Natural Product Synthesis

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A Diels–Alder Macrocyclization Enables an Efficient Asymmetric Synthesis of the Antibacterial Natural Product Abyssomicin C**

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In memory of Murray Goodman

In their pioneering report on the diene synthesis, or the Diels–Alder reaction, Otto Diels and Kurt Alder recognized the profound impact that this pericyclic reaction would have in the syntheses of "complex compounds related to or identical with natural products" and speculated that this process may also be involved in the biosyntheses of natural products.[1] As the premier method for the construction of functionalized and stereochemically complex six-membered-ring systems,[2] the Diels–Alder reaction is the foundation of some of the most important achievements in chemical synthesis, and the question concerning its relevance in biosynthesis is the subject of much active research.[3] There is a wealth of natural products that could conceivably arise from biosyntheses that feature the Diels–Alder reaction.[4] We reasoned that much of the architectural complexity of the polycyclic marine natural product abyssomicin C (**1**) could arise from a Diels–Alder macrocyclization step and were intrigued by the possibility that such a transformation may also occur in the biogenesis of this natural product.

Süssmuth and co-workers recently described the isolation of abyssomicin C and two related compounds from a sediment sample collected 289 m beneath the surface of the Sea of Japan.[5] These natural products are produced by the rare actinomycete *Verrucosispora* and possess complex polyketide-like structures that were elucidated through extensive NMR spectroscopic studies and an X-ray crystallographic analysis. Abyssomicin C is unique within this new class of marine natural product in its ability to inhibit Gram-positive bacteria, including pathogenic methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* strains.[5,6] Although its biomolecular target in bacteria is not yet known, abyssomicin C blocks the conversion of chorismate to *para*-aminobenzoic acid (*p*ABA) and is thus an early-stage inhibitor of the biosynthesis of tetrahydrofolate (Scheme 1).

Inhibitors of the biosynthesis of *p*ABA are highly attractive as potential antibacterial drugs because *p*ABA is produced in many microorganisms but not in humans. As the first bacterial metabolite that inhibits the biosynthesis of *p*ABA, abyssomicin C is an attractive lead structure for the development of new inhibitors of pathogenic bacteria and a compelling objective for research in chemical synthesis.[7] Herein, we describe a remarkably diastereoselective Diels–Alder macrocyclization in the context of a convergent asymmetric synthesis of (−)-abyssomicin C (**1**). Our preferred design reduced the complexity of the target structure to three fragments and called for two carbonyl addition reactions to achieve key bond formations (Scheme 2).

In this scenario, an intermolecular aldol reaction between the hypothetical ketone enolate **2** and commercially available *trans*,*trans*-2,4-hexadienal (**3**) would be followed by the addition of a lithiated tetronate **4** to an aldehyde carbonyl group. A simple adjustment of the oxidation state would then furnish the needed γ-methylene-β-tetronate derivative **5** for the crucial intramolecular Diels–Alder step.[8] Some impressive large-ring formations that were achieved by the Diels–Alder method[9] bolstered our confidence in the idea that **5** might cycloisomerize to tricycle **6**. If successful, this transformation would establish a substantial portion of the architecture of abyssomicin C and afford a valuable cyclohexenyl double bond for a late-stage epoxidation reaction. Provided that such an oxidation reaction could be achieved in a site- and diastereoselective fashion, we hoped to form the

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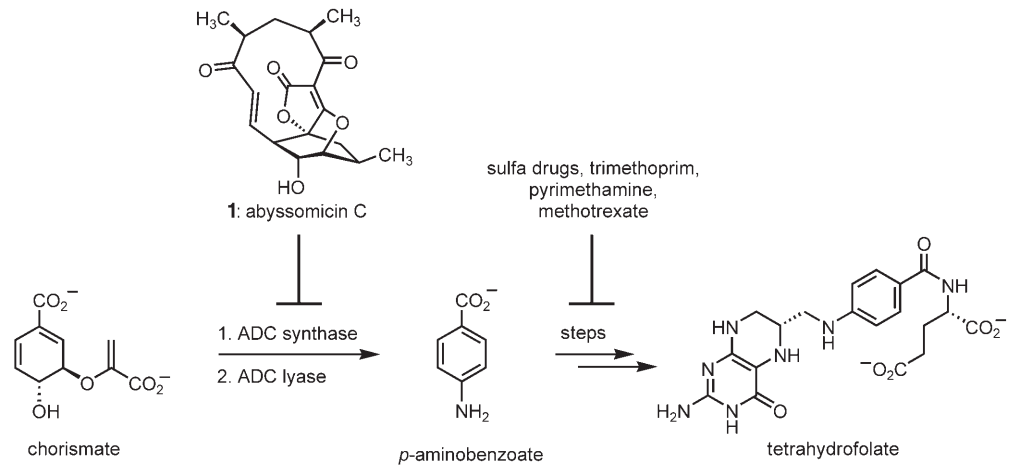
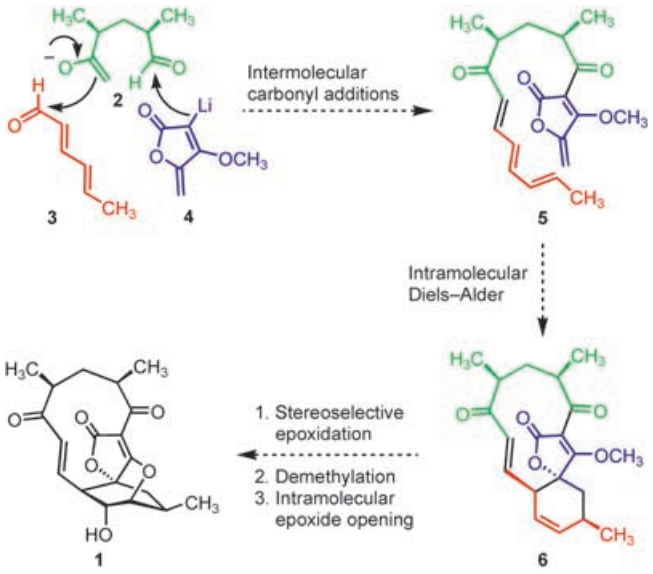
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. The marine natural product abyssomicin C (**1**) inhibits the conversion of chorismate into *para*-aminobenzoic acid (*p*ABA). ADC = aminodeoxychorismate.[6]



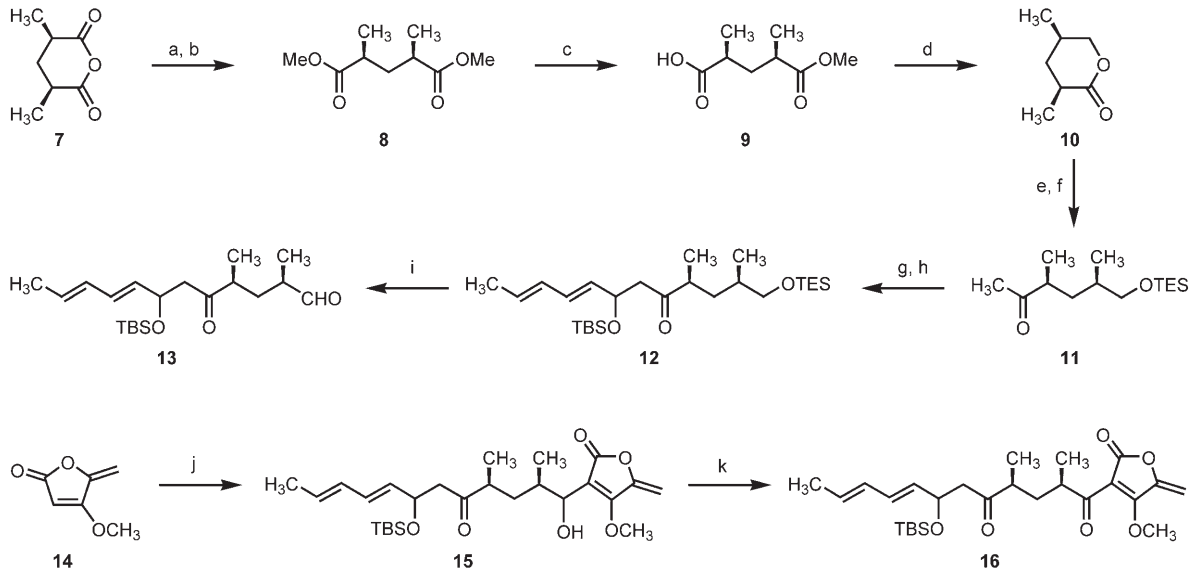
Scheme 2. Design for a synthesis of abyssomicin C which features a Diels–Alder macrocyclization.

rigid oxabicyclo[2.2.2]octane substructure of **1** by a *trans*-diaxial opening of the epoxide by a tetronic acid function that would be exposed by demethylation. The successful execution of this general plan is described below.

Because of the symmetrical nature of the hypothetical species **2**, *meso*-2,4-dimethylglutaric anhydride (**7**) was considered to be an ideal starting material for our synthesis (Scheme 3). This substance was prepared on a 100-gram scale by a combination of the procedures developed by Paquette and Boulet[10] and Lautens and co-workers[11] and was subsequently advanced to the known prochiral dimethyl ester **8** in the straightforward fashion shown. The enzymatic desymmetrization procedure of Lautens and co-workers, which had previously been applied to the acyclic *meso*-diester **8**,[11] provided a smooth high-yielding route to the optically active monocarboxylic acid **9**. A chemoselective reduction of the ester function with lithium borohydride was followed by an acid-catalyzed lactonization to **10**, a known substance[12] that was judged to have an optical purity of 93% *ee* by HPLC analysis. The action of methyllithium on lactone **10** gave the corresponding lactol, after which a simple alcohol silylation step caused ring-opening and afforded methyl ketone **11**.

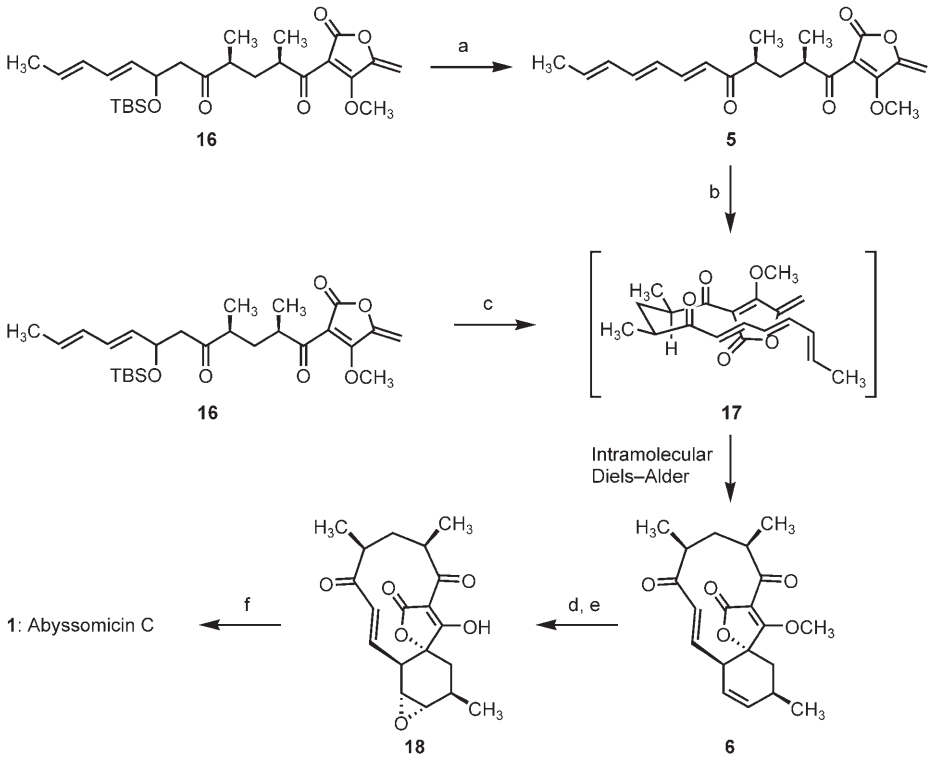
Our aim was to utilize **11** in an intermolecular aldol addition reaction with **3**. The commercially obtained dienal **3** is admixed with as much as 10 mol% of the 4-*cis* geometrical isomer, so we opted to produce this compound from all-*trans* 2,4-hexadien-1-ol through a Swern oxidation.[13] Aldehyde **3**, prepared in this manner, was taken forward into the key aldol step in crude form. Under the reaction conditions shown, **3** joined efficiently with the kinetic lithium enolate derived from **11**, thus resulting in the formation of a 1:1 mixture of secondary alcohol epimers. A straightforward alcohol silylation step then gave a diastereoisomeric mixture of silyl ethers, shown as **12**. Our intent was to unveil the sensitive triene array of the targeted Diels–Alder substrate immediately before (or perhaps during) the key cycloaddition event through a simple β elimination. Therefore, the production of epimers in the aldol construction of **12** was ultimately inconsequential.

It was pleasing to discover that the triethylsilyl ether in **12** could be directly transformed to keto aldehyde **13** by a Swern oxidation.[14] Our expectation that this electrophilic compound would react chemoselectively with organolithium reagent **4**, the conjugate base derived from the known methyl tetronate **14**,[15] was justified by the construction of intermediate **15** under the conditions shown. This reaction, which established a key carbon–carbon bond and afforded material that contains all of the carbon atoms of abyssomicin C, can be performed on gram scales, although its yield is typically modest and variable (e.g., 35–55%).[16] This aldehyde addition process also yielded a mixture of alcohol diastereoisomers that could be resolved by chromatography on silica gel. However, it was our custom to convert this mixture of four diastereoisomers into two through an alcohol oxidation with the Dess–Martin periodinane reagent.[17] This oxidation proceeded efficiently and yielded the desired acyl tetronate **16**.



Scheme 3. a) MeOH, reflux, 24 h; b) MeOH, H_2SO_4 (cat.), benzene, reflux, 18 h (87%, 2 steps); c) α-chymotrypsin, phosphate buffer pH 7.8, 23 °C, 4 days (96%); d) $LiBH_4$ (2 equiv), THF, 50 °C, 5 h; then HCl, H_2O, 23 °C, 15 h (60%, 93% *ee*); e) MeLi (1.3 equiv), THF, −78 °C, 1.5 h; f) TESCl (1.1 equiv), imidazole (2 equiv), DMF, 0 °C, 1.5 h (79%, 2 steps); g) LDA, THF, −78 °C, 2.5 h; then *trans,trans*-2,4-hexadienal (1.1 equiv), 1.5 h (94%, d.r. = 1:1); h) TBSOTf (1 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, 0 °C, 0.5 h (85%); i) $(COCl)_2$ (5 equiv), DMSO (10 equiv), Et_3N (10 equiv), CH_2Cl_2, −40→−78 °C, 5 h (60–70%); j) LDA, toluene, −78 °C, 6 min; then aldehyde **13**, 1.5 h (35–55%, d.r. = 1:1); k) DMP (1.5 equiv), CH_2Cl_2, 0→23 °C, 1.5 h (84%). TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, DMP = Dess–Martin periodinane.

The decision to utilize a β-*tert*-butyldimethylsilyloxy keto function as a progenitor to the required trienone array proved to be well founded. Preliminary observations indicated that trienone **5** is a rather unstable substance. Fortunately, we could generate this compound upon exposure of a solution of intermediate **16** in dichloromethane to 5 mol% of the Lewis acid scandium(III) triflate (Scheme 4). Much to our delight, the crude trienone **5** underwent a remarkably efficient and highly diastereoselective cycloisomerization to tricycle **6** when heated to 100 °C in toluene. To avoid handling the sensitive trienone **5**, we searched for reaction conditions that would permit the β-elimination/Diels–Alder sequence to be conducted in a one-pot process. We hoped to find a Lewis acid catalyst that would effect the required elimination of *tert*-butyldimethylsilanol on heating and that this event would trigger the desired Diels–Alder cyclization of the intermediate trienone **5** to **6**. Among the metal triflates that were examined, lanthanum(III) triflate was capable of inducing the direct conversion of **16** into tricycle **6** under the conditions shown. This transformation was also highly diastereoselective; **6** formed cleanly, and we did not observe any other regioisomeric or diastereoisomeric cycloadducts. In an effort to gain some insight into this interesting and fortunate selectivity, we located the transition states for all of the possible intramolecular Diels–



Scheme 4. a) $Sc(OTf)_3$ (5 mol%), CH_2Cl_2, 0 °C, 40 min (65%); b) toluene, 100 °C, 4 h (79%); c) [La(OTf)$_3$] (10 mol%), toluene, 100 °C, 4 h (50%); d) DMDO (1 equiv), acetone, 0→23 °C, 18 h (67%); e) LiCl (10 equiv), DMSO, 50 °C, 2 h (quant.); f) *p*-TsOH (1.2 equiv), LiCl (5 equiv), CH_3CN, 50 °C, 2 h (50%). DMDO = dimethyldioxirane, *p*-TsOH = *para*-toluenesulfonic acid monohydrate.

Alder reactions at the HF/3-21G level of theory.[18] The lowest-energy transition-state conformation clearly resembled **17**, and the next lowest transition-state conformation was 5.7 kcal mol^{-1} higher in energy. This analysis predicts that **5** should cycloisomerize through conformer **17**, an asynchronous transition state that has an *anti* relationship between the two carbonyl groups that are part of the acyl tetronate moiety.

From the vantage of **6**, only three seemingly straightforward transformations were needed to reach the target structure. Fortunately, dimethyldioxirane was well suited to the oxidation of the newly formed cyclohexenyl double bond.[19] This site- and diastereoselective oxidation produced the desired epoxide and was followed by a quantitative nucleophilic demethylation of the acyl methyl tetronate substructure. This two-step reaction sequence afforded **18**, a compound that appeared to be an ideal precursor to abyssomicin C (**1**). Because of its carboxylic acid like nature, the hydroxy group in **18** is a weak nucleophile. Compound **18** is essentially impervious to basic reagents; all efforts to achieve base-induced heterocyclizations to abyssomicin C were unsuccessful. After much experimentation, we found that warming a solution of **18**, *para*-toluenesulfonic acid monohydrate, and lithium chloride in acetonitrile to 50 °C for 2 h resulted in the formation of abyssomicin C (**1**) and a regioisomeric substance that we named "iso-abyssomicin C". Under these conditions, the ratio of these two compounds is 1:1, but they are readily separated by chromatography on silica gel. Optical rotation studies of our sample of synthetic abyssomicin C (**1**) showed an $[\alpha]_D^{20}$ value of -40 ($c = 0.1$, MeOH), and spectroscopic studies (^{1}H and ^{13}C NMR, UV, and IR) resulted in data that matched those reported by Süssmuth and co-workers.[5]

In summary, a concise enantioselective synthesis of (−)-abyssomicin C was achieved in 15 steps from the known *meso*-2,4-glutaric anhydride (**7**) by a reaction sequence that features a highly diastereoselective Diels–Alder macrocyclization. We can procure significant amounts of the natural product by this route, which should facilitate an investigation of the intriguing biological properties of abyssomicin C. It was proposed that the rigid oxabicyclo[2.2.2]octane substructure of abyssomicin C (**1**) may serve as a structural surrogate for the conformation of chorismate in solution and that its electrophilic enone system may inactivate one of the enzymes involved in the biosynthesis of *p*ABA in bacteria (Scheme 1) through covalent alkylation.[5] By adapting the chemistry described herein, we anticipate that it will be possible to synthesize affinity-tagged variants of abyssomicin C for studies of its potential chemical reactivity and binding properties in human-tissue proteomes.[20,21] This information would be part of a comprehensive analysis of the potential of abyssomicin C as an antibacterial drug candidate. Further studies of this fascinating early-stage inhibitor of the biosynthesis of tetrahydrofolate in bacteria are clearly warranted.

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