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Synthesis of substituted 3-furan-2(5*H*)-ones via an anthracene Diels–Alder sequence

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Abstract—Deprotonation then electrophilic quench of the lactone derived from the Diels–Alder addition adduct of anthracene and maleic anhydride gave α-substituted lactones in good yield. Of particular note was the reaction with chlorotrimethylsilane which gave only the *C*-silylated product. Flash vacuum pyrolysis (FVP) of the alkylated products afforded 3-substituted furan-2(5*H*)-ones in good overall yield.

The furan-2(5*H*)-one or butenolide motif is a common structural feature found in a large number of bioactive natural products from cembranolides, such as the anti-tumour compound sarcophine **1**, to simple lactones themselves, for example, **2** which displays antifungal activity (Fig. 1).[1]

This, coupled with the ability to functionalise many of the core butenolide atoms, have triggered numerous developments aimed towards the synthesis of these molecules.[2] One of the more generally applicable approaches involves the cyclisation of allenic esters and acids promoted by $AgNO_3$, IBr or I_2.[2b,c] This allows access to 4-iodo-3,5-disubstituted butenolides which can be further elaborated through the vinyl iodide. More recently an extremely attractive approach has been disclosed that involves the ring-closing metathesis of acrylate esters.[2d] However, at this time, this is restricted to only 4,5-substituted butenolide targets. 3-Substituted butenolides have been accessed by alkylation of enolates of bicyclic lactones formed from the Diels–Alder reaction of cyclopentadiene and the appropriate enone, followed by a retro Diels–Alder reaction.[3] Although these reactions gave the desired butenolides in excellent yields, there are limitations with this methodology. Any Diels–Alder reaction with cyclopentadiene provides a mixture of both *exo* and *endo* cycloadducts. This in itself is not detrimental to the methodology other than complicating the analysis of intermediates. However, the *endo* isomer was found to be significantly more reactive than the *exo*, the latter requiring 10–20 equiv of alkylating agent to obtain yields in excess of 85%.

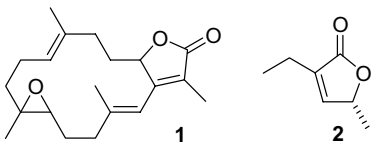

Figure 1. Naturally occurring 3-furan-2(5*H*)-ones.

Previous and ongoing research, from this group and others has investigated the use of substituted anthracenes as potential chiral auxiliaries.[4] Pivotal to this work is the highly diastereoselective Diels–Alder cycloaddition of substituted anthracene derivatives with dienophiles. Having established that both addition and cleavage of substrates is indeed viable, work has now focused on exploring the asymmetric transformations that can be carried out. Of particular interest is the functionalisation of enolates of the anthracene cycloadducts. Although there have been reports of the generation of enolates of anthracene–acrylate cycloadducts,[5] to our knowledge there has only been one record of the generation and reaction of enolates at such a fused bicyclic position.[4i] This species was subsequently trapped with a range of aldehydes and benzoyl chloride in poor to moderate yield. Thus the development of an alkylation strategy would complement this existing methodology, and additionally provide an alternative route to

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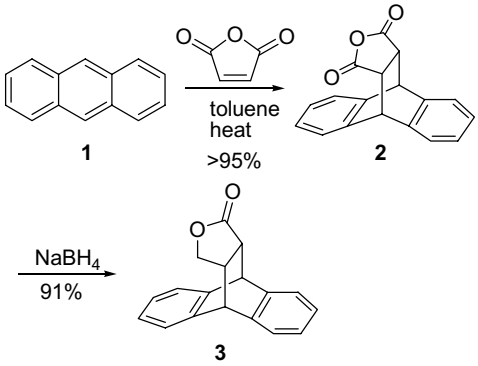
butenolides that circumvents the *endo*/*exo* and reactivity issues associated with the use of cyclopentadiene.

The starting material for these transformations was lactone **3** which was prepared on a multi-gram scale following literature precedent.[6] Thus, Diels–Alder addition of maleic anhydride with anthracene **1**, followed by reduction of the anhydride **2** with sodium borohydride afforded lactone **3** in excellent yield (Scheme 1).

The sparse solubility of lactone **3** in THF precluded enolate formation at −78 °C. However, treatment of a slurry of the lactone **3** with lithium diisopropylamide in THF at 0 °C led to complete solubilisation and generation of an intense yellow solution. Addition of a slight excess of methyl iodide, allyl iodide, butenyl bromide or benzyl bromide afforded *C*-alkylated lactones **4**–**7** in good yields after silica gel chromatography (Table 1, entries 1–4, respectively). Since this enolate has previously been quenched with carbonyl electrophiles,[4i] a number of non-carbon based electrophiles were also considered. Thus, reaction with tributyltin chloride gave the stannane **8** in a disappointingly low yield (Table 1, entry 5). However, reaction with diethyl chlorophosphate (entry 6) gave the α-phosphonate **9** in good yield, while chlorotrimethylsilane (entry 7) yielded the *C*-silyl lactone **10** as the sole product in excellent yield (84%).[7] Conclusive evidence of silylation at carbon rather than at oxygen were the ^{13}C NMR signal of the new quaternary carbon at δ 47.2 ppm and a strong IR carbonyl band at 1741 cm^{-1}. Enolates generated by treatment with lithium amides followed by quenching with trimethylsilyl chloride generally provide *O*-silyl ethers,[8] however, esters and lactones can be *C*-silylated by judicious choice of the appropriate silyl chloride[9] or hydrosilylation of diazo carbonyl compounds.[10]

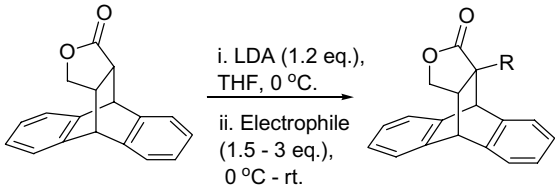


Scheme 1. Preparation of the key lactone **3**.

Examination of the minimised structures of lactone **3** and γ-butyrolactone **11** indicates that both adopt similar conformations with H–C–C=O bonds angles of 64.9° and 58.9°, respectively (Fig. 2),[11] ruling out a stereoelectronic requirement for the reduced acidity of this proton. However, the calculated structure of the enolate of γ-butyrolactone **11** appears to exist in an almost planar conformation that lactone **3** cannot possibly adopt due to the inherent bicyclic structure. This leads to a tetrahedral-like α-keto carbanion that cannot adopt a completely coplanar arrangement with the adjacent π system. This inefficient overlap reduces the 'effective' delocalisation through the carbonyl group, resulting in a more carbon-centred carbanion that reacts through carbon instead of oxygen.

Problems were initially encountered when trying to effect the retro Diels–Alder cleavage of the lactones. Heating the parent lactone **3** in toluene, mesitylene or xylene failed to promote cycloreversion. The lactone **3** was also heated with an excess of maleic anhydride in the hope that any trace quantities of anthracene formed in an equilibrating mixture would be trapped out. However, once again only starting material **3** was returned. Application of other methods known to effect the retro Diels–Alder reaction of anthracene adducts such as heating in high boiling silicone oil[12] or using ultra-violet[4d] or microwave[13] irradiation all proved ineffective. However, application of flash vacuum pyro-

Table 1. Deprotonation and reaction of lactone **3** with electrophiles



Entry	Electrophile	R	Product	Yield[a]
1	CH_3I	CH_3	**4**	76
2	$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2$	**5**	71
3	$CH_2{=}CHCH_2CH_2Br$	$CH_2{=}CHCH_2CH_2$	**6**	75
4	$PhCH_2Br$	$PhCH_2$	**7**	78
5	Bu_3SnCl	Bu_3Sn	**8**	21[b]
6	$(EtO)_2P(O)Cl$	$(EtO)_2P(O)$	**9**	74
7	$(CH_3)_3SiCl$	$(CH_3)_3Si$	**10**	86

[a] Based on isolated product.
[b] Unoptimised yield.

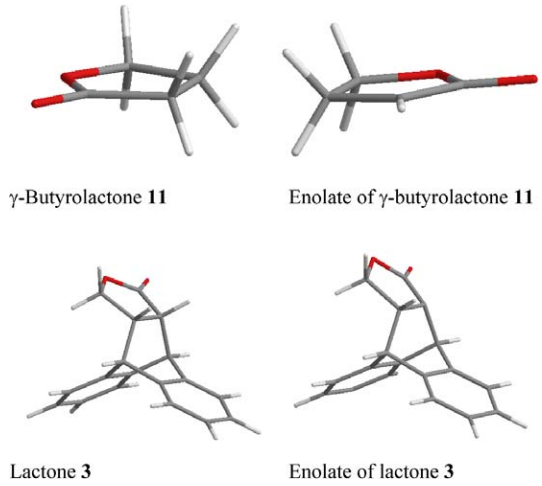
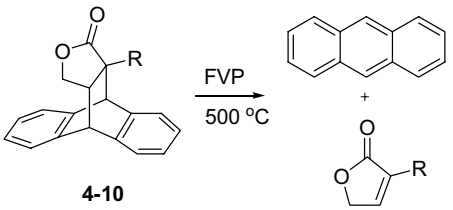


Figure 2. Calculated structures of lactones **3** and **11** and their enolates.[11]

Table 2. Flash vacuum pyrolysis of lactones **4–10**



4-10 **12-18**

Entry	Lactone	Product	R	Yield[a]
1	**4**	**12**	CH_3	78
2	**5**	**13**	$CH_2{=}CHCH_2$	83
3	**6**	**14**	$CH_2{=}CHCH_2CH_2$	70
4	**7**	**15**	$PhCH_2$	79
5	**8**	**16**	H	78[b,c]
6	**9**	**17**	$(EtO)_2P(O)$	67[c]
7	**10**	**18**	$(CH_3)_3Si$	82

[a] Based on isolated product.
[b] 2(5*H*)-Furanone obtained instead of vinyl stannane.
[c] Refers to conversion to product as noted from the ^1H NMR spectrum.

lysis at ~500 °C readily cycloreverted lactones **4–7** to yield 3-alkyl butenolides **12–15** in good to excellent yields (Table 2, entries 1–4) that are generally comparable to those obtained with the cycloadduct of cyclopentadiene. Interestingly, the homo-allyl lactone **14** (Table 2, entry 3) did not appear to undergo a Cope rearrangement under the FVP conditions.

Somewhat disappointingly, stannane **8** failed to survive FVP treatment and afforded only destannylated furanone **16** in good conversion together with unidentified decomposition products (entry 5). However, attempts to purify this material led to loss of product, presumably due to the inherent volatility of the lactone **16**. Vinyl stannanes have been previously prepared using FVP techniques, although these have been unsubstituted, inferring that the α-stannyl enones prepared here are thermally unstable.[14] More encouraging results were obtained with the phosphonate **9**, leading to quantitative cleavage to the vinyl phosphonate **17** (entry 6). However, this material could not be isolated, decomposition occurring on attempted purification by silica gel chromatography or Kugelröhr distillation. Phosphonate **17** has been previously prepared via an oxidative deselenation procedure, however, this compound was found to decompose by polymerisation even while standing at room temperature.[15] In spite of the problems with the two previous α-hetero substituted lactones, the *C*-trimethylsilyl lactone **10** cleanly afforded 3-(trimethylsilyl) 2(5*H*)-furanone **18** in excellent yield (entry 7). Although a few other routes exist to vinyl silanes of this type,[16] this two-step *C*-silylation/retro Diels–Alder sequence represents a simpler and more efficient route than those currently employed.

In summary, we have demonstrated that bridgehead lactones of type **3** can indeed be deprotonated and functionalised with a variety of electrophilic species. This has led to a much improved and efficient route for the synthesis of 3-(substituted) furan-2(5*H*)-ones that overcomes the stereoselectivity issues and excess reagents used when employing cyclopentadiene adducts.

Supplementary data

A list of experimental procedures and characterisation data for all new compounds is included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.097.

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