A Versatile and General One-Pot Method for Synthesizing Bis-spiroketal Motifs

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ABSTRACT

A versatile and general method for the biomimetic construction of [5,5,5]- and [6,5,6]-bis-spiroketal motifs, starting from easily accessible furan nuclei, by means of a powerful one-pot singlet oxygen-mediated cascade sequence is reported.

Nature has seen fit to include the delicate bis-spiroketal functionality in a wide range of interesting natural products. Several different classes of marine toxins including the spiriolides,1 pinnatoxins,2 pteriatoxins,3 and the azaspiracids4 contain this motif. It is also a subunit present in certain terrestrially derived ionophore antibiotics.5 Since interest in the syntheses of these architecturally complex molecules abounds, much work has already been undertaken directed toward finding elegant ways to synthesize the bis-spiroketal moiety in its various forms. Not surprisingly the majority of existing research in this field has focused on using acid-catalyzed ketalization reactions to achieve the goal.6 While this approach has on rare occasions been successful in producing a cascade reaction capable of zipping up the three rings simultaneously,7 more often than not it has required two independent cyclization steps separated by at least one deprotection and/or oxidation reaction(s).6 Furthermore, as a strategy it always requires both the engineering of a complex linear precursor and the difficult orchestration of multiple oxidations and protecting group manipulations in order to prepare the requisite oxygen functionalities for participation in the envisaged cyclisations.6 Aside from this not unproblematic ketalization strategy, several other spirocycle formation reactions of note have been employed.6 Brimble et al. have used an elegant oxidative cyclization procedure wherein hypervalent iodine, molecular iodine, and light are comandeered to assist in forming a plethora of different bis-spiroketals; again this approach requires several steps to affect the desired double cyclization.6,8 Alternatively, a small number of strategies reliant on the oxidation of a furan nucleus have appeared in the literature sporadically over the past 4 decades. Indeed, the first reported synthesis (1) (a) Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A. S.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C. J. Chem. Soc., Chem. Commun. 1995, 2159–2169. (b) Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A. S.; Walter, J. A.; Wright, J. L. C. J. Nat. Prod. 2001, 64, 308–312. (2) (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zeng, S.-Z.; Chen, H.-S. J. Am. Chem. Soc. 1995, 117, 1155–1156. (b) Chou, T.; Kamo, O.; Uemura, D. Tetrahedron Lett. 1996, 37, 4023–4026. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. Tetrahedron Lett. 1996, 37, 4027–4030. (d) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. Tetrahedron Lett. 2001, 42, 3491–3494. (3) Takada, N.; Umemura, N.; Suenaga, K.; Uemura, D. Tetrahedron Lett. 2001, 42, 3495–3497. (4) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Fruey, A.; McMahon, T.; Silke, J.; Yasumoto, T. J. Am. Chem. Soc. 1998, 120, 9967–9968. (5) Dutton, C. J.; Banks, B. J.; Cooper, C. B. Nat. Prod. Rep. 1995, 12, 165–181. (6) For a review of bis-spiroketal syntheses, see: Brimble, M. A.; Farès, F. A. Tetrahedron 1999, 55, 7661–7706.

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of a bis-spiroketal ring system used electrochemistry to oxidize a simple furan bearing pendant hydroxyl groups to yield the corresponding bis-spiroketal in one step.9 Later Albizati,10 Kocienski,11 and Stockman12 all deployed electrophilic bromine as the oxidant to transform various furans into the corresponding bis-spiroketal moiety. Only in the latter case were both spiroketal forms in a single step.12

After surveying the methods reported for the formation of bis-spiroketal, we were left in no doubt that there was a pressing need for a more direct and general method for the one-pot formation of these spirocycles from simple precursors. Our experience in using singlet oxygen (1O2) as a biomimetic synthetic tool13 (especially for synthesizing spirocyclic compounds14) led us to believe that this objective could be readily attained by the deft application of some powerful 1O2 chemistry. Furthermore, given that naturally occurring furans are known and that 1O2 is readily available in the natural environment as a result of the existence of ideal conditions for its generation (abundant molecular oxygen, visible spectrum light, and sensitizers such as tannins, porphyrins, and chlorophylls), we felt that it was highly probable that our postulate was biomimetic. Our ambitious blueprint for the syntheses of these compounds was devoid of cumbersome intermediary protection and oxidation steps and was one wherein broad variation in the cyclization precursors could be readily entertained. Herein, we report our success in employing this design, involving a highly efficient cascade reaction sequence initiated by the [4+2]-cycloaddition between an easily accessible furan nucleus and 1O2,15 for the synthesis of various bis-spiroketal.

The elegant concept that we were able to successfully implement, wherein the [4+2]-cycloaddition is followed by two successive intramolecular trapping reactions in order to furnish both of the targeted spirotetal rings in one synthetic operation, is detailed in Scheme 1. Thus, our analysis can be summarized as follows: we proposed that the product of the cycloaddition between 1O2 and furans of type A, endoperoxide B, might be the subject of an intramolecular attack16 by a suitably positioned pendant hydroxyl group to afford the spirotetal hydroperoxide C. Hydroperoxide C might then be reduced in situ to yield the corresponding hemiketal, which could, in turn, be coaxed into cyclizing under the influence of traces of acid to furnish the desired bis-spiroketal D.

Scheme 1. Outline of Our Concept for the One-Pot Formation of Bis-spiroketals

To begin our investigation, we took the simple diester 2 (made previously for the purposes of a different project) and reduced it with LAH to form the corresponding diol 3 in good yield (82%). This diol 3 was then subjected to the 1O2 oxidation conditions routinely used in our laboratories13,14 to affect such transformations: oxygen was bubbled through the reaction solution, 10–4 M Methylene Blue was added as sensitizer, and the solution was irradiated with visible spectrum light until complete consumption of the starting material was observed by TLC (2 min). After the addition of dimethyl sulfide as in situ reductant and passing of the crude material through a short pad of silica, we were most gratified to observe the formation of the sought after [5,5,5]-bis-spiroketal 4 (80%) as a 1:1 mixture of diastereoisomers12 (measured by 1H NMR, taken in CDCl3). It should be noted that retrospective study of this reaction revealed that the desired bis-spiroketal product 4 could be formed directly from the hydroperoxide intermediate (not shown) upon standing in CDCl3, without the need to employ dimethyl sulfide.

Having obtained the exciting proof of principle for this attractive cascade sequence, we set about devising a faster and more efficient means by which to access the furan

Scheme 2. Proof of Principle: Successful One-Pot Formation of the [5,5,5]-Bis-spiroketal 4 from Dihydroxyfuran 3
oxidation precursors. To this end, we sought to implement a simple strategy in which two successive alkylations of appropriate furyllithium anions with suitable alkyl iodides would provide the desired compounds (Scheme 3). Starting from furan itself and using n-BuLi as base, this procedure could readily be employed to furnish first monosubstituted furan 7 and then diol 8 (after TBAF-mediated deprotection) in an overall yield of 62% (over three steps). The alkylating agent, iodide 6, had been made in one step from tetrahydrofuran, using NaI and TBSCl, by following a literature procedure. Upon subjecting this diol 8 to the \( \text{O}_2 \)-mediated oxidation and in situ reduction conditions described above, once again the double spirocycle formation cascade proceeded smoothly, successfully providing the desired [6,5,6]-bis-spiroketal product 9 (77%, as a 55:45 mixture of diastereoisomers).

In order for our method to be more generally applicable to complex natural product synthesis as we desired, we next looked at synthesizing differentially substituted furans, bearing suitable handles for further manipulations, to test as reaction substrates. We deemed that introducing a trisubstituted double bond into the oxidation substrates would furnish us with the most useful handle for the introduction of the requisite tertiary alcohol present in the natural products of interest (vide supra). To this end, a simple Wittig reaction was employed to append an unsaturated side chain onto 2-furaldehyde (1, Scheme 4A). The lithium anion of the product of this reaction was then acylated using the commercially available Weinreb amide, N-methoxy-N-methylacetamide. The resulting methyl ketone was subjected to a second Wittig reaction employing the same phosphonium salt 10. This facile reaction sequence yielded the bis-unsaturated furan 13 in an overall yield of 43% with a ratio of Z:E geometric double bond isomers of 4:1. The fate of 13, upon column chromatography after TBAF-mediated deprotection, confirmed our suspicions regarding the source of furan 11’s instability (i.e., degradation via formation of the furylic cation). For when 13 was exposed to the Lewis acidic conditions of column chromatography, the sole product isolated was tetrahydrofuran 14. This unwanted product was assumed to arise by intramolecular trapping of the readily formed and highly stabilized furylic cation under the mildly acidic conditions of the column. Given our experience regarding the instability of furans 11 and 13 upon deprotection, we felt that the inclusion of trisubstituted double bonds or tertiary furylic alcohols (also suitable for the targeted natural products but even more susceptible to furylic cation formation) in these substrates was going to be problematic, but we also felt that this obstacle was not insurmountable. If acidic conditions, including column chromatography, could be avoided or postponed, the desired cyclization precursors might be attainable.

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To test this postulate we reverted to the use of 2-substituted furan 7 as a starting material. This furan was further functionalized using the, by now, standard reaction sequence to furnish diol 15 in an overall yield of 52% and as a mixture of geometric isomers (85:15 Z:E, confirmed by NOE studies, Scheme 5). To avoid unwanted degradation, we took the precaution of not attempting to purify the product of the TBAF-mediated deprotection step; instead the diol 15 was used crude. When diol 15 was subjected to the established cascade reaction conditions, after the reduction step mediated by dimethyldisulfide, the hemiketal 17 (2:1 mixture of diastereoisomers) could be isolated, purified, and fully characterized (proving that the intramolecular trapping reaction was completely regioselective). The relative stability of hemiketal 17 provided a stark contrast to the previously encountered hemiketals, which were all transient species that snapped shut immediately on being exposed to any form of acid (including silica). Hemiketal 17 had to be exposed to catalytic amounts of p-TsOH before it could be caged into cyclizing to form the desired [6,5,6]-bis-spiroketal 18 (1:1 mixture of diastereoisomers, 1H NMR in CDCl3) in 80% yield (from diol 15, yield based on only the Z-isomer of 15 reacting in this sequence). The regiochemistry of hemiketal 17 was deduced on the basis of the coupling pattern seen in 1H NMR for the vinylic proton; in the oxidation precursor 15 the vinylic proton had appeared as a triplet, but in the hemiketal 17 it was present as a broad doublet. It should be noted that it was not necessary to isolate hemiketal 17, the whole double cyclization cascade sequence could be done in one pot if p-TsOH was added after the reduction was shown to be complete by TLC.

With the highly successful cyclization of diol 15 to yield bis-spiroketal 18 now accomplished, we were afforded with further proof that the method we had developed for the formation of variable bis-spiroketal ring systems was general and amenable to incorporation of suitable handles potentially allowing for its ready application to the synthesis of certain natural products. In summary, the work described in this communication meets the rigorous goals we had designated at the outset of our investigation. In short, a method was developed that (1) accomplished the facile one-pot formation of both spiroketal rings of various bis-spiroketal units, (2) was devoid of complex functional group manipulations and cumbersome cyclization precursor syntheses, and (3) employed one of nature’s favorite synthetic tools, O2, in an elegant and highly efficient biomimetic cascade reaction sequence.

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Supporting Information Available: Experimental procedures and 1H and 13C spectra for all relevant compounds plus HRMS for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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