

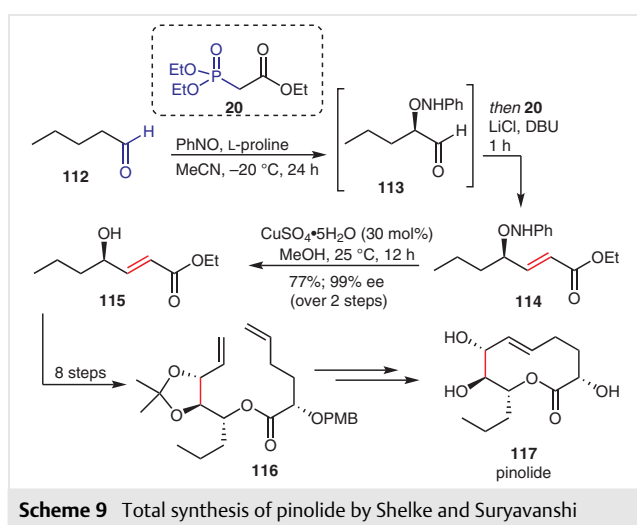
2.3 Synthesis of α,β -Unsaturated Carbonyl Groups

α,β -Unsaturated esters and enones are common motifs in chemical building blocks and natural products. Here, we highlight five recent natural product syntheses that required the introduction of α,β -unsaturated carbonyl groups via HWE reactions.



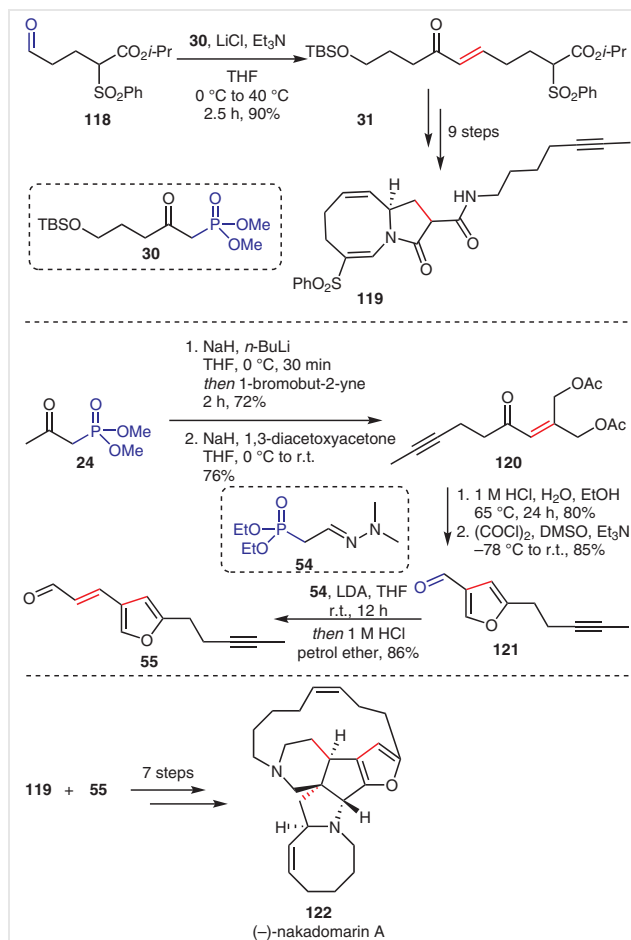
Scheme 8 Synthesis of (–)-flueggeine C by Jeon and Han

The first example is pinolide (**117**), which is a member of naturally occurring decanolides isolated in 2012⁷³ and was synthesized in 2016 by Shelke and Suryavanshi (Scheme 9).⁷⁴ The synthesis started with asymmetric α -aminoxylation of pentanal (**112**) using L-proline and nitrosobenzene as an electrophilic oxygen source. α -Anilinoxy aldehyde **113** was subjected to HWE olefination (LiCl and DBU) in the second step with phosphonoacetate **20** to yield γ -anilinoxy- α,β -unsaturated ester **114**, which underwent copper-mediated N–O bond cleavage to produce secondary alcohol **115** in 77% yield (99% ee). Total synthesis of pinolide **117** was accomplished in 10 additional steps.

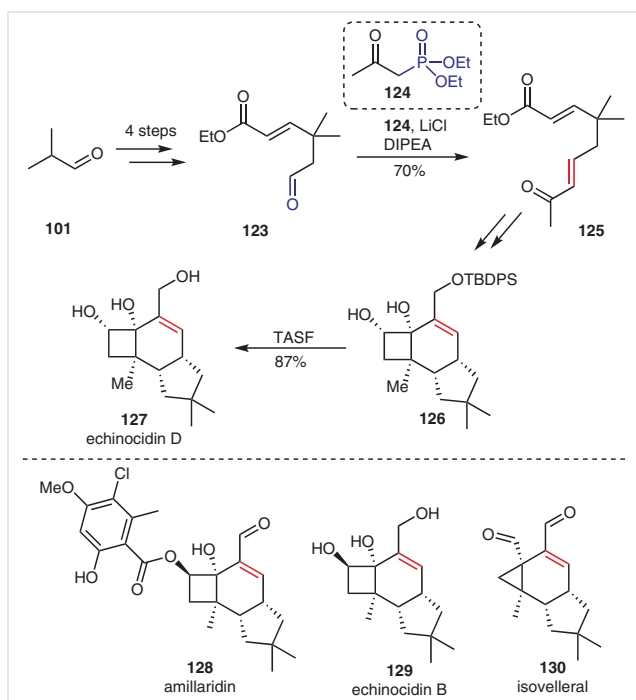


In the 2016 total synthesis of nakadomarin A by Boeckman and co-workers, an HWE reaction was employed to construct necessary building blocks.²³ Nakadomarin A belongs to the manzamine alkaloid family and was isolated from marine sponges by Kobayashi and co-workers.⁷⁵ Members of this compound family exhibit a broad range of bioactivities, such as cytotoxicity, antimicrobial, antileishmanial, antimalarial, and many more.⁷⁶

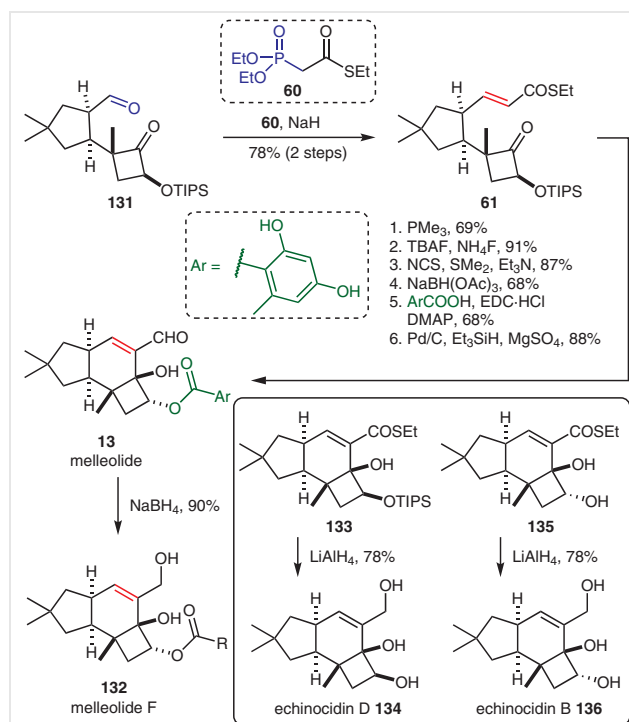
As shown in Scheme 10, transformation of aldehyde **118** and phosphonate **30** under Masamune and Roush conditions (LiCl/Et₃N) resulted in the formation of the α,β -unsaturated ketone **31** in 90% yield.²⁵ A second reaction sequence started with the dianion of phosphonate **24** being propargylated and converted into enone **120** via an HWE olefination with 1,3-diacetoxyacetone (55% yield over 2 steps). After deprotection and Swern oxidation the resulting furancarbaldehyde **121** was again subjected to an HWE reaction with iminophosphonate **54** in the presence of LDA and subsequent deprotection yielded **55**. With both **119** and **55** building blocks in hand, the total synthesis of (–)-nakadomarin A (**122**) was accomplished in 17 steps (longest linear sequence) with an overall yield of 3%.



Another example for the use of Masamune and Roush's HWE conditions for the synthesis of linear unsaturated carbonyl units in a natural product synthesis was described in 2017 by Scheidt and co-workers.⁷⁷ They reported the total synthesis of four sesquiterpenoids belonging to the protoiludane, mellolide, and marasmane families (Scheme 11). The synthesis of these bioactive natural products was based on an HWE olefination of aldehyde **123** with phosphonate **124** in the presence of LiCl and DIPEA, which produced enone **125** in good overall yield (70%). Intramolecular reductive pinacol coupling was subsequently employed to synthesize the key intermediate *cis*-cyclobutanediol **126**. The total synthesis of echinocidin D (**127**) was accomplished by desilylation of **126** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). Intermediate **126** was also used to synthesize isovelleral (**130**) (3 additional steps), amillaridin (**128**), and echinocidin B (**129**).



Scheme 11 Synthesis of isovelleral, amillaridin, and echinocidins B and D and by Scheidt and co-workers



Scheme 12 Total synthesis of melleolide, melleolide F, and echinocidins B and D by Takasu and co-workers

Takasu and co-workers also described the synthesis of protoilludane sesquiterpenes melleolide (**13**), melleolide F (**132**), echinocidins B (**136**) and D (**134**) (Scheme 12).¹⁸ Here, an HWE reaction of ketoaldehyde **131** with phosphonate **60** yielded α,β -unsaturated thioester **61** (78% yield over 2 steps). Subsequent intramolecular Morita–Baylis–Hillman reaction with trimethylphosphine yielded the cyclized precursor **133**.

The synthesis of protoilludane by Takasu and co-workers was accomplished by using a redox sequence including a Corey–Kim oxidation to cyclobutanone, reduction with $\text{NaBH}(\text{OAc})_3$ to **135**, esterification of the alcohol with orsellinic acid, and Fukuyama reduction of the thioester to obtain melleolide (**13**). Reduction of the aldehyde **13** with NaBH_4 yielded melleolide F (**132**). The synthesis of other natural products of the protoilludane family from intermediate **133** was also achieved. This includes echinocidin D (**134**) by reduction and desilylation with lithium aluminum hydride and echinocidin B (**136**) from reduction of intermediate **135** with LiAlH_4 .

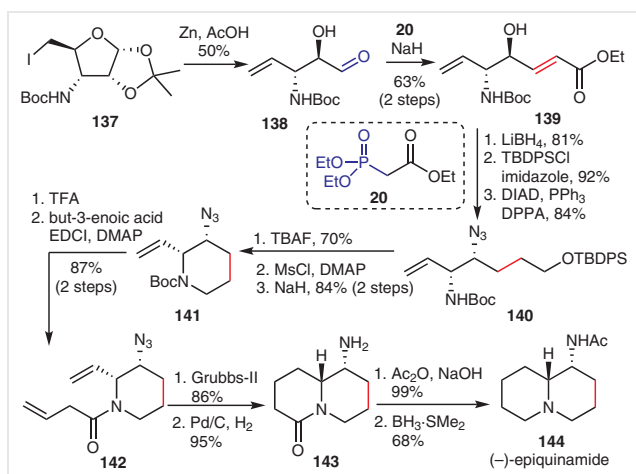
Kongkathip and co-workers described the asymmetric total synthesis of (–)-epiquinamide (**144**) in 2019,^{78a} which is a quinolizidine alkaloid isolated from the skin of an Ecuadorian frog^{78b} (Scheme 13). Quinolizidines are an important group of natural products, which show a broad range of biological activity. For the total synthesis, furanoside **137**,⁷⁹ derived from D-glucose, was subjected to a Zn-mediated Bernet–Vasella reaction. The resulting aldehyde **138** was

subjected to an HWE reaction with **20** in the presence of NaH in toluene to obtain unsaturated ester **139** in 63% yield (2 steps). After reduction of ester **139** to a primary alcohol and silyl-protection, the secondary alcohol was transformed into the respective azide **140** under Mitsunobu conditions with inversion of the stereocenter. Mesylation of the alcohol and intramolecular carbamate N-alkylation after cleavage of silyl group with TBAF resulted in 2,3-*cis*-disubstituted piperidine **141**. Boc-deprotection and coupling of the amine with but-3-enoic acid provided diene **142**, which was subjected to ring-closing metathesis using the 2nd generation Hoveyda–Grubbs catalyst yielding an unsaturated quinolizidinone. The total synthesis of (–)-epiquinamide (**144**) was completed by hydrogenation of the saturated amine **143**, followed by N-acetylation and reduction of lactam with $\text{BH}_3\cdot\text{SMe}_2$ complex.

2.4 Synthesis of Substituted C=C Bonds

The following two examples illustrate the formation of substituted double bonds by HWE olefinations.

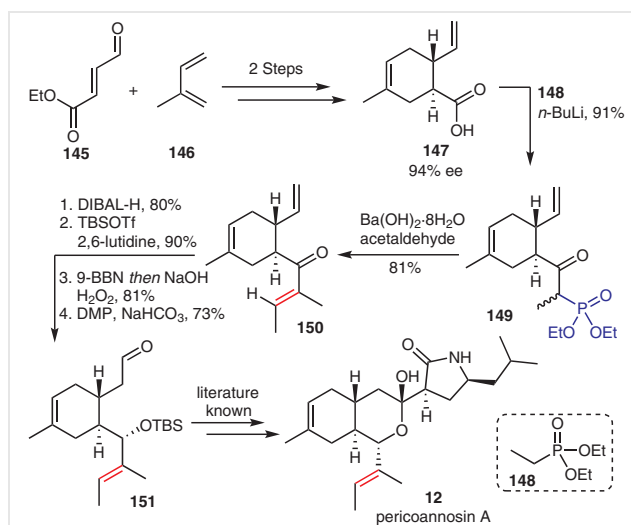
Lindsley and co-workers described the formal total synthesis of pericoannosin A (**12**) in 2019 (Scheme 14),⁸⁰ which was isolated in 2015 from *Periconia* sp. F31 as a new PKS–NRPS hybrid metabolite with a 3-(hexahydro-1*H*-isochromen-3-yl)-5-isobutylpyrrolidin-2-one core structure.⁸¹ The new synthetic route included an HWE reaction to install the substituted olefin and required fewer steps with



Scheme 13 Total synthesis of (-)-epiquinamide by Kongkathip and co-workers

improved overall yield in comparison to the total synthesis of **12** described by Lücke, Kalesse, and co-workers in 2018.⁸² In short, an asymmetric Diels–Alder reaction with **145** and isoprene (**146**) yielded an α,β -unsaturated aldehyde, which was subjected to a Wittig reaction to give terminal alkene **147**. The corresponding β -ketophosphonate **149** was obtained by treatment of **147** with excess lithiated diethyl ethylphosphonate **148** in 91% yield. An HWE reaction of acetaldehyde with phosphonate **149** and $\text{Ba}(\text{OH})_2$ as base produced enone **150** in 81% yield. A Felkin–Anh stereoselective reduction of enone **150** with DIBAL-H afforded the secondary alcohol. Protection of the alcohol followed by selective hydroboration of the terminal alkene and basic oxidizing work-up resulted in an alcohol, which underwent Dess–Martin oxidation to aldehyde **151**.

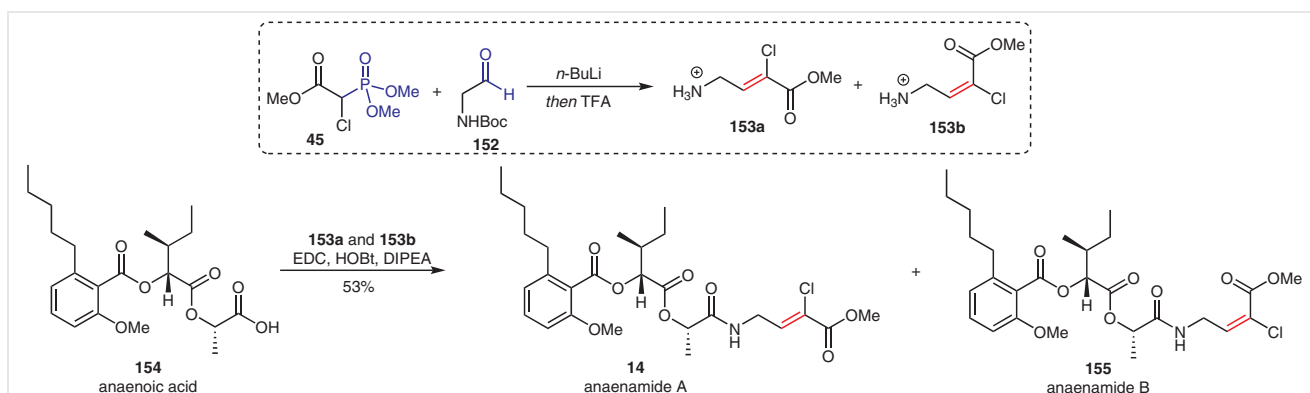
Anaenamides A (**14**) and B (**155**) are new anticancer cyanobacterial depsipeptides containing a chlorinated pharmacophore and were isolated from a marine cyanobacterium derived from the Anaë Island reef system in Guam in 2020.³¹ Their scaffold has an unusual α -chlorinated α,β -un-



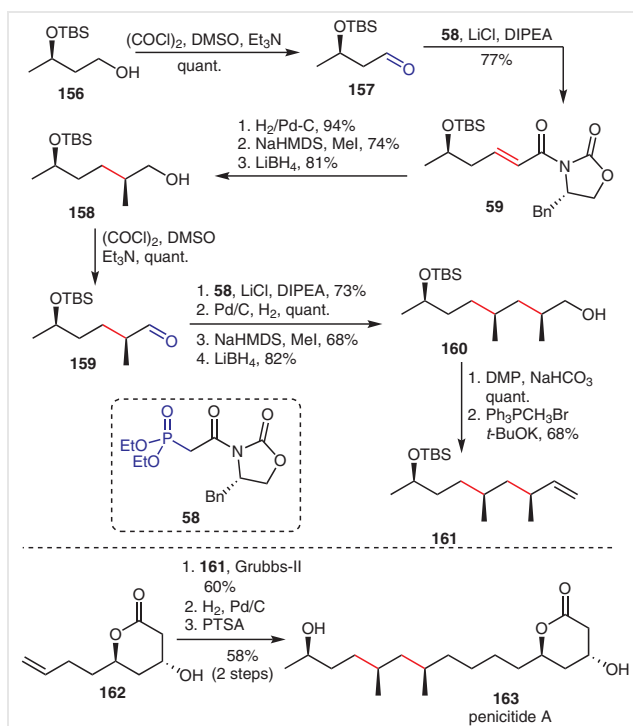
Scheme 14 Formal synthesis of pericoannosin A by Lindsley and co-workers

saturated ester and its double bond geometry impacts the cytotoxicity. Luesch and co-workers achieved the synthesis of anaenoic acid (**154**) in 9 steps that included an HWE reaction to introduce the vinyl halide moiety (Scheme 15).³¹ Building blocks **153a** and **153b** were synthesized from commercially available **152** and phosphonate **45** via HWE olefination, followed by Boc deprotection under acidic conditions. Final coupling of anaenoic acid (**154**) with a crude mixture of **153a** and **153b** by the use of EDC, HOBT, and DIPEA led to the *E*- and *Z*-isomers (**14** and **155**, respectively) of anaenamide.

Goswami and co-workers described the first total synthesis and stereochemical assignment of penicitide A (**163**) in 2020, which is a marine secondary metabolite (Scheme 16).³⁶ Penicitide A (**163**) was isolated from a marine red algal species by Wang and co-workers in 2011 and showed moderate cytotoxicity against pathogen *Alternaria brassicae* and human hepatocellular liver carcinoma cell lines.⁸³



Scheme 15 Total synthesis of anaenamides A and B by Luesch and co-workers



Scheme 16 Total synthesis of penicidine A by Goswami and co-workers

The syntheses commenced with alcohol **156**, which was first subjected to Swern oxidation and the resulting aldehyde **157** transformed by an HWE olefination with phosphonate **58** in the presence of LiCl and DIPEA to obtain primarily *E*-isomer **59** in 77% yield. Alcohol **158** was obtained after hydrogenation, Evans methylation, and reduction with LiBH₄. After another Swern oxidation aldehyde **159** was treated again with phosphonate **58** under Masamune and Roush conditions (LiCl, DIPEA) yielding the olefin in 73%. A second sequence of Evans methylation and reduction following hydrogenation resulted in compound **160**. A final

Dess–Martin oxidation and one carbon Wittig olefination led to the first building block **161**. Alkenes **161** and **162** were subjected to cross olefin metathesis, hydrogenation, and deprotection to obtain penicidine A (**163**) in 15 linear steps with an overall yield of 4.3%. Their synthesis allowed a divergent synthetic approach with easy access to all possible stereoisomers, which led to confirmation of the stereochemical assignments in penicidine A (**163**).

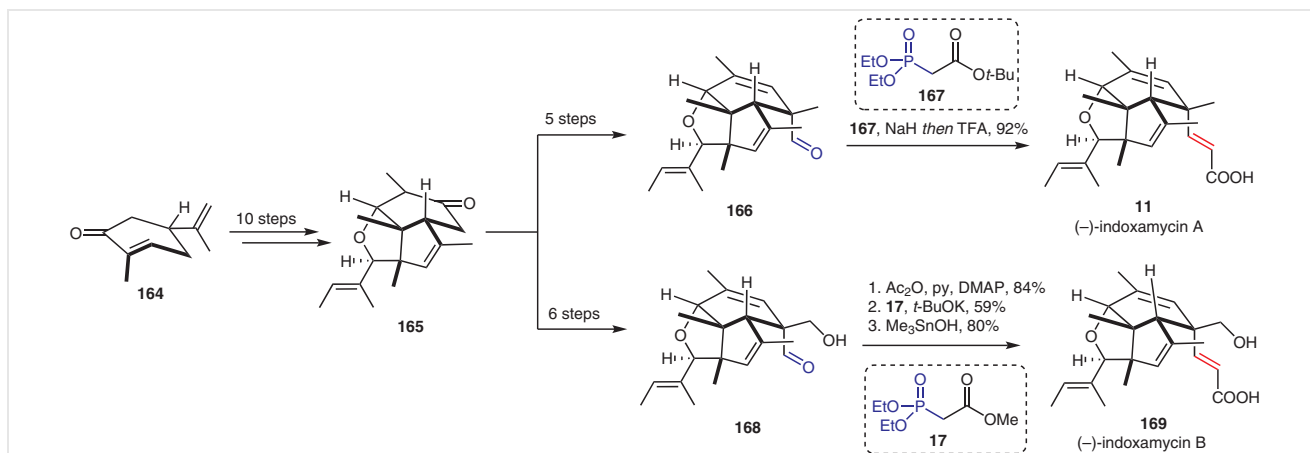
2.5 Late-Stage Modifications by HWE Reactions

Indoxamycins A–F were isolated in 2009 from a saline culture of marine-derived actinomyces by Sato and co-workers as new members of the polyketide structure class.⁸⁴ The structure elucidation of indoxamycins revealed a highly congested [5.5.6] tricyclic carbon skeleton featuring an α,β -unsaturated carboxylic acid side chain and a trisubstituted alkene. The congested core structure consists of six stereogenic centers with three quaternary carbons. This intriguing structure along with the remarkable biological activity makes the indoxamycin family a captivating target for total synthetic approaches.

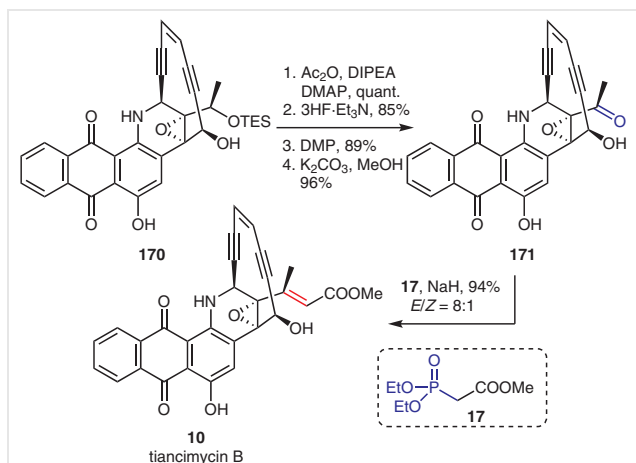
Liang and co-workers successfully used the HWE reaction in 2019 to install an α,β -unsaturated ester at a late stage in the total synthesis of (–)-indoxamycins A (**11**) and B (**169**).⁸⁵

The synthesis of indoxamycins required the generation of **165** from (*R*)-carvone **164** (Scheme 17). This was done in 10 steps including acylation under KH/dimethyl carbonate conditions, methylation of the generated potassium enolate salt, addition of Comins' reagent, and Pd-catalyzed reductive deftriflation.

HWE olefination with **166**, phosphonate **167**, and NaH followed by in situ removal of the *tert*-butyl group resulted in the formation of (–)-indoxamycin A (**11**) in 92% yield. A similar procedure was applied for the synthesis of indoxamycin B (**169**). Reduction and oxidation were used to obtain



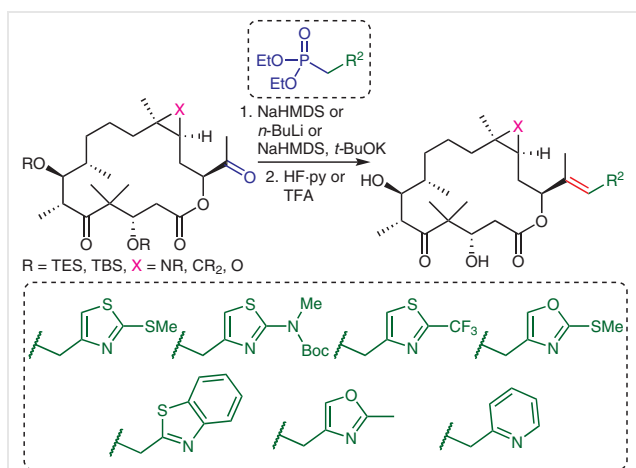
Scheme 17 Total synthesis of (–)-indoxamycins A and B by Liang and co-workers



Scheme 18 Total synthesis of tiancimycin B by Nicolaou and co-workers

aldehyde **168**. Next acetylation of the primary alcohol was followed by HWE reaction with phosphonate **17** to give the product with low conversion due to steric hindrance around the aldehyde. Several bases were screened (NaH, *n*-BuLi, and *t*-BuOK) and *t*-BuOK was relatively effective in the HWE reaction giving the corresponding unsaturated ester in 59% yield. Simultaneous hydrolysis of the methyl ester and acetyl group removal with Me₃SnOH led to (–)-indoxamycin B (**169**).

Another example for late-stage introduction of α,β -unsaturated esters using HWE reactions was reported in 2020 by Nicolaou and co-workers in the total synthesis of tiancimycin B (**10**) (Scheme 18).¹⁶ TES-protected unciamycin **170** was synthesized in 2016 from hydroxyisatin in 22 steps.⁸⁶ It was transformed to unciamycin analogue **171** in four steps with a newly introduced ketone moiety. HWE



Scheme 19 Synthesis of epothilone B analogues by Nicolaou and co-workers

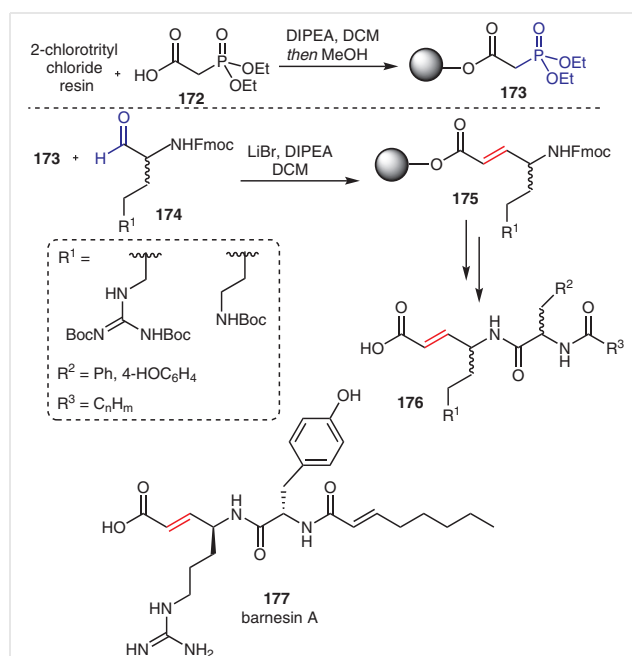
olefination of **171** with phosphonate **17** and NaH as a base provided the *E*- and *Z*-isomers of tiancimycin B (**10**) in 84% and 10% yield, respectively.

Late-stage HWE olefinations were also used in the modification of epothilone B analogues designed by Nicolaou and co-workers to improve their potencies and pharmacological properties as anticancer drugs (Scheme 19).³⁵ Introduction of different heterocycle side chains to the macrocyclic core was achieved via HWE reactions in the presence of NaHMDS, *n*-BuLi, or NaHMDS/*t*-BuOK, followed by desilylation.

2.6 HWE Reactions on Solid Supports

Solid phase synthesis (SPS) is mainly applied in the synthesis of longer and difficult to purify peptides and nucleotides. However, this method has increasingly been used for SP-supported HWE reactions in the synthesis of other small molecules.⁸⁷ Most notably, the synthesis of α,β -unsaturated amides,⁸⁸ esters and nitriles,⁸⁹ macrocycles,⁹⁰ olefins,⁹¹ triazolopyridazines, and peptides containing *E*-alkene amide linkages have been reported.⁹² Furthermore, several reports on the synthesis of *Z*- α,β -unsaturated esters,⁹³ solvent-free reactions,⁹⁴ and crosslinking polysulfones under phase transfer catalysis (PTC)⁹⁵ have been published.

Beemelmans and co-workers reported the application of SP-based HWE reagents to prepare the vinylogous amino acid containing natural product barnesin A (**177**) (Scheme 20),⁹⁶ which was previously isolated from anaerobic bacte-



Scheme 20 Solid-phase based synthesis of cysteine proteases inhibitor barnesin A and derivatives by Beemelmans and co-workers

rium *Sulfurospirillum barnesii* as the first secondary metabolite from Epsilonproteobacteria and the first NRPS-PKS hybrid molecule from this bacterial family.⁹⁷

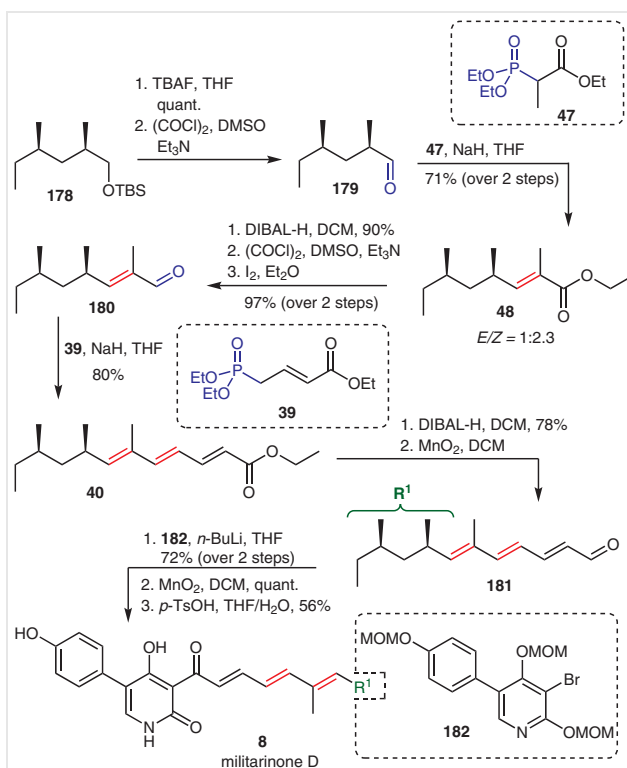
The synthesis began with loading a 2-chlorotriptyl chloride resin (CTC resin) with diethylphosphonoacetic acid (**172**),⁸⁸ which served as a linker, and phosphonate for the HWE reaction. Resin-bound phosphonate **173** was deprotonated with DIPEA and subjected to an HWE reaction with Fmoc-protected aldehyde **174** (LiBr and DIPEA) yielding solid-bound olefin **175**, which allowed for further peptide coupling steps. Subsequent global deprotection produced 14 lipodipeptides with micromolar to nanomolar inhibitory activity against different cysteine proteases.

2.7 Synthesis of Poly-Conjugated C=C Bonds

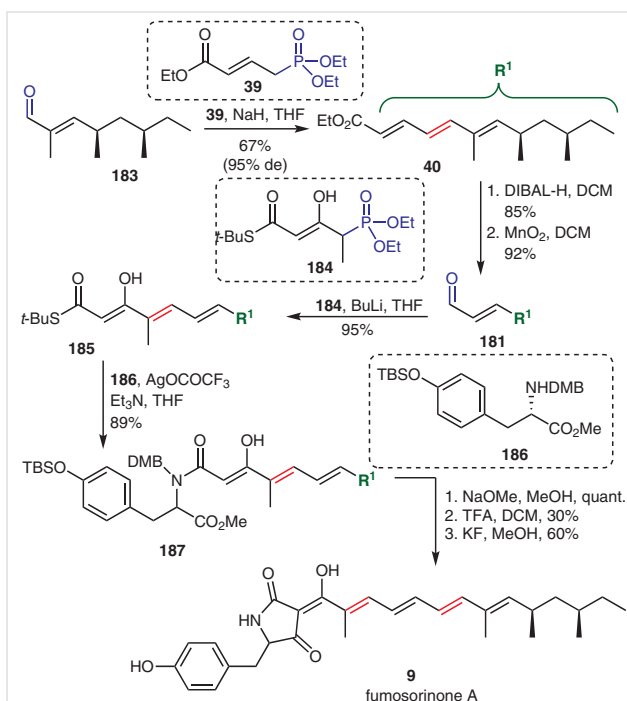
Conjugated π -bond systems allow delocalization of π -electrons through alternating single and double bonds. This concept was introduced by Claisen in 1926 and later named vinylogy.⁹⁸ HWE reactions play a central role in the construction of vinylogous systems and polyconjugated double bonds, especially in natural product synthesis as shown in the following eight examples.^{99,100}

The polyunsaturated side chain of the alkaloids militarinone D (**8**) (Scheme 21), isolated in 2003 from *Paecilomyces militaris*,¹⁰¹ was accomplished by Sim and co-workers in 2015 using a sequence of HWE reactions.³² The first HWE reaction (NaH in THF) of aldehyde **179** with phosphonate **47** yielded unsaturated ester **48** in 71% yield (2 steps, *E/Z* 1:2.3). A subsequent reduction/oxidation sequence produced the aldehyde as an *E/Z* mixture where the *Z*-isomer was converted into the *E*-isomer **180** by treatment with catalytic iodine. The second HWE olefination (NaH in THF) of unsaturated aldehyde **180** and phosphonate **39** yielded triene **40** in 80% yield, which was again transformed into aldehyde **181** in a reduction/oxidation sequence. Aldehyde **181** was added to lithiated pyridine **182** in the final sequence and the resulting allylic alcohol was oxidized to a ketone. This was followed by a global MOM removal to complete the synthesis of militarinone D (**8**) in 5% overall yield.

A structurally related NRPS-PKS based fungal-derived natural product, fumosorinone A (**9**),¹⁰² was isolated in 2017, and shown to contain a pentaene moiety attached to a pyrrolidine-2,4-dione. Due to its potent protein tyrosine phosphatase 1B inhibitor activity and intriguing structure, it was synthesized in 2018 by Schobert and co-workers (Scheme 22).²⁸ The required aldehyde **183** was prepared from commercially available (*S*)-citronellol in 10 steps to synthesize the polyunsaturated PKS side-chain, which was then subjected to the chain elongating HWE reaction with phosphonate **39** and NaH as base to produce elongated olefin **40** in 67% yield. Ester **40** was subjected to a reduction/oxidation sequence yielding aldehyde **181**, which was



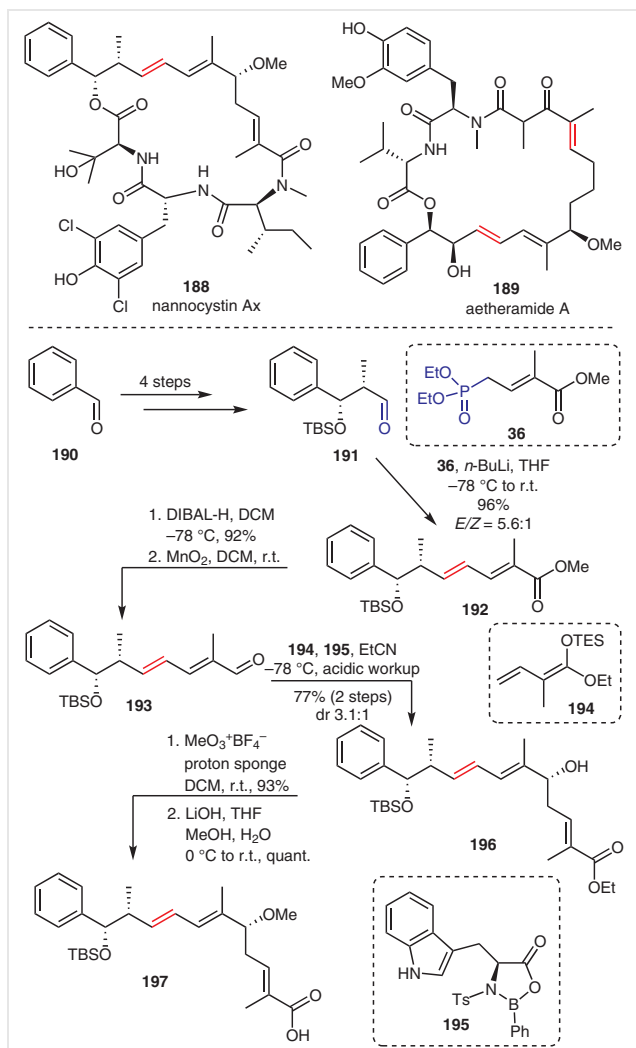
Scheme 21 Total synthesis of militarinone D by Sim and co-workers



Scheme 22 Total synthesis of fumosorinone A by Schobert and co-workers

subjected to a second HWE olefination following Loscher's protocol¹⁰³ giving thioester **185** in a 95% yield as a 2:3 keto/enol mixture. Silver-mediated acylation with amino acid **186** resulted in ketoamide **187**. Subsequent cyclizations followed by a partial TBS deprotection with TFA and global desilylation with KF completed the first total synthesis of fumasatinone **9**.

Another application of an HWE reaction in the synthesis of conjugated C=C bonds was described by Gerstmann and Kalesse in their total syntheses of nannocystin Ax (**188**) and aetheramide A (**189**) (Scheme 23).¹⁰⁴ Chiral aldehyde **191** [4 steps from benzaldehyde (**190**)] was subjected to an HWE reaction using phosphonate **36** and *n*-BuLi to yield acrylic ester **192** in 96% yield in favor of the desired *E*-isomer (5.6:1). Ester **192** was reduced and subsequently oxidized to aldehyde **193**, which was used in a vinylogous Mukaiyama aldol reaction with acetal **194** in the presence of catalyst



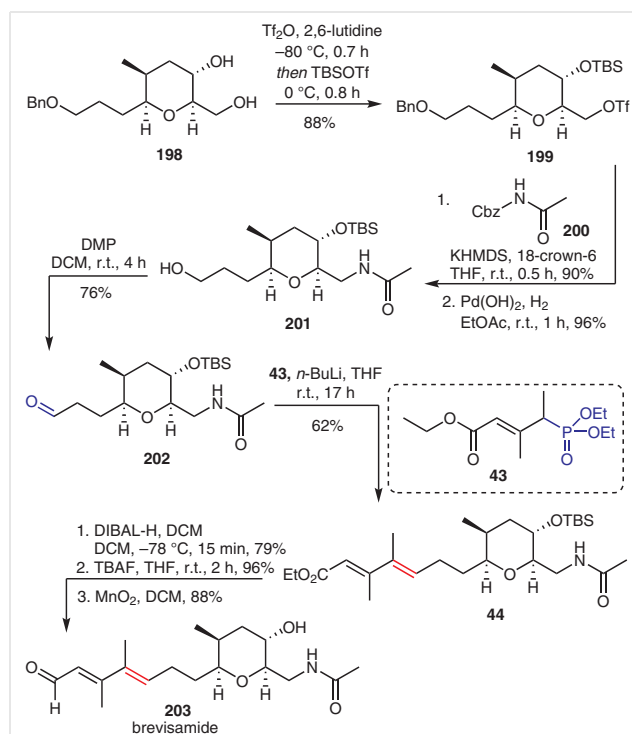
Scheme 23 Structure of nannocystin Ax and aetheramide A and the total synthesis of a building block by Gerstmann and Kalesse

195 to give product **196**. The alcohol **196** was then methylated and the ester was hydrolyzed to carboxylic acid **197**, which was used for completion of the total synthesis of nannocystin Ax (**188**).

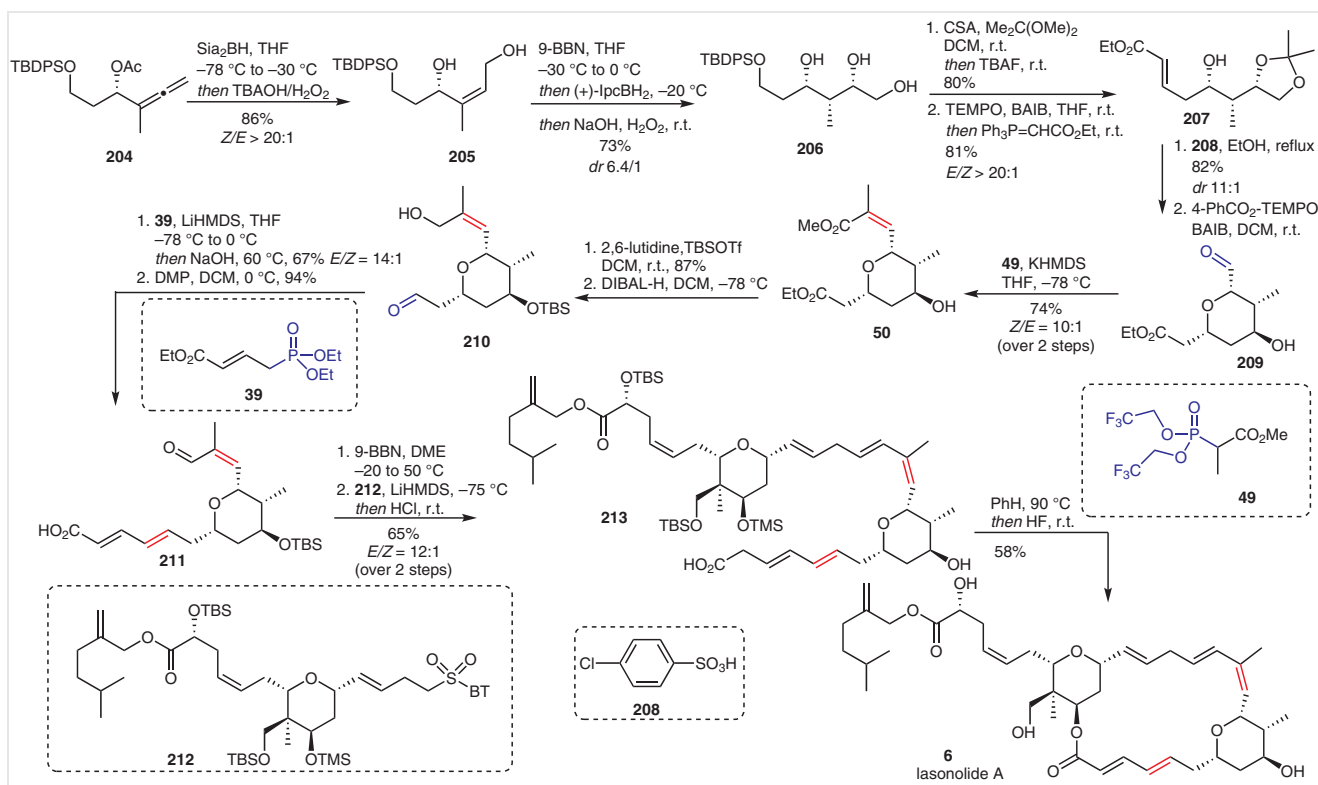
Similarly, the HWE reaction was used by Mori and co-workers in their total synthesis of brevisamide (**203**) (Scheme 24),³⁰ a natural marine product isolated from dinoflagellate containing a tetrahydropyran (THP) ring incorporated into a conjugated carbon chain.

The synthesis of the unsaturated side chain started from commercial 4-(benzyloxy)butanol, which was converted into diol **198** in 10 steps. A short reaction sequence afforded mono-TBS deprotected alcohol **201**. The primary alcohol **201** was oxidized with Dess–Martin periodinane to yield Lindsley's aldehyde **202** as a precursor for the HWE reaction.^{100a,105} The olefination of **202** was accomplished using the vinylogous phosphonate **43** and *n*-BuLi at room temperature to provide dienolate **44** in 62% yield. Ethyl ester **44** was subsequently reduced to the corresponding alcohol using DIBAL-H. This was followed by desilylation of the secondary alcohol and final oxidation of the primary alcohol with MnO₂ gave brevisamide (**203**).

Hong and co-workers reported an extraordinary synthetic strategy towards the total synthesis of lasonolide A (**6**) in 2018 (Scheme 25).³³ This is a natural product contains two functionalized tetrahydropyran moieties and exhibits high and selective cytotoxicity against cancer cells.



Scheme 24 Synthesis of brevisamide by Mori and co-workers



Scheme 25 Total synthetic strategy lasonolide A by Hong and co-workers

A hydroboration-oxidation sequence starting from alkene **204** provided polyhydroxy alkane **206** in good overall yields. The alcohol in **206** was first subjected to an oxidation-Wittig elongation sequence to produce ester **207**. Acidic tetrahydropyran formation was followed by the oxidation to aldehyde **209** that allowed the first HWE reaction with Still-Gennari phosphonate **49** yielding trisubstituted *cis*-conjugated methyl ester **50** in good yields (Z/E 10:1). Silylation of the secondary alcohol in **50** proceeded smoothly and DIBAL-H mediated reduction of the ester delivered aldehyde **210**, which was again subjected to HWE olefination with a vinylogous phosphate **39** and LiHMDS as a base.

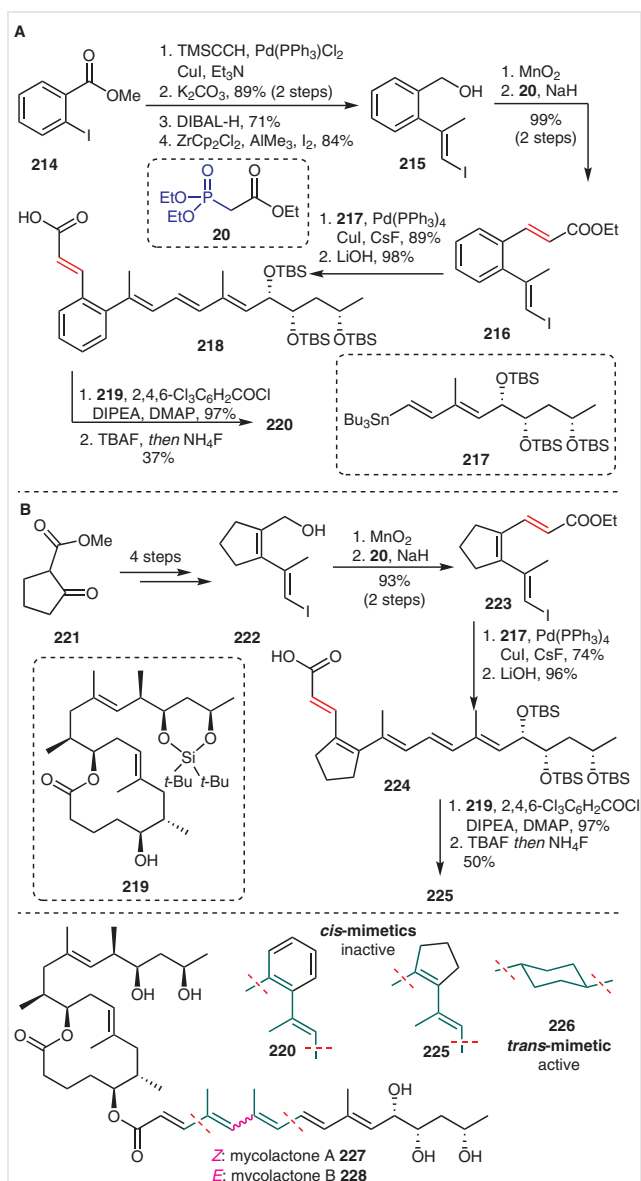
Subsequent Dess–Martin oxidation of the allylic alcohol provided *Z*-enone **211** in 94% yield. An unusual 9-BBN complexation of free carboxylic acid allowed successful Julia olefination with sulfone **212** to give **213**. Lactonization was employed to complete the total synthesis of (–)-lasonolide A (**6**).

The synthesis of polyconjugated mycolactone mimetics by Altmann and co-workers in 2019 represents an addition example for the efficient application of HWE reactions (Scheme 26).¹⁰⁶ Mycolactones A (**227**) and B (**228**) feature a common 12-membered macrolactone core, which can interact with several cellular targets, such as mTor,¹⁰⁷ Sec61 translocon,¹⁰⁸ Wiskott–Aldrich syndrome protein,¹⁰⁹ and the angiotensin II receptor.¹¹⁰ Their synthesis targeted mycolactone analogues **220**, **225**, and **226** as configurationally

stable mimetics to investigate the importance of the double bond for the activity and the mode of action in *Buruli ulcer* pathogenesis (Scheme 26).

Their synthesis started from methyl 2-iodobenzoate (**214**), which was converted into vinyl iodide **215** via Sonogashira coupling with TMS-acetylene, desilylation, reduction of the ester, and zirconium-catalyzed carboalumination/iodination of the terminal alkyne moiety. After oxidation of the primary alcohol **215** with MnO_2 the resulting aldehyde was subjected to an HWE reaction with triethyl phosphonoacetate (**20**) to yield α,β -unsaturated ester **216** (99% over 2 steps). Stille coupling of vinyl iodide **216** with stannane **217** followed by saponification gave acid **218**. Final esterification with macrolactone **219** and desilylation yielded **220**. Analogous syntheses for cyclopentene-derived acids **224** and **225** starting from 2-oxocyclopentane-1-carboxylate (**221**) and 1,4-bis(hydroxymethyl)cyclohexane were also reported.

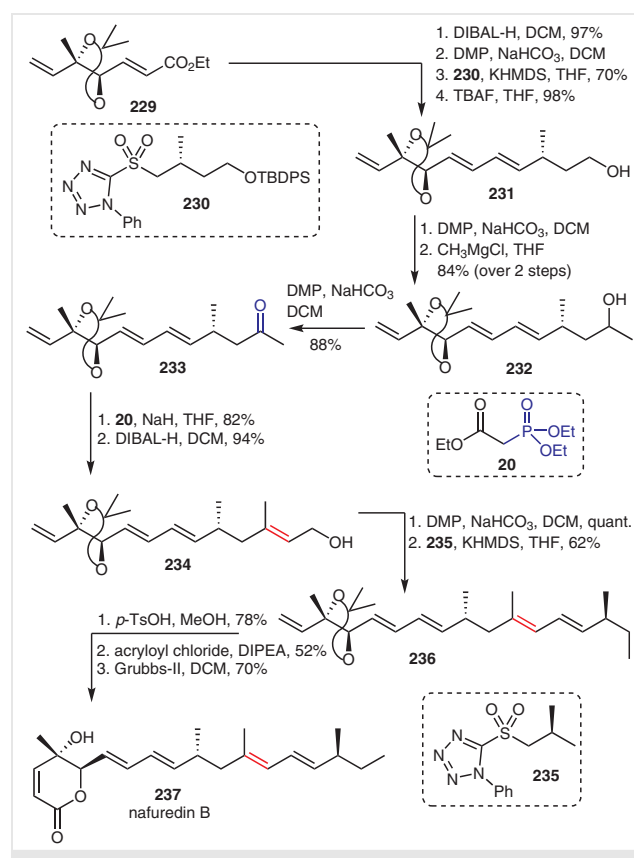
The marine secondary metabolite nafuredin B (**237**) was isolated in 2017 from deep-sea-derived *Talaromyces aculeatus* and *Penicillium variable* together with penitalarins A–C and known nafuredin A.¹¹¹ Nafuredins contain a linear skeleton with an unsaturated chain linked to α,β -unsaturated lactone and showed cytotoxicity against several cell lines in the micro-molar range thus making them attractive synthetic targets.



Scheme 26 Synthesis of mycolactone analogues by Altmann and co-workers

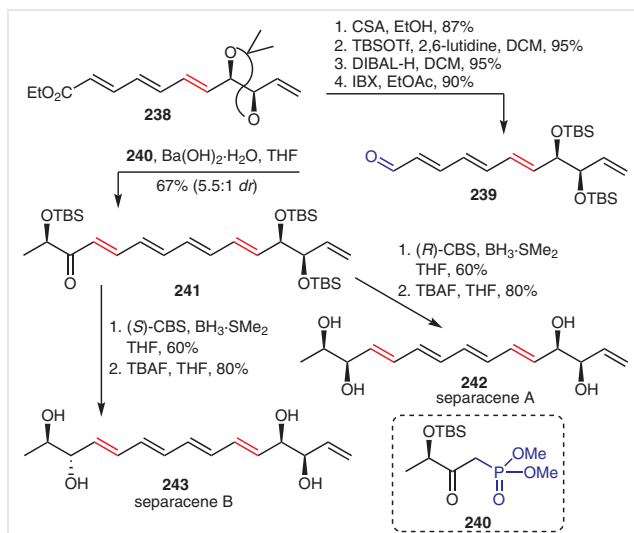
The first total synthesis of nafuredin B (**237**) was accomplished by Goswami and co-workers (Scheme 27)¹¹² and was based on an elongation sequence of one HWE reaction and two Julia–Kocienski olefinations. Commercially available prenyl was converted into unsaturated ester **229** using a known procedure. Ester **229** was then reduced with DIBAL-H and oxidized with Dess–Martin periodinane and the intermediate aldehyde was directly subjected to Julia–Kocienski olefination with sulfone **230** to obtain the olefin (*E/Z* 4:1). The isomers were separated and the *E*-isomer was treated with TBAF to produce primary alcohol **231**, which was again oxidized and treated with Grignard reagent to

give the secondary alcohol **232**. Subsequent oxidation to ketone **233** and an HWE reaction (NaH) with triethyl phosphonoacetate (**20**) produced the elongated unsaturated side chain in **234** (82% yield, *E/Z* 6:1). The final elongation via Julia–Kocienski olefination was pursued after another reduction/oxidation sequence and transformation with sulfone **235** to obtain **236**.^{113,114} The last three steps involved treatment with *p*-toluenesulfonic acid to afford a diol, subsequent acrylation, and then ring-closing metathesis provided the desired nafuredin B (**237**).



Scheme 27 Total synthesis of nafuredin B by Goswami and co-workers

Separacenes A (**242**) and B (**243**) were isolated in 2013 from a marine actinomycete¹¹⁵ and contain an unusual tetraene moiety with a diols on both ends. Goswami and Das reported the first convergent stereoselective total synthesis (Scheme 28) shortly afterwards in 2017.²⁹ The synthesis started from D-tartaric acid which was transformed to unsaturated ester **238** (see Table 1, Entry 14). A deprotection/protection and reduction/oxidation sequence yields TBSOTf-protected aldehyde **239**. They screened several conditions for the HWE reaction of aldehyde **239** and ketophosphonate **240**, such as LiCl, DIPEA, THF (0%, 24 h); LiCl, DBU, THF (0%, 24 h); Cs₂CO₃, MeCN (60%, 5.5:1 dr, 12 h), and were finally able to react **239** with **240** in the presence of



Scheme 28 Total synthesis of separacenes A and B by Goswami and Das

Ba(OH)₂ to yield elongated ketone **241** (80%, 5.5:1 dr, 12 h). They obtained **242** and **243** by stereoselective reduction of ketone **241** with the Corey–Bakshi–Shibata reagent *R*-CBS and *S*-CBS, respectively, and global deprotection with TBAF.

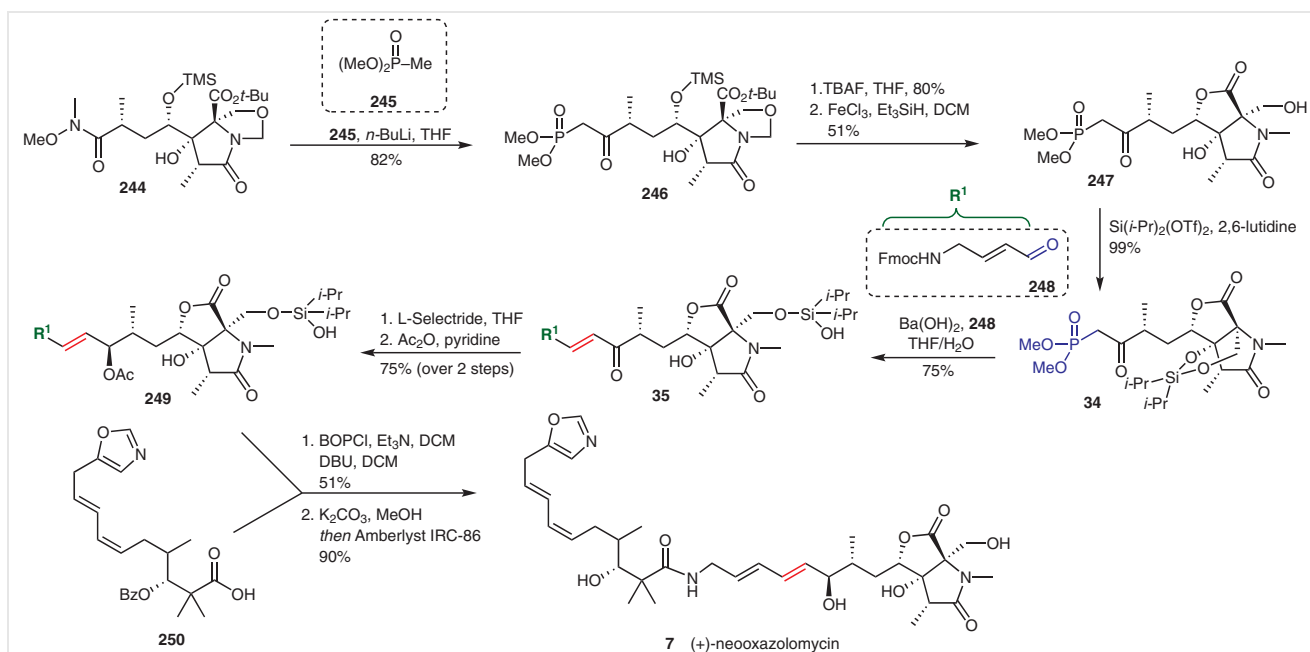
The asymmetric total synthesis of (–)-neooxazolomycin (**7**) (Scheme 29) reported by Kim and co-workers is the final example.²⁵ The structurally complex natural product consists of a unique lactam–lactone structure and an unsaturated polyketide-based sidechain that exhibits potent bio-

logical activities.¹¹⁶ The key substrate **244** was obtained from D-serine in 16 steps and reacted with dimethyl lithiomethylphosphonate to give phosphonate **246** in 82% yield. Further modifications yielded dioxasilinane-protected phosphonate **34**,¹¹⁷ which was then reacted with aldehyde **248** in a temperature-sensitive Ba(OH)₂-mediated HWE reaction to afford the partially deprotected and elongated **35** in 75%. Ketone **35** was subsequently reduced to the corresponding alcohol and acetylated to give **249**. The second fragment, **250**, was synthesized in 13 steps and coupled with **249**. This was then treated with K₂CO₃ and MeOH to produce globally deprotected (+)-neooxazolomycin (**7**).

2.8 HWE-Mediated Coupling of Larger Building Blocks

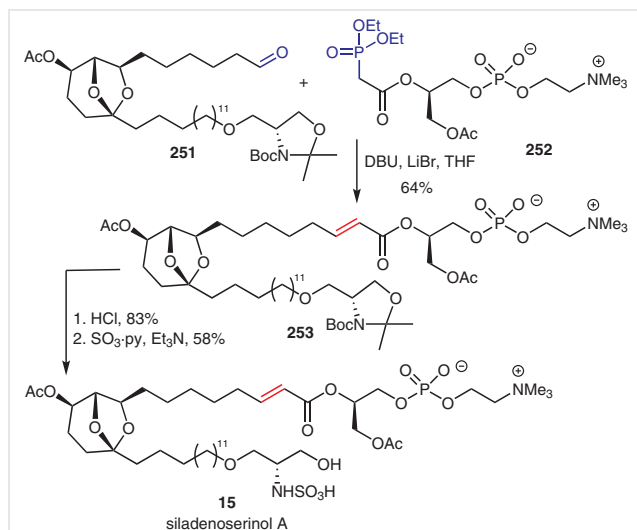
The intramolecular HWE reaction, where one building block contains a phosphonate moiety and the other has an aldehyde or ketone, has found immediate application in synthetic chemistry and natural product synthesis. Here, we give four recent examples.

Siladenoserinol A (**15**) was isolated in 2013 from a tunicate collected in Indonesia,¹¹⁸ and found to contain a 6,8-dioxabicyclo[3.2.1]octane skeleton with two long chains that each contain a sulfamated serinol or glycerophosphocholine moiety. Doi and co-workers reported the first total synthesis of siladenoserinol A (**15**) in 2018 (Scheme 30).¹¹⁹ Their synthetic strategy started with commercially available D-malic acid, which was converted into aldehyde **251** in 21 steps. The glycerophosphocholine moiety was intro-



Scheme 29 Total synthesis of (+)-neooxazolomycin accomplished by Kim and co-workers

duced by an HWE reaction using the previously prepared phosphonate **252** yielding the unsaturated ester **253** in 64% yield. The Boc group was removed with HCl and sulfamate formation finished the synthesis of siladenoserinol A (**15**).

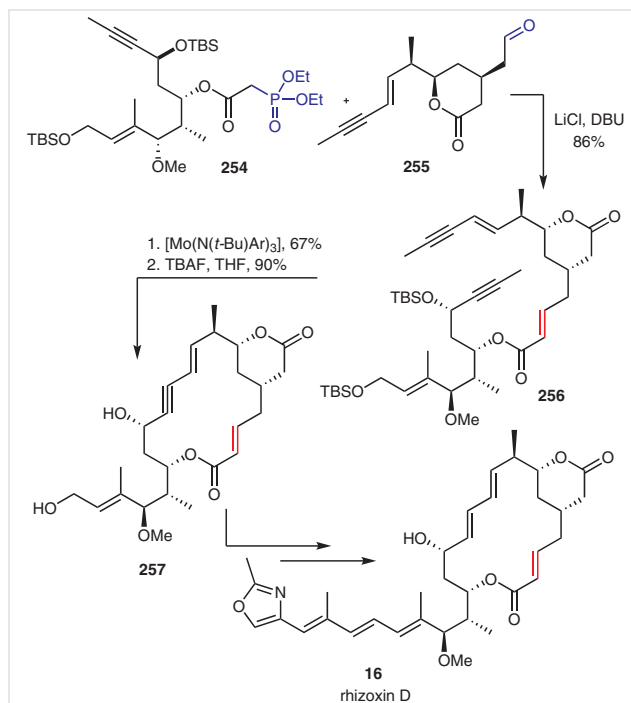


Scheme 30 Total synthesis of siladenoserinol A **15** by Doi and co-workers

Tong, Qian, and co-workers described a second asymmetric synthesis of **15** in 2019 (see Table 1, formation of **19**).¹⁷ They also applied an HWE reaction for the construction of the α,β -unsaturated ester moiety and included the synthesis of siladenoserinol H, which is a structural analogue, to test for antibacterial activity of this compound class.¹²⁰

Rhizoxin is a natural product produced by species of the bacterial genus *Burkholderia*.¹²¹ It was isolated in 1984 and showed high *in vitro* cytotoxicity and *in vivo* antitumor activity.¹²² Fürstner and co-workers presented their own synthetic effort in 2019 that extended earlier studies and resulted in a different modern strategy (Scheme 31).¹²³ The synthesis was based on intermolecular HWE olefination for coupling **254** and **255** followed by macrocyclization to form a 16-membered ring through ring-closing alkyne metathesis.

Their synthesis started from commercially available (*R*)-oct-1-en-3-ol in its optically pure form, which was converted into substrate **254** in 14 steps. The second segment **255** was prepared from crotyl alcohol in 11 steps. A straightforward HWE reaction between phosphonate **254** and aldehyde **255** in the presence of LiCl and DBU was performed to couple both segments and afforded cyclization precursor **256** in 86% yield. Ring-closing alkyne metathesis was followed by TBAF deprotection of silyl groups and yielded de-

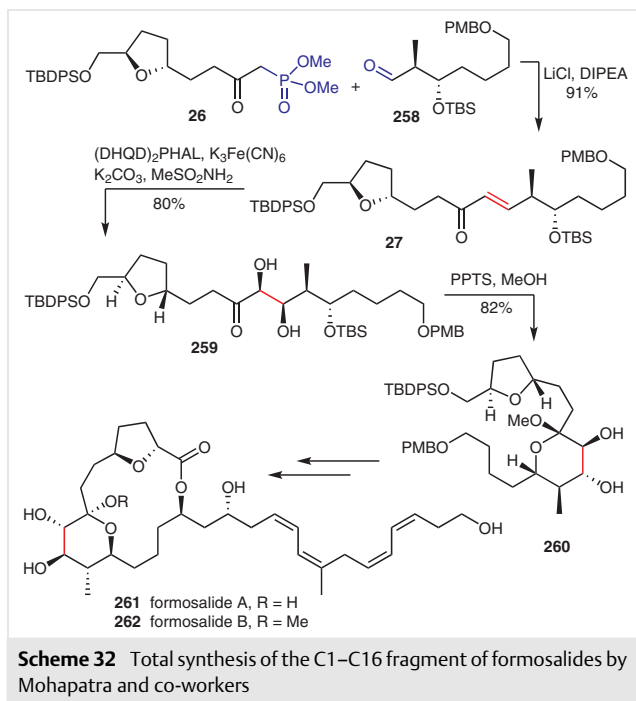


Scheme 31 Total synthesis of rhizoxin D by Fürstner and co-workers

sired macrolactone **257**. Next steps such as *trans*-hydrostannation, C-methylation, and other known procedures led to rhizoxin D (**16**).

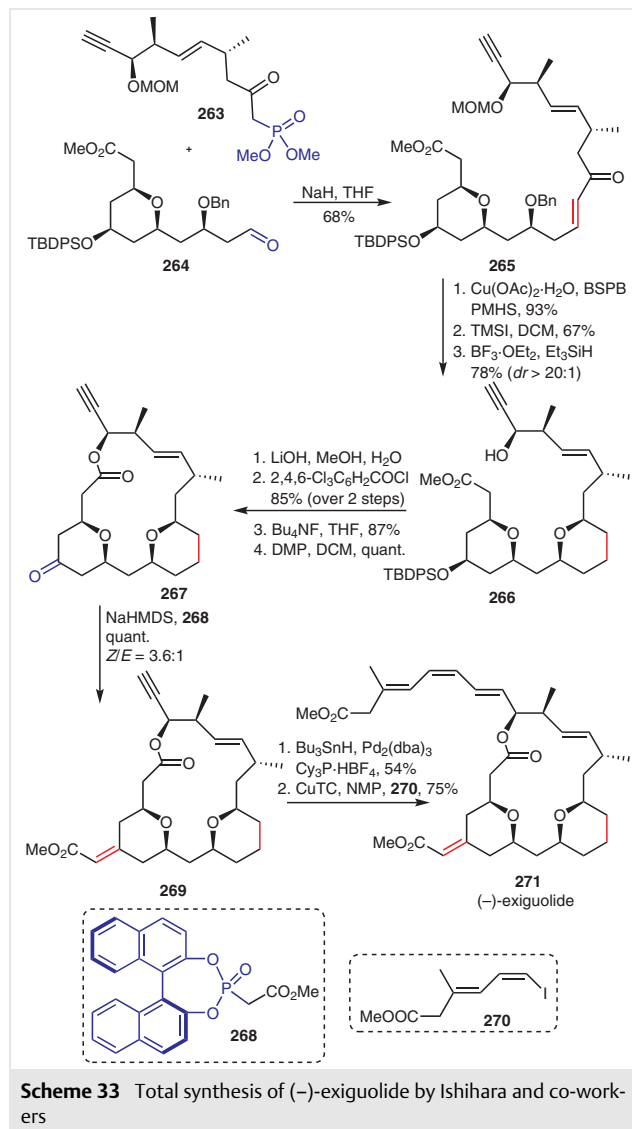
Formosalides A (**261**) and B (**262**) were isolated in 2009 by Lu and co-workers from the dinoflagellate *Prorocentrum* sp. from southern Taiwan.¹²⁴ These macrolides consist of substituted tetrahydropyran (THP), a tetrahydrofuran ring, and a C-14 linear unsaturated chain containing four *cis*-double bonds.¹²⁵ Both compounds exhibited good cytotoxic activity against human T-cell, acute leukemia cells, and human colon adenocarcinoma cells and were thus selected for total synthesis.

Mohapatra and co-workers reported a simple and efficient synthesis of the C1–C16 fragment of the proposed structure of formosalide B (**262**) (Scheme 32).²¹ The synthesis started from commercially available materials and was completed in 9 steps. Aldehyde **258** was prepared from pentane-1,5-diol in 5 steps. Both building blocks were then coupled using an HWE reaction in the presence of LiCl and DIPEA in acetonitrile to furnish the *E*-isomer enone **27** in 91% yield. Olefin **27** underwent dihydroxylation using a Sharpless ligand to give diol **259** (dr 9:1). Finally, **259** was subjected to acid-mediated ketalization to form the THP ring **260** and complete the fully functional C1–C16 fragment of formosalide B (**262**).



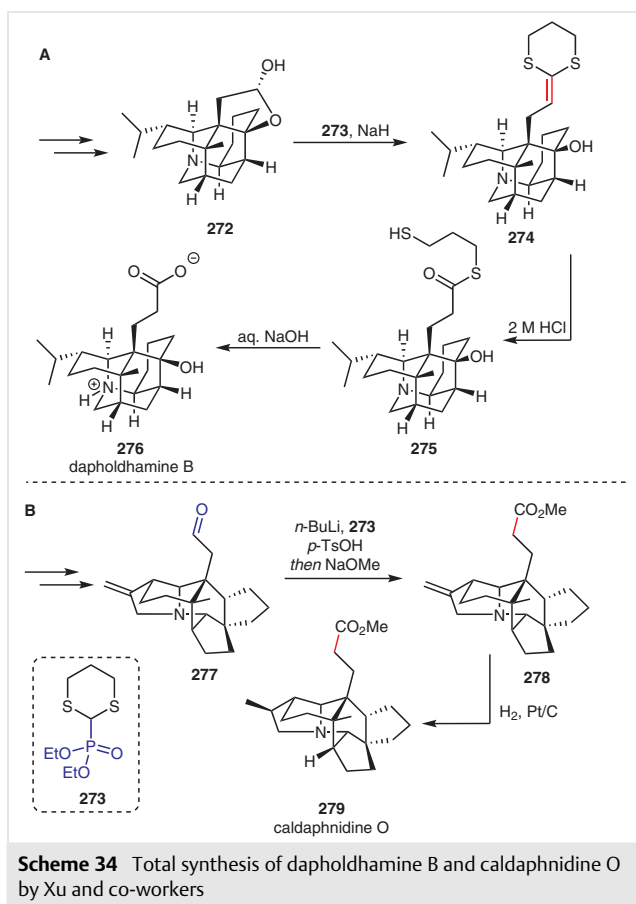
Exiguolide (**271**) was isolated in 2006 from a marine sponge *Geodia exigua* Thiele by Ohta, Ikegami, and co-workers.¹²⁶ It contains a unique 20-membered macrolide core and two tetrahydropyran rings and was shown to have inhibitory activity against human lung cell carcinoma, human lung adenocarcinoma cells, pancreatic cancer, and breast cancer cells.¹²⁷ Exiguolide (**271**) has been a captivating target for synthesis due to its interesting structure and remarkable biological properties. The first total synthesis of it was accomplished in 2010 by Sasaki and Fuwa.¹²⁸ Several synthetic strategies have since been developed and described.¹²⁹ In 2020, Ishihara and co-workers reported an asymmetric total synthesis of **271** (Scheme 33).¹³⁰ The first building block, **263**, was prepared in 8 steps and the THP-based fragment, **264**, was prepared from propane-1,3-diol in 7 steps. Phosphonate **263** and aldehyde **264** were then subjected to an HWE reaction using NaH to give enone **265** in a 68% yield. This was then reacted with Stryke's reagent to provide a saturated compound.¹³¹ Cleavage of MOM and Bn groups by treatment with trimethylsilyl iodide was accomplished, which was followed by silane reduction that yielded *bis*(tetrahydropyran) **266** as single isomer.¹³² Saponification, macrolactonization, removal of the TBDPS group, and subsequent oxidation of the secondary alcohol to the corresponding aldehyde yielded compound **267**. An asymmetric HWE reaction based on Fuji's method was employed to convert aldehyde **267** with chiral phosphonate

268 in the presence of NaHMDS to obtain **269** in a quantitative yield (*Z/E* 3.6:1). Hydrostannylation and Stille coupling produced pure (–)-exiguolide **271** (*Z*-isomer).



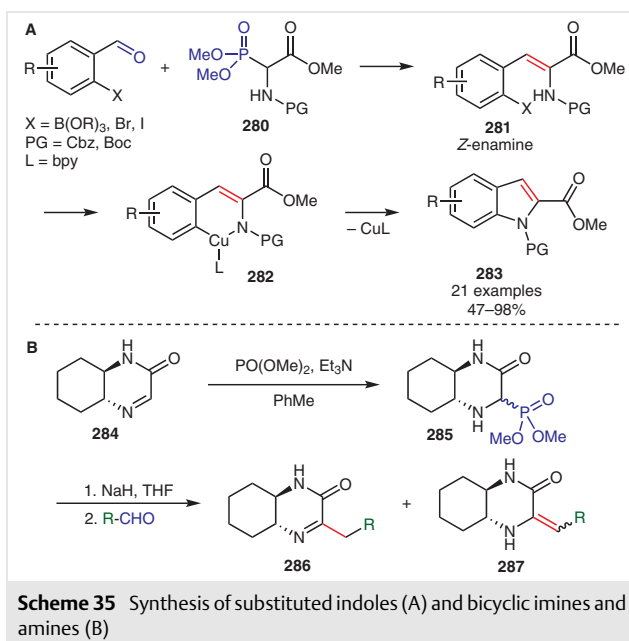
2.9 Miscellaneous

Xu and co-workers described the first enantioselective total synthesis of dapholdhamine B (**276**) in 2019, an alkaloid with a rare aza-adamantane core skeleton (Scheme 34A).¹³³ The critical homologation of the key building block **272** was achieved via an HWE reaction with **273** in the presence of NaH to give intermediate **274**, which then underwent a one-pot acidic hydrolysis to obtain thioester **275**. This was followed by basic hydrolysis to obtain dapholdhamine B (**276**) (21 steps).



Xu and co-workers also reported the total synthesis of alkaloid (-)-caldaphnidine O (**279**) in 22 steps from cyclohexane-1,3-dione (Scheme 34B).¹³⁴ After the synthesis of aldehyde **277**, they employed an HWE reaction with thio-ketal phosphonate **273** and *n*-BuLi followed by acidic and basic workup to produce methyl ester **278**. After diastereoselective hydrogenation of the alkene motif they obtained (-)-caldaphnidine O (**279**).

In a second example, Lim and Choi employed an HWE reaction for synthesis of indoles and azaindoles (Scheme 35A).¹³⁵ In detail, reaction of commercially available *N*-Cbz-protected phosphonoglycine trimethyl ester **280** and substituted 2-bromobenzaldehydes afforded enamines **281**, which were converted into indole **283** via Cu-catalyzed cyclization. This method was also envisaged for the synthesis of thiophene- and benzothiophene-linked pyrroles, which makes it a versatile tool in drug discovery.



Another application is the synthesis of bicyclic imines **286** and amines **287** of the hexahydroquinoxaline-2(1*H*)-one class by Wojaczyńska, Olszewski, and co-workers (Scheme 35B). These compounds show broad pharmacological properties.¹³⁶ Subsequent HWE reactions of chiral phosphonate **285** with different aldehydes in the presence of NaH resulted in a tautomeric mixture of imine **286** and enamine **287**, in favor of the imine form. Additional reduction of the imine or enamine with NaBH₄ led to bicyclic amines.

3 Summary and Outlook

In recent decades, the HWE reaction has been an active area for applications to natural product synthesis. To solve increasingly challenging synthetic problems the required phosphonate reagents have been diversified from simple phosphonates to highly activated, branched, and modified phosphonate reagents. Here, we have summarized representative examples of functionalized reagents used in natural product synthesis reported in 2015–2020. Our comprehensive review will support future synthetic approaches and serve as guideline to find the best HWE conditions for the most complicated natural products.

Conflict of Interest

The authors declare no conflict of interest.

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