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Novel applications of functionalised orthoesters: towards the synthesis of various natural products

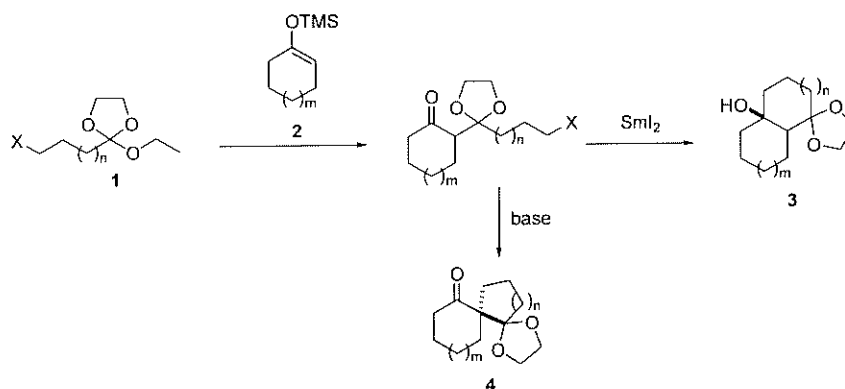
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Though orthoesters have been mostly employed as carboxylic acid protecting groups and acylating agents, their synthetic utility as annelating partners in novel ring forming reactions has been little investigated.¹

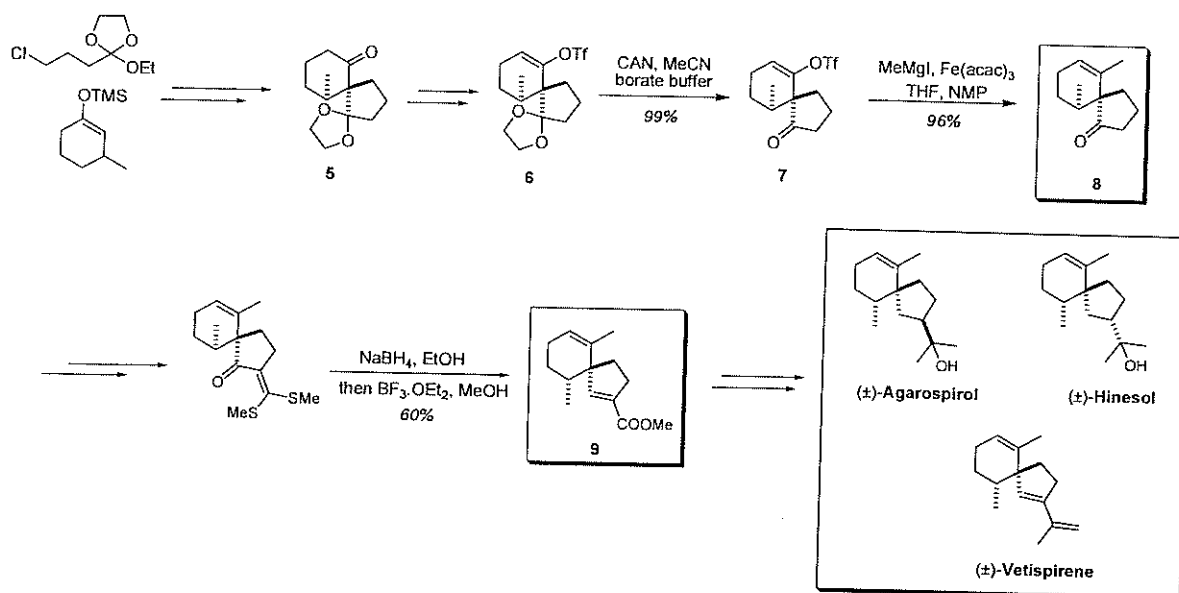
Our laboratory has recently been interested in the preparation and use of functionalised orthoesters **1** (X=halogen) in annelation reactions (Scheme 1). We have previously succeeded in the preparation of bicycloalkanols **3** and spirocyclic diketones **4** from cyclic silyl enol ethers **2**, by taking advantage of the unique reactivity profile provided by our ω -halo orthoesters.²



Scheme 1.

The research project undertaken by the author (Ph.D. candidate, 4th year) is aimed at building upon these initial observations and expanding the reaction manifolds and products available from orthoesters such as **1**.

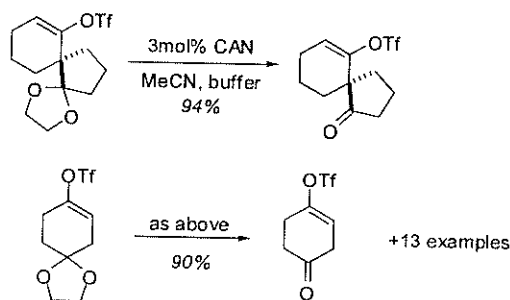
Initially, we demonstrated the usefulness of the aforementioned spiroannulation methodology by performing an efficient total synthesis of members of the Spirovetivane family of sesquiterpenes (Scheme 2).



Scheme 2.

Our successful synthetic endeavour features a number of remarkable transformations, namely: (i) a completely stereoselective two-step construction of the spirocyclic core **5**, (ii) the application of our laboratory's mild CAN-catalysed deprotection procedure in the stringent unmasking of dioxolane **6**, (iii) a chemoselective Fe(III)-catalysed coupling of enol triflate **7** to install an otherwise elusive endocyclic, trisubstituted double bond in **8** and (iv) an elegant rearrangement towards unsaturated ester **9**, from which diverse members of the Spirovetivane family can be readily accessed.³

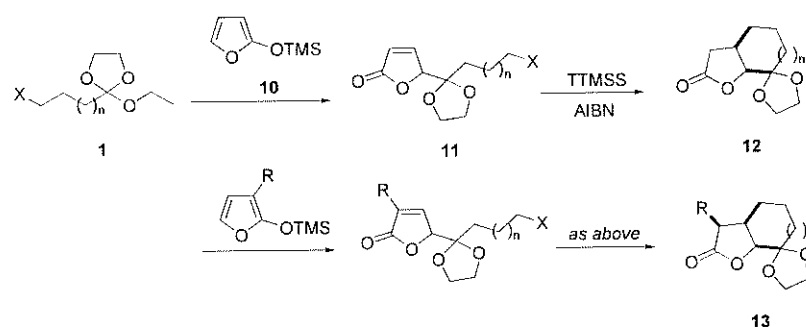
As usually occurs in the frame of total synthesis, we had the opportunity to develop novel and useful synthetic methodology (Scheme 3) that enables, for the first time, the deprotection of a variety of functional groups in the presence of the acid- and base-sensitive enol triflate moiety.^{4,5}



Scheme 3.

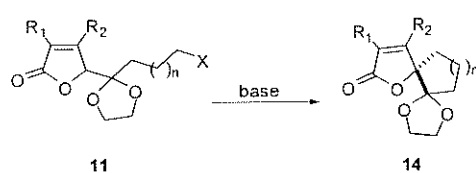
Subsequently, our efforts were aimed at evaluating the use and synthetic potential of extended silyl enol ether **10** (Scheme 4). In spite of scarce literature precedents, we were able to successfully

prepare a wide variety of condensation products **11**. We have shown that a number of these adducts readily undergo radical-type cyclisations onto the proximal, electron-deficient double bond, and this even when the ring thus formed is a four-membered one ($n = -1$)! Through application of this procedure, we were able to prepare a variety of fused, bicyclic lactones **12**. Interestingly, complete stereoselectivity was observed when substituted butenolides were employed, leading to the stereocontrolled generation of up to 3 contiguous stereocenters in a single-step (cf. **13**).⁶ Preliminary applications of these adducts were surveyed.



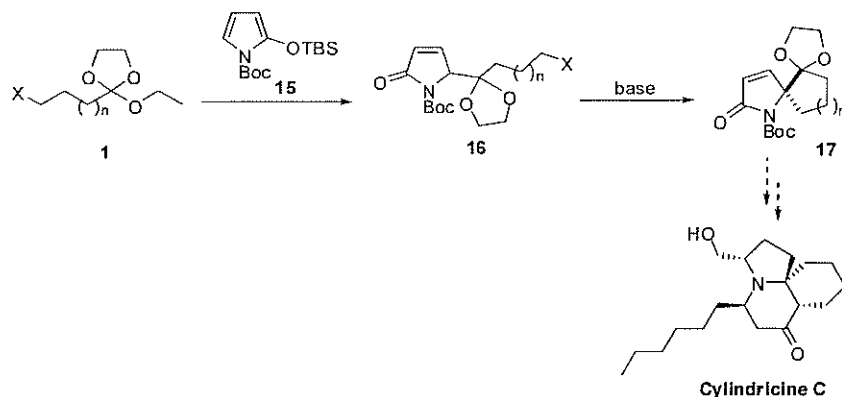
Scheme 4.

On the other hand, the possibility of effecting an unprecedented base-promoted spiroannulation to provide spirocyclic butenolides **14** was demonstrated (Scheme 5). Due to the biological and industrial value of spirobutenolides, this two-step procedure, providing butenolides suitably functionalised for further elaboration, should find broad utility in synthesis. Preliminary applications of these adducts were also investigated.⁷



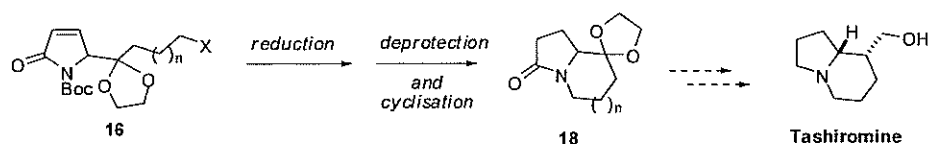
Scheme 5.

In analogous fashion, the corresponding silylated pyrrole **15** is also a competent nucleophile for our orthoesters. We have demonstrated that the synthesis of azaspirocycles **17** by this procedure is a general reaction (Scheme 6) which constitutes one of the most efficient preparations of **17** known to date. We are currently exploiting short routes to complex bioactive natural products, such as Cylindricine C, from **17**.⁸



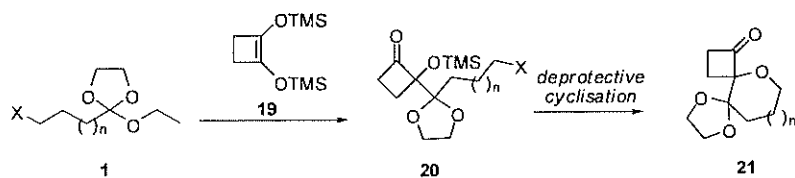
Scheme 6.

Interestingly enough, the presence of a nucleophilic nitrogen atom on adducts **16** provides an additional cyclisation mode, leading to fused alkaloids **18**. We have established this route as a short synthesis of functionalised indolizidines (Scheme 7) and are currently pursuing the synthesis of Tashiromine and other analogues by this approach.



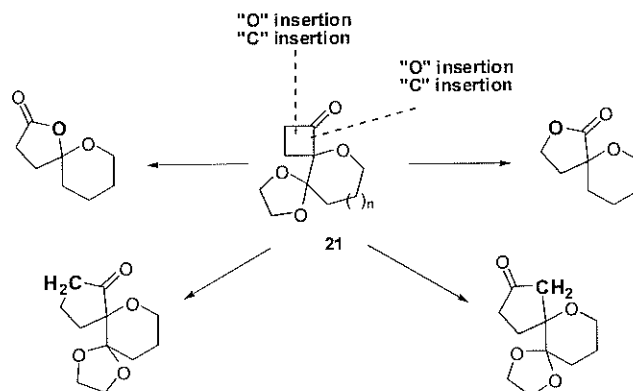
Scheme 7.

On a different note, we have been interested in the application of cyclobutene-derived silyl enol ethers such as **19**. Indeed, we have performed the first known condensation of such compounds with orthoesters, yielding adducts **20** in synthetically useful yields.⁹ The polyfunctionalised products **20** can be readily elaborated to spiroethers **21** in a single step (Scheme 8).



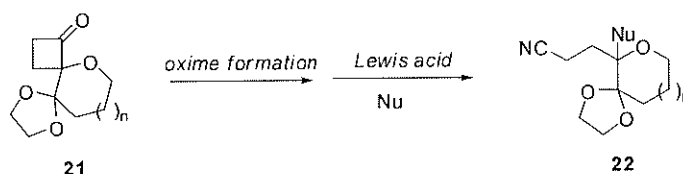
Scheme 8.

Taking advantage of the rich chemistry of cyclobutanones, we have, *inter alia*, realised all possible $\text{-CH}_2\text{-}$ (methylene) and -O- (oxygen) insertions into spiroethers **21** (Scheme 9), with excellent selectivity.



Scheme 9.

Particularly interesting were the results of attempted nitrogen insertion into spiroethers of the general structure **21**. Instead of the anticipated ring-expansion reaction, we were surprised to observe a very selective and high-yielding Beckmann-like fragmentation reaction providing substituted tetrahydropyrans **22** (Scheme 7). A host of different nucleophiles (including C- and O- nucleophiles) could be used to capture the putative oxonium intermediate, allowing the preparation of a wide range of products **22**.



Scheme 10.

Current research focuses on expanding the use of these (and related) orthoester derivatives in synthesis. Among others, we have recently succeeded in an electrochemical version of the general process depicted in Scheme 4. Theoretical calculations have allowed us to gain insight (*inter alia*) into the nature of some unexpected reactions, such as the highly selective Beckmann fragmentation shown above (Scheme 10).¹⁰ Furthermore, there is continued work towards the total synthesis of other biologically active compounds as well as the development of asymmetric versions of these and other orthoester-based methodologies.

References:

- ¹ See, e.g. : C. Huart, L. Ghosez, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 634.
- ² (a) A. Ates; I. E. Markó, *Synlett* **1999**, 1033; (b) I. E. Markó, J.-C. Vanherck, A. Ates, B. Tinant, J.-P. Leclercq, *Tetrahedron Lett.* **2003**, *44*, 3333.
- ³ N. Maulide, J.-C. Vanherck, I. E. Markó, *Eur. J. Org. Chem.* **2004**, *19*, 3962; N. Maulide, J.-C. Vanherck, I.E. Markó, *Chim. Nouv.* **2005**, *89*, 95.
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- ⁵ N. Maulide, J.-C. Vanherck, A. Gautier, I.E. Markó, *Acc. Chem. Res.* **2007**, in press.
- ⁶ N. Maulide, I.E. Markó, *Chem. Commun.* **2006**, *11*, 1200.
- ⁷ N. Maulide, I.E. Markó, *Org. Lett.* **2006**, *8*, 3705.
- ⁸ N. Maulide, S. Songarsa, I.E. Markó, manuscript in preparation.
- ⁹ N. Maulide, I.E. Markó, manuscript in preparation.
- ¹⁰ N. Maulide, I.E. Markó, L. Veiros, manuscript in preparation.