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Short Flow-Photochemistry Enabled Synthesis of the Cytotoxic Lactone (+)-Goniofufurone

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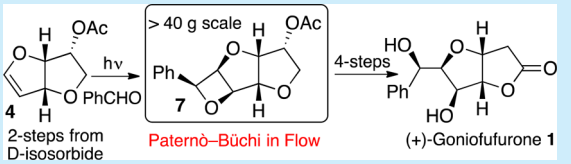
Supporting Information

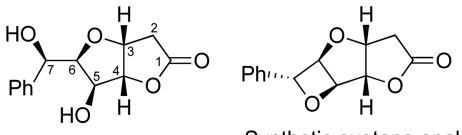
ABSTRACT: A photochemical approach to the cytotoxic lactone (+)-goniofufurone (**1**) is reported. Paternò–Büchi [2 + 2] photocycloaddition from known enol ether **4**, derived from the readily available sugar D-isosorbide, yielded oxetane **7**. This slow, dilute reaction was scaled up by using flow photochemistry to yield >40 g of **7**. Installation of the key lactone ring was achieved via a unique Wacker-style oxidation of an enol–ether bond. Acid-catalyzed aqueous ring opening provided **1** in five steps from **4** (11.5% overall).



(+)-Goniofufurone (**1**) is an example of a number of styryl-lactone containing natural products isolated from *Goniothalamus* trees of the plant family Annonaceae in South East Asia.[1] Extracts from these plants have been used as traditional medicines in the treatment of edema and rheumatism as well as mosquito repellents. A number of total synthesis of **1** and its congeners have been reported,[2] as well as progress in the synthesis and evaluation of biological activity of analogues. Of particular significance is the extensive work of Popsavin et al.[3] who have demonstrated that analogues of **1** have potent antiproliferative effects against a number of human cell lines. In particular, the oxetane **2**, which was formed from 7-*epi*-(+)-goniofufurone, had a cytotoxic potency greater than that of the natural product and, with some cell lines, even greater activity than the anticancer drug standard doxorubicin (Figure 1).

As part of a program exploring the use of synthetic photochemistry in drug discovery, we were intrigued with the possibility of synthesizing **1** by hydrolysis of the oxetane **3**, which as an epimer of **2** should undergo hydrolytic inversion of the benzylic C-7 center during ring opening (Scheme 1). An efficient synthesis of **3** would also prove useful for the preparation of a range of ring-opened analogues for use in drug discovery (**1**, Nu = OR, NHR, SR, CN, etc.). If successful ring-opening protocols could be developed, then a diverse range of nucleophiles could be investigated under protic or Lewis acid conditions. In order to achieve this, we proposed a route toward **3** that involved a Paternò–Büchi [2 + 2] photocycloaddition between the bicyclic enol ether **4** and benzaldehyde (Scheme 1).

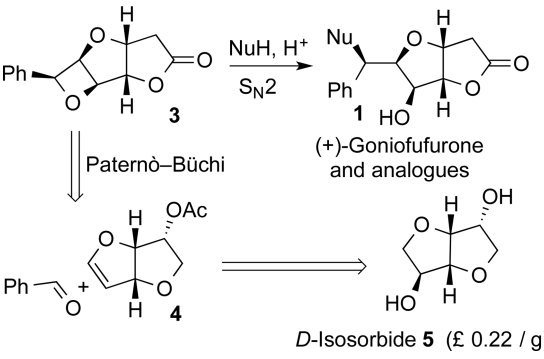
There have been many reports on the scope of the Paternò–Büchi reaction in the synthesis of oxetanes and their subsequent ring-opening reactions.[4] Although this photocycloaddition has some significant limitations, it often provides the most direct and economic route to this class of four-membered heterocycle.[5] Although at this stage the stereoselectivity of **4** to **3** was



compound	K562	HL-60	Jurkat	Raji
1	0.41	>100	32.45	18.45
2	0.39	0.11	0.03	3.65
DOX	0.25	0.92	0.03	2.98

Figure 1. IC_{50} values of (+)-goniofufurone (**1**) and oxetane analogue **2** and their comparison to anticancer drug standard doxorubicin (DOX).

Scheme 1. Proposed Oxetane Ring-Opening Strategy to (+)-Goniofufurone and Analogues and a Concise Route from D-Isosorbide via a Paternò–Büchi Photocycloaddition Synthetic Strategy



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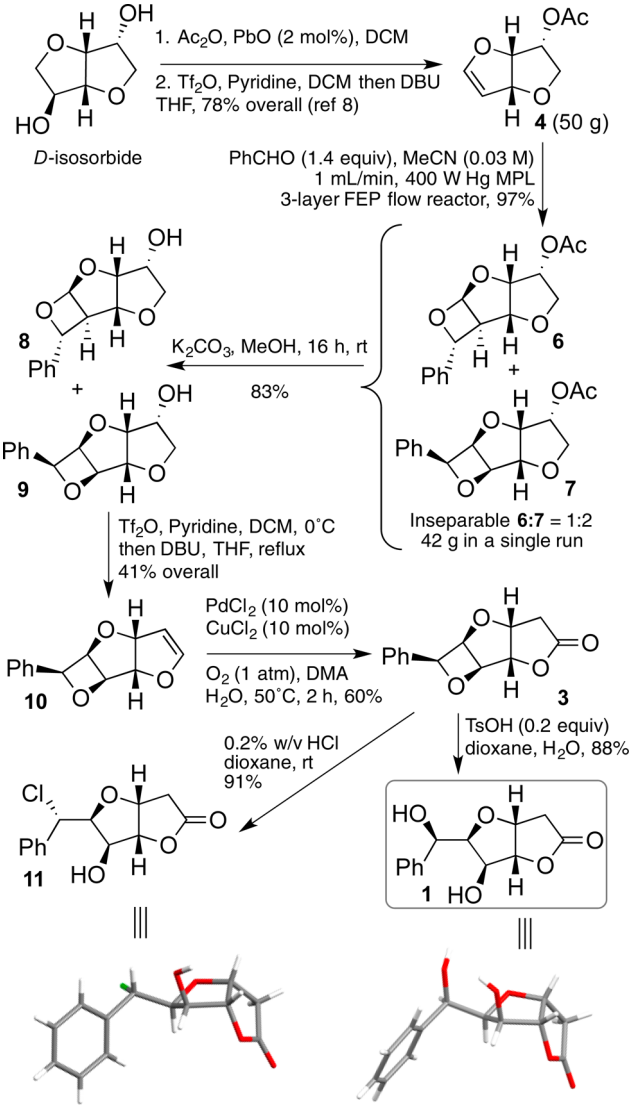
untested, the regiochemistry of a model photocycloaddition of benzaldehyde with dihydrofuran[6] was clearly in our favor. Furthermore, we have shown that the model cycloaddition of benzaldehyde with dihydrofuran could be scaled up very effectively (e.g., 150 g/24 h) using our FEP flow photochemical reactors.[7] Thus, if the Paternò–Büchi photochemistry to **3** could be realized, then a short and scalable route to **1** and analogues could be developed.

The requisite enantiomer of the enol ether **4** is conveniently available from D-isosorbide **7** in a two-step sequence according to the protocol of Berini and Deniau.[8] In our hands, this was found to be highly scalable, and 50 g batches of **4** could be produced routinely. Irradiation of **4** with benzaldehyde in acetonitrile in a batch immersion well (400 mL) with a 400 W medium-pressure lamp gave a 2:1 inseparable mixture of the desired oxetane **7** and a structural regioisomer **6**. Although the batch irradiation proceeded in good overall yield (93%), the reaction was slow and required running at fairly high dilution. This meant that meaningful scale up in batch was rather restricted. Previously, we demonstrated[7] that FEP continuous flow reactors can be useful in the scale up of organic photochemistry, especially in the case of high dilution reactions where the large volumes of solvent are not compatible with fixed volume batch reactors. Using a three-layer FEP flow reactor in conjunction with a 400 W medium-pressure lamp, we were able to considerably upscale the productivity of this key reaction, enabling the formation of over 40 g of the **6**/**7** mixture (97% isolated yield) in a single 83 h run (1 mL/min, 70 min residence time). We were pleased to observe the formation of **7** not only as the major regioisomer but also with the correct C-7 stereochemistry. Basic methanolysis gave a 2:1 mixture of the alcohols **8** and **9**, which were easily separable at this stage (Scheme 2).

With multigram quantities of **9** in hand, we then explored the installation of the lactone ring. Triflation of **9** immediately followed by DBU elimination of the resulting triflate gave the enol ether **10** in 41% yield. The intermediate triflate of **9** proved to be rather unstable and on one occasion decomposed exothermically on standing at room temperature. Unfortunately, the corresponding less labile mesylate and tosylate of **9** were unreactive toward basic elimination. Despite this, we were able to carry out the triflation/elimination of **9** on up to an 8.0 g scale to prepare 2.6 g (35%) batches of **10**.

At this stage, we attempted to investigate the installation of the lactone ring by direct oxidation of **10**. There are a number of reports in the literature regarding the direct oxidation of 5- and 6-membered enol ethers to the corresponding lactones. The most common of these is a chromate-based oxidation system.[9] Unfortunately, a number of the chromate systems explored (e.g., PCC, PDC, Jones oxidation) gave rise to rapid decomposition of **10**, and none of the lactone–oxetane **3** could be isolated. We then screened **10** under a variety of different oxidation conditions, but despite a study of *over 20 oxidants*[10] we were unable to isolate any of the desired lactone **3**. It became frustratingly clear that many of the conditions required to oxidize the enol–ether bond in **10** would always be incompatible with the acid-sensitive oxetane ring. In a change of strategy, we postulated that a Wacker-type oxidation may be more successful as the initial step would involve a metal–π interaction under mild conditions. On treatment of **10** under standard Wacker conditions, we were delighted to see rapid and clean oxidation to the elusive lactone **3** in 60% yield. Pleasingly,

Scheme 2. Total Synthesis of (+)-Goniofufurone and X-ray Crystallography of 1 and 11



this reaction could be carried out on gram scale; e.g., 2.6 g of **10** gave 1.62 g of **3** (58%).

Initial attempts to complete the synthesis of **1** by oxetane ring opening proved to be very interesting. Treatment of **3** with dilute aqueous HCl in dioxane yielded the chloride **11** (91%), which after confirmation by X-ray crystallography appeared to have undergone substitution with overall retention of C-7 stereochemistry. However, as traces (≤5%) of **1** were also isolated from the reaction mixture it is likely that **1** is formed initially and then undergoes subsequent acid-catalyzed chloride substitution in an overall double-inversion sequence. Repeating the sequence with the less nucleophilic TsOH yielded (+)-goniofufurone (**1**) in 88% yield (Scheme 2).

In light of the extreme difficulty faced in the oxidation of enol ether **10** to lactone **3**, the surprisingly effective Pd(II)-mediated oxidation deserves further comment. Although Pd(II) Wacker style oxidations of enol ethers to enones are well documented,[11] we believe that the present result represents the first example of a Wacker style oxidation of a cyclic enol ether to a lactone. It has been reported that the oxidation of dihydrofuran with $PdCl_2$ leads to a mixture where the major

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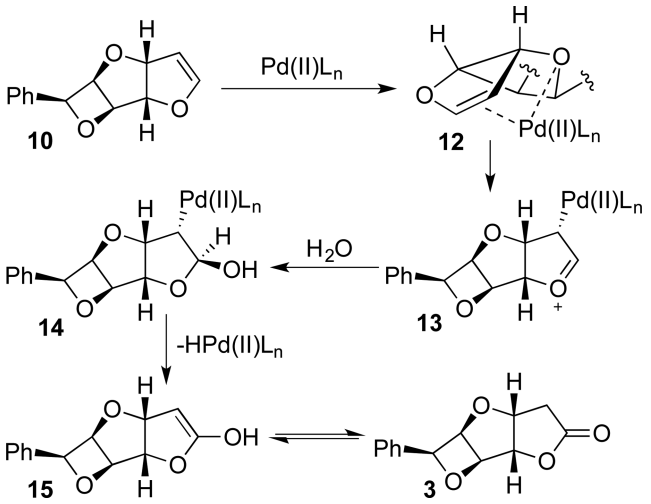
product is 2-hydroxy-3-chlorotetrahydrofuran.[12] This suggests that the mode of oxidation to lactone **3** is specific to the particular structural features present in **10**. It is reasonable to propose that coordination of the alkene to Pd(II) is facilitated by the furan oxygen such that it proceeds from the concave face of **10** to give the complex **12** (Scheme 3). Metalation proceeds

Scheme 3. Proposed Mechanism for Selective Enol−Ether Oxidation to Lactone 3 under Wacker Conditions



to give oxonium ion **13**, which is unable to undergo *syn* β-hydride elimination and as such is attacked by water from the convex face to give **14**. This then undergoes β-hydride elimination to the enol **15** and then tautomerization to **3**.

In conclusion, we have developed a short and scalable synthesis of (+)-goniofufurone (**1**) in just five steps from the enantiopure enol ether **4**, itself a readily available starting material sourced from the abundant and low cost sugar derivative D-isosorbide. Key features include formation of the oxetane **7** by a photochemical Paternò−Büchi reaction. The batch limitations of this step were overcome by the use of a flow photoreactor allowing the synthesis of >40 g of intermediates in a single run. Considering the issues faced in subsequent steps, there is no doubt that it would have been extremely difficult to complete a meaningful total synthesis of **1** without this level of productivity in the Paternò−Büchi step. This highlights the power of flow chemistry techniques when applied to the up-scaling of photochemistry, an area that is often criticized for low productivity levels. Due to the acid sensitivity of the oxetane ring, we were faced with a seemingly intractable enol ether to lactone oxidation problem (**10** to **3**), only to find that a Pd(II) Wacker type oxidation was surprising effective. This novel Pd(II)-catalyzed transformation appears to be specific to **10** as enol ethers are traditionally oxidized to enones under Wacker conditions. Finally this study should allow for the production of quantities of the oxetane−lactone **3** and the chloro lactone **11** as key intermediates for the synthesis of C-7 analogues of (+)-goniofufurone as part of a possible cancer drug-discovery program. For example, as the synthetic oxetane **2** prepared by Popsavin[3] has displayed high cytotoxicity against human cell lines, access to large quantities of **3** and other Paternò−Büchi-derived oxetanes could prove to be medicinally important.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00067.

Experimental procedures and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Oxidation of **10** was investigated under the following, unsuccessful, conditions: (a) PCC, DCM; (b) PCC, NaOAc, DCM; (c) PDC, DCM; (d) CrO_3, MeCN; (e) $KMnO_4$, H_2O; (f) RuO_2, $NaIO_4$, EtOAc, H_2O; (g) $RuCl_3$, Oxone, acetone; (h) TEMPO, $NaIO_4$; (i) *m*-CPBA, DCM; (j) $Pb(OAc)_4$, DCM; (k) TPAP, DCM; l) TPAP, NMO, MeCN; (m) CAN, DCM; (n) IBX, DCM; (o) DMP, DCM; (p) H_2O_2, acetone; (q) Oxone, $NaHCO_3$, acetone; (r) TBHP, ^{t}BuOH, H_2O_2; (s) $NaIO_4$, $RuCl_3$; (t) O_2, Rose Bengal, *hν*, Hunig's base; (u) K_2OsO_4, acetone; (v) OsO_4, ^{t}BuOH; (w) ZnO_2, THF, O_2, DMA, H_2O.

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