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A comparative analysis of the total syntheses of the amphidinolide T natural products

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In this article we compare and contrast the strategies and tactics used in the syntheses of the amphidinolide T family of natural products that have been reported by Fürstner, Ghosh and ourselves. Similar approaches to the trisubstituted THF ring present in the targets are utilized in all of the syntheses, but each strategy showcases a different means of macrocyclization.

1 Introduction

In the search for novel bioactive compounds, natural products isolated from marine organisms have shown a wealth of pharmacological and structural diversity.[1] The sources of the active compounds (sponges in particular) contain very small amounts of the desired products, limiting the quantities that may be isolated and studied. During the 1980s, Jun'ichi Kobayashi and coworkers undertook the isolation of natural products originating from marine symbiotic microorganisms (such as bacteria, fungi, and microalgae) with the intent to cultivate the microorganisms and subsequently isolate larger amount of active compounds.[1a] Early on, Kobayashi focused on a marine microalga dinoflagellate from the genus *Amphidinium*, found in the inner tissue of the Okinawan flatworm *Amphiscolops*. Four novel bioactive macrolides were originally isolated, amphidinolides A–D[2] (Chart 1), exhibiting cytotoxicity against murine lymphoma cells (L1210) and human epidermoid carcinoma KB cells.

Additional species of *Amphidinium* were subjected to the extraction procedure, leading to the discovery of amphidinolides E–H. During the process of isolation, several fractions were found to exhibit cytotoxicity of greater potency than any of the amphidinolides A–H. Further investigation of these cultures led to the discovery of related macrolides, amphidinolides J–Y.[3] Of all the amphidinolides, the most potent anticancer activities are displayed by amphidinolides B, C, G, H, and N (IC_{50} values against L1210 and KB cells <0.006 μg mL^{-1}).

In addition to the striking biological activity of the amphidinolides, they possess several interesting structural features. This family of macrolides shows diversity in size, including lactones of odd-numbered ring size. They display an abundance of stereogenic centers, exo- and endocyclic double bonds, and oxygen-containing substituents (including epoxides, THF and TFP rings, hydroxyl groups, and ketones). Due to their remarkable biological activity and structural functionality, the amphidinolides are challenging and attractive synthetic targets. Since the first reports of the amphidinolide family, considerable effort has been focused on synthesizing these macrolides, resulting in several innovative and efficient total syntheses.[4]

The discovery of the amphidinolide T class (Chart 2) was first reported in 2000.[5] Five members of this subclass, amphidinolides T1–5 (**1–5**), have been identified and characterized thus far. These natural products are 19-membered macrolides, each possessing seven or eight stereogenic centers (seven in the case of **1** and **3–5**; eight in the case of **2**), a highly substituted tetrahydrofuran ring, and exo-methylene. Amphidinolide T1 (**1**) features a ketone at C12 flanked by a hydroxyl group at C13. Interestingly, **3–5** are constitutional isomers of **1**, displaying a reversal of the hydroxy ketone pattern (ketone at C13, hydroxyl group at C12), and amphidinolides **3–5** possess a diastereomeric relationship at C12 and C14. Amphidinolide T2 (**2**) is the sole member of the T family that is not an isomer of another member. The structural and stereochemical features of **2** at C1–C17 are identical to **3**, but the C18 position of **2** is substituted with a

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Tim Jamison was born in San Jose, CA and grew up in neighboring Los Gatos, CA. He received his undergraduate education at the University of California, Berkeley, where he conducted research with Professor Henry Rapoport for nearly three years. A Fulbright scholarship supported ten months of research in Professor Steven A. Benner's laboratories at the ETH in Zürich, Switzerland, and thereafter he undertook his PhD studies at Harvard University with Professor Stuart L. Schreiber. He then moved to the laboratory of Professor Eric N. Jacobsen at Harvard University, where he was a Damon Runyon–Walter Winchell postdoctoral fellow. In July 1999, he began his independent career at MIT, where his research program focuses on the development of new methods of organic synthesis and their implementation in the total synthesis of natural products.

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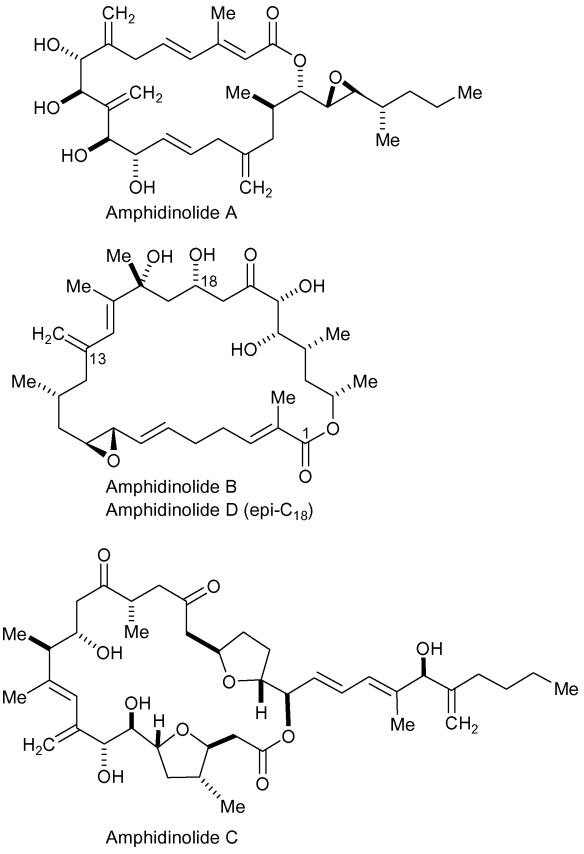
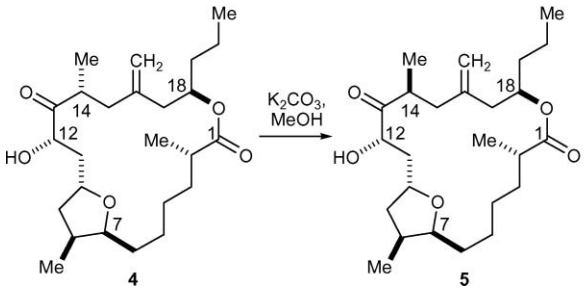


Chart 1

(3*S*)-hydroxybutyl group, in contrast to the *n*-propyl group exhibited by the other T amphidinolides.

The intriguing isomeric relationship of amphidinolides **1** and **3**–**5** attracted our attention, as it is likely that these natural products are biosynthesized through related processes or through a common pathway that diverges to yield the discrete natural products. Adding credence to this hypothesis is the observation that amphidinolide T4 (**4**) can be directly converted to amphidinolide T5 (**5**)[5c] *via* C14 epimerization simply by treatment with K_2CO_3 in MeOH (eqn. 1). In a different vein, we believed that we might be able to employ a divergent strategy in the laboratory in order to access several of these natural products rapidly.



(1)

It became clear shortly after we commenced our synthetic studies of the amphidinolide T family that a number of other research groups were also interested in the T family. In 2002, the Fürstner laboratory reported a total synthesis of amphidinolide T4 (**4**),[6] and shortly after this report, Ghosh and Liu disclosed their total synthesis of amphidinolide T1 (**1**).[7] A full account from Fürstner appeared in late 2003 that described the total syntheses of **1** and **3**–**5**[8] just as we had completed a synthesis of **1**.[9] We recently disclosed our comprehensive synthetic studies of the amphidinolide T family which culminated in the synthesis of amphidinolide T4 (**4**).[10] The syntheses from Fürstner, Ghosh, and our group present three approaches to the amphidinolide T family that rely on very different strategies to effect macrocycle formation but, interestingly, make use of a similar route to the key tetrahydrofuran ring in the targets. The objective of this account is to compare and contrast these published routes to amphidinolides T1, T3, T4 and T5, highlighting significant contributions that each offers to the general field of synthetic chemistry.

2 Fürstner's syntheses of amphidinolides T1 and T3–T5

2.1 Retrosynthetic analysis: common late-stage intermediate approach

It was clear from Fürstner's initial T4 communication[6] (and delineated in the later full account)[8] that the synthetic strategy hinged upon a late-stage intermediate that would ultimately provide a point of divergence to both the T1 and T3–5

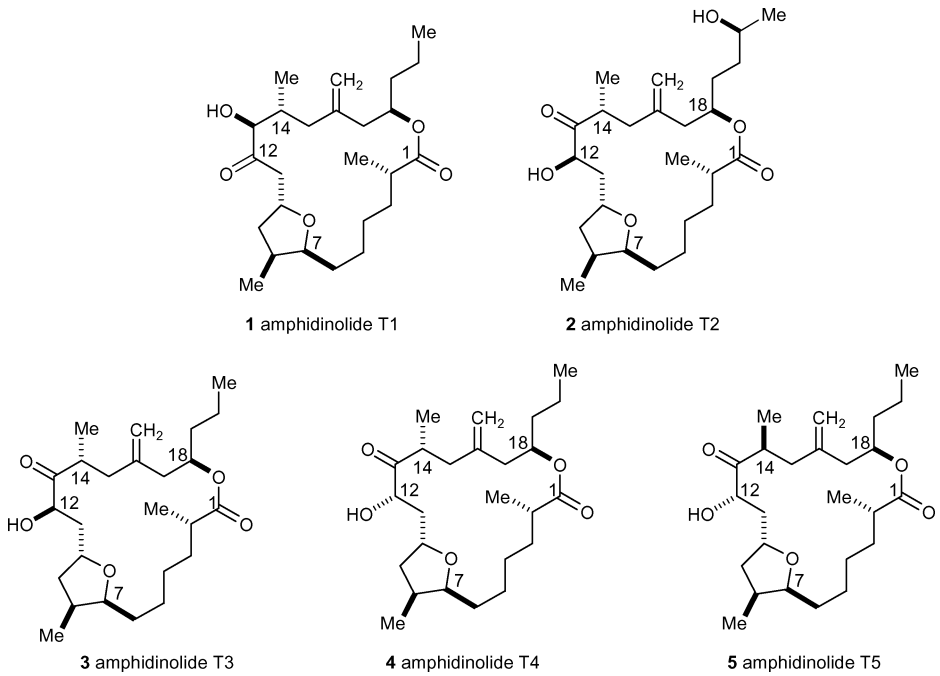
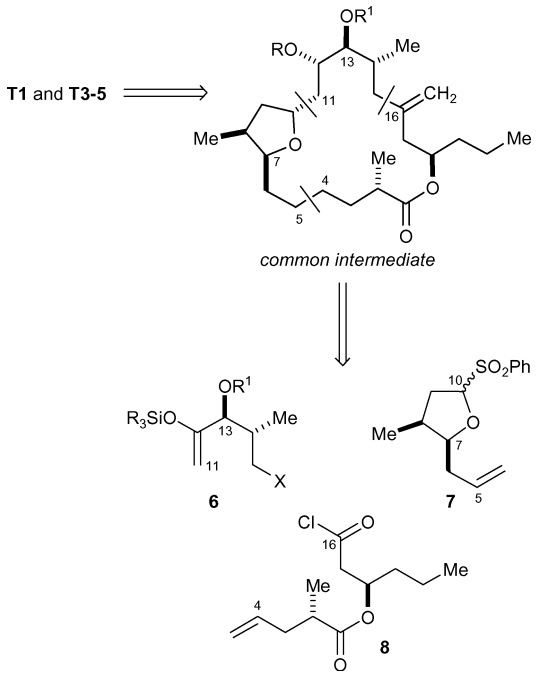


Chart 2



Scheme 1 Fürstner's strategy for amphidinolides T1 and T3–T5.

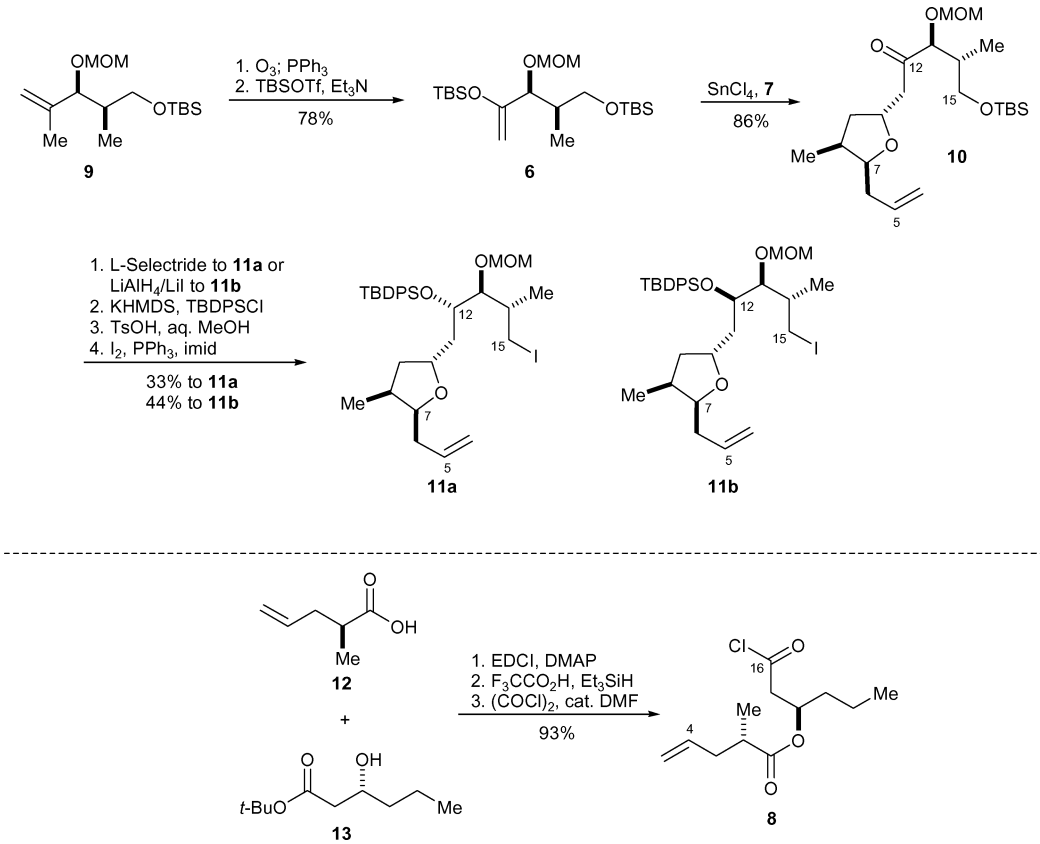
frameworks (Scheme 1). This key intermediate bears hydroxyl groups at both C12 and C13; ostensibly simple deprotection and oxidation state adjustment was predicted to provide access to **1** and **3**–**5**. The common intermediate was envisioned to be assembled rapidly from three simpler fragments (**6**, **7** and **8**).

2.2 Synthesis of T1, T3, T4 and T5

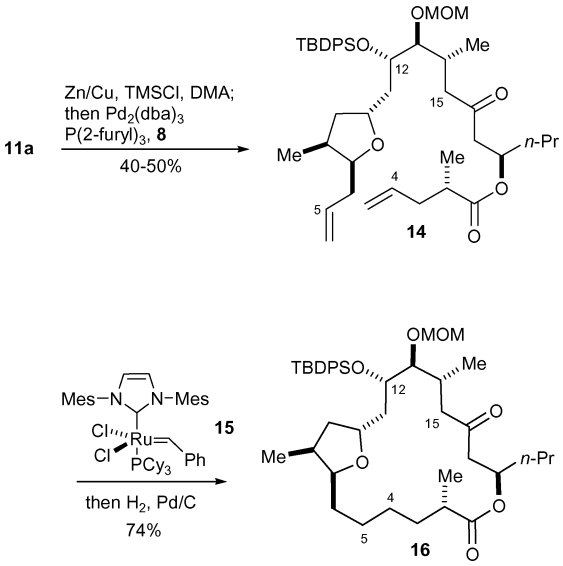
Alkene **9**, easily prepared using an auxiliary-based diastereoselective aldol reaction, was ozonolyzed to the ketone and silylated under basic conditions to produce silyl enol ether **6** (Scheme 2). Lewis acid-mediated coupling with sulfone **7** proceeded smoothly and in very high diastereoselectivity, affording ketone **10**. Selective reduction using L-Selectride produced the C12 *S* diastereomer (24 : 1 dr), while reduction with $LiAlH_4$–LiI afforded the *R* configuration at C12 (7 : 1 dr). The newly-formed secondary alcohol was protected as a TBDPS ether, allowing for selective deprotection of the primary alcohol and subsequent iodination, giving **11a** or **11b** depending on the protocol used for reduction of ketone **10**. Fragment **8** was synthesized through the esterification of carboxylic acid **12** with alcohol **13**, deprotection of the *t*-Bu ester and conversion to an acid chloride. (Coupling partners **12** and **13** were readily prepared through an auxiliary-based, diastereoselective alkylation and catalytic enantioselective reduction, respectively).

Union of alkyl halide **11a** and acid chloride **8** was accomplished by a palladium-catalyzed acylation (Scheme 3). Ring closing metathesis using ruthenium catalyst **15**[11] proceeded smoothly and in high yield (86%); subsequent hydrogenation delivered macrolactone **16**.

Methylenation of ketone **16** using Nysted's reagent (**17**, Scheme 4) produced alkene **18**, which was originally intended to be the key common intermediate in syntheses of **1** and **3**–**5**. To this end, a sequence of steps from **18** indeed resulted in the synthesis of **1**. The silyl protective group was selectively removed by treatment with a fluorosilicate reagent, and the alcohol was oxidized to the C12 ketone. Deprotection of the MOM ether by exposure to acidic Dowex resin produced amphidinolide T1 (**1**). Complementing this sequence and leading to the reversed hydroxy ketone array of **3**–**5**, the order of deprotection was reversed so that the MOM ether was first removed from **18** to liberate the C13 hydroxyl group. Oxidation and desilylation produced amphidinolide T4 (**4**). As **4** is known to be partially epimerized to **5** when treated with K_2CO_3–MeOH,[5c] a formal synthesis of amphidinolide T5 was also achieved. Attempts to access T3 from common intermediate **18** *via* cleavage of the MOM ether at C13, oxidation to the ketone, and C12 epimerization were unsuccessful. However, elaboration of iodide



Scheme 2



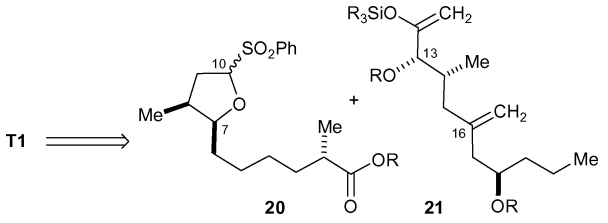
Scheme 3

11b and elaboration in analogy to the sequence used for **11a** (a notable exception being the use of a different catalyst (**15b**)[12] for ring closing metathesis) culminated in the successful synthesis of **3**.

3 Ghosh's synthesis of amphidinolide T1

3.1 Retrosynthetic analysis: ring formation *via* macrolactonization

Shortly after Fürstner's synthesis of T4 was published, Ghosh reported the first total synthesis of amphidinolide T1. The target was dissected into two fragments of approximately the same complexity, sulfone **20** and silyl enol ether **21** (Scheme 5).



Scheme 5 Ghosh's strategy for amphidinolide T1.

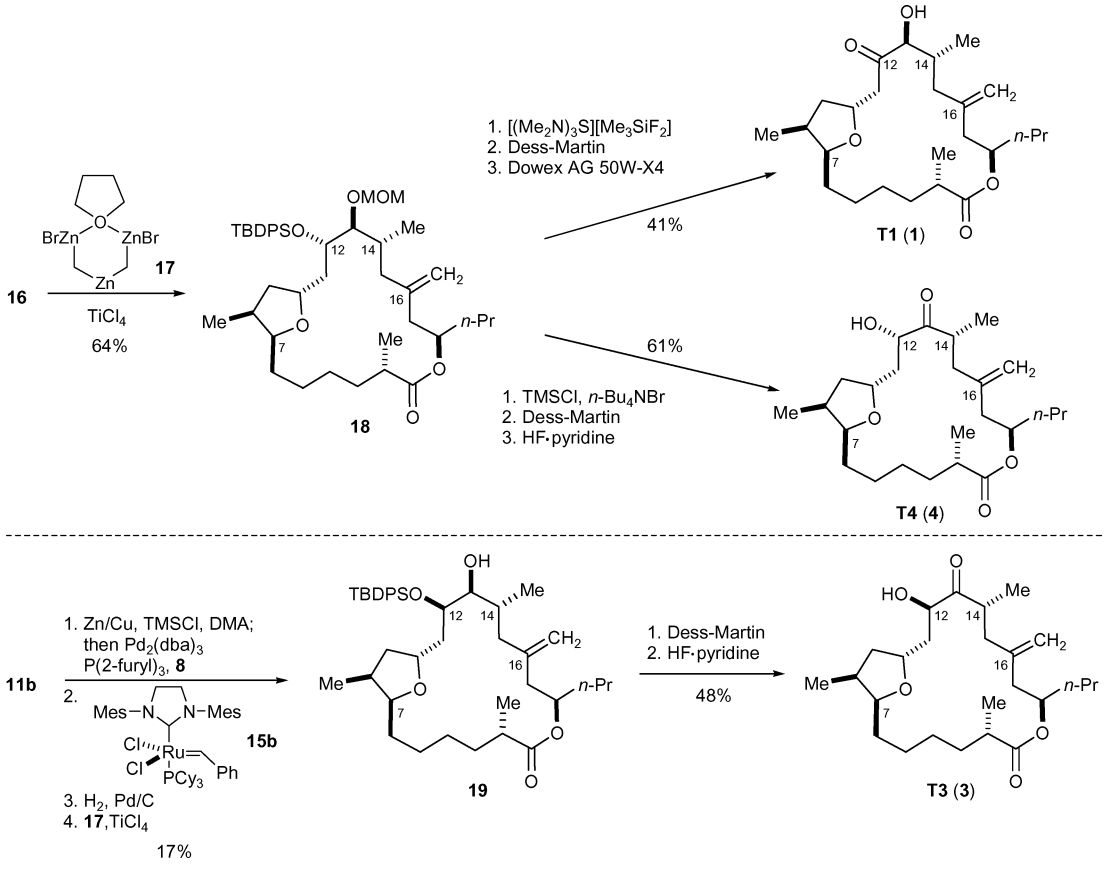
Fragment coupling *via* oxocarbenium ion alkylation and later macrolactonization were envisioned to give access to **1**.

3.2 Synthesis of amphidinolide T1

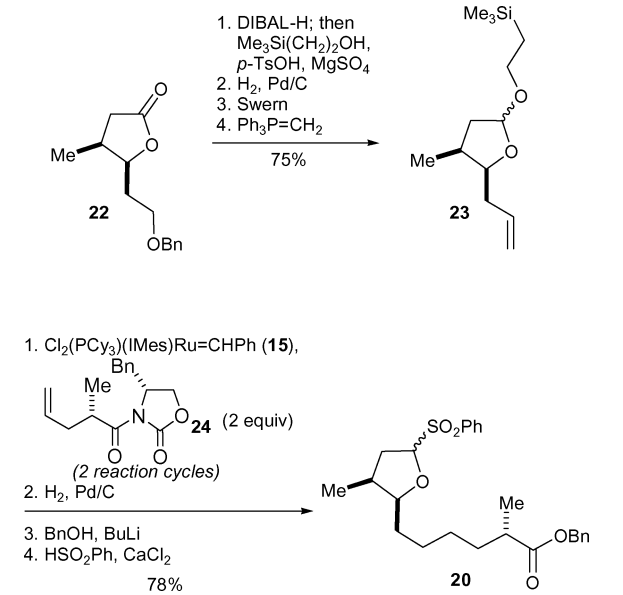
In the forward direction (Scheme 6), lactone **22** was partially reduced, and a mixed acetal with trimethylsilylethanol was formed. Subsequent removal of the benzyl protecting group, oxidation and methylenation produced acetal **23**. Cross metathesis with alkene **24** using catalyst **15**[11] and hydrogenation of the newly-formed alkene proceeded in 94% yield. Cleavage of the auxiliary and exchange of the 2-trimethylsilylethoxy substituent with phenylsulfinic acid provided the target sulfone **20**.

The other key fragment was constructed from intermediate iodide **25**, prepared using an auxiliary-based diastereoselective aldol reaction (Scheme 7). Lithiation, addition to aldehyde **26** (derived from (*S*)-glycidol), and oxidation provided ketone **27**. Subsequent methylenation and deprotection furnished diol **28**. Treatment of **28** with *N*-bromosuccinimide promoted cyclization to bromotetrahydrofuran **29**. Oxidation of the primary alcohol, addition of methylmagnesium bromide and re-oxidation furnished ketone **30**, which was then converted to silyl enol ether **31**.

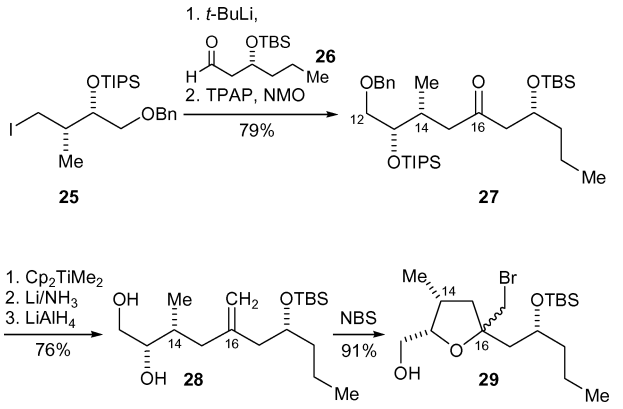
Fragment coupling was achieved by a Lewis acid-mediated alkylation reaction of **20** and **31** (Scheme 8). Removal of the TBS and benzyl groups was followed by macrolactonization,



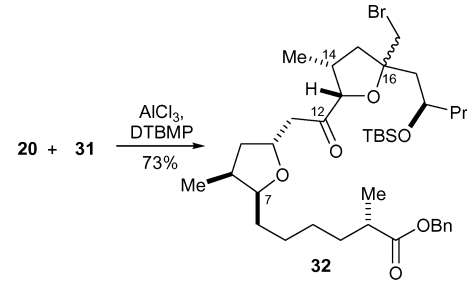
Scheme 4

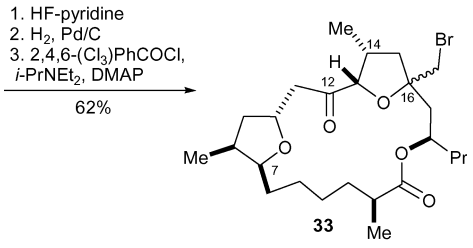


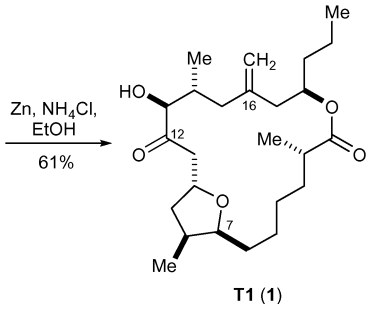
Scheme 6



Scheme 7







Scheme 8

affording macrocycle **33** in 71% yield. Finally, reductive cleavage of the bromotetrahydrofuran moiety by treatment with Zn unveiled amphidinolide T1 (**1**).

4 Jamison's syntheses of amphidinolides T1 and T4

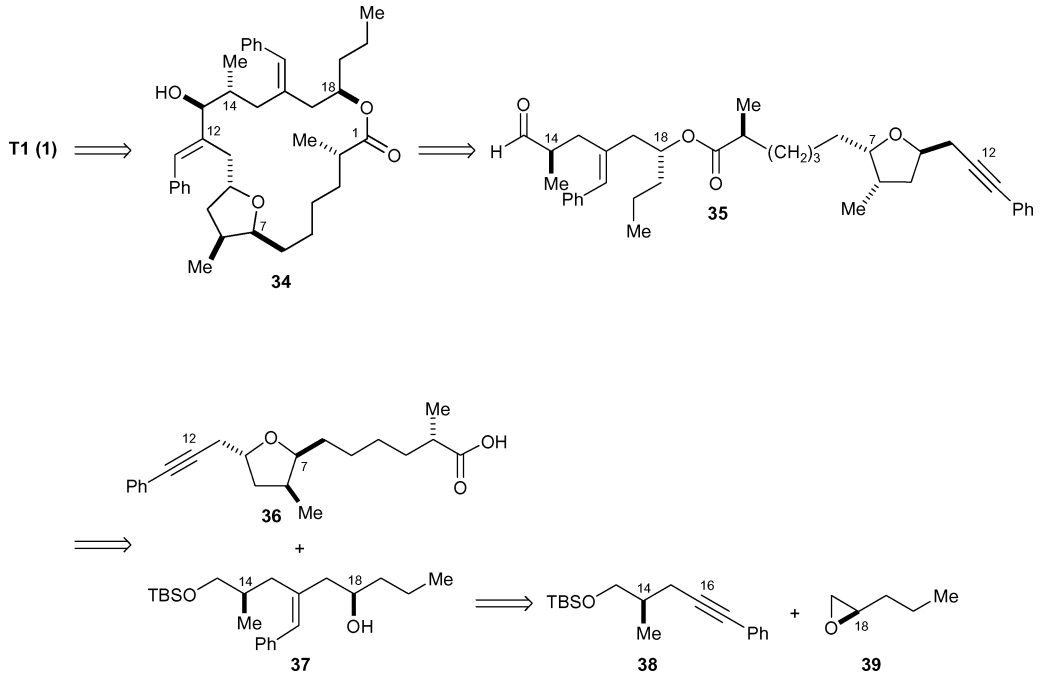
4.1 Retrosynthetic analysis of T1 and T4

Our synthetic approach to amphidinolides T1 and T4 rested upon the use of nickel-catalyzed reductive coupling reactions of alkynes developed in our laboratory (shown for **1** in Scheme 9). Specifically, we envisioned an intramolecular variant of our alkyne–aldehyde reductive coupling[13,14] that would form the C12–C13 bond to produce a macrocyclic allylic alcohol (**34**) (*i.e.*, a reductive macrocyclization of alkynal **35**) and then be elaborated to the hydroxy ketone array found in **1**. Dissection of the requisite alkynal provided two precursors, carboxylic acid **36** and homoallylic alcohol **37**. We predicted that a key alkyne–epoxide fragment coupling reaction[15] of alkyne **38** and (*R*)-propyloxirane (**39**) would install the homoallylic alcohol moiety of **37** and assemble the C13–C21 portion of the natural products.

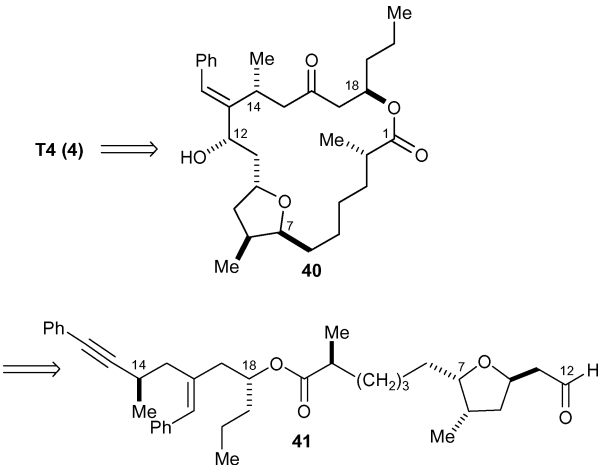
The synthesis of the reversed hydroxy ketone array found in **4** would require a different macrocyclic allylic alcohol (**40**, Scheme 10) possessing an alkene at C13. While the corresponding alkynal **41** differs from the T1 alkynal **36** in that the positions of the aldehyde and alkyne are reversed (aldehyde at C12 and alkyne at C13), we predicted that many of the intermediates necessary to provide cyclization substrate **41** would either be exact T1 intermediates or closely related structures.

4.2 Synthesis of amphidinolide T1

We were pleased to find that alkyne **38** (produced by an auxiliary-based diastereoselective alkylation reaction) did indeed undergo nickel-catalyzed reductive coupling with epoxide **39** to afford homoallylic alcohol **37** in good yield (Scheme 11). The other key fragment, acid **36**, was synthesized from lactol **42**. The C10–C11 bond was formed by treating **42** with $BF_3{\cdot}OEt_2$ and allenyltriphenylstannane (**43**) as a propargyl anion equivalent. This reaction not only promoted the desired propargyl addition, but removed the primary TBS protective group. Elaboration of the terminal alkyne *via* Sonogashira coupling with iodobenzene produced aryl alkyne **44**. Conversion to the corresponding alkyl iodide and subsequent auxiliary-based diastereoselective



Scheme 9 Jamison's strategy for amphidinolide T1.



Scheme 10 Jamison's strategy for amphidinolide T4.

alkylation proceeded in high yield. Finally, cleavage of the auxiliary afforded the necessary carboxylic acid **36**.

The fragments were coupled using a DCC-mediated esterification reaction. Removal of the TBS protective group and oxidation provided alkynal **35**. Reductive macrocyclization of this alkynal was accomplished by heating with triethylborane in the presence of a catalyst system composed of $Ni(cod)_2$ and PBu_3 affording allylic alcohol **34** in 44% yield. While the yield of the cyclization was modest, the diastereoselectivity was remarkably very high (>10 : 1 dr at the newly formed carbinol center, C13).

With the formation of **34**, all of the stereogenic centers carbon atoms in the ring of **1** had been installed. Further elaboration of allylic alcohol **34** to amphidinolide T1 (**1**) was accomplished by TBS protection of the hydroxyl group at C13 and ozonolysis to diketone **45** (Scheme 12). Finally, conversion to **1** proceeded *via* selective methylenation of the C16 ketone and subsequent removal of the TBS protective group.

4.3 Synthesis of amphidinolide T4

We sought to apply our reductive macrocyclization strategy to the synthesis of other amphidinolide T natural products containing the reversed hydroxy ketone pattern at C12 and C13. As mentioned above, this goal required an α,ω-alkynal (**41**) with the positions of the aldehyde and alkyne reversed with respect to **35**. Despite this difference, several intermediates used in the T1 synthesis were used to access **41**. As shown in Scheme 13, chiral alcohol **46** was oxidized to the aldehyde and converted to the corresponding dibromo olefin. Treatment with methyllithium followed by chlorotrimethylsilane afforded diyne **47**. This diyne underwent a group selective nickel-catalyzed reductive coupling with epoxide **39** (no reductive coupling was observed at the C13 position adjacent to the silicon substituent). Removal of the TMS group and coupling with iodobenzene furnished homoallylic alcohol **48**. The other coupling partner, carboxylic acid **50**, was synthesized in analogy to the T1 acid (**36**) by allylation of lactol **42**. Iodination, diastereoselective alkylation and cleavage of the auxiliary afforded **50**.

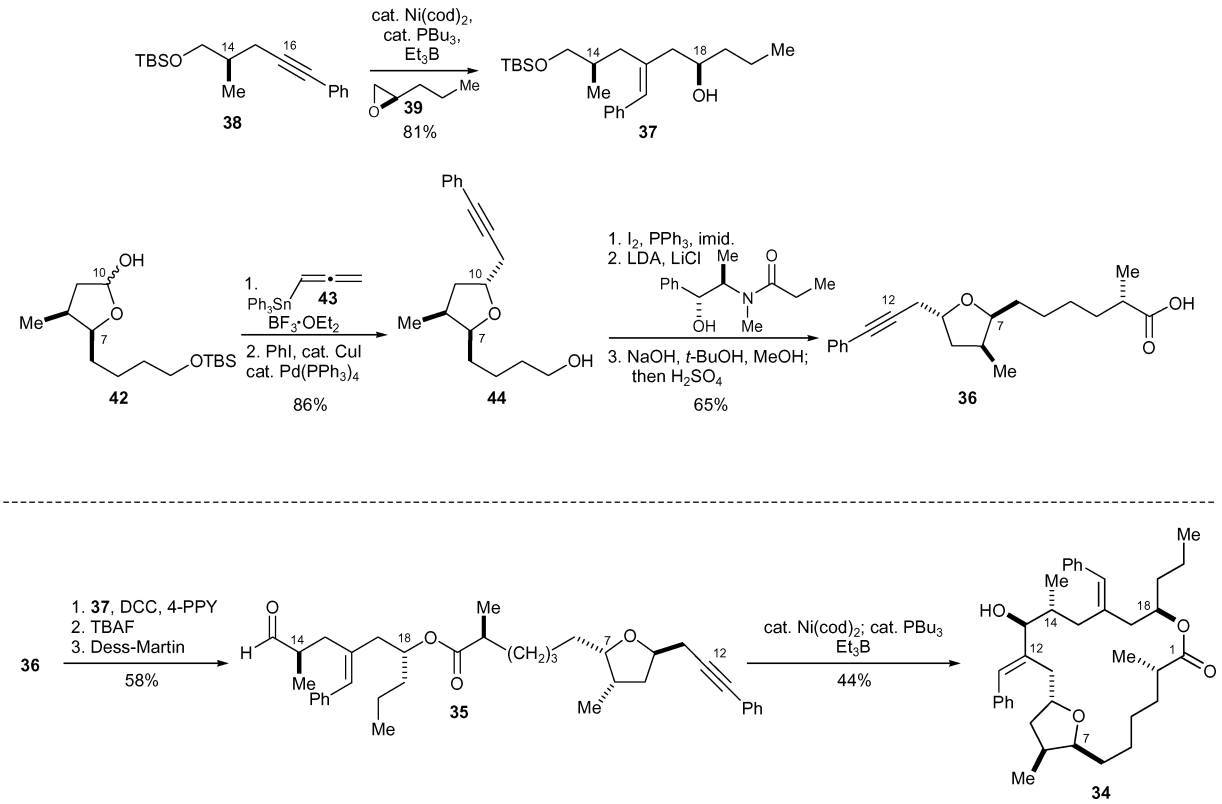
The key fragments were, as before, joined by an esterification reaction, and subsequent ozonolysis produced ketoalkynal **41**. Nickel-catalyzed reductive macrocyclization again proceeded in very high diastereoselectivity (>10 : 1 dr) and in 58% yield to afford allylic alcohol **40**. This allylic alcohol was elaborated to amphidinolide T4 in analogy to the T1 endgame sequence (Scheme 14). Protection of the hydroxyl group followed by ozonolysis produced diketone **51**. Selective methylenation and deprotection afforded amphidinolide T4 (**4**).

5 Comparison of the total syntheses of amphidinolide T natural products

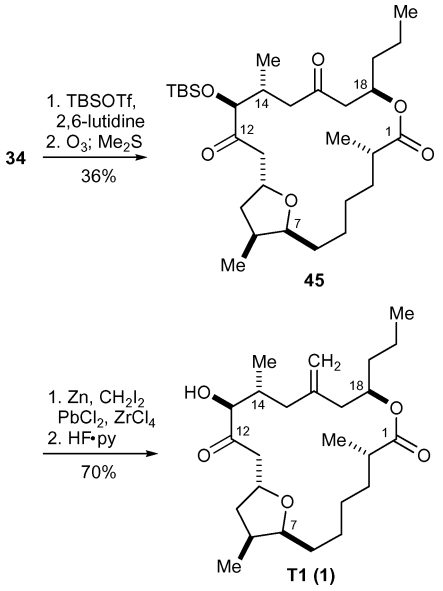
The strategies taken by our group and the laboratories of Fürstner and Ghosh certainly represent conceptually distinct approaches to the 19-membered macrocycle present in the amphidinolide T natural products. Particularly striking, however, is the degree of commonality in several of the bond formations made by all three research groups, despite the unique strategies taken. In the remainder of this article, we have attempted to compare and contrast these routes.

5.1 Formation of the macrocycle

The aspect that differs the most among the three synthetic strategies is the method of macrocycle formation (Scheme 15).



Scheme 11



Scheme 12

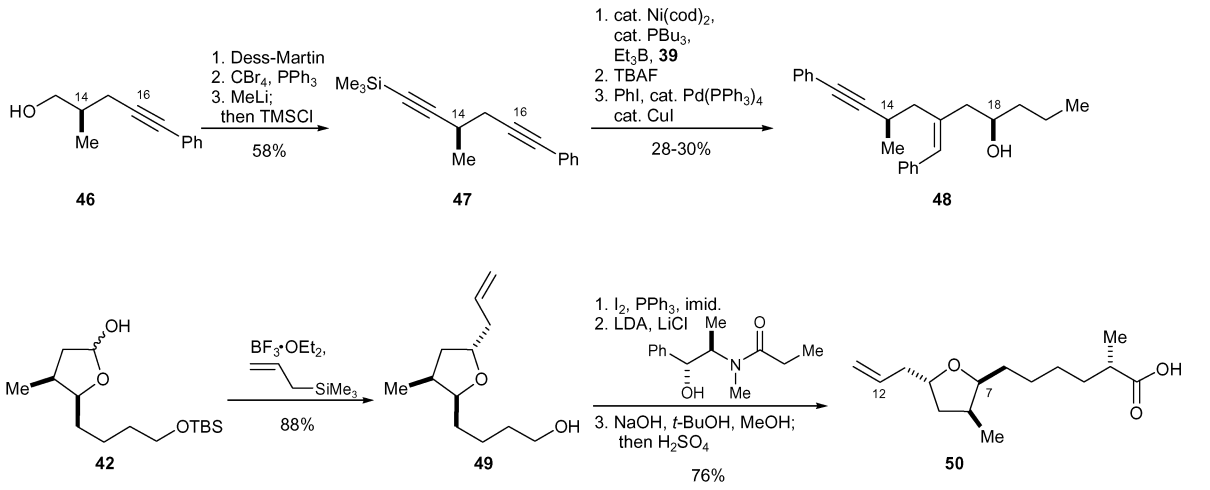
In the syntheses of **1** and **3**–**5**, Fürstner chose to form the C4–C5 bond and construct the macrocyclic framework *via* ring closing metathesis. This reaction proved to be very powerful, proceeding in high yield (86%) at 40 °C. Ghosh took an alternative approach to **1** by closing the ring using a C1–O bond formation reaction. The desired macrolactonization was smoothly accomplished under Yamaguchi conditions[16] with mild heating (50 °C) to afford the lactone in very good yield (71%). In our retrosynthetic analyses of **1** and **4**, we disconnected the macrocycle in yet another way. We utilized nickel-catalyzed reductive macrocyclizations of two different alkynals to form the C12–C13 bonds found in the natural products while concomitantly setting the stereogenic centers bearing hydroxyl groups. The yields of the reductive macrocyclizations were modest (44% for **1** and 58% for **4**), but in both cases, the hydroxyl groups (at C13 in the case of **1** and at C12 in the case of **4**) were installed with complete stereocontrol (>10 : 1 dr).

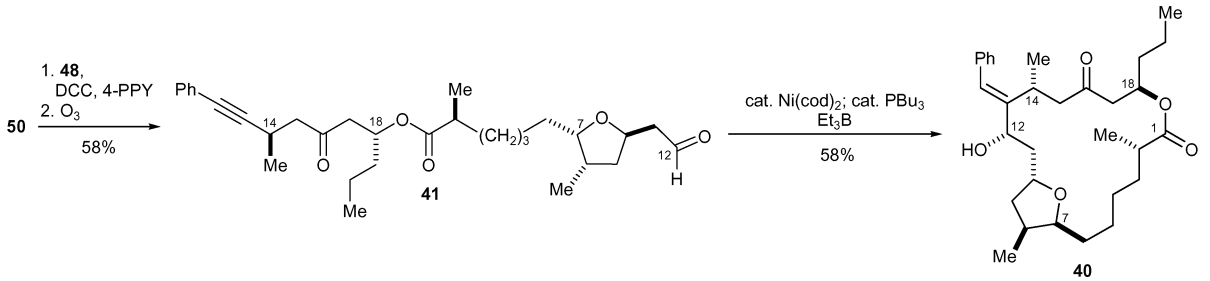
5.2 Formation of the C4–C5 bond *via* olefin metathesis

The first of many similarities between some or all of the syntheses is the method for C4–C5 bond formation. As previously mentioned, Fürstner formed this bond *via* ring closing metathesis (Schemes 3 and 4).[17] Interestingly, while the Ghosh synthesis of T1 did not close the ring forming this bond, the C4–C5 bond was formed using related methodology, that is, by ruthenium-catalyzed olefin cross metathesis. This reaction was performed using relatively closely matched terminal alkene coupling partners (type I according to Grubbs' classification),[18] mixed acetal **23** and oxazolidinone **24** (Scheme 6). The lack of electronic and steric difference in the olefins was overcome by employing excess **24** (2.0 equiv) and performing two reaction cycles. That is, after the initial reaction, the undesired alkene homodimers were isolated and resubjected to the reaction conditions. The end result was a very high overall yield of the desired cross metathesis product (96% combined yield). In our syntheses of **1** and **4**, we did not form the C4–C5 bond as we used a known aldehyde possessing the C4 and C5 carbons embedded within an alkyl chain (*vide infra*).

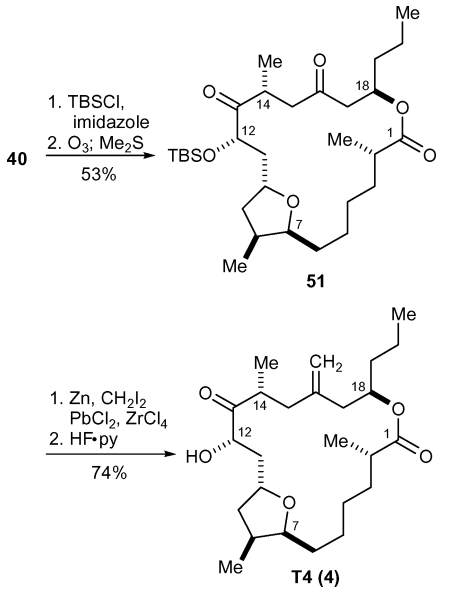
5.3 Methylenation of a C16 ketone

A common theme of all three synthetic approaches to T1 and T4 was the use of a carbonyl at the C16 position to construct the C13–C21 portion of the natural products. Ghosh and Liu used aldehyde **26** (aldehyde at the final C16 position) for a key fragment coupling reaction with the alkyllithium reagent derived from iodide **25** (Scheme 7). Oxidation of the resulting alcohol furnished ketone **27**, which was methylenated using the Petasis protocol[19] to ultimately install the exo-methylene moiety at C16 found in **1**.

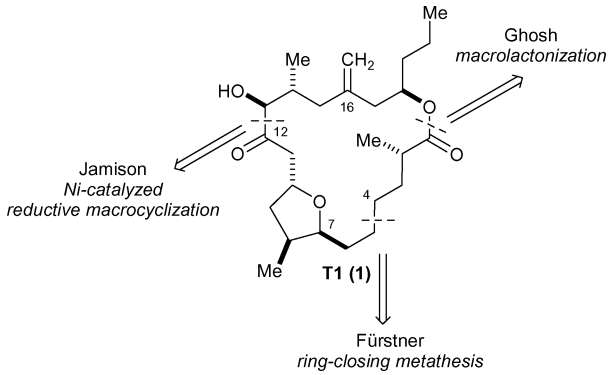




Scheme 13



Scheme 14



Scheme 15

The Fürstner group also performed a fragment coupling reaction in which one partner contained a carbonyl at the C16 position. An acid chloride (**8**) provided the functional group for fragment coupling, undergoing a palladium-catalyzed acyl–Negishi coupling[20] with iodides **11a** and **11b** (Schemes 3 and 4) to provide unsymmetrical ketones. After further elaboration, an advanced macrocyclic intermediate (**16** in the case of **1,4**, and **5**) containing a ketone at C16 was methylenated using Nysted's reagent (Scheme 4). Notably, this ketone was extraordinarily difficult to methylenate, attributed to its highly compact conformation (confirmed by semiempirical calculations performed by Fürstner and subsequent comparison to the crystal structure[5c] of **1**).

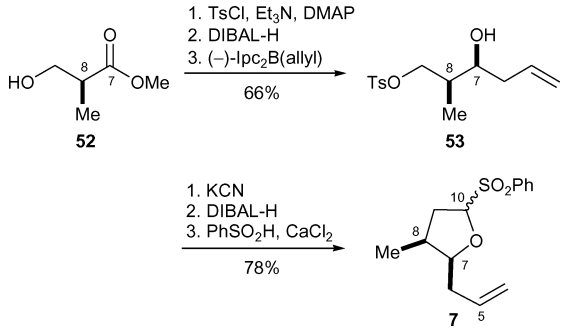
While we did not directly use the carbonyl functionality to perform a fragment coupling reaction, our syntheses of **1** and **4** did rely on the use of advanced macrocyclic intermediates containing a ketone at C16 to install the final methylidene olefin present in the natural products. Our approach was to form the C16–C17 bond using a nickel-catalyzed reductive fragment coupling reaction of an alkyne and epoxide. This reaction produced a homoallylic alcohol possessing a benzylidene group at C16 (**37** (for T1) and **48** (for T4), Schemes 11 and 13). In both cases, this functional group was eventually converted to the exo-methylene by oxidative cleavage to the corresponding C16 ketone and subsequent methylenation of a macrocyclic intermediate (**45** in the case of T1 and **51** in the case of T4).

In this respect, our macrocyclic ketones differed significantly from Fürstner's in that they contained an additional ketone at

C12 or C13, the functional group present at the corresponding site in **1** and **4**. Accordingly, selective methylenation of the C16 carbonyl would be required. In analogy to Fürstner's observations, we also found these macrocyclic diketones to be particularly unreactive under many standard methylenation conditions and prone to decomposition under basic conditions. However, using a modified Takai reaction[21,22] (Schemes 12 and 14), we were able to selectively methylenate at the C16 ketone to access **1** and **4**. The rationale for this site selectivity is most likely the difference in steric bulk about the two carbonyl groups.

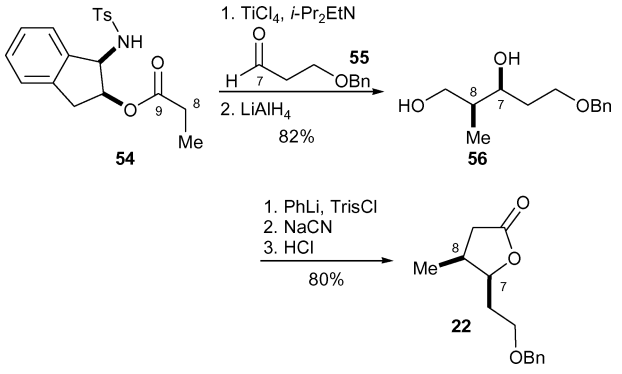
5.4 Assembly of the substituted THF ring

5.4.1 Control of the C7–C8 stereochemical relationship. Each of the three groups approached the installation of the C7–C8 stereogenic centers in a different manner. The Fürstner syntheses utilized a diastereoselective Brown allylation[23] of an aldehyde (derived from commercially available ester **52**) to form the C6–C7 bond and install the C7 stereogenic center (Scheme 16). The product of this reaction, alcohol **53**, was treated with potassium cyanide to displace the primary tosyl group. Subsequent reductive cyclization and sulfonylation provided the key fragment **7**.



Scheme 16

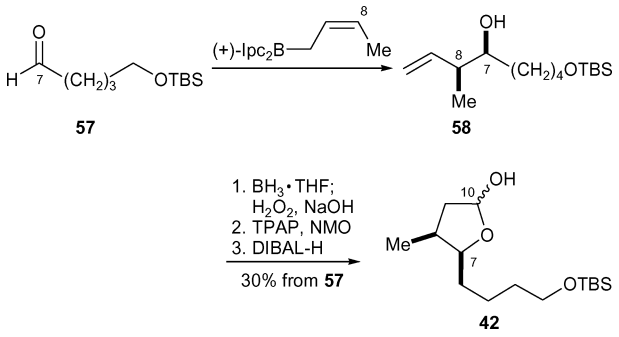
Ghosh took a different approach, performing a diastereoselective aldol reaction of the titanium enolate of ester **54**[24] and aldehyde **55** to form the C7–C8 bond and concomitantly set the absolute and relative stereochemistry at these positions (Scheme 17). The product of this reaction was reduced to diol **56**. The primary hydroxyl group was selectively sulfonylated and displaced with sodium cyanide. Acid-promoted cyclization afforded lactone **22**.



Scheme 17

We employed a Brown crotylation[25] of aldehyde **57** to form the C7–C8 bond while simultaneously introducing the relative and absolute stereochemical relationship at these positions (Scheme 18). The product of this reaction, alkenyl alcohol **58**, was hydroborated to a diol, oxidatively cyclized, and partially reduced to afford lactol **42**.[26]

5.4.2 Addition to an oxocarbenium ion to establish the C10 configuration. All three groups approached the problem of



Scheme 18

constructing the trisubstituted tetrahydrofuran ring present in the amphidinolide T natural products in a similar manner: a Lewis acid-mediated addition to an oxocarbenium ion. Both Ghosh and Fürstner employed sulfones as oxocarbenium ion precursors (**23** and **7**, respectively) and silyl enol ethers as nucleophiles using $AlCl_3$ and $SnCl_4$ as Lewis acids, respectively. We used a slightly different precursor, lactol **42**, and installed a propargyl group using allenyltriphenylstannane (**43**) as the nucleophile and $BF_3{\cdot}Et_2O$ as the Lewis acid. In all cases, the diastereoselectivity of the alkylation reaction was very high, installing the third stereogenic center of the THF ring in >95 : 5 dr. Both the sense and degree of stereoselectivity matched that observed by Reißig[27] and Woerpel[26,28] in studies of 5-membered cyclic oxocarbenium ions, corresponding to nucleophilic attack on the inside face of an oxocarbenium ion.

5.5 Comparison of the longest linear sequences and overall yields

All of the reported syntheses of the amphidinolide T natural products are highly convergent. The longest linear sequence of Ghosh's synthesis of amphidinolide T1 (**1**) was 19 steps (6.6% yield over this sequence), and our synthesis of T1 required 17 linear steps (1.1% overall yield). Interestingly, four of the syntheses (Fürstner's syntheses of T1, T3 (**3**), and T4 (**4**), and our synthesis of T4) were "exactly convergent". That is, in each of these cases, there are two longest linear sequences that are the same number of steps. Accordingly, the overall yield of the synthesis depends on which of the two sequences is used to calculate the yield. For example, Fürstner's T1 and T4 syntheses were both accomplished using 18 linear steps in the longest sequence. In his T1 synthesis, the overall yield from intermediate **7** was 1.4% and 1.5% from intermediate **9**. For T4, the overall yield from **7** was 2.1%, and from intermediate **9** the yield was 2.3%. Our synthesis of T4 was carried out in 15 linear steps (2.7% yield from aldehyde **57** or 1.7% yield from alcohol **46**). Finally, Fürstner's synthesis of T3 was 17 linear steps (1.6% yield from **7** and 1.7% yield from **9**).

6 Conclusions

In conclusion, several contributions to synthetic organic chemistry were made by the three laboratories (Fürstner, Ghosh, and Jamison) in their syntheses of several of the amphidinolide T natural products. All syntheses highlight the power of nucleophilic additions to oxocarbenium ions for the stereocontrolled assembly of substituted tetrahydrofuran rings. Notably, all of the approaches include the methylenation of a ketone at the ultimate C16 position. In our syntheses and those of Fürstner, this methylenation is carried out on a late-stage, hindered macrocyclic ketone. Interestingly, Ghosh installed the methylene unit earlier in the synthesis and protected it through several steps as a novel cyclic bromoether.

Several important methods for fragment coupling were established to be very effective by all groups. Fürstner's syntheses

of **1** and **3**–**5** highlighted the utility of palladium-catalyzed acylation reactions using highly functionalized coupling partners. Ruthenium-catalyzed olefin cross metathesis was shown by the Ghosh synthesis of T1 to be very successful even with two electronically and sterically similar terminal alkenes. In our syntheses of **1** and **4**, we demonstrated the utility of regioselective nickel-catalyzed reductive coupling reactions of epoxides and alkynes.

Finally, each group demonstrated a different method of 19-membered ring formation. We used nickel-catalyzed reductive macrocyclizations to form the C12–C13 bond and set the stereogenic center of **1** and **4** bearing a hydroxyl group. Fürstner used olefin metathesis (RCM) in a very efficient macrocyclization to form the C4–C5 bond in **1** and **3**–**5**. Taking yet a different approach to **1**, Ghosh formed the C1–O bond in a very successful macrolactonization reaction.

In summary, the amphidinolide T natural products present several challenges to the synthetic organic chemist. The fact that some of these were solved in a similar way by all three groups suggests that the methods used were ideally suited for the issues at hand. Finally, in contrast, that different solutions were devised for some of the problems demonstrates that natural products often stimulate the development of and provide a proving ground for new strategies and methods of organic synthesis.

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