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Further explorations on bridged 1,2,4-trioxanes

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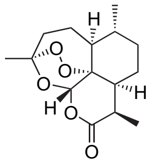
Abstract—Three new bicyclo[3.2.1]-type 1,2,4-trioxanes have been designed and synthesized. One of them demonstrates better tolerance of the intramolecular hemiketals to steric crowding in hydroperoxidation. The other represents a prototype for possible manipulation of the transient radicals generated in cleavage reactions. A new substitution pattern in the bridged system is explored through synthesis of the third molecule. The configurations of all stereogenic centers in the bridged system can be effectively controlled by the chirality of the allyl alcohol as illustrated by the enantioselective synthesis of the fourth molecule. Finally, similar bicyclo[3.3.1]-type 1,2,4-trioxanes are shown very difficult to be synthesized because of the involvement of a conformer with two substituents at axial positions at the same time.

1. Introduction

World-wide recognition of qinghaosu[1] (artemisinin) and its derivatives as effective weapons in the battle against malaria has led to a dramatically renewed interest in organic peroxides, a rather old class of organic compounds known[2a] since 1850s, and thus has greatly stimulated the studies[2b–x] on such compounds.



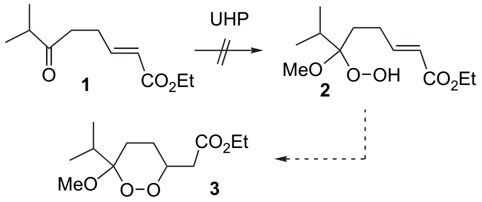
Qinghaosu
(Artemisinin)

Peroxy bonds are the central functionality of organic peroxides. Compared with other covalent bonds commonly found in organic compounds, peroxy bonds are very fragile because their average bond energy is only approximately half of that for a C–C single bond. This decides that peroxy bonds cannot survive a range of reaction conditions as well as reagents commonly employed in organic synthesis and thus makes synthesis of organic peroxides more difficult than otherwise. Besides, peroxy bonds are practically impossible to form from two alkoxyls or related species. It is therefore not surprising that the existing methods for 'making' peroxy bond(s) in an organic molecular framework are rather limited in number. Under such circumstances, making use of one of the known methods for introducing peroxy bonds in different molecular systems has become the most common practice in the synthesis of organic peroxides.

One of the practical methodologies for incorporating peroxy bond(s) into organic molecules is that introduced by Kobayashi[3] and co-workers, which utilizes UHP (urea–hydrogen peroxide complex) as the source of the peroxy functionality. By employing this protocol we have made a range of new organic peroxides, including monocyclic, fused bicyclic, spiro, and bridged ones.[4] In this paper we describe our further explorations on the bridged trioxanes.

2. Results and discussions

One of the major purposes of our studies here is to exploit the facile formation of intramolecular hemiketal in the incorporation of a hydroperoxyl group. In the previous molecular setups we already demonstrated that intramolecular hemiketals were superior to the intermolecular ones. These observations encouraged us to re-examine the possibility to include a bulky isopropyl group at ketone carbonyl group, which was shown[4b] to be impossible in an intermolecular hemiketal system (Scheme 1) with either **1** or its dimethyl ketal as the starting material.



Scheme 1.

Keywords: Antimalarials; Hemiketals; Peroxides; Cyclization; Heterocycles.

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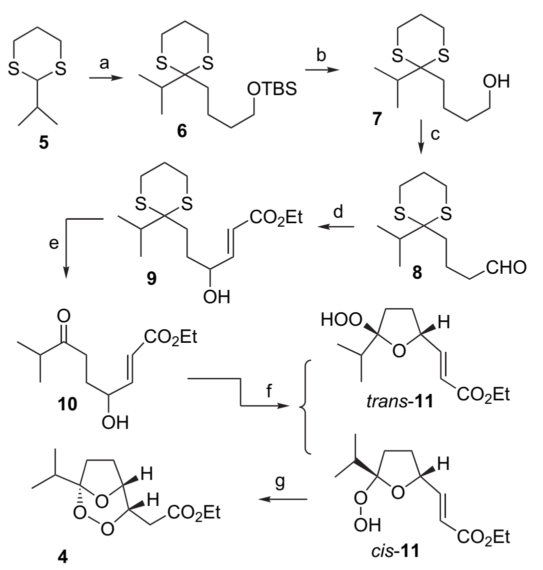
An additional thing that we wish to examine through this molecule is whether the cis/trans ratio of the hydroperoxyl intermediate could be improved by a bulkier substituent so that more desired cis isomer (with –OOH cis to the Michael acceptor) could be formed in the hydroperoxidation.

The synthesis of the first target (**4**) of this work is outlined in Scheme 2. The known dithiane **5**[5] was deprotonated with *n*-BuLi at −25 °C followed by treatment with $I(CH_2)_4OTBS$[6] to give **6** in 84% yield. The TBS protecting group was then removed with TBAF to afford alcohol **7**. A $SO_3\cdot Py$ oxidation gave the corresponding aldehyde **8**, which on treatment with $PhSOCH_2CO_2Et$ via the SPAC[7] reaction (Sulfoxide Piperidine And Carbonyl reaction) yielded alcohol **9**.

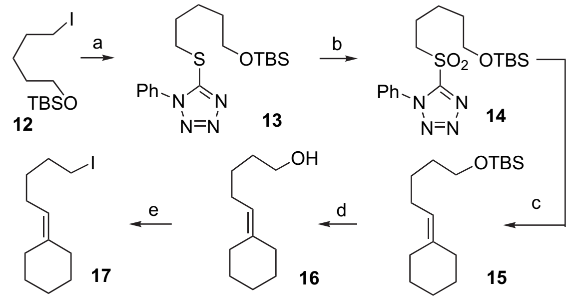


Scheme 2. (a) (i) *n*-BuLi/−25 °C/4 h; (ii) $HMPA/I(CH_2)_4OTBS$/0 °C/17 h, 84%; (b) TBAF/THF/rt/4 h, 70%; (c) $SO_3\cdot Py/DMSO/NEt_3/CH_2Cl_2$/0 °C/0.5 h, 86%; (d) $PhSOCH_2CO_2Et$/piperidine/CH_3CN/rt/17 h, 62%; (e) $I_2/NaHCO_3$/acetone–H_2O/0 °C/0.5 h, 82%; (f) UHP (ca. 7.5 equiv)/*p*-$TsOH\cdot H_2O$/DME/rt/12 h, 90% (*trans*-**11**/*cis*-**11**=1.3:1); (g) cat. $HNEt_2/CF_3CH_2OH$/rt/24 h, 30%.

The sulfur protecting group was then removed to release the carbonyl group to set up a stage for incorporation of a hydroperoxyl group. To our gratification, when treating **10** with *p*-TsOH/UHP[4d] the reaction did take place as anticipated, giving **11** as a 1.3:1 mixture of the trans and cis isomers. This result proves again that with a transient intramolecular hemiketal as an immediate precursor, the driving force for the incorporation of the hydroperoxyl group is significantly increased compared with those in intermolecular cases. Thus, for the first time we are able to include an isopropyl at the carbonyl group in the ketal exchange reaction. And the content of the desired cis isomer (with the –OOH cis to the C–C double bond) in the product mixture reached an unprecedented 44%. Further treatment of *cis*-**11** with $HNEt_2$ in CF_3CH_2OH at ambient temperature for 24 h led to the desired end product **4** in 30% yield.

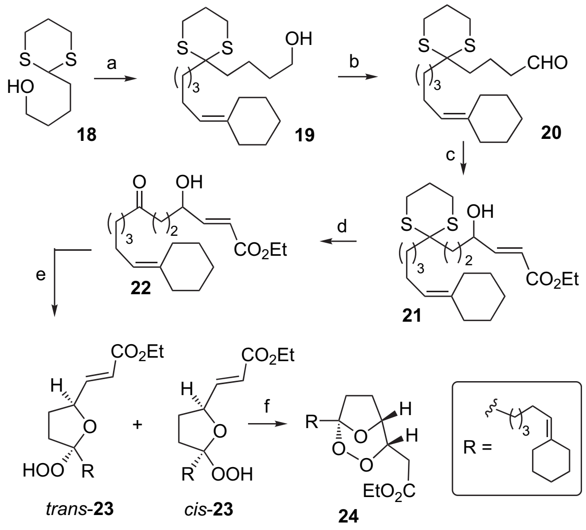
We also designed a similar trioxane that carries a different substituent in place of the isopropyl group in **4**. The side chain in this case is a substituted pentyl group with a cyclohexylidene group at the terminal, which may allow the carbon-centered radical generated in a single electron reducing species induced cleavage reaction (a likely model for in vivo antimalarial action) to evolve further into a secondary radical through an intramolecular addition[3c] and thus improve the antimalarial potency.

The synthesis is shown in Scheme 3. Reaction of the known iodide **12**[8] with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation with *m*-CPBA led to sulfone **14**. Deprotonation of **14** with NaHMDS and reaction with cyclohexanone afforded **15**. The TBS protecting group was readily removed by treatment with TBAF. The resulting alcohol (**16**[9]) was then converted into the corresponding iodide **17**.



Scheme 3. (a) NaH/1-phenyl-1*H*-tetrazole-5-thiol/rt/overnight, 97%; (b) *m*-CPBA/$NaHCO_3$/rt/1 d, 91%; (c) NaHMDS/cyclohexanone/−78 °C/6 h, 74%; (d) TBAF/THF/0 °C/1 h, 96%; and (e) I_2/imid./PPh_3/0 °C/30 min, 85%.

With the side chain in hand, we set out to build up the framework of the second target molecule (Scheme 4). The known dithiane **18**[10] was first converted into the corresponding dianion by treatment with slightly more than 2 equiv of *n*-BuLi at −20 °C. The above mentioned iodide **17** was then introduced along with HMPA. After reaction at ambient temperature for 15 h, the desired alcohol **19** was obtained in 70% overall yield.



Scheme 4. (a) (i) *n*-BuLi/−20 °C/4 h, (ii) HMPA/**17**/rt/15 h, 70%; (b) $SO_3\cdot Py/NEt_3$/DMSO/0 °C, 30 min, 89%; (c) $PhSOCH_2CO_2Et$/piperidine/CH_3CN/rt/overnight, 63%; (d) $I_2/NaHCO_3$/acetone–H_2O/0 °C/0.5 h, 78%; (e) UHP/*p*-$TsOH\cdot H_2O$/rt/20 h, total yield 88% (*trans*-**23**/*cis*-**23**=1.6:1); and (f) $HNEt_2/CF_3CH_2OH$/rt/15 h, 28%.

A subsequent $SO_3\cdot Py$/DMSO oxidation transformed the terminal alcohol into an aldehyde, which on exposure to