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# Concise Synthesis of the Multiply Oxygenated ABC-Ring System of the Dihydro-β-agarofurans

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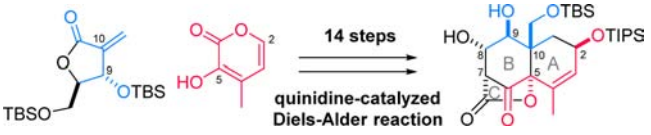
## ABSTRACT




**The multiply oxygenated ABC-ring system of the dihydro-β-agarofurans was synthesized by employing two highly stereoselective reactions. The quinidine-catalyzed Diels–Alder reaction between a chiral dienophile and 3-hydroxy-4-methyl-2-pyrone simultaneously installed the C2-stereogenic center and two contiguous tetrasubstituted carbon centers (C5 and C10) of the A-ring. After 12 additional transformations, the aldol reaction of the resulting spiral AC-ring cyclized the B-ring with stereoselective introduction of the C7- and C8-centers.**

Numerous dihydro-β-agarofuran sesquiterpenoids have been isolated from plants of the Celastraceae family over the years (Scheme 1A).[1] While dihydro-β-agarofurans share a common tricyclic skeleton comprised of a *trans*-decalin (A- and B-rings) and a tetrahydrofuran ring (C-ring), these compounds differ in the oxidation states, stereochemistries, and functionalization patterns of the oxygen-based functional groups. Reflecting these structural variations, they exhibit diverse biological activities, such as antitumor promoting, cytotoxic, anti-HIV, multidrug resistance reversing, anti-inflammatory, and immunosuppressive activities. To develop a general synthetic route applicable to these pharmacologically useful agarofurans, triptofordin F-2[2] and emarginatine B[3] were chosen as initial synthetic targets.[4,5] Here we report the development of an expeditious route to the fused ABC-ring system **1** with multiple oxygen functional groups.

The densely functionalized structures of triptofordin F-2 and emarginatine B pose a formidable synthetic challenge. We designed tricycle **1** as an advanced intermediate for the total synthesis (Scheme 1B). As the five stereocenters (C5, 7, 8, 9, 10) of the ABC-ring of **1** correspond directly to those of the targets, appropriate functional group manipulations of **1** at the C3-olefin, C2-alkoxy, and C6- and C11-carbonyl groups would lead to the targeted molecules. Compound **1** would in turn be assembled by the stepwise ring formation from chiral α,β-unsaturated ester **2** and 3-hydroxy-4-methyl-2-pyrone **3**, which possess the C9-alkoxy and C15-methyl groups in place, respectively. Diels–Alder reaction between **2** and **3** would construct the

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(2) (a) Takaishi, Y.; Ujita, K.; Nakano, K.; Tomimatsu, T. *Chem. Pharm. Bull.* **1988**, *36*, 4275. (b) Takaishi, Y.; Ujita, K.; Tokuda, H.; Nishino, H.; Iwashima, A.; Fujita, T. *Cancer Lett.* **1992**, *65*, 19.

(3) Kuo, Y.-H.; Chen, C.-H.; Kuo, L.-M. Y.; King, M.-L.; Wu, T.-S.; Haruna, M.; Lee, K.-H. *J. Nat. Prod.* **1990**, *53*, 422.

(4) For synthetic studies on related compounds, see: (a) Barrett, H. C.; Büchi, G. *J. Am. Chem. Soc.* **1967**, *89*, 5665. (b) Asselin, A.; Mongrain, M.; Deslongchamps, P. *Can. J. Chem.* **1968**, *46*, 2817. (c) Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435. (d) Heathcock, C. H.; Kelly, T. R. *Chem. Commun.* **1968**, 267a. (e) Büchi, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546. (f) Huffman, J. W.; Raveendranath, P. C. *Tetrahedron* **1987**, *43*, 5557. (g) Li, W.-D. Z.; Zhou, G.; Gao, X.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 4649. (h) Mehta, G.; Kumaran, R. S. *Tetrahedron Lett.* **2003**, *44*, 7055. (i) Boyer, F.-D.; Prangé, T.; Ducrot, P.-H. *Tetrahedron: Asymmetry* **2003**, *14*, 1153. (j) Siwicka, A.; Cuperly, D.; Tedeschi, L.; Vézouët, R. L.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron* **2007**, *63*, 5903. (k) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528. (l) Iwatsu, M.; Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Heterocycles* **2012**, *86*, 181. (m) Webber, M. J.; Warren, S. A.; Grainger, D. M.; Weston, M.; Clark, S.; Woodhead, S. J.; Powell, L.; Stokes, S.; Alanine, A.; Stonehouse, J. P.; Frampton, C. S.; White, A. J. P.; Spivey, A. C. *Org. Biomol. Chem.* **2013**, *11*, 2514.

(5) For a total synthesis of euonyminol, see: (a) White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780. (b) White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404.

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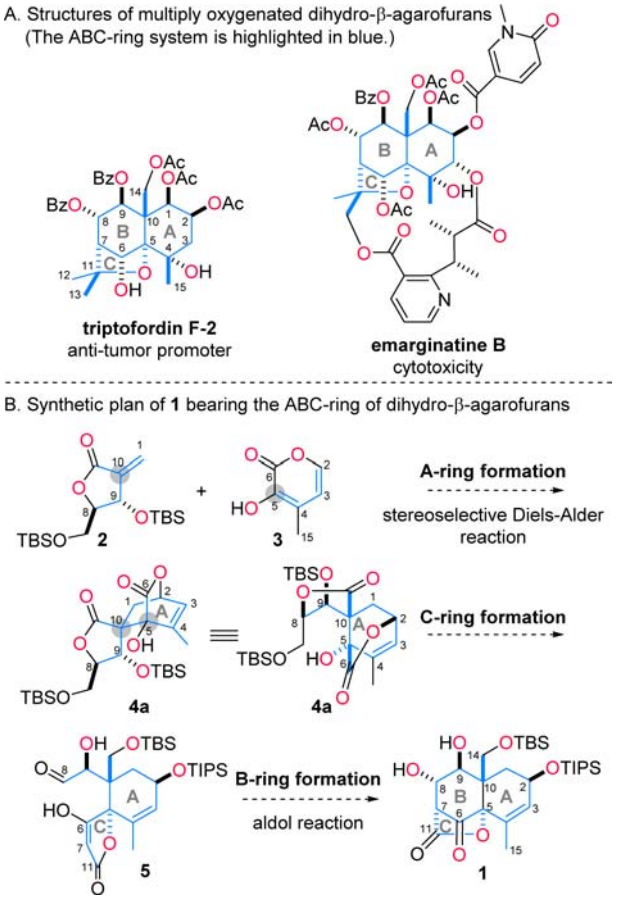
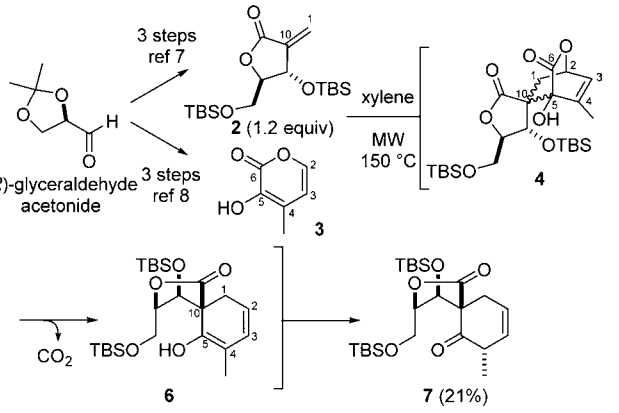
A-ring structure **4a** with establishment of the three new stereocenters (C2, 5, 10).[6] Next, the C-ring would be attached to **4a** via introduction of the C7,11-carbon unit at the C6 position to produce spiral bicycle **5**. Lastly, intramolecular aldol reaction of **5** would form the B-ring through stereoselective introduction of the C7,8-centers.

**Scheme 1.** Structures of Multiply Oxygenated Dihydro-β-agarofurans and Synthetic Plan of **1**




After preparation of both dienophile **2**[7] and diene **3**[8] from (*R*)-glyceraldehyde acetonide in three steps, their Diels–Alder reaction was investigated (Scheme 2). This intermolecular reaction was envisioned to stereoselectively introduce the two contiguous tetrasubstituted (C5 and 10) and C2-hydroxylated carbons. To realize this demanding task, **2** and **3** were first heated to 150 °C in xylene. However, significant amounts of **2** and **3** were recovered, and cycloadduct **4** underwent decarboxylative retro-Diels–Alder reaction, resulting in formation of undesired **7** (21% yield).

**Scheme 2.** Thermal Diels–Alder Reaction of **2** and **3**




Acceleration of the cycloaddition was apparently necessitated to prevent thermal $CO_2$-loss from the adduct **4**. We thus adopted the base-promoted Diels–Alder reaction.[9] A base was expected to enhance the reactivity of **3** by increasing its HOMO energy through deprotonation of the hydroxy group. In fact, treatment of **2** (1.2 equiv) and **3** with 1 equiv of $Et_3N$ in $CHCl_3$ at rt resulted in high yielding formation of the two diastereomeric adducts **4a** and **4b** (**4a**:**4b** = 2.4:1, 87% combined yield, entry 1),[10] and **7** was not detected. To further improve the stereoselectivity of the desired isomer **4a** over **4b**, a set of tertiary amines were screened. Among DABCO (entry 2), quinine **A** (entry 3), and its pseudoenantiomer quinidine **B** (entry 4), **B** was found to be superior in terms of selectivity. The Diels–Alder reaction was also promoted by the presence of **A** or **B** in catalytic amounts (20 mol %, entries 5 and 6). Remarkably, the conditions in entry 6 exclusively produced **4a** in almost quantitative yield (**4a**:**4b** = 29:1). On the other hand, replacement of $CHCl_3$ with MeOH (entry 7) and use of methylated quinidine **C**[11] instead of **B** (entry 8) lowered the selectivity for **4a**.

The correct constructions of the C2-, C5-, and C10-stereochemistries of **4a** reflected the high regio-, face-, and *exo*-selectivity of the quinidine-catalyzed Diels–Alder reaction. The regioselectivity is controlled by the favorable

(6) For representative examples of the Diels–Alder reactions of 3-hydroxy-2-pyrone, see: (a) Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, *16*, 2389. (b) Gladysz, J. A.; Lee, S. J.; Tomasello, J. A. V.; Yu, Y. S. *J. Org. Chem.* **1977**, *42*, 4170. (c) Middlemiss, D. *Synthesis* **1979**, 987. (d) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171. (e) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

(7) (a) Depezay, J.-C.; Merrer, Y. L. *Carbohydr. Res.* **1980**, *83*, 51. (b) Urabe, D.; Yamaguchi, H.; Someya, A.; Inoue, M. *Org. Lett.* **2012**, *14*, 3842. See Supporting Information for the synthesis of **2**.

(8) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364. See Supporting Information for the synthesis of **3**.

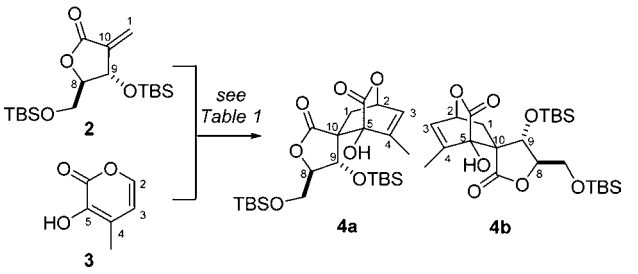
(9) For amine-accelerated Diels–Alder reactions of 3-hydroxy-2-pyrone derivatives, see: (a) Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1995**, *36*, 5939. (b) Okamura, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Chem. Lett.* **1996**, *25*, 193. (c) Okamura, H.; Morishige, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1998**, *39*, 1211. (d) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. See also ref 8. For a review on the amine-accelerated Diels–Alder reaction, see: (e) Shen, J.; Tan, C.-H. *Org. Biomol. Chem.* **2008**, *6*, 3229.

(10) See Supporting Information for the structure determination.

(11) (a) Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641. (b) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537.

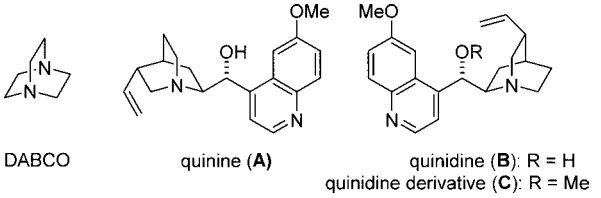
(12) The high regioselectivity of the Diels–Alder reaction using 3-hydroxy-2-pyrone derivatives has been described in literature. See refs 6a–6c and 9.

**Table 1.** Amine-Promoted Diels–Alder Reaction of **2** and **3**[a]




| entry | amine | solvent | yield (**4a**:**4b**) |
|---|---|---|---|
| 1 | $Et_3N$ | $CHCl_3$ | 87% (2.4:1) |
| 2 | DABCO | $CHCl_3$ | 71% (4.0:1) |
| 3 | **A** | $CHCl_3$ | 99% (8.3:1) |
| 4 | **B** | $CHCl_3$ | 92% (15:1) |
| 5 | **A**[b] | $CHCl_3$ | 91% (8.3:1) |
| 6 | **B**[b] | $CHCl_3$ | 99% (29:1) |
| 7 | **B**[b] | MeOH | 68% (3.5:1) |
| 8 | **C** | $CHCl_3$ | 80% (4.0:1) |

[a] Conditions: **2** (1.2 equiv), **3** (1 equiv), amine (1 equiv), solvent (1 M), rt. [b] 20 mol % of amine was used.




interaction of the large coefficient of the LUMO at C1 of dienophile **2** and that of the HOMO at C2 of diene **3**,[12] while the sterically cumbersome C9-TBS-oxy group of **2** blocks one face of the C1-olefin to induce complete face selectivity (Figure 1). These two selectivities dictate generation of only *exo*-adduct **4a** and *endo*-adduct **4b** out of the eight potentially generating isomers of the reaction. The excellent *exo*-selectivity in the presence of quinidine **B** would be influenced by the tight complex between **B** and **3** through the hydrogen-bonding (OH of **B** and C=O of **3**) and ion-pair interactions ($NR_2$ of **B** and OH of **3**). The *endo*-approach via **TS-2** would be impeded by the steric repulsion between the **3**/**B**-complex and the C8-oxymethylene group of **2**,[9b] and the more sterically favorable *exo*-approach via **TS-1** resulted in exclusive generation of **4a**. The lower *exo*-selectivity upon employing the alcoholic solvent (Table 1, entry 7) or the amines bearing no hydroxyl group (entries 1, 2, and 8) supported the importance of the hydrogen bond between the secondary hydroxy group of **B** and the carbonyl group of **3**. Judging from the similar stereochemical outcome in entries 3–6, the proper distance of the hydroxy and tertiary amino groups appears to be more consequential than the chiral centers within **A** and **B**.

Having constructed the A-ring structure with the C5- and C10-tetrasubstituted carbons, introduction of the carbon unit at C6 corresponding to the C-ring was the next

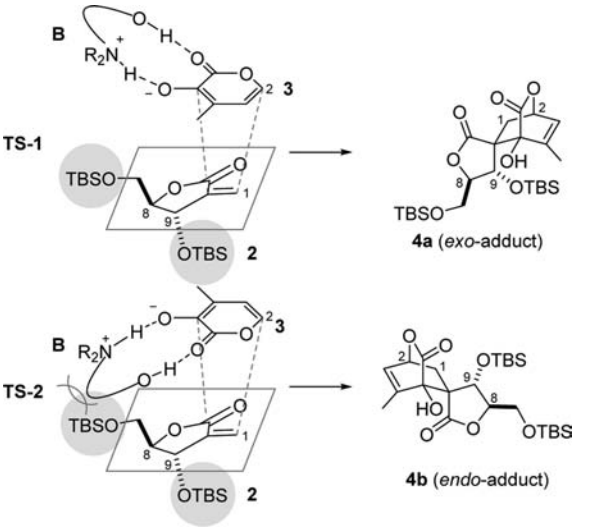



**Figure 1.** Rationale for the stereoselective Diels–Alder reaction.

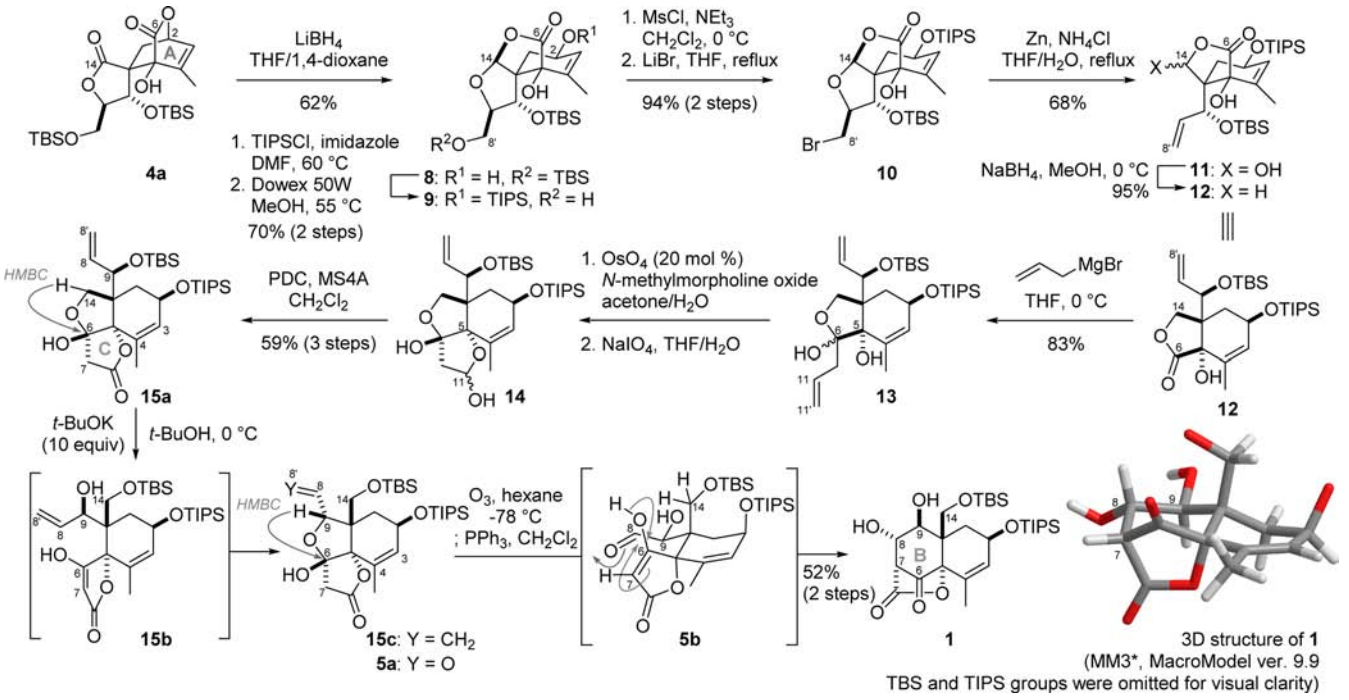
task (Scheme 3). Before doing so, it was necessary to differentiate the oxidation levels of the C6- and C14-carbons. The more sterically exposed C14-carbonyl group of **4a** was chemoselectively reduced with $LiBH_4$ in the presence of the C6-carbonyl group. Under these conditions, the six-membered C6-lactone was reorganized into the five-membered one to produce **8**. TIPS-protection of the liberated C2-hydroxy group of **8**, followed by selective removal of the TBS group at C8′–OH, afforded **9**. The C8′-primary hydroxy group was in turn converted to the bromide by mesylation and subsequent LiBr treatment. The zinc-induced reductive opening of the cyclic ether of **10** in refluxing THF gave **11**, and the C14-hemiacetal of **11** was reduced by the action of $NaBH_4$ to deliver the five-membered C6-lactone **12**.

With C6-lactone **12** in hand, C6-homologation and subsequent C-ring construction were investigated. Despite the negligible reactivity of the C6-carbonyl group toward a number of carbon nucleophiles, allylmagnesium bromide was found to react with **12** to provide the adduct **13** in 83% yield. Next, osmylation transformed the most sterically accessible C11-olefin of triene **13** to the corresponding 1,2-diol, which was oxidatively cleaved to generate the C11-hemiacetal **14**. The cyclized lactol of **14** was then converted to the corresponding lactone of **15a**, thereby completing the construction of the C-ring.

The last remaining challenge for assembly of the ABC-ring system was cyclization of the B-ring through the stereoselective aldol reaction between C7 and C8. To do so, the C8-olefin had to be oxidized into the corresponding aldehyde. However, ozonolysis of diene **15a** led to non-site selective cleavage of the monosubstituted C8- and trisubstituted C3-olefins, presumably because the bulky

(13) The migration of a TBDPS group under the basic conditions was reported; see: Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed.* **1990**, *29*, 431.

**Scheme 3.** Synthesis of the Multiply Oxygenated ABC-Ring **1** of Dihydro-$\beta$-agarofurans




C9-TBS ether shielded the neighboring C8-olefin. After extensive efforts, we found an appropriate structural isomer of **15a** for the C8-selective ozonolysis. Namely, *t*-BuOK in *t*-BuOH effected the TBS-transposition of **15a** from the C9-secondary OH to the less hindered C14-primary OH to produce **15b**,[13] and subsequent ring closure from **15b** generated **15c**. The isomeric structures of **15a** and **15c** were determined by the HMBC correlations shown in Scheme 3. Migration of the TBS group enabled discrimination of the reactivity between the C8- and C3-olefins, since the C8-olefin of **15c** was free from the steric interference of the TBS ether. Treatment of **15c** with ozone in hexane[14] and the following reductive workup with $PPh_3$ indeed promoted the requisite C8-oxidation. Furthermore, the aldol reaction between the aldehyde and the highly enolizable 1,3-dicarbonyl moiety occurred in situ, giving rise to **1** as the sole isomer (**5a**→**5b**→**1**).[15] In this cyclization, the C7−H of the presumed intermediate **5b** is structurally fixed to the pseudoequatorial position by the C5-spiral ring system, and the C8-carbonyl group adopts the pseudoequatorial conformation to avoid unfavorable steric interaction with the C14-oxymethylene group. These two controlling factors likely realized introduction of the contiguous C7- and C8-stereocenters of the ABC-ring system.

In conclusion, we developed a synthetic route to the fused ABC-ring system of agarofurans **1** in 14 total steps from the known material **2** with the correct C9-stereochemistry. The key features of the route include (i) the quinidine-catalyzed Diels−Alder reaction between **2** and **3** to establish the C5- and C10-tetrasubstituted and C2-alkoxy-substituted stereocenters of the A-ring, (ii) a highly chemoselective reaction sequence to construct the C-ring structure, and (iii) a B-ring annulation by the intramolecular aldol reaction to install the C7- and C8-stereocenters. Further efforts on the total synthesis of highly oxygenated dihydro-$\beta$-agarofurans from **1** are currently underway in our laboratory.

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**Supporting Information Available.** Experimental procedures, characterization data, and $^1H$ and $^{13}C$ NMR spectra of all newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The yield of the ozonolysis of **15c** was only 20% when the reaction was performed in $CH_2Cl_2$.

(15) The structure of **1** was determined from the large coupling constant between H8 and H9 ($J$ = 8.2 Hz).

The authors declare no competing financial interest.