

# Stereoselective synthesis of bicyclic lactones by annelation with functionalised orthoesters†

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Received (in Cambridge, UK) 18th January 2006, Accepted 30th January 2006

First published as an Advance Article on the web 14th February 2006

DOI: 10.1039/b600677a

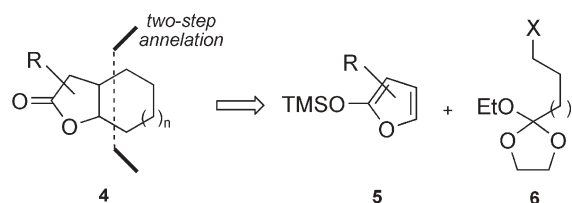
An efficient two-step annelation of functionalised orthoesters with trimethylsilyloxyfuran derivatives, which delivers suitably decorated bicyclo[3.*n*.0]lactones in high overall yields and with complete diastereocontrol of up to three contiguous stereocenters, is reported.

Oxabicyclic and oxatricyclic systems are among Nature's preferred building blocks for the elaboration of varied biological activities through chemical diversity. In particular, the  $\gamma$ -butyrolactone/lactol moiety is a recurrent feature of many naturally occurring substances. Some representative examples are depicted in Fig. 1.<sup>1</sup>

Although approaches to the synthesis of bicyclic lactones have been imaginative and numerous,<sup>2</sup> there is a continued demand for connective and concise methods for the assembly of these important subunits that can deal with the following issues: (a) provide high levels of stereoselectivity, (b) cope with the preparation of a variety of ring sizes and (c) allow an increase in complexity through introduction of reactive functionalities. In this communication, we wish to report some of our preliminary results in the establishment of such a methodology.

As presented in Scheme 1, we envisioned that a variety of bicyclo[3.*n*.0]lactones **4** might become readily available through the annelation of 2-trimethylsilyloxyfuran derivatives **5** by the functionalised orthoesters **6**.<sup>3</sup> Although these annelating agents have been previously condensed with cyclic silyl enol ethers,<sup>4</sup> to the best of our knowledge, this is the first time that such a direct two-step annelation is envisaged on a silyloxyfuran template.

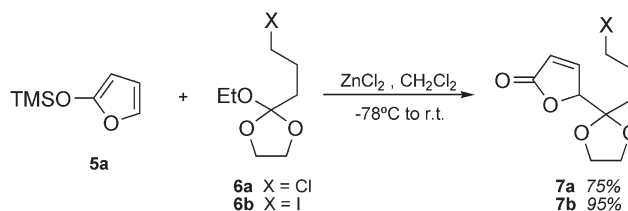
The success of this synthetic strategy required the fulfilment of two crucial conditions, namely, i) the viability of the condensation between extended silyl enol ethers such as **5** and our orthoesters **6**



Scheme 1 Proposed antithetic analysis of bicyclic lactones **4**.

had to be demonstrated, and ii) the ring closure of the initial adducts into the desired bicyclic structures had to proceed efficiently. Inspired by the seminal work of Pelter and Asaoka, who successfully condensed trimethyl orthoformate, acetate and benzoate with trimethylsilyloxyfuran derivatives,<sup>5</sup> we treated **5a** with orthoester **6a**, in the presence of substoichiometric amounts of zinc chloride (0.7 eq.  $\text{ZnCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to rt). Pleasingly, the condensation product **7a**, bearing an  $\omega$ -chlorine atom, could be isolated in good yields. The crystalline iodinated analogue **7b** was also prepared by the same procedure in comparably high yields (Scheme 2).

With adducts **7a** and **7b** in hand, attention was then focused on the crucial ring closure step.<sup>6</sup> Accordingly (Scheme 3), both compounds were separately exposed to the action of tris(trimethylsilyl)silane (TTMSS) in refluxing benzene solution containing catalytic amounts of AIBN.<sup>7</sup> Interestingly, whilst chlorinated **7a** was recovered unchanged, its iodinated counterpart **7b** smoothly



Scheme 2 Initial results on the condensation of trimethylsilyloxy furan with functionalised orthoesters.



Scheme 3 Radical-mediated cyclisation of adducts **7a** and **7b**.

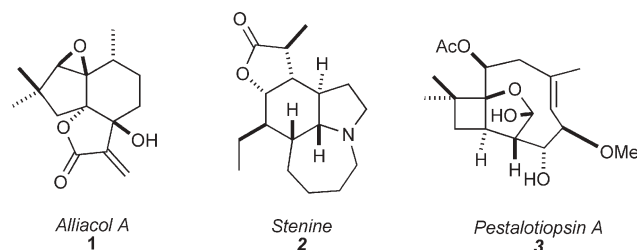


Fig. 1 Selected natural products embodying a  $\gamma$ -butyrolactone/lactol subunit.

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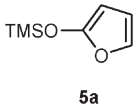
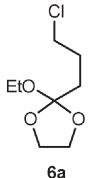
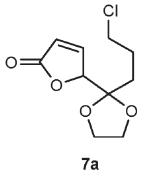
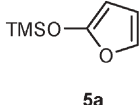
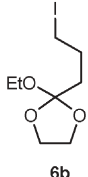
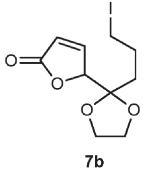
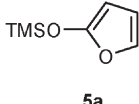
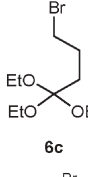
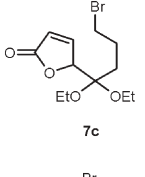
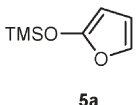
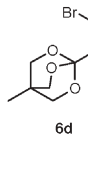
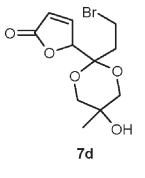
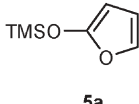
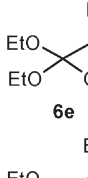
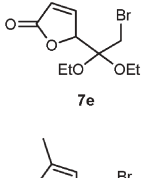
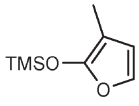
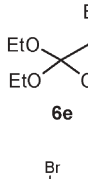
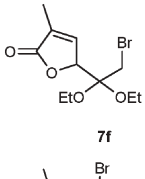
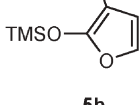
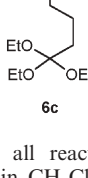
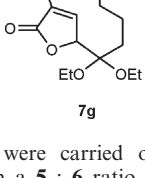
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b600677a

provided bicyclo[4.3.0]lactone **8a** in excellent yield and as a single diastereomer.

Encouraged by the efficiency of this process, which constituted an operationally simple two-step annelation of trimethylsilyloxy furan **5a**, we prepared a range of condensation products, bearing different tether lengths. The results are collected in Table 1.

Particularly noteworthy is the observation that this condensation reaction is not limited to the use of dioxolane-containing orthoesters (e.g. **6a** and **6b**). Indeed, the simpler trialkoxy orthoester derivatives **6c** and **6e** also underwent smooth coupling

**Table 1** Results of the condensation reactions between trimethylsilyloxy furan derivatives and functionalised orthoesters<sup>a</sup>

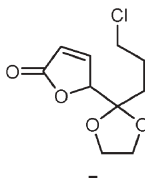
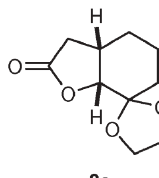
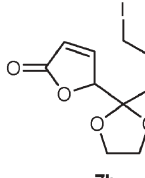
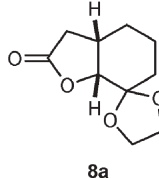
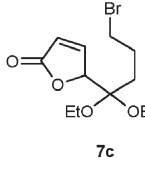
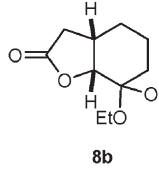
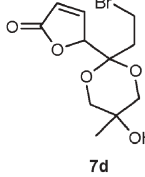
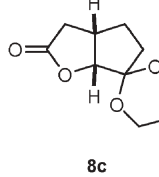
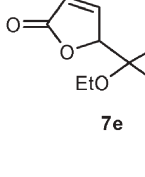
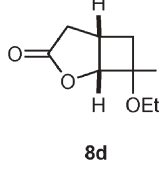
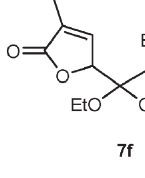
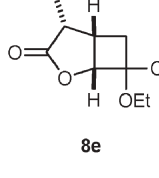
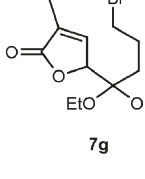
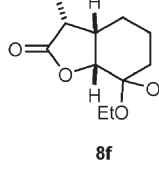
| Entry | Furan derivative                                                                    | Orthoester                                                                          | Product                                                                             | Yield <sup>b</sup> |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|
| 1     |    |    |    | 75%                |
| 2     |    |   |   | 95%                |
| 3     |  |  |  | 95%                |
| 4     |  |  |  | 47% <sup>c</sup>   |
| 5     |  |  |  | 94%                |
| 6     |  |  |  | 80%                |
| 7     |  |  |  | 86%                |

<sup>a</sup> Unless otherwise stated, all reactions were carried out in the presence of 0.7 eq. ZnCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> with a **5** : **6** ratio of 1 : 1.5, from -78 °C to r.t. <sup>b</sup> Yields refer to pure, isolated products.

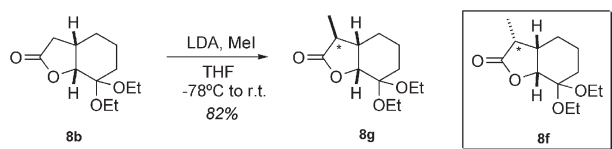
<sup>c</sup> Reaction performed with 5 eq. TMSOTf as the Lewis acid.

with **5a** and **5b** (entries 3 and 5).<sup>8</sup> However, the ensuing adducts display a somewhat lower stability than ketals **7a** and **7b**, which can complicate their purification and lead to decomposition over large periods of time. Conversely, most of the products bearing a dioxolane protecting group are perfectly stable upon chromatography on silica-gel and can be stored without any noticeable change of properties.

**Table 2** Radical-mediated cyclisations of condensation products **7a**

| Entry | Condensation product                                                                 | Bicyclic lactone                                                                      | Yield <sup>b</sup> |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------|
| 1     |    |    | — <sup>c</sup>     |
| 2     |    |    | 98%                |
| 3     |   |   | 88%                |
| 4     |  |  | 72%                |
| 5     |  |  | 65%                |
| 6     |  |  | 90%                |
| 7     |  |  | 97%                |

<sup>a</sup> All reactions performed in the presence of 1.5 eq. TTMS, 0.15 eq. AIBN, in refluxing benzene. In all cases, a single diastereomer of the product was detected in the crude mixture. <sup>b</sup> All yields refer to pure, isolated products. <sup>c</sup> No reaction was observed.



**Scheme 4** Complementary routes to diastereomeric lactones **8f** and **8g**.

It should be noted that, although the yield reported for product **7d**, containing a 3-carbon tether (entry 4), is slightly lower than the remaining examples, the preparation of this compound represents, to the best of our knowledge, the first example of an *intermolecular* condensation employing the Corey OBO-orthoester **6d**.<sup>9</sup> This observation is particularly significant as it establishes the latter compounds as potentially valuable intermolecular acylating agents rather than mere, inert, protecting groups in synthesis.

Having secured an efficient access to the halogenated adducts **7a–g**, we then turned our attention to their radical-mediated cyclisation reactions. The results of these experiments are compiled in Table 2.

Apart from Entry 1, all the ring-forming reactions proceeded in an efficient manner. Particularly worthy of comment is the otherwise rare 4-*exo*-trig cyclisation leading to **8d**.<sup>10</sup> Indeed, such a compound embodies the suitably functionalised bicyclo[3.2.0]heptane core present in Pestalotiopsis A **3**. These cyclisations appear to benefit from a moderate Thorpe–Ingold effect induced by the ketal substituent, which accelerates the ring closure.

Importantly, all these cyclisations take place with complete diastereocontrol, foremost when substituted furan derivatives were employed in the initial condensation step (entries 6–7). In these cases, 3 contiguous stereocenters are generated in one step with > 95% stereoselectivity. Furthermore, as shown in Scheme 4, adduct **8g**, prepared by alkylation of **8b**, and cyclisation product **8f** are epimeric at the  $\alpha$ -lactone carbon centre (marked with \*).<sup>11</sup> The efficient access to both stereoisomers with complete control of their relative stereochemistry further broadens the scope of this methodology.

In summary, we have disclosed a concise, two-step annelation methodology that proceeds with high efficiency and complete diastereocontrol. Using this protocol, a wide variety of bicyclo[3.*n*.0]lactones **8** can be easily assembled from readily available trimethylsilyloxyfuran derivatives and functionalised orthoesters, in high overall yields. Importantly, the added functionality introduced by the orthoester as a ketal protecting group renders these bicyclic lactones particularly interesting scaffolds for subsequent elaboration. Current efforts are now aimed at delineating the full scope of this original methodology, installing an enantioselective version and applying it to the synthesis of biologically relevant substances. The results of these investigations will be reported in due course.

We are grateful to Professor Reinhard Brückner (Institut für Organische Chemie und Biochemie der

Albert-Ludwigs-Universität, Freiburg) for providing us with experimental details for the preparation of **5a** and **5b**. Financial support for this work by the Université catholique de Louvain, the Fonds pour la Recherche dans l'Industrie et l'Agriculture (F.R.I.A., studentship to N.M.) and Merck, Sharp and Dohme (Merck Academic Development Award to I.E.M.) is gratefully acknowledged. N.M. is grateful to the Fond National de la Recherche Scientifique (F.N.R.S.) for receiving an “Aspirant F.N.R.S.” research fellowship.

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- In stark contrast, orthoesters **6c** and **6e** do not provide similar adducts when reacted with silyl enol ethers derived from cyclic ketones.
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- Interestingly, inspection of product **8d** reveals it to be the opposite regioisomer of a formal [2 + 2] cycloaddition of ketene to a dihydrofuran derivative.
- The envelope-like topology of these bicyclic systems directs the hydrogen delivery to the intermediate cyclic radical from the less congested convex-face. Similarly, methylation occurs from the least hindered, exocyclic face.