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Synthesis of Cyclic Hemiketals and Spiroketals from Dioxanorbornanes

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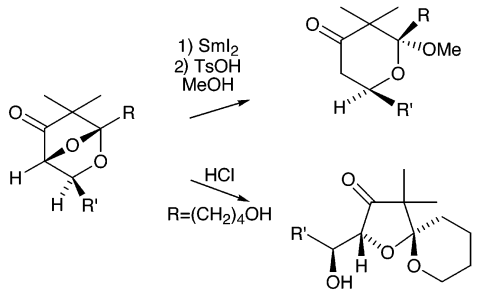
ABSTRACT

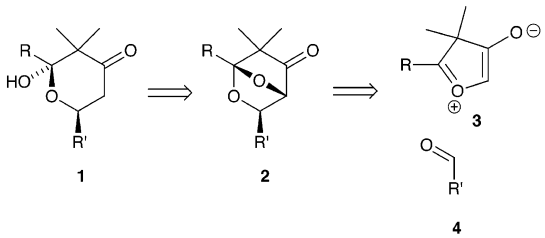


A new method for the synthesis of substituted pyranone hemiketals from dioxanorbornanes via SmI_2 is described. Also reported is a synthesis of spiro[4.5]ketals from analogous intermediates via acid-promoted deprotection/ketalization.

Cyclic hemiketals such as **1** (Scheme 1) are ubiquitous components in naturally occurring compounds.[1,2] Elegant studies by Padwa[3] and others[4] have established that dipolar cycloaddition of carbonyl ylids with carbonyl compounds leads to the formation of the dioxanorbornanone nucleus **2**, as outlined in Scheme 1. We now demonstrate a novel approach to the generation of pyranone hemiketal **1** that underscores the utility of dioxanorbornanones **2** in the construction of oxygenated ring systems.

The construction of dipole **3** (R = *n*-C_6H_{13}) is outlined in Scheme 2. Dimethylation of benzyl 3-ketononanoate (NaH, MeI) led to the formation of **5** in 84% yield. The diazoketone **6** could be prepared in a one-pot reaction sequence, via (1) hydrogenolysis of **5** to generate the unstable β-ketoacid, (2) formation of the corresponding mixed anhydride with methyl chloroformate and triethylamine, and (3) reaction of the derived mixed anhydride with diazomethane to give diazoketone **6** in 69% yield from **5**. Reaction of **6** with pivaldehyde in the presence of 5 mol % $Rh_2(OAc)_4$ gave **7** in excellent yield. The assignment of the *exo* orientation of the *tert*-butyl group on the dioxanorbornanone ring system

Scheme 1



(1) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.
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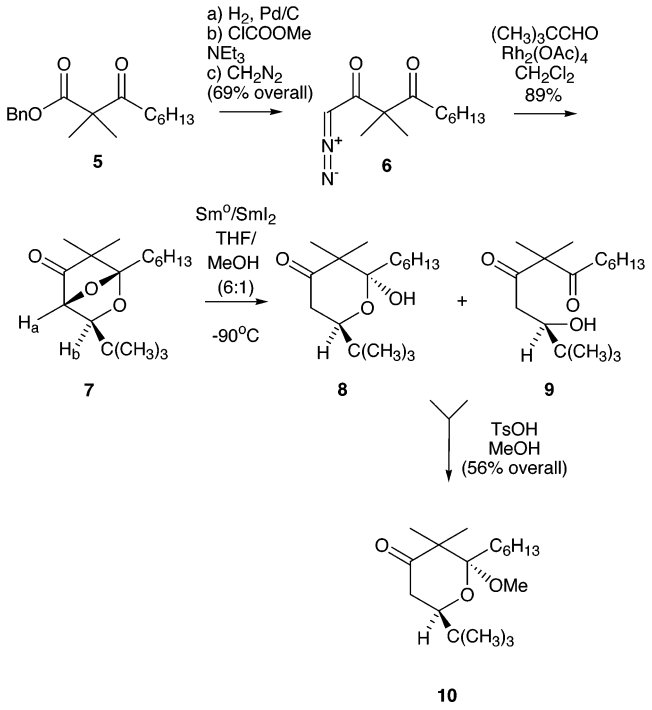
Scheme 2



was based on extensive precedent for related transformations[4] and could be confirmed by ^{1}H NMR analysis, which revealed an absence of coupling between H_a and H_b in **7**, a result that is consistent only with *exo*-cycloadduct **7**.

Exposure of **7** to samarium diiodide (in the presence of samarium metal) in MeOH/THF (1:6) at −90 °C led to the predominant formation of **9**, which corresponds to the opening of the desired hemiketal ring, along with hemiketal **8** (ca. 4:1). Exposure of the mixture of **8** and **9** resulting from the SmI_2 reduction of **7** to TsOH in MeOH gave **10** as the sole product in 56% yield over the two steps (reduction and ketalization). The exclusive formation of **10** is consistent with the anomeric effect,[5] i.e., axial orientation of the methoxy group and equatorial orientation of the *tert*-butyl substituent in **10**, and was confirmed by ^{1}H NMR analysis, in which the cis relative stereochemistry of the methoxy and the methine shown in **10** was established by NOESY.

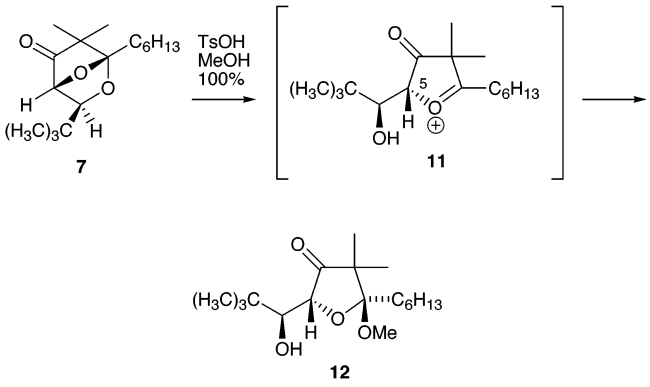
We have also examined acidic hydrolysis of the dioxanorbornanone cycloadduct **7**. Reaction of **7** with TsOH in methanol leads to the quantitative formation of **12**. The stereoselective addition of methanol anti to the C-5 carbinol substituent in oxonium ion **11** proceeds in the same sense as that observed by Veyrières in a closely related system.[6,7]

We reasoned that intramolecular addition of an alcohol moiety to the oxonium ion intermediate **11** derived from **7** would lead to an efficient synthesis of spirocyclic ketals.[8] The preparation of the key intermediate **15** is shown in

(5) Beaulieu, N.; Dickinson, R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531−2536.

(6) (a) Jaouen, V.; Jégou, A.; Lemée, L.; Veyrières, A. *Tetrahedron* **1999**, *55*, 9245−9260. (b) Goursaud, F.; Peyrane, F.; Veyrières, A. *Tetrahedron* **2002**, *58*, 3629−3637.

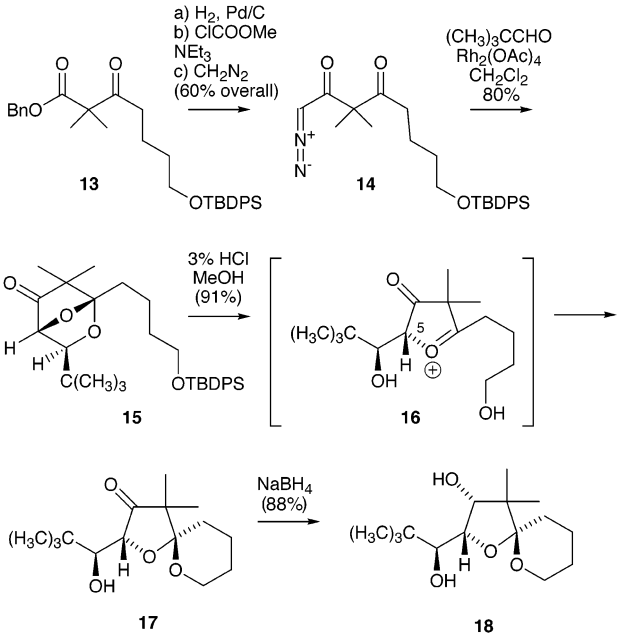
Scheme 3



Scheme 4. Subjection of **13** to the same reaction conditions employed for the formation of **6** (Scheme 2) led to the formation of dipole precursor **14**. Reaction of **14** with pivaldehyde in the presence of $Rh_2(OAc)_4$ led to the synthesis of **15** in excellent yield. Treatment of **15** with 3% methanolic HCl led to the exclusive formation of **17**. The stereoselectivity of the cyclization of **15** can be attributed to the addition of the hydroxybutyl group anti to the C-5 carbinol substituent in the oxonium ion intermediate **16**. The stereochemistry of **17** was confirmed by reduction to the corresponding α-alcohol **18**, the structure and stereochemistry of which was established by X-ray crystallographic analysis.

We have demonstrated that dioxanorbornanone cycloadducts can be selectively transformed into pyranone hemiketals and furanone-based spiroketals, respectively. The application of this methodology to the synthesis of oxygenated ring systems is currently underway in our laboratory, and our results will be reported in due course.

Scheme 4



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Supporting Information Available: Spectroscopic data and experimental procedures for the preparation of **5**−**18** and X-ray data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For the addition of carbon nucleophiles 5-substituted tetrahydrofuran-based oxonium ions, see: (a) Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339−6342. (b) Schmitt, A.; Reissig, H. *Synlett* **1990**, 40−42. (c) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747−8756. (d) Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675−3686.

(8) For the synthesis of spirocyclic ketals via intramolecular capture of a tetrahydropyrilium ion, see: Keller, V. A.; Martinelli, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467−470.