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Intramolecular Carboxylic Acid Trapping of Pyran-4-one Derived Zwitterions: A Novel Synthesis of Fused Bicyclic Lactones

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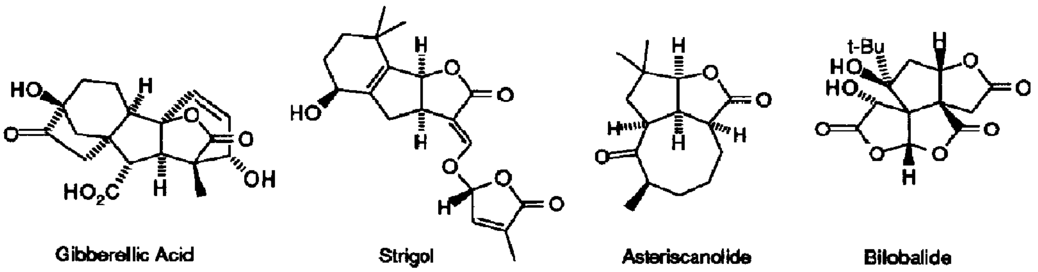
Abstract: *Pyran-4-ones bearing carboxylic acid side chains were prepared either by direct carboxylation with carbon dioxide or through oxidative cleavage of side chain olefins. Irradiation in a non-nucleophilic solvent yielded fused bicyclic lactones. The efficiency of the reaction was not dependent on ring substitution.*

Methods for the annulation of a lactone ring onto a carbocycle have received considerable attention, due to the frequency with which this structural motif is encountered. Figure 1 shows several natural product targets in which a lactone is fused to an adjacent cyclopentane ring. Closure of the lactone ring has been effected via both C-O and C-C bond formation. Among the former methods, addition of a pendant carboxyl group to an electrophilic carbon (e.g., iodo- or selenolactonization) has proven to be among the most useful. We report here a new variation on this approach, in which the electrophilic carbon center resides at one terminus of a photochemically generated oxyallyl zwitterion.

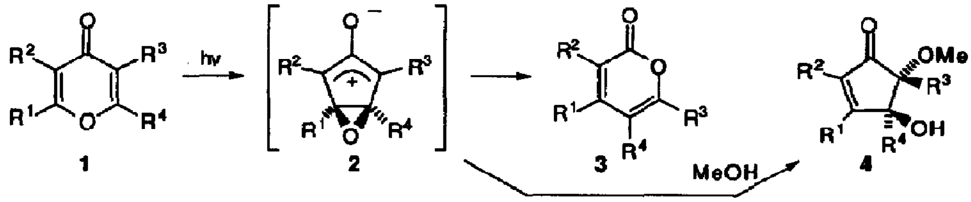


Gibberellic Acid Strigol Asteriscanolide Bilobalide

Figure 1. Natural products containing cyclopentane-fused lactones.

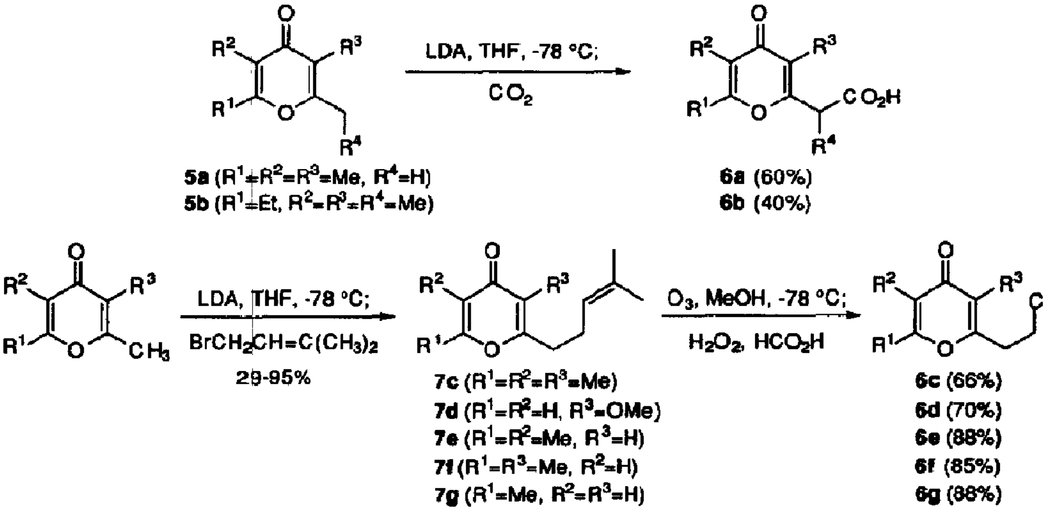
Study of the pyran-4-one photochemistry[1,2] has revealed a variety of interesting mechanistic problems and considerable synthetic potential. Early work demonstrated that, upon irradiation in hydroxylic solvents, pyran-4-ones **1** produced both rearranged pyrone **3** and solvent adducts **4** (Scheme 1).[3] This observation provided evidence for a transient oxyallyl zwitterion intermediate **2**. More recently, we have attempted to develop a variety of zwitterion trapping reactions as useful synthetic processes. A particularly attractive feature of these reactions is the substantial increase in molecular complexity that is realized. We have shown that the zwitterion may be productively trapped by both hydroxylic solvents[4] and acetonitrile.[5] Inter- and intramolecular [4+3]-cycloaddition of 1,3-dienes can also be effected.[6] Finally, several classes of pendant nucleophiles have been demonstrated to effectively capture the zwitterion, including alcohols,[7] olefins[8] and arenes.[9] In the process, fused bicyclic ethers, diquinanes, hydrindans or benzohydrindenes are directly generated from simple precursors. In the present study, we have sought to extend this trapping process to carboxyl nucleophiles.

Scheme 1



The carboxylic acid derivatives required for the key photocyclization could be easily prepared from simple polyalkylated pyran-4-ones in one or two steps. Tetrasubstituted pyrones **5a** and **5b** could be cleanly deprotonated at the γ-position using LDA at -78°C. The resulting enolates were quenched with carbon dioxide to produce the desired acids **6a-b** in moderate yields (Scheme 2). Analogous carboxylation of 2,6-disubstituted 4-pyrones was complicated by the lability of the derived enolates. Previous work[8,10] has shown that efficient generation and electrophilic trapping of these enolates requires the use of cosolvents such as HMPA or DMPU. Separation of the highly polar carboxylic acid product from the cosolvent was difficult, rendering this route unsuitable for the more lightly substituted examples.

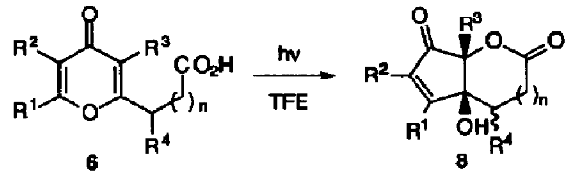
Scheme 2



The one-carbon homologs could be prepared via a two-step procedure, and this method proved to be applicable to any ring substitution pattern. The previously described prenylated pyran-4-ones **7** are readily available from simple 2-methyl pyran-4-ones via standard anion alkylation chemistry.[8] Ozonolysis of the side chain olefin and oxidative work-up gave the desired carboxylic acids **6c-n** in good yield. The products could be used in the subsequent photoreactions without further purification.

In preliminary experiments, irradiations were carried out in trifluoroethanol (TFE) using a 450W Hanovia medium pressure mercury lamp, resulting in fair yields (Table). Prior solvent trapping studies had indicated that a low pressure mercury lamp gave cleaner reactions,[4] presumably as a result of diminished levels of secondary photoreactions. For the conversion of **6** to **8**, yields were improved by 4 to 18% with a low pressure lamp, although longer irradiation times were necessary to consume the pyran-4-ones.[11] Irradiation at lower temperature was also examined in one case (**6g**), but led to much longer reaction times and diminished yield (0 °C, 10 h, 35%). In general, the best results were obtained with permethylated substrates, which cyclized in 70% yield for both n=0 (**6a**) and n=1 (**6c**). For the remaining substrates, with the exception of 3-methoxy substrate **6d**, the efficiency of the ring closure was comparable (ca. 50%).[12] These results parallel those obtained when using pendant alcohol nucleophiles,[6] in that the yield of cyclized product does not appear to be dependent on the ring substituion pattern. As expected, little diastereoselectivity was observed in the case of substrate **6b**, bearing a preexisting stereogenic center in the side-chain.

Table. Photochemical Conversion of Pyran-4-ones 6 to Bicyclic Lactones 8.[a]

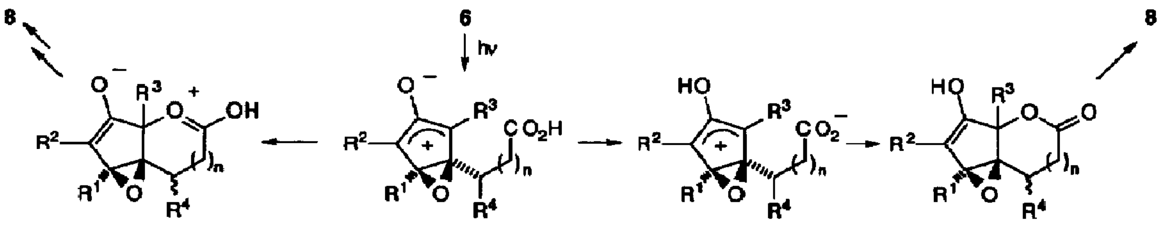


Substrate	R¹	R²	R³	R⁴	n	t (min)	product	yield (%)[b]
6a	Me	Me	Me	H	0	65	**8a**	70[c]
6b	Et	Me	Me	Me	0	45	**8b**	56[c,d]
6c	Me	Me	Me	H	1	60	**8c**	70[c]
6d	H	H	OMe	H	1	150	**8d**	25[e]
6e	Me	Me	H	H	1	120	**8e**	45[e]
6f	Me	H	Me	H	1	180	**8f**	53[e]
6g	Me	H	H	H	1	180	**8g**	48[e]

[a] For a representative procedure, see reference 11. [b] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR and combustion analyses were obtained for all products. [c] A Hanovia medium pressure mercury lamp was used. The mixture was irradiated for ca. 1 h. The solvent was removed and the crude product purified by radial chromatography. [d] Isolated as an inseparable 3 : 2 mixture of diastereomers. [e] A Hanovia low pressure mercury lamp was used. The mixture was irradiated for 2-3 h after which solvent was removed. The crude product was dissolved in EtOAc and washed with saturated $NaHCO_3$.

The nature of the reactive groups in these examples deserves comment. While trapping of the zwitterion by protonated carboxylic acid is a possibility (Scheme 3), a more likely scenario would involve prior proton transfer to generate the more electrophilic hydroxyallyl cation and the more nucleophilic carboxylate ion. Inclusion of catalytic quantities of protic acid has previously been shown to enhance inefficient oxyallyl zwitterion trapping processes.[4,9] Collapse to the tricyclic lactone and epoxide opening would then furnish the observed bicyclic lactones.

Scheme 3



In summary, readily prepared carboxyl-substituted pyran-4-ones **6** are converted to reactive oxyallyl zwitterions upon irradiation. Efficient cyclization of the pendant carboxyl onto the electrophilic terminus of the oxyallyl system leads to fused bicyclic cyclopentenone-lactones **8**. These products should be useful in the synthesis of lactone containing targets or highly oxygenated cyclopentanoids. Further applications of this chemistry will be reported elsewhere.

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11. Representative procedure: **6-Hydroxy-7-methyl-3-oxo-2-oxabicyclo[4.3.0]non-7-en-9-one (8g).** 2-(2'-Carboxyethyl)-6-methyl-4H-pyran-4-one (**6g**) (100mg, 0.55mmol) was dissolved in TFE (75mL, ca. 7.3 mM). Dry N_2 was bubbled through the resulting solution for 30 min. The reaction mixture was then irradiated in a quartz vessel at ambient temperature using a Hanovia 3.5 W low pressure mercury lamp until the starting material was consumed (3 h). The mixture was concentrated and the residue dissolved in EtOAc (30 mL). The organic solution was washed with saturated $NaHCO_3$ (2 mL), dried over $MgSO_4$ and concentrated to leave a yellow oil. The oil was purifed by radial chromatography (silica gel, 1 mm, hexanes/EtOAc 1:1) to give 48 mg (48%) of **8g** as a white solid: mp 111-113°C; IR (thin film) 3400, 2951, 1761, 1719, 1616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (q, J = 1.3 Hz, 1H), 4.78 (s, 1H), 4.3 (br s, 1H), 2.58 (ddd, J = 16.6, 7.0, 3.7 Hz, 1H), 2.28-2.18 (m, 1H), 2.17 (d, J = 1.3 Hz, 3H), 2.10-1.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 176.3, 171.3, 129.2, 86.4, 76.4, 30.2, 26.5, 13.8; Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.12; H, 5.57.

12. The remainder of the mass consisted of intractable, highly polar material which resisted characterization. A representative cyclization product (**6e**) was inert to reaction conditions either with (2 h) or without (4 h) irradiation.

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