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## Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea

Adriana Lorente,<sup>†,‡</sup> Janire Lamariano-Merketegi,<sup>†,‡</sup> Fernando Albericio,<sup>†,‡,§,#</sup> and Mercedes Álvarez\*,<sup>†,‡,§,⊥</sup>

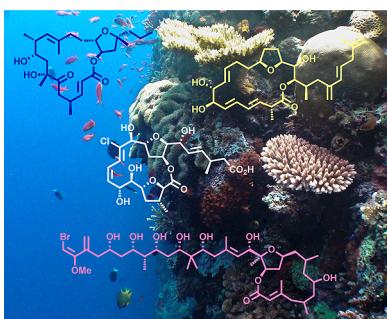
<sup>†</sup>Institute for Research in Biomedicine, Barcelona Science Park, University of Barcelona, Baldí Reixac 10, 08028 Barcelona, Spain

<sup>‡</sup>CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Barcelona Science Park, Baldí Reixac 10, 08028 Barcelona, Spain

<sup>§</sup>Department of Organic Chemistry, University of Barcelona, 08028 Barcelona, Spain

<sup>#</sup>School of Chemistry, University of KwaZulu-Natal, 4001-Durban, South Africa

<sup>⊥</sup>Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain



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### 1. INTRODUCTION

Marine organisms have produced a big number of structurally diverse secondary metabolites with important biological activities as a defense mechanism to the persistent aggression of their environment.<sup>1</sup> This structural diversity makes marine natural products excellent candidates for the investigation of new bioactive molecules with high pharmacological potential.<sup>2</sup>

A significant number of marine polyketide macrolides have been isolated in the last years from sponges, algae, dinoflagellate, and other marine invertebrates, characterized by their structural novelty. From a chemical structure point of view, marine polyketide macrolides are fascinating, many of them being highly oxygenated and stereochemically elaborate, such as, for instance, the oxazole containing polyketides kabiramide C,<sup>3</sup> halichondramide,<sup>4</sup> and ulapualide A<sup>5</sup> or the complex polyketide family of the spongistatins<sup>6</sup> (Figure 1).

The determination of full bioactivity, mechanism of action, and further medical application of marine polyketide macrolides is usually unfeasible because their isolation from natural sources very often furnishes very small sample amounts. Thus, synthesis is necessary for further development of these macrolides as pharmacological leads, not only in terms of their supply, but also for structural and stereochemical assignments. Several reviews focusing on the isolation, structure determination, and synthesis of polyketide macrolides have been published until now.<sup>7</sup>

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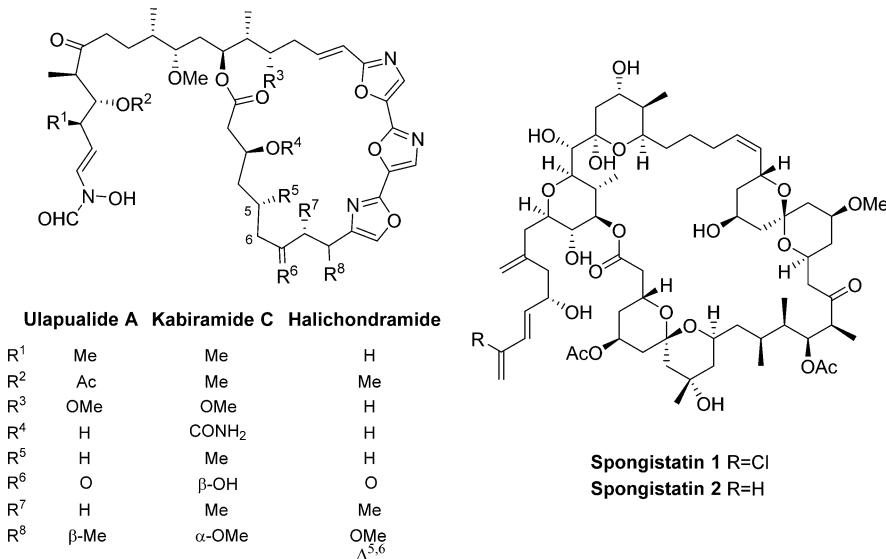


Figure 1. Structures of ulapualide A, kabiramide C, halichondramide, and spongistatin 1 and 2.

Large molecular size tetrahydropyran (THP)-containing polyketide macrolides are a class of marine macrolides with diverse and interesting biological activities. Some of them have reached the clinical trial stage or the market, as is the case of the

atoms with the macrolide. The revision starts with those compounds for which only isolation and structure determination were described and follows with the isolation, structure determination, and synthesis of the rest of the families.

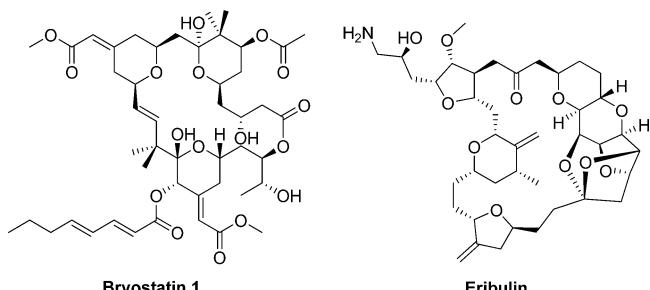


Figure 2. Structures of bryostatin 1 and eribulin.

promising anticancer agents bryostatin 1<sup>8</sup> or eribulin,<sup>9</sup> the analogue of the marine macrolide halichondrin B, respectively (Figure 2). Large molecular size THP-containing macrolides rarely include tetrahydrofuran (THF) rings in their structure. Nevertheless, some natural products are found where both systems are included, such as the above-mentioned eribulin, pectenotoxins,<sup>10</sup> and prorocentrolide<sup>11</sup> toxins, the family of the halistatins,<sup>9a</sup> the family of the antimitotic spirastrellolides,<sup>12</sup> or the actin-targeting marine polyether goniodomin A.<sup>13</sup>

More recently, THF rings instead of THP rings have occurred in structures of new bioactive compounds. Large molecular size polyketide macrolides with THP and THF rings in their structure were the first reported THF-containing macrolides. Over the last 20 years, more THF-containing polyketide macrolides have been described, and their potential as drug candidates has increased exponentially. It is worth mentioning that THF-containing macrolides are often of smaller molecular weight and less complex than their THP congeners.

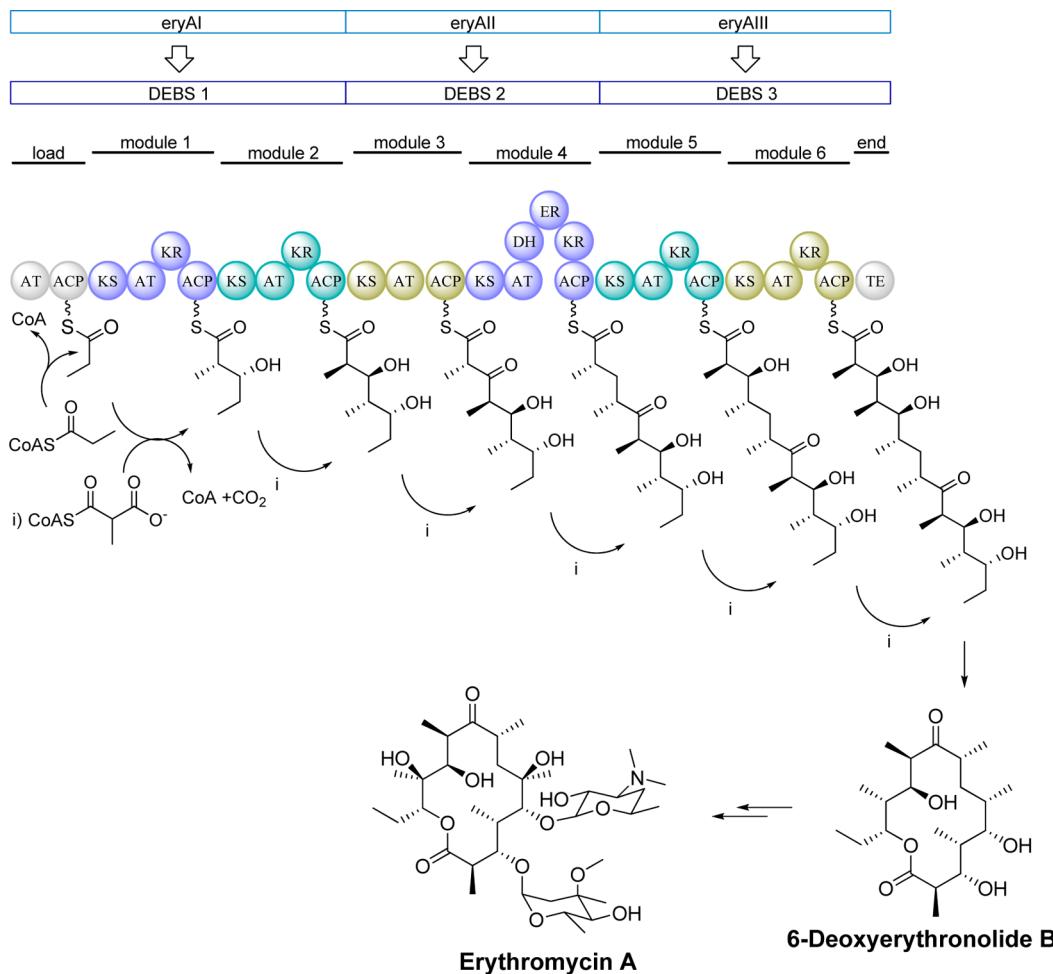
This review focuses on the chemical efforts aimed at achieving the isolation and total synthesis of specific marine macrolides, such as macrolides that contain a fused or bridged THF ring, up to 2012. Macrolides containing a fused THF ring share two common carbons with the macrolide, while macrolides containing a bridged THF ring share three or four common

## 2. BIOSYNTHESIS

On the basis of their biosynthetic origin, metabolites are divided into six classes: ribosomal and nonribosomal peptides, alkaloids, phenylpropanoids, polyketides, terpenoids and steroids, and carbohydrates. Members of each class of metabolites have been shown to exhibit interesting biological activities. Ribosomal peptides and carbohydrates are often referred to as primary metabolites, due to their lack of structural complexity; on the other hand, nonribosomal peptides, alkaloids, phenylpropanoids, polyketides, and terpenoids and steroids are classified as secondary metabolites, because they are formed from a series of enzymatic transformations that employ a much more diverse set of precursors and more sophisticated biosynthetic reactions.<sup>14</sup>

The main push into the investigation of polyketide biosynthesis came from Arthur Birch in the 1950s. His contributions were decisive, recognizing that polyketones could be generated from acetate units by repeated condensation reactions. He tested his theory by feeding an isotopically labeled acetate with <sup>14</sup>C at C-1 to a suitable polyketide-producing organism.<sup>15</sup> Later, with the development of genetic techniques in the 1980s and the discovery of enzymes, a new field based on gene sequencing and manipulation appeared.<sup>16</sup> Nowadays, the predictable relationship between the structure and function of modular-type polyketide synthases (PKSs) has enabled the genetic manipulation of biosynthetic pathways for production of novel variants of naturally occurring compounds, such as macrolide antibiotics and antitumor compounds.<sup>17</sup>

Polyketide natural products are constructed by large multifunctional protein complexes PKSs, which use acetate and propionate as building blocks. Different families of PKSs generate very distinct classes of polyketides, but irrespective of the producing organism, polyketides are always formed by decarboxylative Claisen-type 1,2-head-to-tail condensations of thioesters with malonyl-derived extender units. Type I PKSs, or modular PKSs, construct polyoxygenated aliphatic compounds,



**Figure 3.** Domain arrangement of erythromycin synthase.

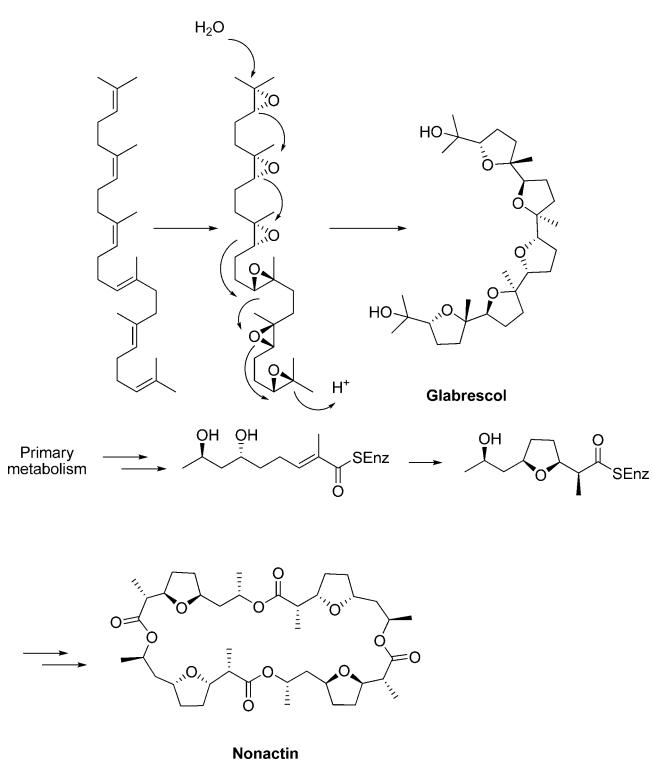
which is the subject of our review. An acyl transferase (AT) domain catalyzes thioester bond formation between an acyl carrier protein (ACP) domain and a coenzyme A (CoA)-bound starter unit. Then, a ketosynthase (KS) domain catalyzes the binding of its cysteine-bound malonyl elongation unit to the growing ACP-bound polyketide. Acetate units are loaded onto cysteine residues of adjacent KS domains, and the chain is elongated via successive Claisen condensations. Complexity and diversity are added to the polyketide chain through ketoreductase (KR), dehydratase (DH), and enoyl reductase (ER) domains. Moreover, PKS and nonribosomal peptide synthase (NRPS) modules can work together to form hybrid PKS–NRPS molecules. The sequence ends in the thioesterase (TE) domain, although the absence of this domain in some PKSs suggests the existence of alternative releasing mechanisms.<sup>18</sup> Figure 3 shows an example of chain elongation; 6-deoxyerythronolide B synthase (DEBS) is the PKS that forms the backbone of erythromycins and is encoded by the three *eryAI-III* genes.<sup>19</sup> Once the resulting linear carbon backbone is released from the PKS, the carbon framework is further processed and modified by various tailoring enzymes, which enhance its functionality to yield biologically active compounds. This post-PKS processing is another source of diversity in polyketide biosynthesis, as there is enormous scope for mixing and matching the tailoring enzymes to produce altered structures. For example, the skeleton can be oxidized or reduced to introduce hydroxy or carbonyl groups (oxygenases [OXs] and ketoreductases [KRs]), methylated at

oxygen, nitrogen or carbon centers (methyl transferases [MTs]), or decorated with deoxysugar molecules (glycosyltransferases [GTs]).<sup>20</sup>

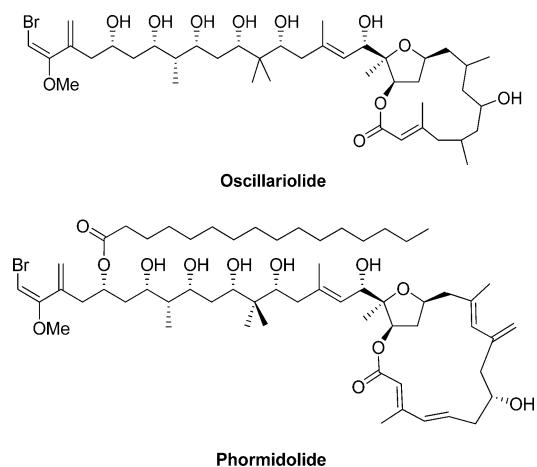
Macrolactones are normally formed upon termination/cyclization, provided that the TE domains attached to the terminal modules of PKSs are tolerant toward polyketide chain length as well as substitutions at the C-2 and C-3 positions of the lactone, although with varying efficiencies.<sup>21</sup> On the other hand, the formation of oxacyclic ethers normally occurs in post-PKS processing; (bio)chemically, ether bond formation is not straightforward, but nature has evolved many ways to furnish these structures with high efficiency, and, when necessary, with high enantio- or regioselectivity.<sup>22</sup> Enzymes, such as peroxidases or alkene mono-oxygenases (AMOs), are able to form epoxides from double bonds. The subsequent opening of these epoxides furnished cyclic ethers. This process sometimes occurs in a cascade fashion forming polycyclic natural products, for instance, in the biosynthesis of glabrescol (Scheme 1).<sup>23</sup> Another approach to the formation of oxaheterocycles is the addition of hydroxyl groups to activated double bonds involving the Michael addition reaction, as in the case of the antitumor agent nonactin (Scheme 1).<sup>24</sup>

Another important subject in polyketide biosynthesis is stereochemistry. The PKS-catalyzed assembly process generates stereochemical diversity, because carbon–carbon double bonds may have either *cis*- or *trans*- geometry, and because of the chirality of centers bearing hydroxyl groups and branching

**Scheme 1. THF Ring Formation in the Biosynthesis of Glabrescol and Nonactin**



methyl groups. More recently, aspects of stereochemistry in polyketide biosynthesis are becoming better understood.<sup>25</sup> Nevertheless, the knowledge around the stereochemical outcome of complex polyketide biosynthesis is still expanding.

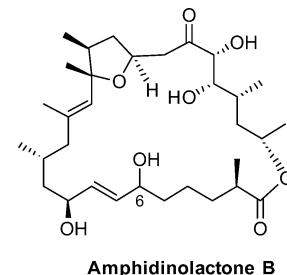


**Figure 4. Structures of oscillariolide and phormidolide.<sup>26,27</sup>**

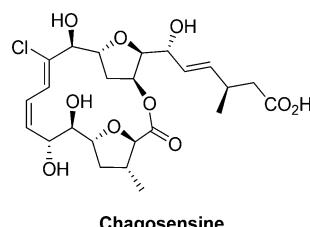
### 3. OVERALL OF THF-CONTAINING MACROLIDES

#### 3.1. Oscillariolide<sup>26</sup> and Phormidolide<sup>27</sup>

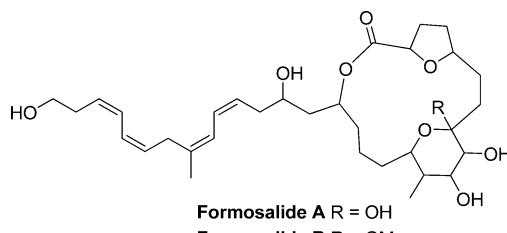
Oscillariolide was isolated from a marine blue-green alga *Oscillatoria* sp. collected from Gokashowan-Bay, Mie Prefecture,



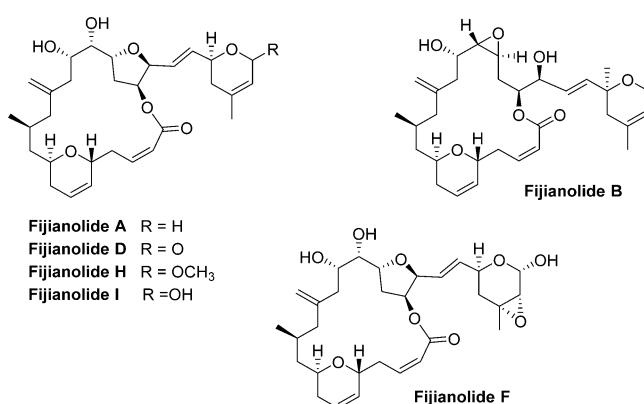
**Figure 5. Structure of amphidinolactone B.<sup>29</sup>**



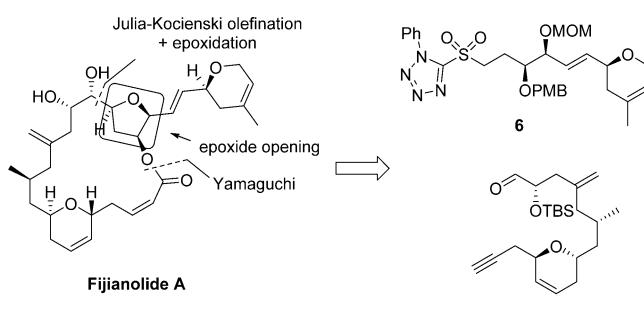
**Figure 6. Structure of chagosensine.<sup>30</sup>**



**Figure 7. Structures of formosalides A and B.<sup>31</sup>**

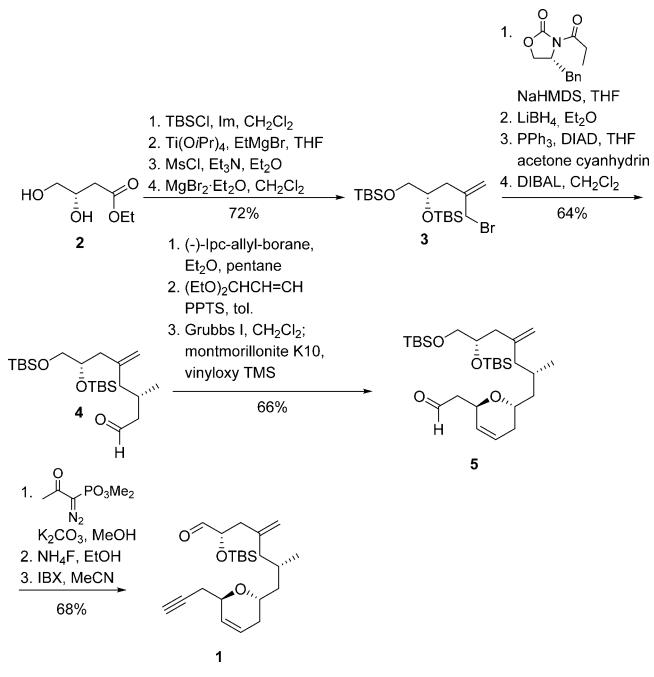


**Figure 8. Structures of fijianolides A, B, D, H, I, and F.<sup>32–34</sup>**

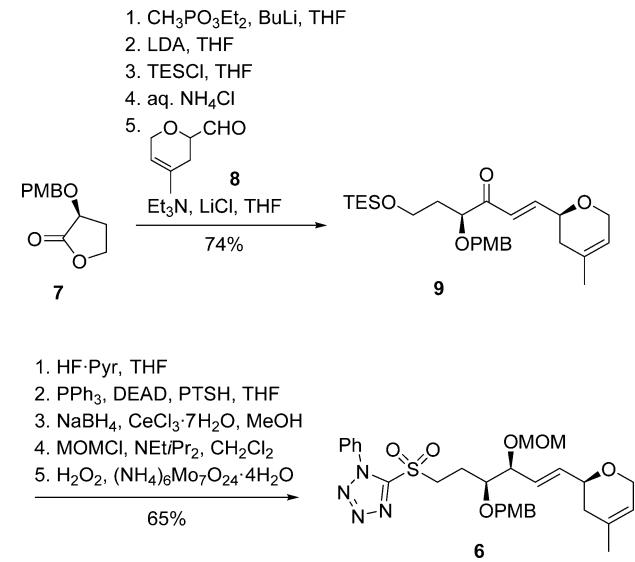


**Figure 9. Fijianolide A retrosynthetic analysis by Mulzer.<sup>35</sup>**

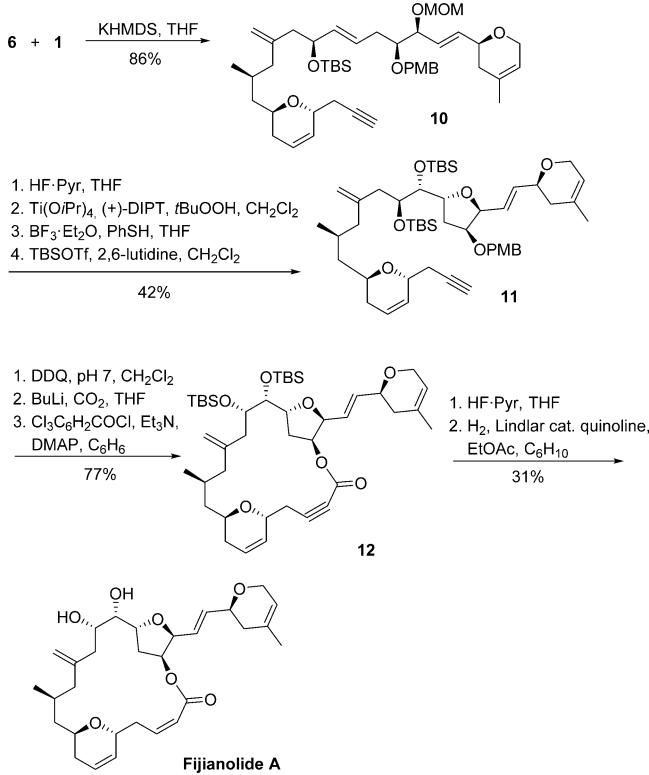
Scheme 2. Synthesis of Aldehyde 1



Scheme 3. Synthesis of Sulfone 6



and was shown to cause inhibition of cell division of fertilized starfish eggs.<sup>26</sup> Its structure was elucidated on the basis of spectral data, but the stereochemistry was not defined. A few years later, phormidolide was isolated from the cyanobacteria *Phormidium* sp. and was shown to be toxic to brine shrimp at micromolar concentration.<sup>27</sup> The structure of phormidolide was elucidated using various spectroscopic methods, mostly advanced nuclear magnetic resonance (NMR) techniques. Comparison of spectroscopic data of both compounds demonstrated the same stereochemistry for the polyhydroxy chain and the THF ring (Figure 4). Both compounds share the characteristic structure of a trisubstituted bridged THF macrolactone with a long polyhydroxy chain containing a unique terminal bromo diene. It is worth mentioning that halogenated natural products are compounds typically isolated from cyanobacteria.<sup>28</sup>

Scheme 4. Total Synthesis of Fijianolide A<sup>35</sup>

### 3.2. Amphidinolactone B<sup>29</sup>

Amphidinolactone B was isolated from a marine dinoflagellate *Amphidinium* sp., and was shown to have modest cytotoxicity. The structure and relative stereochemistry of amphidinolactone B was elucidated on the basis of spectroscopic data. It is constituted by a 26-membered macrocycle containing a 2,5-bridged-tetrasubstituted THF with a quaternary center, a keto carbonyl, four hydroxyl groups and six branched methyls. It affords complex stereochemistry because it has eleven stereocenters and two double bonds (Figure 5). The C-6 stereocenter was not defined due to the limited amount of the sample.

### 3.3. Chagosensine<sup>30</sup>

Chagosensine was isolated from the Red Sea calcareous sponge *Leucetta chagosensis*, and was described as a chlorinated 16-membered macrolactone containing two 2,3,5-trisubstituted THF rings (Figure 6). The structure and absolute configuration of chagosensine were elucidated by chemical derivatization and spectroscopic techniques.

### 3.4. Formosalides<sup>31</sup>

Formosalides A and B were isolated from a dinoflagellate, *Procentrum* sp., strain PL040104002. They exhibited cytotoxicity against acute lymphoblastic leukemia cells and human colon adenocarcinoma cells. Detailed analysis of NMR spectra was the basis for the structure determination as 17-membered ring macrolides (Figure 7). The compounds have an all-*cis* tetraene system, a tetrahydropyran ring and a tetrahydrofuran ring. Formosalide A has five hydroxyl groups, and formosalide B has four hydroxyl groups and one methoxy group. Both compounds have two branched methyls and a C14 linear side-chain. The stereochemistry of the nine stereocenters was not determined, only the relative stereochemistry of five- and six-bridged rings was established. The substitution of THF and THP rings was elucidated to be a 2,5-*anti*- and 8,12-*syn*-bridged system.

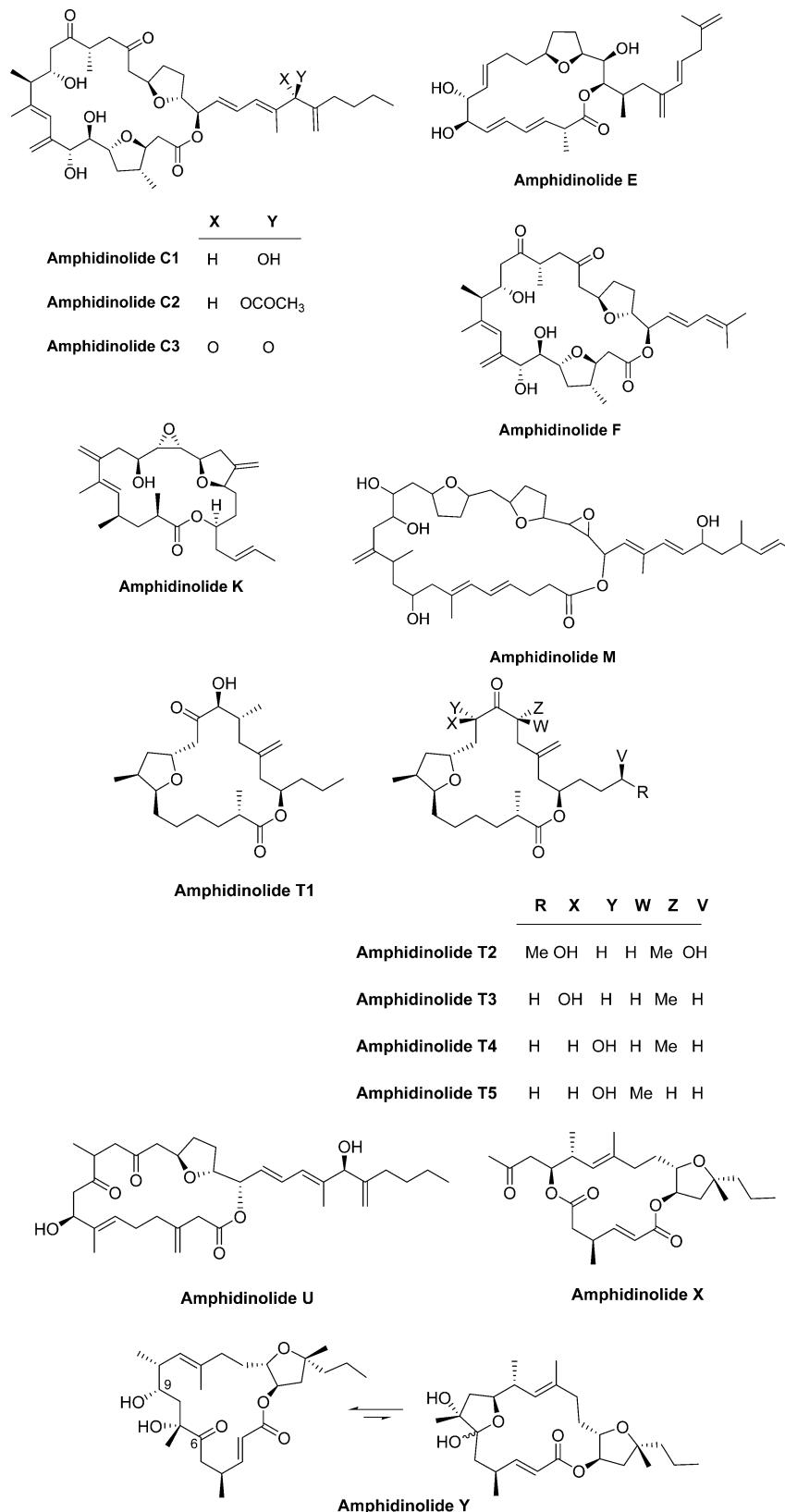
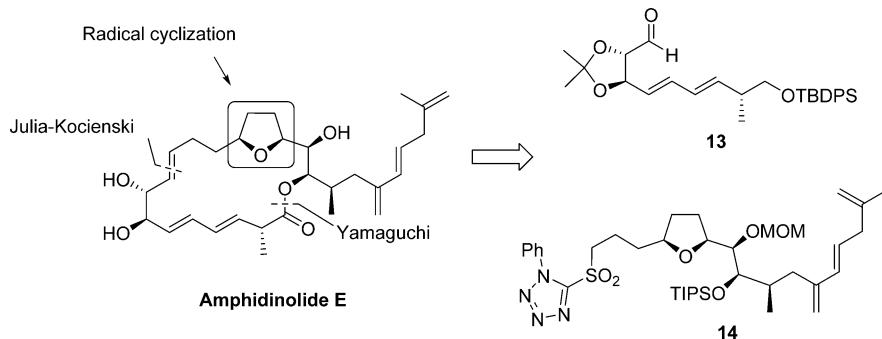


Figure 10. Structure of THF-containing amphidinolides.<sup>39g–u</sup>

### 3.5. Fijianolides<sup>32–34</sup>

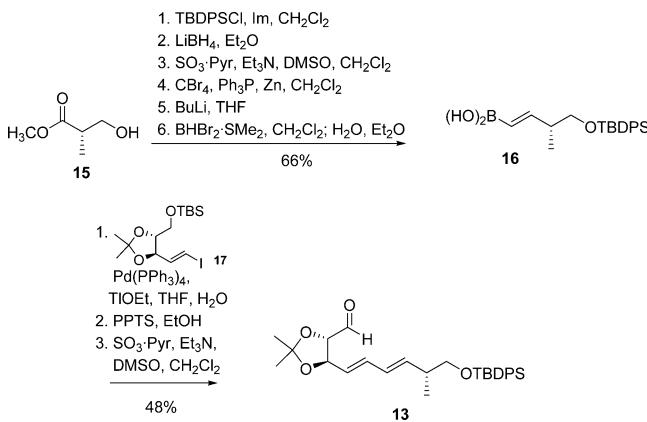
These 20-membered ring macrolides were characterized simultaneously in 1988 as fijianolides A and B from the marine sponge *Cacospongia mycofijiensis*<sup>32</sup> and as isolaulimalide and

laulimalide from a *Hyatella* sponge.<sup>33</sup> Several years later new minor components of *C. mycofijiensis* collected from Vanuatu and Indonesia were identified as fijianolides D–I.<sup>34</sup> Fijianolides A and B showed cytotoxicity against two human cancer cell lines, MDA MB 435 and HCT 116, at micromolar concentration.



**Figure 11.** Amphidinolide E retrosynthetic analysis by Lee.<sup>46</sup>

### Scheme 5. Synthesis of Aldehyde 13



Fijianolide B was active in the same cancer cell lines at nanomolar concentration. This increase of activity was attributed to the epoxide ring. The structure of these compounds was established by one- and two-dimensional NMR studies. From a structural point of view, these fijianolides were divided into two groups: fijianolides A, D, F, H, and I containing one THF in addition to one dihydropyran (DHP) in the macrolactone ring, whereas the remaining fijianolides were related to fijianolide B containing only one DHP ring in the macrocycle. Fijianolides A, D, H, F, and I have identical macrocycle constitution and configuration and only differ in the functionalization of the pyran lateral chain (Figure 8).

Synthetic efforts toward this family of compounds have focused on the synthesis of fijianolide B (laulimalide), and, to a lesser extent, on the synthesis of the THF-containing macrocycle fijianolide A (isolaulimalide) and related fijianolides D–I. Nevertheless, Mulzer and co-workers have described the synthesis of fijianolide A.<sup>35</sup>

**3.5.1. Mulzer's Synthesis of Fijianolide A.**<sup>35</sup> Their strategy was developed envisioning a final macrolactonization and the formation of an epoxide precursor of the THF ring from a double bond formed by a Julia–Kocienski olefination (Figure 9).

Aldehyde C2–C16 fragment **1** was synthesized by diprotection of commercially available diol **2** and Kulinkovich reaction,<sup>36</sup> followed by mesylation and MgBr<sub>2</sub>·Et<sub>2</sub>O mediated cyclopropylallyl rearrangement to obtain allyl bromide **3** (Scheme 2). Transformation of compound **3** into aldehyde **4** was obtained by Evans alkylation, reduction to remove the chiral oxazolidinone, Mitsunobu conversion into the nitrile, and final reduction. Transformation of **4** into dihydropyran **5** was afforded by allylation of **4** with (−)-isopinocampheyl-allyl-borane, followed

by one-pot ring closing metathesis (RCM) and addition of vinyloxytrimethylsilane and montmorillonite K10 for side chain introduction. Conversion of aldehyde **5** into the terminal alkyne was achieved using the Bestmann–Ohira reagent.<sup>37</sup> Further selective removal of the *tert*-butyldimethylsilyl (TBS) protecting group and oxidation furnished aldehyde **1**.

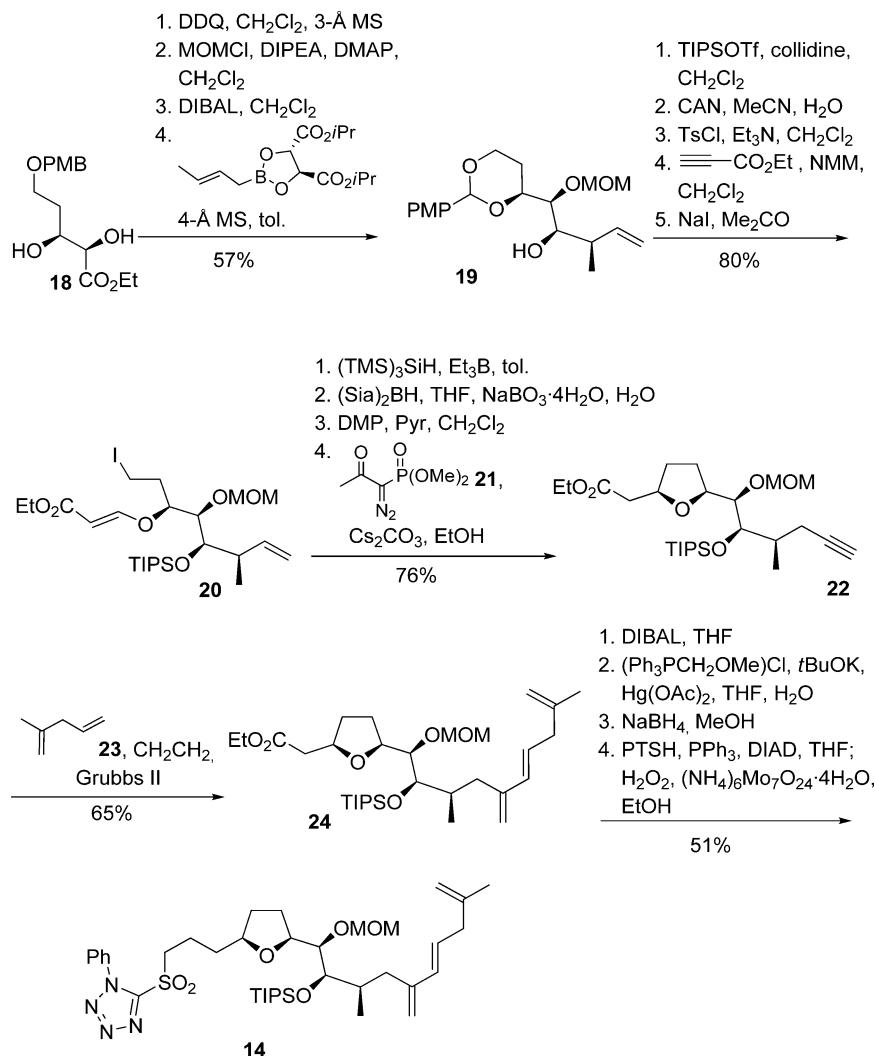
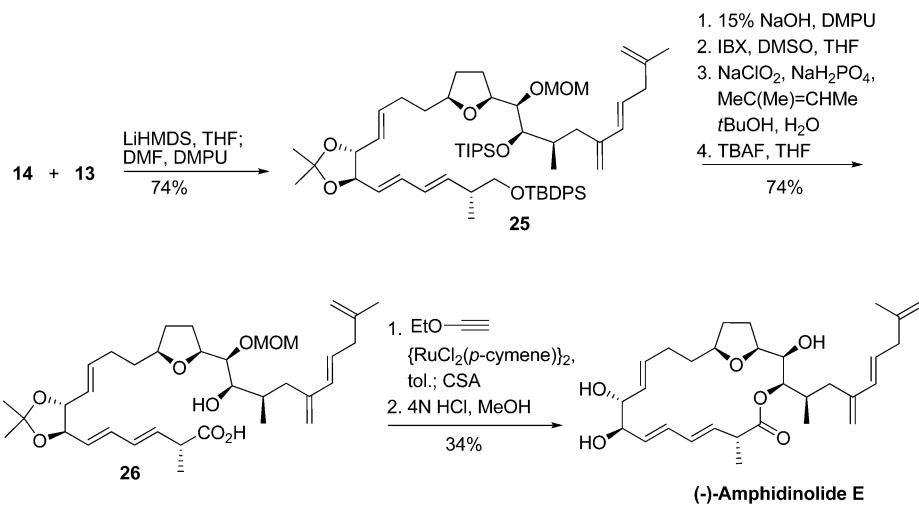
Sulfone **6** was obtained from protected  $\alpha$ -hydroxy butyrolactone **7**, which was treated with an equimolar amount of the lithium salt of diethyl methanephosphonate. Further deprotection led to the dianion that was then silylated with triethylsilyl (TES) chloride. Hydrolysis of the silyl enol ether and Horner–Wadsworth–Emmons (HWE) reaction with aldehyde **8**,<sup>38</sup> under Masamune–Roush conditions, led to enone **9** (*E/Z* > 40:1). Selective deprotection of primary alcohol and conversion to the sulfide, followed by Luche reduction, yielded *syn*-alcohol with a good diastereomeric ratio (*dr* > 17:1). MOM protection and oxidation to the sulfone furnished **6** (Scheme 3).

Condensation of sulfone **6** and aldehyde **1** afforded coupled compound **10**. TBS deprotection and epoxidation, followed by removal of the methoxymethyl (MOM) protecting group, intramolecular epoxide opening, and TBS protection, afforded THF derivative **11**. *p*-Methoxybenzyl (PMB) removal and C1 elongation led to a seco acid that was then cyclized under Yamaguchi conditions to obtain **12**. Further deprotection of the TBS ethers and reduction of the triple bond to obtain (*Z*)-enoate furnished fijianolide A (Scheme 4).

### 3.6. Amphidinolides

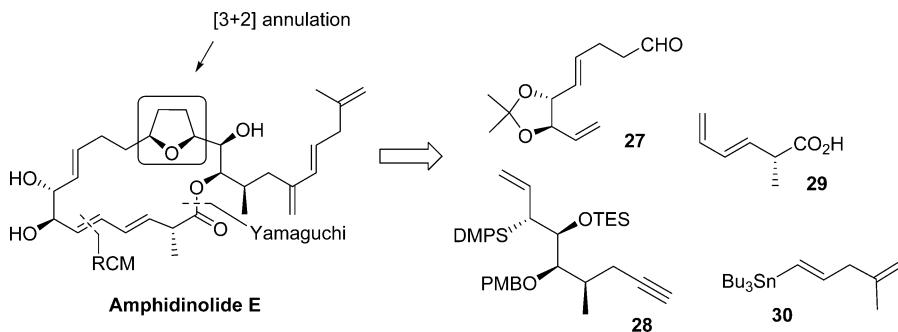
Amphidinolides are metabolites isolated from *Amphidinium* sp., of a genus of symbiotic marine dinoflagellates of Okinawan marine flatworms *Amphiscolops* sp. Forty members of this big macrolide family have been isolated up to 2010, but only 15 of them have an additional fused or bridged THF in their macrolactone ring (Figure 10). An interesting member of the family is amphidinolide C, which shows potent cytotoxicity in the nanomolar range against murine lymphoma L1210 and human epidermoid carcinoma KB cells ( $IC_{50}$  = 5.8 and 4.6 ng/mL, respectively) in vitro. Unique structural features are the presence of exomethylidene units and polyene side chains, as well as the presence of fused or bridged THF systems. Their structural and stereochemical complexity, combined with their important bioactivity, all exhibiting potent cytotoxic activity, make them attractive targets to apply new synthetic methods, thereby encouraging the work of different groups. The isolation, structure elucidation, and activity of this family of macrolides, as well as its biosynthesis, have been extensively reviewed since the discovery of the series was first reported. The last reported macrolide, named amphidinolide C3, was isolated in 2010.<sup>39</sup>

Scheme 6. Synthesis of Sulfone 14

Scheme 7. Total Synthesis of (-)-Amphidinolide E<sup>46</sup>

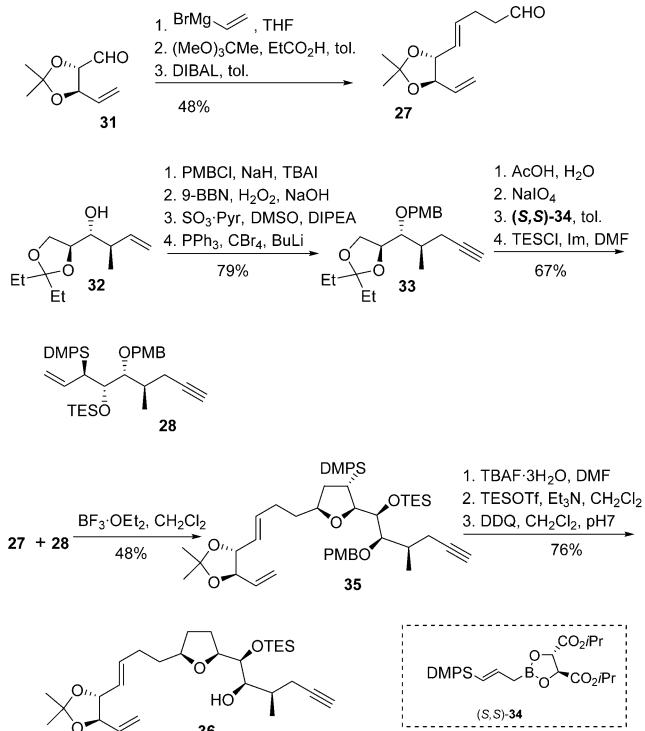
Synthetic work on amphidinolides up to 2000 has been reviewed.<sup>41</sup> Nevertheless, during the past decade, a major effort has been made on the synthesis of this family of compounds, and several total syntheses have been compiled.<sup>42</sup>

**3.6.1. Amphidinolide E.** Amphidinolide E is a 19-membered macrolide isolated from the Y-5' strain of the dinoflagellate *Amphidinium* sp.<sup>39g,h</sup> Several studies aimed at the synthesis of amphidinolide E have been described: Gurjar published the synthesis of the C12–C19 fragment in 2004,<sup>43</sup>

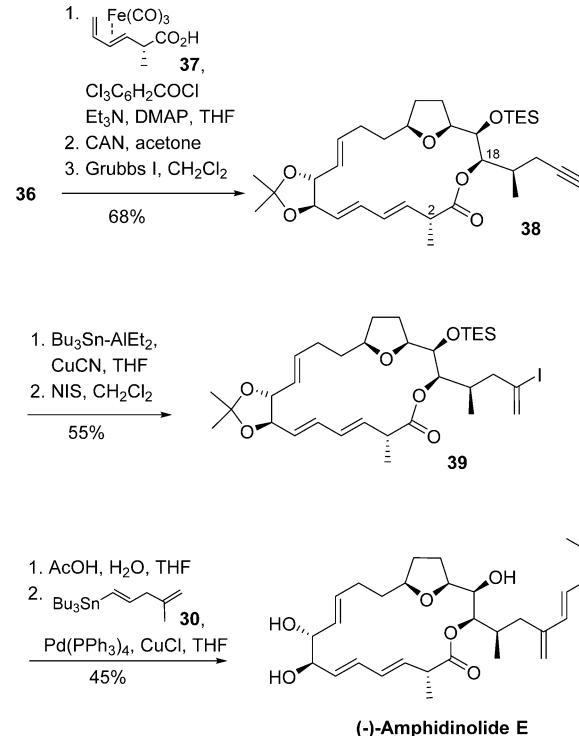


**Figure 12.** Amphidinolide E retrosynthetic analysis by Roush.<sup>47</sup>

**Scheme 8. Synthesis of THF Derivative 36**



**Scheme 9. Synthesis of (−)-Amphidinolide E<sup>47</sup>**



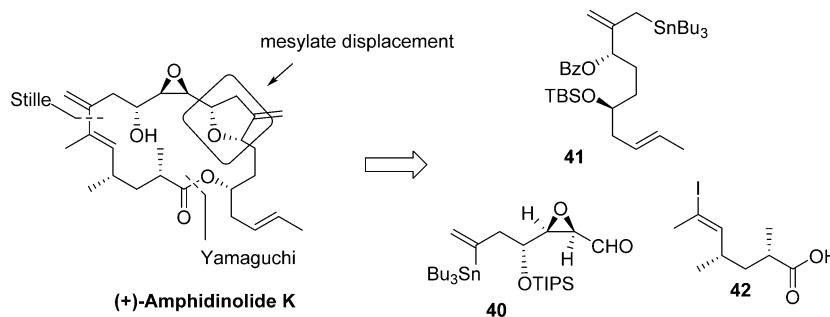
Marshal published the synthesis of the C6–C21 fragment in 2005,<sup>44</sup> and Vilarrasa and co-workers published the synthesis of fragments C1–C7 and C10–C26 in 2008.<sup>45</sup> Total syntheses of amphidinolide E to date are those reported by Lee<sup>46</sup> and Roush.<sup>47</sup>

**3.6.1.1. Lee's Synthesis of Amphidinolide E.**<sup>46</sup> In 2006, Lee and co-workers described the total synthesis of amphidinolide E; later, they published a detailed account of their attempts toward the synthesis, including pathways that led to a dead end but which were also synthetically interesting.<sup>48</sup> The successful strategy to amphidinolide E focused on lactonization at a late stage, to avoid lability problems at C2. The key intermediates were C1–C9 and C10–C26 fragments 13 and 14 (Figure 11).

Aldehyde 13 was prepared starting from methyl (S)-3-hydroxy-2-methylpropanoate 15 and was then converted into vinyl boronic acid 16 by protection as a *tert*-butyldiphenylsilyl (TBDPS) ether, reduction, oxidation, Corey-Fuchs homologation, and hydroboration-hydrolysis. Suzuki cross-coupling of 16 with vinyl iodide 17,<sup>49</sup> removal of the TBS group, and oxidation afforded aldehyde 13 (Scheme 5).

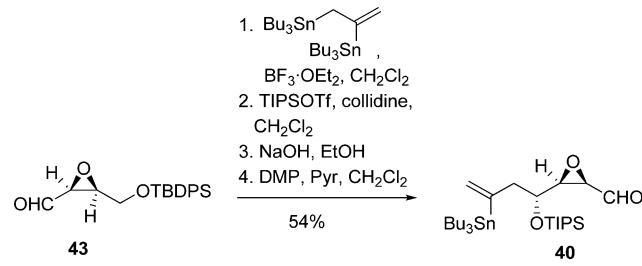
Fragment C10–C26, sulfone 14, was prepared from diol 18<sup>50</sup> by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation to furnish the *p*-methoxyphenyl (PMP) acetal. Protection of the remaining hydroxyl group and reduction, followed by Roush crotylation, led to homoallylic alcohol 19 with good dr (16:1). Triisopropylsilyl (TIPS) protection and removal of the cyclic PMP acetal led to a diol, which was then tosylated at the primary hydroxyl and treated with ethyl propiolate at the secondary hydroxyl. Subsequent substitution of the tosylate with iodide provided 20. Radical cyclization of iodide 20 permitted the formation of the THF ring. Hydroboration–oxidation and further oxidation led to an aldehyde that treated with diazophosphonate 21 provided alkyne 22. Cross metathesis with diene 23 led to triene 24. Reduction of ester 24, followed by homologation of the resulting aldehyde by Wittig methoxymethylidenation and hydrolysis, reduction with NaBH4, Mitsunobu type introduction of thiol, and oxidation, provided sulfone 14 (Scheme 6).

Julia–Kocienski olefination between sulfone 14 and aldehyde 13 furnished the desired *E*-alkene 25 in good yield (*E/Z* 10:1). After removal of the TBDPS group and oxidation to acid, the



**Figure 13.** (+)-Amphidinolide K retrosynthetic analysis by Williams.<sup>55</sup>

**Scheme 10. Synthesis of Aldehyde 40**



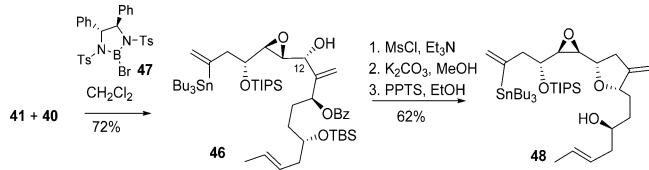
TIPS protecting group was also removed and seco acid **26** was obtained. Macrolactonization was possible using the Kita protocol,<sup>51</sup> and removal of the remaining protecting groups led to (−)-amphidinolide E (Scheme 7).

**3.6.1.2. Roush's Synthesis of Amphidinolide E.**<sup>47</sup> Roush and co-workers described the synthesis of amphidinolide E, and three of its diastereomers. An unexpected and highly selective C2 inversion observed during an esterification reaction over the course of the natural product synthesis gave to the process an important advantage, enabling a straightforward synthesis of some of its diastereomers.<sup>52</sup> Roush and co-workers envisaged that amphidinolide E could be accessed by elaboration of the THF via a [3 + 2] annulation reaction of aldehyde **27** and allylsilane **28** (Figure 12). The remaining building blocks were dienacid **29** for the lactone construction and tin derivative **30** for the side chain introduction.

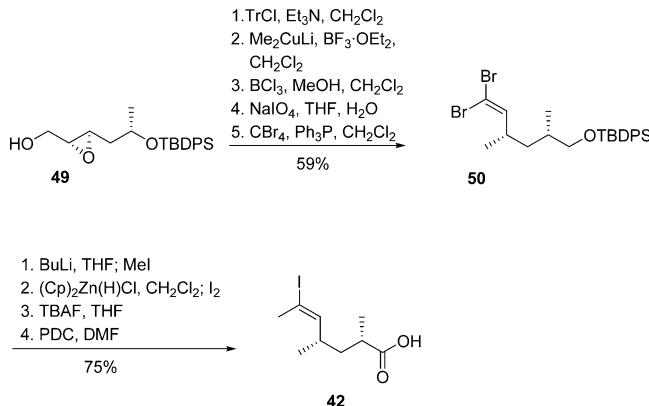
Aldehyde **27** was synthesized starting from aldehyde **31**,<sup>53</sup> which was treated with vinyl magnesium bromide, followed by a Johnson orthoester Claisen rearrangement of the mixture of diastereomeric allylic alcohols. Reduction of the resulting methyl ester afforded aldehyde **27**.

Allylsilane **28** was prepared from homoallylic alcohol **32**.<sup>54</sup> Protection of the hydroxyl of **32** as a PMB ether and hydroboration–oxidation furnished an alcohol that was oxidized

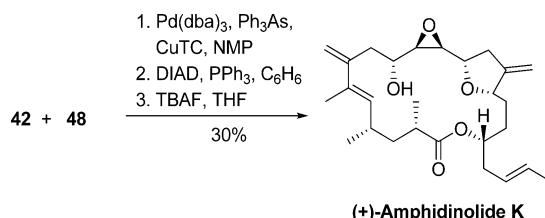
**Scheme 12. Synthesis of THF Building Block 48**



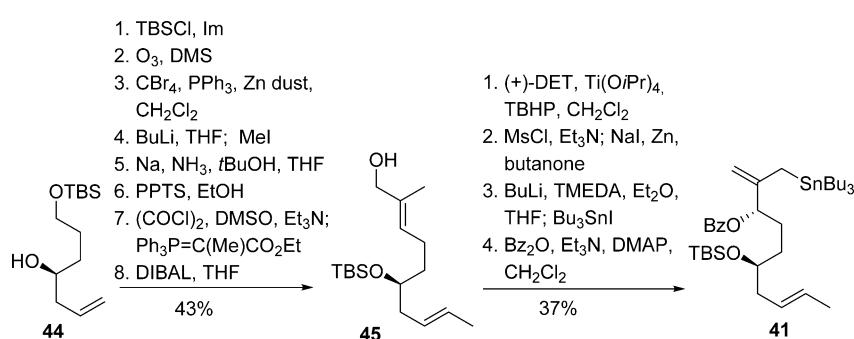
**Scheme 13. Synthesis of Vinyl Iodide 42**

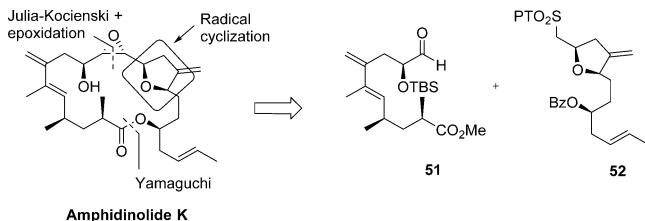


**Scheme 14. Total Synthesis of (+)-Amphidinolide K<sup>55</sup>**



**Scheme 11. Synthesis of Stannane 41**



Figure 14. Amphidinolide K retrosynthetic analysis by Lee.<sup>57</sup>

and Corey–Fuchs homologation led to alkyne 33. Acid hydrolysis of the ketal protecting group and oxidative cleavage of the resulting diol provided an aldehyde. Subsequent treatment with (*S,S*)-34 afforded silylallylboration with 9:1 selectivity. The protection of the resulting alcohol as a TES ether furnished allylsilane 28.

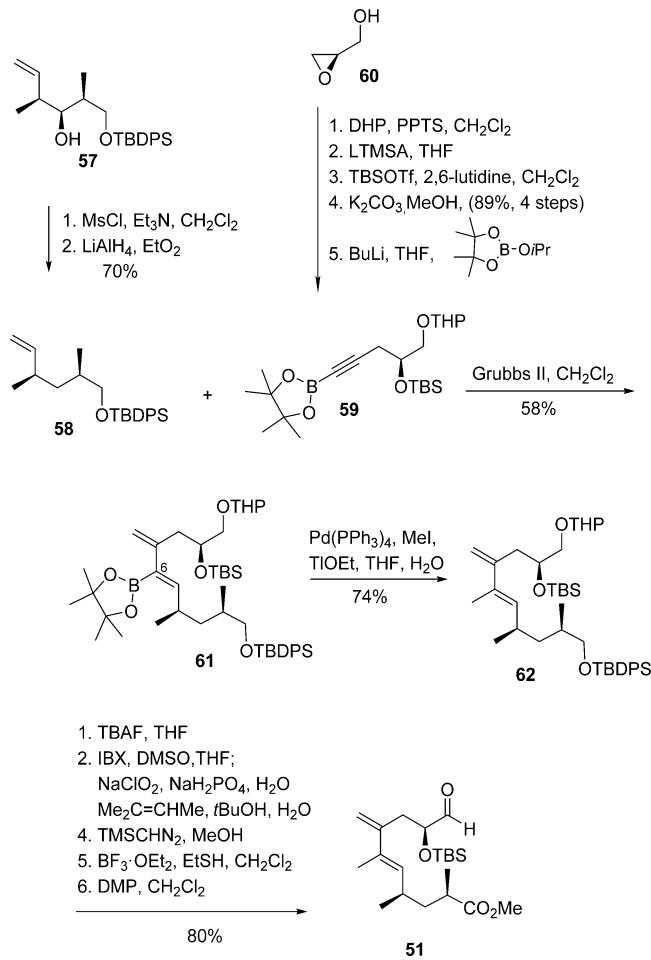
With both fragments in hand, [3 + 2] annulation catalyzed with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  afforded 35 with  $\text{dr} > 20:1$ . Cleavage of C–Si bond by treatment with tetrabutylammonium fluoride (TBAF) was not selective and also produced removal of the TES protecting group, which was reintroduced; further removal of the PMB protecting group afforded alcohol 36 for esterification (Scheme 8).

Esterification of the C18 hydroxy group was achieved using “diene protected” acid 37 only to avoid lability problems at C2. Oxidative removal of the  $\text{Fe}(\text{CO})_3$ -unit provided the free diene ready for the Grubbs’ first generation catalyzed RCM to obtain macrolactone 38. Vinyl iodide 39 was obtained after stannylation–protonolysis and treatment with NIS. After acidic removal of the acetonide and TES protecting groups, Stille cross-coupling with vinyl stannane 30 afforded (−)-amphidinolide E (Scheme 9).

Several diastereomeric amphidinolide E analogues were prepared with the same strategy changing the acid 37 and allylsilane 28 stereochemistry.<sup>52</sup>

**3.6.2. Amphidinolide K.** Amphidinolide K is a 19-membered macrolide, the structure of which was described with undetermined stereochemistry at C2, C4, and C18.<sup>39i</sup> Synthetic efforts toward this natural product carried out by Williams and co-workers led to the elucidation of relative and absolute configuration by the synthesis of up to 25 distinct diastereomers.<sup>55</sup> Further work on amphidinolide K consisted of

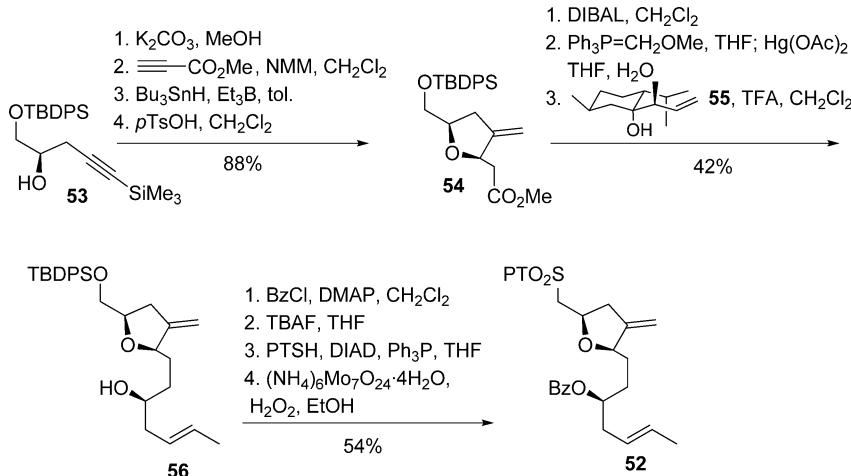
Scheme 16. Synthesis of Fragment 51

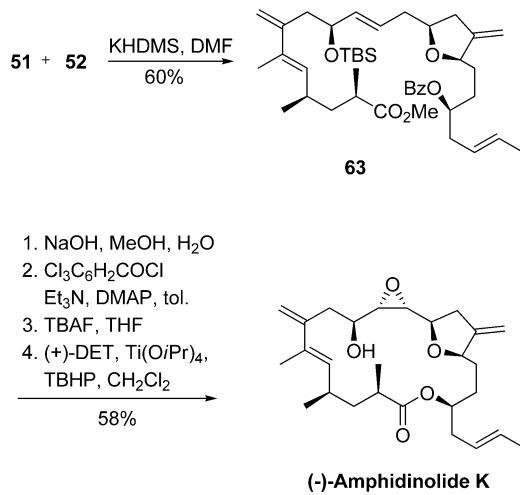


the synthesis of the C9–C22 fragment by Vilarrasa,<sup>56</sup> and the total synthesis of the natural product achieved by Lee.<sup>57</sup>

**3.6.2.1. Williams’s Synthesis of (+)-Amphidinolide K.**<sup>55</sup> This work permitted the assignment of the relative and absolute configuration of the isolated natural product. Williams’s strategy relied on the synthesis of three building blocks, compounds 40, 41, and 42, which allowed flexibility for the intricate stereochemical issues (Figure 13).

Scheme 15. Synthesis of THF Derivative 52

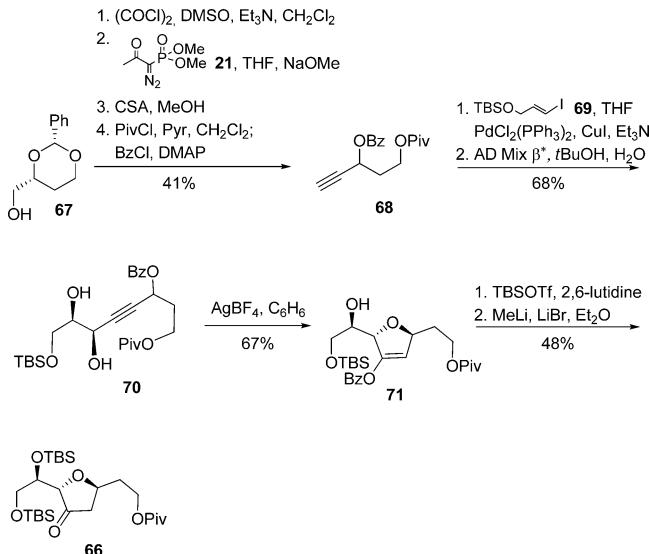


Scheme 17. Synthesis of (−)-Amphidinolide K<sup>57</sup>

Aldehyde **40** was prepared by allylation of epoxy aldehyde **43** under Felkin-Ahn control (6.9:1 *anti:syn*). The resulting alcohol was protected as a TIPS ether followed by removal of the TBDPS protecting group and oxidation to provide aldehyde **40** (Scheme 10).

Known alcohol **44**,<sup>58</sup> containing the proper configuration, was the starting material for the synthesis of C13–C22 fragment. The eight-step transformation of **44** into allylic alcohol **45** included protection of the free hydroxy group, ozonolysis and homologation to the triple bond, methylation of the terminal triple bond, stereoselective reduction of the triple bond, selective deprotection of the primary alcohol, oxidation, Wittig reaction, and ester reduction. Asymmetric Sharpless epoxidation of **45** and reductive transposition, followed by an alkoxide-assisted allylic deprotonation, furnished stannane **41** (Scheme 11).

Coupling of fragments **41** and **40** to give alcohol **46** was achieved in high diastereomeric control (dr 17:1) by transmetalation of the stannane with borane **47** and subsequent addition of the aldehyde. The desired 2,5-*cis*-tetrahydrofuran was obtained by mesylation of **46** and nucleophilic displacement at

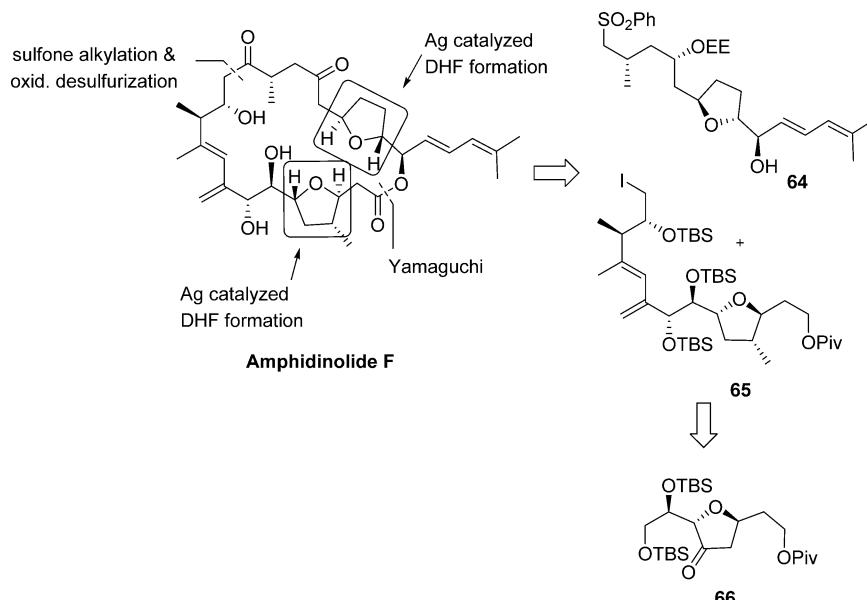
Scheme 18. Synthesis of THF Derivative **66**

C12 on methanolysis of the benzoate. Mild TBS hydrolysis furnished alcohol **48** (Scheme 12).

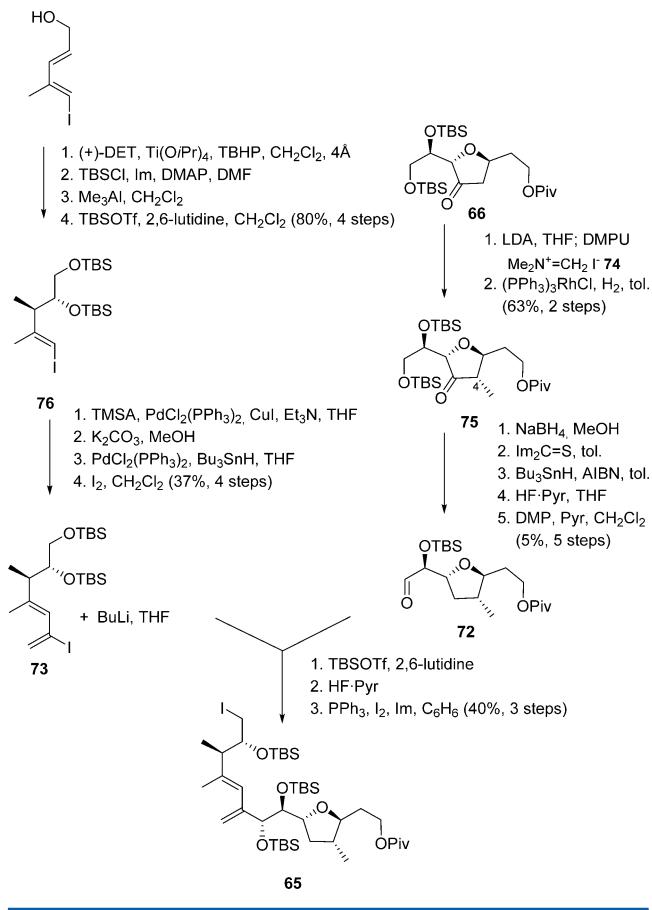
Acid **42** was prepared from known epoxide **49**<sup>59</sup> by protection as a trityl (Tr) ether, Me<sub>2</sub>CuLi addition, and removal of the triphenylmethyl (Tr) protecting group to provide a diol that was subjected to oxidative cleavage and converted to dibromoolefin **50**. Transformation of dibromo compound **50** into the iodo acid **42** was afforded by elimination, methylation, *syn* hydrozirconation–iodination (9:1), removal of the TBDPS group, and oxidation (Scheme 13).

Stille coupling between tin derivative **48** and iodide **42** afforded a seco acid that was subjected to Mitsunobu conditions for macrolactonization, followed by elimination of the TIPS protecting group to afford (−)-amphidinolide K (Scheme 14).

**3.6.2.2. Lee's Synthesis of (−)-Amphidinolide K.**<sup>57</sup> Lee and co-workers' total synthesis of (−)-amphidinolide K followed a convergent strategy, which divided the molecule into two main fragments C1–C10 and C11–C22, **51** and **52**, as precursors of

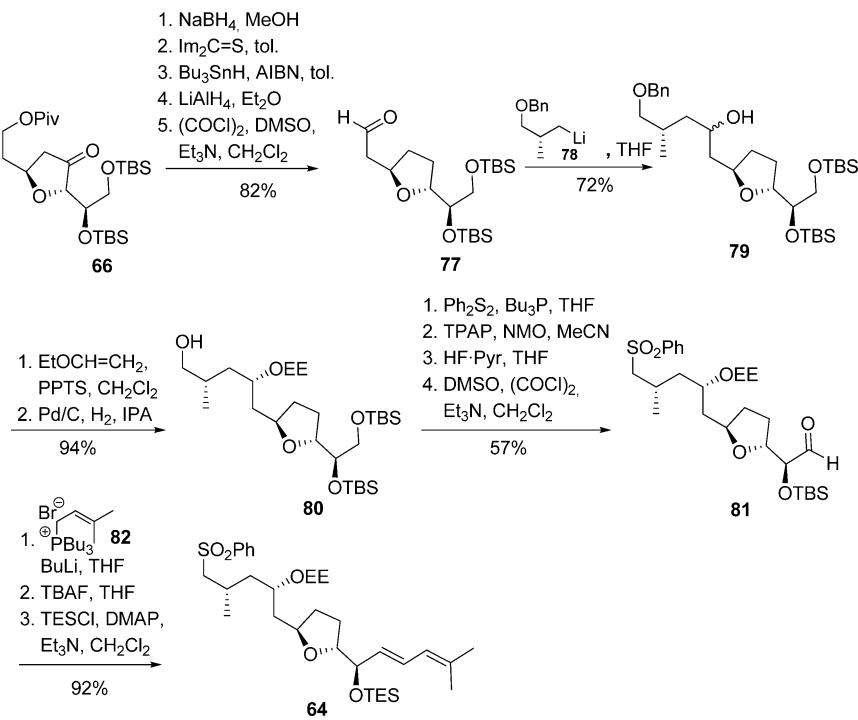
Figure 15. Amphidinolide F retrosynthetic analysis by Carter.<sup>70</sup>

Scheme 19. Synthesis of Building Block 65



olefin bond formation by Julia–Kocienski reaction and final macrolactonization (Figure 14).

Scheme 20. Synthesis of Building Block 64



The THF ring of fragment **52** was formed by a stereoselective radical cyclization of a  $\beta$ -alkoxyacrylate with tributylstannane. The known homopropargylic alcohol **53**<sup>60</sup> was the starting material to obtain a  $\beta$ -alkoxyacrylate, which by reaction with tributylstannane and triethylborane, followed by acidic destannylation, gave the *cis*-2,5-disubstituted oxolane **54** (16:1). Reduction of **54** to the aldehyde and Wittig reaction to obtain the homologous aldehyde, followed by reaction with alcohol **55**,<sup>61</sup> furnished the homoallylic alcohol **56**. Protection of the alcohol as a benzoate derivative and functionalization of the deprotected primary alcohol to the sulfone by Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by oxidation, afforded compound **52** (Scheme 15).

Fragment C1–C10, **51**, was synthesized as shown in Scheme 16 by a reaction sequence in which the key step was the enyne cross-metathesis between olefin **58** and alkynyl boronate **59** to give an enriched mixture of the desired *E*-isomer **61** (7.5:1). Olefin **58** was obtained from known alcohol **57**<sup>62</sup> by reduction of the mesyl (Ms) derivative. Alkynyl boronate **59** was prepared from (*R*)-glycidol **60**, via protection of the hydroxyl as a THP acetal, treatment with lithium trimethylsilylacetyleide (LTMSA), TBS protection, removal of the trimethylsilyl (TMS) protecting group, and formation of the boronate. Introduction of the methyl group at C6 of *E*-**61** was achieved by Suzuki–Miyaura reaction in the presence of thallium ethoxide to give diene **62**. This reaction was not possible using alternative strategies. Transformation of **62** into **51** was performed by successive selective deprotection of the TBDPS alcohol, oxidation, methyl esterification, removal of the THP protecting group, and oxidation.

*E* olefin **63** was obtained by Julia–Kocienski reaction of aldehyde **51** and sulfone **52** (Scheme 17). Further transformation into the 19-membered macrocycle was performed by hydrolysis of the ester and Yamaguchi lactonization. After removal of the TBS protecting group and asymmetric

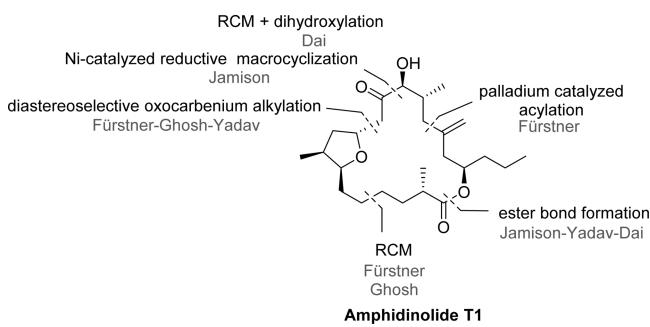
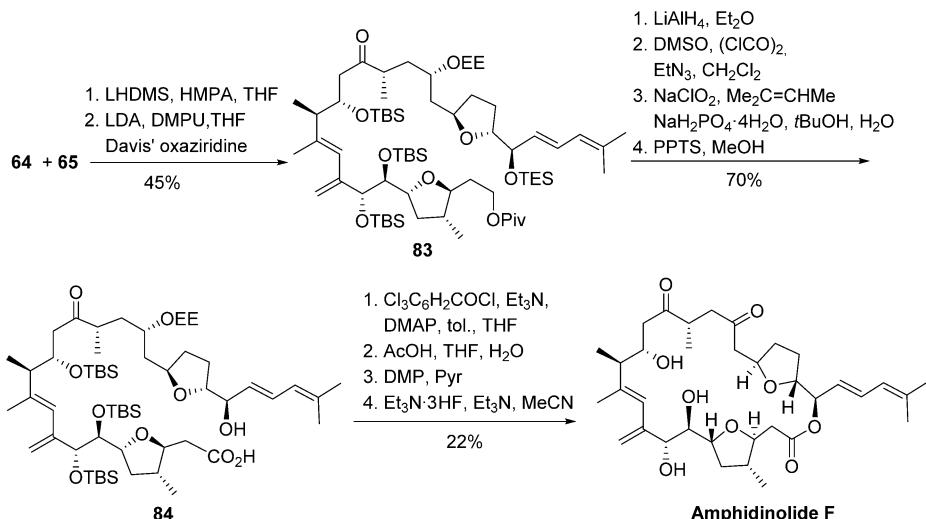
Scheme 21. Total Synthesis of Amphidinolide F<sup>70</sup>

Figure 16. Main bond disconnections for the synthesis of amphidinolide T1.

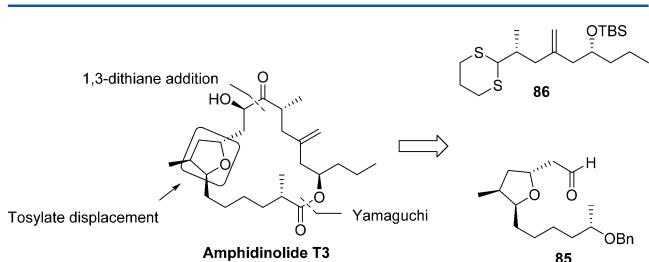


Figure 17. Amphidinolide T3 retrosynthetic analysis by Zhao.

epoxidation of the disubstituted endocyclic double bond, (-)-amphidinolide K was obtained.

**3.6.3. Amphidinolides C1, C2, C3, F, and U.** Amphidinolides C1, C2, C3 and F are 25-membered macrolactones containing two *trans*-2,5-disubstituted THF rings.<sup>39j–n</sup> Amphidinolide U is a 20-membered macrolactone containing one *trans*-2,5-disubstituted THF ring (Figure 10).<sup>39p</sup> The similarity in their structure and stereochemistry leads to the conclusion that they are biogenetically closely related and the strategies for their synthesis may proceed by similar pathways.

Synthetic work on these amphidinolides compiles several publications where the syntheses of fragments were achieved. Of interest are those published by Roush,<sup>63</sup> Mohapatra,<sup>64</sup> Armstrong,<sup>65</sup> Spilling,<sup>66</sup> Frigadère and Ferrié,<sup>67</sup> and Pagenkopf.<sup>68</sup> Finally, Carter described the total synthesis of the C7–C20 subunit<sup>69</sup> and the total synthesis of amphidinolide F.<sup>70</sup>

**3.6.3.1. Carter's synthesis of Amphidinolide F.<sup>70</sup>** The retrosynthetic analysis of Carter's group is based on the macrocyclization by lactone formation at the end of the process from a linear precursor containing the two THF rings. They developed a smart strategy where the two building blocks C15–C29 and C1–C4, 64 and 65, could be synthesized from the same THF intermediate 66 (Figure 15).

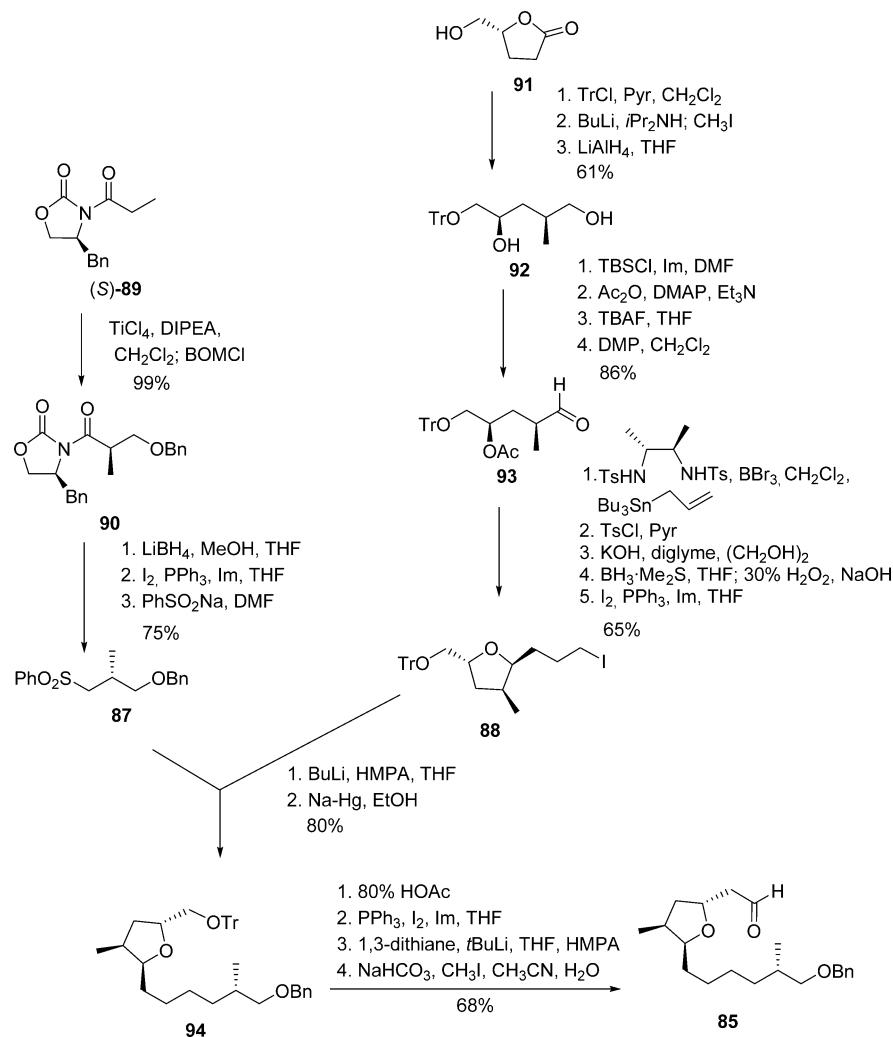
Common intermediate 66 was synthesized starting from known alcohol 67.<sup>71</sup> Oxidation and Bestmann–Ohira reaction, followed by benzylidene acetal removal and orthogonal protection of the free hydroxy-group, furnished 68, which was subjected to Sonogashira cross-coupling with 69 and Sharpless asymmetric dihydroxylation, to obtain diol 70. Formation of dihydrofuran (DHF) 71 was achieved with AgBF<sub>4</sub> with excellent stereoselectivity (dr > 20:1). Subsequent protection of the free alcohol and removal of the enol benzoate furnished intermediate 66 (Scheme 18).

The synthesis of fragment 65 was performed by stereoselective transformation of 66 into 72, followed by its condensation with the lithium derivative of vinyl iodide 73 and functional group transformation. The key step for the synthesis of 72 was the introduction of a methylidene in the  $\alpha$ -position of the keto-group using the iminium salt 74, followed by its stereoselective hydrogenation with Wilkinson's catalyst to give the correct stereochemistry at C4 of the desired 75. Transformation of 75 into aldehyde 72 was performed by deoxygenation, selective deprotection of the primary TBS, and oxidation. Fragment 73 was synthesized from known iodide 76,<sup>69</sup> by a regioselective hydrostannation of a Sonogashira formed enyne, followed by iodo vinyl formation (Scheme 19).

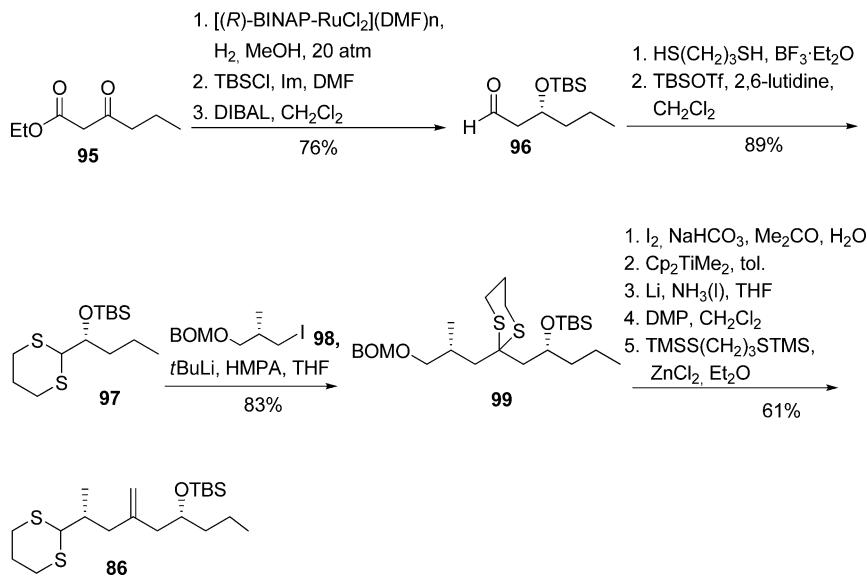
Subunit 64 was obtained from 66 by keto-deoxygenation and removal of the pivaloyl (Piv) protecting group, followed by oxidation to furnish aldehyde 77, which was then reacted with lithium derivative 78,<sup>72</sup> to obtain epimeric alcohols 79 (1.5:1). Protection as ethoxyethyl acetal (EE) permitted separation, and the synthesis went on with 80, which was obtained after deprotection of the benzyl ether. Alcohol 80 was converted into 81 by introduction of the sulfone, deprotection of the primary TBS alcohol, and oxidation. Reaction of 81 with Vedejs-type tributyl phosphonium salt 82,<sup>73</sup> and silyl protecting group exchange, led to the desired *E* fragment 64 (Scheme 20).

Coupling of building blocks 64 and 65 was performed successfully with lithium hexamethyldisilazane (LHMDS) and

Scheme 22. Synthesis of Trisubstituted THF Building Block 85

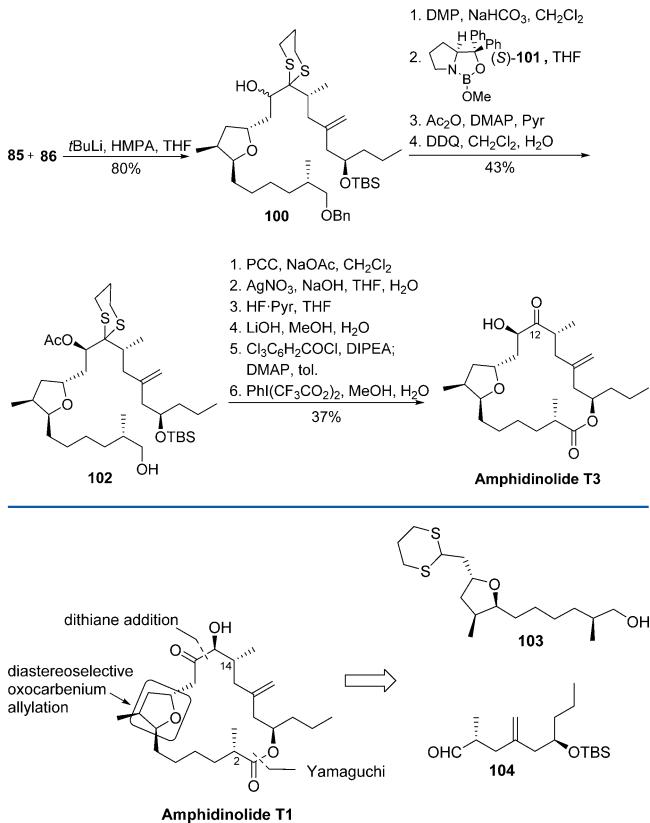


Scheme 23. Synthesis of Building Block 86



hexamethylphosphoramide (HMPA). After oxidative desulfurization,<sup>74</sup> ketone 83 was obtained along with Piv-deprotected product. The mixture was converted to seco acid 84, which,

under Yamaguchi conditions, after selective deprotection of the EE ether, oxidation, and desilylation furnished amphotinolide F (Scheme 21).

**Scheme 24.** Total Synthesis of Amphidinolide T3<sup>77</sup>Figure 18. Amphidinolide T1 retrosynthetic analysis by Yadav.<sup>78</sup>

**3.6.4. Amphidinolides T1, T2, T3, T4, and T5.** Amphidinolide T series are 19-membered macrolactones containing a *cis,trans,trans*-2,3,5-trisubstituted THF ring and an exocyclic methylenic group.<sup>39p-s</sup> The fact that they are all structurally related permits a diverted strategy for the synthesis of more than one natural product following the same synthetic route.

Synthesis of amphidinolides T was reviewed until 2005,<sup>42a</sup> when the work done by Fürstner, Ghosh and Jamison was compiled. Later in 2011, Fürstner presented a revision of the work done by his own group on the synthesis of amphidinolides, including the T series, and amphidinolides X and Y.<sup>42b</sup>

Further work includes the synthesis of the C1–C12 subunits by Iqbal<sup>75</sup> and Clark<sup>76</sup> and the total syntheses published by Zhao,<sup>77</sup> Yadav,<sup>78</sup> and Dai.<sup>79,80</sup> Figure 16 summarizes the main bond disconnections for the total syntheses of amphidinolide T1.

**3.6.4.1. Zhao's Synthesis of Amphidinolide T3.**<sup>77</sup> Key steps in this synthesis were the macrolactonization and the 1,3-dithiane addition, which meant the construction of two fragments, aldehyde 85 and dithiane 86 (Figure 17).

Aldehyde 85 was synthesized by condensation of sulfone 87 with iodide 88 (Scheme 22). Enantioselective synthesis of sulfone 87 was performed using oxazolidinone compound 89 as chiral auxiliary to obtain protected alcohol 90. Removal of the chiral auxiliary and introduction of the sulfone led to compound 87 as shown in Scheme 22. The synthesis of 88 started with the protection of alcohol 91 as a Tr ether. Further alkylation provided good diastereoselectivity (dr 11:1) and reduction with LiAlH<sub>4</sub> afforded diol 92. Aldehyde 93 was obtained by selective protection of 92 as a TBS ether, followed by acetylation of the secondary hydroxyl, desilylation, and oxidation. Asymmetric

allylation of 93, followed by tosyl (Ts) introduction and cyclization, produced the trisubstituted THF ring with the correct stereochemistry. Hydroboration–oxidation and subsequent iodine substitution provided iodide 88. Addition of lithium derivative of 87 to 88, followed by reductive removal of the sulfonyl group, furnished 94. Removal of the Tr protecting group, iodine exchange, and substitution by 1,3-dithiane, followed by removal of dithiane, afforded segment 85.

Synthesis of dithiane segment 86 started by stereoselective hydrogenation of ethyl 3-oxohexanoate 95, protection of the formed alcohol, and reduction of the ester to obtain aldehyde 96. Formation of the dithiane resulted in loss of the TBS ether, so re-protection was mandatory at this stage. The resulting dithiane 97 was reacted with iodide 98 to obtain 99. Removal of dithiane, Petasis olefination, reductive elimination of BOM protecting group and oxidation, followed by dithiane constitution from the aldehyde, resulted in the formation of segment 86 (Scheme 23).

The assembly of 85 and 86 led to epimeric alcohols 100 (1:7:1). Despite the effort of the authors to obtain 100 as a unique stereoisomer, the only possibility was to oxidize the alcohol to the ketone and perform a stereoselective reduction with (S)-101. Acetylation of the formed hydroxyl and oxidative removal of benzyl protecting group afforded alcohol 102. A two-step oxidation process was necessary to maintain the dithiane moiety. Removal of TBS and acetyl protecting groups was performed prior to Yamaguchi macrocyclization, and final removal of the dithiane afforded amphidinolide T3 (Scheme 24).

This synthesis of amphidinolide T3 describes the basis for the synthesis of amphidinolide T4, by simply inverting the stereochemistry at C12 in the last steps of the synthesis.

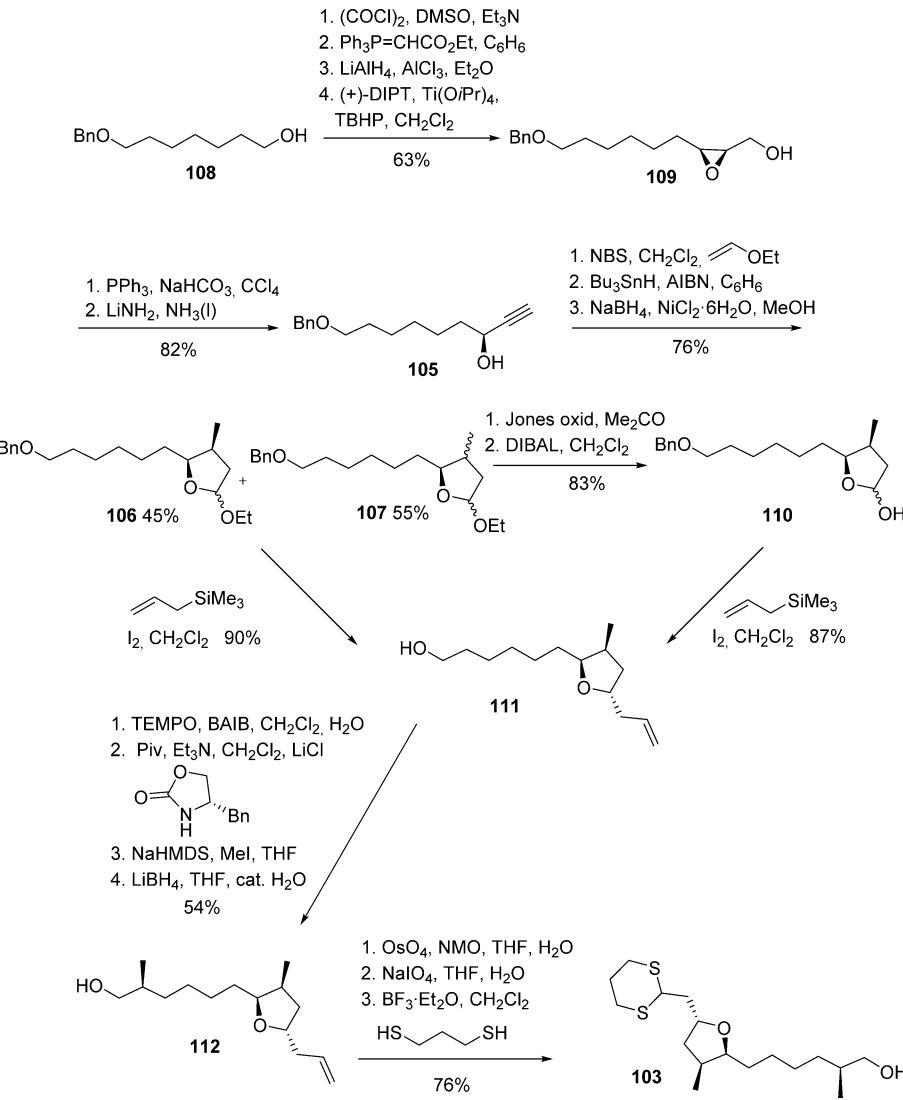
**3.6.4.2. Yadav's Synthesis of Amphidinolide T1.**<sup>78</sup> Yadav's retrosynthesis of amphidinolide T1 depicted two subunits, 103 and 104. They based their assembly on a dithiane addition and a macrocyclization. The formation of the THF system was achieved by a new allylation strategy developed in their group (Figure 18).

The key steps for the synthesis of building block 103 were the transformation of alkynol 105 into a bromo acetal that was subjected to radical cyclization and hydrogenation to give ethoxy-THFs 106 and 107. Alcohol 108 was transformed into 109 by oxidation, Wittig olefination, reduction of the ester to an allylic alcohol, and asymmetric epoxidation. Reaction of 109 with PPh<sub>3</sub> in CCl<sub>4</sub> with NaHCO<sub>3</sub>, followed by base-induced elimination, resulted in alkynol 105. Alkynol 105 with NBS and ethyl vinyl ether gave a bromo acetal that was subjected to radical cyclization and hydrogenation to obtain ethoxy-THFs 106 and a diastereomeric mixture of 107. Mixture 107 was partially recovered for total synthesis by oxidation separation of epimers and reduction of the *syn*-lactone to obtain 110. Allylation of either lactol ether 106 or lactol 110 was performed using a methodology developed by Yadav,<sup>81</sup> based on the reaction with allyltrimethylsilane in the presence of iodine; the yield and diastereoselectivity of this step proved that it was an effective methodology. Interestingly, the loss of the benzyl protecting group was observed in the presence of 1.2 equiv of iodine.

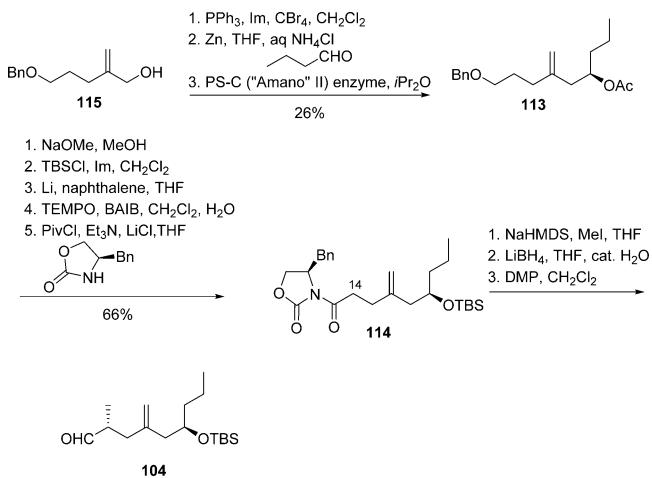
Oxidation of the free alcohol of 111, followed by introduction of a chiral auxiliary, permitted diastereoselective methylation, and the removal of the chiral auxiliary with LiBH<sub>4</sub> afforded alcohol 112. Dihydroxylation, oxidative cleavage of the diol with NaIO<sub>4</sub>, and dithiane formation led to segment 103 (Scheme 25).

Enantioselective synthesis of fragment 104 had two important steps for stereochemical results: the enzymatic acetylation of

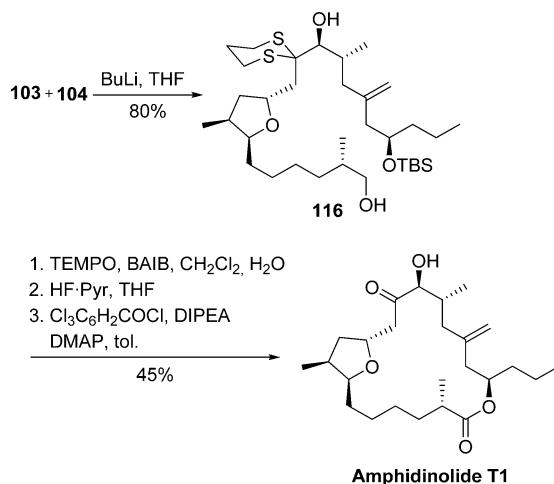
Scheme 25. Synthesis of Trisubstituted THF Derivative 103



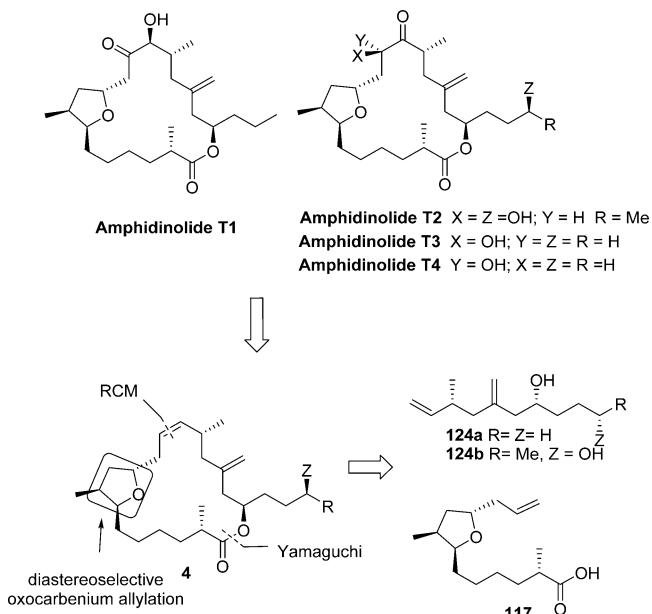
Scheme 26. Synthesis of Aldehyde 104



epimeric alcohols to give 113 and the stereoselective C14 methylation of the acyloxazolidinone 114 precursor of aldehyde 104 (Scheme 26). Alcohol 115 was prepared by malonate synthesis from 3-benzyloxy-1-iodopropane<sup>82</sup> and diethyl malo-

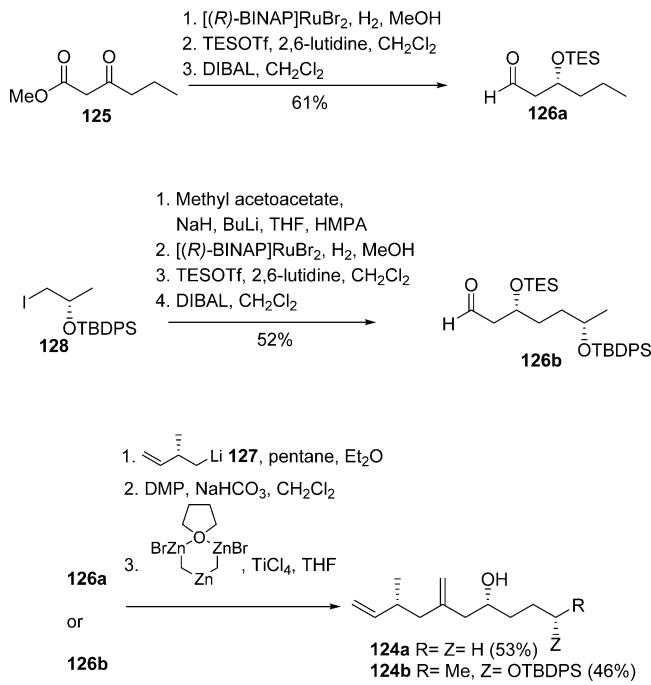
Scheme 27. Total Synthesis of Amphidinolide T1<sup>78</sup>

nate followed by reductive elimination. After bromination and allylation of butyraldehyde, the obtained racemic mixture of alcohols was subjected to enzymatic kinetic resolution to give 113. Successive deacetylation, protection as a TBS ether, removal

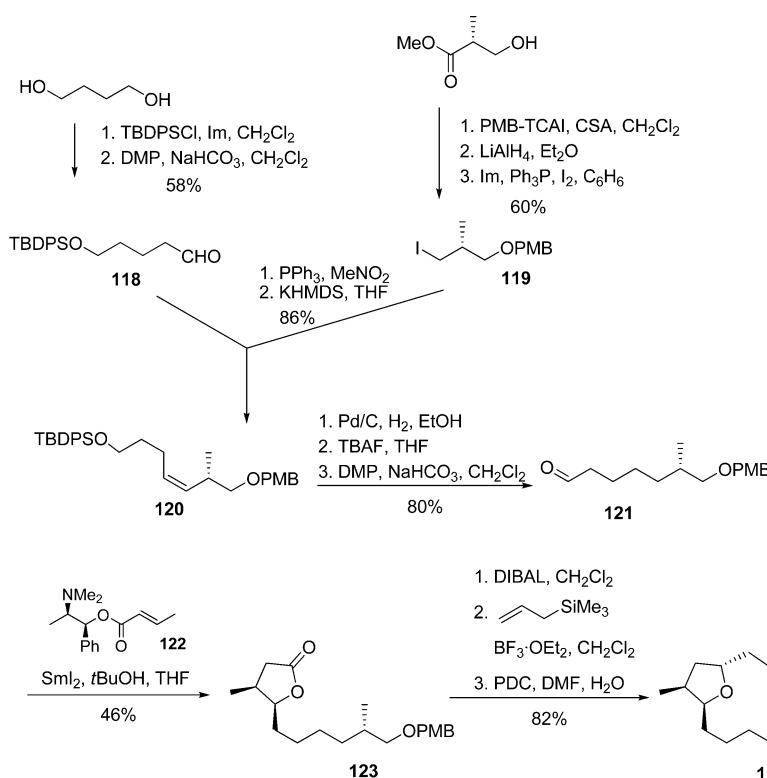
Figure 19. Retrosynthetic analysis of amphidinolides T by Dai.<sup>80</sup>

of the benzyl group, oxidation, and introduction of a chiral oxazolidinone afforded derivative **114**, which, upon methylation and removal of the chiral auxiliary in a two-step process, gave aldehyde **104**.

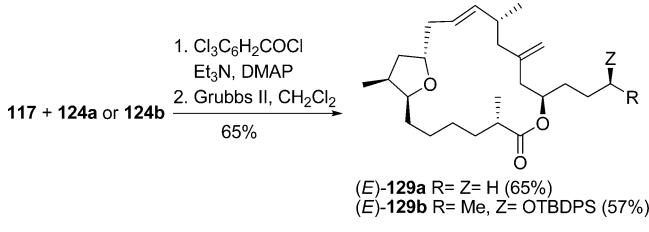
Addition of the lithium derivative of dithiane **103** to aldehyde **104** gave a 4:1 mixture of diastereomers of **116** favoring the *syn* adduct. Chromatographic separation permitted isolation of the major isomer. Selective oxidation of the primary hydroxyl group with loss of the dithiane moiety, removal of the TBS ether, and Yamaguchi lactonization led to amphidinolide **T1** (Scheme 27).

Scheme 29. Synthesis of Alcohols **124a** and **124b**

**3.6.4.3. Dai's Syntheses of Amphidinolides T1, T2, T3, and T4.**<sup>80</sup> The total synthesis of amphidinolides **T1**, **T2**, **T3**, and **T4** by Dai and co-workers took advantage of the components similarity to develop a diverted strategy from an advanced intermediate **117** (Figure 19). The synthesis is based on the union of two fragments by ester formation and RCM to prepare a common macrocyclic possessing a double bond precursor of  $\alpha$ -

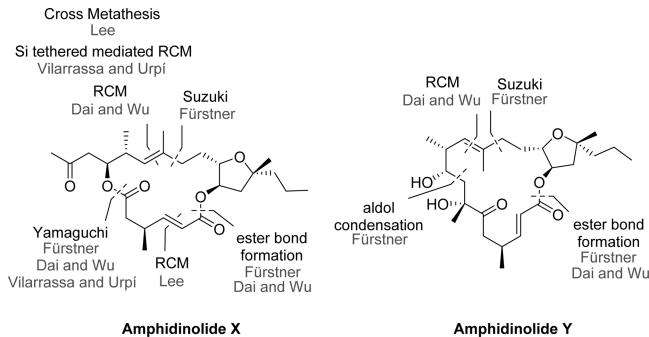
Scheme 28. Synthesis of Acid **117**

**Scheme 30.** Synthesis of Macrolactones 129a and 129b



hydroxyketone, which is characteristic of the T series amphenidinolide natural products.

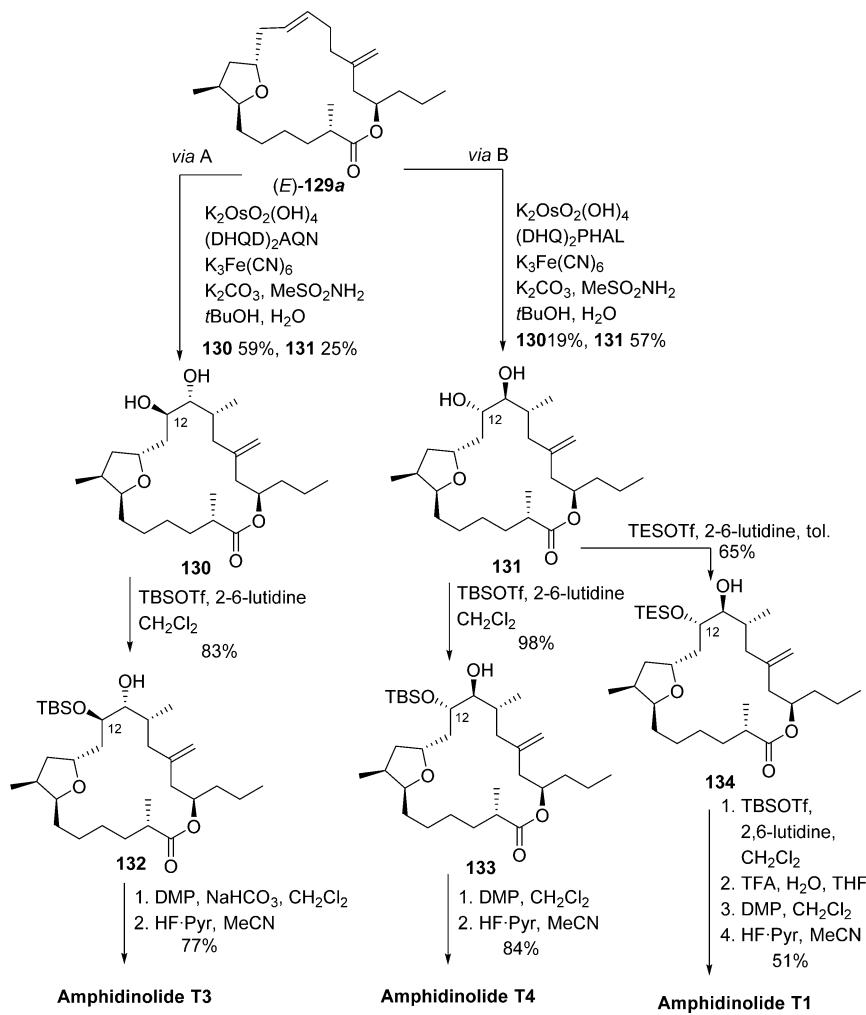
Fragment **117**, shared by the four amphenolides T1, T2, T3, and T4, was synthesized as shown in Scheme 28. Phosphonium salt of iodide **119**, synthesized by known procedures,<sup>83</sup> was reacted with KHMDS and aldehyde **118** to yield alkene **120**, which was then transformed into aldehyde **121** by hydrogenation, removal of TBDPS ether, and oxidation. The stereoselective construction of the trisubstituted THF ring present in fragment **117** was afforded by SmI<sub>2</sub>-mediated enantioselective reductive coupling between aldehyde **121** and crotonate **122** to give lactone **123**, which was then transformed into fragment **117** by reduction, allylation–deprotection, and oxidation.

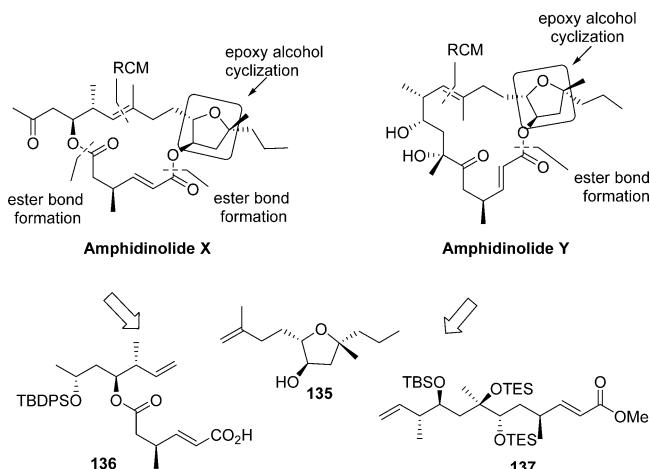


**Figure 20.** Strategic disconnections for amphotericin B and its analogues.

For the synthesis of amphidinolides T1, T3, and T4, fragment **124a** was produced starting from  $\beta$ -keto ester **125**.<sup>80b</sup> Asymmetric reduction of the keto-group, protection of the hydroxyl, and reduction of the ester, afforded aldehyde **126a**. Further reaction of **126a** with lithium derivative **127**, followed by oxidation and methylenation with Nysted's reagent, which resulted in the loss of the TES ether, furnished **124a**. Amphidinolide T2 was synthesized from fragment **124b**.<sup>80a</sup> Protection of methyl (S)-lactate, reduction of the ester to the alcohol, and iodine exchange, gave iodine **128**. Methyl acetoacetate was alkylated with **128**. Enantioselective hydro-

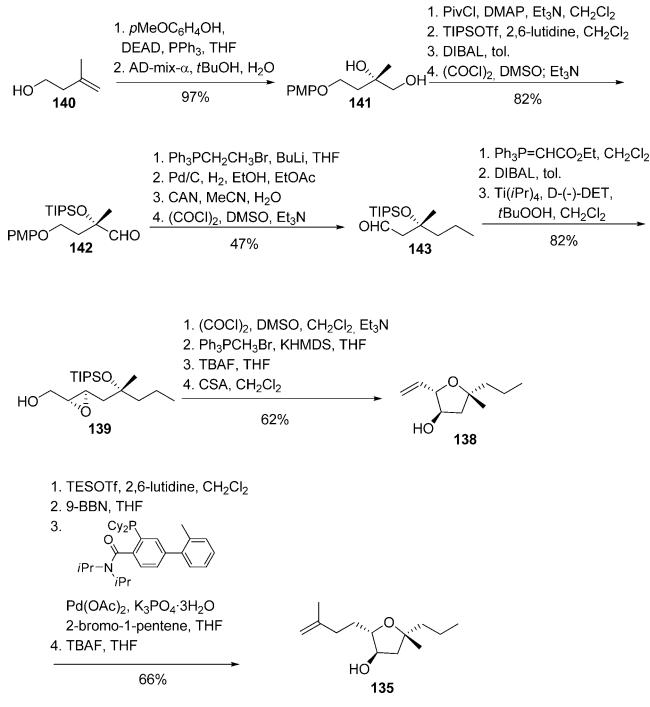
**Scheme 31.** Total Syntheses of Amphidinolides T1, T3, and T4<sup>80</sup>





**Figure 21.** Amphidinolides X and Y retrosynthetic analysis by Dai and Wu.<sup>88</sup>

**Scheme 32. Synthesis of Tetrasubstituted THF Building Block 135**



genation, TES ether formation, and controlled reduction of the ester, furnished aldehyde **126b**. This aldehyde was transformed into **124b** in a similar reaction sequence as in **124a** (Scheme 29).

Fragments **124** and **117** were condensed by ester formation and further RCM using Grubbs II catalyst to yield macrolactones **129a** and **129b** (Scheme 30).

(E)-**129a** was the common synthetic intermediate for the total syntheses of amphidinolides T1, T3, and T4.<sup>80b,c</sup> Asymmetric dihydroxylation of (E)-**129a** was performed to obtain either **130**, using 1,4-bis(dihydroquinidine)anthraquinone [(DHQD)<sub>2</sub>AQN] as a ligand, or **131** with 1,4-bis(9-o-dihydroquinalyl)phthalazine [(DHQ)<sub>2</sub>PHAL]. Transformation of **130** into amphidinolide T3 and **131** into amphidinolides T1 or T4 is based on a monoprotection, oxidation, and deprotection process that takes advantage of the selectivity in the protection of

the less hindered C12 hydroxyl group of **130** or **131**, obtaining **132**, **133**, or **134** (Scheme 31).

Similar asymmetric dihydroxylation of **129b** using (DHQD)<sub>2</sub>AQN protection, oxidation, and deprotection (via A, Scheme 31) afforded amphidinolide T2.<sup>80a</sup>

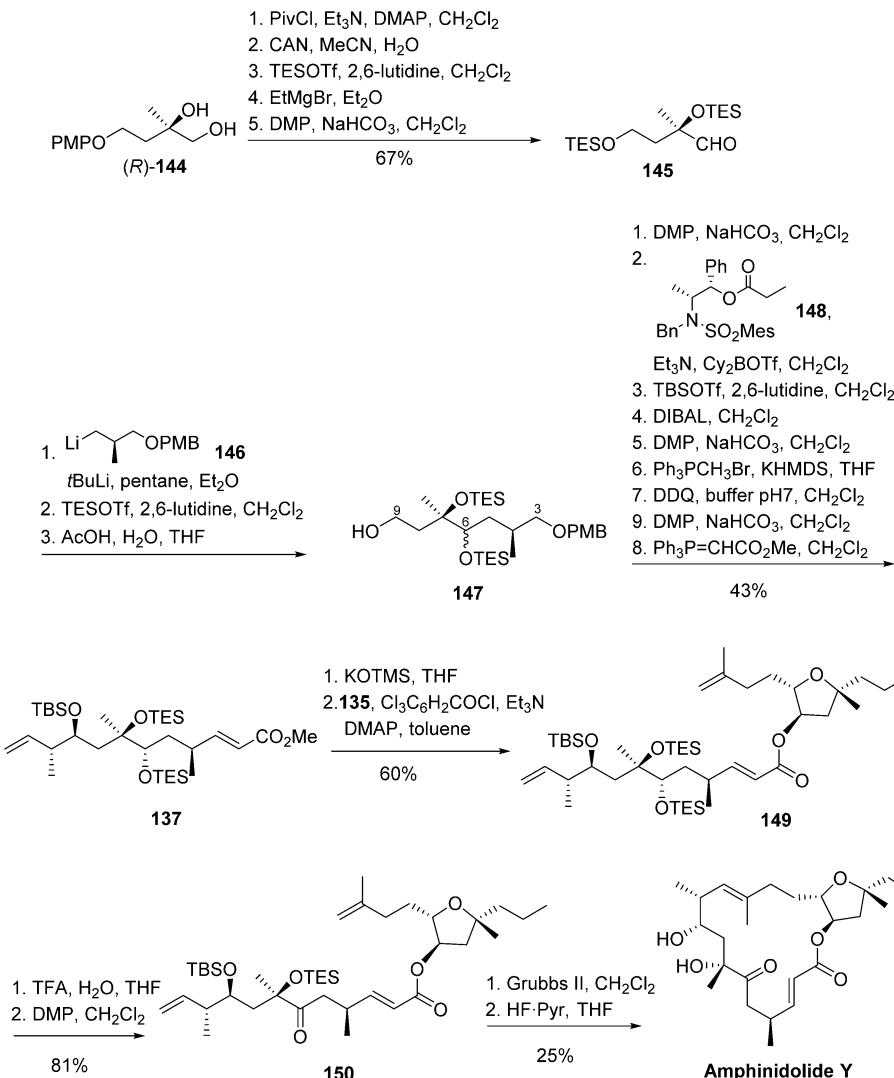
**3.6.5. Amphidinolides X and Y.** Amphidinolides X and Y are 16- and 17-membered macrolides, whose structural similarity suggests a close biogenetic relation. Structural characteristics are the 2,3-*trans*-fused 2,3,5,5-tetrasubstituted THF ring and trisubstituted and conjugated *E*-double bonds in both amphidinolides. Amphidinolide Y exists as an equilibrium mixture of 6-keto and 6(9)-hemiacetal form (9:1) in CDCl<sub>3</sub> (Figure 10).<sup>39t,u</sup>

Several groups have been working in the synthesis and mechanism of action of amphidinolides X and Y since they were first reported in 2003. Of interest is the partial synthesis of the THF segment reported by Vatèle,<sup>84</sup> and by Gurjar and Mohapatra.<sup>85</sup> Fürstner and co-workers described the synthesis of amphidinolide X and Y,<sup>86</sup> both compiled in a revision published in 2011,<sup>42b</sup> which reported the synthesis and biological evaluation of some analogues as well.<sup>87</sup> The total synthesis performed by Dai and Wu,<sup>88</sup> Vilarrasa and Urpí,<sup>89</sup> and Lee<sup>90</sup> was reported at a later date. The main bond disconnections for the synthesis of amphidinolides X and Y are summarized in Figure 20.

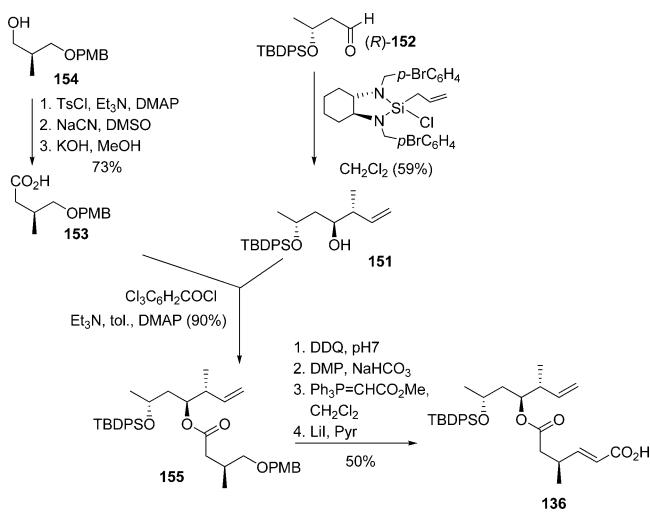
**3.6.5.1. Dai and Wu's Synthesis of Amphidinolides X and Y.**<sup>88</sup> The strategy to synthesize amphidinolides X and Y was based on the same THF building block **135**. The main disconnections were macrolactonization and RCM. As shown in Figure 21, three building blocks were proposed for amphidinolide X and amphidinolide Y: the tetrasubstituted THF **135** and the acid derivatives **136** and **137**.

Enantioselective synthesis of tetrasubstituted THF **138** with the appropriate configuration of the four stereocenters was the key for the total synthesis.<sup>88a</sup> Epoxide **139** was synthesized from homoallylic alcohol **140**, using Corey's procedure<sup>91</sup> to obtain diol **141**. Manipulation of protecting groups and oxidation of the primary alcohol led to aldehyde **142**. This aldehyde was subjected to Wittig olefination and reduction, followed by removal of the PMP protecting group and oxidation to obtain aldehyde **143**. Olefination of **143** and reduction, followed by Sharpless epoxidation, furnished epoxy alcohol **139** in high enantioselectivity. Attempts to obtain a cyclized product from epoxy alcohol **139** failed to produce the desired THF fragment.  $\pi$ -Orbital activation by oxidation of the alcohol and Wittig olefination, followed by removal of the TIPS protecting group, and camphorsulfonic acid (CSA) catalyzed cyclization, led to **138**. Transformation of **138** into fragment **135** was afforded by protection of the alcohol, followed by hydroboration, Suzuki cross-coupling, and removal of the protecting group (Scheme 32).

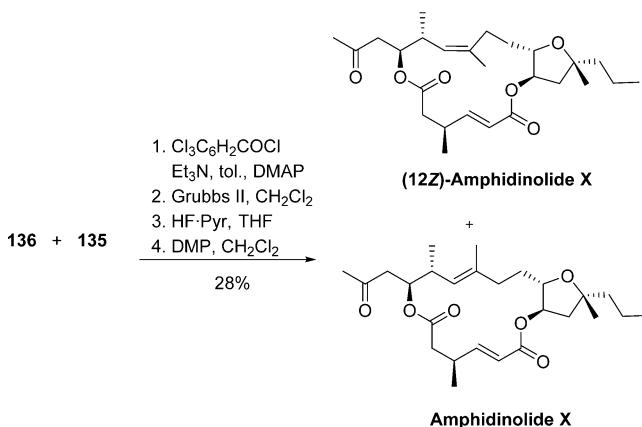
**Synthesis of Amphidinolide Y.**<sup>88b</sup> Monoprotected triol **144**<sup>91</sup> was transformed to aldehyde **145** by exchanging protecting groups and oxidation. Reaction of **145** with the lithium derivative **146**<sup>83</sup> produced, after protection and selective desilylation, an epimeric mixture of alcohols **147** (3:1.2). The major alcohol (*6S*)-**147** was transformed into **137** by elongation at the two ends. Sequential selective oxidation at C9, aldol reaction with chiral ester **148**, followed by protection of the free hydroxyl, reduction of the ester to the alcohol, oxidation to the aldehyde, Wittig olefination, and oxidation at C3, followed by Wittig reaction, afforded **137**. Methyl ester cleavage and Yamaguchi lactonization with fragment **135** led to RCM precursor **149**. The same procedure was used to obtain **149** 6-epimer from the

Scheme 33. Total Synthesis of Amphidinolide Y<sup>88b</sup>

Scheme 34. Synthesis of Acid 136



minority alcohol (6*R*)-147. Ketone 150 was obtained from either 149 or its 6-*epi*-149 by selective desilylation and oxidation. RCM was possible with ketone 150 in a 40% yield. After desilylation, amphidinolide Y was obtained as a 5:1 mixture (Scheme 33).

Scheme 35. Synthesis of Amphidinolide X and (12*Z*)-Amphidinolide X<sup>88c</sup>

*Synthesis of Amphidinolide X.*<sup>88c</sup> Building block 136 for the synthesis of amphidinolide X was prepared starting from homoallylic alcohol 151 and acid 153. Alcohol 151 was obtained by asymmetric crotylation of known (R)-152.<sup>92</sup> Acid 153 was synthesized from alcohol 154<sup>83b</sup> in three steps. Condensation of

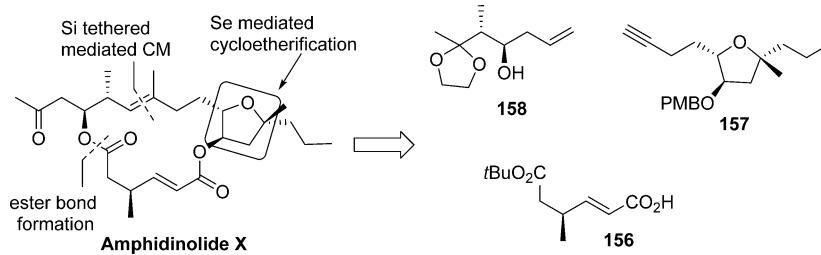
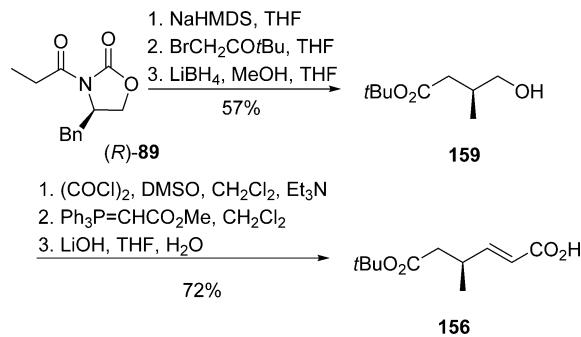


Figure 22. Amphidinolide X retrosynthetic analysis by Vilarrasa and Urpi.<sup>89</sup>

**Scheme 36. Synthesis of Building Block 156**



151 with 153 was performed under Yamaguchi conditions to obtain 155. Removal of the PMB protecting group, oxidation, and subsequent Wittig olefination, provided an ester that was transformed into acid 136 (Scheme 34).

Acid 136 was condensed with THF fragment 135. Further RCM afforded a mixture of Z/E-macrodiolides (71:29).

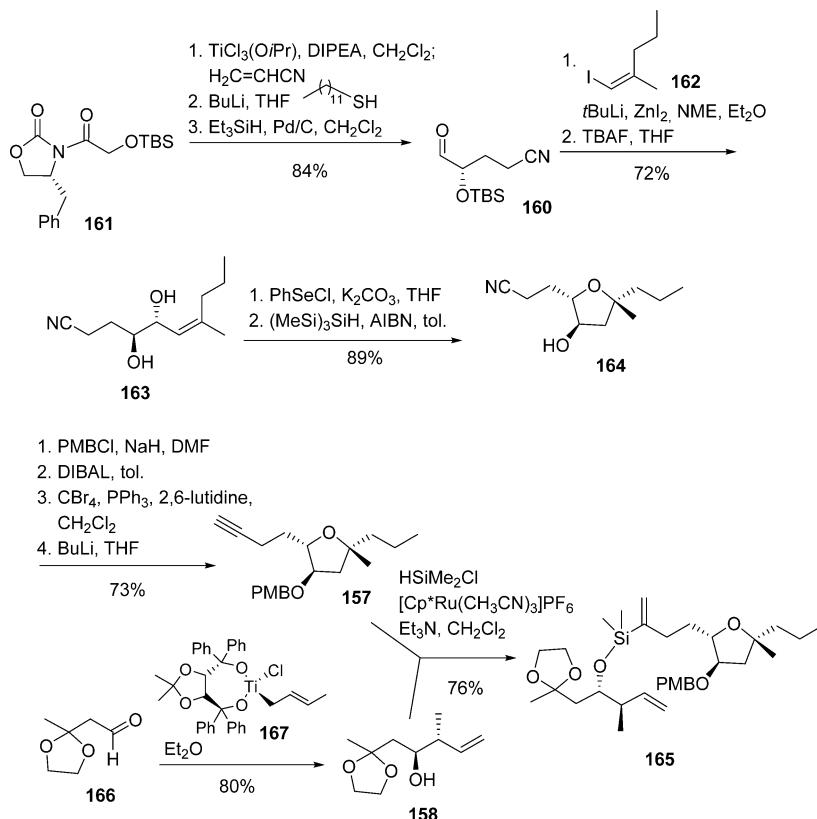
Desilylation and oxidation of the mixture produced (12Z)-amphidinolide X and amphidinolide X itself (Scheme 35).

**3.6.5.2. Vilarrasa and Urpi's Synthesis of Amphidinolide X.**<sup>89</sup> Vilarrasa and Urpi's strategy for the synthesis of amphidinolide X depicted three main disconnections to form building blocks 156, 157, and 158 (Figure 22). Two ester bond formations and a silicon tethered cross metathesis (CM) reaction were used to build the final macrolide. Authors describe their efforts toward a strategy based on a RCM, but the low reactivity of the 1,1-disubstituted olefin led to a dead end. The construction of a silicon tether proved to be a reasonable solution to the CM problem.

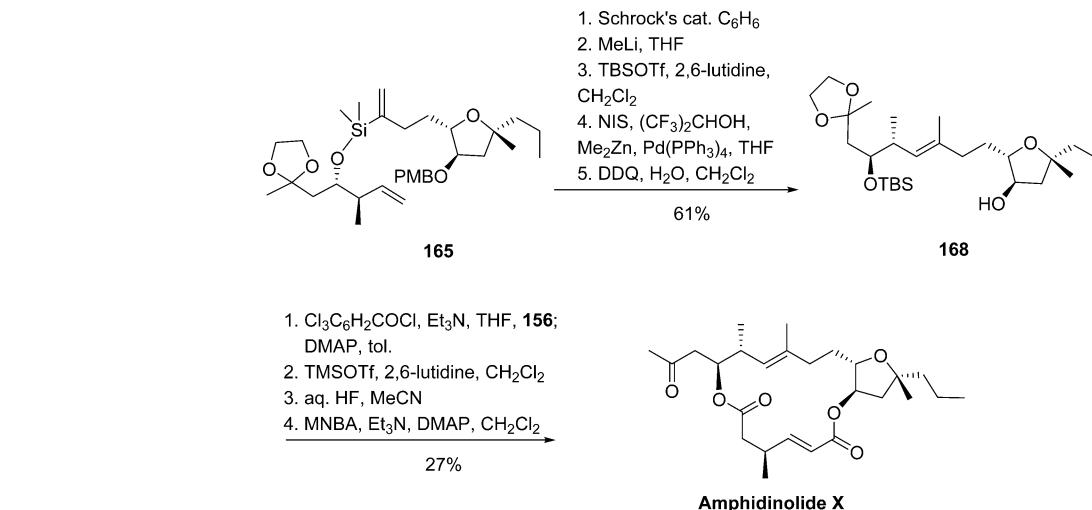
Monoprotected diacid derivative 156 was synthesized by an asymmetric enol alkylation. Elimination of the chiral auxiliary to obtain alcohol 159, further oxidation, and Wittig reaction, followed by selective hydrolysis, gave 156 (Scheme 36).

Aldehyde 160 was obtained from oxazolidinone 161 by asymmetric addition of the titanium enolate with acrylonitrile and reduction. Reaction of 160 with the alkenylzincate derived from iodide 162 using N-methylephedrine (NME) as organic

**Scheme 37. Synthesis of Silicon-Tethered Diene 165**

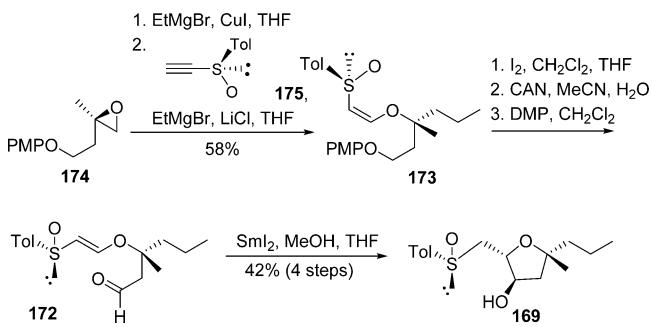


**Scheme 38.** Total Synthesis of Amphidinolide X<sup>89</sup>



**Figure 23.** Amphidinolide X retrosynthetic analysis by Lee.<sup>90</sup>

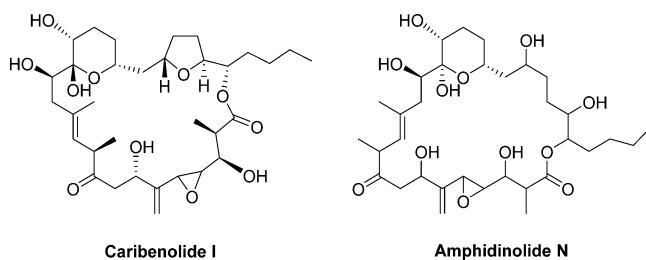
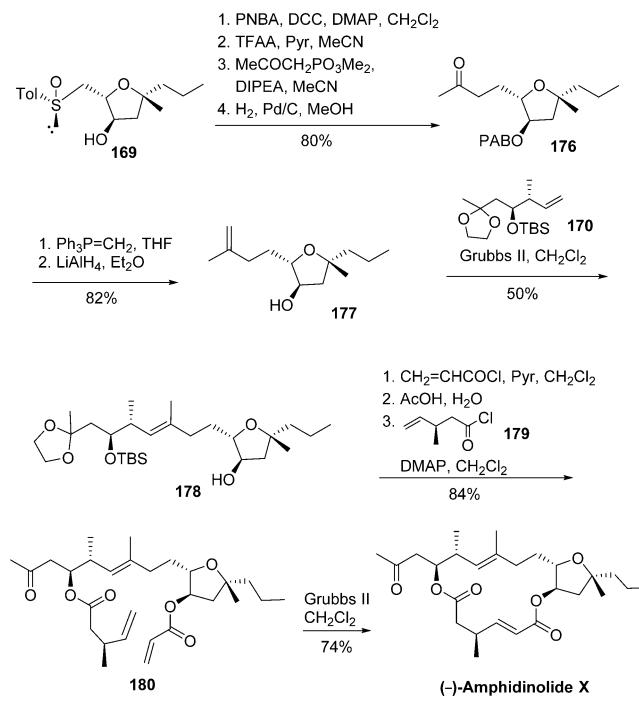
**Scheme 39. Stereoselective Synthesis of Tetrasubstituted THF Derivative 169**



asymmetric inductor, followed by deprotection of the TBS ether, afforded enantiopure **163**. The synthesis of tetrasubstituted THF **164**,<sup>89a</sup> the key step of this process, was afforded by stereocontrolled PhSeCl-induced cyclization of the *anti-Z*  $\alpha,\beta$ -dihydroxy-trisubstituted olefin **163**, followed by deselenylation. Transformation of **164** into **157** was obtained by protection of the free hydroxyl group and homologation of the cyano group to the terminal triple bond. Silicon-tethered fragment **165** was obtained using Trost's catalyst<sup>93</sup> from the addition of dimethylchlorosilane to the triple bond of **157**, followed by silyl ether formation with alcohol **158** (Scheme 37). Alcohol **158** was obtained from aldehyde **166** in a process using Ti-derivative **167**.<sup>94</sup>

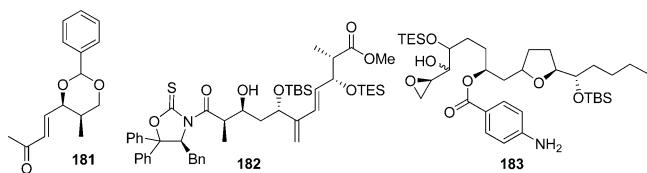
Dialkene **165** was reacted with Schrock's catalyst, and the silicon tether was removed by reaction with MeLi. This was followed by protection of the hydroxyl, iododesilylation with *N*-iodosuccinimide (NIS), and Negishi coupling with Me<sub>2</sub>Zn. Benzyl removal provided alcohol **168** that was condensed with

**Scheme 40.** Enantioselective Total Synthesis of (-)-Amphidinolide X<sup>90</sup>



**Figure 24.** Proposed structures of caribenolide I<sup>97</sup> and amphidinolide N.<sup>39</sup>

building block 156. Further removal of the *t*Bu ester and the TBS ether, followed by macrolactonization, led to amphotinolide X (Scheme 38).



**Figure 25.** Structures of C1–C6, C1–C11, and C13–C29 building blocks of caribenolide I.<sup>101,102</sup>

**3.6.5.3. Lee's Synthesis of Amphidinolide X.**<sup>90</sup> The last synthesis of amphidinolide X published to date is the one carried out by Lee and co-workers. They based the construction of the THF onto a cyclization of an aldehydo  $\beta$ -alkoxyvinyl sulfoxide derived from a tertiary alcohol. The retrosynthetic analysis shown in Figure 23 depicts building blocks 169, 170, and 171.

THF 169 was obtained with good stereocontrol by Sm<sub>2</sub> mediated cyclization of vinyl ether 172. (*Z*)-Alkoxyvinyl sulfoxide 173 was obtained by nucleophilic addition of EtMgBr to known epoxide (R)-174,<sup>95</sup> followed by reaction of the resulting alkoxide with (S)-alkynyl sulfoxide 175. Isomerization to the (*E*)-alkoxyvinyl sulfoxide by treatment with iodine, followed by ceric ammonium nitrate (CAN) deprotection of the benzyl group, and final oxidation to the aldehyde, led to cyclization precursor 172 (Scheme 39).

Protection of 169 and Pummerer rearrangement afforded an aldehyde that was subjected to a HWE olefination. Hydrogenation produced the double bond as well as the nitro group reduction to give ketone 176. After Wittig methylenation and LiAlH<sub>4</sub> deprotection, hydroxyolefin 177 was obtained. Grubbs II-catalyzed CM between 177 and known olefin 170,<sup>89b</sup> afforded (*E*)-178. Alcohol 178 was condensed with acryloyl chloride, TBS deprotection, condensation with the acid chloride 179,<sup>96</sup> and subsequent RCM of 180, furnished (−)-amphidinolide X (Scheme 40).

### 3.7. Caribenolide I<sup>97</sup>

Caribenolide I is an important cytotoxic metabolite obtained from cultured cells of *Amphidinium* sp. in enriched seawater, under fluorescent illumination, and harvested at the stationary phase in a 0.026% yield from dried cells.<sup>97</sup> Caribenolide I was a

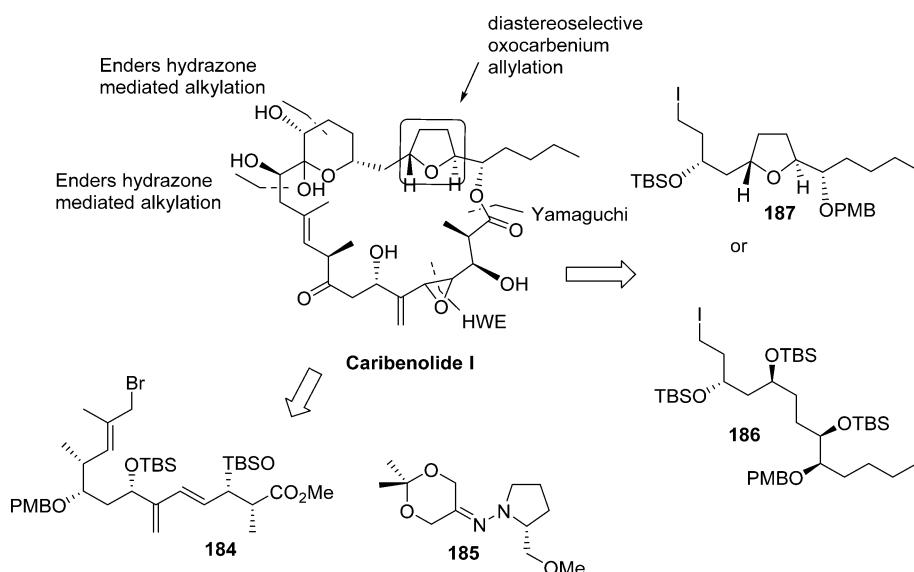
cytotoxic agent in the human colon carcinoma cell line (HCT 116) and the corresponding drug-resistant HCT 116 VM/46 with 1.6 nM values for the IC<sub>50</sub>. Caribenolide I was found to be 100 times more potent than amphidinolide B. This natural compound represents a new type of macrocyclic lactone, which contains one  $\alpha$ -methylidene epoxide, one disubstituted THF, one tetrasubstituted THP ring, one keto group, one *E*-double bond, four hydroxyl groups, and one butyl lateral chain (Figure 24). Stereochemical configuration of the natural product, except for the two epoxide stereocenters, was determined by synthetic studies.

Work on the synthesis of caribenolide I is often related to amphidinolide N,<sup>39</sup> due to their similar structure. Nicolaou<sup>98,99</sup> and Franck and Frigadère<sup>100–102</sup> have worked on the complex challenge posed by the synthesis of these structures.

Franck and Figadère's group published an interesting contribution to the total synthesis of caribenolide I.<sup>101,102</sup> They described the stereoselective synthesis of building blocks C1–C6,<sup>100</sup> C1–C11,<sup>101</sup> and C13–C29<sup>102</sup> 181, 182, and 183 of caribenolide I using as key steps asymmetric aldol reactions, to control the absolute configurations of stereogenic centers (Figure 25).

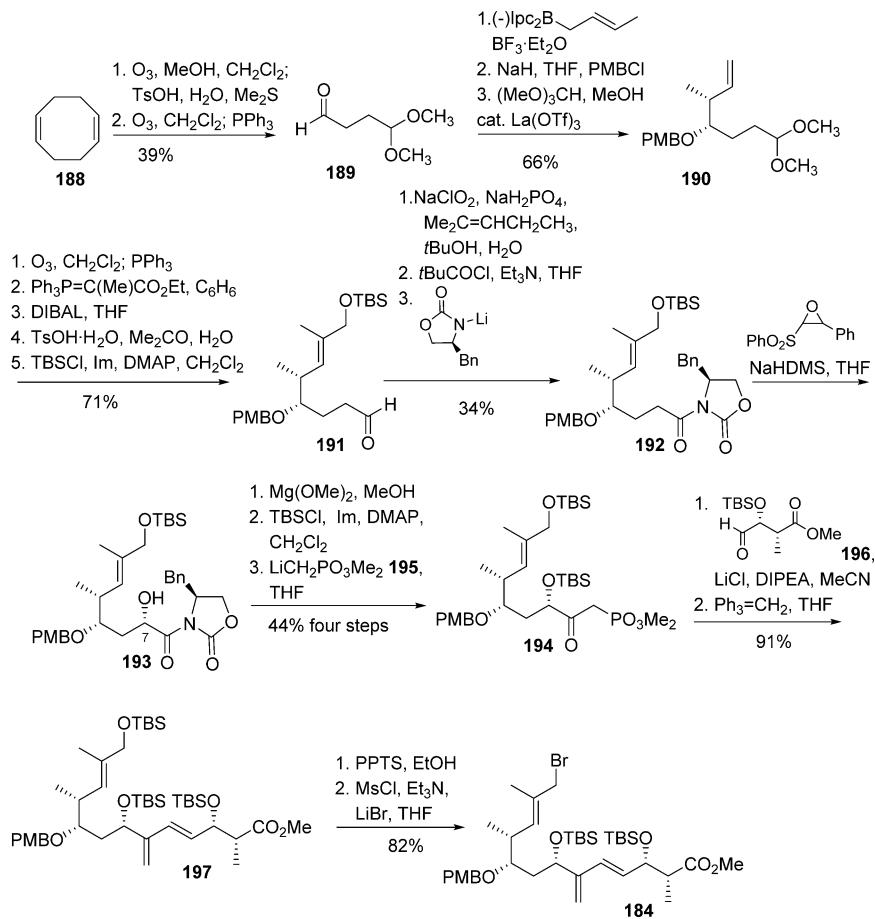
The last contribution to the study of this natural product has been recently published by Trost,<sup>103</sup> who, based on synthetic studies, stated that caribenolide I and amphidinolide N could have more common structural features than those previously reported, since amphidinolide N could also present the THF structural motif.

**3.7.1. Nicolaou's Synthesis of Caribenolide I.**<sup>99</sup> Nicolaou and co-workers tested three alternative procedures for the synthesis of caribenolide I. The last procedure afforded the enantioselective synthesis of *des*-epoxy-caribenolide I. This work was important to confirm the constitution of the molecule and to establish the configuration of 11 stereocenters and the *E*-alkene. The first strategy tested by Nicolaou's group was based on an enyne metathesis for C5 and C6 bond formation. However, following the synthesis of the complete C6–C29 carbon skeleton possessing the terminal acetylene, it was not possible to introduce the C1–C5 chain either intermolecular or intramolecularly.<sup>98</sup> The second strategy focused on a palladium-

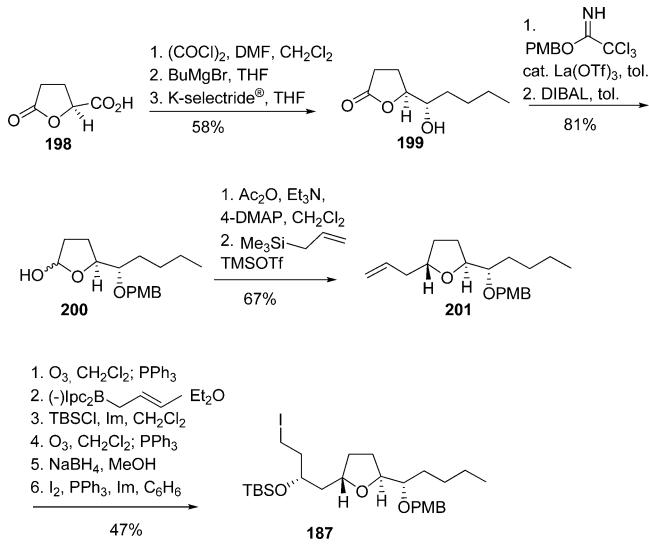


**Figure 26.** Caribenolide I retrosynthetic analysis by Nicolaou.<sup>99</sup>

Scheme 41. Synthesis of Bromide 184



Scheme 42. Synthesis of Iodide 187



catalyzed cross-coupling to generate the C5–C6 bond by reaction between a vinyl bromide and several functionalized forms of the C1–C5 skeleton.<sup>98</sup> The last strategy, called by the authors the ‘HWE approach’, has, as a key intermediate, bromide 184 (see Figure 26). The stereoselective assembly of the Enders hydrazone<sup>104</sup> C14–C16 185 with bromide 184 and iodide 186 affords the full skeleton of amphidinolide N. A similar procedure using iodide 187 affords the full skeleton of caribenolide I.<sup>99</sup>

The 1,5-cyclooctadiene 188 was converted into aldehyde 189 via two sequential ozonolysis reactions.<sup>105</sup> The introduction of the C9–C10 fragment by a Brown crotylboration reaction<sup>106</sup> of aldehyde 189, followed by secondary alcohol protection as the corresponding PMB ether, gave 190. Unexpectedly, a significant degree of hydrolysis of the dimethyl acetal group occurred during this step; therefore, the crude reaction mixture was subjected to acetalization prior to purification. Ozonolysis of the terminal alkene in compound 190 then provided the aldehyde, which was subjected to an (E)-selective Wittig reaction using stabilized phosphorane, to give trisubstituted alkene as a single geometrical isomer. The alkene was converted into aldehyde 191 by a three-step sequence of ester reduction, acetal hydrolysis, and TBS alcohol protection. The C7 hydroxyl group was introduced through enantioselective  $\alpha$ -oxygénéation chemistry of *N*-acyl oxazolidinones on 192.<sup>107</sup> *N*-Acyl oxazolidinone 193 was transformed into the  $\beta$ -ketophosphonate 194 in three steps based on methanolysis, removal of the auxiliary group, TBS protection of the C7-OH, and reaction with the lithium derivative 195. HWE reaction between 194 and 196 gave exclusively the C4–C5 (E)-isomer, which underwent Wittig methylenation to yield diene 197. Bromine 184 was obtained from 197 by chemoselective deprotection of the primary alcohol and substitution of the hydroxyl group by bromine via mesyl derivative (Scheme 41).

L-Glutamic acid was chosen as the starting material for the synthesis of the C17–C29 fragment 187 (Scheme 42). It was converted into lactone 198, with retention of configuration, via diazotization and internal displacement.<sup>108</sup> Formation of acid

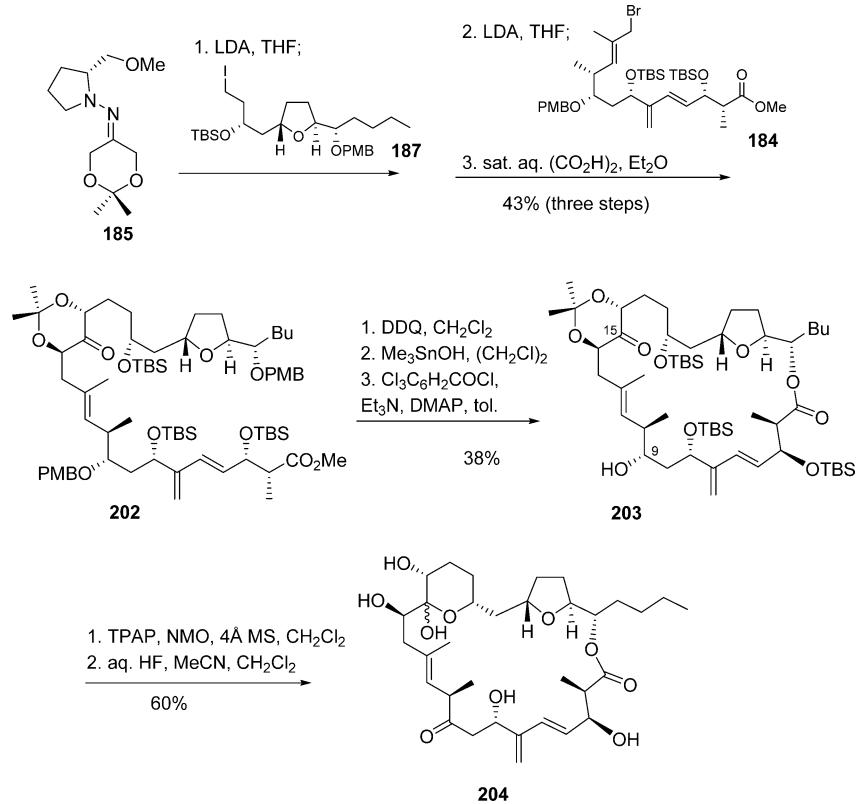
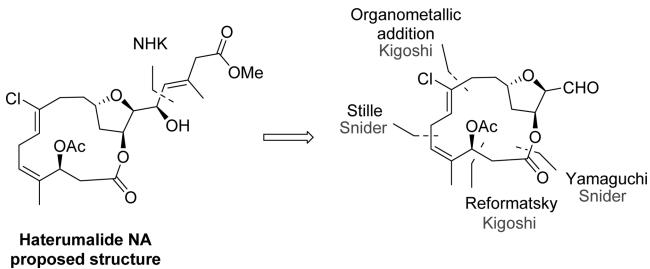
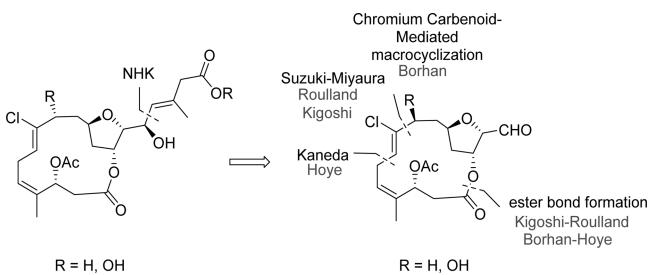
Scheme 43. Synthesis of C15 Epimeric Mixture of *des*-Epoxy-caribenolides I 204<sup>99</sup>

Table 1. Structures of Haterumalides and Biselides

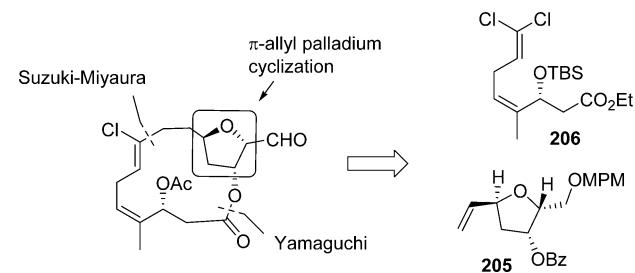
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Ref.	isolation
<b>Haterumalide NA</b>	H	Ac	H	OH	111	
<b>Haterumalide NB</b>	H	Ac	H	OBu	111	
<b>Haterumalide NC</b>	H	Ac	OH	OBu	111	
<b>Haterumalide ND</b>	H	Ac	OH	OH	111	
<b>Haterumalide NE</b>	H	H	H	OH	111	
<b>Haterumalide B</b>	H	Ac	H		110	
<b>Biselide A</b>	OAc	Ac	H	OH	114a	
<b>Biselide B</b>	OAc	Ac	H		114a	
<b>Biselide C</b>	OH	Ac	H	OH	114b	
<b>Biselide D</b>	H	Ac	H		114b	



**Figure 27.** Retrosynthetic disconnections for proposed haterumalide NA.



**Figure 28.** Retrosynthetic disconnections for haterumalide NA/oocydin A, haterumalide B and haterumalide NC.

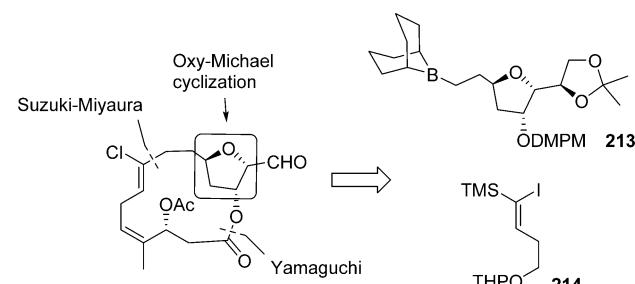
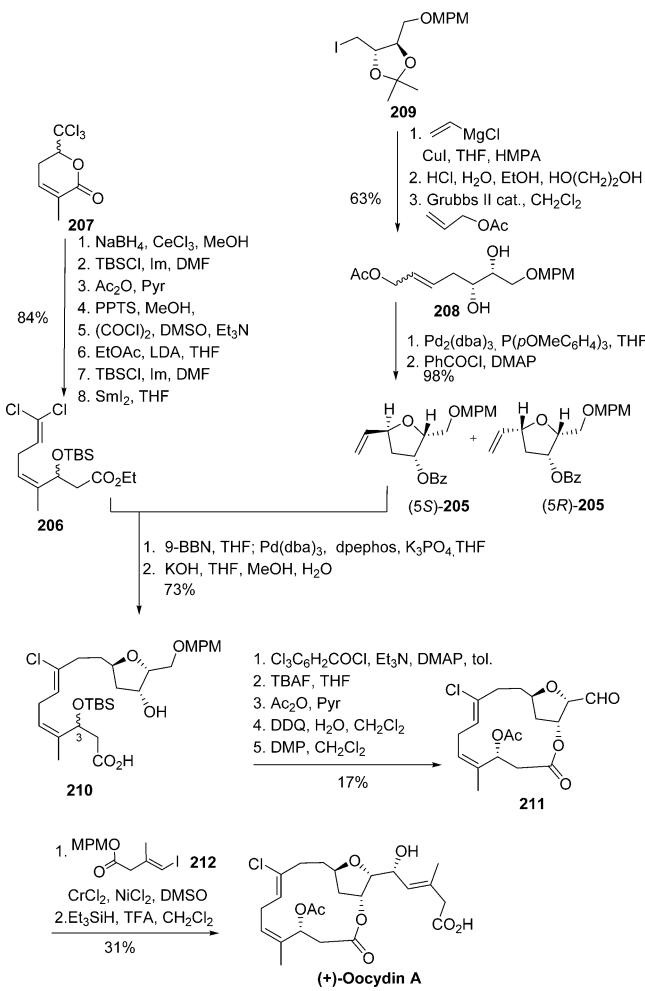


**Figure 29.** Oocydin A retrosynthetic analysis by Roulland.<sup>123</sup>

chloride, followed by the careful chemoselective addition of butylmagnesium bromide at low temperature, gave a ketone, which, upon reduction using K-Selectride, furnished alcohol **199** as a single stereoisomer. Protection of alcohol as the PMB ether, followed by reduction of lactone using DIBAL, gave lactol **200**, which was converted into anomeric acetate. Further allylation of this acetate, catalyzed with TMSOTf at low temperature to give the (21S)-THF product **201**, was then achieved (96%, dr 3.5:1). Iodide **187** was prepared from alkene **201** with a good global yield through a sequence of six further transformations consisting of chain integration and exchange of protecting and functional groups.

The complete carbon framework of target caribenolide I was furnished by the assembly of the building block fragments using Enders chiral hydrazone<sup>104</sup> alkylation methodology. The optimum conditions for the alkylation of hydrazone **185** were depicted as smooth coupling, first with C17–C29 iodide building block **187** and then with C1–C13 bromide building block **184**, following cleavage of the hydrazone auxiliary using aqueous oxalic acid to obtain ketone **202** as a single observable stereoisomer (Scheme 43). From ketone **202**, the fully deprotected core structure of caribenolide I was obtained by removal of both PMB protecting groups by treatment with DDQ, followed by hydrolysis of the ester to the corresponding acid using  $\text{Me}_3\text{SnOH}$ . Macrolactonization of the resulting acid under standard Yamaguchi conditions<sup>109</sup> afforded compound **203**.

**Scheme 44.** Enantiomeric Total Synthesis of (+)-Oocydin A<sup>123</sup>



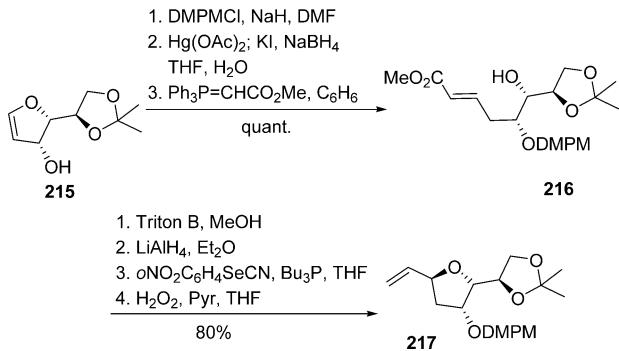
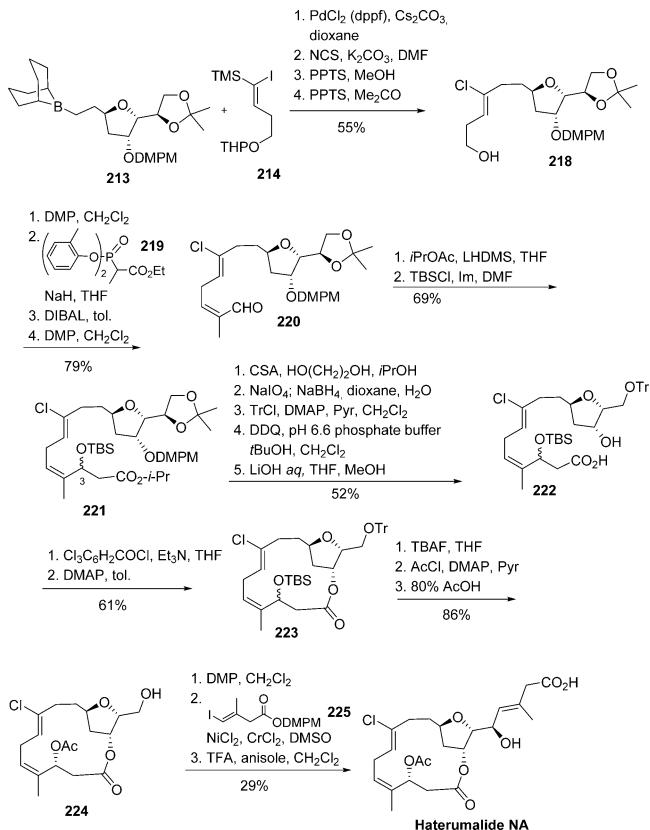
**Figure 30.** Haterumalide NA retrosynthetic analysis by Kigoshi.<sup>119</sup>

Oxidation of C9-OH group and deprotection of the ketone moiety was accompanied by spontaneous intramolecular hemiacetal formation at the C15 carbonyl group, to generate tricyclic compound **204** (a *des*-epoxy-caribenolide I stereoisomer) as an inseparable 6:1 mixture of anomers. From diene **204**, completion of the first total synthesis of caribenolide I stereoisomer then required the selective epoxidation of the C4–C5 alkene. The oxidation has not yet been described to date.

### 3.8. Haterumalides, Oocydin A, and Biselides

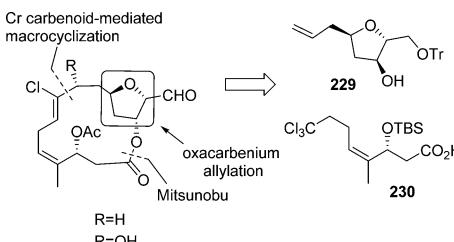
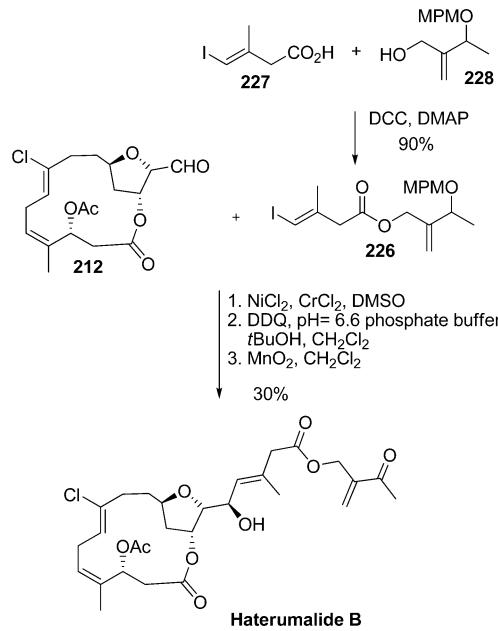
Haterumalides are a series of chlorinated macrolides isolated for the first time in 1999 from an Okinawan sea sponge of the species *Ircinia* and Okinawan ascidian *Lissoclinum* sp.<sup>110,111</sup> In isolation, haterumalide NA was demonstrated to be a strong cytotoxic

Scheme 45. Synthesis of Trisubstituted THF 217

Scheme 46. Total Synthesis of Haterumalide NA<sup>119a</sup>

agent against leukemia cell line (P338) and haterumalide B inhibited fertilized sea urchin eggs at micromolar concentration. Initial proposed stereochemistry was revised upon synthetic production of the proposed haterumalide NA.<sup>112</sup> In the same year, oocydin A, a haterumalide NA diastereomer, was isolated from the South American epiphyte *Serratia marcescens*.<sup>113</sup> Several years later the first biselides were isolated from the Okinawan ascidian *Didemnidae* sp. and after spectroscopic analysis, their structures were established as oxygenated analogs of haterumalides.<sup>114</sup> Researchers at the Fujisawa Pharmaceutical company isolated FR177391 from the soil bacterium *Serratia liquefaciens* and determined its structure as a diastereomer of haterumalide NA.<sup>115</sup> It is worth mentioning that some of the haterumalides were also isolated from the soil bacterium *Serratia plymuthica*.<sup>116</sup>

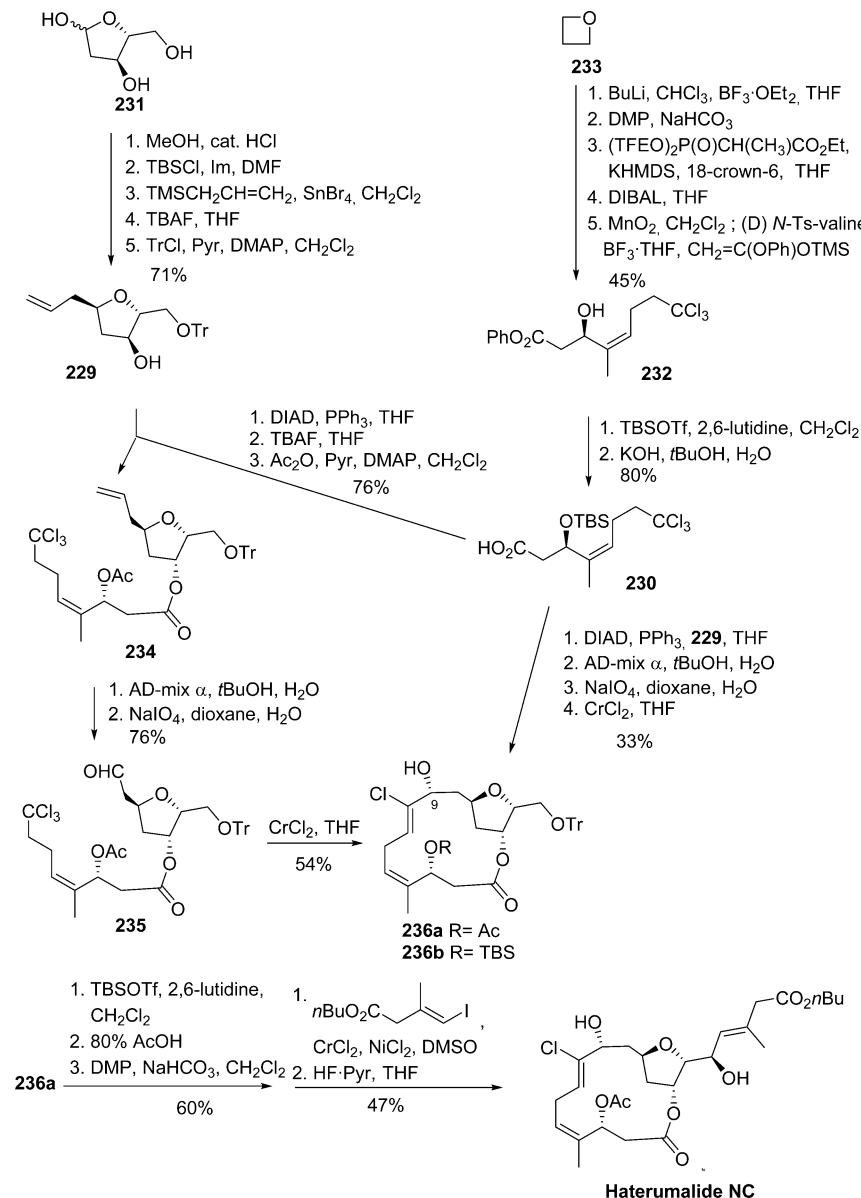
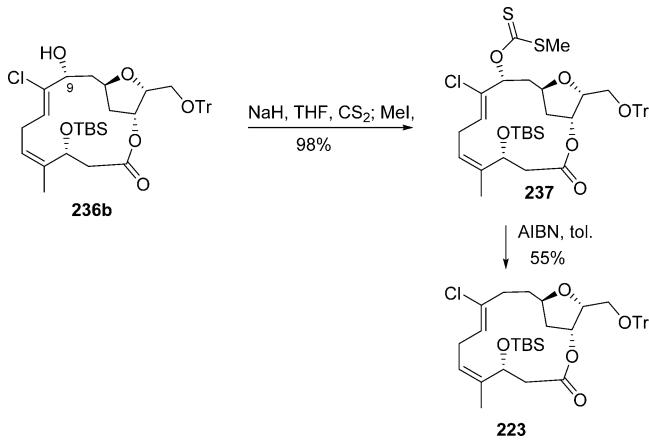
Spectroscopic data for haterumalide NA, oocydin A, and FR177391 seem to be identical, but there are differences in their reported optical rotations. Therefore, whether the bioactive

Scheme 47. Total Synthesis of Haterumalide B<sup>119b</sup>Figure 31. Retrosynthetic analysis of haterumalides NA and NC by Borhan.<sup>124</sup>

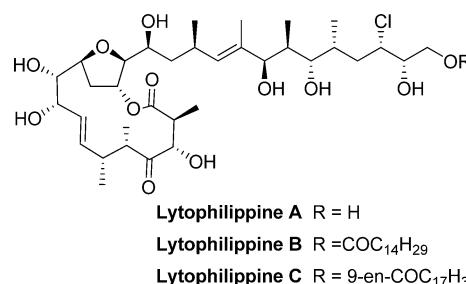
metabolite from *Serratia* species is the enantiomer of that derived from the sponge remains unclear. Finally, some advances have been made recently regarding the study of the oocydin A gene cluster and its biosynthesis from a four-plant associated enterobacteria.<sup>117</sup> From a structural point of view, these molecules display many interesting motifs in their complex frameworks, such as the THF ring bridged with a macrocyclic lactone, a Z chlorovinyl functionality, two allylic alcohols, and several stereogenic centers (Table 1). Helpful and complete reviews were published in 2007 and 2009<sup>118</sup> about the isolation, structures, bioactivities, and total synthesis of haterumalides, biselides, and related natural products. In our review, mention is made only to papers after Kigoshi's review.

The widespread family of haterumalides, biselides, oocydin and FR177391 has attracted attention from numerous groups of synthetic chemists who have developed different strategies for the synthesis of these compounds. The synthetic work carried out by Kigoshi and co-workers helped the structural reassignment<sup>112</sup> and later achieved the total synthesis of haterumalides NA and B using two different routes.<sup>119</sup> Recently, the same group has described their results toward the synthesis of biselides A and B.<sup>120</sup> Of interest are also the syntheses developed by Snider,<sup>121</sup> Hoye,<sup>122</sup> Roulland,<sup>123</sup> and Borhan.<sup>124</sup> Figures 27 and 28 summarize the retrosynthetic disconnections in the successful total syntheses of haterumalides and biselides.

The aldehyde itself is the common synthetic precursor in all the total syntheses. Different key strategic bonds have been

Scheme 48. Borhan's Total Synthesis of Haterumalide NC<sup>124</sup>Scheme 49. Formal Synthesis of Haterumalide NA<sup>124</sup>

chosen for the syntheses of the aldehydes: macrolactonization,<sup>112,119–124</sup> Suzuki-Miyaura coupling,<sup>112,119,123</sup> Stille cou-

Figure 32. Proposed structures for lytophilippines A–C.<sup>133</sup>

pling,<sup>121</sup> Reformatsky reaction,<sup>112</sup> haloallylation reaction,<sup>122</sup> or the use of chlorovinylidene chromium carbenoids.<sup>124</sup>

**3.8.1. Roulland's Synthesis of Oocydin A.**<sup>123</sup> The key step for Roulland's total synthesis of oocydin A was the Suzuki–Miyaura cross-coupling of the vinyl THF building block 205 and in situ obtained alkylboronate of the dichlorovinyl derivative 206,<sup>125</sup> followed by macrocyclization (Figure 29).

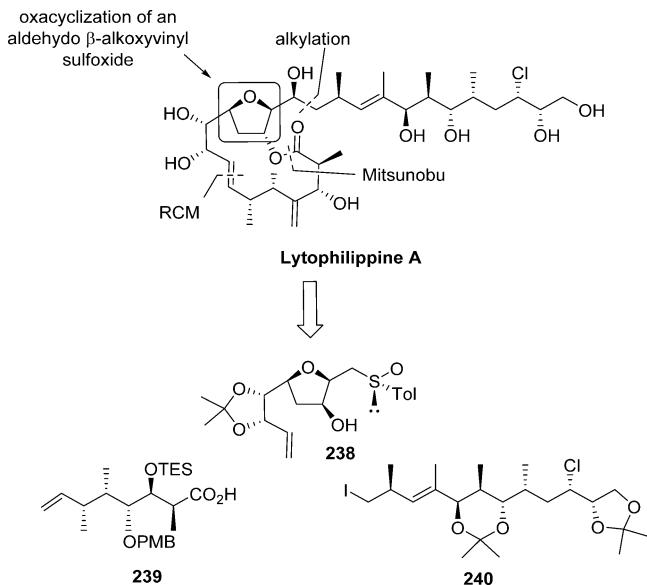
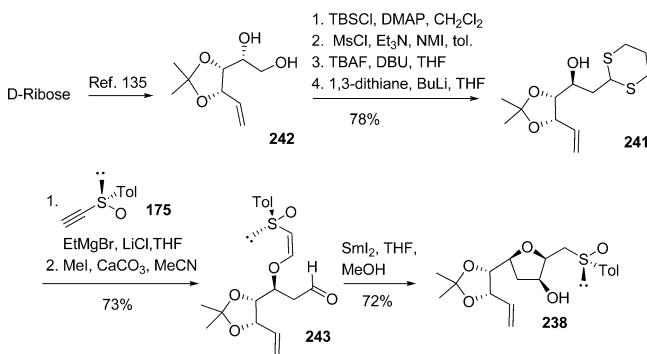


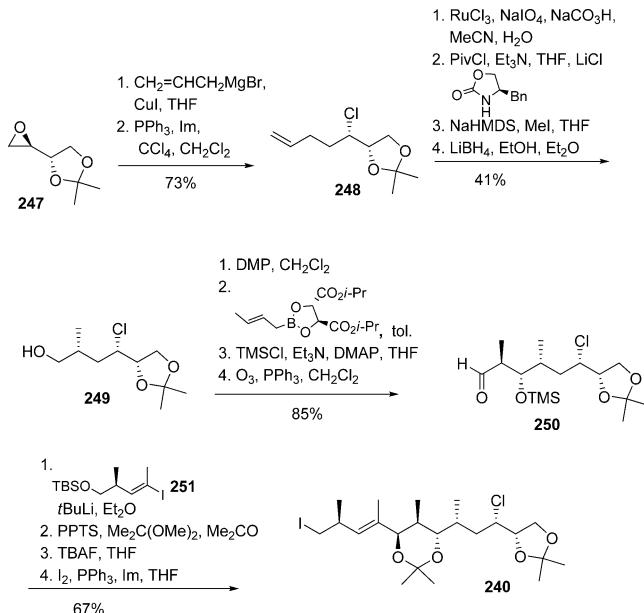
Figure 33. Proposed lytophilippine A retrosynthetic analysis by Lee.<sup>134</sup>

#### Scheme 50. Synthesis of Trisubstituted THF Building Block 238



The two synthetic precursors of oocydin A **205** and **206** were obtained as shown in Scheme 44.  $\alpha,\beta$ -Unsaturated lactone **207** was the precursor of dichloroalkene **206** by a sequence of eight synthetic steps performed with good yield. THF **205** was obtained in turn, as a C-5 epimeric mixture (96:4), via intramolecular cyclization of the alcohol over the  $\pi$ -allyl palladium of acetate **209**. Separation of the epimers (*SS*)-**205**

#### Scheme 52. Synthesis of Building Block 240

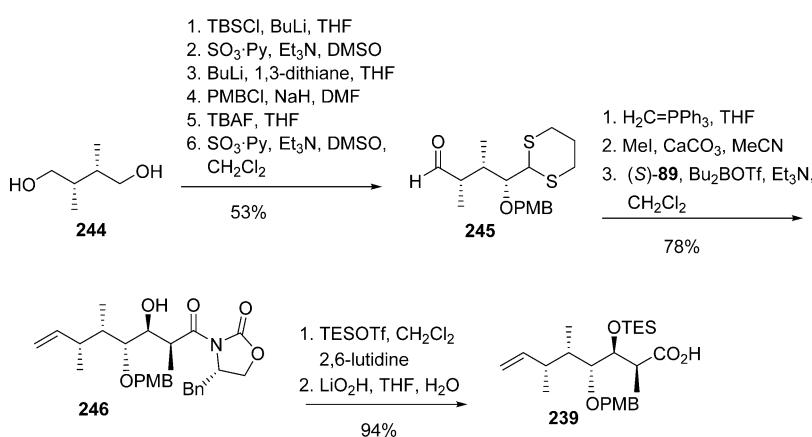


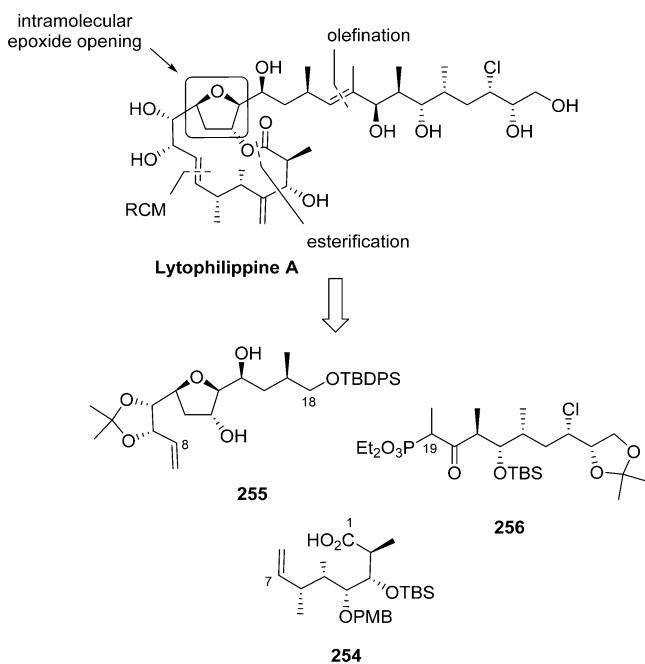
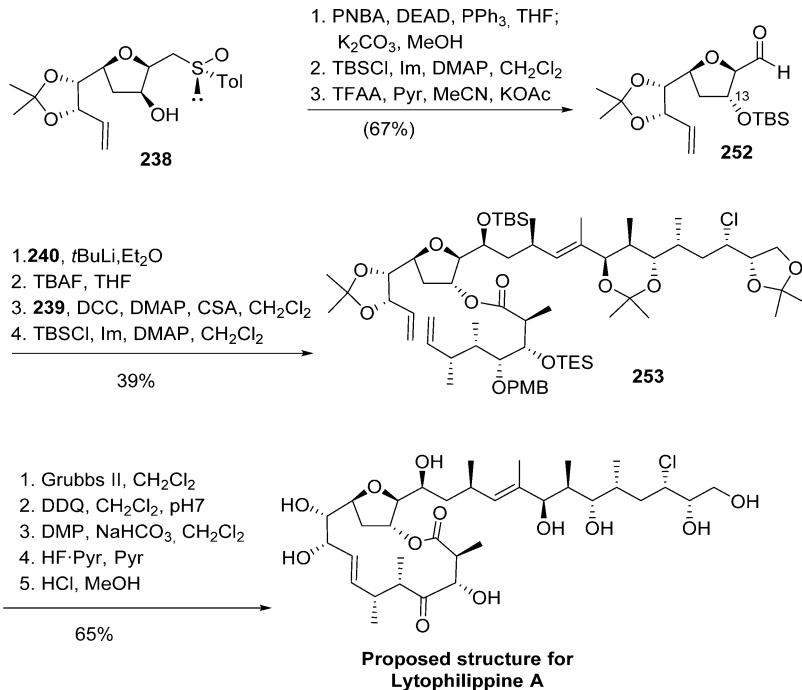
and (*SR*)-**205** was afforded after benzylation. Acetate **208** was prepared as an *E/Z* mixture (95:5) from the iododerivative **209** by copper-catalyzed substitution of iodide with vinylmagnesium chloride, followed by deprotection, and cross-metathesis reaction with allyl acetate using Grubbs II catalyst.

Cross-coupling of (*SS*)-**205** and the epimeric mixture of **206** gave a diester, which was saponified to seco acid **210**. Macrolactonization of **210** under Yamaguchi conditions, removal of TBS protecting group, separation of C3 epimers, and acetylation before *p*-methoxybenzyl (MPM) group removal and oxidation, afforded **211**; the unwanted C3 isomer was recycled under oxidation and Luche reduction to also obtain aldehyde **211**. The condensation of fragment **212**<sup>21</sup> with aldehyde **211** under Nozaki–Hiyama–Kishi (NHK)<sup>126</sup> conditions, furnished an alcohol, which upon final deprotection<sup>127</sup> of the masked carboxylic acid, supplied the target compound (+)-oocydin A, whose chemical data were identical to those of the naturally occurring compound.

**3.8.2. Kigoshi's Synthesis of Haterumalides NA and B.**<sup>119</sup> A parallel route for haterumalide NA was developed by H. Kigoshi and published in the same year as Roulland's synthesis. Kigoshi's total synthesis of haterumalide NA followed the same

#### Scheme 51. Synthesis of Building Block 239



Scheme 53. Synthesis of Proposed Structure for Lytophilippine A<sup>134</sup>Figure 34. Proposed lytophilippine A retrosynthetic analysis by Hiersemann.<sup>139</sup>

strategy as the one described by the same group when the reassignment of the stereochemistry was done.<sup>112</sup> The two precursor building blocks of the aldehyde were THF 213 with a masked formyl and vinyl iodide 214 (Figure 30).

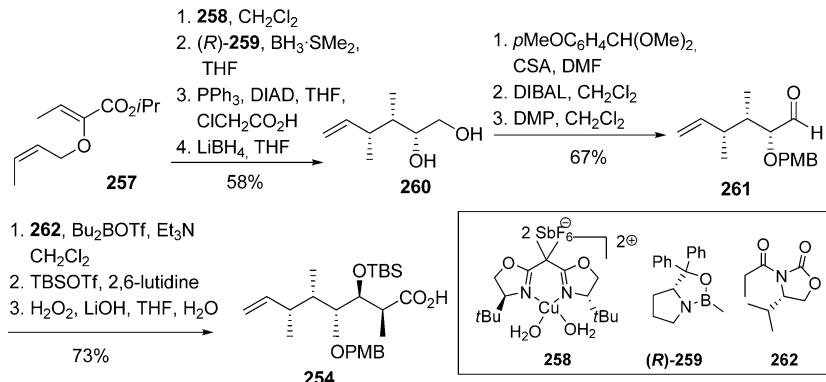
Known glycal 215<sup>128</sup> was protected as a 3,4-dimethoxybenzyl (DMPM) ether, followed by an oxymercuration–reduction sequence, and Wittig olefination to afford ester 216. Oxy-Michael cyclization, reduction of the ester, and elimination, provided the trisubstituted THF 217 with the proper configuration at the three stereocenters (Scheme 45).

Hydroboration of olefin 217 afforded compound 213. Suzuki–Miyaura cross-coupling between 213<sup>129</sup> and 214, followed by transformation of alkenyli silyl ether into the chloroolefin and acidic removal of THP protecting group, produced the acetonide intermediate 218. Oxidation of 218 to aldehyde, followed by modified HWE reaction with phosphonate 219 and diisobutylaluminium hydride (DIBAL) reduction, gave an allylic alcohol, which was oxidized to the conjugated aldehyde 220. The aldol reaction of 220 with isopropyl acetate, followed by protection of the resulting alcohol, yielded ester 221 as a diastereomeric mixture at C-3. A sequence of interchange of protecting groups, oxidative cleavage of the diol, protection of the resulting alcohol, removal of the DMPM protecting group, and hydrolysis of the isopropyl ester gave acid 222. Macro-lactonization by Yamaguchi conditions<sup>109</sup> gave the desired lactone 223. Removal of the TBS group in 223 permitted the separation of C-3 isomers by silica gel column chromatography. The undesired isomer was transformed into the desired isomer by oxidation and Luche reduction. The key intermediate 224 was obtained by acetylation of the hydroxyl group at C-3 and removal of the trityl group. 224 was converted into haterumalide NA by oxidation with Dess–Martin periodinane and Nozaki–Hiyama–Kishi coupling with iodide 225 to afford, after ester removal, haterumalide NA (Scheme 46).

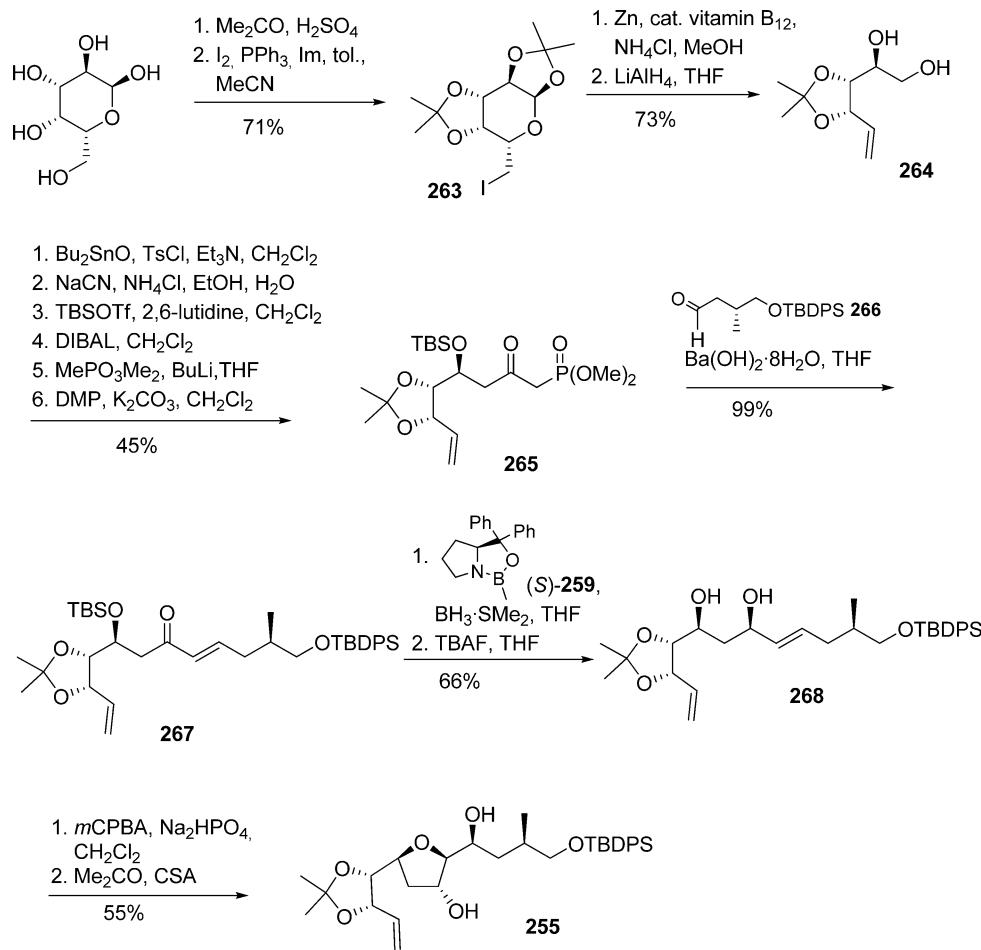
The relative stereochemistry of haterumalide B was established by synthesis.<sup>119b</sup> The synthetic process was performed using the racemic iodide 226 in the NHK coupling reaction with aldehyde 212 to give a diastereomeric mixture of alcohols (dr 5.5:1), followed by removal of the MPM group and subsequent selective oxidation of allylic alcohol with MnO<sub>2</sub> (Scheme 47). Iodide 226<sup>120</sup> was obtained by condensation of (*E*)-iodo-acid 227 with the monoprotected diallyldiol 228.<sup>130</sup>

**3.8.3. Borhan's Total Synthesis of Haterumalide NC and Formal Synthesis of Haterumalide NA.**<sup>124</sup> The total synthesis of haterumalide NC was accomplished via an unprecedented macrocyclization of an aldehyde and a chlorovinylidene chromium carbenoid to construct the C8–C9 bond.

Scheme 54. Synthesis of Building Block 254



Scheme 55. Synthesis of Building Block 255



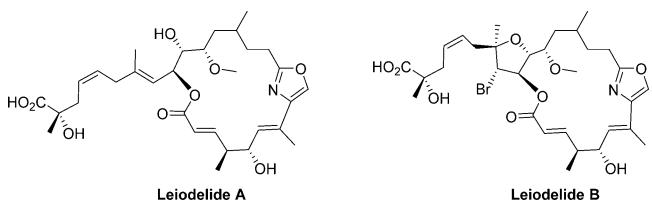
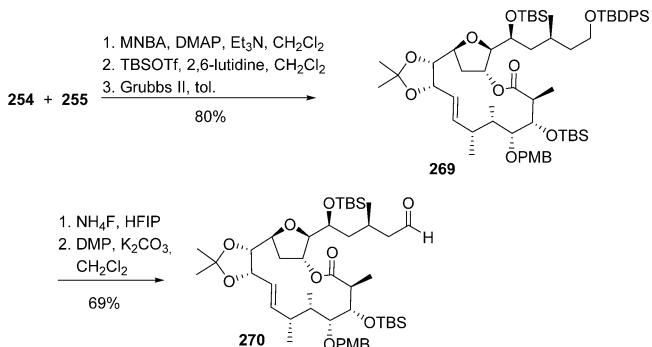
The retrosynthetic analysis shown in Figure 31 depicts two building blocks: trisubstituted THF 229 and trichloroacid 230. Deoxygenation of the latter product led to the formal synthesis of haterumalide NA.

Enantioselective synthesis of trisubstituted THF 229 was afforded from 2-deoxy-D-ribose 231 by convenient protection, allylation, deprotection, and final protection of the primary alcohol as a Tr ether to yield 229 (Scheme 48).

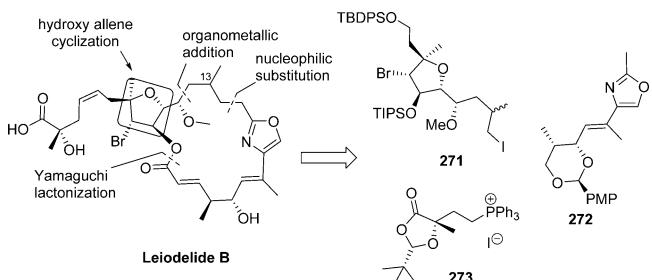
Preparation of protected hydroxyacid 232 began with the opening of the ring of oxetane 233 with the anion of chloroform, followed by oxidation of alcohol to aldehyde, which was immediately subjected to a Still Gennari olefination<sup>131</sup> to yield

the desired Z-acrylate. The ester function was reduced to the allylic alcohol. Subsequent oxidation to the unsaturated aldehyde and subsequent asymmetric Mukaiyama aldol reaction<sup>132</sup> furnished 232. Acid 230 was obtained by protection of the secondary alcohol as a TBS ether and phenyl ester hydrolysis. Mitsunobu esterification of alcohol 229 and carboxylic acid 230 yielded, after exchange of protecting groups, ester 234. Selective dihydroxylation and oxidation of the terminal alkene afforded aldehyde 235 ready for the intramolecular CrCl<sub>2</sub>-mediated coupling that furnished 236a. The stereochemistry of the newly generated C9 center matched the stereochemistry of the natural product, haterumalide NC. The final installation of the side chain

**Scheme 56. Synthesis of Lactone 270 Containing the Macrocyclic Core of Lytophilippine A<sup>139</sup>**



**Figure 35.** Proposed structures of leiodelides A and B.<sup>141</sup>



**Figure 36.** Proposed leiodelide B retrosynthetic analysis by Fürstner.<sup>142</sup>

of haterumalide NC was prepared as illustrated in Scheme 48 in a fashion similar to that reported in prior syntheses for haterumalide NA.<sup>112</sup>

Analogue compound 236b was subjected to deoxygenation of C9-OH, obtaining 223, an advanced intermediate of the synthesis of haterumalide NA. This was produced via radical-induced fragmentation of xanthate 237 with azobis(isobutyro)-nitrile (AIBN) in refluxing toluene as shown in Scheme 49.

### 3.9. Lytophilippines<sup>133</sup>

Lytophilippines A–C are chloro-containing macrolactones isolated from the Red Sea hydroid *Lytocarpus philippinus* in 2004 by Řezanka and co-workers. Lytophilippines A–C showed positive results in the crown gall tumor inhibition test and brine shrimp toxicity assay and demonstrated antibacterial activity against *Escherichia coli*, but were inactive against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*.

The structure of lytophilippines was elucidated by spectroscopic methods and by chemical degradation (Figure 32). The proposed structure for these compounds was based on a 14-membered macrolactone bridged with a trisubstituted THF containing three methyl ramifications, an *E*-double bond, a ketone and three hydroxyl groups. In addition, lytophilippines possess a chloro-unsaturated-polyhydroxy side chain. The difference between the three members of this group lies in the fatty acid present in lytophilippines B and C. However, further synthetic studies of lytophilippine A claimed that the proposed

structure did not correspond to that of the natural compound and that further work should focus on elucidating the correct structure.<sup>134</sup>

### 3.9.1. Lee's Synthesis of Proposed Lytophilippine A.<sup>134</sup>

The work presented by Lee and co-workers in 2011 established, on the basis of total synthesis, that the proposed structure for lytophilippine A was not matching that of the natural product. Its retrosynthetic analysis divided the molecule into three building blocks, trisubstituted THF derivative 238, carboxylic acid 239, and side chain 240 (Figure 33).

Enantioselective transformation of D-ribose into alcohol 241 was afforded by protection as a 2,3-acetonide, followed by Wittig olefination to obtain diol 242.<sup>135</sup> Diol 242 was then converted to the corresponding epoxide and finally reacted with 2-lithio-1,3-dithiane, to give 241. Oxiaddition of 241 to alkynyl sulfoxide 175 and hydrolysis of the dithiane unit provided aldehyde 243 (Scheme 50). 5-Exo cyclization of 243 with SmI<sub>2</sub> led to 3-hydroxyoxolane 238 (dr 9:1).

Monoprotection and oxidation of diol 244<sup>136</sup> furnished an aldehyde that was reacted with 2-lithio-1,3-dithiane with moderate stereocontrol (dr 4.6:1). The resulting alcohol was protected as PMB ether. Further deprotection of the TBS and oxidation provided aldehyde 245. Wittig olefination and dithiane hydrolysis provided an aldehyde ready to be reacted with boron enolate to furnish compound 246 in good yield and stereoselectivity (dr > 19:1). Acid 239 was obtained by TES protection and removal of the chiral inductor (Scheme 51).

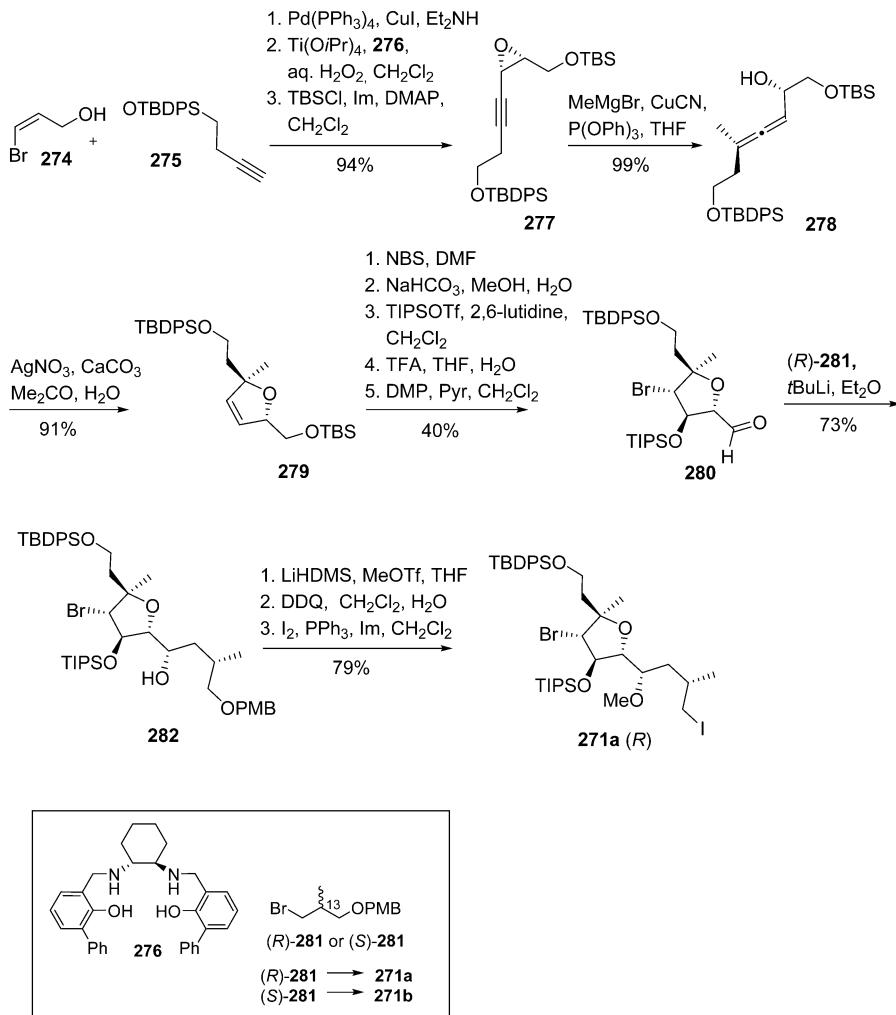
Side chain 240 was obtained starting from the known epoxide 247<sup>137</sup> by reaction with allylmagnesium bromide, followed by substitution of the hydroxyl with the chloride, to give 248. The terminal double bond was oxidized to the acid. Stereoselective  $\alpha$ -methylation via Evans oxazolidinone induction and reduction with lithium borohydride afforded alcohol 249. Aldehyde 250 was obtained by oxidation of alcohol 249, Roush croylation (dr > 19:1), protection of the obtained alcohol as a TMS ether, and reductive ozonolysis. Building block 240 was obtained by addition of the vinyl lithium reagent prepared from known vinyl iodide 251,<sup>138</sup> followed by acetonide formation, TBS ether cleavage and iodide substitution of the resulting terminal hydroxyl group (Scheme 52).

Condensation of building blocks 238 and 239 by a Mitsunobu reaction, followed by ring closing metathesis, and introduction of side chain 240, furnished protected lytophilippine A with only a 10% yield and low diastereoselectivity (dr 4:1).

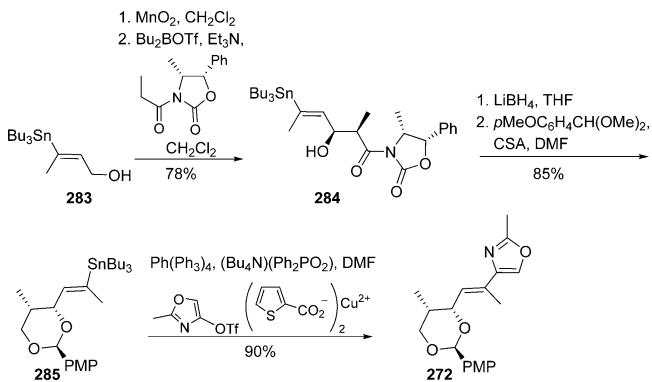
An alternative route, based on the introduction of the side chain before macrocyclization, was developed starting from THF 238 (Scheme 53). Inversion of the stereochemistry at the C-13 via a Mitsunobu reaction, followed by protection of the hydroxyl group as a TBS ether, and subsequent Pummerer rearrangement, led to formyl hydroxyoxolane 252. Side chain 240 was introduced at this stage with moderate yield and diastereoselectivity (dr 1.6:1). Deprotection of the TBS ether provided a diol that was converted to diene 253 by condensation with acid 239 and TBS ether formation of the free alcohol. A single macrolactone was then obtained via RCM, removal of the PMB protecting group, oxidation of the free alcohol with Dess–Martin periodinane (DMP), and final elimination of the remaining protecting groups (Scheme 53).

Dramatic <sup>1</sup>H and <sup>13</sup>C NMR differences between the isolated lytophilippine A and the synthesized product led to the conclusion that the structure proposed by Řezanka and co-workers was not adequate.

Scheme 57. Synthesis of the Northern Sector of Proposed Leiodelide B

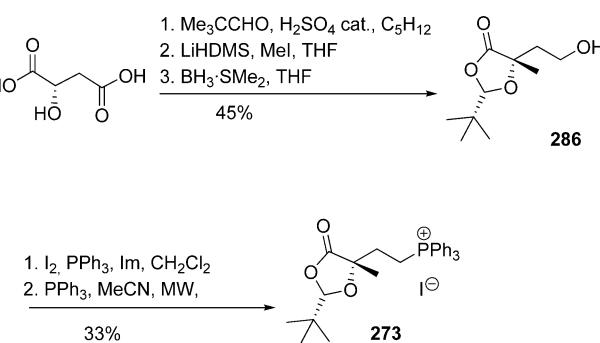


Scheme 58. Synthesis of Oxazole Building Block 272



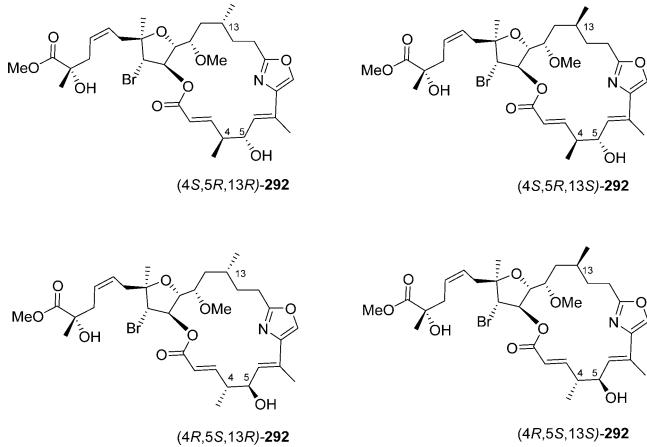
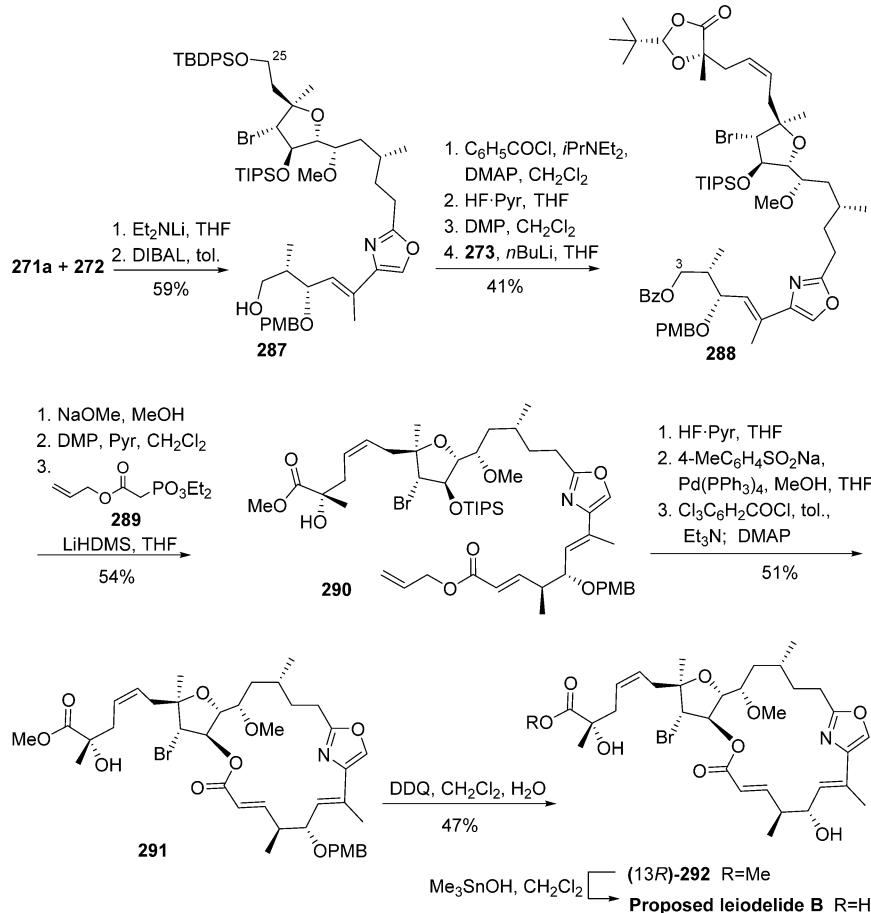
**3.9.2. Hiersemann's Synthesis of C1–C18 Building Block of Proposed Lytophilippine A.<sup>139</sup>** In 2010 Hiersemann and co-workers described the synthesis of the C1–C18 building block. The synthesis of this fragment is introduced in this review because it is an advanced building block of the natural product containing the macrolactone and lacking only the side chain introduction. Its retrosynthetic analysis shown in Figure 34 proposes three building blocks: the C1–C7 segment 254, the C8–C18 segment 255, and the appropriate C19–C27 segment 256.

Scheme 59. Enantioselective Synthesis of Phosphonium Iodide 273

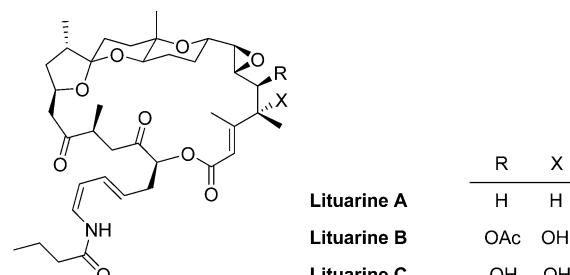


Building block 254 was synthesized starting from allyl vinyl ether 257 by a reaction sequence based on asymmetric Gosteli–Claisen rearrangement, configuration inversion, and further reduction to provide diol 260. Transacetalization with *p*-methoxybenzaldehyde dimethyl acetal, followed by reductive cleavage, and oxidation of the resulting primary alcohol gave aldehyde 261. Diastereoselective Evans aldol reaction, protection of the hydroxyl group, and removal of the chiral auxiliary led to fragment 254 (Scheme 54).

Building block 255 was synthesized starting from D-galactose by bis(acetonide) protection, followed by substitution of the

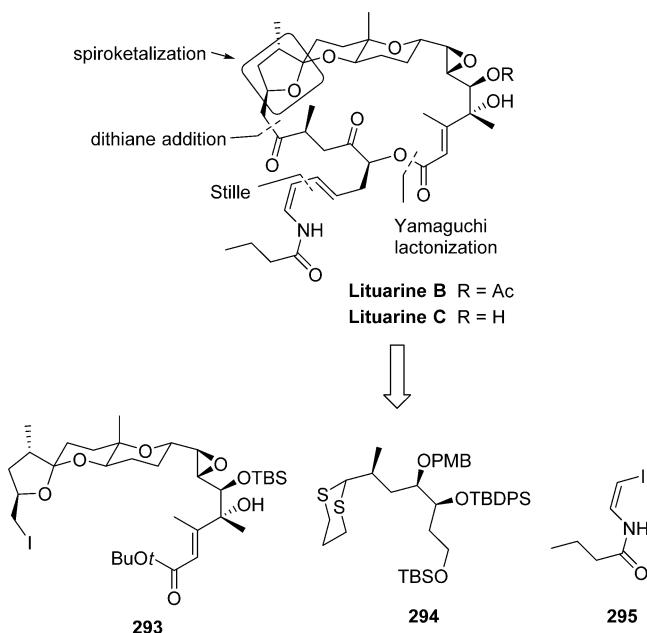
Scheme 60. Synthesis of Proposed Leiodelide B<sup>142</sup>Figure 37. Four stereoisomers of leiodelide B.<sup>142</sup>

remaining hydroxyl group by iodide to obtain **263**.  $\beta$ -Elimination led to a cyclic hemiacetal that was reduced to diol **264**. The primary alcohol was subjected to a Kolbe nitrile synthesis, and the secondary hydroxyl group was protected as TBS ether. Reduction of the nitrile was followed by transformation of the resulting aldehyde into  $\beta$ -keto phosphonate **265** for HWE reaction with known aldehyde **266**<sup>140</sup> to give enone **267**. Compound **267** containing the C8–C18 fragment of lytophilipine A was reduced at the enone carbonyl with a dr > 95:5, and chemoselective removal of the silyl protecting group delivered diol **268**. Diastereoselective epoxidation of the double bond was

Figure 38. Proposed structures of lituarines A–C.<sup>147</sup>

not possible in reasonable diastereomeric ratios, and thus the best conditions were obtained with 3-chloroperoxybenzoic acid (CPBA) to give a 3:2 mixture of the corresponding diastereomeric oxiranes in 95%. Finally, chromatographic separation was mandatory after diastereomeric differentiating acetalization of the mixture with CSA to obtain the desired enantiomerically pure segment **255** (Scheme S5).

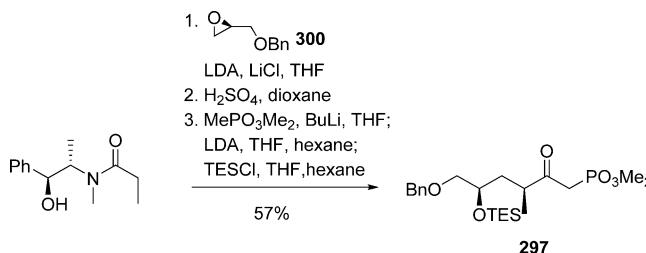
The targeted macrolide was formed by regioselective ester bond formation between acid **254** and alcohol **255**, followed by subsequent RCM, obtaining **269**. Selective removal of the primary TBDPS protecting group in front of the secondary TBS ethers was achieved with NH<sub>4</sub>F in hexafluoroisopropanol (HFIP), and oxidation of the resulting alcohol furnished aldehyde **270** containing the macrocyclic core of lytophilipine A (Scheme S6). Authors claim the preparation of the side chain is under construction for introduction.

Figure 39. Retrosynthetic analysis of lituarines B and C by Smith III.<sup>150</sup>

### 3.10. Leiodelides<sup>141</sup>

Leiodelides A and B (also named leiodolides A and B) are cytotoxic macrocyclic lactones extracted from a sponge, identified as a member of the rare genus *Leiodermatium* (order Lithistida, Azoricidae family) and collected at a depth of 720 feet near Uchelbeluu Reef in Palau. Leiodelide B represents the first member of a new class of 19-membered ring macrolides and incorporates several unique functional groups including a pentasubstituted THF with four stereocenters, a conjugated oxazole ring, a bromine substituent, and a  $\alpha$ -hydroxy- $\alpha$ -methyl carboxylic acid side-chain terminus. Leiodelide B was found to be active against HCT 116 human colon carcinoma. The structure of leiodelides A and B was established by spectroscopic analysis, chemical modification, and degradation. The relative and absolute stereochemistries at most chiral centers were assigned on detailed interpretation of spectroscopic data, coupled with chemical degradation and application of the modified Mosher ester method. Structure of leiodelide B was established by comparison of spectral data for leiodelide B with data for leiodelide A, suggesting that leiodelide B was a related macrolide (Figure 35). The authors proposed a bromonium ion induced formation of the THF ether bridge in leiodelide B from leiodelide A. Synthetic work on this natural product concluded that the proposed structure is in error and should be revised.<sup>142</sup>

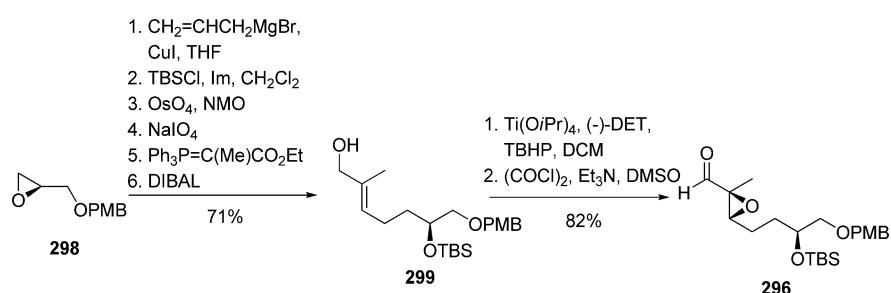
**3.10.1. Fürstner's Synthesis of Proposed Leiodelide B.**<sup>142</sup> Only one synthetic approach to leiodelide B has been

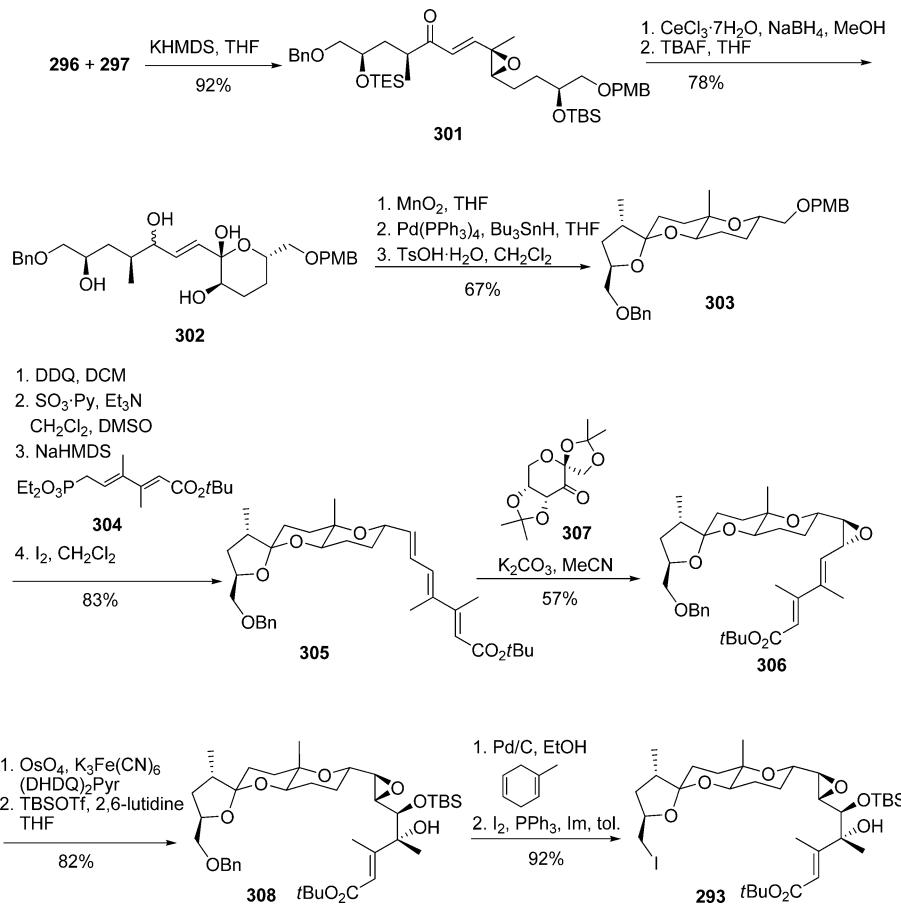
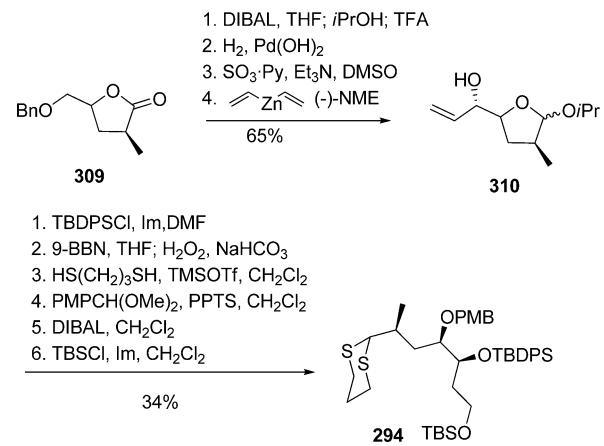
Scheme 62. Synthesis of Phosphonate 297<sup>149a</sup>

published until now by Fürstner's group. Their synthesis was based on the disconnections shown in Figure 36, considering the union of building blocks 271, 272, and 273. Because the configuration of C-13 stereocenter was not established, two building blocks with the precursor of (*R*)-C13 and (*S*)-C13 were tested in this work. Of interest in this synthesis is the enantioselective preparation of the pentasubstituted THF moiety by Ag-induced cyclization of a  $\alpha$ -allenol to give a DHF ring with the proper configuration at positions 2 and 5 of the ring. The subsequent step was stereoselective bromo-esterification of the ring double bond to the proper pentasubstituted THF.

The polysubstituted THF 271 containing four stereocenters was afforded starting from the allylic alcohol 274 and alkyne 275 as building blocks for the construction of 277 (Scheme 57). This epoxide was transformed into the axially chiral allene intermediate 278 by conjugate addition of the reagent derived from  $\text{MeMgBr}$ , a stoichiometric amount of  $\text{CuCN}$ , and  $\text{P}(\text{OPh})_3$ . Subsequent  $\text{AgNO}_3$ -induced cyclization of allenol 278 to DHF 279,<sup>143</sup> bromo-esterification, protecting-group manipulations, and oxidation gave aldehyde 280. After chain extension with the building block (*R*)-281<sup>144</sup> by metal–halogen exchange with  $t\text{BuLi}$  in  $\text{Et}_2\text{O}$ , followed by transmetalation with freshly prepared  $\text{MgBr}_2$ , epimeric alcohols at C15 were obtained in 73% yield in a 1:4 ratio. The minor isomer could be recycled by oxidation/Luche reduction to 282. Subsequent *O*-methylation, oxidative cleavage of the PMB ether, followed by conversion of the resulting alcohol into the corresponding iodide 271a, completed the preparation of the northern sector of proposed leiodelide B in one of the two possible diastereomeric forms. Epimer 271b was obtained in a similar way using (*S*)-281 for the reaction with aldehyde 280.

Oxazole building block 272 was obtained as indicated in Scheme 58 from stannylated alcohol 283. Oxidation of 283 to the aldehyde, which was then subjected to an Evans boron-aldol reaction,<sup>145</sup> yielded 284. Reductive cleavage of the auxiliary and protection of the resulting diol as acetal gave product 285, which was then prepared for cross-coupling with the known 2-methyl-oxazol-4-yl triflate<sup>146</sup> to finally give building block 272.

Scheme 61. Synthesis of Aldehyde 296.<sup>149a</sup>

Scheme 63. Synthesis of Building Block 293<sup>149</sup>Scheme 64. Synthesis of Building Block 294<sup>150</sup>

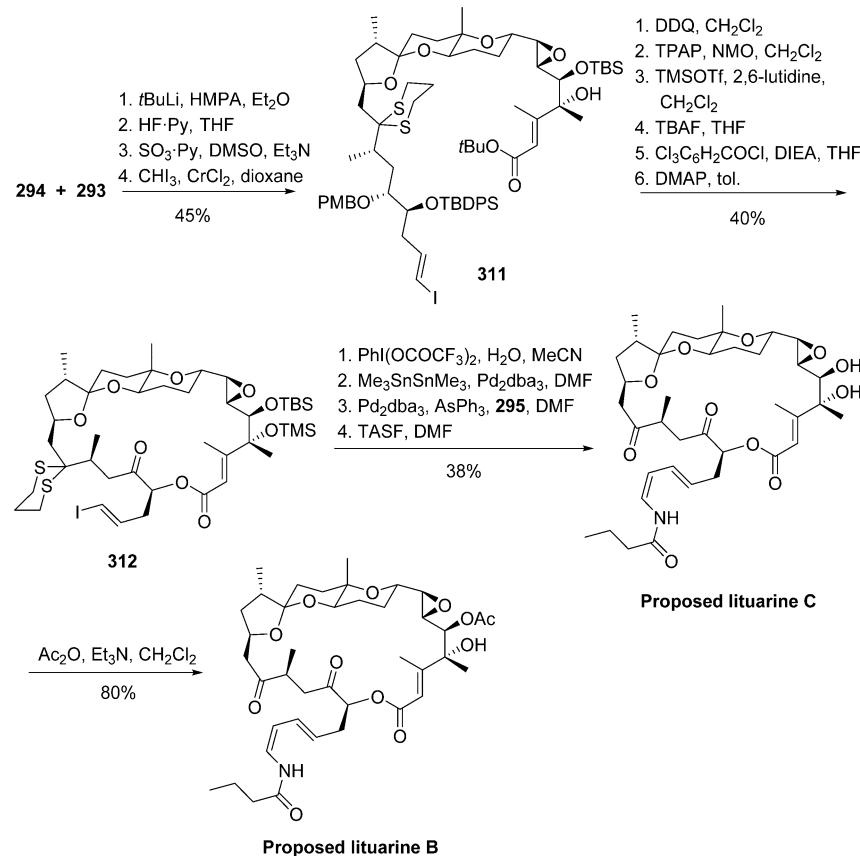
The third building block 273 was prepared from L-malic acid by a reaction sequence based on the simultaneous protection of the acid and the  $\alpha$ -hydroxy groups, followed by diastereoselective  $\alpha$ -methylation and reduction, to give alcohol 286. Transformation of 286 into 273 was performed using the normal procedures (Scheme 59).

The connection of the three building blocks started with the alkylation of 272 with iodide 271a using Et<sub>2</sub>NLi as the optimal base. Reductive opening of the PMP acetal released primary alcohol 287. Further exploratory macrocyclization studies showed that the installation of the side chain should have been

given priority, and consequently macrocyclization was depicted as the final step of the synthesis (Scheme 60).

Protection of 287 as benzoate ester, selective removal of the TBDPS ether at C25 and oxidation, followed by reaction of the resulting aldehyde with the ylide derived from 273, gave alkene 288 in good yield. Benzoate at C3 was removed and the cyclic acetal was converted at the acid terminus into the corresponding methyl ester. DMP oxidation of the primary alcohol at C3, followed by a HWE olefination with phosphonate 289, gave product 290, which comprised the complete carbon backbone of leiodelide B. Selective TIPS deprotection and Pd-catalyzed cleavage of the allyl ester, followed by Yamaguchi lactonization<sup>109</sup> of the resulting seco acid, gave the desired macrocycle 291. Removal of the residual PMB protecting group completed the total synthesis of the putative leiodelide B methyl ester (13R)-292. The epimeric product (13S)-292 was prepared analogously from 271b and 272. Authors describe that neither of the synthesized methyl esters matched the reported data of leiodelide B, with small but non-negligible deviation being scattered over the entire framework. The free acid (13R)-leiodelide B obtained by saponification of (13R)-292 with excess Me<sub>3</sub>SnOH showed important differences in the chemical shifts in the C2–C9 region of the molecule. To check the originally assigned configuration of 4S and 5R, enantiomeric oxazole building block ent-272 was prepared (Figure 37).

The four isomers (Figure 37) were synthesized; however, none of them reproduced the published data of the natural product well enough to claim identity.

Scheme 65. Synthesis of Proposed Lituarines B and C<sup>150</sup>

### 3.11. Lituarines<sup>147</sup>

Lituarines A–C were isolated from the New Caledonian sea pen, *Litaria australasiae* and exhibited antifungal, antineoplastic, and significant cytotoxicities. The IC<sub>50</sub> of lituarines A–C toward KB cells are 3.7–5.0 nM, 1.0–2.0 nM, 5.0–6.0 nM, respectively. Their relative stereochemistry and connectivity was described based on spectroscopic techniques, although absolute stereochemistry remains unknown. Unusual structural features of these natural products are the C(8–18) tricyclic core, based on [6,5] spiroketal and *trans*-bridged tetrahydropyran rings. In addition, they possess an exocyclic dienamide moiety (Figure 38). Robertson<sup>148</sup> worked on the synthesis of these complex compounds, achieving partial synthesis of the proposed structures. Smith III<sup>149,150</sup> achieved the total synthesis of the proposed structures of lituarines B and C and upon comparison of synthetic, and isolated compounds stated that the proposed stereochemistry was erroneous.

**3.11.1. Smith III's Synthesis of Proposed Lituarines B and C.<sup>149,150</sup>** The retrosynthetic analysis of lituarines B and C gave three building blocks: the most challenging tetracyclic core fragment 293, dithiane fragment 294, and iodoenamide 295 (Figure 39).

Fragment 293 was synthesized from aldehyde 296 and phosphonate 297.<sup>149a</sup> Epoxide 298 was converted to alcohol 299 through the following reaction sequence: copper catalyzed allylmagnesium bromide addition, protection of the resulting alcohol, terminal double bond oxidative cleavage, Wittig olefination, and reduction. Asymmetric Sharpless epoxidation and oxidation of the alcohol resulted in aldehyde 296 (Scheme 61).

Phosphonate 297 was obtained by alkylation of (S,S)-pseudoephedrine amide with epoxide 300<sup>151</sup> and acid mediated cyclization, followed by treatment with the lithium anion of dimethyl methanephosphonate and in situ protection as a TES ether (Scheme 62).

HWE olefination between 296 and 297 produced 301 with exclusive *E*-selectivity. Luche reduction and treatment with TBAF afforded self-cyclized product 302. Oxidation of 302 to give a conjugated ketone, followed by double bond reduction and acetalization with *p*-toluenesulfonic acid, afforded tricyclic core 303 in high yield and stereocontrol.<sup>149a</sup> Transformation of 303 into unsaturated ester 305 was performed via oxidative cleavage of the PMB protecting group, oxidation to the aldehyde, HWE olefination with phosphonate 304, and equilibration with iodine of the obtained mixture of trienes. Epoxide 306 was obtained by Shi's protocol using 307 as a catalyst. Asymmetric dihydroxylation of 306 and protection of the less hindered hydroxyl afforded 308.<sup>149b</sup> Removal of PMB protecting group and iodine substitution gave fragment 293 (Scheme 63).

Dithiane building block 294 was obtained from known lactone 309,<sup>152</sup> upon reduction, removal the benzyl ether, oxidation to aldehyde, and addition of vinyl zinc to obtain alcohol 310 (Scheme 64). Subsequent protection, hydroboration, TMSOTf mediated dithiane formation, and orthogonal protection of the free hydroxyl groups gave fragment 294.

Reaction of lithium derivative of 294 and iodide 293 was achieved in a reasonable good yield (Scheme 65). Removal of the TBS ether protecting group, oxidation to the aldehyde, and Takai olefination led to vinyl iodide 311. The next steps included the removal or interchange of protecting groups, oxidation, and cyclization under Yamaguchi conditions to give macrolactone

312. Removal of the dithiane, installation of the stannane, Stille coupling with iodoenamide **295**,<sup>150</sup> and subsequent removal of silicon protecting groups afforded proposed lituarine C. Selective acetylation of proposed lituarine C led to proposed lituarine B.

With both synthetic targets in hand, the authors realize that neither of them matched the described natural products.

#### 4. BIOACTIVITY

During the past few years, bioguided isolation of marine organisms furnished macrolides with important biological activities. Most of them are cytotoxic compounds; however, other interesting activities, most significantly antimicrobial and antibacterial activities, have been found as well.

Oscillariolide,<sup>26</sup> phormidolide,<sup>27</sup> and the family of the lytophilippines<sup>133</sup> showed potential antitumoral activity, although more assays should be done to assess their value as anticancer leads. Formosalides,<sup>31</sup> amphidinolides,<sup>39</sup> haterumalides,<sup>110,111,113,114,116,119b</sup> amphidinolactone B,<sup>29</sup> and leiodelide B<sup>141</sup> showed moderate to good antitumoral activity against a variety of cancer cell lines such as murine leukemia cells, human epidermoid carcinoma cells, human colon cancer cells, or human breast cancer cells. However, the more active compounds among the ones described in this review were caribenolide I,<sup>97</sup> amphidinolide C,<sup>39</sup> and the lituarines,<sup>147</sup> which showed high antitumoral activity against HCT 116 cells (caribenolide I), L1210 cells (amphidinolide C1), and KB cells (lituarines). As mentioned before, antimicrobial and antibacterial activities are also found in some THF-containing macrolides, such as in lytophilippines, haterumalides, and their related family compounds.<sup>115a,116a</sup>

A rational comparison of bioactivity among the families described in this review would be ineffective due to the diversity of biological tests and the different experimental conditions published until now for their evaluation.

#### 5. CONCLUSIONS

Our knowledge and tools to synthesize natural products are far from nature's ability to create these same complex compounds with high efficiency and selectivity, through the combination of evolution and thermodynamics. Marine macrolides are only an example of these elaborate natural products which have high pharmacological potential. Nevertheless, isolation from the natural sources often furnishes small amounts of the product, which makes the determination of the structure and the preparation of enough sample of compounds for clinical trials a dead end for their development. In this context, the total synthesis of natural products is the more reasonable and useful tool. Furthermore, synthesis of compounds such as those described in this work, with complex structures and a high number of stereocenters, requires the development of new reagents as well as full synthetic strategies, which are being further applied to the synthesis of other complex compounds. Thus, the continued efforts that several groups are putting into marine research sciences should fuel the identification of new chemical entities as new active pharmaceutical ingredients and the discovery of new synthetic tools, which will be applied to the synthesis of a broad range of molecules. All these advances should translate into new drug families in the near future, which will face unmet therapeutic indications and needs.

#### AUTHOR INFORMATION

##### Corresponding Author

\*E-mail: mercedes.alvarez@irbbarcelona.org.

##### Notes

The authors declare no competing financial interest.

##### Biographies



Adriana Lorente was born in Barcelona in 1985. She studied chemistry at the University of Barcelona, where she received her B.S. degree in 2008, and her M.S. degree in 2009 under the supervision of Dr. Fèlix Urpí and Dr. Pedro Romea. Adriana is currently a doctoral student at the Institute for Research in Biomedicine at the Barcelona Science Park under the supervision of Dr. Mercedes Álvarez and Dr. Fernando Albericio. Her research interests include the development of new methodologies for synthesis of natural products as well as its structure determination.



Janire Lamariano-Merketegi was born in 1985 in Antzuola. In 2008, she got her B.S. degree in chemistry at the University of Basque Country (UPV/EHU). After, she moved to Complutense University of Madrid (UCM) where she received her M.S. degree under the supervision of Dr. Carmen Avendaño. In 2010, she joined for one year the Janssen-Cilag pharmaceutical division in Toledo. At this time, she is a doctoral student at the Institute for Research in Biomedicine at the Barcelona Science Park under the supervision of Dr. Mercedes Álvarez and Dr. Fernando Albericio. Her research interests are focused on stereoselective synthesis of polyketide chains present in marine natural products.



Professor Fernando Albericio received his Ph.D. in Chemistry at the University of Barcelona, in 1981. Following postdoctoral work at Tufts University (Boston), at the Université d'Aix-Marseille (France), and at the University of Minnesota (1981–1984), he returned to Barcelona as Associate Professor. During the 1992–1994 period, he was Director of Peptide Research with Millipore/Waters at Boston. He rejoined the University of Barcelona, where he was promoted to Professor in 1995. He participated in the foundation of the Barcelona Science Park, taking on different responsibilities, and served as General Director of the park (2005–2012). Nowadays, he is holding various appointments: Professor at the University of Barcelona, Research Professor at the University of KwaZulu-Natal (Durban, South Africa), and Group Leader at the Institute for Research in Biomedicine. Professor Albericio is deeply involved in the development of the third mission of the University, the transference of knowledge and technology to the society. He has founded several biotech companies and is acting on the board of directors of several foundations and companies. Furthermore, he is a consultant for several companies in the chemical and pharmaceutical areas. Professor Albericio's major research interests cover practically all aspects of peptide synthesis and combinatorial chemistry methodologies, as well as synthesis of peptides and small molecules with therapeutic activities. He has published over 600 papers, several review articles, more than 40 patents, and co-author of three books. He is editor of several scientific journals and acting on the editorial board of several others. Recently, Professor Albericio was honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires (Argentina) and the Vincent du Vigneaud Award (American Peptide Society).



Professor Mercedes Álvarez received her Ph.D. in chemistry at the University of Barcelona under the supervision of Prof. Ricardo Granados. She has a permanent position in the Faculty of Pharmacy of the University of Barcelona, as Associate Professor first and later as full Professor. In 1990 she spent a sabbatical year in The Manchester University working with Prof. John A. Joule. After that period a long

collaboration began between Manchester and Barcelona Universities for developing new procedures for the synthesis of marine natural products with polyheterocyclic structure and biological activities. In 2002, she was invited to join with the group led by Prof. Fernando Albericio and to move her research group to the Science Park of Barcelona. Currently, she holds a double appointment as Professor at the University of Barcelona and Researcher at the Institute for Research in Biomedicine in the Barcelona Science Park (IRB). Her major research interests cover synthesis of natural products, heterocyclic chemistry, combinatorial chemistry and solid phase methodology, as well as synthesis of small molecules with therapeutic activity.

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## ABBREVIATIONS

Ac	acetyl
ACP	acyl carrier protein
AIBN	azobis(isobutyro)nitride
AMO	alkene mono-oxygenase
AT	acyl transferase
BAIB	bis(acetate)phenyliodine
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOM	benzoyloxymethyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cat	catalytic
CM	cross metathesis
CoA	coenzyme A
Cp	cyclopentyl
CPBA	3-chloroperoxybenzoic acid
CSA	camphorsulfonic acid or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonic acid
Cy	cyclohexyl
dba	di(benzylidene)acetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEBS	6-deoxyerythronolide B synthase
DET	diethyl tartrate
DH	dehydratase
DHF	dihydrofuran
DHP	dihydropyran
(DHQ) <sub>2</sub> PHAL	1,4-bis(9- <i>o</i> -dihydroquininyl)phthalazine
(DHQD) <sub>2</sub> AQN	1,4-bis(dihydroquinidine)anthraquinone
(DHQD) <sub>2</sub> Pyr	1,4-bis(9- <i>o</i> -dihydroquininyl)pyridine
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide

DMP	Dess Martin periodinane or 1,1,1-tris-(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1 <i>H</i> )-one	PNBA	<i>p</i> -nitrobenzoic acid
DMPM	3,4-dimethoxybenzyl	PPTS	pyridinium <i>p</i> -toluenesulfonate
DMPS	dimethylphenylsilyl	PTSH	1-phenyltetrazole-5-sulfonic acid
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidinone	Pyr	pyridine
DMSO	dimethyl sulfoxide	RCM	ring closing metathesis
dpephos	bis[2-(diphenylphosphino)phenyl] ether	SAE	Sharpless asymmetric epoxidation
dppf	1,1'-ferrocenediyi-bis(diphenylphosphine)	Sia	siamyl or 1,2-dimethylpropyl
dr	diastereomeric ratio	TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
EE	ethoxyethyl	TBAF	tetrabutylammonium fluoride
ER	enoyl reductase	TBDPS	<i>tert</i> -butyldiphenylsilyl
Grubbs II	[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro-(phenylethylene)-(tricyclohexylphosphine)ruthenium	TBHP	tetrabutyl hydroperoxide
Grubbs I	bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride	TBS	<i>tert</i> -butyldimethylsilyl
GT	glycosyltransferase	TC	thiophenecarboxylic acid
HCT 116 VM/46	human colon carcinoma resistant cell line	TCAI	trichloroacetimidate
HCT 116	human colon carcinoma cell line	TE	thioesterase
HFIP	hexafluoroisopropanol	TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
HMDS	hexamethydisilazane	TES	triethylsilyl
HMPA	hexamethylphosphoramide	Tf	triflate or trifluoromethanesulfonyl
HWE	Horner-Wadsworth-Emmons	TFA	trifluoroacetic acid
IBX	1-hydroxy-1,2-benziodoxol-3(1 <i>H</i> )-one 1-oxide	TFAA	trifluoroacetic anhydride
Im	imidazole	TFE	2,2,2-trifluoroethyl
Ipc	isopinocampheyl	THF	tetrahydrofuran
KB	epidermoid carcinoma	THP	tetrahydropyran
KHMDS	hexamethydisilazane potassium salt	TIPS	trisopropylsilyl
KR	ketoreductase	TMEDA	<i>N,N,N',N'</i> -tetramethylethane-1,2-diamine
KS	ketosynthase	TMS	trimethylsilyl
K-selectride	potassium tri- <i>sec</i> -butylhydroborate	TMSA	trimethylsilyl acetilene
L1210	murine leukemia cell line	tol	toluene
LDA	lithium diisopropylamide	TPAP	tetrapropylammonium perruthenate
LHMDS	hexamethydisilazane lithium salt	Tr	triphenylmethyl or trityl
LTMSA	lithium trimethylsilylacetyllide	TRITON B	<i>N,N,N</i> -trimethyl-benzenemethanaminium
MDA MB 435	melanoma cell line	Ts	hydroxide
MNBA	2-methyl-6-nitrobenzoic acid anhydride		tosyl or <i>p</i> -toluensulfonyl
MOM	methoxymethyl		
MPM	4-methoxybenzyl		
MS	molecular sieve		
Ms	mesyl or methanesulfonyl		
MT	methyl transferases		
NCS	<i>N</i> -chlorosuccinimide		
NHK	Nozaki-Hiyama-Kishi		
NIS	<i>N</i> -iodosuccinimide		
NME	<i>N</i> -methylephedrine		
NMI	<i>N</i> -methylimidazole		
NMM	<i>N</i> -methylmorpholine		
NMO	<i>N</i> -methylmorpholine oxide		
NMR	nuclear magnetic resonance		
NRPS	non-ribosomal peptide synthetase		
OX	oxygenase		
PAB	<i>p</i> -aminobenzoyl		
PCC	pyridinium chlorochromate		
PDC	pyridinium dichromate		
Piv	pivaloyl		
PKS	polyketide synthases		
PMB	<i>p</i> -methoxybenzyl		
PMP	<i>p</i> -methoxyphenyl		

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