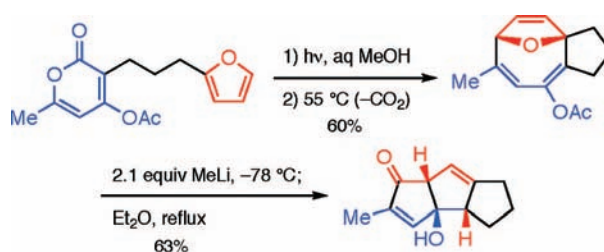


Concise Route to Triquinanes from
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ABSTRACT



Treatment of ether-bridged cyclooctatrienes (formed via intramolecular [4 + 4]-photocycloaddition of pyran-2-ones bearing pendent furans, followed by thermal decarboxylation) with excess MeLi furnishes triquinane ring systems via an apparent sequence of β -elimination, 1,5-hydrogen shift, and transannular aldolization.

Polyquinanes have been frequent synthetic targets¹ as a result of their wide distribution in nature, as well as their value in the construction of theoretically interesting hydrocarbons. The dense connectivity and infrequent occurrence of functionality handles found in most of these structures present special challenges, driving the development of many clever and highly effective synthetic strategies. Many new methods, although originally developed to address the polyquinane problem, have enjoyed widespread use in chemical synthesis targeting a diverse range of important target compounds.

We have previously reported that irradiation of pyran-2-ones possessing tethered furan groups furnishes cyclooctadienes containing ether and lactone bridges.² This process occurs via a crossed intramolecular [4 + 4]-photocycloaddition, and the resultant adducts may serve as advanced

intermediates in the synthesis of cyclooctane-containing targets.³ Here we describe an unanticipated alternative application of these products, providing access under anionic conditions to substituted linearly fused triquinanes from the pyran-2-one starting materials in just three steps.⁴

To date, successful examples of pyran-2-one crossed [4 + 4]-photocycloadditions have been limited to cases in which the diene partner is a furan (Scheme 1). While these reactions furnish cyclooctadienes in good yield, their suitability for the construction of cyclooctanoid natural products depends upon the availability of convenient methods for opening the lactone and ether bridges of the resulting adducts **2**. Reductive cleavage of the lactone to give 1,5-diols **3** is efficient and can provide access to advanced intermediates in the synthesis of diterpenes of the fusicocin class.³ Another strategy for lactone removal is the thermal decarboxylation of the initial adducts to give cyclooctatrienes **4**. This process

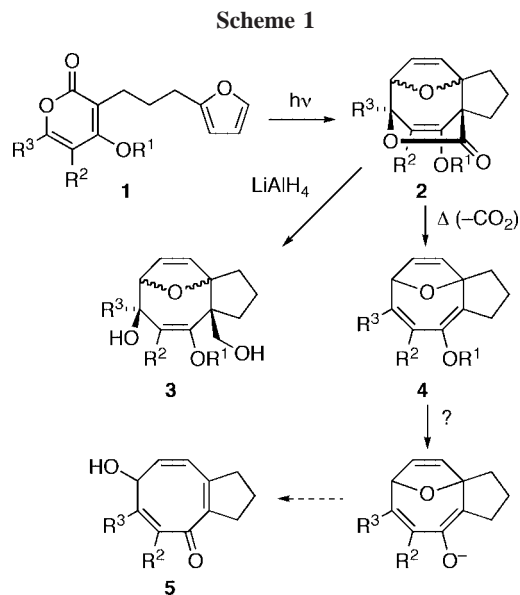
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(1) Reviews: (a) Paquette, L. A. *Recent Synthetic Developments in Polyquinane Chemistry*; Springer-Verlag: Berlin, 1984. (b) Gupta, A. K.; Fu, X.; Snyder, J. P.; Cook, J. M. *Tetrahedron* **1991**, *47*, 3665–3710. (c) Marchand, A. P. *Synlett* **1991**, 73–79. (d) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–719.

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(3) Song, D.; McDonald, R.; West, F. G. *Org. Lett.* **2006**, *8*, 4075–4078.

(4) Reorganization of 2-pyridone photoadducts into diquinane frameworks via *electrophilic* activation has been described by Sieburth and co-workers: (a) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. McN. *Org. Lett.* **2001**, *3*, 2165–2167. (b) Lim, Y.-H.; Li, T.; Chen, P.; Schreiber, P.; Kuznetsova, L.; Carroll, P. J.; Lauher, J. W.; Sieburth, S. McN. *Org. Lett.* **2005**, *7*, 5413–5415.



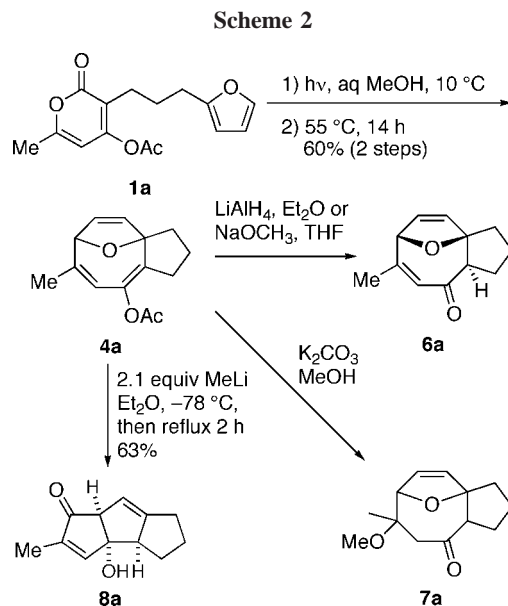
was initially observed as an undesired side reaction during photocycloadditions conducted without adequate cooling;^{2b} however, more recently we have found that deliberate heating of the reaction mixture following irradiation furnishes **4** in good yields.⁵

Effective processing of the bridging ether is somewhat more challenging, as has been noted in other approaches to medium-sized rings.⁶ We saw a possible solution to this problem via triene, given the incipient enolate functionality at the bridgehead adjacent to the ether oxygen. If R^1 could be cleaved under anionic conditions, eliminative opening of the ether bridge might occur to give **5**.

Initial studies were conducted using triene **4a**, available in 60% yield over two steps⁵ from the previously described pyran-2-one **1a** (Scheme 2). A variety of conditions were investigated for cleavage of the acetate group, including MeONa/THF , LiAlH_4 , and $\text{K}_2\text{CO}_3/\text{MeOH}$; however, although these reagents effected deacetylation, no evidence for eliminative opening of the ether was seen, and either enone **6a** or Michael adduct **7a** were isolated as the sole product. After extensive optimization, treatment with excess methyl lithium in Et_2O at low temperature followed by warming to reflux was found to produce one main new product. Careful characterization revealed that this product was not the expected cyclooctatrienone; only two alkenes were present, one part of an apparent conjugated enone and the other an isolated trisubstituted alkene. Moreover, although the compound contained a hydroxyl moiety, it was found to be a tertiary alcohol seemingly at a bridgehead position. Careful analysis of HMBC and TROESY spectral data led to the structural assignment as linearly fused triquinane **8a**.

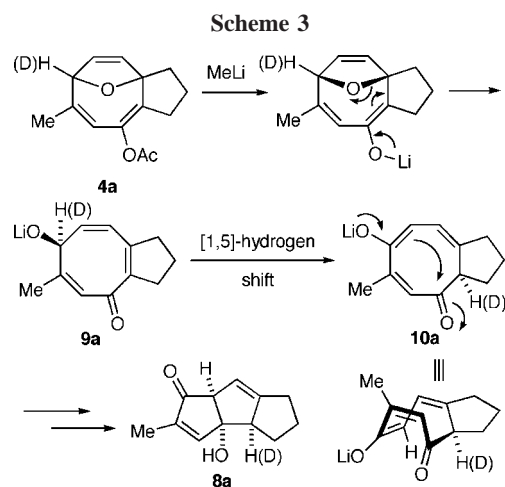
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Subsequent X-ray crystallographic analysis confirmed this assignment.⁷

Formation of a triquinane skeleton from a bicyclo[6.3.0]undecatriene precursor implied the involvement of a transannular reaction. However, it was not immediately apparent how the expected elimination product could participate in such a process. Further inspection of the presumed anionic intermediate **9a** suggested the possibility of a [1,5]-hydrogen shift to give the isomeric **10a** (Scheme 3).⁸ With an enolate center established directly across the



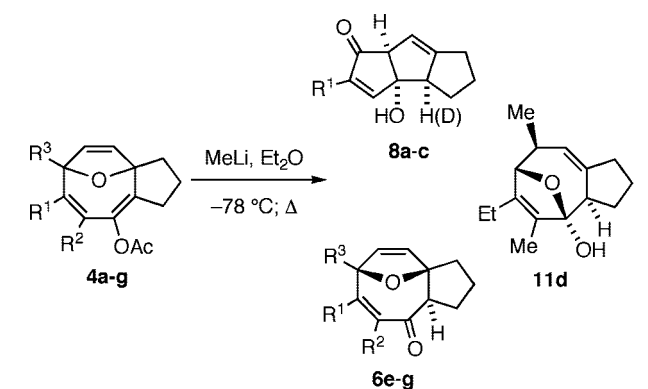
eight-membered ring from a carbonyl group, transannular aldol addition should be facile to give **8a** after workup.⁹ To evaluate this mechanistic proposal, substrate **4a** was prepared with a deuterium label at the C-5 position of

(7) See Supporting Information for a discussion of the structural assignment of **8a**.

the former furan. Exposure to the identical MeLi conditions furnished deuterated triquinane **8a** in a yield comparable to that of the unlabeled case, with specific introduction of deuterium at the bridgehead carbon. This regio- and stereospecific deuterium transfer is consistent with the [1,5]-shift mechanism. The observed *cis-syn* ring-fusion stereochemistry is presumed to result from reaction via the lowest energy tub-like conformation for enolate **10a**.¹⁰

To test the generality of this unexpected and substantial reorganization process, we next examined cyclooctatrienes **4b–g**, available from the corresponding pyran-2-ones in moderate to good overall yields (Table 1).⁵ In the event, substrate **4b** gave comparable amounts of triquinane product

Table 1. Deacetylation of Dienones **4**^a



entry	substrate	R ¹	R ²	R ³	product	yield (%) ^b
1	4a	Me	H	H	8a	63 ^c
2	4b	Et	H	H	8b	60
3	4c	Ph	H	H	8c	trace
4	4d	Et	Me	H	11d	67 ^d
5	4e	Me	Me	H	6e	90
6	4f	(CH ₂) ₃		H	6f	80
7	4g	Me	H	Me	6g	91

^a General procedure: Triene **4** was dissolved in diethyl ether at $-78\text{ }^{\circ}\text{C}$, and 2.1 equiv of MeLi was added. After 30 min the reaction mixture was heated at reflux for 2 h. ^b Yields given are for isolated product after chromatographic purification. ^c Deuterium-labeled **8a** was obtained in 61% yield from **4a** ($\text{R}^3 = \text{D}$). ^d Trace amounts ($<5\%$) of a product tentatively identified as enone **6d** were also isolated.

(entry 2), while traces of this product were obtained with phenyl-substituted triene **4c**. In the latter case, extensive decomposition to a plethora of uncharacterizable products was observed. Three other cases furnished ether-bridged

(8) For related [1,5]-hydrogen shift behavior in medium-ring substrates, see: (a) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972–3974. (b) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411–4423. (c) Eggert, U.; Stohrer, I.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1992**, *33*, 3465–3468.

(9) For a review of cascade processes terminated by transannular aldolization in eight-membered rings, see: (a) Paquette, L. A. *Eur. J. Org. Chem.* **1998**, 1709–1728.

(10) Geometries of possible reactive conformers were minimized using DFT (B3LYP 6-31G** level) starting from AM1 optimized structures (Spartan). We thank Professor Dennis Hall for assistance with these calculations.

cyclooctadienones **6** in excellent yield (entries 6–8), while one substrate (entry 5) underwent an alternative ether cleavage process to furnish hemiketal **11d**. The relative configuration of the new stereocenter of enone **6f** was ascertained via detection of a transannular NOE correlation between the bridgehead methine and one of the dihydrofuran protons, and the others were assigned by analogy (see Supporting Information for additional discussion of structural assignments).

Clearly, the effectiveness of the dihydrofuran elimination step is sensitive to the degree of substitution at the R¹ and R² positions on the cyclooctatriene ring. Disubstituted (entries 5 and 6) substrates returned only the deacetylated enone **6**. Failure to observe elimination in these cases may result from substituent effects on the conformer populations of the intermediate enolates generated immediately after loss of acetyl, preventing optimal orbital overlap for elimination. However, the isolation of enone **6g** in high yield (entry 7) is instructive. Substrate **4g** differs from **4a** only in the presence of a methyl at the R³ position (site of the hydrogen that would be expected to undergo 1,5-hydrogen shift; Scheme 3). Not surprisingly, this example shows no evidence of the corresponding [1,5]-methyl shift, but the absence of any trienone elimination product corresponding to **5** (see Scheme 1) suggests that ring-opened alkoxide **9** may be in equilibrium with bridged enolate **12**, with the equilibrium favoring **12**. When [1,5]-hydrogen shift of **9** is facile, a pathway to triquinane products **8** would then be available, while substrates either unable to undergo [1,5]-shift (**9g**) or slow to do so (**9e,f**) would revert to **12** and furnish ether-bridged enones **6**.

The isolation of hemiacetal **11d** is unique among these examples. We presume this product to arise from an S_N2'-type opening of the dihydrofuran at the less hindered alkene carbon to give **13d**.^{11,12} Upon workup, transannular hemi-

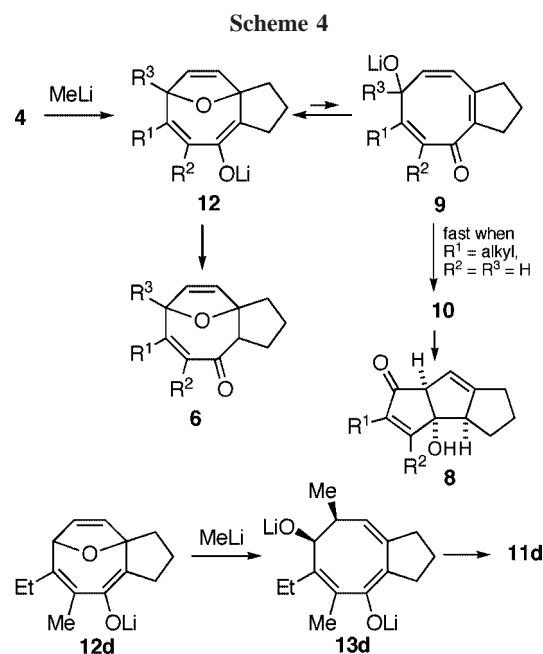
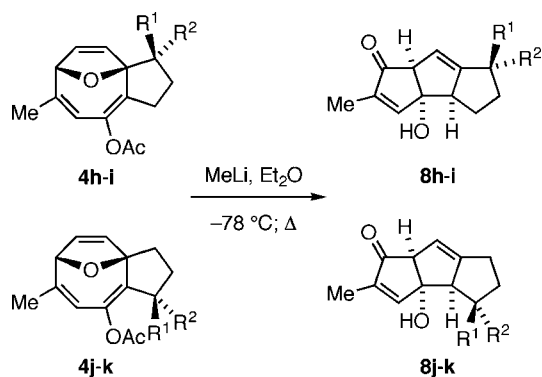


Table 2. Triquinane Formation from Branched Substrates **4h–k**^a



entry	substrate	R ¹	R ²	product	yield (%) ^b
1	4h	Me	H	8h	56
2	4i	H	Me	8i	68
3	4j	Me	H	8j	52
4	4k	H	Me	8k	63

^a The general procedure described in Table 1 was followed. ^b Yields given are for isolated products after chromatographic purification.

acetal formation should be facile.¹³ The relative stereochemistry of the bridgehead methine is presumed to be *trans* to the bridging ether and methyl groups in analogy to enones **6**.

Finally, four examples with the cyclooctatriene substitution pattern of **4a** but substituted with a methyl branch in the fused cyclopentane ring were examined to probe the

effect of remote stereocenter on triquinane formation (Table 2). In the event, the four triquinanes **8h–k** were obtained in 52–68% yield, *each formed cleanly as a single diastereomer*. The absence of any stereochemical erosion is consistent with a 1,5-shift mechanism for the introduction of the bridgehead hydrogen atom, as an alternative proton transfer mechanism would not be expected to display complete stereospecificity.

Fused bicyclic cyclooctatrienes are readily available from pyran-2-ones bearing linked furans via a two-step [4 + 4]-photocycloaddition and thermal decarboxylation sequence. In a number of cases, deacetylation with MeLi and heating leads to triquinane products via an apparent elimination/1,5-shift/aldolization cascade. However, this pathway appears to be sensitive to triene substitution. One example of apparent S_N2' opening of the dihydrofuran by MeLi was also observed. We continue to probe the scope of these novel processes, and the results of these studies will be described elsewhere.

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Supporting Information Available: Experimental procedures, physical data, and NMR spectra for trienes **4** and their products **6e–g**, **8a–c,h–k** and **11d**, as well as CIF data for **8a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) This product could also conceivably arise from 1,6-addition of methyl lithium to elimination product **9e**; however, the S_N2' mechanism seems more probable absent copper ion and in light of the considerable precedent for this reactivity in related oxabicyclic systems (see ref 11).

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