

Rearrangement of 2-Dienylcyclobutenones. Synthesis of Highly Substituted Annulated Furans

Philip Turnbull,[†] Matthew J. Heileman, and Harold W. Moore*

Department of Chemistry, University of California, Irvine, California 92717

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The independent discovery by Liebeskind and Moore that 4-alkenyl(or aryl)cyclobutenones readily ring expand to aromatic systems has led to a number of useful synthetic applications.^{1,2} Such rearrangements stem from torquoselective ring opening³ of these cyclobutenones **1** to the dienylketene intermediates **2**, which then electrocyclicize to the corresponding arenes **3** (Scheme 1). Documented here is a complementary method in which 2-dienylcyclobutenones **4** lead to related dienylketenes **5** and thus to annulation products **7** and **8**, which would be difficult to access from the 4-alkenyl(or aryl)cyclobutenone methods. The stereochemistry of the 2-dienyl group is of no major consequence since vinylketenes **5(E)** and **5(Z)** apparently equilibrate under the reaction conditions *via* cyclobutenone **6**.⁴ Thus, the dienylketene **5(Z)** required for 6 π electrocyclization is available from either **4(Z)** or **4(E)**. This initial account outlines progress on the synthesis of 2-dienylcyclobutenones and their rearrangements to highly substituted naphthols, phenols, and annulated furans.

Two methods, beginning with readily available alkyne-substituted cyclobutenones **9** and **10**, were developed to furnish ethenylcyclobutenediones, precursors to the desired cyclobutenones of general structure **4**. The first method involves stereospecific *cis* reduction of the alkyne moiety in 4-(phenylethynyl)cyclobutenone **9** under Lindlar conditions (PdCaCO₃, Pb, quinoline)⁵ followed by acid hydrolysis of the β -hydroxyenol ether group to afford 3-isopropoxy-4-((*Z*)-2-phenylethenyl)cyclobutenedione (**11a**) in 85% yield (Table 1, entry 1, method A).

Conjugate additions to the vinylogous alkynone functionality in **10a** and **10b** provided a second method for synthesizing a variety of alkenylcyclobutenediones.⁶ Reaction with alkyl, vinyl, and arylcuprates, generated by the addition of 2 equiv of the corresponding lithium reagent to a copper bromide dimethyl sulfide complex,⁷

Scheme 1

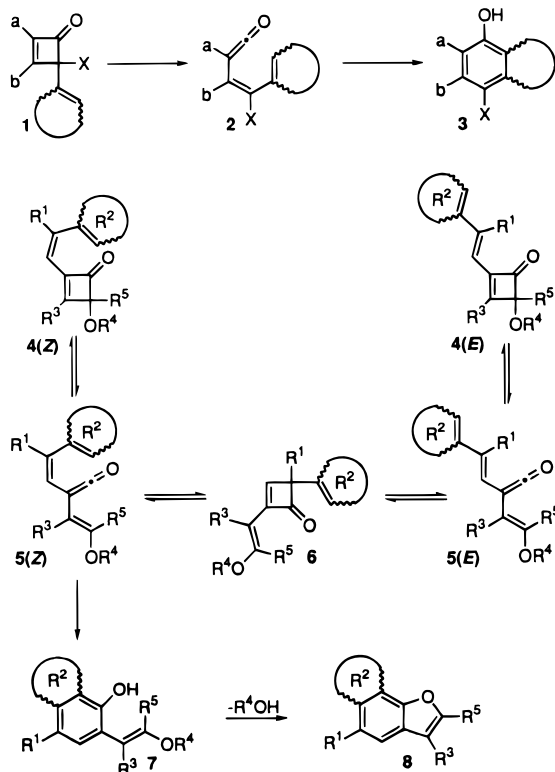
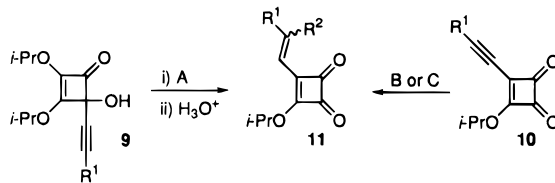


Table 1. Synthesis of Dienylcyclobutenediones



method A = H₂, PdCaCO₃, Pb, quinoline and gives the *Z*-product.
method B = (R²)₂CuLi and gives a *Z/E* mixture; ca. 1:1.
method C = PhSH and gives the *E*-isomer predominantly (20:1).

entry	sm	method	R ¹	R ²	product	% yield
1	9	A	Ph	H	11a	85
2	10a	B	Ph	<i>n</i> -Bu	11b	77
3	10b	B	<i>n</i> -Bu	Me	11c	75
4	10b	B	<i>n</i> -Bu	OMe	11d	86
5	10a	C	Ph	SPh	11e	85

[†] National Needs Fellow 1994–1995.

(1) (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Liebeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3065.

(2) For reviews on the ring expansions of cyclobutenones see: (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (b) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (c) Bellus, D.; Ernst, B. *Angew Chem.* **1988**, *100*, 820.

(3) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

(4) The concept of vinylketene/cyclobutenone equilibrium is supported by the following works: (a) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 644. (b) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.

(5) This reduction method was adopted from a similar example: Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.

(6) For examples of conjugate additions to ethenylcyclobutenones see: (a) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129. (b) Liu, H.; Gayo, L. M.; Sullivan, R. W.; Choi, A. Y. H.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 3284.

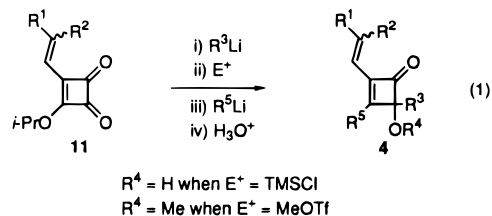
(7) For a good review of the synthetic utility of copper reagents see: Lipshutz, B. H.; Sengupta, S. *Org. React. (New York)* **1992**, *41*, 135.

gave good yields of the *E*- and *Z*-isomers of the desired cyclobutenediones in 1:1 ratios (Table 1, entries 2–4, method B). The geometric isomers were readily separable in all cases, and the stereochemistry of the individual isomers was established by NOE studies.

Addition of heteroatom nucleophiles to alkenylcyclobutenediones is also a viable route to alkenyl derivatives as demonstrated by the formation of **11e** (85%) upon treatment of **10a** with thiophenol (Table 1, entry 5, method C). Here again, the adduct is formed as a 1:1 mixture of *E*- and *Z*-isomers. However, in the presence of silica gel the isomers equilibrate to give a 20:1 mixture of **11e(E)** to **11e(Z)**.

An efficient "one-pot" synthetic elaboration of the above-described 4-ethenyl-3-isopropoxycyclobutenediones

11 provided 3,4-dialkyl-2-ethenyl-4-hydroxy(and alkoxy)-cyclobutenones **4** suitable for ring expansion (eq 1).⁸ In



essence, treatment of **11** with an alkyl lithium reagent followed by chlorotrimethylsilane or methyltriflate gave the respective 4-alkyl-2-ethenyl-3-isopropoxy-4-[(trimethylsilyl)oxy]- or -4-methoxycyclobutenone, which was not isolated but treated directly with a second alkyl-lithium.⁹ The resulting cyclobutenone was then quenched with 1.2 M HCl, causing hydrolysis of the β -hydroxyenol ether, as well as subsequent removal of the trimethylsilyl group where appropriate, to give the desired cyclobutenones **4a–g** in good to excellent yields (Scheme 2).

Cyclobutenones stemming from the *cis* reduction method were thermolyzed as the corresponding 4-hydroxycyclobutenones to give excellent yields of annulated furans (Scheme 2). For example, thermolysis of 2(*Z*)-alkenylcyclobutenones **4a** and **4b** followed by treatment with trifluoroacetic acid (TFA) proceeds cleanly to the respective naphthofurans **8a** (88%) and **8b** (86%). It was possible to isolate the naphthol intermediate **7a** resulting from the preliminary thermolysis of **4a** in 67% yield despite its propensity to undergo the second ring closure. Exposure of **7a** to TFA gave a quantitative yield of naphthofuran **8a**. Higher overall yields were realized by one-pot thermolysis and acid treatment.

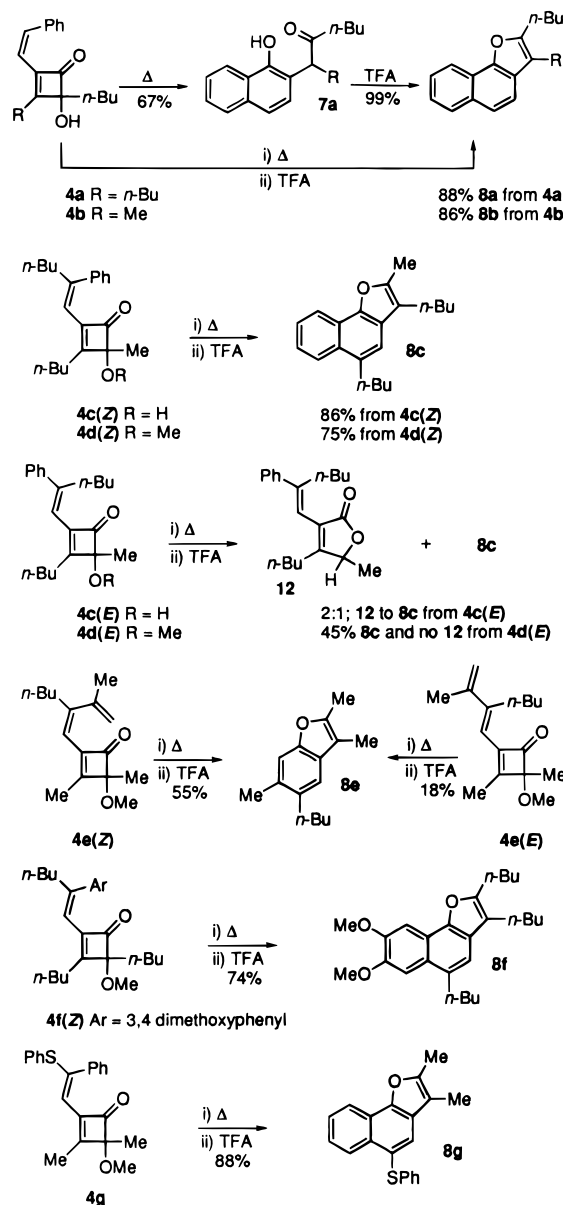
The *E*- and *Z*-isomers **4c–g**, resulting from conjugate additions, were thermolyzed separately to determine the feasibility of arene construction through the equilibrating cyclobutenone intermediate **6**. Indeed, both geometrical isomers give the desired furan (Scheme 2). Ring expansion of (*Z*)-hydroxycyclobutenone **4c** afforded an 86% yield of naphthofuran **8c**. The (*E*)-hydroxycyclobutenone **4c** gave a 2:1 ratio of furanone **12**¹⁰ to naphthofuran. Lactone formation was easily circumvented by starting instead with 4-methoxycyclobutenones **4d–g**. The protected cyclobutenone **4d** gave a 75% yield of naphthofuran for the *Z*-isomer and a 45% yield for the *E*-isomer. In all cases the *E*-isomer took significantly longer to react than did its stereoisomer [e.g., 28 min for **4d(Z)** and 4.5 h for **4d(E)**]. Interestingly, **4f(E)** possessing a highly electron rich aromatic functionality did not provide any annulated furan while its *Z*-isomer gave a 74% yield of the desired arene. As delineated in Scheme 2, a variety of furans **8** can be constructed by starting with the conjugate addition route.

(8) For other methods of synthesizing highly substituted cyclobutenones see: (a) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482. (b) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (c) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942.

(9) Addition of lithium reagents to 2-alkynyl-4-arylcyclobutenones results in ring opening: Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 3274.

(10) Butenolide formation has been observed in other cases: (a) Perri, S. T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, *29*, 3529. (b) Pollart, D. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 5444. (c) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.

Scheme 2



In conclusion, the significant points to arise from this study include the following: (1) 2-dienylcyclobutenones can be readily constructed from reductions of and conjugate additions to alkyne-bearing dialkylsquarate derivatives, (2) rapid synthetic elaboration of these diones is possible through a “one-pot” double organolithium reagent addition, and (3) 2-dienylcyclobutenones with both *E*- and *Z*-diene configurations give the desired annulations to benzo- and naphthofurans upon heating followed by treatment with acid. The wide variety of carbo- and heterocycles available through this methodology is under current investigation; details of these studies are forthcoming.

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Supporting Information Available: General experimental procedures and characterization data are given (12 pages).