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COMMUNICATION

Functionalized 3(2*H*)-furanones *via* photooxygenation of (β-keto)-2-substituted furans: Application to the biomimetic synthesis of merrekentrone C†

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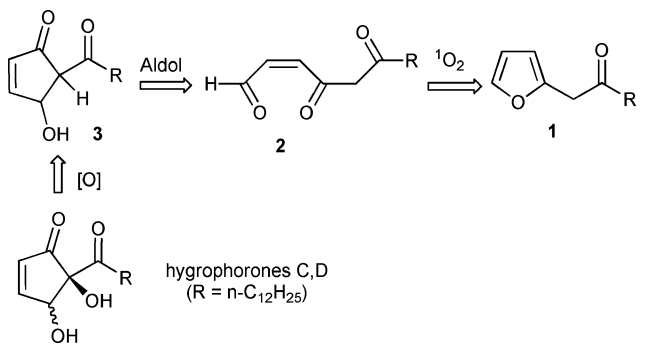
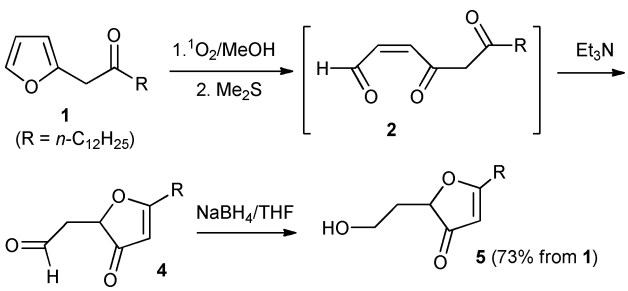
Photooxygenation of (β-keto)-2-substituted furans leads, in a one pot operation, to functionalized 3(2*H*)-furanones with good to excellent yields. This methodology was applied as a key-step to the concise and biomimetic synthesis of the sesquiterpene merrekentrone C. The precursor to merrekentrone C, keto difuran, was synthesized using a cross coupling of α-iodo-3-acetylfuran with an alkenyl furan under Fenton-type conditions.

Recently, we became interested in synthesizing members of the hygrophorone[1] family of natural products. These cyclopentenones exhibit fungicidal activity. Following the retrosynthetic analysis shown in Scheme 1, β-keto-2-furan **1** was proposed as the starting material. Phootoxygenation[2] of **1** should provide triketone **2**, which in turn might be a reasonable precursor to the hygrophorone's skeleton *via* an intramolecular aldol reaction.[3] However, when we first investigated this proposed reaction, we found that the only product formed upon reaction of **1** with singlet oxygen ($^1O_2$) in MeOH, followed by treatment with Me_2S (4 equiv) and Et_3N (1 equiv), was the 3(2*H*)-furanone-substituted aldehyde **4**[4] (Scheme 2). The anticipated aldol product **3** was not detected. Clearly, the intermediate triketone **2** undergoes an intramolecular oxa-Michael reaction,[5] instead of the envisaged aldol reaction. Prompted by this observation, we undertook a systematic study of this transformation (Scheme 3) and found that all the (β-keto)-2-substituted furans provide, after singlet oxygen photooxygenation, treatment with Me_2S and Et_3N (one pot), 3(2*H*)-furanones in good to excellent yield.



Scheme 1 Retrosynthetic analysis for hygrophorones C–D, *via* photooxygenation of keto furan **1**.



Scheme 2 Formation of a 3(2*H*)-furanone (**4**) *via* photooxygenation of keto furan **1**.

The 3(2*H*)-furanone core skeleton appears in a significant number of natural products[6] and bioactive substances.[7] As a result, a variety of methodologies have been developed for the synthesis of functionalized 3(2*H*)-furanones, including metal-,[8] and non-metal-catalyzed procedures.[9] Moreover, an enantioselective version was recently presented.[10] Closely related to the 3(2*H*)-furanone forming reaction shown in Scheme 2, are the photooxygenation of an α-furyl β-keto acetate[11] (a single example), and the oxidation of some (β-keto)-2-furans with *m*-CPBA.[12] The latter reaction often yields a significant quantity of by-products *via* lateral over-oxidation[13] of the products.

In a typical experiment, the keto furan was photooxygenated at 0 °C in methanol using methylene blue as a sensitizer. Upon consumption of the starting material (typically a few minutes), the solvent was evaporated, and replaced by CH_2Cl_2 or $CDCl_3$. Then Me_2S (4 equiv) were added (16 h, 25 °C), followed by Et_3N (1 equiv). After 10 h the solvent was evaporated and the residue was chromatographed to provide the 3(2*H*)-furanones in good to excellent yield (57–83%). In the case of the chromatographically

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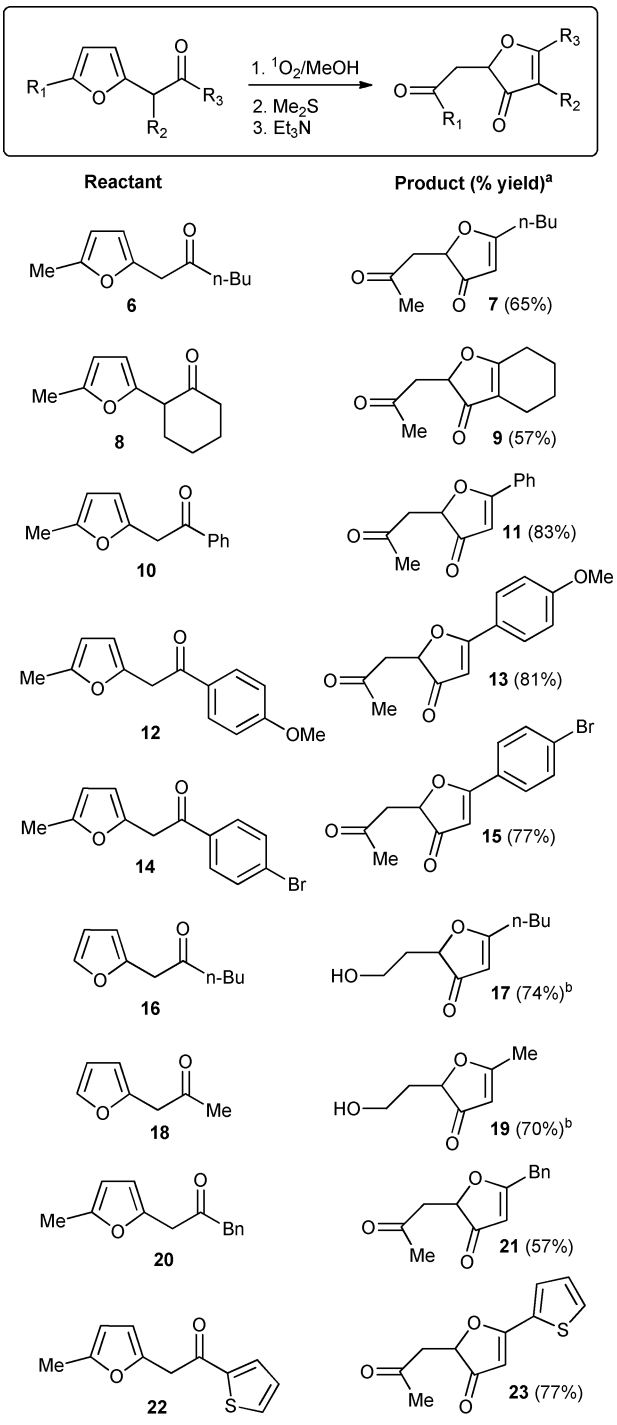
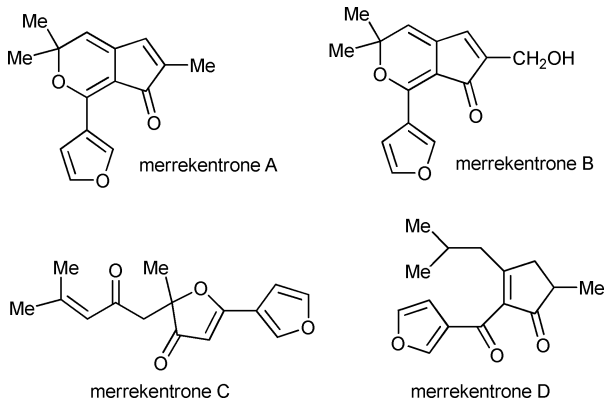


[a] Isolated yield. [b] The crude reaction mixture of the initially formed 3(2*H*)-furanone substituted aldehyde was reduced with 1.2 equiv of $NaBH_4$ in moistened THF (see SI).

Scheme 3 Synthesis of functionalized 3(2*H*)-furanones *via* photooxygenation of β-keto-2-substituted furans.

labile 3(2*H*)-furanone-substituted aldehydes (not shown) formed by the photooxygenation of monosubstituted furans **16** and **18**, direct reduction of the crude reaction mixture with $NaBH_4$ (1.2 equiv, 0 °C, 10 min) in moistened THF provided the alcohols **17** and **19** in yields of 74% and 70%, respectively. This methodology offers an advantageous alternative route to 3(2*H*)-furanones, because it effects the reaction in one pot starting from simple precursors, in high yield, and using the clean green oxidant—singlet oxygen.

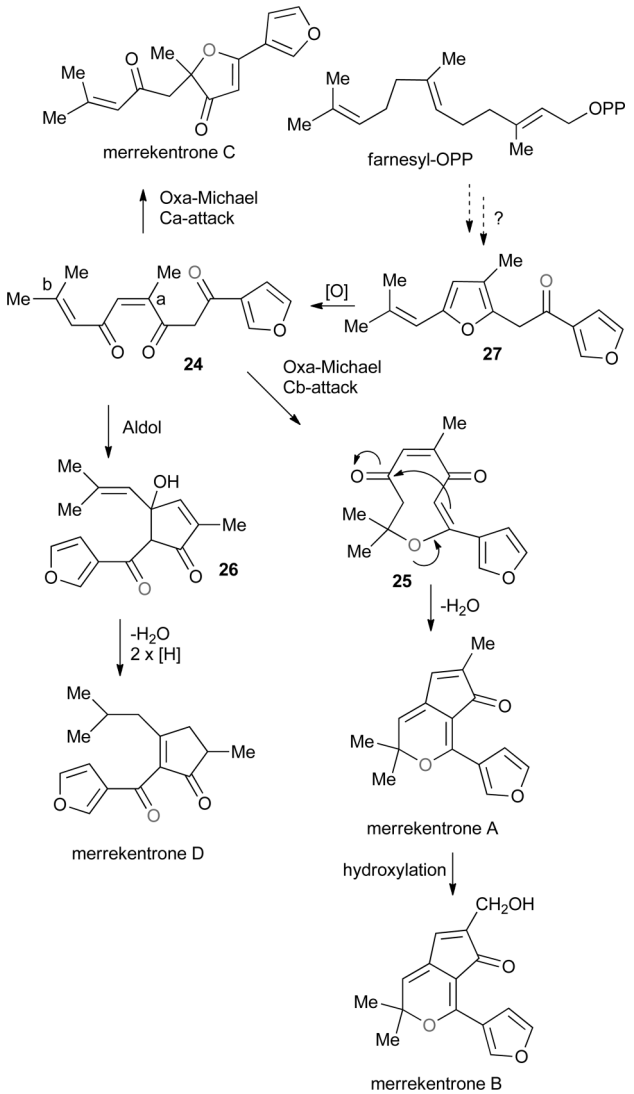
To apply this methodology to a natural product synthesis we chose merrekentrone C (Scheme 4),[14] a furano sesquiterpene isolated from the roots and rootstocks of *Merremia kentrocaulos*. It possesses the characteristic 2-(β-keto)-3(2*H*)-furanone moiety appearing in all the products shown in Scheme 3. By examining the structural motifs of all the co-isolated merrekentrones A–D (Scheme 4), we postulate a biosynthetic scenario, based on which the acyclic triketone **24** is their common biogenetic precursor (Scheme 5).



Scheme 4 Merrekentrones A–D.

Thus, we propose that an intramolecular oxa-Michael of the α-furyl carbonyl to enone carbon atom C_a should provide merrekentrone C (from this common precursor **24**). Macrocyclic oxa-Michael of the same carbonyl oxygen atom of **24** to the enone carbon atom C_b should provide the nine-membered ring oxacycle **25**, which after an intramolecular Prins-type reaction accompanied by a dehydration should lead to merrekentrone A. Merrekentrone A could be the precursor of merrekentrone B, which should be obtained after an allylic hydroxylation. Finally, an intramolecular aldol reaction of **24**, to yield **26**, followed by dehydration and two C–C double bond reductions will lead to merrekentrone D. Triketone **24** could possibly result in Nature from the oxidation of keto difuran **27**,[15] which has the typical C–C connectivity of a linear acyclic sesquiterpene (*e.g.* farnesyl diphosphate).

Following this analysis, we focused on the synthesis of difuran **27**, and examination of the fate of its oxidation product **24**. The synthesis was accomplished (Scheme 6), after much experimentation, using as a key-reaction, a Fenton-type coupling between an α-iodo ketone and an alkenyl furan. Thus, addition of the *in situ* prepared lithium enyne **28**[16] to hydroxyacetone acetate in THF initially afforded hydroxy acetate **29** (GC-MS). To our delight, under the quenching conditions (10 equiv H_2O), the LiOH produced cleanly hydrolyzed **29**, on standing after 3 h, to diol **30** (75% isolated yield). Subsequently, enyne diol **30** afforded in almost quantitative yield alkenyl furan **31** by reacting with $AgNO_3$ (10% mol) in hexane for 1 h.[17] The use of AgOTf or $AgBF_4$ resulted in product decomposition. Finally, **31** underwent cross coupling with α-iodo ketone **32**, under Fenton-type conditions ($FeSO_4$, H_2O_2, DMSO) to form the desired keto difuran **27**. It is worthy of note that in the literature[18] there are sporadic examples of

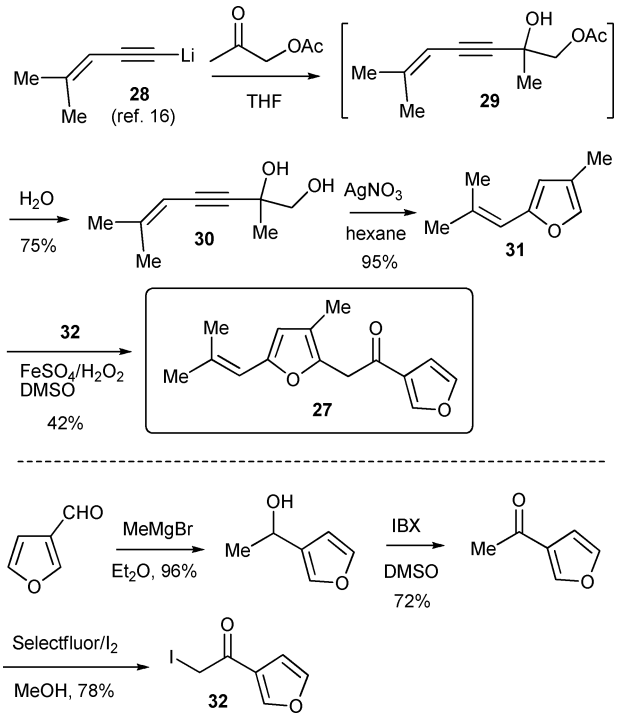


Scheme 5 A plausible biogenetic proposal for merrekentrones A–D.

pyrrole or furan cross coupling with α-iodo esters, but no examples with α-iodo ketones. We found that the optimum conditions to achieve the desired coupling were the initial use of a ratio of **31** : **32** = 5 : 1. Under these conditions no by-products (such as C–C dimerization of **32**) are formed. To improve the yield, we performed four additional cycles into the same reaction mixture by adding successively 0.8, 0.6, 0.5 and 0.4 equiv of iodo ketone **32**, accompanied by the necessary amounts of $FeSO_4/H_2O_2$. Through this modification, the isolated yield of **27** was 42% relative to the alkenyl furan **31**. The α-iodo ketone **32**, was easily synthesized in 78% yield by iodination of 3-acetylfuran (I_2, Selectfluor®).[19]

In the final crucial step, the keto difuran **27** underwent photooxygenation in MeOH. To our disappointment, a mixture of undesired products were isolated in very low yield.

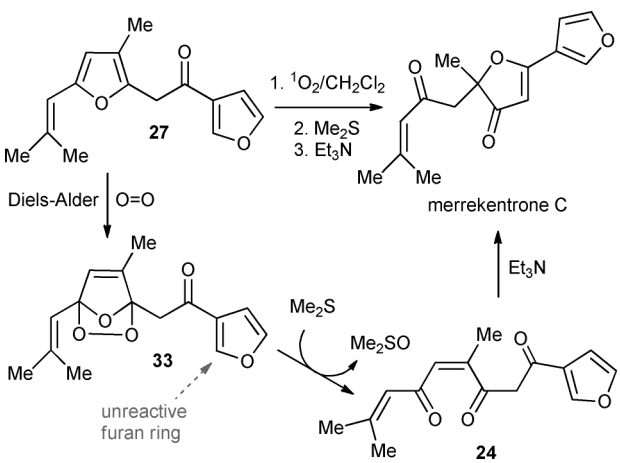
We believe that both furan rings were being oxidized. Although, the furan ring bearing the carbonyl group at its α-position is electron deficient, it is known that α-carbonyl substituted furans can be oxidized by singlet oxygen if the reaction is carried out in methanol.[20] Therefore, we decided to use a non-protic/non-nucleophilic solvent.[21] The photooxygenation of **27** in dichloromethane at 0 °C was completed after a few minutes.



Scheme 6 Synthesis of keto difuran **27**.

Following the addition of dimethyl sulfide (4 equiv, 30 min, stirring) and then of Et_3N (1 equiv, 3 h, stirring), a single product was formed which was merrekentrone C (48% isolated yield).

We propose that the initially formed endoperoxide[22] **33** (Scheme 7), yields, after the addition of dimethyl sulfide, the desired triketone **24** (with concomitant formation of DMSO). The triketone then undergoes, exclusively, a 5-*exo*-trig oxa-Michael reaction affording merrekentrone C. No other products were seen by ^1H NMR in the crude reaction mixture. By performing the photooxygenation of **27** at −60 °C, again merrekentrone was isolated as the only product, yet in a greatly improved 82% yield, and we propose that the lower isolated yield when performing the reaction with $^1O_2$ at higher temperature is associated with the thermal instability of endoperoxide **33** towards undergoing an undesirable polymerization.



Scheme 7 Transformation of keto difuran **27** to merrekentrone C upon photooxygenation.

In conclusion, we have presented an efficient protocol for the synthesis of functionalized 3(2*H*)-furanones based on the singlet oxygen photooxygenation of β-keto-2-substituted furans. The methodology was applied to a concise and efficient synthesis of merrekentrone C.

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