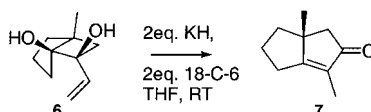# The First Reported Anionic Oxy Retro-Ene Reaction

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ABSTRACT

Treatment of the diol **6** with KH and 18-C-6 at room temperature gives the cyclopentenone **7** in good yields. Mechanistic analysis reveals that this is the first case of an anionic oxy retro-ene reaction followed by a tandem intramolecular aldol condensation.

The synthetic utility and application of ene and retro-ene reactions has been extensively documented.[2] Recently, the accelerating effect of alkoxides on concerted reactions has attracted considerable attention, with particular interest being focused on the ene reaction. The first successful examples of anionic oxy-ene reactions were reported earlier this year by Schmid and Borschberg.[3] Cohen et al. also applied the alkoxide accelerating effect of the metallo-ene reaction to a synthesis of (±)-Matatabiether.[4] In addition, a presumed alkoxide-assisted retro-ene reaction was reported by Murray et al. but was reconsidered on the basis of mechanistic studies of deuterated analogues and calculations.[5] In this communication, we report the first example of an anionic oxy retro-ene reaction followed by an intramolecular aldol condensation.

To model the key anionic oxy [1,3] sigmatropic shift to set the *cis*-ring juncture of the C and D rings of ouabain, we prepared the diol **6** from the well-known enoate **1** (Scheme 1).[6] The ester was reduced to the diol **2** quantitatively with

Scheme 1
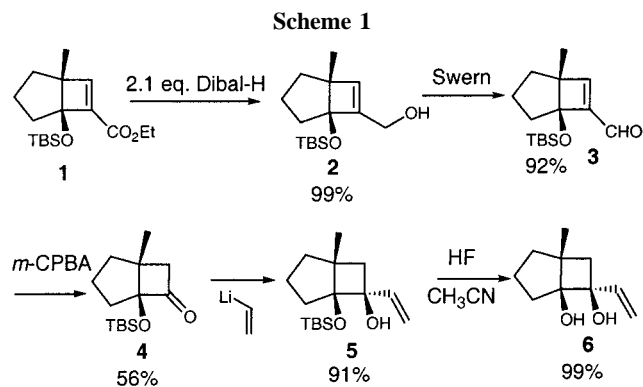
2.1 equiv of DIBAL-H and further oxidized to the enal **3** in 92% yield using Swern conditions. Oxidation of the aldehyde to the formate with recrystallized *m*-CPBA and catalytic amounts of sulfuric acid, followed by hydrolysis upon aqueous workup, yielded the desired ketone **4** in 56% yield. Unexpectedly, addition of vinyllithium occurred predominantly from the concave face of the molecule, furnishing the tertiary alcohol **5** in 91% yield. The tertiary silyl ether resisted deprotection under normal conditions but was removed easily upon treatment with concentrated HF·CH$_3$-CN to give the *cis*-diol **6**.[7]

(1) 2000−2001 American Chemical Society Division of Organic Chemistry Graduate Fellow, sponsored by DuPont Pharmaceuticals, Inc.

(2) (a) Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1992**, *57*, 1904. (b) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (d) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (e) Alder, K.; Pascher, F.; Schmitz, A. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 27.
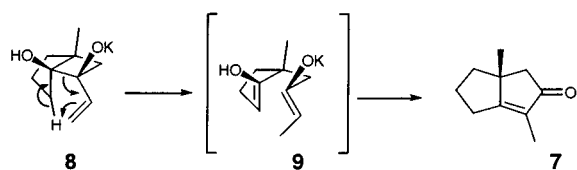
(3) Schmid, G. A.; Borschberg, H. J. *Helv. Chim. Acta* **2001**, *84*, 401.

(4) Cheng, D.; Zhu, S. R.; Yu, Z. F.; Cohen, T. *J. Am. Chem. Soc.* **2001**, *123*, 30.

(5) Murray, W. V.; Turchi, I. J.; Bussolari, J. C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2715.

(6) (a) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248. (b) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1992**, *33*, 3879.

Treatment of the *cis*-diol **6** with 2 equiv of iodine-pretreated potassium hydride[8] and 18-crown-6 did not yield the desired [1,3] sigmatropic shift product but rather the known cyclopentenone **7**. This known compound is presumably formed by an intramolecular aldol condensation of the corresponding dione, which must presumably be formed during the treatment of the diol **6** with base. The proposed mechanism as shown in Scheme 2 is that the alkoxide **8** undergoes a facile anionic oxy retro-ene reaction, which yields the enol enolate **9** (although Scheme 2 shows the reaction proceeding through a monoanion, the intermediacy of a dianion cannot be ruled out), which is perfectly set up for the postulated intramolecular aldol condensation.

To demonstrate the alkoxide accelerating effect we submitted the *cis*-diol **6** to a week of refluxing in deuterated toluene only to recover the starting material intact. For further evidence of the retro-ene mechanism we then explored deuterium-labeling experiments, reasoning that if the hydrogen being transferred was replaced by a deuterium atom, it should therefore be easily detected on the allylic methyl. The deuterium labeling experiment began with the ketone **10** prepared from alkylation of the thermodynamic enolate, as we have previously described (Scheme 3).[9] Treatment of the

Scheme 3
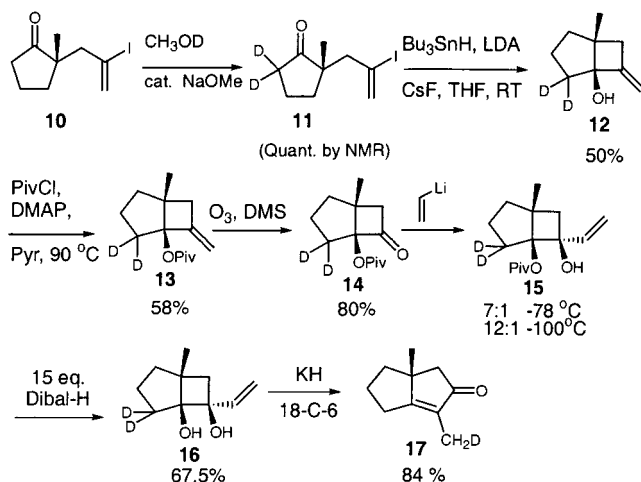
ketone with catalytic amounts of sodium methoxide in deuterated methanol gave by NMR a quantitative yield of

the deuterated product **11**. Using our previously reported conditions, we were able to obtain the strained cyclic product **12** in reasonable yields.[9] Protection of the tertiary alcohol with pivalic anhydride and DMAP in pyridine yielded the pivaloate **13**. Ozonolysis followed by reductive workup produced the ketone **14** in 80% yield. Addition of vinyllithium at −100 °C again occurred mainly from the concave face to give a mixture of alcohols in a 12:1 ratio affording the alcohol **15** as the major isomer. Removal of the pivaloate protecting group was accomplished by subjecting it to 15 equiv of DIBAL-H,[10] thus procuring the desired deuterated substrate **16** in 67.5% yield.

Treatment of the diol **16** under identical conditions as reported previously gave predominantly the monodeuterated cyclopentenone **17**.[11] We observed predominantly the mono-deuterated product presumably because the remaining deuterium is lost by deprotonation−reprotonation by the excess base during the reaction. Mass spectrometry reveals the presence of both the mono- and bisdeuterated products. These findings provide strong evidence to support our proposed mechanism.

Although it is highly likely that the reaction follows the suggested pathway, it was nevertheless an interesting prospect to try to isolate the simple retro-ene product rather than the ensuing aldol product. Under basic conditions the tandem aldol condensation is inevitable. However, if one could effect the reaction thermally, one could theoretically isolate the neutral intermediate without a competing pathway. As reported above, the thermal retro-ene did not occur when the *cis*-diol **6** was refluxed in toluene for a week. A survey of the literature reveals that thermal retro-ene reactions tend to occur between 180 and 400 °C.[12] However, if the migrating hydrogen comes from an oxygen atom rather than a carbon, then the transition state is significantly lowered, and rearrangement can occur in the 130 °C range.[13] Combination of this effect with the strain release of a cyclobutan lowers the temperature for the reaction to occur to the 40−60 °C range.[14]

To drive the thermal retro-ene at a reasonable temperature, the *trans*-diol **19** was therefore required. Many analogues of the ketone **4** were prepared by changing the protecting group on oxygen. However, even using various protecting groups on oxygen as well as several alkylating reagents, all of our efforts to achieve selective organometallic attack from the convex face proved unsuccessful. The best results were obtained by adding excess vinyllithium to the rapidly equilibrating hydroxyketone **18a**.[9] In this case, the *trans*-diol **19** was obtained in 10% isolated yield, as shown in Scheme 4. The structure of the diol **19** was assigned using NOE experiments, which showed interaction between the vinylic protons and the methyl group, and IR spectroscopy

(7) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(8) Macdonald, T. L.; Natalie, K. J.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124.

(9) Jung, M. E.; Davidov, P. *Org. Lett.* **2001**, *3*, 627.

(10) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

(11) In theory, the reaction requires only 1 equiv of base; however, the yields are poorer and a longer reaction time is required.

(12) Conia, J. M.; Barnier, J. P. *Tetrahedron Lett.* **1971**, 4981.

(13) Wilson, J. W.; Sherrod, S. A. *Chem. Commun.* **1968**, 143.

(14) Barnier, J. P.; Ollivier, J.; Salaun, J. *Tetrahedron Lett.* **1989**, *30*, 2525.

Scheme 4

18a   18b   19

10%

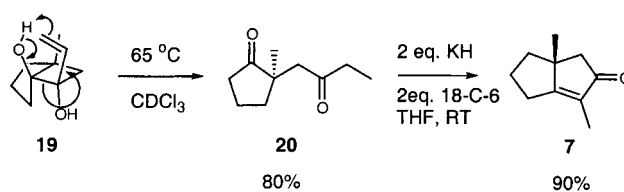**Scheme 5**

19   20   7

80%   90%
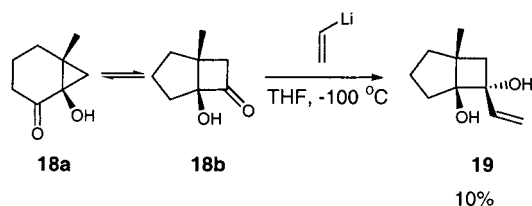
(the diol **19** lacks the sharp hydrogen-bonded hydroxyl stretch present in its epimer **6**).

Heating of the diol **19** in deuterated chloroform produced 80% of the retro-ene product **20** (Scheme 5). Subjecting this newly formed dione to basic conditions would be expected to generate the ketone enolate **9**, which should cyclize via intramolecular aldol condensation as observed in the original anionic oxy retro-ene reaction. Treatment of the diketone **20** with potassium hydride and 18-crown-6 afforded 90% of the cyclopentenone **7**.

Thus, we have observed the first reported alkoxide-accelerated retro-ene reaction of the diol **6**, which ultimately affords the enone **7** via intramolecular aldol condensation of the dione **20**.

Supporting Information Available: 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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