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A convenient new route to enantiopure 3-hydroxy-5-oxo esters and 5,6-dihydropyran-2-ones: intricacies of the trithioorthoester protecting group

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ABSTRACT

3-Hydroxy-5-oxo esters are useful precursors to biologically active compounds. An expedient three-step synthesis of 3-hydroxy-5-oxo esters based on dithiane anion chemistry is presented along with the transformation of the 3-hydroxy-5-oxo esters into 5,6-dihydropyran-2-ones.

Enantiopure 3-hydroxy-5-oxo esters **1** are key intermediates for active pharmaceuticals such as HMG-CoA reductase inhibitors [statins, e.g., Mevastatin (**2**)[1]], which are a top-selling family of cholesterol-lowering drugs.[2] Furthermore, enantiopure esters **1** are potential precursors to the 5,6-dihydropyran-2-one motif that appears in numerous biologically active natural products [e.g., (+)-passifloricin A (**3**)] (Fig. 1).[3]

During the course of our own work, we required an enantiopure 3-hydroxy-5-oxo ester motif. We were surprised when a comprehensive literature search revealed that firstly, only a limited number of methods for accessing this popular moiety in enantiopure form exist, and secondly, these methods are not overly attractive. Contrary to our expectations for a seemingly simple motif, many existing protocols seem to be quite lengthy. For example, a common[4] non-enzymatic approach to HMG-CoA reductase inhibitors involves a Wittig, or a Horner–Wadsworth–Emmons reaction in addition to at least three steps to synthesise the ylide **4** or phosphonate ester **5** (Fig. 2).[5] Other methods for preparing enantiopure 3-hydroxy-5-oxo esters rely on enzymes to introduce chirality at C3.[6] Blandin[7] accessed a 3-hydroxy-5-oxo ester through asymmetric hydrogenation of a 3,5-dioxo ester, and although this methodology is highly promising, the maximum ee achieved to date is 75%. Moreover, autoclave equipment, which is not always available in a synthetic organic chemistry laboratory, was required to generate this result. Accordingly, new methods to assemble rapidly enantiopure 3-hydroxy-5-oxo esters **1** using standard techniques, and readily available enantiopure starting materials, could be of some benefit.

The ring opening of epoxides by dithiane anions, followed by thioketal deprotection, is a well known strategy for constructing enantiopure β-hydroxy ketones.[8] This transformation forms the cornerstone of the Tietze[9]–Smith[10] linchpin reaction (i.e., anion

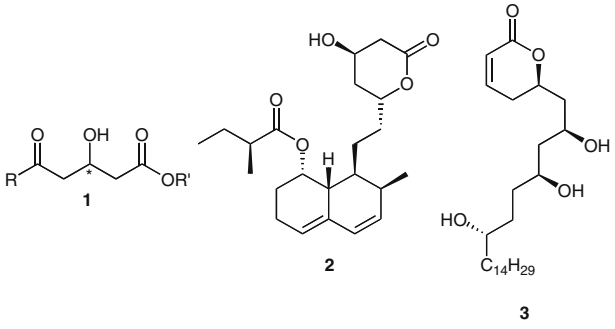

Figure 1.

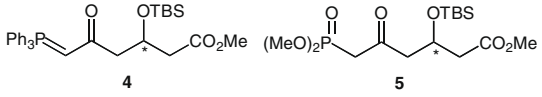

Figure 2.

relay chemistry[11]) that we,[12] and others[13] have utilised in the synthesis of complex natural products. Hence, we wondered whether this powerful methodology could be further extended to encompass enantiopure 3-hydroxy-5-oxo esters **1**. This Letter describes the successful extension of such chemistry to this goal.

More specifically, we envisaged a concise synthesis, featuring the reaction of a dithiane anion with an epoxide linked to the tris(methylthio) masked ester group[14] which culminates in a global deprotection step. The chemistry was initially developed using racemic epichlorohydrin but enantiopure epichlorohydrin was used in the later work. Both (*S*)- and (*R*)-epichlorohydrin are commercially available. The key epoxy trithioorthoester **6** was prepared in good yield by reacting epichlorohydrin (**7**) with

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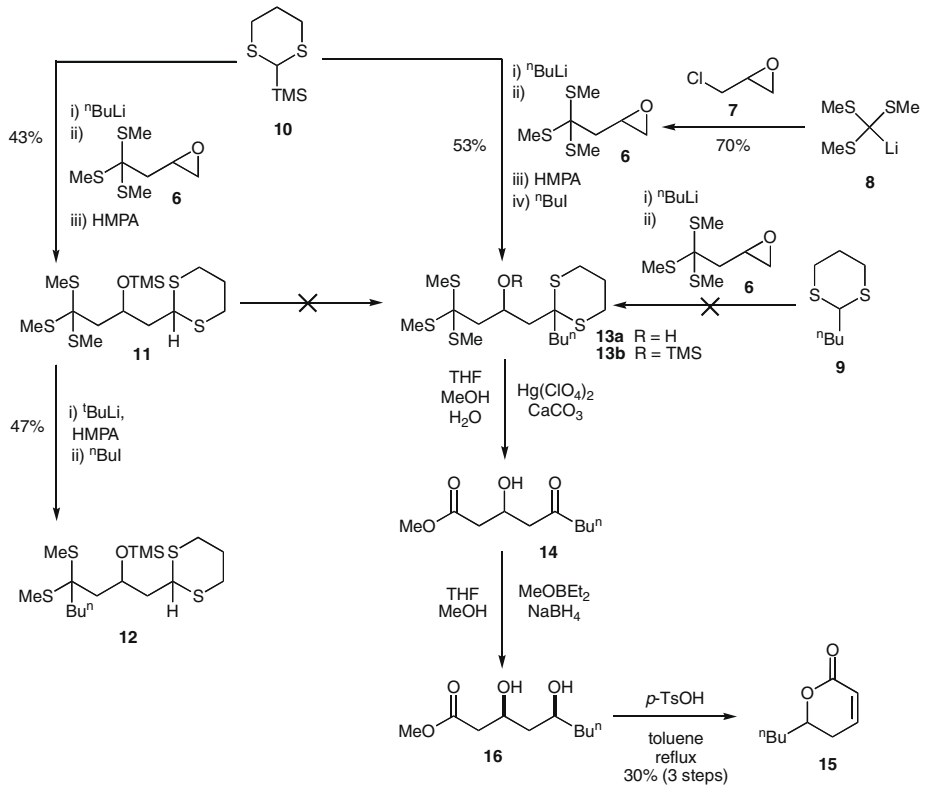


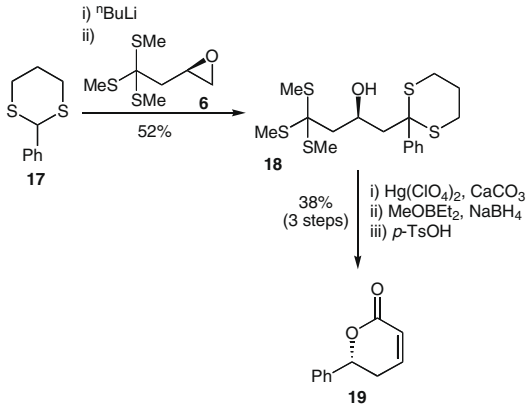
Scheme 1.

tris(methylthio)methyllithium (**8**) (Scheme 1).[15,16] Epoxide **6** failed to react with the anion of 2-butyl-1,3-dithiane (**9**) but did engage with the lithio derivative of TMS-dithiane **10** to afford, after Brook rearrangement, adduct **11**. When compound **11** was treated with ^{t}BuLi and ^{n}BuI, lithium–sulfur exchange rather than dithiane deprotonation occurred, affording the masked ketoaldehyde **12** instead of the desired 3-hydroxy-5-oxo ester precursor **13b**. Lithium–sulfur exchange is well precedented,[17] but to the best of our knowledge, this is the first example of lithium–sulfur exchange in a molecule bearing an acidic dithiane proton.

The problem of competition between lithium–sulfur exchange and dithiane deprotonation was ultimately solved using Smith's three-component linchpin protocol[18] and compound **13b** was accessed from TMS-dithiane **10**, epoxide **6** and 1-iodobutane, in one step, in 53% yield (Scheme 1). Simultaneous removal of all three protecting groups with $HgCl_2/HgO$[15a] afforded the target 3-hydroxy-5-oxo ester **14** in 49% yield. Global deprotection could also be realised with $Hg(ClO_4)_2$.[19] To demonstrate the utility of this dithiane-based approach to 3-hydroxy-5-oxo esters, compound **14** was further elaborated to the 5,6-dihydropyran-2-one **15**. *Syn* selective reduction[20] of **14** furnished diol **16** and treatment with catalytic *p*-TsOH effected lactonisation and dehydration to give lactone **15** in 30% yield from dithiane **13b** (Scheme 1).[21]

Attention turned to making the methodology applicable to 5-aryl-3-hydroxy-5-oxo esters. Pleasingly, the anion of 2-phenyl-1,3-dithiane (**17**) opened epoxide **6** to provide alcohol **18** in moderate yield (Scheme 2), albeit unoptimised. Alcohol **18** was smoothly converted into lactone **19** in the same manner as described for the *n*-butyl derivative (i.e., **15**). Lactone **19** was obtained in good overall yield (38% over three steps)[22] and in 94% ee[23] (the commercially available (*R*)-epichlorohydrin used had an ee of 98% and 98% is a typical de[20] for a diethylmethoxyborane-mediated reduction).

In summary, a new method for accessing 3-hydroxy-5-oxo esters **1** has been described. The protocol developed is shorter than



Scheme 2.

many previously reported non-enzymatic methods. In addition, competition between trithioorthoester lithium–sulfur exchange and dithiane anion generation has been revealed for the first time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.058.

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23. Determined by chiral HPLC (OD, hexane/2-propanol). The observed optical rotation (+188) was in accordance with the optical rotation reported for the other enantiomer (−210, see Ref. 22).