Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5655

www.rsc.org/obc

COMMUNICATION

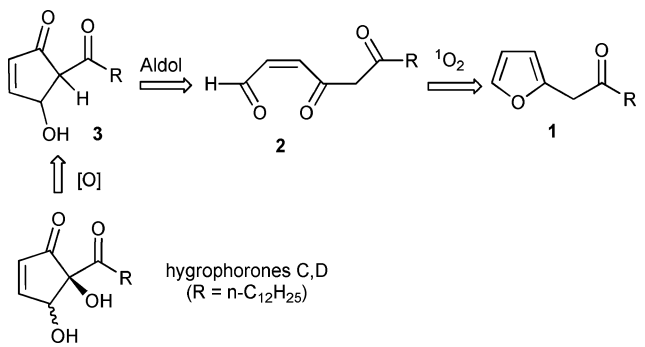
Functionalized 3(2*H*)-furanones *via* photooxygenation of (β-keto)-2-substituted furans: Application to the biomimetic synthesis of merrekentrone C†

Charis Gryparis, Ioannis N. Lykakis,‡ Christina Efe, Ioannis-Panayotis Zaravinos, Theonymphi Vidali, Eugenia Kladou and Manolis Stratakis*

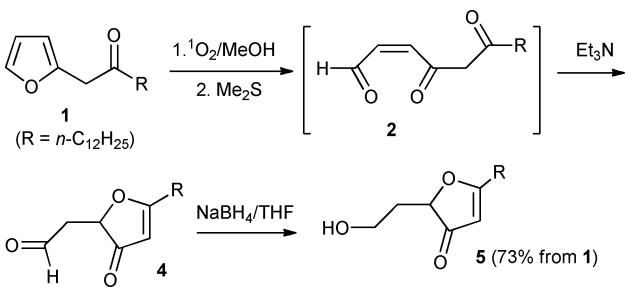
Received 9th April 2011, Accepted 14th June 2011
DOI: 10.1039/c1ob05567d

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**.

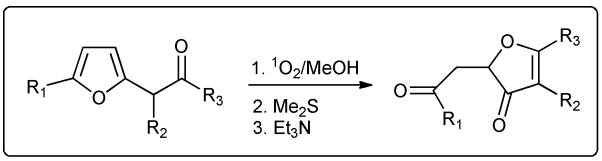
The 3(2*H*)-furanone core skeleton appears in a significant number of natural products[6] and bioactive substances.[7] As a result, a variety of methodologies have been developed for the synthesis of functionalized 3(2*H*)-furanones, including metal-,[8] and non-metal-catalyzed procedures.[9] Moreover, 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.

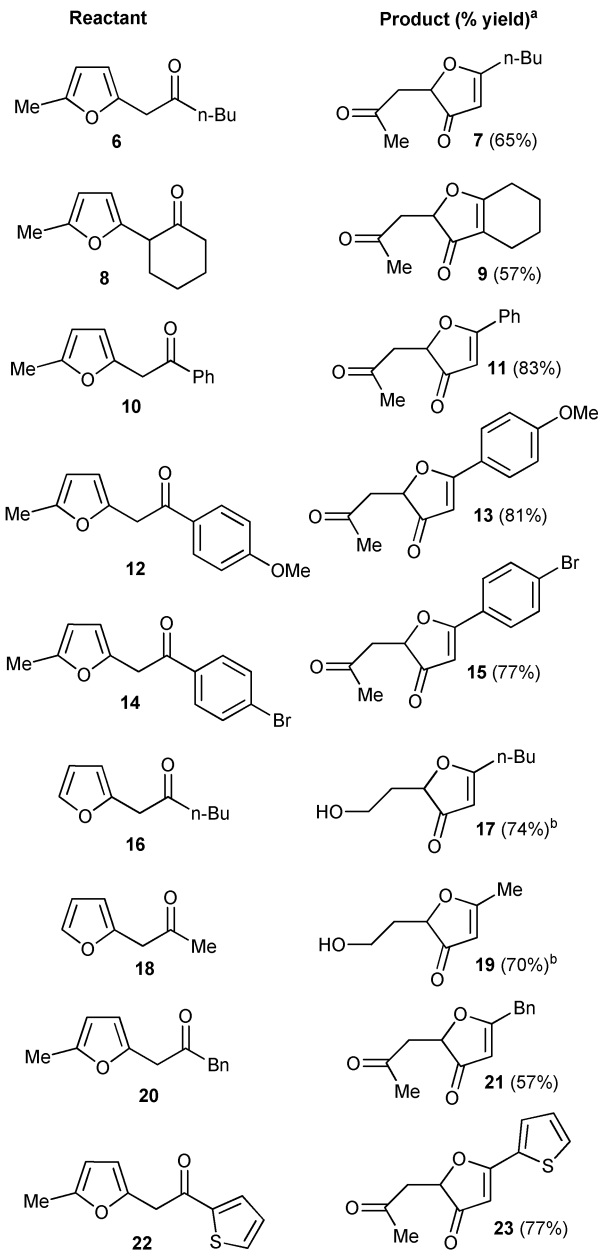
In a typical experiment, the keto furan was photooxygenated at 0 °C in methanol using methylene blue as a sensitizer. Upon consumption of the starting material (typically a few minutes), the solvent was evaporated, and replaced by CH_2Cl_2 or $CDCl_3$. Then Me_2S (4 equiv) were added (16 h, 25 °C), followed 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

Department of Chemistry, University of Crete, Voutes, 71003, Iraklion, Greece. E-mail: stratakis@chemistry.uoc.gr; Fax: +30 2810 545001; Tel: +30 2810 545087

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05567d

‡ Current address: Department of Chemistry, Division of Organic Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece.



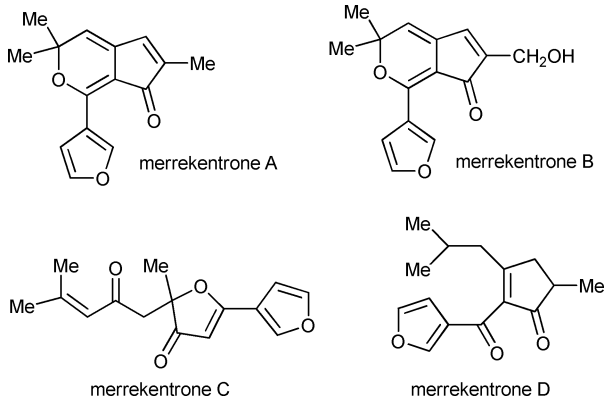


[a] Isolated yield. [b] The crude reaction mixture of the initially formed 3(2*H*)-furanone substituted aldehyde was reduced with 1.2 equiv of $NaBH_4$ in moistened THF (see SI).

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.

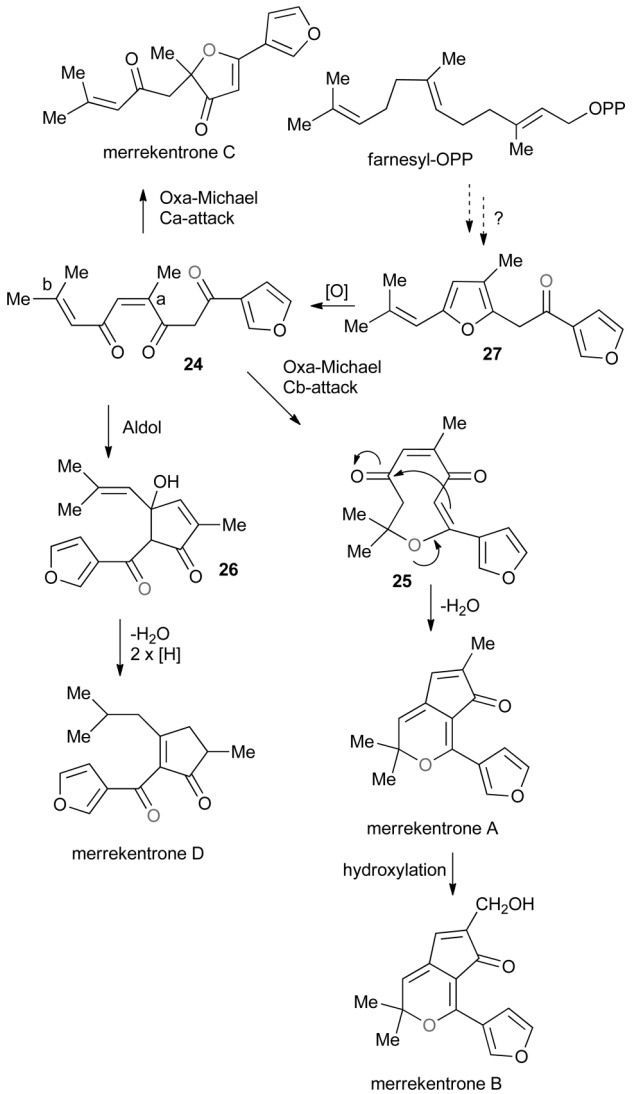
To apply this methodology to a natural product synthesis we chose merrekentrone C (Scheme 4),[14] a furano sesquiterpene isolated from the roots and rootstocks of *Merremia kentrocaulos*. It possesses the characteristic 2-(β-keto)-3(2*H*)-furanone moiety appearing in all the products shown in Scheme 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

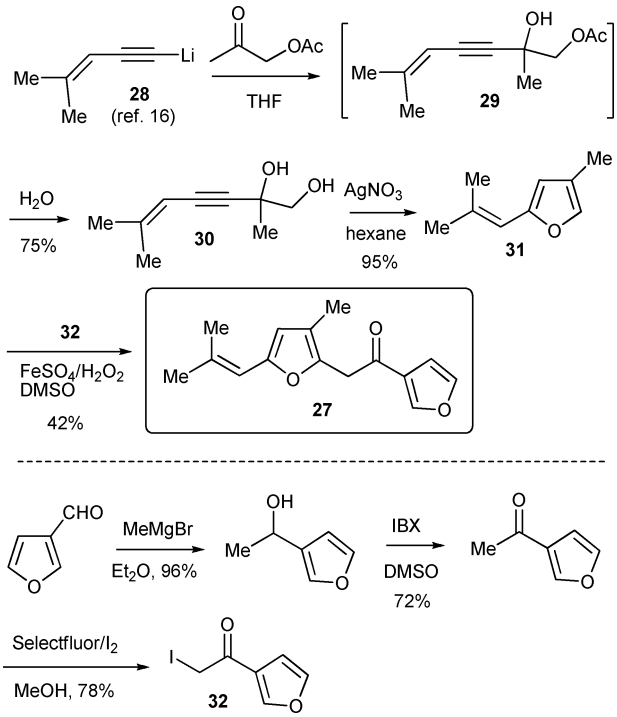


Scheme 5 A plausible biogenetic proposal for merrekentrones A–D.

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.

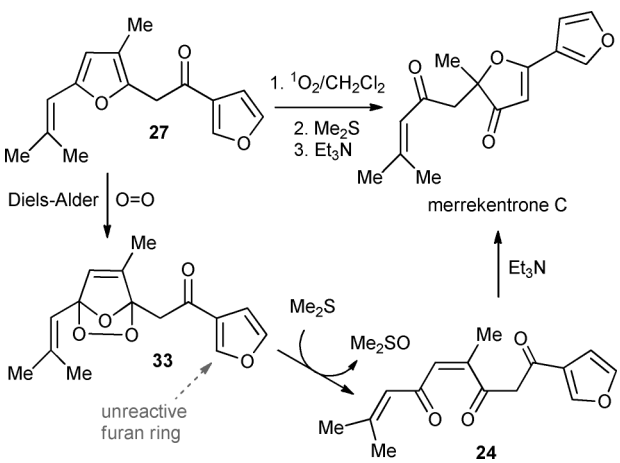
We believe that both furan rings were being oxidized. Although, the furan ring bearing the carbonyl group at its α-position is electron deficient, it is known that α-carbonyl substituted furans can be oxidized by singlet oxygen if the reaction is carried out in methanol.[20] Therefore, we decided to 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.

We thank Dr. Tamsyn Montagnon for assistance during the preparation of this manuscript, and ProFI for obtaining some HRMS spectra.

Notes and references

1 T. Lubken, J. Schmidt, A. Porzel, N. Arnold and L. Wessjohann, *Phytochemistry*, 2004, **65**, 1061.

2 (*a*) T. Montagnon, M. Tofi and G. Vassilikogiannakis, *Acc. Chem. Res.*, 2008, **41**, 1001; (*b*) T. Montagnon, D. Noutsias, I. Alexopoulou, M. Tofi and G. Vassilikogiannakis, *Org. Biomol. Chem.*, 2011, **9**, 2031.

3 (*a*) G. Vassilikogiannakis and M. Stratakis, *Angew. Chem., Int. Ed.*, 2003, **42**, 5465; (*b*) G. Vassilikogiannakis, G. Margaros, T. Montagnon and M. Stratakis, *Chem.–Eur. J.*, 2005, **11**, 5899.

4 Due to the instability of aldehyde **4** under chromatographic conditions, the crude reaction mixture was reduced with $NaBH_4$ to provide alcohol **5**.

5 (*a*) M. Tofi, K. Koltsida and G. Vassilikogiannakis, *Org. Lett.*, 2009, **11**, 313; (*b*) I. N. Lykakis, I.-P. Zaravinos, C. Raptis and M. Stratakis, *J. Org. Chem.*, 2009, **74**, 6339; (*c*) S. J. Hayes, D. W. Knight, A. W. T. Smith and M. J. O'Halloran, *Tetrahedron Lett.*, 2010, **51**, 720.

6 (*a*) A. B. Smith, M. A. Guaciaro, S. R. Schow, P. M. Wovkulich, B. H. Toder and T. W. Hall, *J. Am. Chem. Soc.*, 1981, **103**, 219; (*b*) Y. Li and K. J. Hale, *Org. Lett.*, 2007, **9**, 1267; (*c*) M. Ishikawa, T. Ninomiya, H. Akabane, N. Kushida, G. Tsujiuchi, M. Ohyama, S. Gomi, K. Shito and T. Murata, *Bioorg. Med. Chem.*, 2009, 1457; (*d*) J. McK. R. Woollard, N. B. Perry, R. T. Weavers and J. W. van Klink, *Phytochemistry*, 2008, **69**, 1313; (*e*) Y. Asami, H. Kakeya, R. Onose, A. Yoshida, H. Matsuzaki and H. Osada, *Org. Lett.*, 2002, **4**, 2845; (*f*) A. H. Banskota, J. B. McAlpine, D. Sorensen, M. Aouidate, M. Piraee, A. M. Alarco, S. Omura, K. Shiomi, V. M. Farnet and E. Zazopoulos, *J. Antibiot.*, 2006, **59**, 168; (*g*) R. L. Edwards, D. J. Maitland, C. L. Oliver, M. S. Pacey, L. Shields and A. J. S. Whalley, *J. Chem. Soc., Perkin Trans. 1*, 1999, 715; (*h*) Y. Hayashi, M. Shoji, S. Yamaguchi, T. Mukaiyama, J. Yamaguchi, H. Kakeya and H. Osada, *Org. Lett.*, 2003, **5**, 2287.

7 (*a*) S. Kirmizigul, N. Goren, S.-W. Yang, G. A. Cordell and C. Bozok-Johansson, *J. Nat. Prod.*, 1997, **60**, 378; (*b*) H. T. Sakamoto, D. Flausino, E. E. Castellano, C. B. W. Stark, P. J. Gates and N. P. Lopes, *J. Nat. Prod.*, 2003, **66**, 693; (*c*) S. S. Shin, Y. Byun, K. M. Lim, J. K. Choi, K.-W. Lee, J. H. Moh, J. K. Kim, Y. S. Jeong, J. Y. Kim, Y. H. Choi, H.-J. Koh, Y.-H. Park, Y. I. Oh, M.-S. Noh and S. Chung, *J. Med. Chem.*, 2004, **47**, 792; (*d*) A. Carotti, A. Carrieri, S. Chimichi, M. Boccalini, B. Cosimelli, C. Gnerre, A. Carotti, P.-A. Carrupt and B. Testa, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3551; (*e*) M. Togashi, S. Ozawa, S. Abe, T. Nishimura, M. Tsuruga, K. Ando, G. Tamura, S. Kuwahara, M. Ubukata and J. Magae, *J. Med. Chem.*, 2003, **46**, 4113.

8 (*a*) M. Egi, K. Azechi, M. Saneto, K. Shimizu and S. Akai, *J. Org. Chem.*, 2010, **75**, 2123; (*b*) E. M. Bunnelle, C. R. Smith, S. K. Lee, S. W. Singaram, A. J. Rhodes and R. Sarpong, *Tetrahedron*, 2008, **64**, 7008; (*c*) S. F. Kirsch, J. T. Binder, C. Liebert and H. Menz, *Angew. Chem., Int. Ed.*, 2006, **45**, 5878; (*d*) Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou and H. Gao, *Org. Lett.*, 2006, **8**, 3445; (*e*) K. Kato, H. Nouchi, K. Ishikura, S. Takaishi, S. Motodate, H. Tanaka, K. Okudaira, T. Mochida, R. Nishigaki, K. Shigenobua and H. Akita, *Tetrahedron*, 2006, **62**, 2545; (*f*) M. Reiter, H. Turner, R. Mills-Webb and V. Gouverneur, *J. Org. Chem.*, 2005, **47**, 1519; (*g*) B. Crone and S. F. Kirsch, *J. Org. Chem.*, 2007, **72**, 5435.

9 (*a*) B. A. Trofimov, O. A. Shemayakina, A. G. Mal'kina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Org. Lett.*, 2010, **12**, 3200; (*b*) Y. Inoue, K. Ohuchi, I.-F. Yen and S. Imaizumi, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3518; (*c*) A. B. Smith, P. A. Levenberg, P. J. Jerris, R. M. Jr. Scarborough and P. M. Wovkulich, *J. Am. Chem. Soc.*, 1981, **103**, 1501; (*d*) R. Saxena, V. Singh and S. Batra, *Tetrahedron*, 2004, **60**, 10311; (*e*) J. D. Winkler, K. Oh and S. M. Asselin, *Org. Lett.*, 2005, **7**, 387; (*f*) S. Gogoi and N. P. Argade, *Tetrahedron*, 2006, **62**, 2999; (*g*) T. Kawaguchi, S. Yasuta and Y. Inoue, *Synthesis*, 1996, 1431.

10 C. M. Marson, E. Edaan, J. M. Morrell, S. J. Coles, M. B. Hursthouse and D. T. Davies, *Chem. Commun.*, 2007, 2494.

11 R. Antonioletti, F. Bonadies, T. Prencipe and A. Scettri, *J. Chem. Soc., Chem. Commun.*, 1988, 850.

12 R. Antonioletti, T. Bonadies and A. Scettri, *Tetrahedron Lett.*, 1987, **28**, 2297.

13 In our hands, treatment of some of the keto furans shown in Scheme 2 with *m*-CPBA, formed a mixture of products with 3(2*H*)-furanones seen in a low relative yield (<20%). In addition, $NaClO_2$, a known furan oxidant {(*a*) S. P. Annangudi, M. Sun and R. G. Salomon, *Synlett*, 2005, 1468; (*b*) D. L. J. Clive, Minaruzzaman and L. Ou, *J. Org. Chem.*, 2005, **70**, 3318} provides extensive product decomposition.

14 K. Jenett-Siems, K. Siems, L. Witte and E. Eich, *J. Nat. Prod.*, 2001, **64**, 1471.

15 Several α-keto furanoterpenoids similar to **27** are naturally occurring: Y. Liu, S. Zhang and P. J. M. Abreu, *Nat. Prod. Rep.*, 2006, **23**, 630.

16 L. Commeiras, J. Thibonnet and J.-L. Parrain, *Org. Biomol. Chem.*, 2009, **7**, 425.

17 (*a*) J. A. Marshall and C. A. Seho, *J. Org. Chem.*, 1995, **60**, 5966; (*b*) F. Yoshimura, M. Sasaki, I. Hattori, K. Komatsu, M. Sakai, K. Tanino and M. Miyashita, *Chem.–Eur. J.*, 2009, **15**, 6626.

18 (*a*) E. Baciocchi, E. Muraglia and G. Sleiter, *J. Org. Chem.*, 1992, **57**, 6817; (*b*) F. Loiseau, J.-M. Simone, D. Carcache, P. Bobal and R. Neier, *Monatsh. Chem.*, 2007, **138**, 121.

19 S. Stavber, M. Jereb and M. Zupan, *Chem. Commun.*, 2002, 488.

20 B. L. Feringa, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 469.

21 Methanol adds to the carbonyl group to form a labile hemiacetal, and thus the furan ring becomes significantly more nucleophilic against singlet oxygen.

22 K. Gollnick and A. Griesbeck, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 726.

