

# Synthesis of Furan-Bridged 10-Membered Rings through [8 + 2]-Cycloaddition of Dienylfurans and Acetylenic Esters

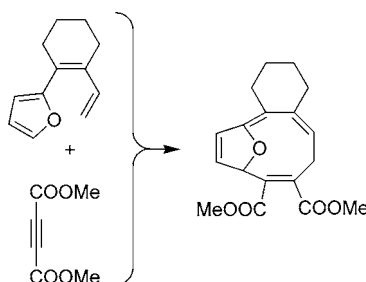
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## ABSTRACT



The coupling of various dienylfurans with dimethyl acetylenedicarboxylate (DMAD) has been examined. In most cases this reaction proceeds via [8 + 2]-cycloaddition to afford furan-bridged 10-membered ring systems as a single diastereomer. Dienylfuran intermediates were generated using either a chromium carbene-based method or aldol-based methods. Reaction of [8 + 2]-cycloadducts with electrophilic reagents occurred selectively at the enol ether alkene.

Furan-bridged 10-membered ring systems are commonly found in a variety of coral-derived cytotoxic compounds.<sup>1</sup> The most potent anticancer agent possessing this substructure is eleutherobin (**1**, Scheme 1), which is active against a variety of cancer cell lines at nanomolar concentrations and operates through stabilization of microtubules. Eleutherobin is obtained in low yield from a rare coral species,<sup>2</sup> and two elegant but lengthy total syntheses of eleutherobin have been reported.<sup>3</sup> Much of the drug development effort has centered on evaluation of the minimal pharmacophore requirements through examination of analogues<sup>4</sup> and the preparation of simpler analogues through organic synthesis.<sup>5</sup> A recently

reported reaction, the [8 + 2]-cycloaddition reaction<sup>6</sup> between dienylisobenzofuran derivatives (e.g., **4**) and dimethyl acety-

(1) For a review, see: Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, 49, 531–556.

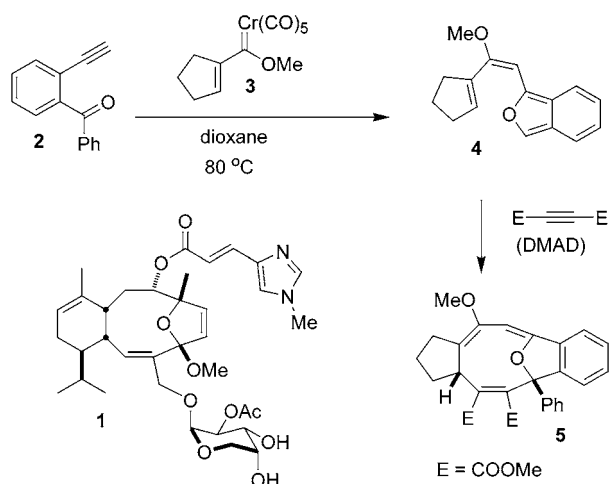
(2) (a) The yield is 0.01% dry weight. Lindel, T.; Jensen, P. R.; Fenical, W.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, 119, 8744–8745. (b) Production of eleutherobin through aquaculture has recently been reported. Taglialatela-Scafati, O.; Deo-Jangra, U.; Campbell, M.; Roberge, M.; Andersen, R. J. *J. Org. Lett.* **2002**, 4, 4085–4088.

(3) (a) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; Van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, 120, 8674–8680. (b) Chen, X. T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, 121, 6563–6579. (c) A formal total synthesis has also been reported. Ritter, N.; Metz, P. *Synlett* **2003**, 2422–2424.

(4) (a) McDaid, H. M.; Bhattacharya, S. K.; Chen, X. T.; He, L.; Shen, H. J.; Gutteridge, C. E.; Horwitz, S. B.; Danishefsky, S. J. *Cancer Chemother. Pharmacol.* **1999**, 44, 131–137. (b) Cinel, B.; Roberge, M.; Behrlich, H.; van Ofwegen, L.; Castro, C. B.; Andersen, R. J. *Org. Lett.* **2000**, 2, 257–260. (c) Roberge, M.; Cinel, B.; Anderson, H. J.; Lim, L.; Jiang, X.; Xu, L.; Bigg, C. M.; Kelly, M. T.; Andersen, R. J. *Cancer Res.* **2000**, 60, 5052–5058. (d) Britton, R.; Dilip de Silva, E.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2001**, 123, 8632–8633. (e) Diederichsen, U. *Org. Synth. Highlights V* **2003**, 317–325.

(5) (a) Chandrasekhar, S.; Jagadeshwar, V.; Narsihmulu, C.; Sarangapani, M.; Krishna, D. R.; Vidyasagar, J.; Vijay, D.; Sastry, G. N. *Bioorg. Med. Chem. Lett.* **2004**, 14, 3687–3689. (b) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, 44, 7913–7919. (c) Beumer, R.; Bayon, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, 44, 681–684.

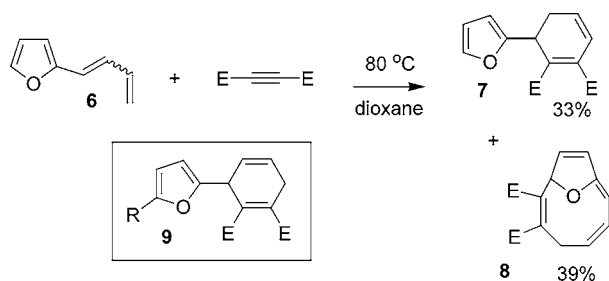
Scheme 1



lenedicarboxylate (DMAD)<sup>7</sup> provides an incredibly simple entry into furan-bridged ten-membered rings (e.g., **5**). The benzo fusion required in this transformation is a serious impediment to use of this reaction for synthesis of eleuthero-bin derivatives or the related eunicellins; however, benzo fusion provides tremendous activation for the [8 + 2]-cycloaddition reaction in Scheme 1.<sup>8</sup> In this paper, we report that simple furandienes lacking the isobenzofuran activation are excellent substrates for this reaction, providing rapid access to the central ring system of eleuthero-bin.

The coupling of 2-butadienylfuran (**6**, Scheme 2) with DMAD was examined for the preliminary evaluation of

Scheme 2



dienylfurans as  $8\pi$  components in cycloaddition reactions. Compound **6** was easily prepared through the Wittig reaction as a nearly 1:1 mixture of *E* and *Z* isomers.<sup>9</sup> Thermal reaction

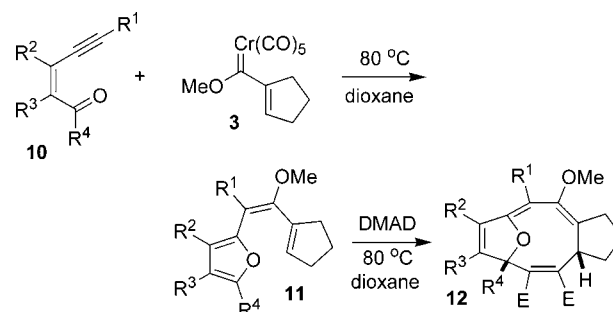
(6) The [8 + 2]-cycloaddition reaction has been primarily restricted to substrates where carbons 1 and 8 of the tetraene system are rigidly held in close proximity (e.g., methylenecycloheptatrienes). For a review, see: Nair, V.; Anilkumar, G. *Synlett* **1998**, 950–957.

(7) Luo, Y.; Herndon, J. W.; Cervantes-Lee, F. *J. Am. Chem. Soc.* **2003**, 125, 12720–12721.

(8) (a) The greatly enhanced reactivity of isobenzofurans (relative to furans) in cycloaddition reactions is well documented. Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, 73, 1–96. (b) Ab initio calculations show that  $\Delta E$  for the [8 + 2]-reaction of butadienylisobenzofuran and acetylene is  $-51$  kcal/mol, while  $\Delta E$  for [8 + 2]-reaction of butadienylfuran and acetylene is  $-22$  kcal/mol.

of this isomeric mixture with DMAD led to [8 + 2] (**8**) and isomerized [4 + 2] cycloadducts (**7**) in a nearly 1:1 ratio. Since the [8 + 2]-cycloadduct can only arise from the pure *Z* isomer of the dienylfuran **6**, the process will likely be more efficient if stereochemically pure *Z* dienylfurans are employed. Stereochemically pure dienylfuran derivatives could be obtained through the coupling of conjugated enyne-carbonyl systems (**10**, Table 1) and  $\alpha,\beta$ -unsaturated Fischer

**Table 1.** Synthesis of [8 + 2]-Cycloadducts through Three-Component Coupling of Carbene Complex **3**, Enyne **10**, and DMAD



entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	furan (%)	[8 + 2] (%)
A	<i>n</i> -Bu	R <sup>2,3</sup> = Y <sup>a</sup>		H		64 <sup>b</sup>
B	<i>n</i> -Bu	R <sup>2,3</sup> = Y <sup>a</sup>		H	78	78 <sup>c</sup>
C	<i>n</i> -Bu	R <sup>2,3</sup> = Y <sup>a</sup>		Me		58 <sup>b</sup>
D	<i>n</i> -Bu	Ph	H	H	72	0 <sup>c</sup>
E	<i>n</i> -Bu	<i>t</i> -Bu	H	H	74	0 <sup>c</sup>
F	H	<i>t</i> -Bu	H	H		62 <sup>b</sup>
G	TMS	H	H	H		60 <sup>b</sup>

<sup>a</sup> Y =  $-(CCH_2)_3-$ . <sup>b</sup> Yield for a one-pot reaction involving furan formation and [8 + 2]-cycloaddition. <sup>c</sup> Yield for [8 + 2]-cycloaddition only.

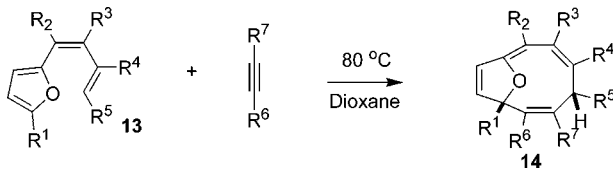
carbene complex **3**.<sup>10,11</sup> The oxygenated dienylfurans (**11**) from this reaction were only moderately stable. Treatment of isolated compound **11** (entry B) with DMAD led to the [8 + 2]-cycloadduct **12** as the exclusive product of the reaction. A one-pot procedure involving heating a mixture of carbene complex and enynecarbonyl compound followed by addition of DMAD was more efficient for the production of [8 + 2]-cycloadducts. As noted in Table 1, the process appears to be quite general. The reaction successfully afforded [8 + 2] cycloadducts as the exclusive reaction products in all cases except entries D and E. In these cases, a steric effect between the bulky R<sup>1</sup> and R<sup>2</sup> group inhibit formation of the conformation required for concerted [8 + 2]-cycloaddition. When the *n*-butyl group in entry E was replaced by H (entry F) the reaction was successful.

Additional stereochemically pure *Z* furan dienes (**13**, Table 2) were also prepared, and their reaction with electron-deficient alkynes was examined. As noted in these examples,

(9) Ben Attra, T.; Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Synth. Commun.* **1992**, 22, 1421–1425.

(10) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, 63, 4564–4565.

(11) For a discussion of enol ether stereochemistry in chromium carbene-alkyne couplings, see: McCallum, J. S.; Kunng, F. A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, 7, 2346–2360.

**Table 2.** Coupling of Dienylfurans with Acetylenic Esters


entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	<b>14</b> (%)
A	H	R <sup>2,3</sup> = Z <sup>a</sup>	H	H	H	E	E	84
B	Me	R <sup>2,3</sup> = Z <sup>a</sup>	H	H	H	E	E	77
C	OMe	R <sup>2,3</sup> = Z <sup>a</sup>	H	H	H	E	E	79
D	H	R <sup>2,3</sup> = Z <sup>a</sup>	H	H	H	E' <sup>b</sup>	COMe	81 <sup>c</sup>
E	H	R <sup>2,3</sup> = Z <sup>a</sup>	H	H	H	H	E	0
F	H	H	H	R <sup>4,5</sup> = Z <sup>a</sup>	E	E	E	56

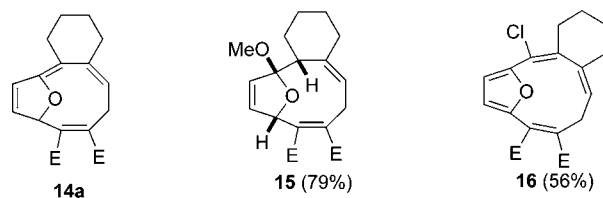
<sup>a</sup> Y = -(CH<sub>2</sub>)<sub>4</sub>-. <sup>b</sup> E' = COOEt. <sup>c</sup> The regioisomer where R<sup>6</sup> and R<sup>7</sup> are reversed was obtained in 6% yield.

the reaction is tolerant of substitution within the furan ring, and the [8 + 2]-cycloadduct **14** was obtained as the exclusive product in all of the cases examined. The reaction is apparently restricted to alkynes that contain two electron-withdrawing groups. The reaction employing the ester-ketone substituted alkyne was remarkably regioselective, resulting in predominantly a single isomer (entry D).<sup>12</sup> The reaction was more efficient in the system where the cyclohexenyl fusion was within the central alkene (entries A–D) than in the one example employing cyclohexenyl fusion at the distal alkene (entry F). This can likely be attributed to the more exposed diene–enol ether system of the product, which was unstable on silica gel and completely decomposed after storage in the refrigerator for 2 weeks in a frozen benzene matrix. The relative reactivity of the compounds where R<sup>2,3</sup> = -(CH<sub>2</sub>)<sub>4</sub>-, R<sup>1</sup> = H (**13a**) or OMe (**13c**) was also tested. Reaction of an excess of these compounds with 1 mol of DMAD led to a 2:1 ratio of the [8 + 2]-cycloadducts **14a/14c**, indicating that steric deactivation by the methoxy group is more important than its electronic activation.

The chemistry of the [8 + 2]-cycloadducts was briefly probed through reaction of cycloadduct **14a** with select

(12) A calculation at the 6-31G\* level reveals that the regiochemistry of the [8 + 2]-cycloaddition reaction is consistent with that predicted by the MO coefficients of the energy-minimized (s-trans) conformation. There is a higher coefficient at the furan terminus of the tetraene system (0.24) than at the diene terminus (–0.21). This calculation was very dependent on the choice of basis set.

electrophiles. As expected, the bridgehead enol ether was the most reactive of the four alkenes in **14a**. Treatment of [8 + 2]-cycloadduct **14a** with methanol and acid led to the ketal **15** (Scheme 3) as a single diastereomer.<sup>13</sup> A ring-

**Scheme 3**

expansion product (**16**) was obtained through treatment of [8 + 2]-cycloadduct **14a** with dichlorocarbene.<sup>14</sup>

In summary, the use of simple dienylfurans as 8 $\pi$ -components in [8 + 2]-cycloadditions has been demonstrated for a variety of furandienes. The parent ring system of a variety of biologically active coral-derived natural products is produced in a single step from readily available components. Subsequent reaction of the cycloadducts with electrophilic reagents is highly selective, occurring exclusively at the bridgehead double bond. Further study of the scope and limit of this reaction is currently underway in our laboratory.

**Acknowledgment.** This research was supported by the NIH SCORE Program.

**Supporting Information Available:** Experimental procedures and spectral data for all compounds in Scheme 2 and Tables 1 and 2. Photocopies of spectra for [8 + 2]-cycloadducts and the products in Scheme 3. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) The product was assigned as the syn double bond addition product derived through protonation and addition of methoxy from the convex face. This isomer is slightly more stable than the anti isomer;  $\Delta E$  syn to anti is +0.3 kcal/mol in a simplified analogue of **15** according to *ab initio* calculations. Trans-bridged furanophanes were not considered due to excessive strain in these systems revealed by MM2 calculations.

(14) Parham, W. E.; Soeder, R. W.; Throckmorton, J. R.; Kuncel, K.; Dodson, R. M. *J. Am. Chem. Soc.* **1965**, 87, 321–328.