Construction of fused bis(pyran) units from enones *via* a hydrosilylation–dihydroxylation–acetalization–reduction sequence†

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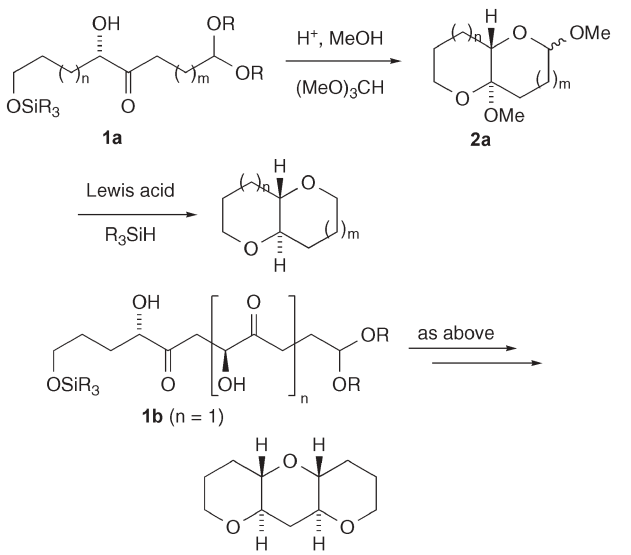
HWE coupling of two simple bifunctional fragments provides enones that can be subjected to a four-step sequence to furnish *trans*-fused bis(pyrans) in good overall yield.

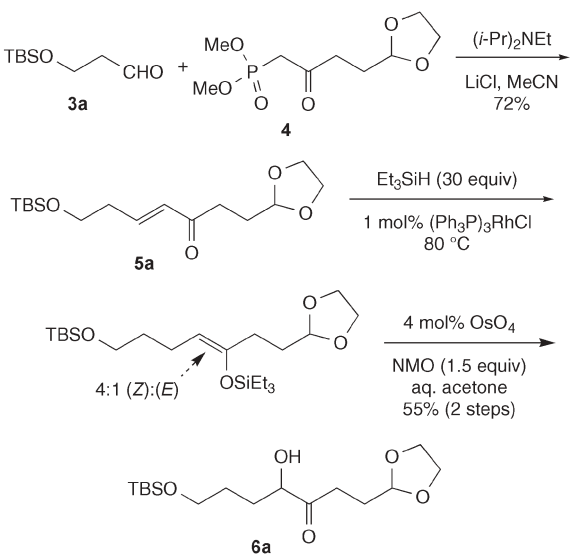
The extreme structural complexity, biological potency, and relative scarcity of the marine polyether ladder toxins make them attractive targets for chemical synthesis.[1] For the larger members of this class, convergent assembly of smaller units is nearly always required. However, alternative strategies for construction of the individual fragments can be envisioned, including iterative synthesis[2] or cascade polycyclization.[3] Application of the latter approach towards ladder toxins is especially attractive, given their proposed biosynthetic polycyclization *via* polyepoxide precursors.[4]

We have sought to develop a polycyclization strategy employing more highly oxidized α-hydroxyketone (acyloin) units in place of epoxides (Scheme 1). For example, substrate **1a** should undergo *in situ* bicyclization to the bis(acetal) **2a** under conditions of acidic deprotection of the terminal alcohol and aldehyde functionalities. Subsequent silane reduction of the acetals *via* Lewis acid activation would then furnish the bis(pyran).[5] One possible advantage of this approach is the avoidance of the regioselectivity problems sometimes seen in epoxide openings, leading to products that have undergone incomplete cyclization.[3] Also of interest are its potential generality with other ring sizes (n or $m > 1$), and the possibility of forming three or more rings by incorporating multiple acyloin moieties into the acyclic precursor (*e.g.*, **1b**). Here we report the results of our initial studies of this process, and demonstrate its applicability to bis(pyran) systems.



Scheme 1 Polyacetal strategy to fused polycyclic ethers.

Implementation of this strategy required straightforward access to acyloins possessing the appropriate terminal groups. Ideally, the method should produce the acyloin(s) with good control of the absolute configuration at the secondary alcohol center. An attractive route would employ dihydroxylation of a suitable enol derivative, which has been shown to occur with good enantioselectivity under the Sharpless asymmetric dihydroxylation conditions.[6] To generate the requisite enol ether with regiocontrol, we settled on enone **5a** as our initial target (Scheme 2). This compound could be easily assembled *via* HWE olefination of protected hydroxypropionaldehyde **3a** with phosphonate **4** under the modified Roush–Masamune conditions.[7] With this material in hand, conjugate reduction could now be examined. We chose to focus on 1,4-hydrosilylation, as this process would directly furnish a silyl enol ether suitable for oxidative processing. In the event, hydrosilylation was achieved using Wilkinson's catalyst and triethylsilane,[8] and the somewhat labile silyl enol ether was immediately subjected to dihydroxylation conditions to furnish acyloin **6a** in 55% yield over two steps.



Scheme 2 Preparation of substrate **6a**.

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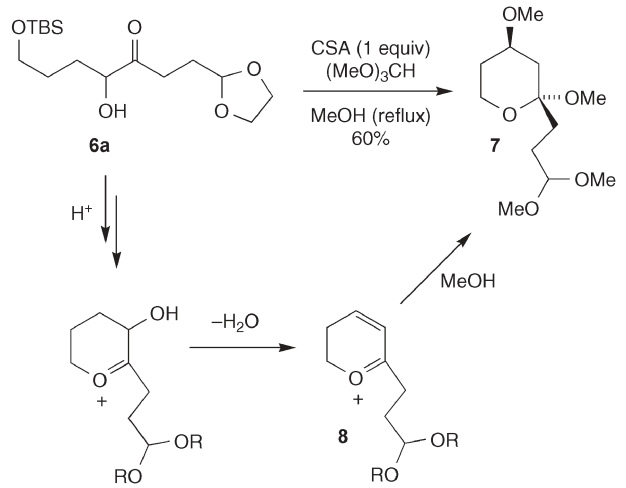
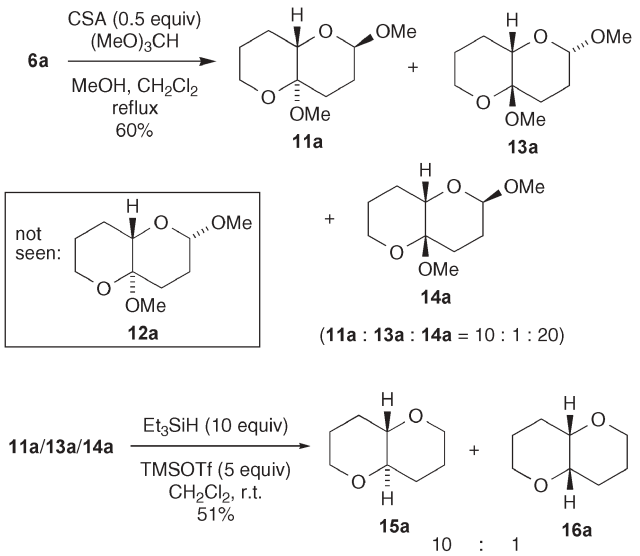


Scheme 3 Attempted cyclization of **6a** in refluxing MeOH.

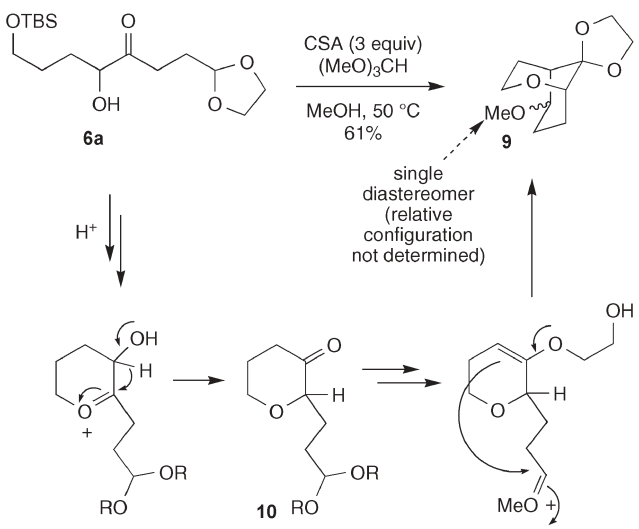


Scheme 5 Bicyclic acetal formation from **6a** and reduction to bis(pyran).

Initial efforts at acetalization of **6a** employed stoichiometric camphorsulfonic acid in the presence of trimethyl orthoformate in refluxing methanol (Scheme 3). However, the major product proved to be pyran **7**.[9] This undesired product is presumed to arise *via* conjugate addition of methanol to unsaturated oxocarbenium ion **8**.

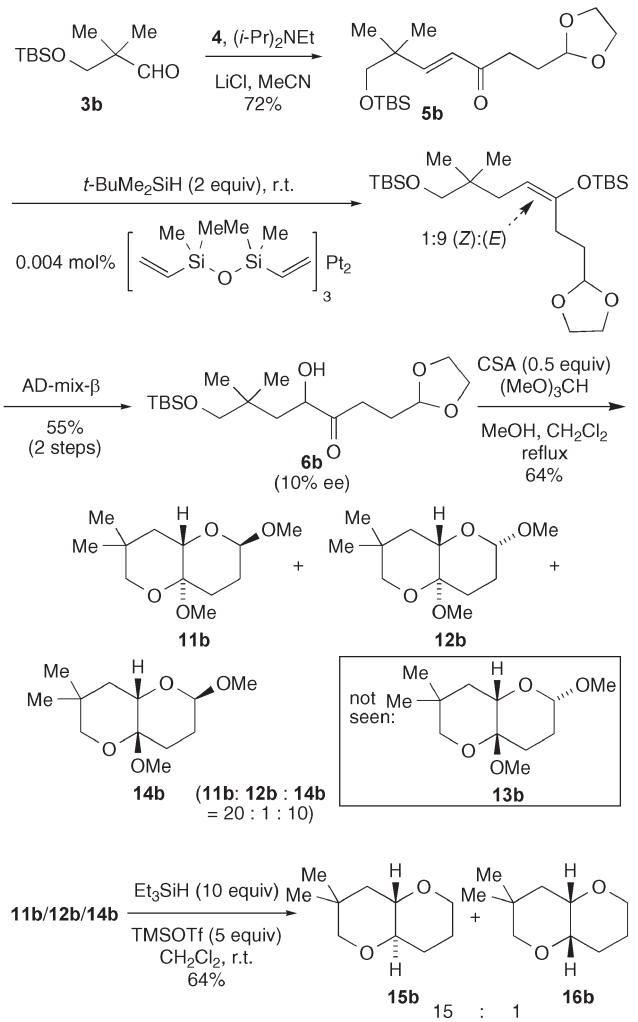
In order to suppress the elimination of water to form **8**, the reaction was run at lower temperature in the presence of three equivalents of acid (Scheme 4). In this case, a good yield of bridged product **9** was obtained.[9] Formation of this compound requires a redox inversion of the acyloin unit, which may occur *via* a hydride shift to give pyranone **10**, followed by transacetalization and intramolecular aldolization.

Successful formation of the desired fused bicyclic acetal was finally achieved (Scheme 5) under relatively mild conditions ($(MeO)_3CH$–MeOH–0.5 equiv. CSA in refluxing dichloromethane). Three diastereomeric products,[9] *trans*-fused isomer **11a** and *cis*-fused isomers **13a** and **14a**, were obtained in a 10 : 1 : 20 ratio in a combined yield of 60%. (The other possible *trans*-fused isomer **12a** was not isolated.) It is surprising that *trans* diastereomer **11a** was not the predominant product, as steric and anomeric effects would be expected to favor this structure.[10] However, the configuration at the two acetal centers was of little consequence, since the subsequent step would involve reduction *via* planar oxocarbenium ion intermediates. Indeed, treatment of any of the pure diastereomers or a mixture of the three with TMSOTf–Et_3SiH furnished the same 10 : 1 ratio of *trans* bis(pyran) **15a** and its *cis* isomer **16a** in moderate yield.[9] The significant preference for the *trans* ring-fusion in this type of reduction is consistent with the observation of selective axial hydride delivery by Kishi and others.[11]



Scheme 4 Attempted cyclization of **6a** with excess CSA.

Because the desired product **15a** is centrosymmetric, efforts to apply asymmetric dihydroxylation in this series were pointless. Therefore, we set out to prepare an acyloin substrate that would lead to an unsymmetrically substituted bis(pyran). Siloxyaldehyde **3b** was condensed with phosphonate **4** as before, to yield enone **5b** (Scheme 6). Hydrosilylation of **5b** under the conditions employed for **5a** was unsatisfactory, as the resulting silyl enol ether was found to be too labile. Use of more bulky silanes with Wilkinson's catalyst was unsuccessful, due to sluggish reactivity. However, use of *t*-$BuMe_2SiH$ in the presence of Karstedt's catalyst furnished the desired (and isolable) enol silane in good yield.[12] In practice, the crude silyl enol ether was carried directly on to the dihydroxylation step, which was accomplished using freshly prepared AD-mix-β (4 mol% $(DHQD)_2PHAL$, 4 mol% OsO_4, 3 equiv. $K_3Fe(CN)_6$ and 1 equiv. $MeSO_2NH_2$). The enantiomeric excess in the production of acyloin **6b** (determined *via* derivatization as the MTP esters) was disappointingly low (10%). A possible explanation for this outcome is the predominance of the (*E*)-silyl enol ether from hydrosilylation with Karstedt's catalyst. Sharpless had previously shown that a (*Z*) geometry was required for good enantioselectivity in the dihydroxylation of some linear enol silanes.[6,13] Regardless of this result, **6b** was subjected to the optimal cyclization conditions and furnished three diastereomeric bicyclic acetals, **11b**, **12b** and **14b**, in a 20 : 1 : 10 ratio in 64% combined yield.[9] (The other possible *cis*-fused diastereomer, **13b**, was not isolated.) As before, the mixture of diastereomeric acetals could be reduced to give bis(pyrans) **15b** and **16b** as a 15 : 1 mixture in 64%



Scheme 6 Preparation and cyclization of substrate **6b**.

yield. NMR analysis of the major product **15b** using the chiral shift reagent Eu(hfc)$_3$ confirmed the 10% ee value measured for **6b**.

We have shown in two examples that easily prepared enones such as **5a** or **5b** can be carried through a convenient, four-step process of conjugate hydrosilylation, dihydroxylation, bicyclization to mixed acetals, and reduction to furnish bis(pyran) products with good diastereoselectivity for the *trans*-fused products **15**. Initial attempts at absolute stereocontrol using asymmetric dihydroxylation indicate that silyl enol ether geometry may be critical. Efforts to controllably form the (*Z*) enol ether, and to apply this sequence to more elaborate substrates, are underway, and will be described elsewhere in due course.

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9 See ESI for discussions of structural assignments for all cyclization products.

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13 Preliminary AD experiments using the 4 : 1 (*Z*)–(*E*) mixture of TES enol ethers obtained from hydrosilylation of **5a** with Wilkinson's catalyst support this hypothesis. An enantiomeric excess of 68% was measured *via* chiral HPLC (Chiralpak OJ-H, IPA–hexane 4 : 96).

