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Rapid Access to the Tricyclic Spirotetronic Core of Abyssomicins

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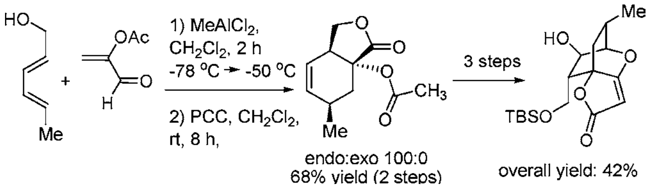
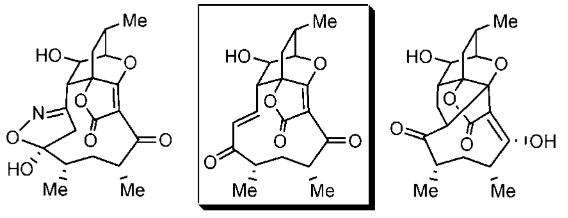
ABSTRACT



Abyssomicins, a novel class of polyketide antibiotics, are characterized by an unprecedented spirotetronic tricyclic subunit in their structure. In this letter, a short synthesis of a suitably functionalized tricyclic precursor of abyssomicins is reported. Key steps of the synthesis are (i) the highly stereoselective Al(III)-tethered Diels–Alder reaction and (ii) the tandem Dieckmann cyclization/TBS trapping of the C9 hydroxyl group followed by a regioselective intramolecular epoxide opening for the assembly of the target tricyclic structure.



Abyssomicin B Abyssomicin C Abyssomicin D

Figure 1. Structure of Abyssomicins B, C, and D.

Most recently, the isolation of abyssomicins, a novel class of macrocyclic polyketides, from the rare marine actinomycete *Verrucosispora* was reported by the research group of R. Süssmuth (Figure 1).[1] Among these secondary metabolites, abyssomicin C can potently inhibit tetrahydrofolate (THF) biosynthesis.[2] This property renders abyssomicin C a promising lead structure for the development of new antibiotics against gram-positive resistant bacteria. From a structural point of view, abyssomicins possess a unique oxabicyclo[2.2.2] octane subunit consisting of a spirotetronic acid which bridges a highly functionalized cyclohexyl ring through an enol ether moiety. All the above features make abyssomicin C an attractive synthetic target. However, no total synthesis of this molecule has been reported yet. While this work was in progress, a first synthetic approach toward abyssomicins' core by Maier et al. appeared in the literature.[3] In this letter, we disclose a short stereoselective synthesis of the main tricyclic nucleus of abyssomicins.

A retrosynthetic approach for abyssomicin C is illustrated in Figure 2. In our analysis, we planned to obtain the macrocycle of abyssomicin C by an acylation/RCM reaction sequence between **1** and **2**. Precursor **2** could be obtained by direct functional group transformations of advanced intermediate **3**, which contains the common core for all abyssomicins tricyclic spirotetronates. Since the C11 and C12 oxygen substituents of the target molecule exhibit an *anti*-stereochemical relationship, we envisioned that this pattern could be the outcome of a regioselective epoxide opening of intermediate **4** by the spirotetronate moiety. We assume

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[1] Bister, B.; Bischoff, D.; Ströbele, M.; Riedlinger, J.; Reicke, A.; Wolter, F.; Bull, A. T.; Zähner, H.; Fiedler, H.-P.; Süssmuth, R. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2574.

[2] Riedlinger, J.; Reicke, A.; Zähner, H.; Krismer, B.; Bull, A. T.; Maldonado, L. A.; Ward, A. C.; Goodfellow, M.; Bister, B.; Bischoff, D.; Süssmuth, R. D.; Fiedler, H. P. *J. Antibiot.* **2004**, *57*, 271.

[3] Rath, J.-P.; Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089.

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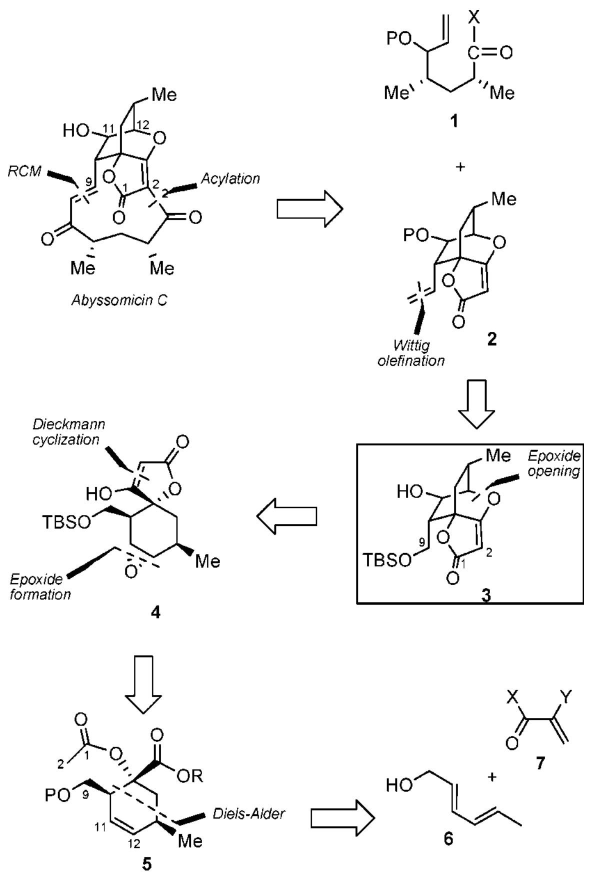
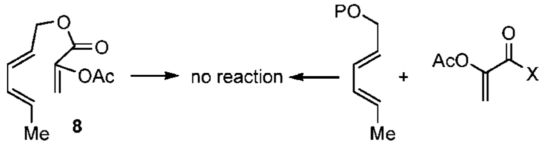


Figure 2. Retrosynthetic analysis.

that such a transannulation could relate to a putative biosynthetic process that leads to abyssomicins' core. Structure **4** was anticipated to result from Dieckmann cyclization−epoxidation of a type **5** compound. Finally, a regio- and stereoselective Diels−Alder (DA) cyclization was chosen to provide the cyclohexyl ring, starting from commercially available dienol **6** and the appropriate dienophile.

Unfortunately, we encountered several difficulties not long after we embarked on our synthetic efforts. In our first unsuccessful approach, we examined an intramolecular DA (IMDA) strategy on ester **8**[4] under various conditions (Scheme 1).[5] Then, we focused on an intermolecular DA between TBS or PMB ethers of **6** with either 2-acetoxy acrolein[6] or 2-acetoxy acrylic esters.[7] Unfortunately, all reactions failed either with thermal or with Lewis acid (LA) catalysis. Failure of the above reactions was attributed to a possible negative effect of the −OAc group on the reactivity of the captodative dienophilic component.[8,9]

Scheme 1. Unsuccessful Attempts for DA Cyclization[a]



[a] P: TBS or PMB protecting groups; X: H or OR.

Recently, Ward et al. reported an elegant LA-catalyzed DA process between **6** and methyl acrylate.[10] Ward suggested that Al(III) or Mg(II) LAs are able to tether hexadienol **6** and methyl acrylate in a preorganized DA intermediate and promote a highly stereoselective DA cyclization. We decided to use Ward's synthetic protocol for the reaction between **6** and 2-acetoxy acrolein (**10**) or acrylic esters (Me$_2$AlCl or MgBr$_2$ catalysis at room temperature), but unfortunately, no detectable DA products were observed in our system. Nevertheless, we insisted on applying the LACASA-DA[11] concept to the case of captodative dienophiles.[12] After screening a variety of conditions, we were finally able to elicit the desired cycloaddition using MeAlCl$_2$ and a precise order of addition. Thus, when 1.5 equiv of MeAlCl$_2$ was added to a mixture of **6** and **10** in CH$_2$Cl$_2$ or toluene at -78 °C, lactol **11** was obtained in high yield as a C1-epimeric mixture (Scheme 2).[13] It is important to note that the reaction was effective *only* (i) when the aforementioned order of reagent addition was followed, and (ii) when low reaction temperatures were used. The latter helps prevent **6** from decomposing. We believe that the above method could extend the scope of LACASA-DA reactions, a subject which is currently under investigation in our laboratory.

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(4) Prepared by a novel selective O-acetylation of the pyruvic ester of **6** (unpublished results).

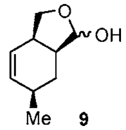
(5) For IMDAs of relevant systems bearing other dienophilic parts, see: (a) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323. (b) Lilly, M. J.; Paddon-Row, M. N.; Sherburn, M. S.; Turner, C. I. *J. Chem. Soc., Chem. Commun.* **2000**, 2213. (c) Kim, P.; Tsuruda, J. M.; Olmstead, M. M.; Eisenberg, S.; Kurth, M. J. *Tetrahedron Lett.* **2002**, *43*, 3963. (d) Cayzer, T. N.; Wong, L. S.-M.; Turner, P.; Paddon-Row, M. N.; Sherburn, M. S. *Chem.*—*Eur. J.* **2002**, *8*, 740.

(6) Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

(7) For DA reactions of 2-acetoxy dienophiles, see: (a) Funk, R. L.; Yost, K. J., III. *J. Org. Chem.* **1996**, *61*, 2598. (b) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402. (c) Takeda, K.; Imaoka, I.; Yoshii, E. *Tetrahedron* **1994**, *50*, 10839.

(8) For a study on the reactivity of captodative acrylates in DA reactions, see: Herrera, R.; Jimenez-Vazquez, H. A.; Modelli, A.; Jones, D.; Soderberg, B. C.; Tamariz, J. *Eur. J. Org. Chem.* **2001**, 4567.

(9) In sharp contrast, unsubstituted acrolein reacted readily with **6** in water, affording a bicyclic lactol with high stereoselectivity as a mixture of C1-epimers. See: Bulman Page, P. C.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, *7*, 1022.



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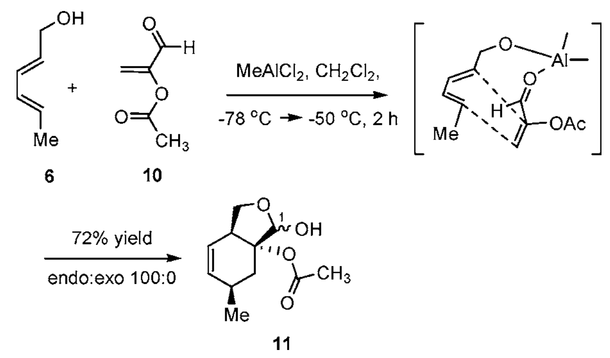
(10) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937.

(11) The term LACASA-DA (Lewis Acid CAtalyzed Self-Assembled Diels−Alder) has been introduced by Ward. See ref 10.

(12) For DA examples with classical dienophiles following a similar mechanistic scenario, see: (a) Snider, B. B.; Phillips, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 1113. (b) Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003. (c) Bienayme, H.; Longeau, A. *Tetrahedron* **1997**, *53*, 9637. (d) Bienayme, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2670.

(13) In fact, ^{1}H NMR of the crude DA product, after nonacidic workup, showed the presence of a single stereoisomer of lactol **11**. This preference could be expected for a lactolization process occurring *after* the stereospecific formation of the cyclohexyl ring. Crude **11** is readily epimerized by silica gel during chromatographic purification, affording finally a mixture of C1-epimers in a ratio $\sim$3.5:1.

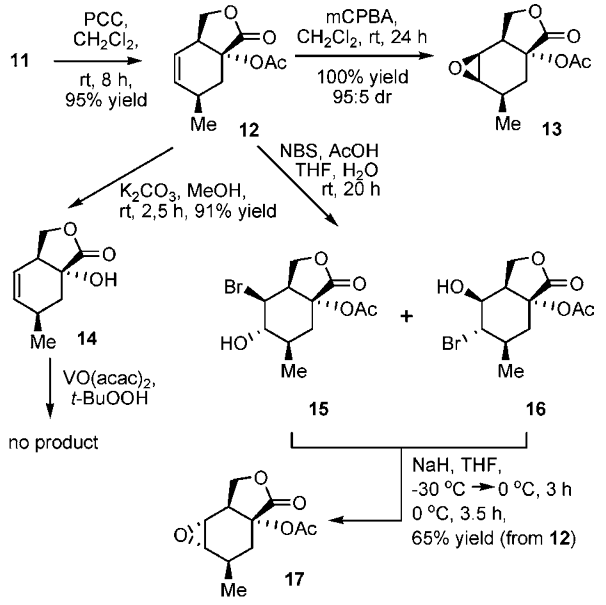
Scheme 2. Application of a LACASA-DA Reaction toward the Synthesis of Lactol **11**



In the next step, lactol **11** was oxidized with PCC to afford smoothly the corresponding lactone **12**. When we attempted to epoxidize lactone **12**, we were surprised to see that epoxide **13** was mainly produced (**13**:**17** ~ 95:5).[14] We tried to invert this unexpected stereochemical preference by saponifying the acetyl ester and then directing the epoxidation syn to the hydroxyl function using VO(acac)$_2$/*t*-BuOOH,[15] but unfortunately, no epoxidation product was observed. Finally, the desired epoxide was synthesized as a single diastereoisomer by converting **12** into a mixture of the two bromohydrin isomers **15** and **16** and inducing cyclization with NaH. Compound **17** was obtained in 65% yield for the two steps.

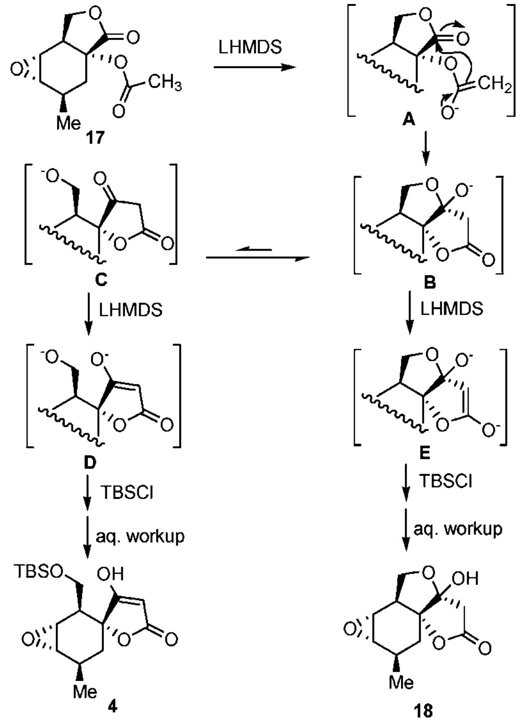
The next step of the synthesis involved a Dieckmann condensation to access the tetronic acid ring system. Surprisingly, the main product of the reaction of **17** with LHMDS at low temperatures was a single epimer of the tricyclic lactol **18** (Scheme 4).[16] Moreover, lactol **18** displayed a remarkable inertness toward all efforts to open its hemiketal group and trap the released hydroxyl with a silicon protecting group under standard protocols.[17] Interestingly, tetronic acid **4** could only be produced when 2 equiv of LHMDS was added to a mixture of lactol **18** and 2 equiv of TBSCl. In light of this, we explored the possibility of combining these last two steps and attempting a sequential Dieckmann reaction/TBS trapping of the C9 hydroxyl group. In an early experiment, 2 equiv of LHMDS was added at −30 °C to a mixture of 2 equiv of TBSCl and **17**, and the reaction was stirred for 3 h between −30 and 0 °C and for 3 h at room temperature and quenched with H$_2$O. After extraction with Et$_2$O and NaHSO$_4$ acidification of the aqueous solution, the tetronic acid **4** was mainly obtained, according to analysis of the 200 MHz ^{1}H NMR spectrum of the crude product in CDCl$_3$.[18] The need for inverse reagent addition can be rationalized by a mechanism that includes a fast trapping of dianion **D**, which would shift the equilibrium between **B** and **C** to the open chain intermediate (Scheme 4). This shift could prevent the irreversible formation of dianion **E**, which would afford lactol **18**.

Scheme 3. Epoxidation of Lactone **14**



A closer inspection of the 200 MHz ^{1}H NMR spectrum of the above reaction (in CDCl$_3$) revealed that small amounts

Scheme 4. Putative Pathway for the Formation of **4** and **16**



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(14) This unexpected preference during mCPBA epoxidation of **12** was observed also by Maier (ref 3), who verified the structure of **12** by X-ray analysis of its Dieckmann cyclization product.

(15) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

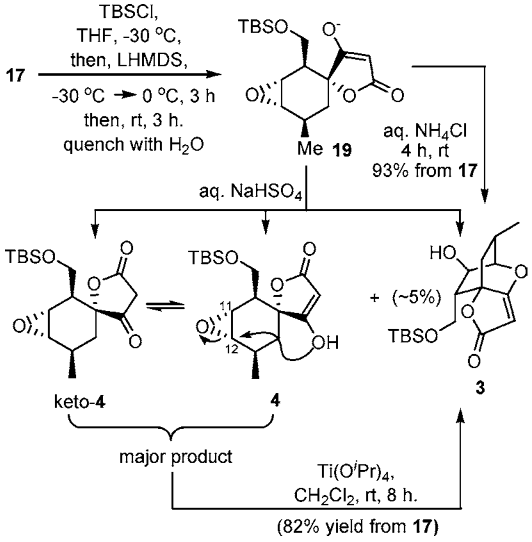
(16) The formation of a single epimer (**18**) is in accordance with the recent work of Maier (ref 3) and also with the observation of Kraus et al. during a similar Dieckmann cyclization toward a three-ring phytuberin precursor. See: (a) Kraus, G. A.; Wang, X. *Synlett* **1999**, *9*, 1395. (b) Guzei, I. A.; Wang, X. M.; Kraus, G. A. *Acta Crystallogr. C* **2000**, *56*, 389.

(17) For similar transformations, see: (a) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563. (b) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (c) Kato, K.; Sasaki, T.; Takayama, H.; Akita, H. *Tetrahedron* **2003**, *59*, 2679.

of lactol **18** and an unknown product with a characteristic singlet at δ 4.92 ppm were also present in the mixture. We observed that when the acidification with dilute $NaHSO_4$ solution and extraction of the aqueous phase with Et_2O were performed quickly the unknown product was still partially obtained but the formation of **18** was totally suppressed. This clearly indicated that lactol **18** was being formed during acidification due to acidic cleavage of the TBS group of **4** and not during the reaction. We attribute this enhanced lability of the TBS group to an intramolecular interaction with the proximal tetronic acid rather than exclusive direct cleavage in the acidic medium. Moreover, we observed that the crude product of the above reaction was quantitatively transformed to the unknown product when treated with 1 equiv of $Ti(O^iPr)_4$ in CH_2Cl_2. Interestingly, NMR analysis of the unknown product revealed that it corresponded to the target molecule **3**. Obviously, $Ti(O^iPr)_4$ was able to catalyze the intramolecular epoxide opening[19] of **4** in a regioselective manner.[20] We assume that the excellent regioselectivity of this reaction is dictated by the perpendicular correlation between the flat tetronic ring and the carbocycle which directs nucleophilic attack exclusively to the opposite carbon center, that is, C12 (Scheme 5).

Finally, we tried to merge the Dieckmann reaction/TBS trapping sequence with the epoxide opening. After several experiments, we succeeded in achieving this transformation using NH_4Cl instead of $NaHSO_4$ during the workup and stirring the aqueous solution for 4 h (Scheme 5). At these conditions (pH ~ 6), **4** exists in its anionic form, thus preventing the TBS cleavage. Nevertheless, the pH of this medium is sufficient to protonate the epoxide, thus promoting the desired nucleophilic opening by the tetronate anion. A simple extraction with Et_2O afforded the target compound in 93% yield starting from epoxide **17**.

Scheme 5. Synthesis of Tricyclic Tetronate **3**



In conclusion, we have developed a stereoselective synthesis of the core structure of abyssomicin C, which affords the target molecule in five steps and 42% overall yield, and which uses only two column chromatographic purifications. The synthesis starts from commercially available hexadienol **6** and 2-acetoxy acrolein and comprises novel transformations, such as the first stereoselective Al(III)-tethered Diels–Alder reaction of a captodative dienophile and an interesting cascade reaction that led to the target molecule. Completion of the synthesis is currently underway.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] We should mention at this point that **4** is in constant tautomerism with its keto form (see Scheme 5), as it was determined by its ^{1}H NMR($CDCl_3$) spectrum.

[19] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

[20] Maier et al. describes a spontaneous intramolecular epoxide opening in a similar intermediate, which was not observed in our case (see ref 3).