Cyclooctatrienes from pyran-2-ones *via* a tandem [4 + 4]-photocycloaddition/decarboxylation process†

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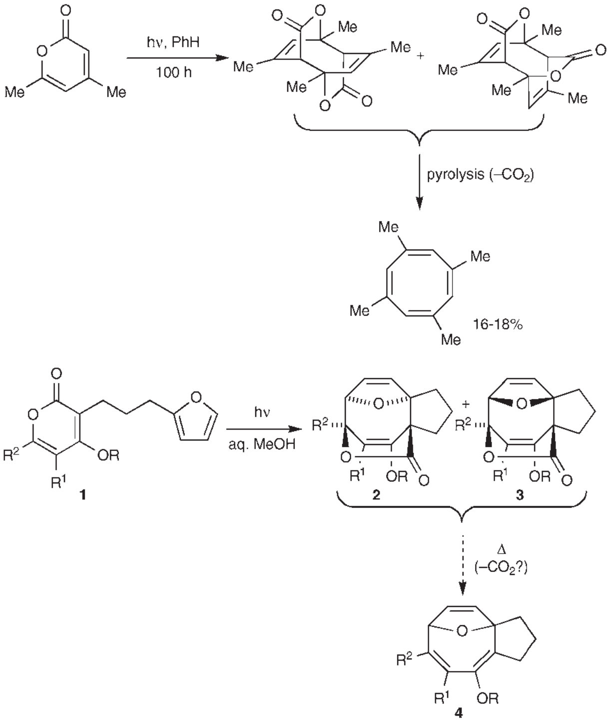
Received (in College Park, MD, USA) 23rd April 2008, Accepted 2nd June 2008
First published as an Advance Article on the web 18th July 2008
DOI: 10.1039/b806871b

Irradiation of pyran-2-ones bearing pendent furans in aqueous MeOH followed by heating furnished fused bicyclic products containing a cyclooctatriene ring.

Appearance of the cyclooctane ring in natural products is surprisingly frequent, given the challenges connected with its direct formation from acyclic precursors in the flask.[1] There has been considerable activity focused on the development of efficient and general methods for the construction of cyclooctanes, especially within a larger polycyclic skeleton.[2,3] Among these, strategies that form the ring through a cycloaddition process are especially attractive, as they allow retrosynthetic disconnection of two cyclooctane bonds and a corresponding simplification to two smaller precursor fragments.[4] In a fascinating example of such a higher-order cycloaddition, 4,6-dimethylpyran-2-one was shown by de Mayo *et al.* to undergo a photochemical dimerization to furnish diastereomeric cyclooctadienes with two lactone bridges (Scheme 1).[5] Pyrolysis effected double decarboxylation by retrograde [4 + 2]-cycloaddition to give tetramethylcyclooctatetraene.

More recently, we have shown that crossed intramolecular [4 + 4]-photocycloadditions can be achieved using readily accessible pyran-2-ones with pendent furan traps, providing cyclooctadienes **2** or **3** with bridging ether and lactone.[6] 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 [4 + 4]-adducts. Reductive opening of the lactone is possible, and this approach is being applied in the synthesis of diterpenes of the fusicoccin class.[7] An alternative method for lactone removal would utilize the decarboxylation process described by de Mayo. Importantly, such a strategy potentially would provide a single triene product **4** regardless of the ratio of diastereomeric cycloadducts **2** and **3**. Here we describe a convenient, one-pot route to cyclooctatrienes *via* a tandem photocycloaddition/decarboxylation process.



Scheme 1 Decarboxylation of pyran-2-one [4 + 4]-photocycloadducts.

Decarboxylation in tandem with Diels–Alder cycloaddition reactions of pyran-2-ones is often seen at the elevated temperatures typically required for these processes,[8] and decarboxylation of pyran-2-one/furan [4 + 4]-cycloadducts was previously noted as a minor side reaction occuring in photocycloadditions conducted without adequate cooling.[6b] With this in mind, we examined the heat induced decarboxylation of the previously described[6b] cyclooctadienes **2a** and **3a** (Scheme 2). Initial pilot-scale experiments were carried out in toluene. *Exo* cycloadduct **2a** underwent slow decarboxylation to give traces of **4a** after extended heating at 80 °C, but underwent quantitative conversion to **4a** after 6 h at reflux. To our surprise, *endo* cycloadduct **3a** was inert to these conditions, returning only starting material. Decarboxylation of **2a** in MeOH at 55 °C was complete after 3 h, while **3a** remained unconsumed after 24 h under these conditions. Finally aqueous MeOH (40% v/v), the solvent system most commonly employed for the photocycloaddition reactions, was examined. Cycloadduct **2a** was cleanly decarboxylated after 3 h at 40 °C. While **3a** was unreactive at this temperature, heating

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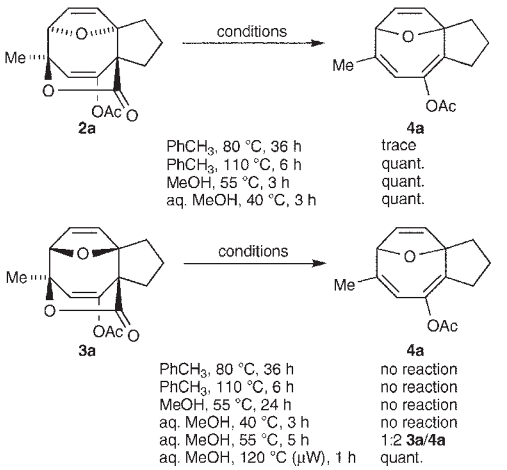
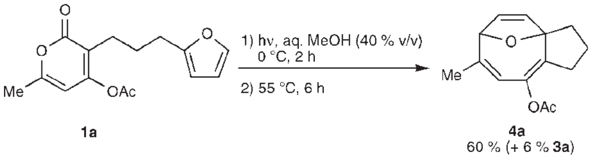
† Electronic supplementary information (ESI) available: Representative experimental procedures and spectral data for photosubstrates and cyclooctatrienes **4**. CCDC 690017. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b806871b



Scheme 2 Thermal behavior of *exo* adduct **2a** and *endo* adduct **3a**.

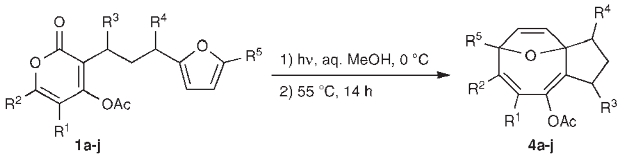
at 55 °C for 5 h effected partial conversion to **4a**. Complete decarboxylation of **3a** could be accomplished by microwave heating at 120 °C (Biotage Initiator) for 1 h.

Since decarboxylation could be effected in aqueous MeOH, we decided to examine the feasibility of a one-pot process entailing initial irradiation of pyran-2-ones, followed immediately by thermal decarboxylation of the photolysate. Substrate **1a** was irradiated under the standard conditions, then heated at 55 °C for 14 h, to furnish **4a** in 60% yield over two steps, along with 6% recovered **3a** (eqn (1)).



(1)

Table 1 Tandem photocycloaddition/decarboxylation[a]



Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Crude **2**:**3** ratio[b]	Yield **4** (%)[c]
1	**1a**	H	Me	H	H	H	1.6 : 1	60[d]
2	**1b**	H	Et	H	H	H	2.7 : 1	62[d]
3	**1c**	H	Ph	H	H	H	1.4 : 1	39[d]
4	**1d**	H	H	H	H	H	Not det.	13[e]
5	**1e**	Me	Et	H	H	H	3.1 : 1	60[d]
6	**1f**	Me	Me	H	H	H	3.0 : 1	63[d]
7	**1g**	–$(CH_2)_3$–		H	H	H	1.4 : 1	63[d]
8	**1h**	H	Me	H	H	Me	1.1 : 1	53[d]
9	**1i**	H	Me	Me	H	H	1.48 : 1[f]	44[g]
10	**1j**	H	Me	H	Me	H	Not det.	48[g]

[a] *General procedure*: Substrates were dissolved in *ca.* 40% (v/v) aq MeOH (1 mg mL^{-1}) in a round bottom flask cooled in an ice-water bath, and irradiated under Ar using a Hannovia 450 W medium-pressure Hg vapor lamp. After 2 h, the reaction mixture was placed in an oil bath and heated at 55 °C for 14 h. Aqueous work-up yielded product as a crude oil, which was purified by flash chromatography. [b] Ratios were obtained by integration of alkene hydrogen resonances in ^{1}H NMR spectra of reaction mixture following irradiation at 0 °C. Trace amounts of [2 + 2]-photoadducts were seen in the crude mixtures from entries 1, 2, 5, 6 and 9, but were not present in detectable quantities following thermolysis. [c] Yields given are for isolated product after chromatographic purification. [d] Varying amounts of unconsumed *endo* adduct **3** were isolated along with **4**: **3a** (6%), **3b** (11%), **3c** (12%), **3e** (10%), **3f** (8%), **3g** (14%) and **3h** (8%). [e] Thermolysis was carried out at 90 °C for 14 h. [f] The major *exo* isomer was formed in a 2 : 1 ratio of methyl epimers (**2i** and **2i′**), while the *endo* isomer was obtained as a single diastereomer (**3i**). [g] Decarboxylation product **4i** was obtained as a 4.5 : 1 mixture of diastereomers, and was accompanied by 20% of **3i**. Decarboxylation product **4j** was obtained as a 1 : 1 mixture of diastereomers, and was accompanied by 12% of **3j**.

To test the generality of this process, we then prepared several additional pyran-2-one substrates‡ and subjected them to the irradiation/thermolysis sequence used with **1a** to furnish cyclooctatrienes **4b–h** (Table 1). Analysis of the crude reaction mixture prior to thermolysis indicated preferential formation of the *exo* cycloadduct in all but one case, in accord with earlier observations. A general trend towards higher *exo* : *endo* ratios was seen for examples with greater substitution on the pyranone ring (entries 2, 5 and 6), while the presence of a C-5 methyl group on the furan ring had the opposite effect. For the most part, the one-pot process occurred in good overall yield, with the exception of the 6-phenyl substrate **1c** and unsubstituted case **1d** (entries 3 and 4), both of which underwent photocycloaddition and thermolytic loss of CO_2 only sluggishly. Notably, additional substitution on the pyran-2-one ring (entries 5–7) did not affect the overall efficiency of this two-step process, and additional substitution on the furan led to only minor diminution in the overall yield (entry 8). In most cases, significant quantities of unreacted *endo* cycloadduct were isolated along with **4**, a result of its slower decarboxylation. However, extended heating to consume unreacted **3** was not desirable, due to slow decomposition of **4** under these conditions. In several cases, microwave heating at 120–130 °C for 1 h could effect complete consumption of **3**; however, because of the large solvent volumes required (typical concentration = 1 mg mL^{-1}) and the apparent sensitivity of **4** to these conditions, simple heating at lower temperature was found preferable.

Two examples with stereogenic centers in the tether were examined (entries 9 and 10). The overall yield of the resulting trienes **4i** and **4j** was somewhat decreased in these cases, although both were accompanied by significant quantities of unreacted **3** (20% of **3i** and 12% of **3j**). Notably, while the presence of a methyl group adjacent to the furan had little apparent effect on the stereochemical outcome (entry 10), branching next to the pyranone ring led to a 4.5 : 1 ratio of trienes **4i** (entry 9). Moreover, *endo* isomer **3i** was obtained as a single diastereomer.§ The origins of this promising diastereoselectivity are under investigation.

These results establish the generality of the one-pot conversion of pyran-2-ones to cyclooctatrienes, but the effect of

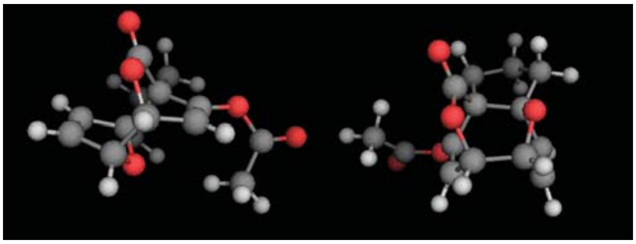


Fig. 1 Minimized structures of *exo* adduct **2a** and *endo* adduct **3a**.

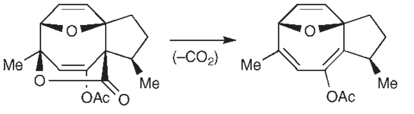
substitution, solvent and relative stereochemical configuration on the efficiency of the decarboxylation step merit further discussion. While additional substitution had little or no negative effect on the overall yield of the two-step process, the unsubstituted example **1d** provided only minor amounts of cyclooctatriene **4d**, and required extended heating at higher temperature. This, together with the increased rate of decarboxylation in polar solvents, suggests that the decarboxylation transition state may possess significant polar character. Importantly, enhanced rates of decarboxylation of pyran-2-one/maleimide [4 + 2]-adducts in protic solvent *vs.* nonpolar or polar aprotic solvents has been noted,[9] and decarboxylation of β-lactones often displays a marked dependence on solvent polarity.[10] The differing reactivity of *endo* and *exo* cycloadducts is more puzzling. In several cases that were examined in detail, the *endo* cycloadduct was found to undergo loss of CO_2 at a substantially lower rate than its *exo* isomer, and only *endo* cycloadduct was isolated in those cases where unreacted cycloadduct was recovered from the one-pot protocol. Molecular modeling of **2a** and **3a** does not suggest a significant difference in ground-state energy (Fig. 1);¶ however, it is possible that the decarboxylation activation barrier for the *exo* cycloadduct may be reduced through neighboring group assistance by the adjacent ether bridge in a polar decarboxylation.

A concise and convenient method to access bicyclo[6.3.0]undecatrienes from simple heterocyclic precursors is described. A tandem photocycloaddition/decarboxylation sequence can be carried out in one pot using aqueous MeOH as solvent. The triene products are expected to be amenable to a variety of productive modification processes. Further studies, including efforts to understand the stereospecific rates of thermal decarboxylation by *endo* and *exo* cycloadducts, are underway and will be reported in due course.

Notes and references

‡ Substrates **1b–h** were prepared *via* palladium(0)-mediated allylation of 4-hydroxypyran-2-ones with 3-acetoxy-1-(2-furyl)propene. Branched tether substrates **1i** and **1j** were prepared by analogous methods using methyl-substituted allylic acetates. See ref. 6*b* and ESI† for details.

§ The single isomer of **3i** that was isolated was a crystalline solid whose X-ray diffraction analysis established its relative stereochemistry to be *syn* (see below). Upon heating, **3i** underwent decarboxylation to give the major diastereomer of triene **4i**. The 4.5 : 1 ratio of **4i** diastereomers is higher than expected based upon the initial mixture of [4 + 4]-adducts following irradiation. This discrepancy may reflect selective decomposition of the minor diastereomer of **4i** during chromatographic purification. (See ESI† for additional discussion of structural determination.)



3i(syn) (x-ray) **4i (major)**

¶ Molecular mechanics calculations used the MMFFaq force field running in Spartan '06. Energies of **2a** and **3a** were calculated to be within 1 kcal mol^{-1} with or without correction for aqueous solvent.

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