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Synthesis of 1,6,7-trioxa-spiro[4.5]decanes

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Abstract—As potential antimalarial agents, four novel spiro-peroxides were designed and synthesized with the peroxy bond introduced employing the Kobayashi's methodology (with modifications). The results showed that by using cyclic hemiketal as substrates the incorporation of the hydroperoxyl group could be achieved in high yields without recourse to the expensive $Sc(OTf)_3$ catalyst.

Although even back in the 19th century organic peroxides were already known,[1] the value of this class of compounds was never fully recognized by the scientific communities around the world until the late 1980s, when qinghaosu (artemisinin, an outstanding antimalarial agent discovered[2] in China) was made broadly known to the West. Now, with the great potential of organic peroxides as a novel class of antimalarial agents demonstrated through many qinghaosu derivatives and various simple analogues,[3] design and synthesis of new organic peroxides have gradually grown into an active area in organic chemistry.

Recently, Kobayashi and co-workers[4a,b] reported a very convenient way to construct six-membered monocyclic peroxides using UHP (H_2O_2–urea complex, a commercially available solid reagent) as the peroxy bond source. In their methodology the hydroperoxyl group (–OOH) was incorporated into the substrate structure through a $Sc(OTf)_3$-catalyzed OH/OOH exchange. Hence, the presence of a hemiketal formed in situ from a ketone and MeOH (solvent) was apparently a pre-requisite for the OOH incorporation. We reasoned that if the hemiketal formed intramolecularly, the corresponding hemiketal would be available times for the subsequent exchange. The introduction of OOH might be significantly facilitated and the expensive $Sc(OTf)_3$ perhaps could be replaced with a commonly utilized acid.[4c] An additional advantage to use intramolecular[4d] hemiketals as the precursors is that the products would carry a new structural feature—a spiro framework with the peroxy bond and the hemiketal alkoxy bond in different rings. Besides, we were also interested in examining whether other Michael acceptors than α,β-unsaturated esters could serve well in the ring-closure step. All these prompted us to conduct the work reported below.

We first designed simple targets **1** and **2**, which were synthesized using the route shown in Scheme 1. The known[5] dithiane **3** was protected as a MOM ether before being deprotonated and alkylated at the dithiane C-2 position to yield acetal **4**. The masked aldehyde carbonyl group was then freed by hydrolysis in acetone in the presence of a catalytic amount of PPTS (pyridinium *p*-toluenesulfonate). The resulting aldehyde was immediately treated with $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Bn$ in CH_2Cl_2 to give **5** or **6**, respectively. The sulfur protecting group was then removed with $I_2/NaHCO_3$[6] to afford **7** or **8**, respectively.

Introduction of the OOH group was achieved using Kobayashi's method at very similar substrate concentrations, but the catalyst $Sc(OTf)_3$ was replaced with *p*-TsOH (the commercially available monohydrate). Kobayashi also examined *p*-TsOH. However, the yields for their non-cyclic hemiketal substrates were rather low unless 20-fold excess of UHP was employed. In our cases, the reaction appeared to be much easier to occur. Thus, in the presence of 7.5 equiv of UHP, **9** could be readily obtained in 82% isolated yield after ca. 20 h reaction at the ambient temperature. Further treatment of **9** or **10** with $HNEt_2$ in F_3CCH_2OH gave the end

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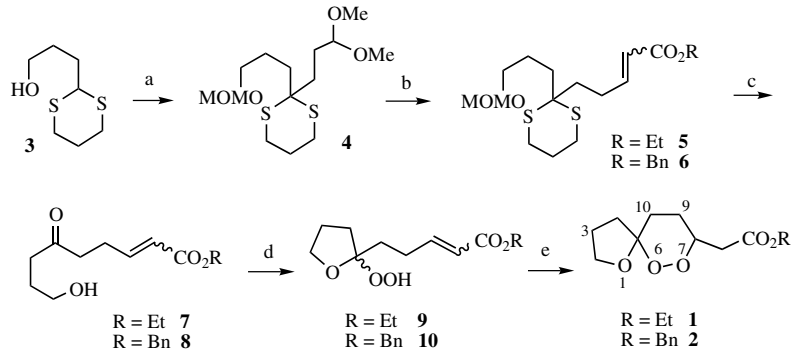
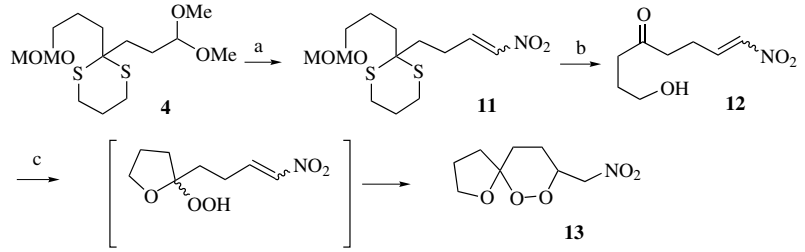


Scheme 1. Reagents and conditions: (a) (i) $CH_2(OMe)_2$, LiBr, TsOH, rt, 48 h; (ii) BuLi, HMPA, $I(CH_2)_2CH(OMe)_2$, 0 °C, 48 h, 71% (over two steps); (b) (i) PPTS, acetone, reflux, 12 h; (ii) $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Bn$, CH_2Cl_2, rt, 12 h, 86% for **5** or 94% for **6** (over two steps); (c) (i) *p*-TsOH, EtOH, reflux or 2 N HCl, THF, 40–50 °C; (ii) I_2, acetone, $NaHCO_3$, 0 °C, 30 min, 75% for **7** or 50% for **8** (over two steps); (d) UHP, *p*-TsOH, MeOH, rt, 82% for **9** or 54% for **10** (not optimized); (e) $HNEt_2$, CF_3CH_2OH, rt, 24 h, 52% for either **1** or **2**.



Scheme 2. Reagents and conditions: (a) (i) PPTS, acetone, reflux, 12 h; (ii) CH_3NO_2, DBU, rt, 15 h; (iii) MsCl, NEt_3, rt, 24 h, 91% (over three steps); (b) (i) I_2, $NaHCO_3$, 0 °C, 30 min; (ii) concd HCl, acetone–H_2O, rt, 17 h, 23% (over two steps); (c) UHP, *p*-TsOH, DME, rt, 10.5 h, 35%.

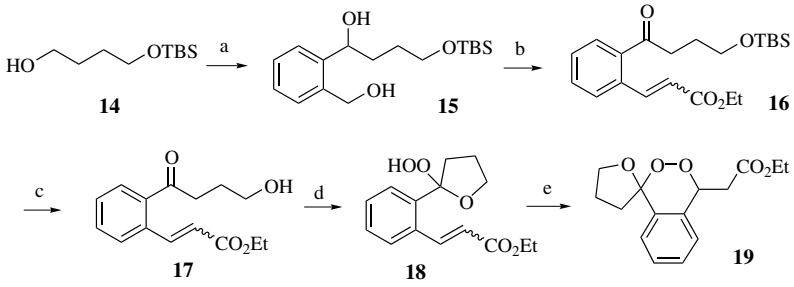
product[4e] **1** or **2**, respectively (presumably as a mixture[4f] of the diastereomers).

As part of our interest in examining the scope and limitation of the Kobayashi's method, we next tried to use a $–NO_2$ as the electron-withdrawing group in place of the $–CO_2R$ (Scheme 2). Thus, the acetal **4** was transformed into **11** by a three-step sequence. First, the acetal was protected as mentioned above. The intermediate aldehyde was then treated with nitromethane in the presence of DBU to give an intermediate alcohol. The OH group β to the nitro group was then eliminated after being converted to the corresponding mesylate, yielding the alkenyl nitro compound **11**. Deprotection of the ketone carbonyl group and the hydroxyl group was rather complicated, presumably because of the presence of the alkenyl nitro partial structure. However, as we were mainly interested whether the final ring-closing could take place, we went on with **12** despite the low yield.

In the subsequent hydroperoxidation of **12**, we modified the reaction conditions slightly (utilizing DME to replace MeOH), because from other closely-related experiments we had already observed that MeOH readily underwent Michael addition to the C–C double bond if a $–NO_2$ group was present. After such an adjustment, the hydroperoxidation did occur as wished. However, due to the presence of the highly reactive $–CH{=}CHNO_2$ partial structure, the resulting hydroperoxy species could not be isolated. Instead, it proceeded directly to yield the end cyclic peroxide **13**.

Apart from changing the electron-withdrawing group on the C–C double bond, we also attempted incorporation of an aromatic ring into the core structures of the targets because presence of an UV chromophore may facilitate future studies (i.e., tracing the molecule) and alter the bioactivity as a consequence of its influence on the radical-mediated cleavage[8] pathways. The synthesis of such a molecule (**19**) is shown in Scheme 3. Thus, the known alcohol **14**[7] was oxidized into the corresponding aldehyde and treated with the lithium reagent[9] generated in situ from *o*-bromophenylmethanol. The intermediate diol **15** was oxidized into an aldehyde–ketone, which was directly treated with $Ph_3P{=}CHCO_2Et$ to give the α,β-unsaturated ester **16**. The terminal TBS protecting group was then removed and the resulting alcohol–ketone **17** was treated with UHP in DME to give the hydroperoxy species **18** in 86% yield. On further treatment with $HNEt_2$ in F_3CCH_2OH, the end product **19** was obtained in 54% yield.

In summary, we have designed and synthesized four novel spiro-peroxides, extending Kobayashi's methodology to cyclic hemiketals. We also examined the feasibility of using a nitro group as the electron-withdrawing group to replace the ester group in the original procedure. The results showed that by using cyclic hemiketals as substrates the hydroperoxidation could be realized in high yields without recourse to the expensive catalyst $Sc(OTf)_3$. DME (1,2-dimethoxyethane) was found to be a good substitute for MeOH as the solvent in the hydroperoxidation, which could eliminate the problem



Scheme 3. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, NEt_3; (ii) BuLi, $BrC_6H_4CH_2OH$, −78 °C, 1 h, then the aldehyde, −78 °C, 40 min, 61% (two steps); (b) (i) $(COCl)_2$, DMSO, NEt_3; (ii) $PhP{=}CHCO_2Et$, rt, 3 h, 74% (over two steps); (c) *p*-TsOH, THF–H_2O (4:1), rt, 5 h, 96%; (d) UHP, CSA, DME, rt, 18 h, 86%; (e) $HNEt_2$, CF_3CH_2OH, rt, 2 h, 54%.

caused by addition of MeOH to the α,β-unsaturated moiety in some substrates (with a strong electron-withdrawing group on the C–C double bond).

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