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Addition of Dithiols to Bis-Ynones: Development of a Versatile Platform for the Synthesis of Polyketide Natural Products

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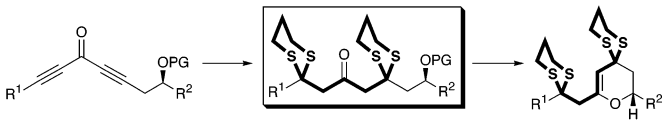
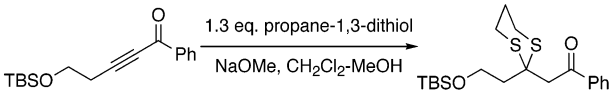
ABSTRACT



The conjugate addition of dithiols to bis-ynones generates a versatile masked 1,3,5-triketone platform. These functional units are useful intermediates for the synthesis of oxygen-containing heterocycles commonly found in polyketide natural products. The tetrahydropyranyl fragments of the marine macrolides Lyngbouilloside and Callipeltoside A have been synthesized with use of this methodology.

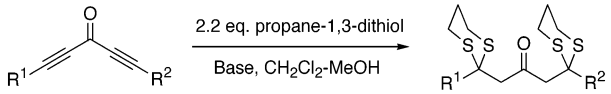
The generation of 1,3-oxygenated functionality in organic molecules is an important process in modern synthetic chemistry.[1] While there have been many advances in this area, and especially for the assembly of polyketide natural products, there remains a constant need to develop new methods for the introduction of 1,3-oxidation patterns with enantio- and diastereocontrol.[2] Through a number of natural product programs we have realized the general utility of β-keto 1,3-dithianes as versatile intermediates for the synthesis of polyketide-type structures. As a result we recently reported a method for the synthesis of β-keto 1,3-dithianes through the conjugate addition of dithiols to ynones, ynoates, and ynals (Scheme 1).[3]

Scheme 1. Conjugate Addition of a Dithiol to an Ynone



It was envisaged that an orthogonally protected 1,3,5-triketone could be generated by this strategy through the conjugate addition of a dithiol to a bis-ynone at β- and β'-alkyne carbon atoms. To the best of our knowledge the synthesis and use of orthogonally masked 1,3,5-triketones has not been employed in the synthesis of complex molecules. However, such a synthetic tactic would provide a highly versatile platform for the synthesis of structural motifs that are often found in polyketide natural products.[4]

Scheme 2. Conjugate Addition of Dithiols to Bis-ynones



In this paper we report the development of a process for the generation of β,β'-bis-1,3-dithiane ketones by the conjugate addition of dithiols to a bis-ynone (Scheme 2). We

(1) (a) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(2) (a) For some recent examples see: Smith, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. (b) Rychnovsky, S. D.; Khire U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (d) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535. (e) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890. (f) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.

(3) Gaunt, M. J.; Sneddon, H. F.; Hewitt, P. R.; Orsini, P.; Hook, D. F.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 15.

(4) (a) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

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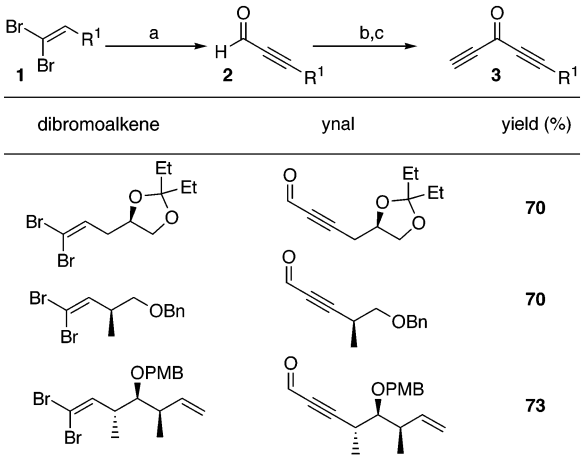
Table 1. Preparation of Ynones from Dibromoalkene[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 to −30 °C, 1 h; (ii) *N*-formylmorpholine, rt, 3 h. (b) HCCMgBr, THF, −78°C. (c) Dess−Martin periodinane, CH_2Cl_2.

also report the use of these masked 1,3,5-triketone units as key intermediates for the preparation of a range of oxygen-containing heterocycles that can be used in natural product synthesis.

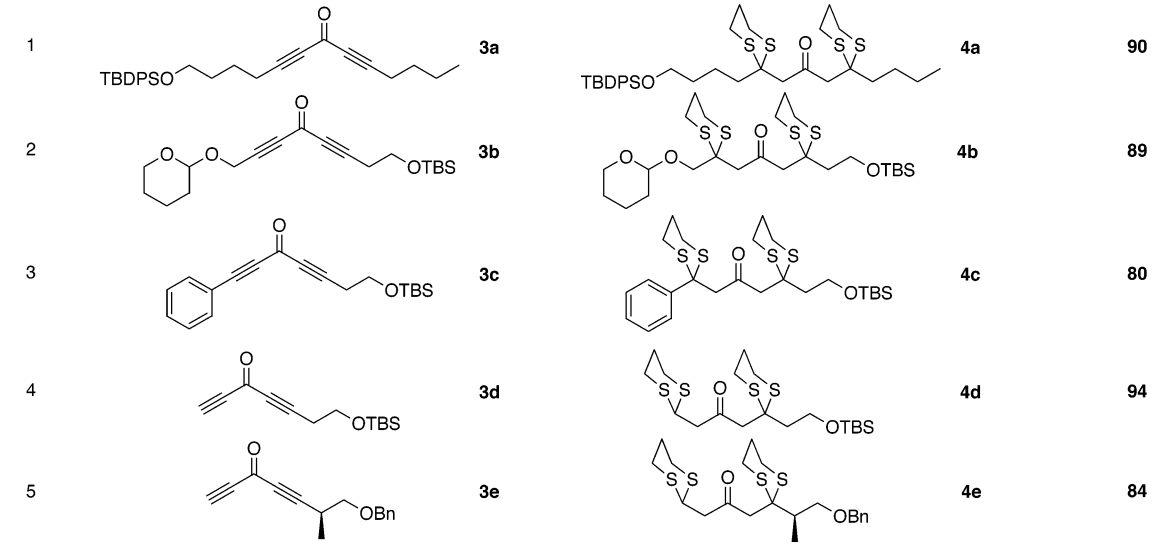
This approach would exploit the effective C−C bond-forming potential of alkynes with the proposed tandem dithiol functionalization of the bis-ynone to rapidly generate a versatile trione fragment. Accordingly, initial studies were aimed at developing a method for the facile assembly of the required bis-ynones **3** (Table 1). Taking advantage of the powerful Corey−Fuchs protocol[5] for the synthesis of alkynes we planned to intercept the resulting acetylide anion with a formylating agent. Standard metalation with *n*-BuLi followed by interception with *N*-formylmorpholine furnished the desired ynals **2** in good yield. Addition of a second alkyne anion followed by oxidation formed the bis-ynone **3** as a simple three-step sequence (for some examples see Table 1).

To investigate the dithiol additions to bis-ynones, initial studies were based on the conditions that had been developed for our earlier work on additions to ynones.[3]

After brief optimization studies the ideal conditions were found to require treatment of the bis-ynone **3** with propane-1,3-dithiol (2.2 equiv) and sodium methoxide (2.2 equiv) in methanol−dichloromethane (1:1, 0.05 M) at −10 °C. In some cases it was found that bases such as sodium hydroxide or tetrabutylammonium hydroxide were required to effect reaction and that tetrahydrofuran was on occasion preferred to dichloromethane to aid the overall solubility of the reaction mixture.

The dithiol addition takes place smoothly on a range of bis-ynones **3** (Table 2). For example, straightforward alkyl groups (entry 1), heteroatom substituents (entries 1−3), and aryl groups (entry 4) are well tolerated and generate the corresponding bis-dithiane ketones **4** in good yield. Of particular importance were the successful reactions of terminal bis-ynones **3d**−**e**. The products **4d**−**e**, which contain a terminal dithiane moiety, can be further utilized in C−C bond-forming processes through interception of their 2-lithio derivative with electrophiles.[6] On the basis of experimental observations it is noticeable that the terminal alkyne unit of the bis-ynone reacts almost instantaneously to form the 1,3-dithiane moiety. However, when the propargylic center is more heavily substituted (**3e**) the addition

Table 2. Dithiol Addition to Bis-ynones[a]



[a] Reagents and conditions: Propane-1,3-dithiol, NaOMe, MeOH−CH_2Cl_2, −10 °C to rt.

is slower but the reaction still proceeds well to form the desired bis-dithiane ketone **4e** in good yield.

In a previous communication it was shown that β-keto dithianes decorated with suitable functional groups could be used to form spiroketals.[3] As part of ongoing natural product programs we were interested in using these substrates to form functionalized tetrahydropyranyl systems that could be applied toward the synthesis fragments of polyketide-derived natural products such as Lyngbouilloside[7] and Callipeltoside A[8] (Figure 1).

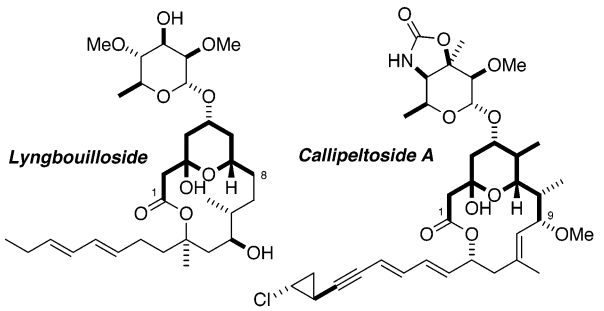


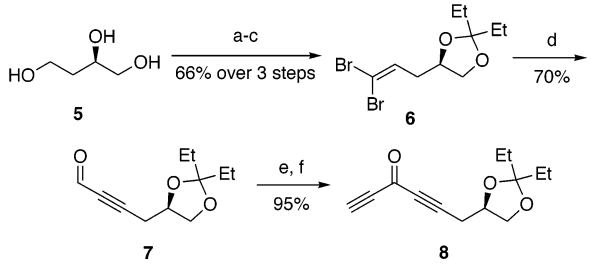
Figure 1. Lyngbouilloside and Callipeltoside A.

Lyngbouilloside is a marine macrolide isolated from *lyngbya bouilonii* and displays a modest cytotoxicity. It comprises a 14-membered macrolide system, a tetrahydropyranyl hemiketal, a rhamnose pyranoside derivative, and a diene side chain. The absolute stereochemistry has not been determined. The C_1-C_8 unit is ideally suited to demonstrate the applicability of the dithiol-bis-ynone addition reaction.

Our progress toward the synthesis of the C_1-C_8 fragment is shown in Schemes 3 and 4. Triol **5** was protected as its 3-pentylidene ketal and the remaining hydroxyl group oxidized to the corresponding aldehyde with pyridinium chlorochromate (PCC). The aldehyde was converted into ynal **7** by using a modified Corey−Fuchs protocol. Formation of the dibromoalkene **6** followed by acetylide formation and interception of the resulting anion with *N*-formylmorpholine furnished ynal **7** in 70% yield. Addition of ethynylmagnesium bromide to ynal **7** formed the bis-ynol and Dess−Martin oxidation[9] generated the bis-ynone **8** in 95% yield over the two steps.

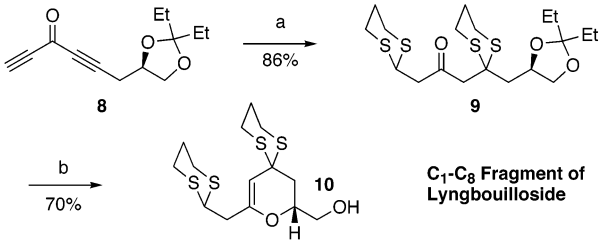
Using the standard conditions, the double addition of propane-1,3-dithiol to bis-ynone **8** proceeded in excellent yield to form bis-dithiane ketone **9** (Scheme 4). Removal of the pentyl ketal with camphorsulfonic acid in methanol and concomitant cyclization afforded the C_1-C_8 fragment **10** of Lyngbouilloside as a 4:1 mixture of the enol ether **10** and the corresponding hemiketal in 70% (82% brsm.).

Scheme 3. Synthesis of Bis-ynone **8**[a]



[a] Reagents and conditions: (a) Pentan-3-one, TsOH, 53 °C, 16 h. (b) PCC, 4 Å mol sieves, CH_2Cl_2, rt, 1 h. (c) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 5 min. (d) (i) *n*-BuLi, THF, −78 °C, 1 h; (ii) *N*-formylmorpholine, rt, 17 h. (e) HCCMgBr, THF, −78 to −30 °C, 30 min. (f) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min.

Scheme 4. Synthesis of the C_1-C_8 Fragment of Lyngbouilloside[a]



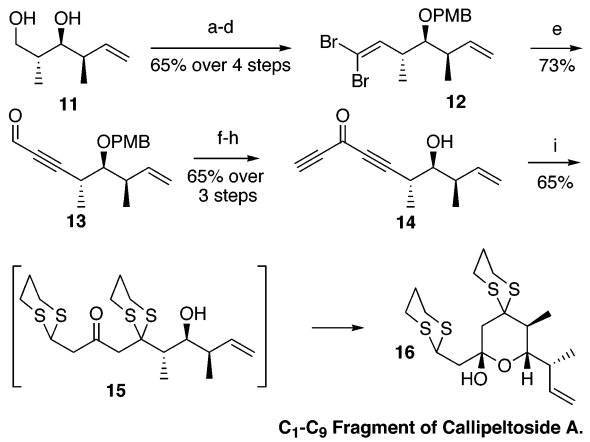
[a] Reagents and conditions: (a) Propane-1,3-dithiol, NaOMe, MeOH−CH_2Cl_2, −10 °C to rt, 17 h. (b) CSA, $HC(OMe)_3$, MeOH, 45 °C, 5 h.

To further highlight the potential of this method the synthesis of the C_1-C_9 fragment of Callipeltoside A was also envisaged (Schemes 5). Diol **11** was converted to dibromoalkene **12** in 65% yield over a four-step sequence. Use of the modified alkynylation protocol (as previously described) generated ynal **13** in good yield. Finally, treatment of **13** with ethynylmagnesium bromide followed by mild oxidation with Dess−Martin periodinane gave the bis-ynone in good yield.

The dithiol addition reaction of the bis-ynone was poor in the presence of the C_7 PMB group; however, when this group was removed the dithiol addition on **14** (C_7−OH) proceeded smoothly. Interestingly, upon isolation we found that the bis-dithiane ketone **15** had in fact cyclized to form the desired tetrahydropyranyl hemiketal **16** in 65% yield. This pleasing result generates the C_1-C_9 Callipeltoside A

(5) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(6) For an example of dithiane coupling in natural product synthesis see: Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350.
(7) Tan, L. T.; Marquez, B. L.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 925.
(8) (a) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085. (b) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C. *Tetrahedron* **1997**, *53*, 3243. (c) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.
(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4383.

Scheme 5. Synthesis of the C_1-C_9 Fragment of Callipeltoside A[a]



[a] Reagents and conditions: (a) $PMPCH(OMe)_2$, *p*-TsOH, $CHCl_3$, rt, 1.5 h. (b) DIBAL-H, CH_2Cl_2, −10 °C, 2 h. (c) Dess−Martin periodinane (DMP), CH_2Cl_2, rt, 2 h. (d) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 1 h. (e) (i) *n*-BuLi, THF, −78 °C, 1 h; (ii) *N*-formylmorpholine, rt, 3 h. (f) HCCMgBr, THF, −78 to −30 °C, 0.5 h. (g) DMP, CH_2Cl_2, rt, 3 h. (h) DDQ, CH_2Cl_2, pH 7 buffer, rt, 14 h. (i) Propane-1,3-dithiol, NaOMe, MeOH−CH_2Cl_2, −10 °C to rt, 17 h.

fragment **16** directly from bis-ynone **14** making the overall processes highly efficient.

The dithiol addition to bis-ynones has enabled the rapid generation of the C_1-C_8 fragment of Lyngbouilloside **10** and the C_1-C_9 fragment of Callipeltoside A **16** and we are currently investigating the synthesis of the remainder of these molecules. This work will be reported in due course.

In summary, we have developed an efficient method for the conjugate addition of dithiols to bis-ynones. The resulting β,β'-bis-1,3-dithiane ketones are isolated in excellent yields across a range of substrates. The potential of these masked 1,3,5-triketone systems as versatile platforms for the synthesis of polyketide natural products is highlighted through the synthesis of the tetrahydropyranyl ring systems of Lyngbouilloside and Callipeltoside A.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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