ORGANIC LETTERS

2005
Vol. 7, No. 22
4939−4941

Synthesis of the Carbocyclic Skeleton of Abyssomicins C and D

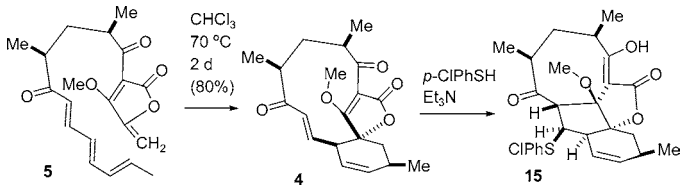
Barry B. Snider* and Yefen Zou

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

snider@brandeis.edu

Received August 6, 2005

ABSTRACT



Intramolecular Diels–Alder substrate trienyl methylenebutenolide 5 was prepared in six steps by coupling 3-methoxy-4-methylenebutenolide (6) with trienone keto aldehyde 7. Heating 5 in $CHCl_3$ for 2 d at 70 °C afforded 80% of a single Diels–Alder adduct 4 with the complete carbon skeleton of abyssomicin C. Addition of thiophenoxide to the enone double bond of 4 followed by an intramolecular Michael addition afforded 15 with the abyssomicin D carbon skeleton.

Abyssomicin C (**1**) was recently isolated from a marine *Verrucosispora* strain collected from sediment at a depth of 289 m in the Japanese sea. It shows antibiotic activity against a variety of Gram-positive bacteria including pathogenic *Staphylococcus aureus* strains and drug-resistant strains.[1] The biologically inactive congener abyssomicin D (**2**) is probably formed from **1** by conjugate addition of hydride to the enone and intramolecular Michael addition.[1]

Abyssomicin C might be accessible by the biomimetic route outlined below in Scheme 1. We thought that abyssomicin C (**1**) could be formed by cyclization of epoxy alcohol **3**, an approach validated by the recent synthesis of the oxabicyclo[2.2.2]octane core by Maier.[2] Epoxy alcohol **3** would be prepared from **4** by epoxidation of the more nucleophilic cyclohexene double bond from the less hindered bottom face and hydrolysis of the vinylogous carbonate.

In the key step, cyclohexene **4** would be formed by an intramolecular Diels−Alder reaction of **5**, which should be readily available by addition of the carbanion formed by deprotonation at C-2 of butenolide **6** to aldehyde **7**. This Diels−Alder reaction is very risky for several reasons. First, three new stereocenters are generated in the cycloaddition so that four products can be formed. Both endo and exo adducts are possible. Facial selectivity is also an issue. Will the two methyl groups on the tether control the approach of the diene and the dienophile? The reactivity of the methylene butenolide as a dienophile is also a concern. Yoshii reported intermolecular Diels−Alder reactions of **6** under forcing conditions by heating in *o*-dichlorobenzene at 180 °C for 7 h to give a modest yield of a 3:1 mixture of isomers in which the major isomer corresponds to **4**.[3] Yoshii also reported that intramolecular Diels−Alder reactions in which the diene was attached to the methylene group of **6** with a three-carbon tether proceeded in benzene at reflux.[4] However, he also found in his synthesis of 24-*O*-methylchlorothricolide that an intramolecular Diels−Alder reaction with a ten-atom

(1) (a) 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*, 2574−2576. (b) 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*, 271−279. (c) Fiedler, H.-P.; Süssmuth, R. D.; Zähner, H.; Bull, A. T. PCT Int. Appl. WO 2005 033114; *Chem. Abstr.* **2005**, *142*, 389059c.

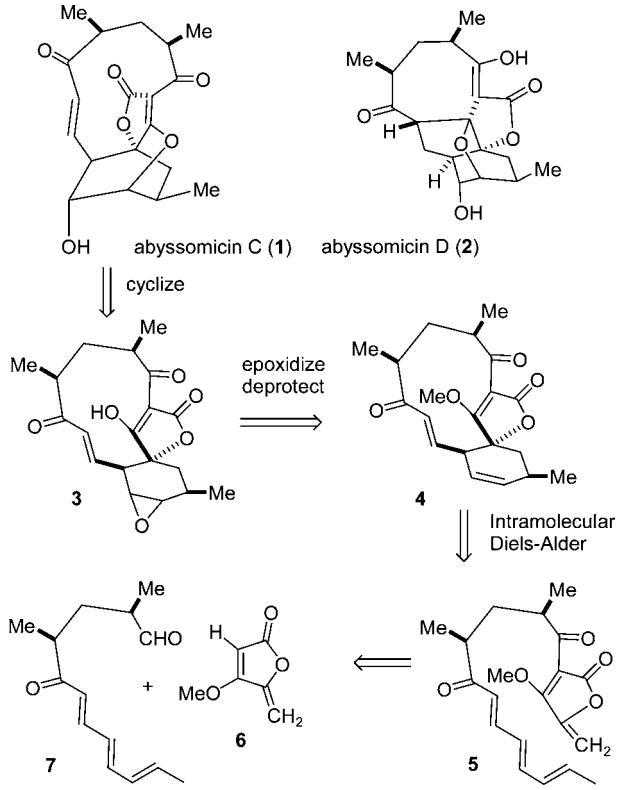
(2) (a) Rath, J.-P.; Eipert, M.; Kinast, S.; Maier, M. E. *Synlett* **2005**, 314−318. (b) Rath, J.-P. Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089−3092.

(3) Takeda, K.; Yano, S.-g.; Sato, M.-a.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135−4137.

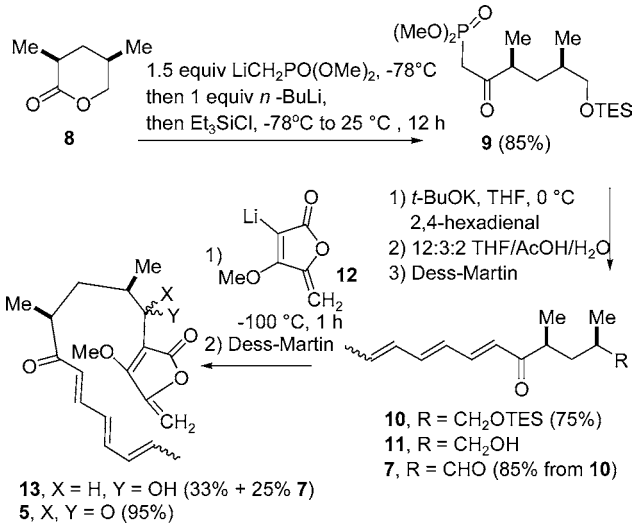
(4) Takeda, K.; Sato, M.-a.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903−3906. See also: Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691−1701.

10.1021/ol0518941 CCC: $30.25
Published on Web 09/24/2005

Scheme 1. Retrosynthesis of Abyssomicin C



Scheme 2. Synthesis of Diels−Alder Substrate **5**



tether attached to **6** as an acyloxy linkage at C-2 proceeded in low yield in *o*-dichlorobenzene at 180 °C to give a mixture of four cycloadducts.[5]

Two factors were more encouraging. The presence of the acyl group in the tether attached to C-2 of the butenolide of **5** should make the dienophile more electron-deficient and therefore more reactive. Finally, the biosynthesis of abyssomicin probably involves a similar Diels−Alder reaction under physiological conditions in which the stereochemistry of the product is controlled by the substrate rather than an enzyme.

Dimethyl lactone **8** was prepared by Andrus' method[6] and converted to keto phosphonate **9** as described by Hoffmann (see Scheme 2).[7] A Wittig reaction of **9** with 2,4-hexadienal afforded 75% of **10** as a 4:1 mixture of *E*- and *Z*-isomers at the terminal double bond.[8] Hydrolysis of the silyl ether of **10** with 12:3:2 THF/AcOH/H_2O afforded alcohol **11**. Dess−Martin oxidation provided aldehyde **7** in 85% yield from **10**. Deprotonation of **6**, which was prepared as described by Paintner,[9] with LDA in THF at −100 °C as described by Yoshii,[10] afforded the carbanion **12**. Reaction of aldehyde **7** with **12** at −100 °C for 1 h afforded alcohol **13** as a mixture of stereoisomers in 33% yield (44% based on recovered **6** and **7**). Dess−Martin oxidation afforded 95% of Diels−Alder substrate **5** still as a 4:1 mixture of *E*- and *Z*-isomers at the terminal double bond. The isomeric mixture should not be a problem because *E,Z*-dienes are much less reactive than *E,E*-dienes in Diels−Alder reactions.

We were pleased to note that **5** slowly underwent a Diels−Alder reaction in $CDCl_3$ at 25 °C with 40% conversion after 1 week indicating that a similar reaction with an OH rather than an OMe substituent on the butenolide could occur under physiological conditions in the biosynthesis without a Diels−Alderase. Heating a solution of **5** in $CHCl_3$ containing 4% hydroquinone in a sealed tube at 70−75 °C for 2 d afforded Diels−Alder adduct **4** in 80% yield based on the reactive stereoisomer **5***E* and recovered **5***Z* in 10% yield (see Scheme 3). Only a single Diels−Alder adduct was isolated. The stereochemistry of **4** about the cyclohexene ring was most convincingly established by an NOE between the methoxy group and the cyclohexene methyl group (H-17), which indicated that the desired adduct was formed in which C-16 is in the endo position. The stereochemistry of the methyl groups in the tether was established by NOE studies on **15** (see below).

Hydrolysis[10] of the vinylogous carbonate of **4** with LiCl in DMSO for 3 d at 25 °C gave vinylogous acid **14** in 88% yield. Unfortunately, attempted epoxidation of the cyclohexene double bond of **14** with *m*-CPBA or DMDO afforded complex mixtures in which the cyclohexene double bond was still present and the enone double bond had reacted. This reactivity of the enone double bond is not surprising.

(5) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431−3434.

(6) Andrus, M. B.; Li, W.; Keyes, R. F. *J. Org. Chem.* **1997**, *62*, 5542−5549.

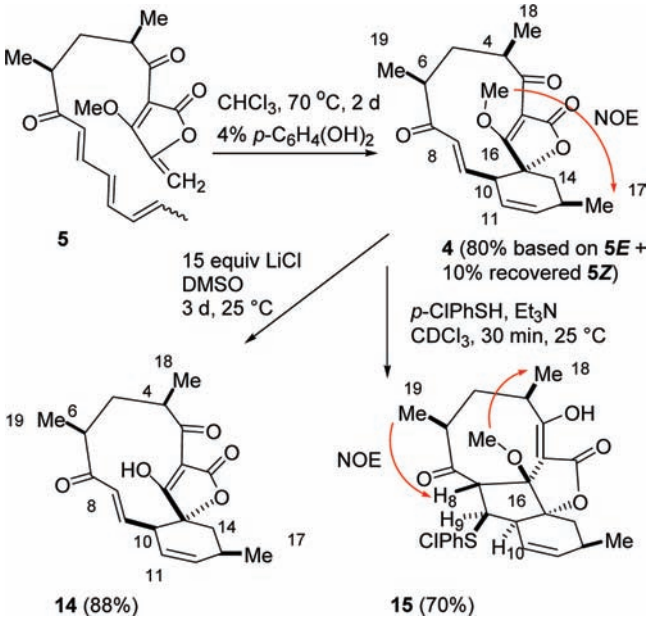
(7) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325−6328. See also: Boeckman, R. K., Jr.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286−8288.

(8) ,4-Hexadienal exists as an equilibrating 4:1 equilibrium mixture of the 2*E*,4*E*- and 2*E*,4*Z*-isomers. See: Gao, X.; Snider, B. B. *J. Org. Chem.* **2004**, *69*, 5517−5527.

(9) Paintner, F. F.; Bauschke, G.; Kestel, M. *Tetrahedron Lett.* **2000**, *41*, 9977−9980. For other preparations of **6**, see ref 3 and: Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. *Tetrahedron* **1991**, *47*, 8285−8296.

(10) (a) Hori, K.; Nomura, K.; Mori, S.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1989**, 712−713. (b) Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925−4928. (c) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888−2902.

Scheme 3. Synthesis of **4** and **15**



Abyssomicins B and D, in which the enone of abyssomicin C has reacted, are biologically inactive, suggesting that the reactive enone double bond of abyssomicin C is crucial for biological activity.[1]

We attempted to protect the enone double bond by conjugate addition of a thiol to give a sulfide, which would later be converted to a sulfoxide or sulfone by oxidation that could be eliminated to regenerate the enone. However, treatment of **4** with *p*-ClPhSH and Et_3N in $CDCl_3$ for 30 min at 25 °C afforded the tetracyclic product **15** in 70% yield. Addition of the thiophenoxide proceeded as expected, but the enolate added to C-16 in an intramolecular Michael addition to give **15** with the carbon skeleton of abyssomicin D. Although **15** is not useful for the synthesis of abyssomicin C, the increased rigidity of **15** allowed us to establish the stereochemistry of the methyl groups in the tether relative to the cyclohexene ring by NOE experiments. An NOE between the methoxy group and one methyl group (H-18) and between H-8 and the other methyl group (H-19) established that the Diels−Alder reaction of **5** proceeded stereospecifically to give **4** with abyssomicin C stereochemistry.

The novel and unexpectedly mild and stereospecific intramolecular Diels−Alder reaction of **5** to give **4** provides facile access to the carbocyclic skeleton of abyssomicin C. We are continuing to explore procedures to epoxidize the cyclohexene to complete the synthesis of abyssomicin C.

Acknowledgment. We thank the NIH (GM50151) for financial support.

Note Added in Proof. While this manuscript was undergoing review, Sorensen reported the preparation of **5** by a related route, the intramolecular Diels−Alder reaction of **5** to give **4**, and further elaboration to complete the synthesis of abyssomicin C: (a) Zapf, C. W.; Harrison, B. A.; Drahl, C. Sorensen, E. J. Abstracts of Papers. *230th National Meeting of the American Chemical Society*; Washington, DC, Aug 28−Sept 1, 2005; American Chemical Society: Washington, DC, 2005; ORGN 234. (b) Zapf, C. W.; Harrison, B. A.; Drahl, C. Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, in press. Georgiadis reported a short synthesis of the oxabicyclo[2.2.2]octane core: Zografos, A. L.; Yiotakis, A.; Georgiadis, D. *Org. Lett.* **2005**, *7*, 4515−4518.

Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0518941