A Challenge for Total Synthesis:
Atom Economy

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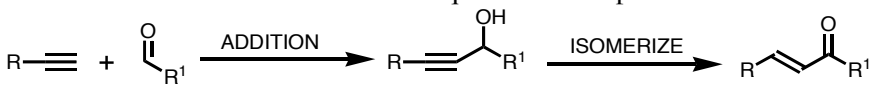
A key aspect of organic chemistry is the ability to design structure for function in which the availability of the designed structure becomes crucial. If the structure does not exist or exists but only in incredibly small amounts, synthesis becomes the only avenue, Making complex structures in a time-efficient manner depends upon the underlying science, synthetic methodology. The effectiveness of any synthetic strategy is interdependent with the core synthetic reactions available. To a first approximation, the chemo-, regio-, diastereo-, and enantio-selectivity of the methodology plays a major in streamlining synthetic strategies. However, also important to the efficiency of a strategy is the maximum use of raw materials and the minimization of the generation of waste which I refer to as "atom economy." The ideal synthetic reaction is one of the form A+B=C with anything else only needed catalytically. Thus, this lecture will deal with the development of new synthetic atom economical reactions and how they impact the design of synthetic strategy to complex targets.

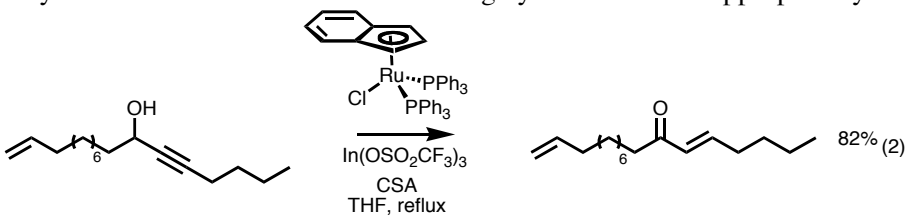
Redox Isomerization

The synthesis of α,β-unsaturated carbonyl compounds frequently involves the use of olefination protocols including but not limited to Wittig, Horner-Emmons-Wadsworth, Julia-Kocienski, etc., protocols. All of these suffer from low atom economy. On the other hand, an attractive atom economic alternative shown in eq. 1 uses a simple addition followed by an



(1)

isomerization. While catalytic additions of alkynes to aldehydes are well developed, a chemoselective redox isomerization of a propargyl alcohol to an enone is not. Eq 2 reveals a highly active catalyst system that effects such reactions in high yields. With an appropriately



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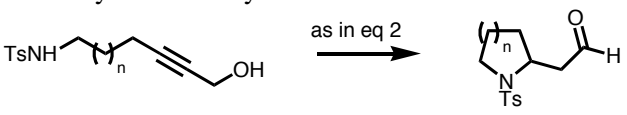
tethered pronucleophile, a facile synthesis of heterocycles emerges. (eq 3). Scheme 1 outlines a retrosynthetic analysis for the synthesis of an intermediates in the arachadonic



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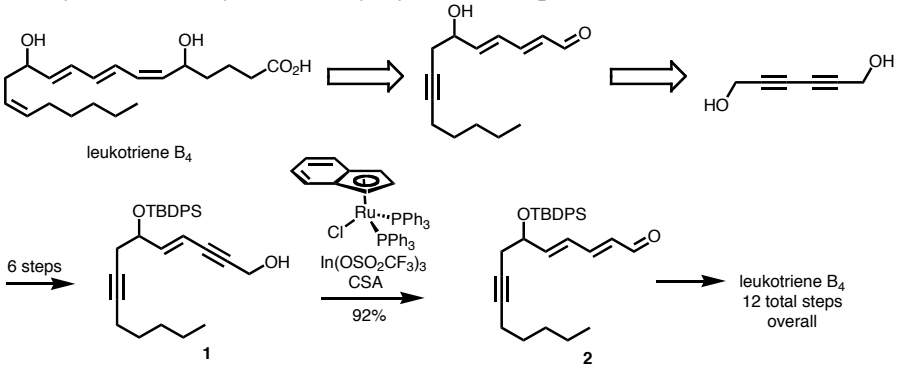
acid cascade, leukotriene B_4. A key step is the chemoselective redox isomerization of the

Scheme 1. Retrosynthetic Analysis and Key Synthesis Step

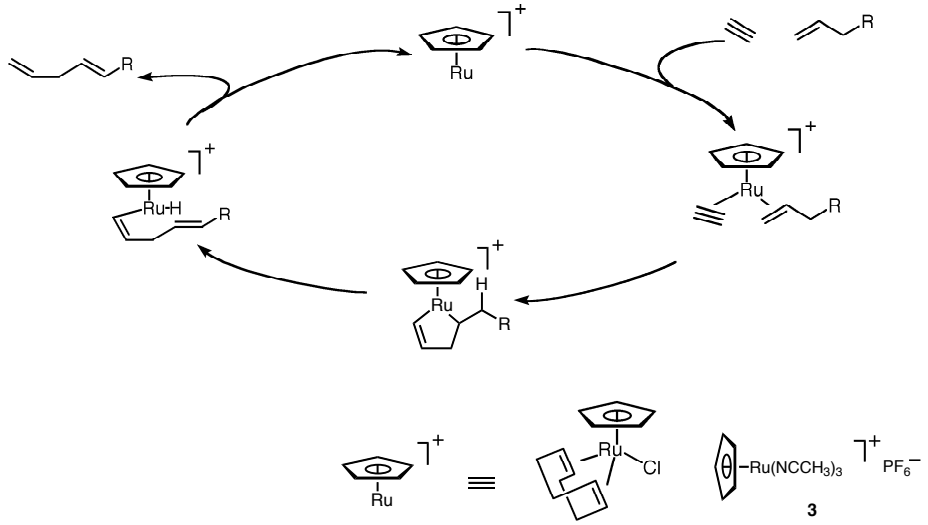


enediynol **1** to the ynedienal **2** in 92 % yield.

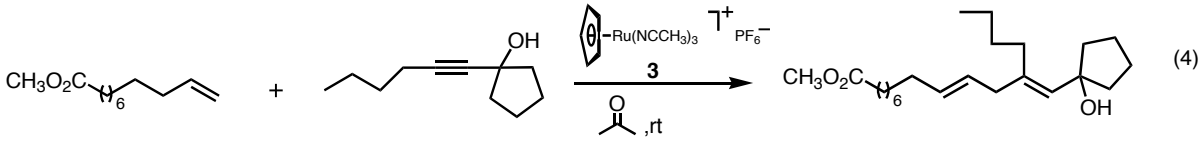
Alkene-Alkyne Coupling

A new type of C-C bond forming reaction envisions the addition of an alkyne across an alkene and an allylic hydrogen to form 1,4-dienes. The key question is how will an alkene couple with an alkyne in lieu of an alkene-alkene or alkyne-alkyne coupling. Scheme 2 outlines a potential

Scheme 2. Alekne-Alkyne Coupling

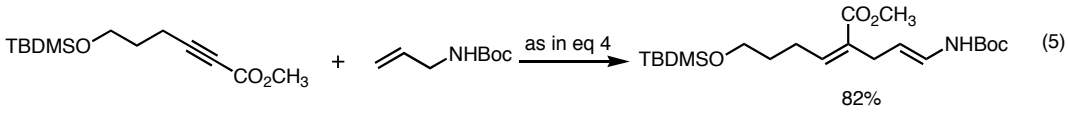


mechanism for a ruthenium catalyzed process. Eq. 4 illustrates such a process wherein 1 eq each of an alkene and an alkyne smoothly add to form the 1,4-diene. A most unusual regioselectivity was



(4)

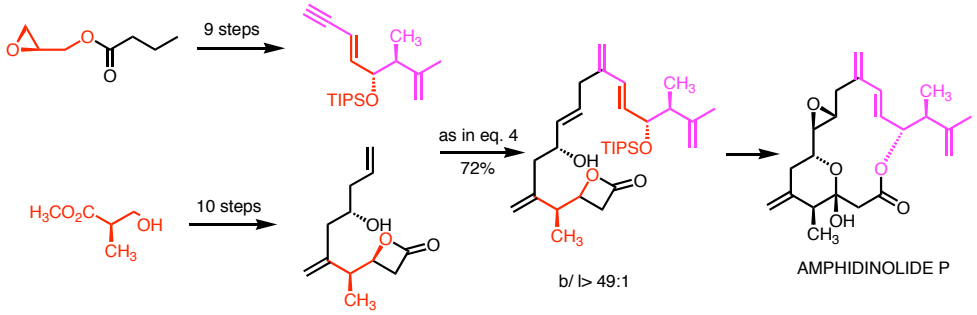
observed with an ynoate wherein, contrary to every known type of addition wherein the new C-C bond formation occurs to the β-carbon of the alkynoate, this Ru catalyzed process occurs regioselectively to the α-carbon as shown in eq. 5. The reaction proceeds with extraordinary chemoselectivity as illustrated in Scheme 3 involving a total synthesis of the anticancer agent amphidinolide P isolated



(5)

from a marine organism. First and foremost, although there are 4 double bonds, only one, the

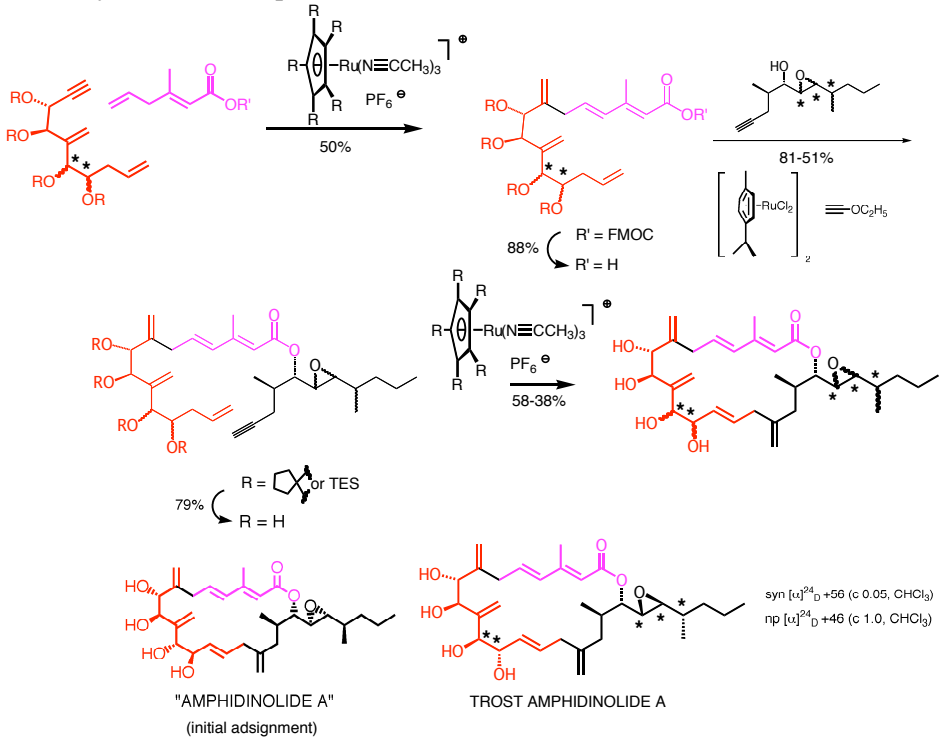
Scheme 3. Synthesis of Amphidinolide P



monosubstituted double bond reacted. Furthermore, a very labile β-lactone as well as unprotected hydroxyl groups remain totally unaffected.

The synthesis of amphidinolide A clearly demonstrated the effectiveness of strategies that emerge from this method. As shown in Scheme 4, the alkene-alkyne coupling was employed twice – initially intermolecularly and subsequently intramolecularly. This case as well, highlights the

Scheme 4. Total Synthesis of Amphidinolide A

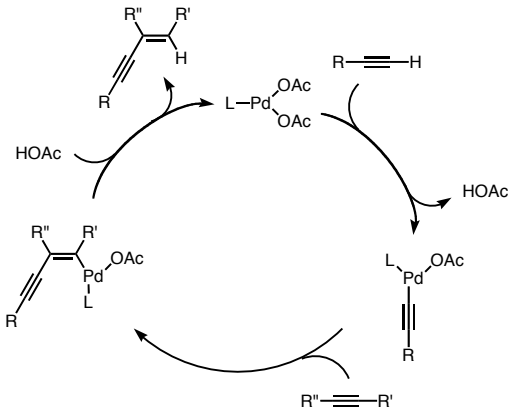


chemoselectivity since the macrocyclization allowed the use of the totally unprotected substrate with 4 free hydroxyl groups, an epoxide, and notably the presence of 5 double bonds. Furthermore, it involved the formation of a 20 membered lactone in yields up to 58%. When the synthesis of the proposed structure proved the assignment of the stereochemistry to be incorrect, the effectiveness of this route permitted the ultimate assignment of the correct structure through total synthesis!

Alkyne-Alkyne Coupling

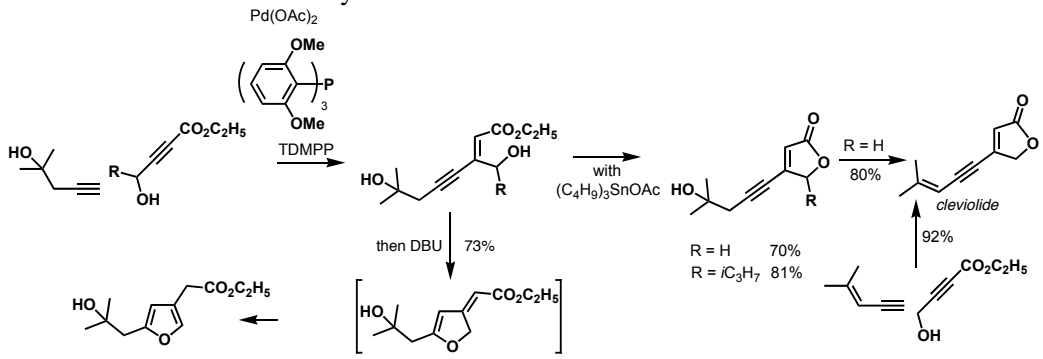
The creation of new synthetic methods derives from the versatility of each individual transition metal. A favorite of ours is palladium. Scheme 5 illustrates a catalytic cycle for coupling of a terminal alkyne coupling with another terminal or internal alkyne. Notably, use of a coordinatively unsaturated Pd(+2) complex with a sterically bulky electron rich ligand facilitates insertion into the terminal C-H bond which, in turn, promotes a carbametalation of the second

Scheme 5. Catalytic Cycle for Alkyne-Alkyne Coupling



alkyne followed by protonation of the vinylpalladium species to give an enyne. Scheme 6 demonstrates the efficiency, chemoselectivity, and versatility of the process. The initial enyne in this case is well suited for lactonization. Surprisingly, the lactonization under the simple conditions of

Scheme 6. Butenolide and Furan Syntheses

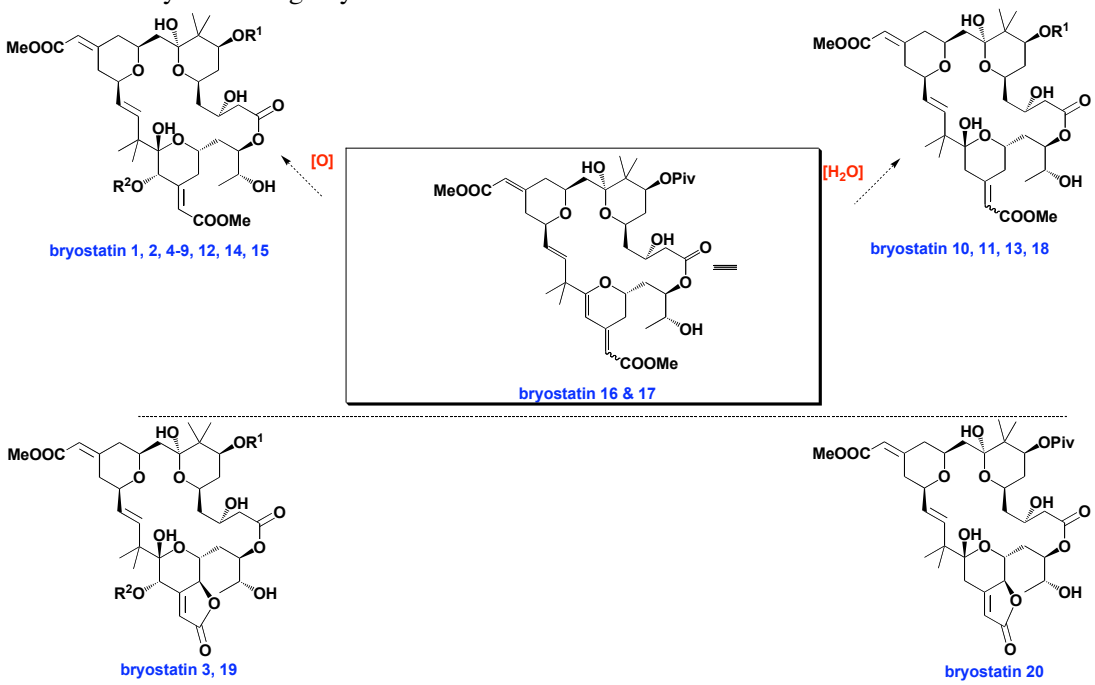


the coupling was slow. To facilitate this step, a trans-esterification catalyst was also used simultaneously wherein the butenolides were directly formed. In the particular case where R=H, simple dehydration served to form the natural product cleviolide isolated from *Senecio clevelandii*. Alternatively, use of 4-methyl-3-penten-1-yne as the terminal alkyne provides this unusual natural product from two commercially available starting materials in one step by a simple addition in which anything else is only used catalytically. Alternatively, treatment of the initial adduct with a base, DBU, promoted furan formation and constitutes an effective atom economic synthesis of such heterocycles.

Total Synthesis of Bryostatins

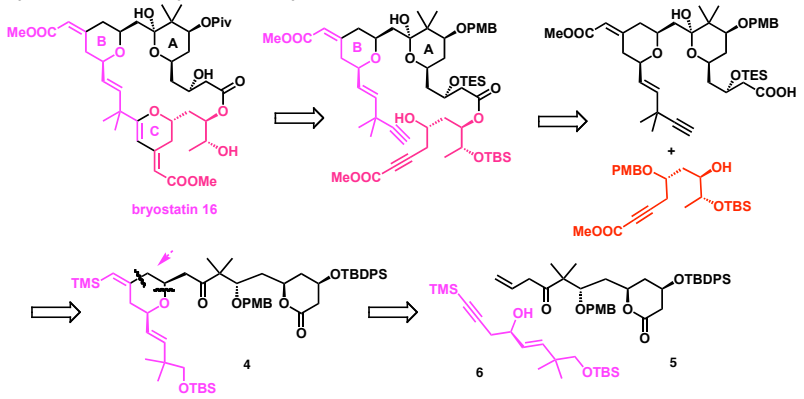
The bryostatins are a family of compounds isolated from the marine bryozoan Bugula *neritina*. While attention has initially focused on their potent anticancer activity, recent studies suggest they may have much broader applications such as in the treatment of Alzheimer's disesase and stroke. Their low availability from natural sources and their intriguing structure make them ideal targets for efficient total syntheses. Prior to our work, only 3 total syntheses which required from 41-43 steps in the longest linear sequence and 72-87 total steps have been reported.

Chart 1. Naturally Occurring Bryostatins



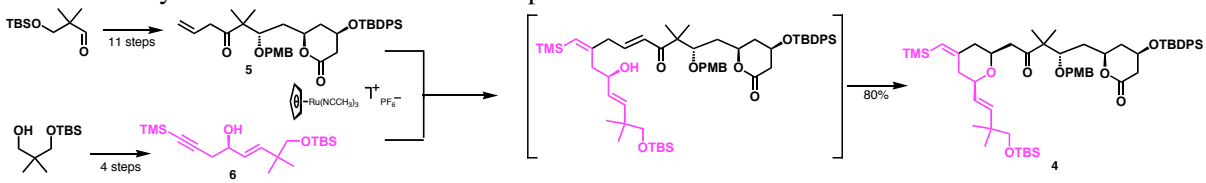
All of the bryostatins have the same core differing only in the oxidation pattern and nature of the esters on the alcohols at C-7 and C-20 as shown in Chart 1. Most intriguing are bryostatins 16 and 17 since they seem to be able to be pivotal intermediates from which all of the known bryostatins may derive. A totally new strategy derives from several of the new synthetic methods outlined above, notably the Pd catalyzed alkyne-alkyne coupling and the Ru catalyzed alkene, alkyne coupling as detailed in Scheme 7. New strategies for the formation of pyrans employing these fundamental methods emerged. Considering pyran ring C leads to the two disconnections pictured in bryostatin 16 invoking pyran formation by addition of an alcohol onto an alkyne in analogy to the furan formation shown in Scheme 6. In this case, the enyne precursor would be generated by a macrocyclization

Scheme 7. Retrosynthetic Analysis of Bryostatin 16.



using the alkyne-alkyne coupling strategy. The second key disconnection is depicted in intermediate **4** wherein the formation of tetrahydropyran ring B would involve a cascade of coupling of alkene **5** and alkyne **6** followed by intramolecular conjugate addition of the hydroxy group on the resultant enone. Scheme 8 details the synthetic direction. Indeed, exposure of a 1.1 : 1 mixture of β,γ-enone

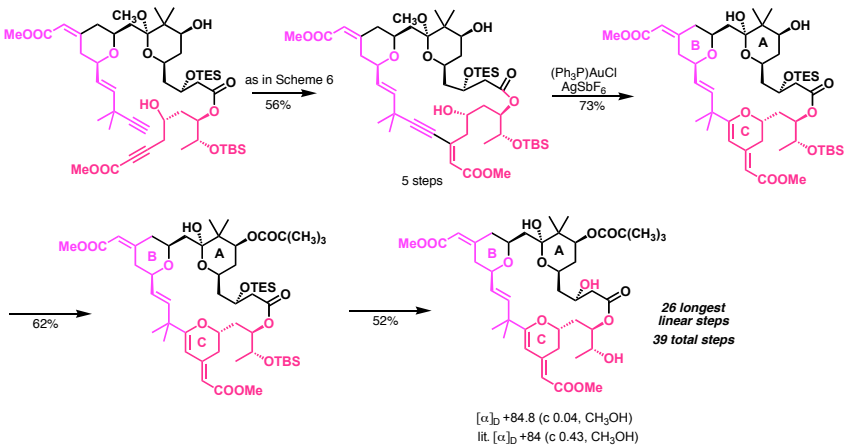
Scheme 8. Synthesis of the Northern Hemisphere



5 and **6** to the catalyst at rt gave an 80% yield of the tetrahydropyran **4** directly. It should be noted that this coupling also sets the geometry of the exocyclic double bond since the vinylsilane can be converted to the unsaturated ester with complete retention of olefin geometry.

Scheme 9 depicts the formation of the macrocycle concommittant with formation of the pyran ring C. The intramolecular terminal alkyne-alkyne coupling proceeded well to produce the 26-

Scheme 9. End Game



membered macrocycle. In our original "one-pot" protocol, palladium was also used to effect the cyclization of the hydroxyl group onto the alkyne. However, the reaction was plagued by many side products. On the other hand, a gold catalyst nicely effected this cyclization to complete the fully elaborated bryostatin 16 which only required attachment of a pivalate ester to the alcohol at C-7 and removal of protecting groups to complete the formation of the natural product. The efficiency of this route is indicated by the facts that only 26 steps for the longest linear sequence and 39 total steps are required. These numbers also show the highly convergent nature of the synthesis which should allow for great flexibility in making bryostatin analogs as well as all the members of the current bryostatin family.

Conclusions

Chemistry is both a science of enablement and of opportunity. The vastness of what we do not know should not be underestimated. At the same time, we are making strides. The invention of new types of reactivity truly becomes enabling. In pursuing such inventions, we must also be sensitive to making synthetic chemistry environmentally benign by design. In achieving this important goal we must begin by making the very reactions themselves as close to the ideal of being simple additions. The ultimate goal must be to make any molecule only by a series of simple addition reactions (ie be chemoselective). Furthermore, each reaction must join the partners with a single orientation (ie be regioselective) as well as a single stereoisomer (ie be diastereo- and enantioselective). Achieving this goal is the ideal. At this point, we cannot know if it is even achievable. Nonetheless, we should not stop trying. Our efforts hopefully are moving us in this direction with the very satisfying benefit that complex molecule synthesis is indeed being made simpler and more efficient.