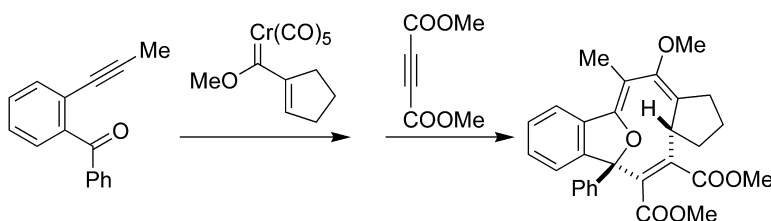


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Synthesis of Furanophane Derivatives through [8+2]-Cycloaddition of Dienylisobenzofurans and Alkynes

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The [8+2]-cycloaddition reaction^{1,2} is a potentially powerful method for the preparation of 10-membered ring systems, although it has been restricted to examples where carbons 1 and 8 of the tetraene are rigidly held in close proximity.³ Although these cycloadditions involve the interaction of 10 π -electrons spread over 10 carbon atoms, the net result in most cases is merely appendage of a five-membered ring onto a preexisting ring.⁴ In this manuscript, the [8+2]-cycloaddition reaction between variously generated dienylisobenzofurans (e.g., **3**, Scheme 1) and dimethyl acetylenedicarboxylate (DMAD) leading to the 11-oxabicyclo[6.2.1]undecane ring system (e.g., **4**) is reported. This represents the first generally successful [8+2]-cycloaddition reaction for conformationally flexible tetraene systems. The 11-oxabicyclo[6.2.1]undecane ring system is a key structural feature of many compounds collectively known as 2,11-cyclized cembranoids or cladiellanes.⁵ Many of these compounds display potent biological activity, including anti-inflammatory and antitumor activity. The reaction in Scheme 1 results in direct synthesis of the complete ring skeleton of the eunicellin diterpenes in a single step.⁶

Initial studies have focused on generation of dienylisobenzofuran intermediates through the coupling of α,β -unsaturated Fischer carbene complexes (**2**) with 2-alkynylbenzophenone derivatives (**1**).⁷ The relatively stable nature of 1-phenyl-3-alkenylisobenzofuran intermediates and their subsequent trapping through Diels–Alder reactions had previously been demonstrated. Prior to the initiation of these studies involving α,β -unsaturated carbene complexes, anticipated reaction pathways included: (1) the Dötz benzannulation reaction resulting in ketone **6**,⁸ and (2) isobenzofuran formation followed by Diels–Alder reaction resulting in **5**. Surprisingly, the coupling of alkenylcarbene complex **2A** (entry A of Table 1, see Table 1 for correlation of substituent letters with R^{1–4}) with benzophenone **1A**, followed by addition of DMAD afforded predominantly the [8+2]-cycloadduct **4A** (76%) and only a minor amount (3%) of the Diels–Alder product **5A**. Compound **6A** was not observed in the reaction mixture. The indicated stereochemistry results from suprafacial addition as is predicted on the basis of orbital symmetry considerations.² Crystals suitable for X-ray analysis could be obtained for closely related structural analogue **4B** (Figure 1). The 11-oxabicyclo[6.4.1]-undeca-1,3,6,9-tetraene ring system has no precedent; however, related examples of 6-carbon-bridged furanophane ring systems have been reported.⁹ Notable sources of strain in this ring system include: (1) twisting of the alkene exocyclic to the furan ring by 14°, and (2) deviation of the endocyclic bond angles at the asterisked carbons by 11° greater than ideal.

Several examples of this reaction using the optimized conditions (alkyne carbene coupling in dioxane at 85 °C followed by addition

Table 1. Three-Component Coupling of Alkynylbenzophenones (**1**), Carbene Complexes (**2**), and DMAD

entry ^a	reactants	R ¹	R ²	R ³	R ⁴	4	5
A	1A + 2A	Bu	Ph	R ^{3,4} = $-(\text{CH}_2)_3-$		76%	3%
B	1B + 2A	Me	Ph	R ^{3,4} = $-(\text{CH}_2)_3-$		61%	0%
C	1C + 2A	H	Ph	R ^{3,4} = $-(\text{CH}_2)_3-$		72%	9%
D	1D + 2A	TMS	Ph	R ^{3,4} = $-(\text{CH}_2)_3-$		5%	62%
E	1E + 2A	Bu	2-benzofuryl	R ^{3,4} = $-(\text{CH}_2)_3-$		45%	30%
F	1A + 2B	Bu	Ph	Me	H	56%	19%
G	1A + 2C	Bu	Ph	R ^{3,4} = $-\text{O}(\text{CH}_2)_3-$		39%	0%

^a Table entry letters correlate with the substituent letters for compounds **3–5**.

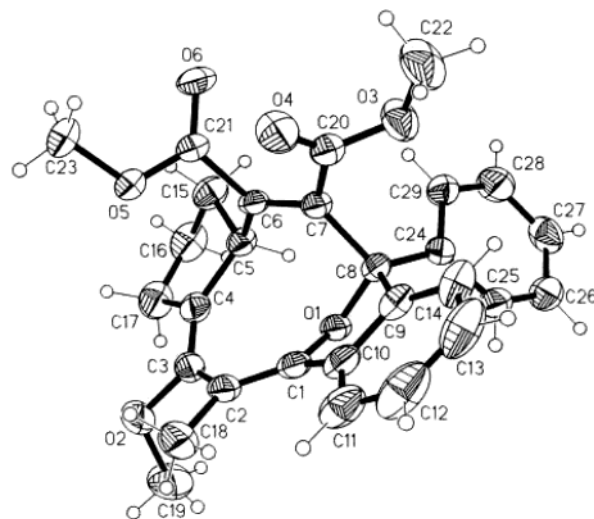


Figure 1. Crystal structure for compound **4B**.

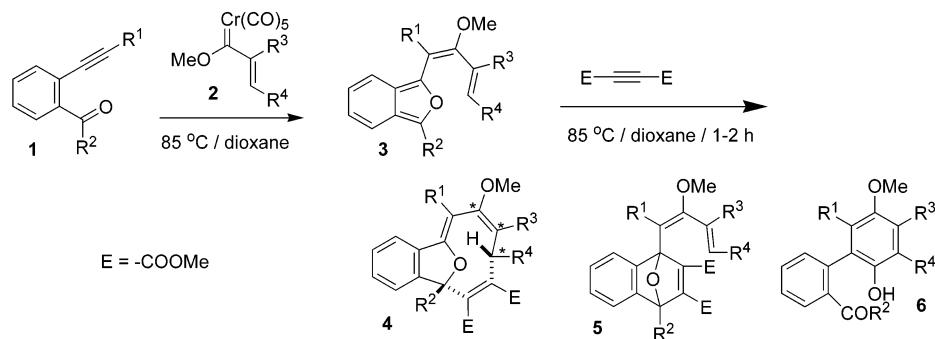
of DMAD) were tested (Table 1). The remaining examples were assigned on the basis of spectral similarity to compound **4B**. In all cases except entry D, the [8+2]-cycloadduct was the major product. This failure can be attributed to a steric effect. The energy-minimized (RHF/6-31G) conformation for isobenzofuran intermediate **3D** features orthogonal enol ether and isobenzofuran groups, versus a more planar orientation in **3C**. An orthogonal orientation between the enol ether and isobenzofuran would prevent [8+2]-cycloaddition. The selectivity for the [8+2]-cycloadduct was noticeably lower using the benzofuranyl ketone derivative **1E** and for the example using the 2-propenylcarbene complex **2B** in entry F. The relatively unstable carbene complex **2C** afforded a lower overall yield of adducts (entry G); however, only the [8+2]-cycloadduct was observed.

To determine if chromium has a unique role,¹⁰ non-chromium-based methods for the generation of dienyl-isobenzofuran intermediates were tested.¹¹ Keto alcohol **8** (Scheme 2) was prepared

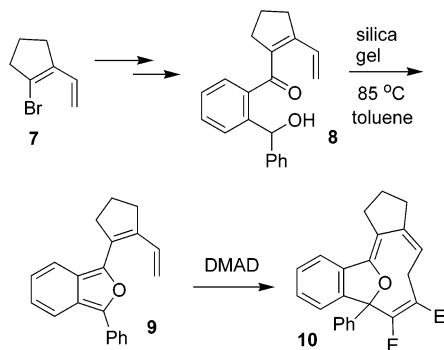
[†] New Mexico State University.

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Scheme 1



Scheme 2



in four steps¹² from readily available bromo-diene **7**.¹³ Compound **8**, which appears to be predominantly hemiketal, converted to yellow isobenzofuran **9** upon attempted purification on silica gel.¹⁴ Treatment of compound **9** with DMAD led to the expected [8+2]-cycloadduct **10** in 64% yield as the exclusive product.

In summary, a novel method for the synthesis of furanophanes has been developed, which might be applicable to all dienylobenzofurans, no matter how they are generated. This reaction is currently under investigation in this laboratory.

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Supporting Information Available: Experimental details for reactions in Table 1 and characterization of major products (PDF). X-ray data for compound **4B**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) First report: Doering, W. v. E.; Wiley, D. W. *Tetrahedron* **1960**, *11*, 183–198.
- (2) Mechanistic work: (a) Liu, C. Y.; Ding, S. T. *J. Org. Chem.* **1992**, *57*, 4539–4544. (b) Liu, C. Y.; Houk, K. N. *Tetrahedron Lett.* **1987**, *28*, 1371–1374. (c) Daub, J.; Hirmer, G.; Kakob, L.; Maas, G.; Pickl, W.; Pirzer, E.; Rapp, K. M. *Chem. Ber.* **1985**, *118*, 1836–1856. (d) Baumler, A.; Daub, J.; Pickl, W.; Rieger, W. *Chem. Ber.* **1985**, *118*, 1857–1867. (e) Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512–517.
- (3) Most examples involve alkydidenecycloheptatrienes or indolizines as the 8 π -component. (a) For the most recent example using alkydidenecycloheptatrienes, see: Pham, W.; Weissleder, R.; Tung, C. H. *Tetrahedron Lett.* **2002**, *43*, 19–20. (b) For the most recent example using indolizines, see: Babaev, E. V.; Simonyan, V. V.; Pasichnichenko, K. Y.; Nosova, V. M.; Kisin, A. V.; Jug, K. *J. Org. Chem.* **1999**, *64*, 9057–9062.
- (4) We are aware of a single example involving six-membered ring formation. Farrant, G. C.; Feldmann, R. *Tetrahedron Lett.* **1970**, *11*, 4979–4982.
- (5) For a review, see: Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531–556.
- (6) Synthetic work since 2002: (a) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652. (b) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543–1546. (c) Chai, Y.; Vivic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, *5*, 1039–1042. (d) Jung, M. E.; Pontillo, J. J. *J. Org. Chem.* **2002**, *67*, 6848–6851. (e) Molander, G. A.; Jeffrey, S. C. *Tetrahedron Lett.* **2002**, *43*, 359–362.
- (7) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269.
- (8) For recent studies of the Dötz reaction using ortho-carbonyl containing phenylacetylenes, see: Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2002**, *43*, 3849–3852.
- (9) Chen, X. T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 185–187.
- (10) Numerous examples of higher order cycloadditions have been reported for chromium systems. Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521–4538.
- (11) For a review of isobenzofurans, see: Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1–96.
- (12) The sequence involves: (i) conversion to the ester with CO, Pd(0), and MeOH, (ii) ester hydrolysis and conversion to the Weinreb amide, and (iii) reaction with 2-LiC₆H₄C(OLi)Ph.
- (13) Sharp, J. T.; Wilson, P.; Parsons, S.; Gould, R. O. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1139–1148.
- (14) For generation of isobenzofurans from similar precursors, see: Smith, J. G.; Fogg, D. E.; Munday, I. J.; Sandborn, R. E.; Dibble, P. W. *J. Org. Chem.* **1988**, *53*, 2942–2953.

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