BICYCLIC KETALS. A TANDEM OXYMERCURATION-SOLVOMERCURATION PROTOCOL

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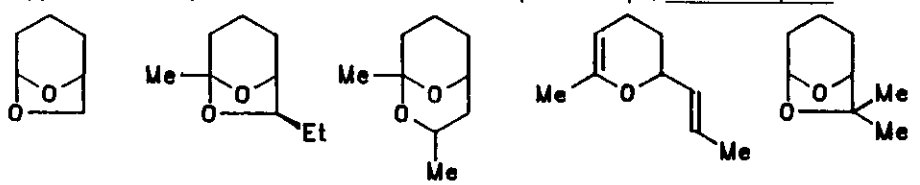
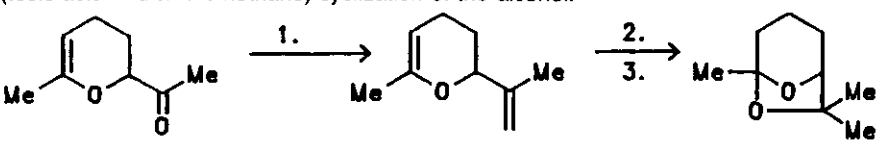
Abstract Oxymercuration of an enol ether takes place faster than oxymercuration of an isolated alkene. When both functional groups are present in the same molecule, one can use a properly oriented hydroxyl group fixed from the oxymercuration process to participate in a solvomercuration of the second site. This **tandem oxymercuration-solvomercuration** protocol was applied to the synthesis of two natural products in the 6,8-dioxabicyclo[3.2.1]octane series.

Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane series, (**1**), have been a focus of research from our group. We recognized the possibility that pheromones (**2**)[1] and (**3**)[2] might be assessable from a common intermediate (**4**) by a tandem oxysolvomercuration reaction. We now report the results of this work and the additional application to a synthesis of **5**, a constituent of Japanese hops, Humulus lupulus.[3]



1 **2** **3** **4** **5**

A model reaction providing credibility to the proposed methodology was found in the conversion of **6** to **8**. Wittig reaction smoothly converted **6** to **7**.[4] Treating **7** with $Hg(OAc)_2$ in aqueous THF, followed by demercuration with NaOH and sodium borohydride provided **8** in 87% yield. The structure of **8** was unambiguously fixed by an independent reaction of **6** with methyl Grignard reagent, followed by acid-catalyzed (tosic acid in dichloromethane) cyclization of the alcohol.

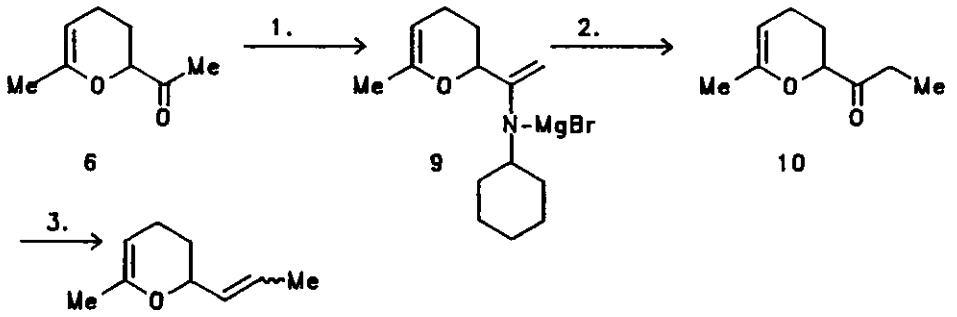


6 **7** **8**

1. $Ph_3P{=}CH_2$ 2. 9.2 g of $Hg(OAc)_2$ in 10 ml of H_2O/ 90 ml of THF, followed by 2 g of 7.

3. 10 ml of 3M NaOH + 10 ml of .5M $NaBH_4$ in 3M NaOH.

We prepared 4 by a route shown in Scheme 1. Treatment of 6 with cyclohexylamine gave 9, which was taken on to 10 using chemistry previously published from our laboratory.[5] Reduction of the enamine of 10 with lithium aluminum hydride/ aluminum chloride gave 4 in 54% yield.



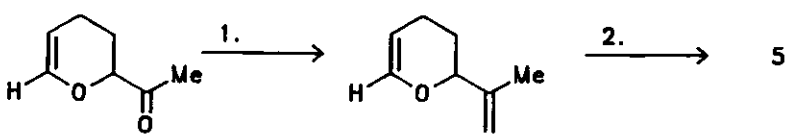
6 9 10 4

1. 20 g of 6 and 14.1 g of cyclohexylamine, 200 ml of benzene to give the imine. MeMgBr (16.8 g) in 150 ml of dry THF, reflux for 5 h. 2. Cool to 0°C, add 20.2 g of MeI; after 24 h hydrolyze with 5% HOAc. 3. 100 ml of benzene, 9.3 g of 10, 4.3 g of pyrrolidine, trace of tosic acid, reflux for 24 h. Distill intermediate enamine (2.1 g, $bp_{0.5mm}$ 103°C. 4. 1.25 g of $LiAlH_4$, 50 ml of Et_2O, 0°C, 1.46 g of $AlCl_3$, 2.1 g of enamine, reflux for 48 h. Cool to 0°C, cautiously add 20 ml of 5% HOAc, chromatograph on silica gel using hexane/ether (9:1); 750 mg of alkene product. **Hrms:** *calculated for $C_9H_{14}O$, 138.1033; found 138.1039.*

Scheme 1.

Submission of 4 to conditions of the oxysolvomercuration protocol gave no 3; however, 15% of 2 was formed in a 45:55 exo-endo ratio, as determined by glc retention times. In retrospect, formation of 2 over 3 comes as no surprise, since Brown has established the overwhelming preference for formation of the furanyl ring system in solvomercuration processes.[6]

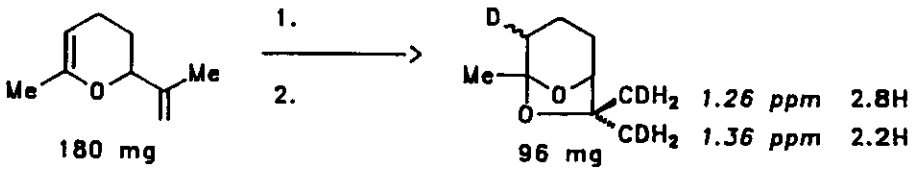
In a similar manner, we carried out the synthesis of 5. Wittig reaction converted the known methyl ketone, (11), to 12. Tandem oxymercuration-demercuration, followed by tosic acid cyclization, gave 5, compared to a sample prepared from an unambiguous synthesis.[3b]



11 12

1. $MeP^+(Ph_3)\ Br^-$ (15.1 g), n-BuLi, THF/Et_2O (1:4), 4.1 g of 11, 21% yield after chromatography (silica gel, pentane/EtOAc, 9:1) 2. $Hg(OAc)_2$ (1.7 g) in 10 ml of H_2O; 314 mg of 12, 45 min, room temperature, then 105 mg of $NaBH_4$ in 4 ml 5% NaOH; tosic acid, 15% yield.

The reactions do provide a new entry to bicyclic ketals; however, this protocol appears to have no advantage over traditional methods. Based on the preferred conformations of the reactant molecules, there should be little facial preference for initial oxymercuration of the enol ether. The question of selectivity of mercuration of the isolated alkene was readily answered by subjecting 7 to conditions of the oxysolvomercuration reaction; followed by demercuration with $NaBD_4$. The C-7 methyl groups both showed incorporation of deuterium, in the approximate ratio of 55:45 (endo:exo), as determined by integration of the proton nmr spectrum.



1. 914 mg of $Hg(OAc)_2$, 2 ml of H_2O, 0.4 ml of THF, 100 mg of 7 in 1 ml of THF, 30 min, room temperature.

2. 55 mg of $NaBD_4$ in 1 ml of 5% NaOH.

ACKNOWLEDGMENTS

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