# The Wittig and Related Reactions in Natural Product Synthesis ☆

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Originally reported in *Liebigs Annalen* in 1953 (then called *Justus Liebigs Annalen der Chemie*), the Wittig reaction has evolved to include the Horner–Wittig and Horner–Wadsworth–Emmons reactions and several other variations. Today, these reactions constitute some of the most powerful processes for the construction of carbon–carbon bond frameworks, facilitating the chemical synthesis of myriads of organic molecules both in research laboratories and industrial settings. The Wittig and related reactions were proven particularly useful in the field of total synthesis, where they enabled the construction of highly complex structures and had a significant impact in shaping the art to its present state of sophistication. In this article the authors focus, after a brief introduction, on total syntheses from their own laboratories that employ such processes. These examples, together with the numerous others adorning the chemical literature, illustrate amply the importance of the Wittig and related reactions and point to their continuing prominence in organic synthesis.

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## 1. Introduction
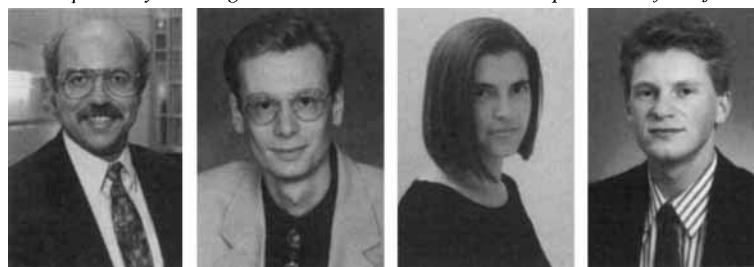
The formation of carbon–carbon bonds is still the most challenging task a chemist faces when synthesizing a molecule. Reactions capable of performing such constructions in a reliable, efficient and stereoselective fashion are, therefore, frequently used and exceedingly valuable in organic



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**MICROREVIEWS:** This feature introduces Annalen's readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.
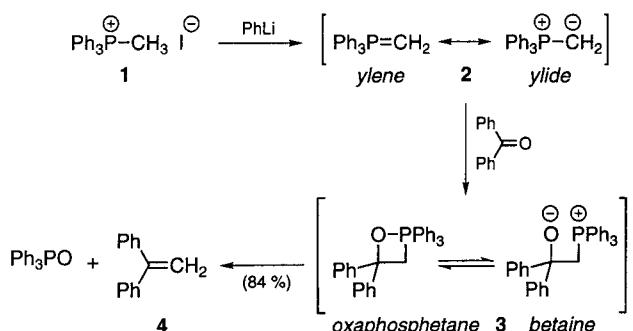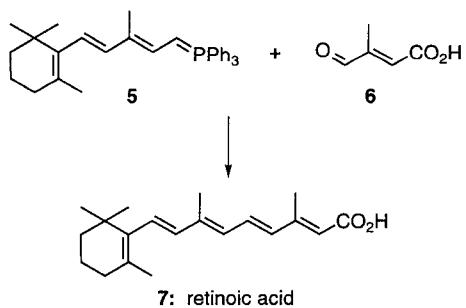
synthesis. Now over 40 years old, the Wittig reaction remains, in this respect, one of the most important reactions yet discovered in organic chemistry.

First reported in 1953 by Wittig and Geissler[1] in a paper in *Liebigs Annalen* that was concerned more with the chemistry of pentacoordinate phosphorus derivatives than with new synthetic methodology, the Wittig reaction was originally exemplified by the reaction of benzophenone with methylidene triphenylphosphorane (**2**) to give 1,1-diphenylethylene (**4**) in 84% yield (Scheme 1). Fortunately, the significance of this discovery was not overlooked and, within a short period of time, scientists at the neighboring BASF plant in Ludwigshafen had used the new reaction in the preparation of retinoic acid (**7**) from the phosphoranylidene **5** and the aldehyde **6** (Scheme 2)[2]. Industry at the time had been actively seeking methods of producing synthetic and naturally occurring vitamins and carotenoids for the foodstuffs market. Within a few years a continuous process
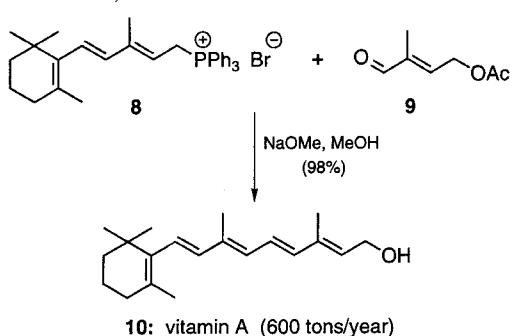
Scheme 1. The first Wittig reaction (1953, Wittig and Geissler)[1]

Scheme 2. Preparation of retinoic acid (**7**) by the Wittig reaction (1953, BASF)[2]
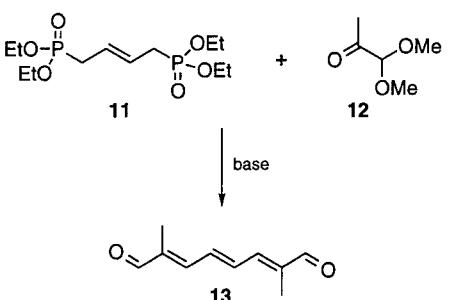
Scheme 3. Industrial preparation of vitamin A (**10**) (1950's, BASF)[2]

based on the Wittig reaction of **8** and **9** (Scheme 3) had been developed that was capable of producing 600 tons of vitamin A (**10**) per year[2]. Subsequently, many more academic and industrial applications of the Wittig reaction were reported and by 1959 the literature on the Wittig reaction had become sufficient to merit the first[3] of many reviews on the subject[4a–d].
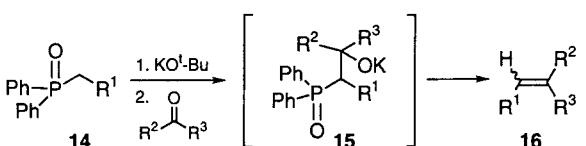
The first variants of the Wittig reaction started to appear around 1957. Pommer and Stilz from BASF described the use of a dialkylphosphonate as an anion-stabilizing group in place of the triphenylphosphonium salt moiety[5]. In the particular case shown in Scheme 4, the corresponding bis-(phosphonium salt) suffered elimination to 1,4-butadiene on attempted ylide formation, whereas the bis(phosphonate) **11** was acceptably stable. Reaction of **11** with methylglyoxaldimethylacetal gave the bis(aldehyde) **13**, an intermediate used industrially in the synthesis of β-carotene[5].

Scheme 4. Use of phosphonate-stabilized anions in olefination reactions (1958, Stilz and Pommer)[5]
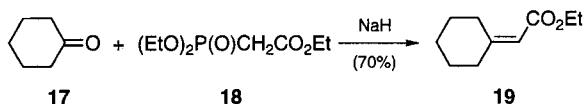
Horner and co-workers described the use of phosphine oxides (e.g. **14**, Scheme 5)[6], and diethyl benzylphosphonate[7] in Wittig-type reactions (Horner–Wittig reaction). If a potassium base was used to generate the phosphine oxide anion, the reaction with a carbonyl compound proceeded to give the alkene, as in the Wittig reaction. However, if a lithium base was used, the intermediate β-hydroxyphosphine oxide could be isolated, which could then be transformed into the alkene in a subsequent step.

Scheme 5. The Horner-Wittig reaction with diphenylphosphine oxide (1958, Horner)[6]

In 1961, Wadsworth and Emmons described their work on phosphonate-stabilized carbanions[8]. This paper pointed out the advantages of increased reactivity that these anions have over the traditional Wittig ylides derived from phosphonium salts (but only when the phosphonate contained an additional α-linked carbanion-stabilizing group), and served to popularize the use of phosphonate-stabilized carbanions for the synthesis of certain alkene classes, particularly α,β-unsaturated esters and ketones (Scheme 6). This reaction is often described as the Horner–Wadsworth–Emmons (HWE) reaction.

Scheme 6. Example for an olefination reaction with a stabilized phosphonate (1961, Wadsworth and Emmons)[8]



A number of other types of phosphoryl-stabilized carbanions have since been described, including thiophosphonates[9] and phosphonamides[10]. In addition, ylides derived from either triphenylarsonium or triphenylstibinium salts undergo olefination reactions with carbonyl compounds, analogous to the Wittig reaction[11]. In contrast, triphenylbismuthonium ylides give epoxides on reaction with carbonyl compounds[12]. Furthermore, in the last decade a number of transition metal derived alkylidenes, such as the Tebbe reagent[13], which bear a superficial structural and mechanistic similarity to simple Wittig reagents, have been described, but currently these look unlikely to surpass the general use of the Wittig reaction in organic synthesis.
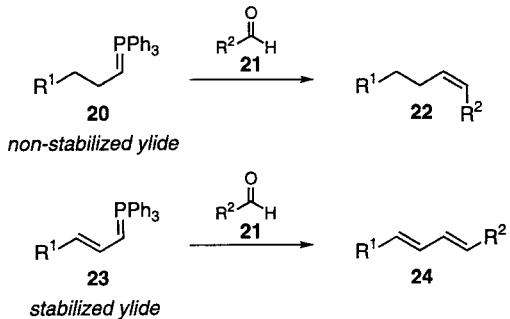
## 2. Selected Aspects of the Wittig and Related Reactions

In this section, we focus on the following aspects of the Wittig reaction: (a) stereoselectivity; (b) the intramolecular Wittig reaction; (c) the Wittig reaction with substrates other than aldehydes and ketones; (d) the catalytic Wittig reaction; (e) asymmetric Wittig reactions; and (f) the Wittig reaction on solid support.

### (a) Stereoselectivity of the Wittig Reaction
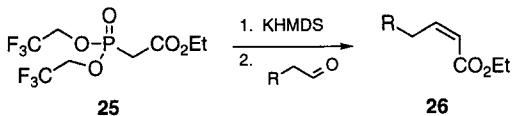
The geometry of the carbon–carbon double bond formed in the Wittig reaction can be controlled in a number of ways. Usually, a non-stabilized ylide (such as **20**, Scheme 7) gives mainly a *cis* double bond in the Wittig reaction with a carbonyl compound, whereas a stabilized ylide (e.g. **23**) gives predominantly a *trans* double bond (Scheme 7). These results have been rationalized in detail many times through investigations into the mechanism of the Wittig reaction[4], but can be generally interpreted in terms of the greater degree of reversibility in the formation of the intermediate betaine from a stabilized ylide as compared to a non-stabilized one. However, these preferences can often be influenced by judicious tuning of the solvent, base and temperature used in the reaction. It is important to note that synthetically useful *cis* selectivities can only be achieved in the absence of soluble salts (in particular, lithium salts) when reactive ylides are involved.

Scheme 7. Stereoselectivity in the Wittig reaction
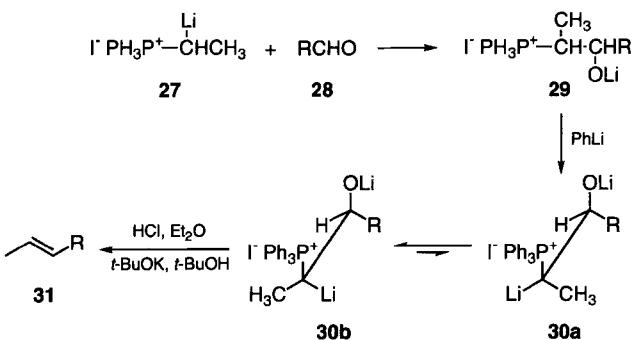


The Still–Gennari modification[14] of the HWE reaction provides a means of synthesizing a *cis* double bond from a stabilized phosphonate carbanion (e.g. **25** → **26**, Scheme 8). The bis(2,2,2-trifluoroethyl) phosphonate grouping is thought to accelerate the elimination of the initially formed adduct such that equilibration to the thermodynamic *trans* alkene is severely restricted. In contrast, the Schlosser modification[15] of the Wittig reaction often enables the preparation of *trans* double bonds from non-stabilized ylides (Scheme 9).

Scheme 8. The Still-Gennari modification of the HWE reaction (1983, Still and Gennari)[14]
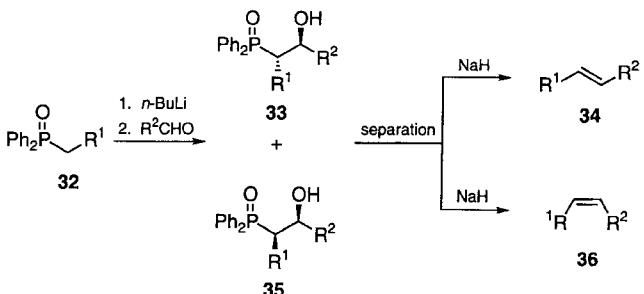


Scheme 9. The Schlosser modification of the Wittig reaction (1966, Schlosser)[15]



Alternatively, as shown by Warren and co-workers[16], the Horner–Wittig reaction provides a way of controlling the double bond geometry in the Wittig reaction (Scheme 10). By stopping the Wittig reaction "half-way" and separating the two diastereomeric β-hydroxy diphenylphosphine oxides (or, preferably, by performing some kind of stereoselective union of the anion and the aldehyde), and then inducing a stereospecific *syn* elimination of diphenylphosphinate, geometrically pure alkenes can be obtained.

Scheme 10. Control of alkene geometry through application of the Horner-Wittig reaction (1985, Warren)[16]



### (b) The Intramolecular Wittig Reaction

The intramolecular Wittig reaction might look rather unlikely at first glance: attempted formation of the ylide with
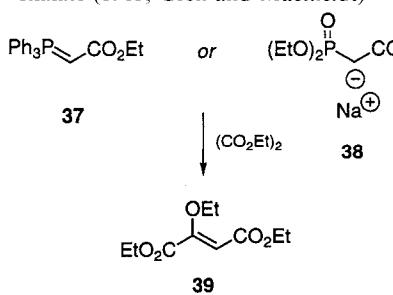
a strong base might be expected to cause competing aldol-type reactions of the carbonyl group at the other end of the molecule. This, to some degree, is correct and most intra-molecular Wittig reactions make use of phosphoryl-stabi-lized carbanions (HWE reaction) since the anions are more reactive. However, a number of heterocycles can be made by the intramolecular Wittig reaction from precursors con-taining suitably unreactive carbonyls. One of the most de-manding examples of such reactions of recent years is that in our synthesis of amphoteronolide B (see Scheme 21 in the next section). The bis-Wittig reaction (in which the first Wittig reaction proceeds inter- and the second intramolecu-larly) has been used extensively by Vollhardt and co-work-ers to synthesize non-benzenoid heteroaromatic systems[17].

**(c) The Wittig Reaction with Substrates Other than Aldehydes and Ketones**
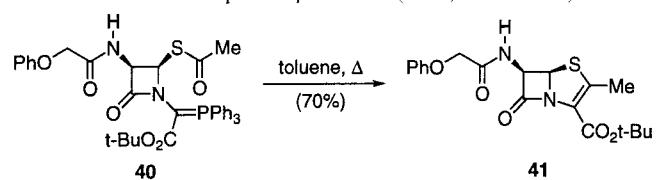
Although phosphonium salt-derived ylides and phos-phonates are generally considered too unreactive to couple with less reactive carbonyl groups like those in esters or amides, such reactions can, nevertheless, occur[18]. For ex-ample in 1966, Grell and Machleidt[19] were the first to re-port the formation of a vinyl ether (**39**) by reaction of a phosphonium ylide (or a phosphonate) with diethyl oxalate (Scheme 11). However, attempted methylenation of simple esters with methylidene triphenylphosphorane does not give the expected vinyl ethers, but instead a β-keto ylide. This transformation could, of course, now be easily achieved by the use of more reactive organometallic species such as the Tebbe or related reagents.

Scheme 11. The stabilized Wittig and HWE reactions with diethyl oxalate (1965, Grell and Machleidt)[19]

In Woodward's approach to the penem β-lactams, an in-tramolecular Wittig reaction between the ylide and the thi-olester functionalities present in **40** was used to make inter-mediate **41** (Scheme 12)[20].

Scheme 12. The intramolecular Wittig reaction in the total synthe-sis of the penem β-lactams (1978, Woodward)[20]
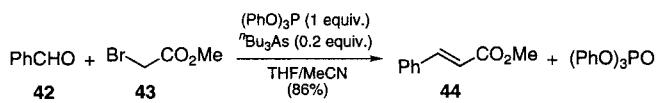
**(d) A Catalytic Wittig Reaction**

Huang and co-workers have described a tri-*n*-butylarsine variant of the Horner−Wadsworth−Emmons reaction

(Scheme 13)[21]. Treatment of an aldehyde, an α-bromo car-bonyl compound and tri(phenyl)phosphite with *n*-Bu₃As (20 mol%) and potassium carbonate in THF/acetonitrile gives the expected *trans* alkene in exellent yield. A catalytic cycle is proposed in which the *n*-Bu₃As reacts with the α-bromocarbonyl compound to give a salt, which is converted to the ylide with potassium carbonate. This reacts with the aldehyde, generating the alkene and *n*-Bu₃AsO. Finally, this is then reduced by the stoichiometric tri(phenyl)phosphite to return the *n*-Bu₃PAs to the catalytic cycle.
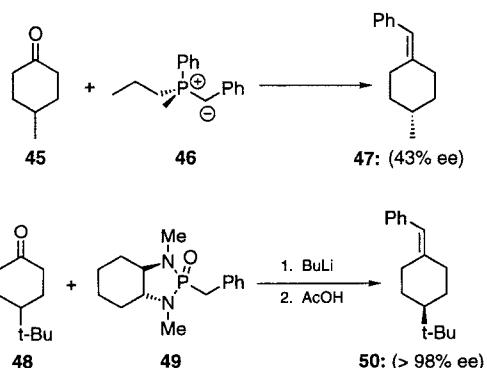
Scheme 13. Example of a catalytic Wittig reaction (1989, Huang)[21]

**(e) Asymmetric Wittig Reactions**
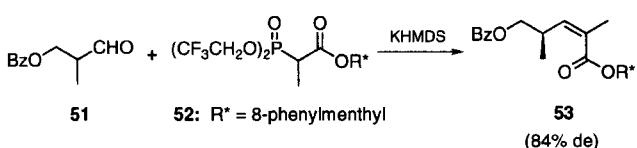
Initially, the concept of an asymmetric Wittig reaction might not seem possible because only sp² centers are formed in the reaction[22]. However, with prochiral sub-strates (e.g. **45**, Scheme 14), the two possible products are enantiomeric, so a suitably designed reagent should be able to favor the formation of either one of them. Bestmann and Lienert achieved reasonable asymmetric induction with the chiral phosphonium ylide **46**[23] better results have since been achieved by Hanessian and co-workers with the phos-phonic bisamide **49** (Scheme 14)[24].

Scheme 14. Examples of asymmetric Wittig reactions (1969, Best-mann[23], 1992, Hanessian[24])

In chiral substrates, an optically active Wittig reagent can sometimes offer an improvement in control of double bond geometry through "matched" asymmetric induction[22]. It is also possible to perform a kinetic resolution of certain chiral racemic aldehydes (e.g. **51**, Scheme 15) through the use of an enantiomerically pure phosphonate (e.g. **51** + **52** → **53**, Scheme 15)[27]. A catalytic, asymmetric version of the Wittig reaction remains, however, elusive.

Scheme 15. Kinetic resolution of racemic aldehydes through a phosphonate-type olefination (1995, Rein and Rei-ser)[25]
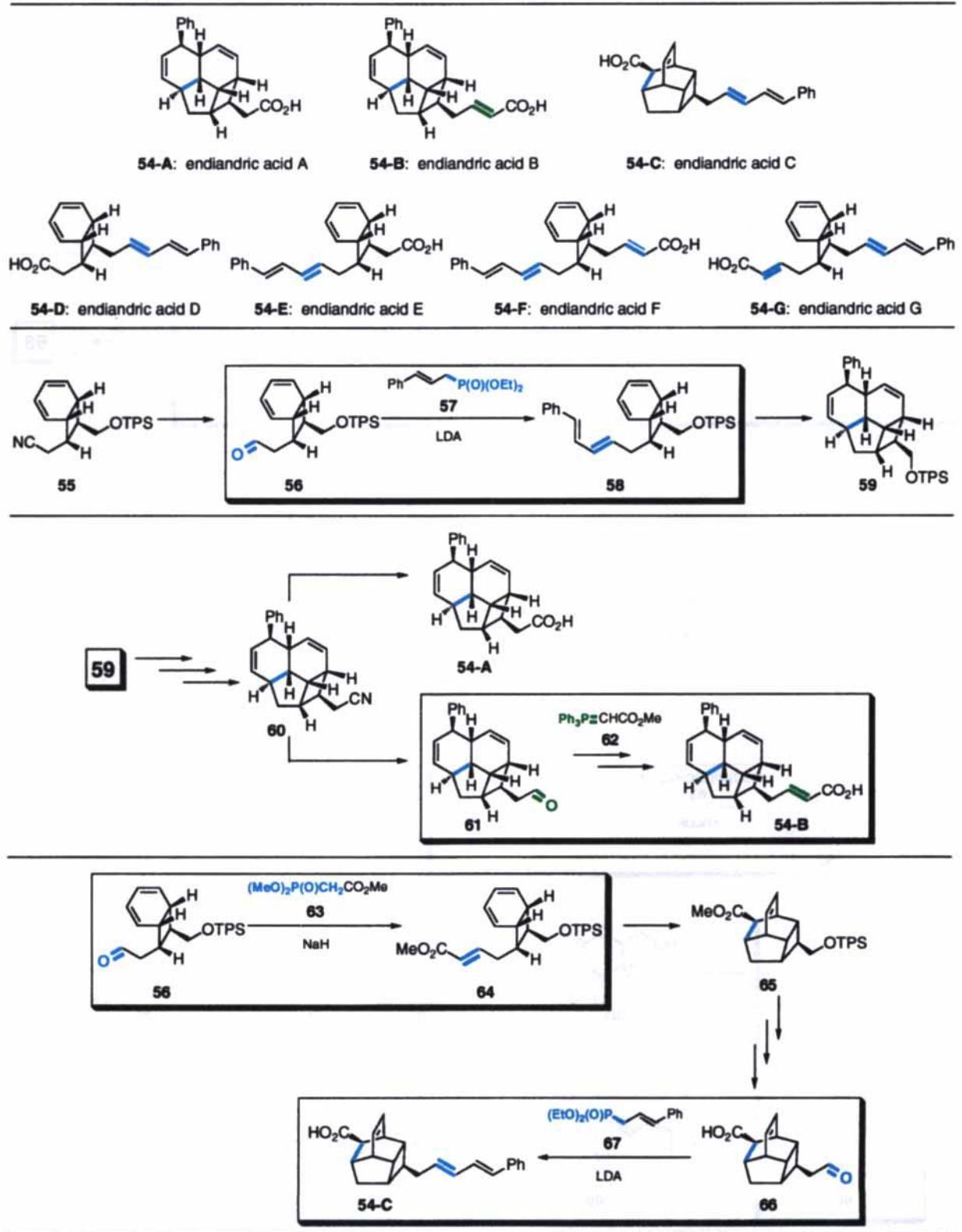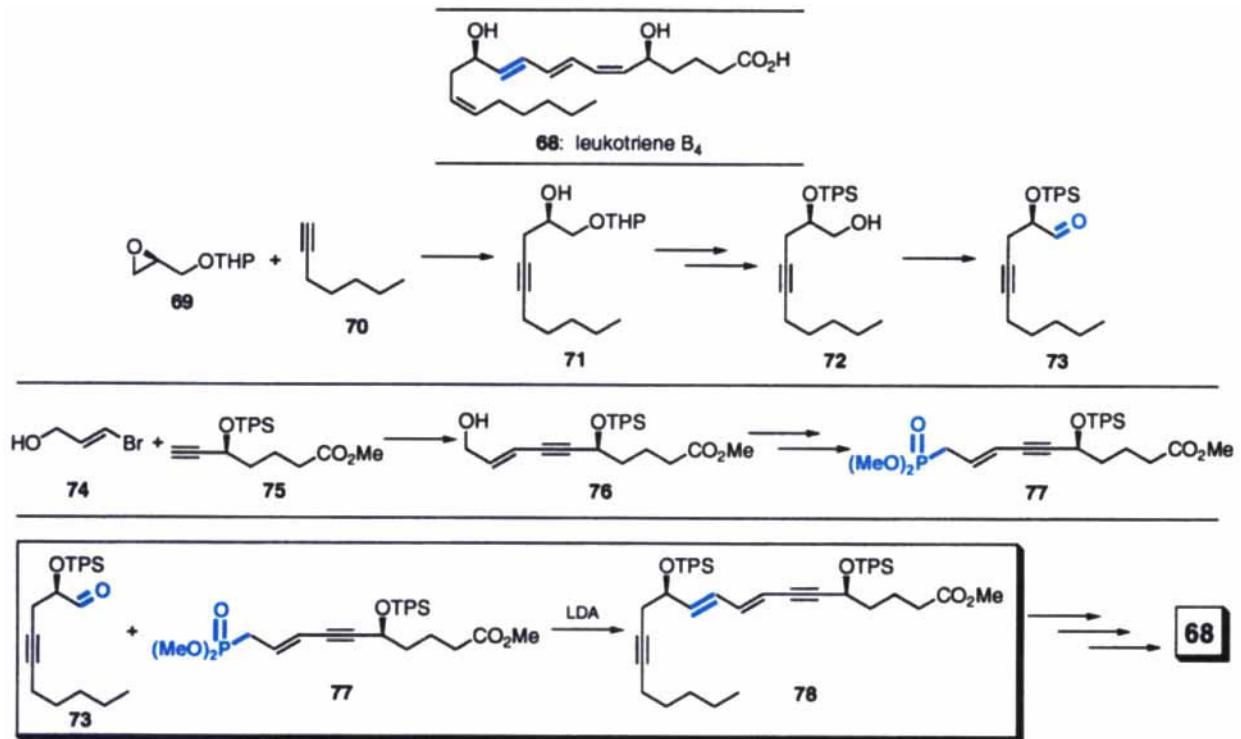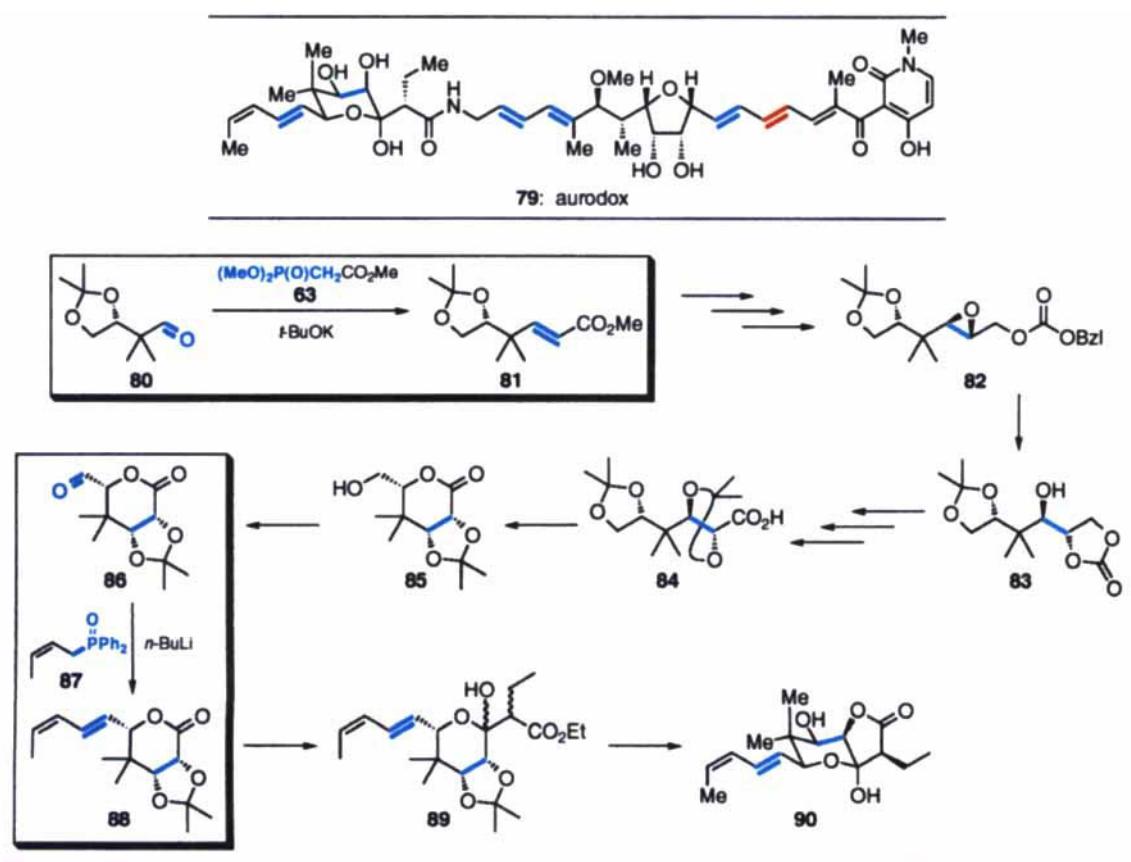
                                                

## (f) The Wittig Reaction on Solid Support

The separation of the triphenylphosphine oxide byproduct from the olefinic product in a Wittig reaction can be a difficult task. Indeed, this is one of the advantages of the Horner−Wadsworth−Emmons reaction over the Wittig reaction. For some years now, it has been possible to perform some Wittig reactions with 1−2% cross-linked 4-polystyryldiphenylphosphine in the place of triphenylphos-

Scheme 16. HWE, stabilized Wittig and Horner−Wittig reactions in the total syntheses of endiandric acids A−G (**54-A−54-G**) (1982)[29]
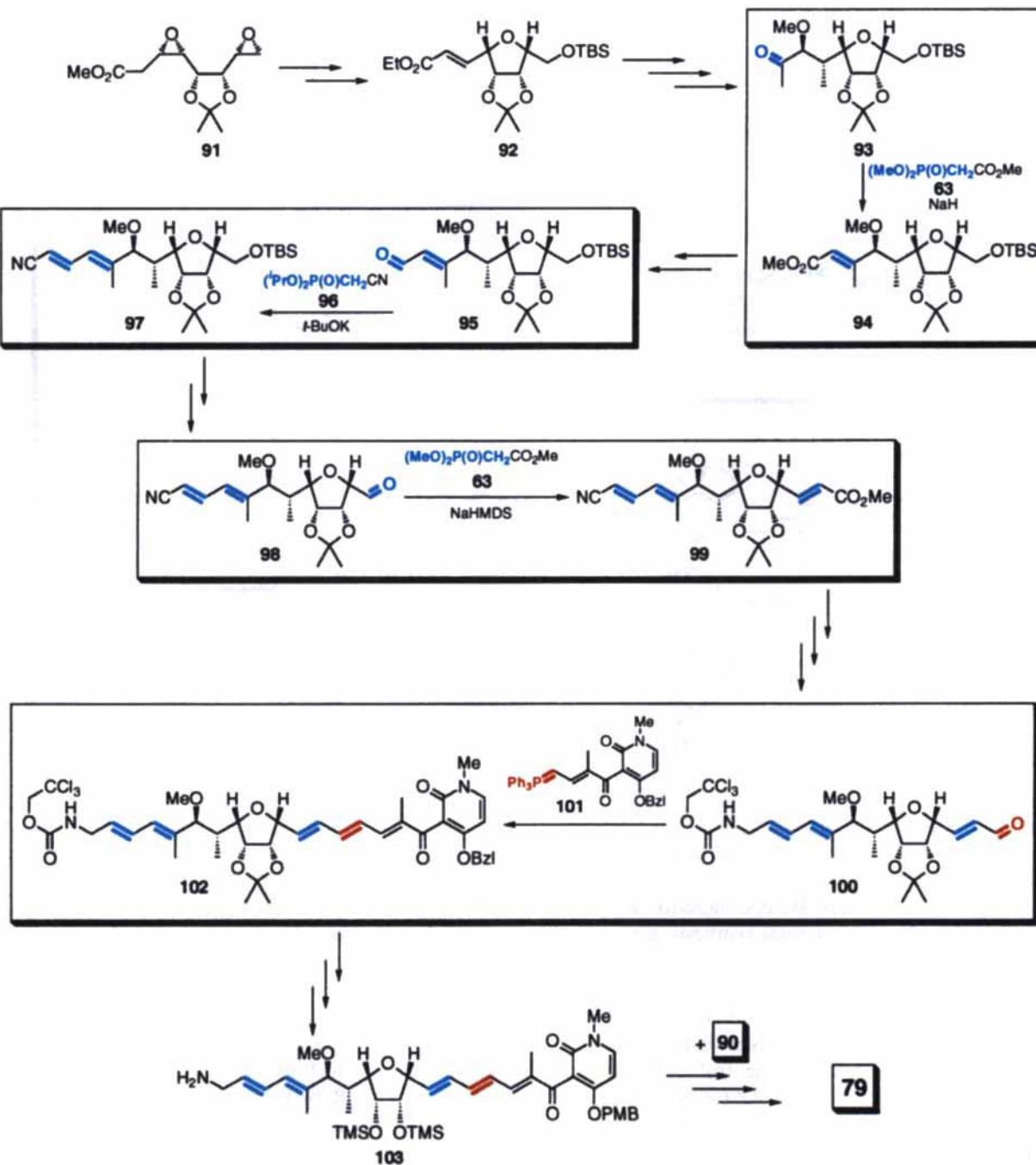
Scheme 17. The Horner−Wittig reaction in the total synthesis of leukotriene B₄ (**68**) (1984)[30]



Scheme 18. The HWE, Horner−Wittig and stabilized Wittig reactions in the total synthesis of aurodox (**79**) (1985)[32]: Part a
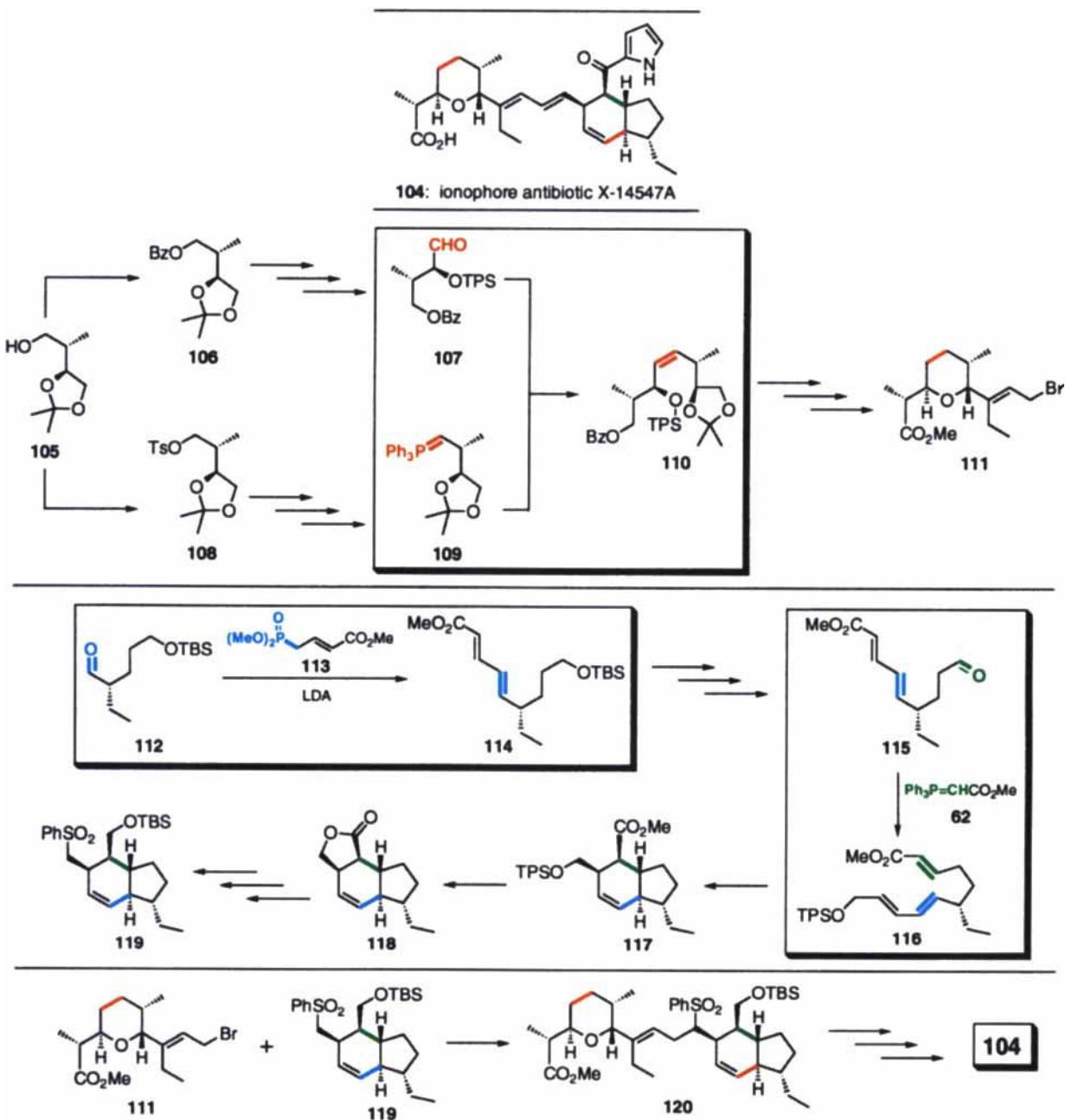
phine[26]. The polymer is readily prepared by bromination of polystyrene, followed by displacement with lithium diphenylphosphide, and is also commercially available. The polymer-supported Wittig reaction itself proceeds well with a variety of substrates, although the stereoselectivity suffers if the cross-linking increases above 2%, and longer reaction times are usually necessary. With the advent of solid-phase combinatorial chemistry, the use of such solid phase reagents is bound to expand. Wittig and related reactions with polymer bound aldehydes have also been described[27].

## 3. Total Syntheses Involving Wittig and Related Reactions: Examples from the Nicolaou Laboratories

The power of the Wittig and related reactions in chemical synthesis is amply demonstrated by the widespread application of these processes in the total synthesis of complex natural products. In this section, we shall describe the use of these reactions at various stages of multi-step syntheses, ranging from the relatively large-scale preparation of early intermediates to the final steps of the sequences leading to highly functionalized targets. Due to the enormous task re-

Scheme 18: Part b

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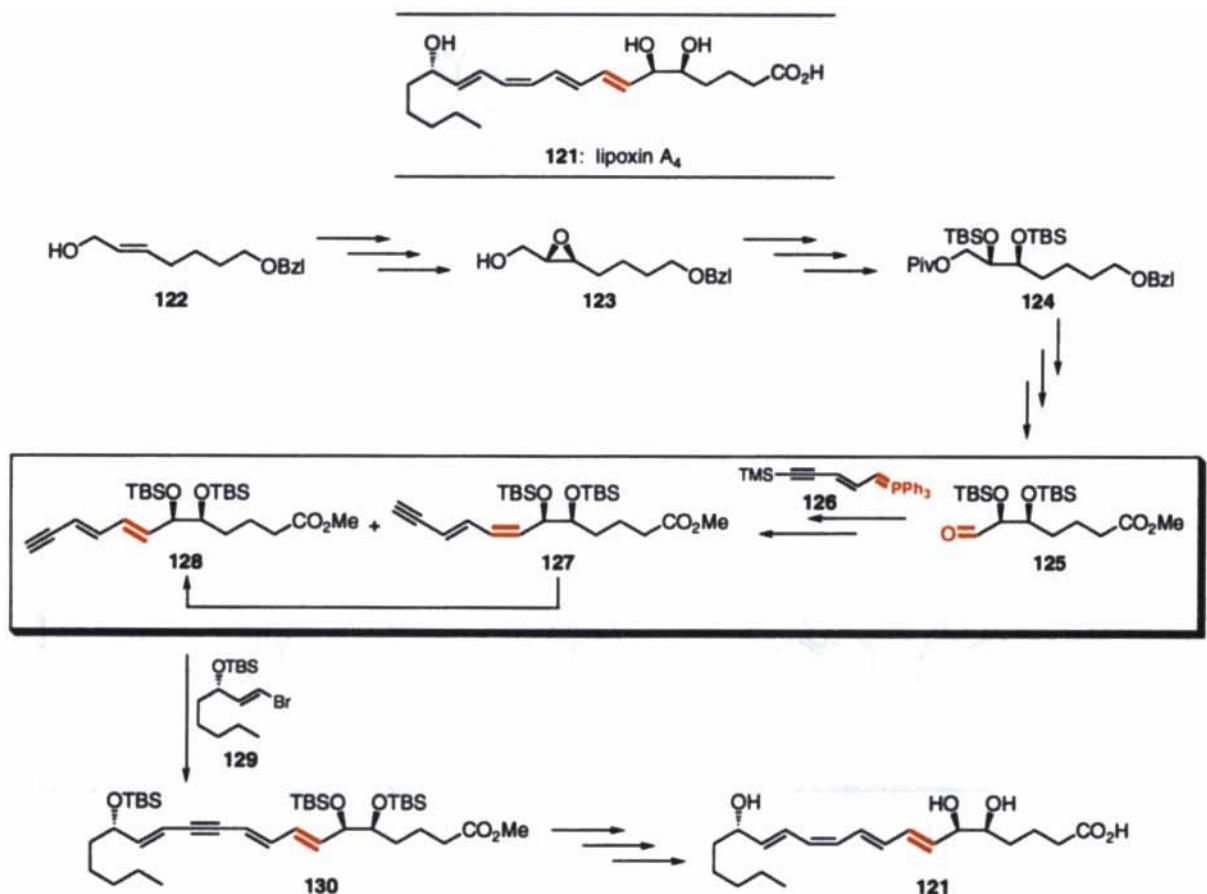
Scheme 19. The Wittig, HWE and stabilized Wittig reactions in the total synthesis of ionophore antibiotic X-14547A (**104**) (1985)[33]



quired for complete coverage of the literature, we have restricted ourselves only to examples from our own laboratories within the last 15 years. We apologize to those whose brilliant works in the field of total synthesis are not mentioned here and refer the reader to our original publications and reviews for the most relevant references[28].

In 1982, we published the total synthesis of a class of naturally occuring compounds known as endiandric acids (compounds **54-A** through **54-G**, Scheme 16)[29]. In these syntheses, cyanide **55**, derived from (2E,4Z,6Z,8E)-deca-2,4,6,8-tetraene-1,10-diol, served as the common intermediate. DIBAL-H reduction of cyanide **55** afforded aldehyde **56**, which

served as the carbonyl component in a Horner–Wittig reaction with the phosphonate anion derived from **57**. The E,E-diene thus formed was suitably positioned to undergo an intramolecular Diels–Alder reaction with one of the double bonds of the 1,3-cyclohexadiene system already present in the molecule. After a number of standard transformations, the advanced intermediate **59** led to endiandric acid A (**54-A**). Following a different sequence, the tetracyclic aldehyde **61** was formed, which was subsequently converted to endiandric acid B (**54-B**) by Wittig reaction with the stabilized ylide methyl (triphenylphosphoranylidene)acetate and ester hydrolysis. Similarly, the synthesis of endiandric acid C (**54-**
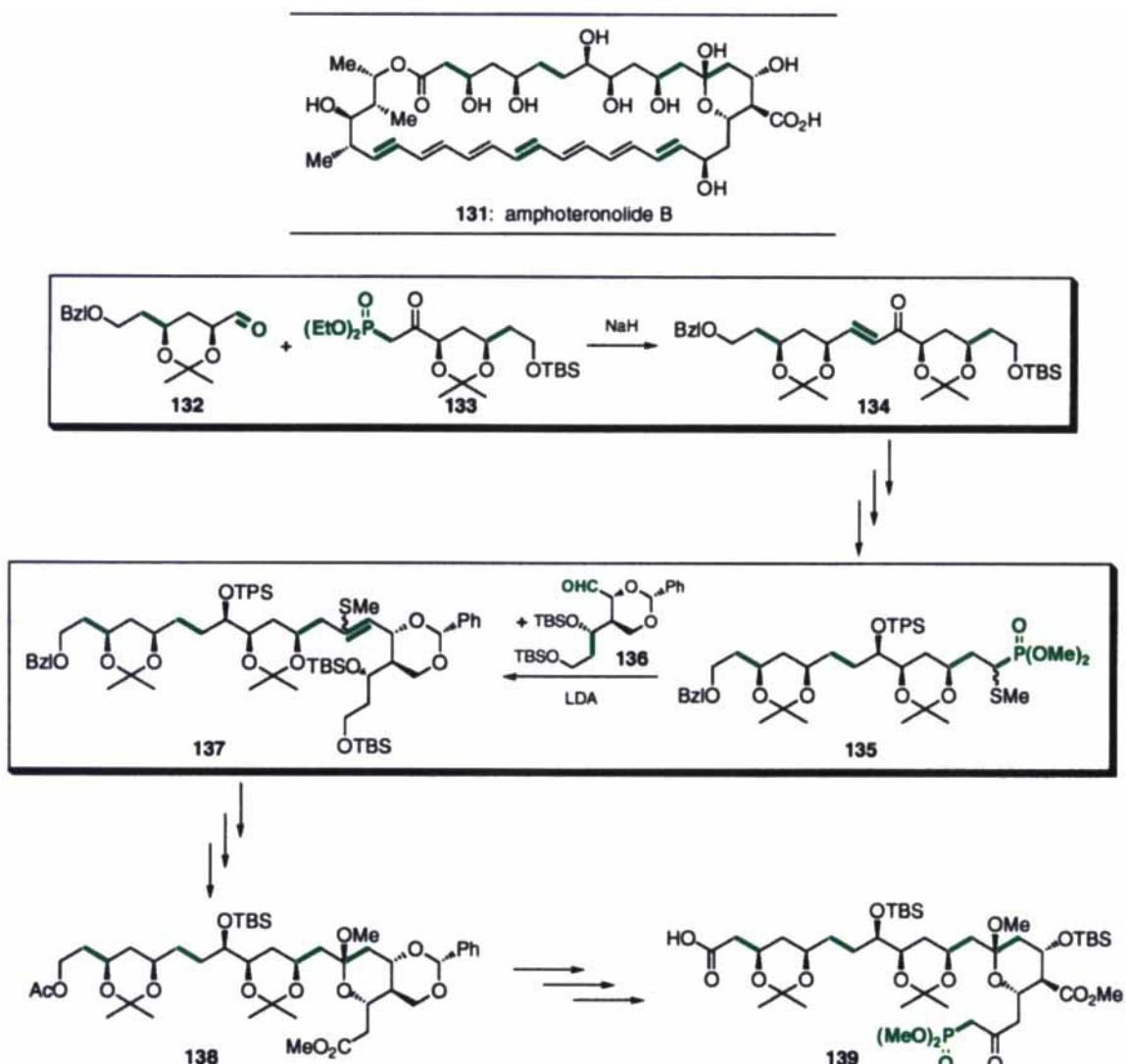
Scheme 20. The Wittig reaction in the total synthesis of lipoxin A$_4$ (**121**) (1985)[34]



C) involved two Wittig-type olefinations. In a HWE reaction, aldehyde **56** was converted to α,β-unsaturated ester **64**, which, upon heating, gave rise to the cage-like compound **65** as the product of an intramolecular Diels–Alder reaction. After chain extension, adjustment of oxidation state and hydrolysis of the methyl ester, the carboxylic acid aldehyde **66** reacted with the anion of (*E*)-diethyl cinnamylphosphonate (**67**), to afford endiandric acid **54-C**. The other members of the endiandric acid family were synthesized by the same basic strategy, utilizing one or two olefinations of the Horner–Wittig type for the attachment of the unsaturated side chains. Their syntheses are omitted here for brevity, but can be found in the original publications[29].

In our next example we will highlight the successful application of phosphonates in the olefination of optically active α-alkoxy- or α-silyloxyaldehydes, which are prone to racemization under basic conditions. A key step in the total synthesis of leukotriene B$_4$ (**68**, Scheme 17)[32] was the coupling of aldehyde **73** with the phosphonate anion derived from **77**, the preparations of which are outlined in Scheme 17. Compared to phosphoranylidenes of the Wittig type, deprotonated phosphonates of the Horner–Wittig and HWE types are stronger bases[31]. Nevertheless, the reaction with easily epimerizable substrates, such as aldehyde **73**, can occur with conservation of stereochemical integrity. Under controlled conditions, the olefination reaction

between **73** and **77** afforded intermediate **78** in 70% chemical yield as a 9:1 *E*/*Z* mixture with regard to the newly formed double bond, and without detectable loss of optical purity.

Aurodox (**79**, Scheme 18a) is a member of the elfamycin family of antibiotics. Our total synthesis of this naturally occurring substance incorporated six olefination reactions of the HWE, Horner–Wittig and stabilized Wittig types[32]. The α,β-unsaturated ester **81** was prepared from aldehyde **80** by a HWE reaction with the anion of trimethyl phosphonoacetate, generating a *trans* double bond. The latter compound (**81**) was transformed by several steps to aldehyde **86**, which was subsequently reacted with lithiated *cis*-2-butenyldiphenylphosphine oxide to afford diene **88** with a *trans* geometry across the newly formed double bond. Another HWE reaction with trimethyl phosphonoacetate was applied to the α-alkoxy ketone **93** (Scheme 18b). Again, the reaction proceeded without any detectable reacemization at the α-center. The *E*/*Z* selectivity, however, was diminished and did not exeed 4:1 in favor of the desired *E* isomer. This observation can be explained by the fact that a ketone served as the substrate, and the decreased selectivity reflects the low energy difference between the two isomeric triply substituted olefins formed, or, more precisely, their oxyphosphonato precursors. The subsequent applications of HWE reactions on aldehydes derived from the unsaturated

Scheme 21. The HWE and Horner−Wittig reaction in the total synthesis of amphoteronolide B (**131**) (1987)[35]: Part a



ester **94** (**95** → **97** and **98** → **99**) led to the intermediate **100**, whose reaction with the stabilized conjugated ylide **101** furnished compound **102** (Scheme 18b) as the major geometrical isomer, and in high yield. Further transformations and coupling with building block **90** via amide bond formation completed the total synthesis of aurodox (**79**).
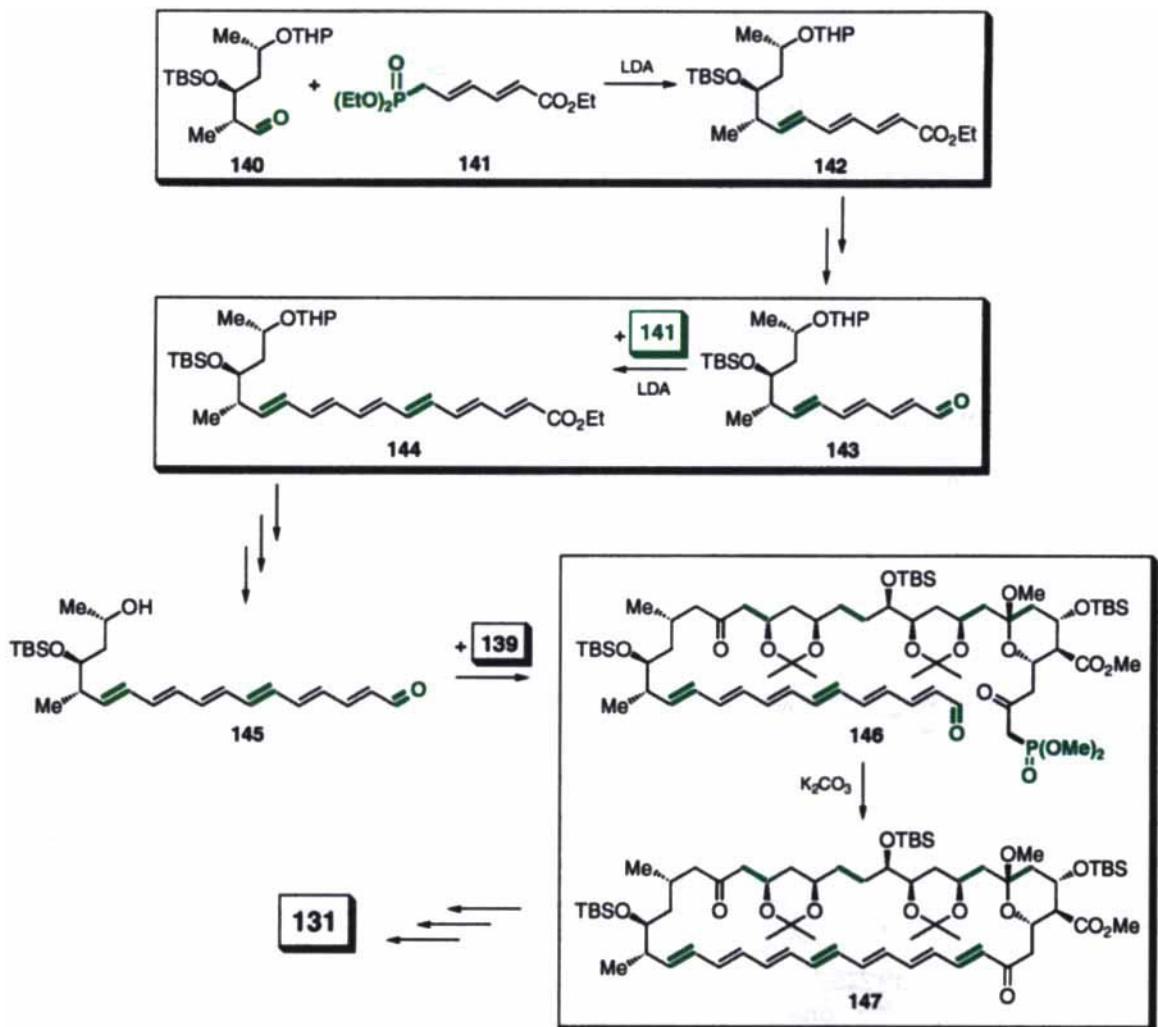
Alcohol **105** served as the starting material for both the carbonyl component (**107**) and the phosphoranylidene (**109**) of a Wittig reaction applied in our total synthesis of the ionophore antibiotic X-14547 A (**104**, Scheme 19)[33]. Due to the well-known effect of α-alkoxy substituents on Wittig reactions[4a], olefin **110** was obtained as a mixture of Z/E isomers (ratio ca. 1:2). Since this double bond was to be hydrogenated at a later stage of the synthesis, the geometry of the double bond was of no consequence and no attempt was made to separate the isomers. For the preparation of the tetrahydroindane building block **119**, an intramolecular Diels−Alder reaction was employed as the key step, and both the diene and the dienophile moieties of the molecule

were constructed by Wittig-related olefinations. The reaction of aldehyde **112** with deprotonated *trans*-trimethyl-4-phosphono-2-butenoate (**113**) afforded diene **114** with the desired E,E geometry. The subsequent elaboration of **114** to **116** included a Wittig reaction between aldehyde **115** and the stabilized ylide methyl (triphenylphosphoranylidene)-acetate (Scheme 19).

Another example where a loss of stereoselectivity is observed in the reaction of a phosphoranylidene with an alkoxy- or silyloxy-substituted aldehyde is provided by the total synthesis of lipoxin A₄ (**121**, Scheme 20)[34]. The aldehyde **125** reacted with the enynephosphoranylidene **126** to give a 1:1 mixture of **127** and **128** in a combined yield of 98%. Fortunately, the Z isomer could easily be converted to the desired E isomer by treatment with catalytic amounts of iodine.

An intramolecular HWE reaction was utilized to achieve the closure of the 36-membered ring present in amphoteronolide B (**131**, Scheme 21a)[35]. The reaction was performed under mildly basic conditions [K₂CO₃, 18-crown-6,

Scheme 21. Part b
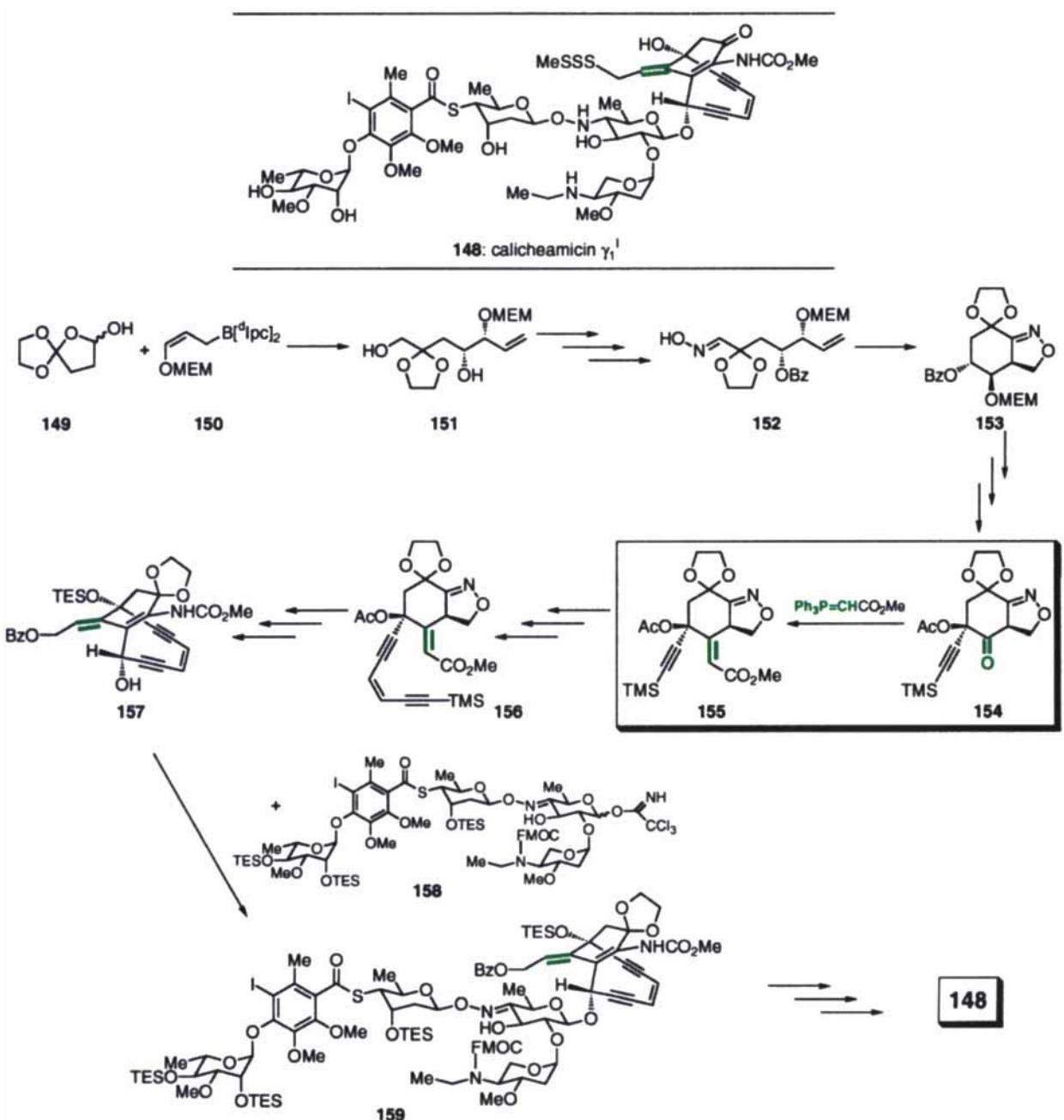


toluene, 65°C or DBU, LiCl, CH₃CN, 25°C, see below for further discussion on these conditions] and proceeded in 70% yield (Scheme 21b). HWE reactions were also employed in the preparation of fragments **139** (Scheme 21a) and **145** (Scheme 21b). The six-fold conjugated unsaturated ester **144** was obtained from aldehyde **140** by two consecutive Horner–Wittig reactions with the doubly unsaturated phosphonate anion of **141**. This chemistry also led to the total synthesis of the antifungal agent amphotericin B[35].

Calicheamicin $\gamma_1^I$ (**148**, Scheme 22) belongs to the enediyne class of anticancer antibiotics. Its fascinating molecular architecture and sophisticated mode of action against tumor cells made it an attractive synthetic target[36]. The first total synthesis of calicheamicin $\gamma_1^I$ (**148**) was completed in our laboratories and published in 1992. A stabilized Wittig reaction between methyl (triphenylphosphoranylidene)acetate and the sterically hindered ketone **154** occurred smoothly and stereoselectively, affording intermediate **155** in 84% yield. The E-α,β-unsaturated ester thus formed set the stage for further elaboration and introduction of the trisulfide moiety which
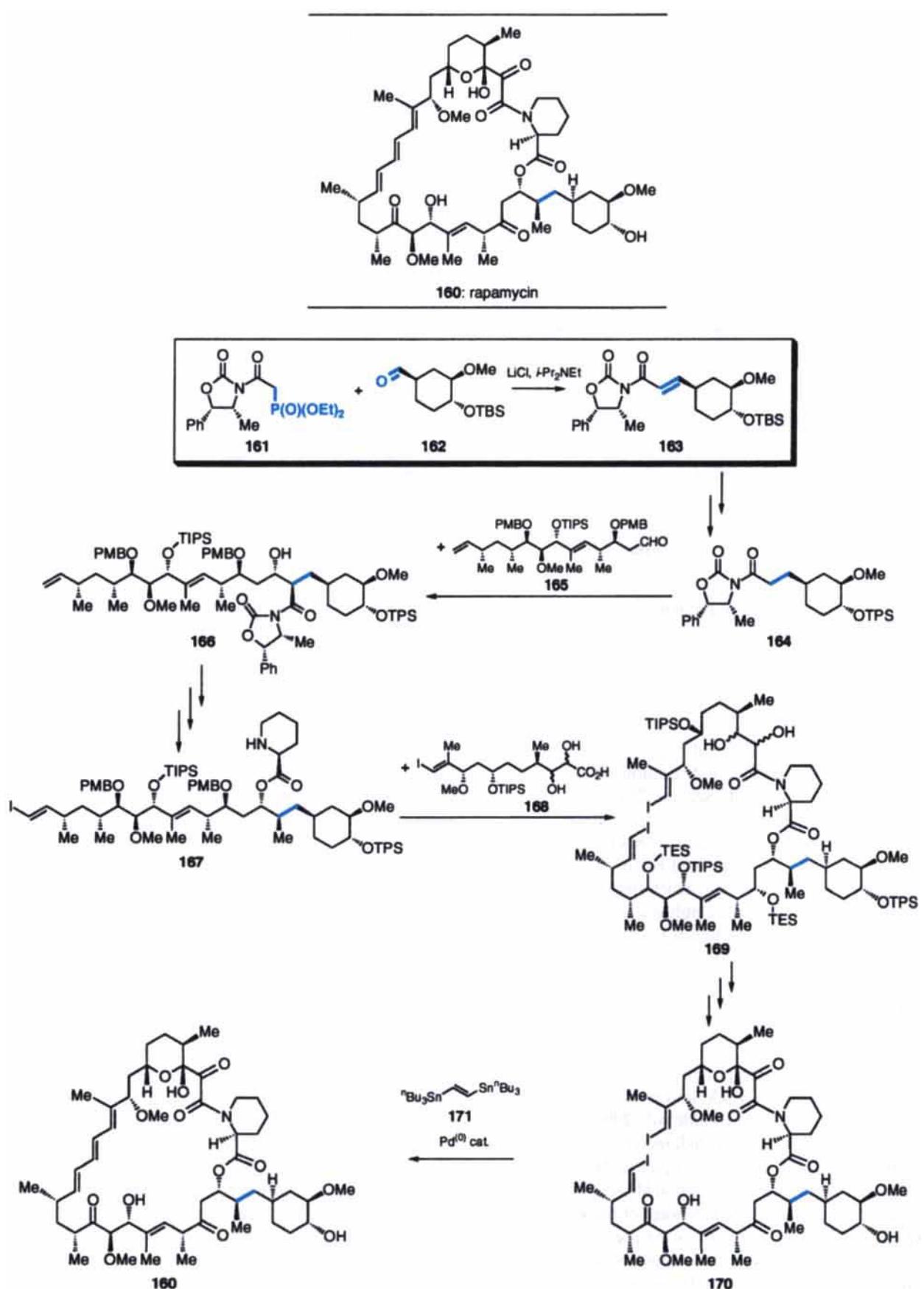
serves as the "triggering device" for activation in calicheamicin's unique mechanism of action.
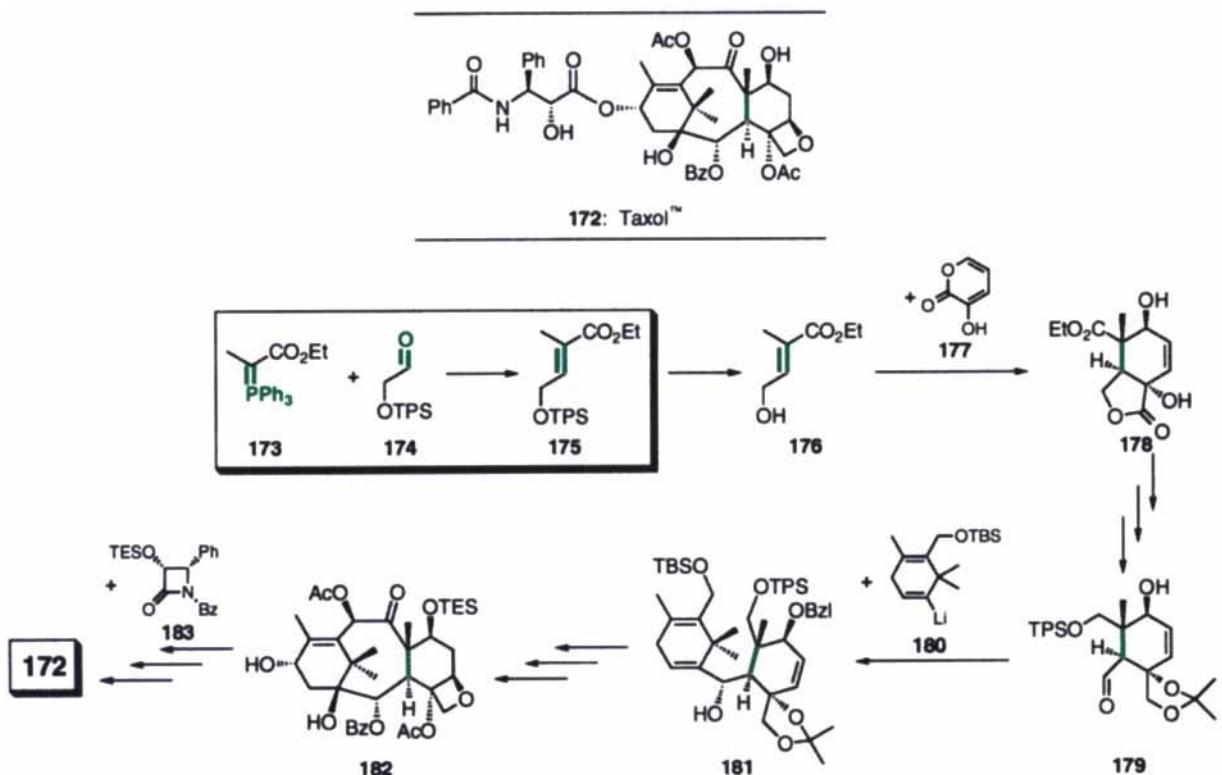
A very mild method for the coupling of a phosphonate with a carbonyl component has been developed by Masamune and Roush and involves the deprotonation of a phosphonoacetate, β-ketophosphonate, or related structure with only weakly basic tertiary amines such as triethylamine or Hünig's base in the presence of a lithium salt (usually LiBr or LiCl)[37]. It is presumed that the β-oxophosphonate is activated by chelation with the lithium cation, thus allowing deprotonation to take place under mild conditions. This procedure is, therefore, the method of choice when base-sensitive substrates are to be utilized in HWE reactions. We took advantage of this protocol in our total synthesis of rapamycin (**160**, Scheme 23)[38]. The imidophosphonate **161** was coupled with aldehyde **162** in the presence of LiCl and Hünig's base. The reaction occured at room temperature in acetonitrile to afford intermediate **163** in 96% yield. Further elaboration, as summarized in Scheme 23, and a final double Stille-type coupling completed the first total synthesis of rapamycin.

Scheme 22. The stabilized Wittig reaction in the total synthesis of calicheamicin $\gamma_1^I$ (**148**) (1992)[36]



In 1994, we published our total synthesis of Taxol (**172**, Scheme 24)[39]. A Wittig reaction of the ylide **173** and the α-silyloxyaldehyde **174** afforded the early intermediate **175** and laid the foundation for the construction of Taxol's C ring, which was one of the two main building blocks in the synthesis. In contrast to some other C–C bond forming reactions, the Wittig and related transformations are reliable both in terms of good yields and selectivities, and in small- as well as large-scale operations, making them powerful tools in the preparation of early intermediates in multi-step syntheses as well as in putting the final touches to complex molecules.

Three Wittig reactions with stabilized and non-stabilized ylides were involved in our synthesis of zaragozic acid A (**184**, Scheme 25)[40], a powerful inhibitor of the enzyme squalene synthase. Building block **189** was obtained by a Wittig reaction between aldehyde **185** and ylide **186**. The preparation of fragment **193** included a Wittig reaction of aldehyde **192** with the stabilized ylide **62** (Scheme 25). Noteworthy is the Wittig reaction between the functionalized ylide **194** and aldehyde **195**. Methyl iodo(triphenylphosphoranylidene)acetate (**194**)[41] reacts with aldehydes to afford vinyl iodides with a predictable geometry across the newly formed double bond. These vinyl iodides are useful inter-

Scheme 23. The HWE reaction in the total synthesis of rapamycin (**160**) (1993)[38]
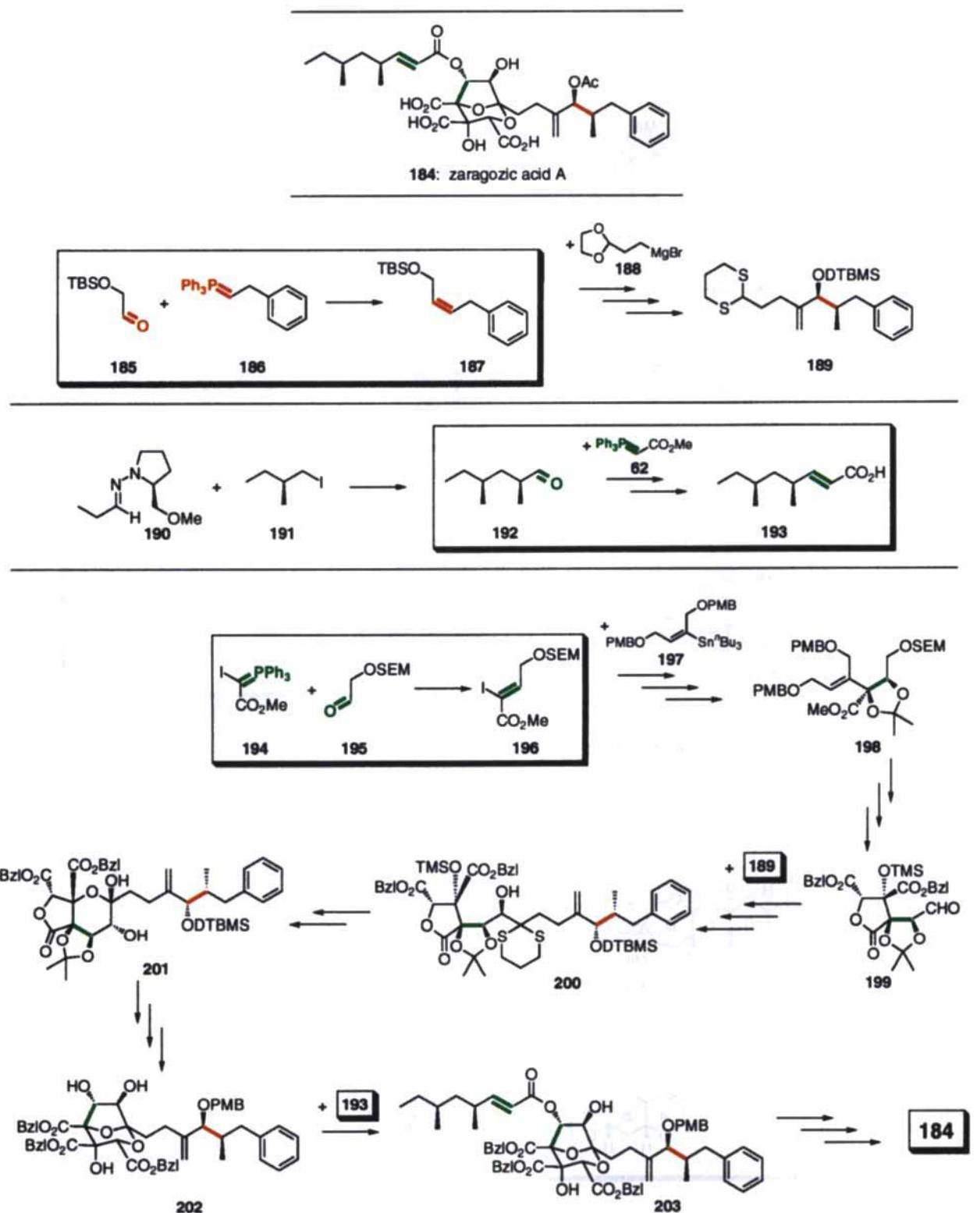
Scheme 24. The stabilized Wittig reaction in the total synthesis of Taxol (**172**) (1994)[39]



mediates because they can participate in a large number of transition metal catalyzed reactions. In the case at hand, the vinyl iodide **196** was obtained in 78% yield ($Z/E >$ 30:1) and subjected to a Stille coupling with vinylstannane **197**, to eventually furnish **198**, which then led to **184** as outlined in Scheme 25.

In our next example, we will highlight the crucial role played by the Wittig and related reactions in the total synthesis of brevetoxin B (**204**, Scheme 26)[42]. No less than twelve carbon–carbon bonds stem from these reactions, that is ca. 25% of all C–C bonds of this molecule and ca. 64% of all the C–C bonds formed by the team during the course of the synthesis! Wittig reactions of the stabilized and non-stabilized type were employed in the construction of the *trans*-fused tetrahydropyran rings, as exemplified in Scheme 26a, by the generation of the G ring. Silylation of the hydroxy group in **205** followed by hydroboration and oxidation afforded aldehyde **206**, which upon treatment with ethyl-2-(triphenylphosphoranylidene)propionate was converted to the α,β-unsaturated ester **208** in 86% yield. Reduction of **208** to the corresponding alcohol, epoxidation of the double bond with *m*CPBA, and oxidation of the epoxy alcohol with SO$_3$ • pyr, led to aldehyde **209**. A Wittig reaction of this aldehyde with methylidene(triphenylphosphorane) **210** gave the 6-*endo* activated epoxide **211** in 81% yield, and set the stage for the anticipated acid-catalyzed hydroxy–epoxy cyclization. After cleavage of the silyl ether with TBAF, the cyclization occurred in the presence of catalytic amounts of PPTS (81% over two steps). Scheme 26b shows the coupling of the two large fragments **213** and **214** as

accomplished by a Wittig reaction. The ylide **213** was generated from the corresponding phosphonium iodide by treatment with *n*-BuLi in THF/HMPA at −78°C. After addition of the aldehyde **214**, the reaction mixture was warmed to 25°C, and the desired coupling product **215** was obtained in 75% yield after acid-induced cleavage of the TMS ether. The formation of the stereoisomeric *E*-alkene was not observed, as expected from the use of HMPA as a co-solvent. With this successful coupling, the Wittig reaction proved once more to be a mild and very effective method for the formation of carbon–carbon bonds in complex situations.
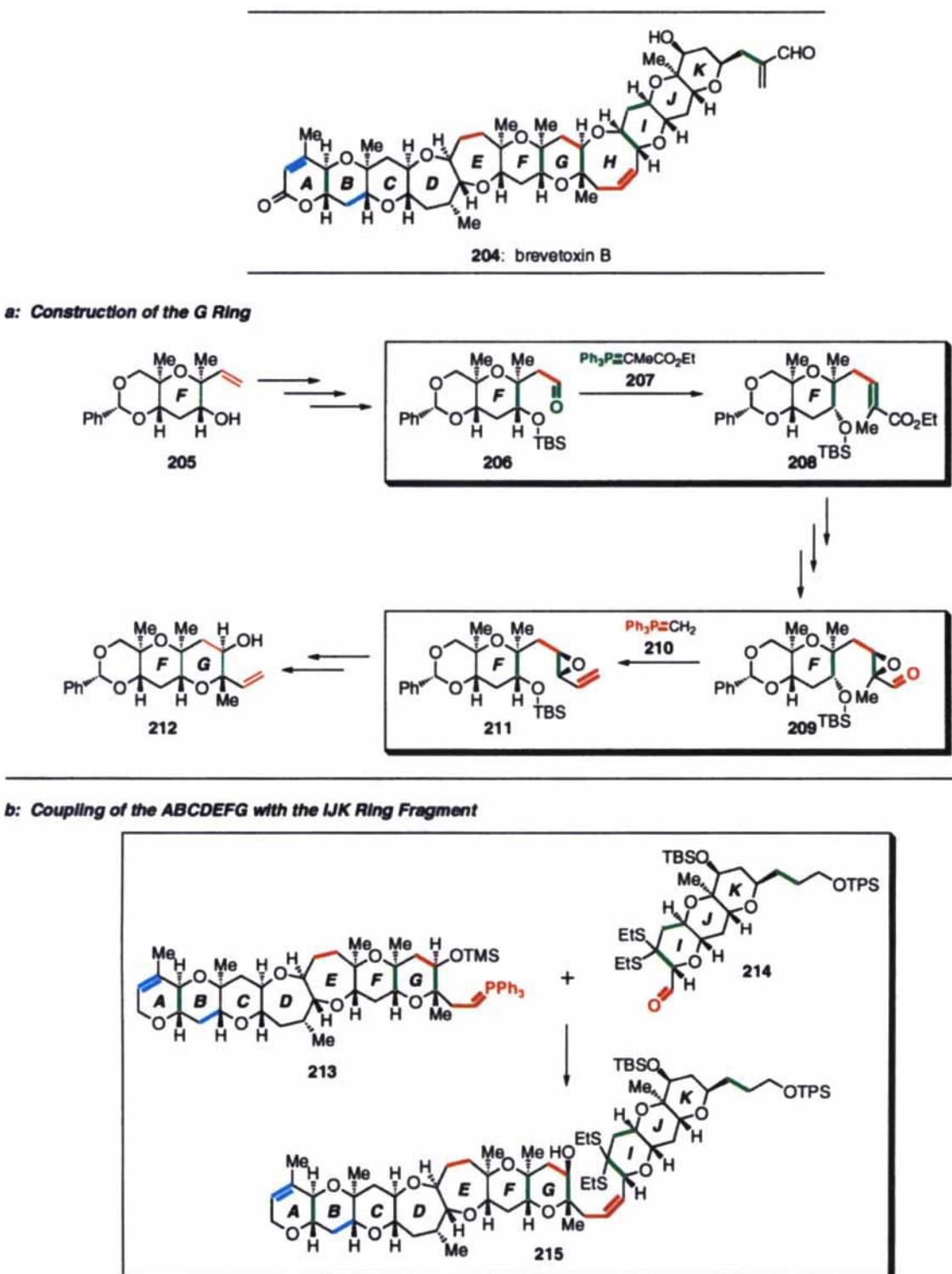
In our last example we will focus on the total syntheses of epothilones A and B (**216-A** and **216-B**, Scheme 27)[43]. Produced from myxobacteria *Sorangium cellulosum*, these compounds became a "hot topic" among chemists, biologists and physicians as soon as their potential in chemotherapy was recognized[44]. Our first total synthesis of epothilone A (**216-A**) was published in January 1997, and was based on an olefin metathesis strategy applying a solution phase methodology[43a]. Shortly thereafter, we reported a second strategy for the total synthesis of epothilones A (**216-A**) and B (**216-B**) based on a macrolactonization approach in solution. Both strategies involved Wittig-type reactions as outlined in Schemes 27a and 27c. A solid-phase synthesis of epothilone A (**216-A**) was also carried out in our laboratories as outlined in Scheme 27b. This sequence featured a Wittig reaction on solid phase (**223** + **224** → **225**), demonstrating the value of this kind of operation in solid-phase and combinatorial chemistry. The ring closure was achieved by an olefin metathesis reaction with

Scheme 25. The Wittig and stabilized Wittig reactions in the toal synthesis of zaragozic acid A (**184**) (1994)[4]



RuCl$_2$(C=CHPh)[P(Cy)$_3$]$_2$ (**229**), a process that liberated precursor **230** as a mixture of four isomers. After deprotection, separation of isomers and epoxidation, epothilone A (**216-A**) and analogs thereof were obtained.
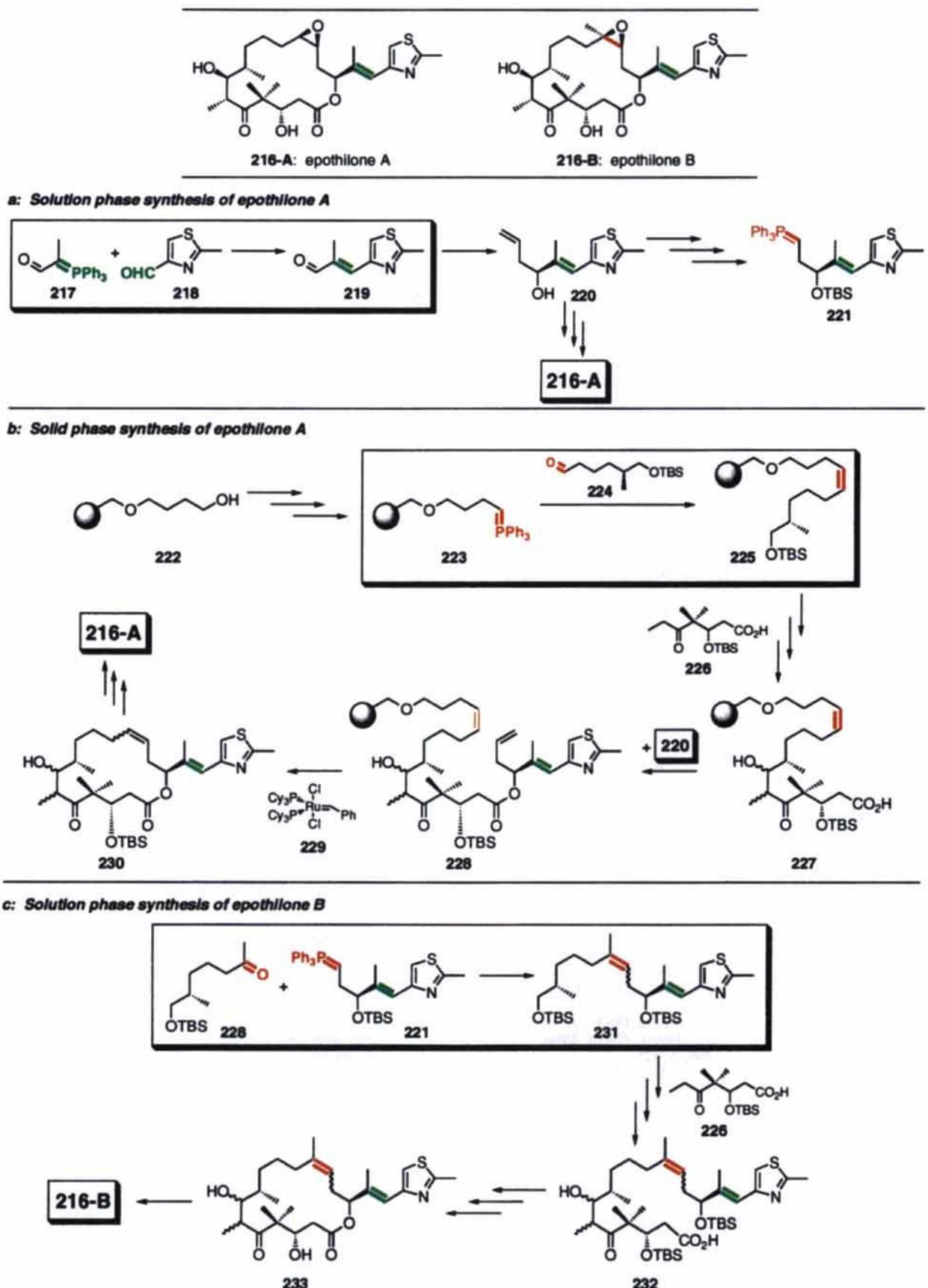
## 4. Conclusion

Having experienced the power of the Wittig and related reactions in total synthesis, one can only attempt to imagine

Scheme 26. The Wittig, stabilized Wittig, and HWE reactions in the total synthesis of brevetoxin B (**204**) (1995)[42]



**204**: brevetoxin B

**a: Construction of the G Ring**



**b: Coupling of the ABCDEFG with the IJK Ring Fragment**



the state of the art without them. Very few reactions can claim similar status to the Wittig reaction in revolutionizing organic synthesis and in enhancing our ability to construct simple or complex carbon frameworks alike. Among them are, perhaps, the Diels−Alder reaction and the numerous reaction involving organometallic coupling reagents (e.g.

magnesium, lithium, copper, zinc, etc.) or coupling reactions mediated by transition metal complexes (e.g. palladium). It is to say that, collectively, these discoveries have changed not only the way we do chemistry today, but, most significantly, the way we live, through developments in chemistry that have found applications in nutrition, cos-

Scheme 27. The Wittig and stabilized Wittig reactions in the total syntheses of epothilones A and B (**216-A**, **216-B**) (1997)[43]



**216-A**: epothilone A     **216-B**: epothilone B

**a: Solution phase synthesis of epothilone A**

**b: Solid phase synthesis of epothilone A**

**c: Solution phase synthesis of epothilone B**

metics, agriculture, clothing, dyestuffs, plastics, high-tech materials, and medicine. For this, we owe much to Wittig, Horner, Wadsworth, Emmons and the many others who contributed so much to our science through their pioneering discoveries.

☆ This article is dedicated to the memory of the late Professor *Georg Wittig* and is based on a lecture given by K. C. Nicolaou at the special symposium "The Research of Georg Wittig – Relevance to Chemistry Today", held in Heidelberg, Germany, July 15–18, 1997, honoring the 100th anniversary of the birth of G. Wittig.

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