Natural Products

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Cycloadditions in the Total Synthesis of Sporolide B

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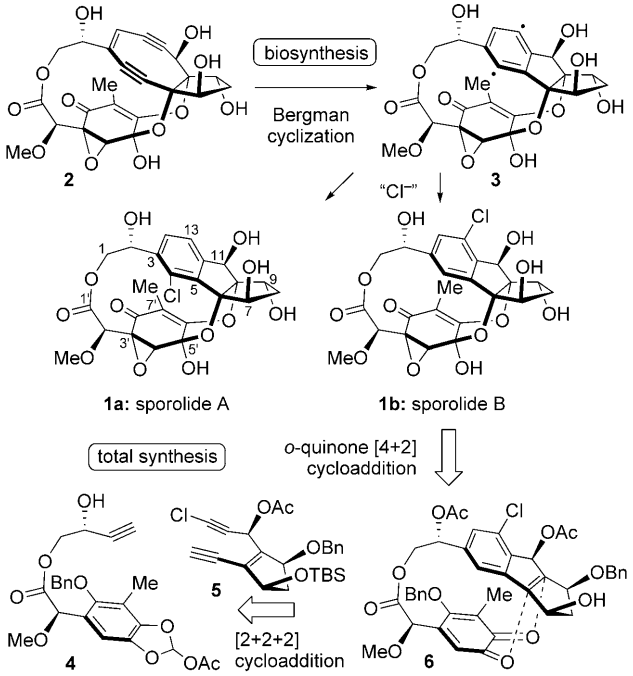
Cycloadditions are among the most powerful synthetic transformations available in modern organic chemistry.[1] The significance of these processes stems from the rapid increase in structural complexity upon the formation of ring systems through the addition of one unsaturated structural unit to another. Starting from relatively simple subunits, several new bonds can be formed in a single step in a highly atom-efficient manner. Consequently, applications in the syntheses of complex natural products are very attractive. However, these reactions often present daunting challenges, as chemo-, regio-, and stereoselectivity must be controlled efficiently to enable concise access to only one of many isomeric products. This requires the availability of robust protocols and catalysts as well as high-level strategic planning. While applications of Diels–Alder reactions of conjugated dienes and alkenes have been well demonstrated in natural product synthesis,[2] other cyclizations are much less common in the assembly of complex targets. In March 2009, the group of Nicolaou reported the total synthesis of sporolide B (**1b**),[3] a complex polycyclic marine macrolide, which is highlighted by two advantageous cyclization reactions, an intermolecular [2+2+2] cycloaddition and an intramolecular [4+2] cyclization of an olefinic *ortho*-quinone.

Marine-derived actinomycetes (*Salinispora tropica*) are the natural source of sporolides A and B (**1a** and **1b**, Scheme 1).[4] The molecular architecture of these chlorinated polyketides, which was elucidated Fenical et al., is characterized by seven rings, ten stereogenic centers, and a very high degree of oxygenation (22 out of the 24 carbon atoms are either oxygenated or sp^2 hybridized). Their biosynthesis[5] is highlighted by an enediyne cyclization of a pentacycle (**2**) mediated by a polyketide synthase and subsequent trapping of the resulting *para*-benzene diradical **3** with chloride.[6]

Interestingly, the retrosynthetic analysis in Nicolaou's total synthesis of sporolide B (Scheme 1) does not rely on such a Bergman cyclization. Instead two remarkable alternative cycloadditions are used. To forge the unusual, highly functionalized benzodioxane subunit, the [4+2] cycloaddition reaction between a trisubstituted *ortho*-quinone and a tetrasubstituted olefin (indene alkene) is perhaps the most understandable in terms of topology and also the most direct access. This synthetic strategy also presents a challenge for chemists because there have been only very limited studies on the [4+2] cycloaddition reaction with *ortho*-quinone as a heterodiene[7] and none at all with this level of substrate complexity and stereoselectivity. Though seemingly bold, it is an opportunity to develop novel synthetic strategies, as the authors state.[8] To secure the desired efficiency (yield and stereoselectivity) of this cycloaddition reaction, the *ortho*-quinone heterodiene and the indene dienophile were positioned in a molecule possessing the full functionalization of the natural products. This strategy may thus be considered to be biomimetic.[5a,b,6] A previous study of this approach with a simplified model substrate had been promising.[8] Thus, an unprecedented intramolecular [4+2] cycloaddition reaction of an *ortho*-quinone (**6**) provided rapid access to the unique complex benzodioxane structure and serves as a new type of macrocyclization as well.[2]

The second key disconnection was based on a reaction type of current interest, the [2+2+2] cycloaddition of alkynes for the rapid construction of highly substituted benzenes.[9]



Scheme 1. Cycloadditions in the biosynthesis and total synthesis of the sporolides.

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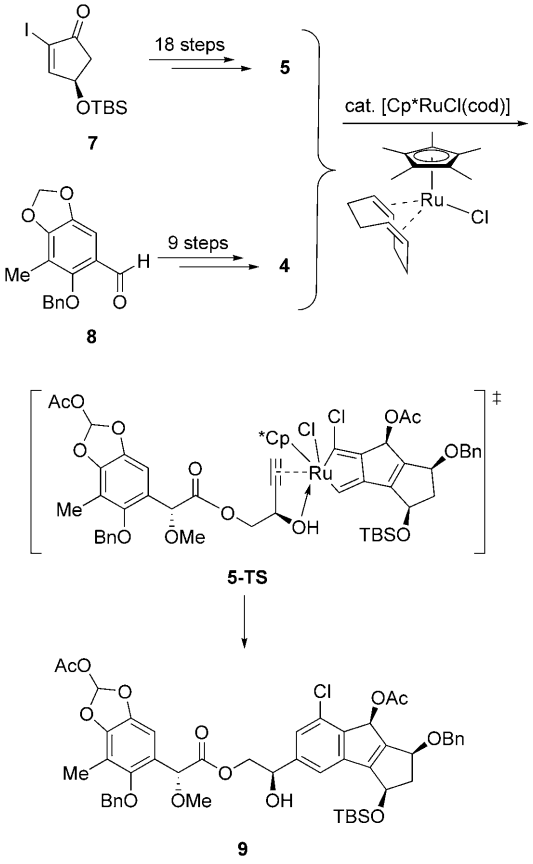
This inherently atom-economical and convergent cyclotrimerization approach has remarkable advantages over conventional strategies for constructing substituted arenes In a recent Highlight[9k] new developments of this reaction were discussed and compared in terms of chemo- and regioselectivity, pertinent topics for chemists when they devise a synthetic plan. As a strategy to overcome the selectivity problem, a partially intermolecular approach (diyne–monoalkyne coupling) has been successfully developed: two of the three alkynes are tethered so as to control the selective formation of the intermediate metallacycle and the geometric course of the reaction. This transition-metal-catalyzed [2+2+2] cycloaddition reaction is very effective when the termini of the third alkyne have significantly different electronic and/or steric properties and when the tether itself is a part of the desired target molecule. The chosen retrosynthetic plan may therefore be seen to exploit the full potential of this still-developing reaction type.

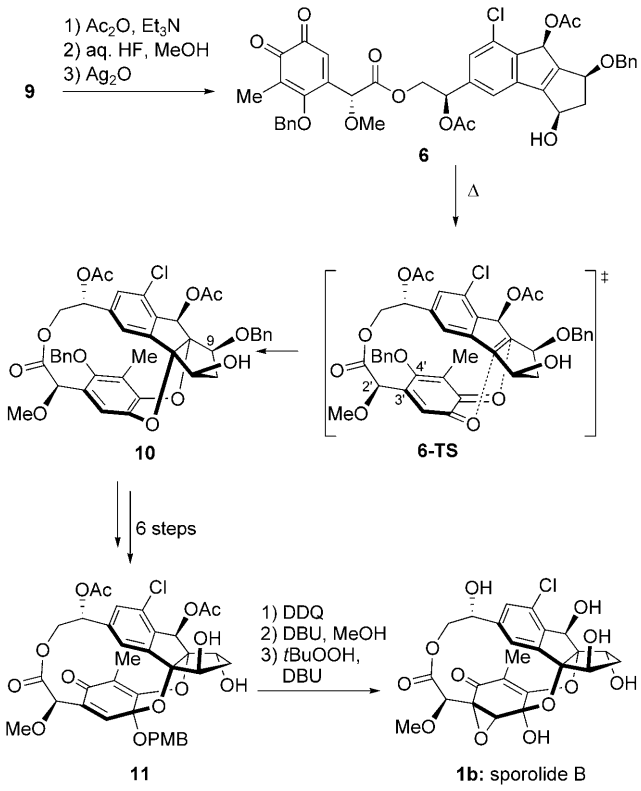
The diyne (**5**) and the monoalkyne (**4**) building blocks for the [2+2+2] cycloaddition dictated by the above retrosynthetic analysis were prepared from the known iodocyclopentenone **7** and the appropriately substituted benzaldehyde **8** through relatively conventional methods in 18 and 9 steps, respectively (Scheme 2).

The critical [2+2+2] cycloaddition turned out to be highly efficient. With 7% mol [Cp*RuCl(cod)] catalyst,[10] the reaction between the two building blocks gave the desired cycloaddition product within 30 minutes in 87% yield as a single regioisomer (Scheme 2). The authors comment that this achievement demonstrates the integration of structural demands and chemical design. In detail, the unusual alkynyl chloride **5** was an ideal starting material for the chlorobenzenoid ring in the structure of sporolide B. Though difficult to visualize, the authors expected good regioselectivity as a result of the steric preference linked with the large chlorine atom together with another possibly more decisive factor, a rarely observed[11] type of regioselective cycloaddition directed by a neighboring hydroxy group (**5-TS**). In this case, both the chlorine and hydroxy functional groups were wanted in the target molecule. Thus, the [Cp*RuCl(cod)]-catalyzed [2+2+2] cycloaddition reaction matched the natural product structure perfectly and excellent results were obtained for this reaction.

The [2+2+2] cycloaddition product was transformed into *ortho*-quinone substrate for the [4+2] cycloaddition by sequential acetate formation, deprotection, and quinone formation (Scheme 3). To implement the planned intramolecular Diels–Alder macrocyclization reaction with the *ortho*-quinone as the heterodiene, a 7.8 mM solution of the substrate in toluene was simply heated at 110 °C for 1.5 h. After flash column chromatography, the expected cycloaddition product was isolated in 21% yield (40% based on recovered starting material). This result was less satisfactory than that in the previous model study[8] but still respectable when one considers the complexity of the substrate. The remarkable



Scheme 2. The key [2+2+2] cycloaddition. Cp* = C_5Me_5, cod = cycloocta-1,5-diene, TBS = *tert*-butyldimethylsilyl.



Scheme 3. The *ortho*-quinone [4+2] cycloaddition and conclusion of the synthesis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PMB = *para*-methoxybenzyl.

diastereoselectivity (facial selection of *ortho*-quinone relative to the indene dienophile) of this reaction may be conveniently rationalized by the steric bias exerted by the neighboring substituents: in **6-TS** all of the substituents on the two five-membered rings point up and block the top face.

Notably, the Nicolaou group chose to pursue their synthetic strategy with the unnatural C9 epimer, presumably to enhance the facial selectivity in this key cyclization. On the other hand, the explanation for the side selectivity of the *ortho*-quinone remains relatively elusive. One would expect, owing to the free rotation around C2′–C3′ bond, that the *ortho*-quinone would adopt a more favorable conformation for the [4+2] addition. Based on previous model calculations,[8] an unfavorable 1,3-benzylic strain between 4′-OBn and 2′-OMe might disfavor the transition state leading to the other possible regioisomer. The successful cycloaddition revealed the complete sporolide ring framework. Subsequent multistep transformations involving an oxidative dearomatization, inversion of the stereogenic center at C9, regio- and diastereoselective epoxidation, and standard functional group conversions proceeded uneventfully to yield sporolide B.

In summary, a sequence of two impressive cycloadditions paved the way for the first total synthesis of sporolide B by the Nicolaou group. Firstly, a regioselective [2+2+2] cycloaddition of two highly elaborate substrates assembled the halogenated aromatic ring. Secondly, an [4+2] cyclization of an *ortho*-quinone stereoselectively closed the dioxane-containing macrocycle. Both reactions clearly demonstrate their power and true applicability in complex natural product syntheses. It is expected that further applications will be pursued.

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