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DOUBLE HYDROXYLATION OF ENOL SILYL ETHERS. A SINGLE-STEP SYNTHESIS OF α, α'-DIHYDROXY KETONES

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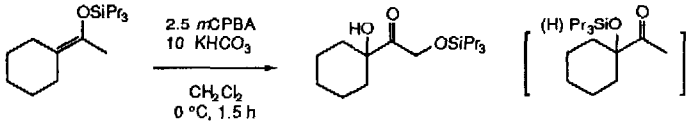
Summary: Oxidation of the more substituted regioisomer of the enol silyl ether of a methyl *sec*-alkyl ketone with 2 equiv of *m*-chloroperbenzoic acid in the presence of $KHCO_3$ gives, after acidic workup, an α,α'-dihydroxylated ketone in high yield. Applications to the synthesis of adrenal hormones and an anthracycline model compound are also described.

Whereas oxygenation of organic compounds represents an important methodology for the synthesis of biologically active compounds, there exist only limited basic repertories for the controlled *poly*oxygenation.[1] We wish to report here an efficient and mild oxidation procedure that creates three contiguous oxygenated carbon centers in a single step. The utility of the reaction has been demonstrated in steroid and anthracycline chemistry.

Since Hassner's initial report in 1975,[2] oxidation of enol silyl ether with peracid has made a reliable method for the preparation of α-siloxy and α-hydroxy ketones. We now have found that, if the enol silyl ether possesses certain structural features, the reaction affords α,α'-dihydroxylated ketones (i.e., introduction of two oxygen atoms in a single-step) instead of the expected monohydroxylated compounds.

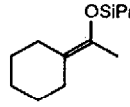
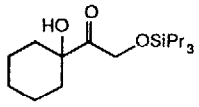
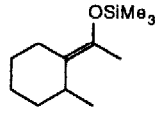
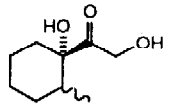
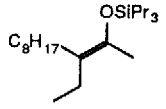
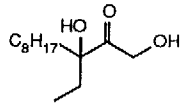
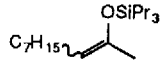
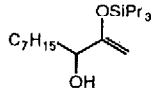
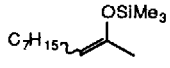
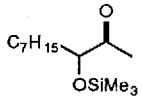
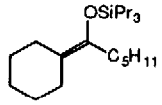
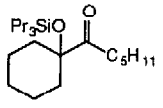
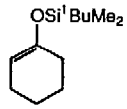
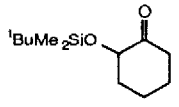
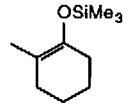
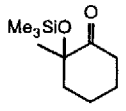
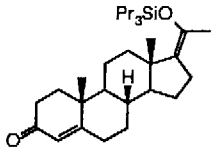
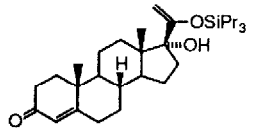


(1)

1 2 3

A typical example is shown in eq 1. When a mixture of the enol silyl ether **1** and finely powdered dry $KHCO_3$ (10 equiv) in methylene chloride was treated with ca. 2.5 equiv of *m*-chloroperbenzoic acid (mCPBA) at 0 °C (added during 1.5 h as a methylene chloride solution), hydroxy siloxy ketone **2** was obtained in 72% isolated yield after aqueous (sodium thiosulfate) workup. There was found no trace of the "normal" oxidation product **3**. Upon brief acidic treatment, **2** could be quantitatively converted to the corresponding dihydroxy ketone.

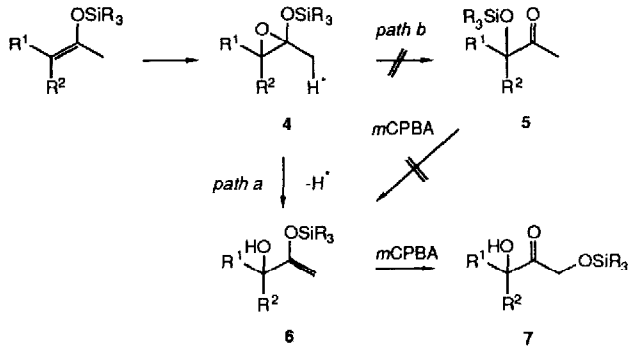
Table I. Double Hydroxylation of Enol Silyl Ethers

entry	substrate	*m*CPBA (equiv)	"abnormal": "normal"	combined %yield	major product
1		2.5	100:0	72	
2		2.5	100:0	79[a]	
3		3.3	100:0	74[a]	
4		1.0	65:35	75	
5		1.0	32:68	94	
6		2.0	25:75	88	
7		2.0	0:100	nd[b]	
8		2.0	0:100	nd[b]	
9	 **8**	1.0	100:0	91	 **9**

[a]Isolated after acidic workup. [b]Not determined. A major portion of the initially monooxygenation product was lost by further oxidation with excess mCPBA

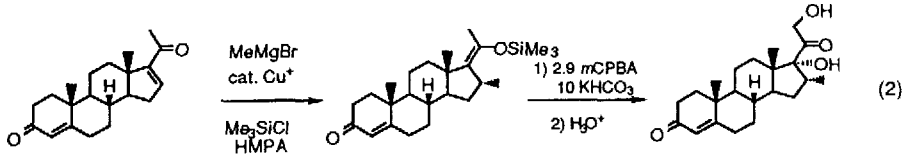
Mechanistic investigations carried out in some depth suggested an interesting reaction pathway (path a, **Scheme I**), in which the rearrangement of an intermediate epoxide **4** to the allylic alcohol **6** (with loss of H*)[3] represents the crucial event. In the normal Hassner reaction (path b), rearrangement of the epoxide **4** to the siloxy ketone **5** proceeds through migration of the silyl group from the enol oxygen to the epoxide oxygen.[2] The inertness of **5** under the present conditions indicated that the "normal" and the "abnormal" pathways are independent reactions. The alcohol **6** has been shown to be the primary product of the reaction by its isolation upon use of only one equiv of the oxidant,[4] and its subsequent conversion to **7** upon addition of another equivalent of the oxidant.

Scheme I



Examples of the double hydroxylation reaction observed for several representative substrates illustrate the scope of this reaction. The "abnormal" pathway is generally preferred by the internal olefinic isomer of the enol silyl ether of methyl alkyl ketones (entries 1-4 and 9), among which that of methyl *sec*-alkyl ketones (entries 1-3 and 9) overwhelmingly prefer the "abnormal" reaction. Choice of the silyl group considerably affects the "normal" vs. "abnormal" ratio: the "abnormal" reaction becomes the favored pathway when bulky *tripropylsilyl* group was used in place of *trimethylsilyl* group (cf. entries 4 and 5). Thus, steric hindrance at the site of the initial oxidation, nature of the site of the proton removal (i.e., H* in **4**), and steric effect of the silyl group all contribute to the balancing of the two pathways.

The example in entry 9, taken from the steroid field, illustrates the strikingly chemoselective, high-yield preparation of enol silyl ether **9** from **8**, which in turn was prepared by regioselective hydrosilation[5] of the bis-enone **10** (94% yield). It is remarkable that the overall sequence realized selective enolization of the C(21) position under almost neutral conditions.

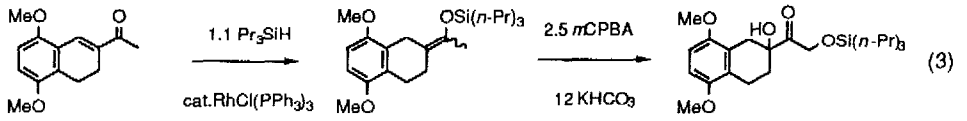


(2)

Finally, we describe the applications of the double hydroxylation reaction to the synthesis of compounds with pharmacological interests. Combined use of the Me3SiCl-accelerated conjugate addition of catalytic

organocopper reagent,[7] and the present double hydroxylation procedure realized rapid construction of pharmacologically important 16-methyl-17,21-dihydroxy structure of corticosteroid.[6,8,9] Thus, the enone **10** was treated with one equiv of MeMgBr in the presence of cat. Cu^+/Me_3SiCl/HMPA, and the resultant silyl ether **11** was oxidized to obtain **12** in nearly quantitative overall yield.[6b]

Another example illustrates the utility in the anthracycline chemistry.[10] The combined hydrosilation/double oxidation sequence converted the enone **13**[11] in 51% overall yield to the compound **14**, which represents a model compound for the adriamycin CD ring portion.[12]



13 **14** 51% overall

References and Notes

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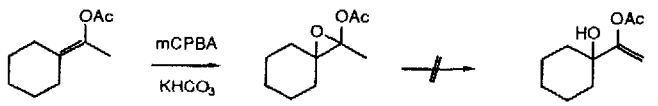

15 **16** **17**

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12. E.N. thanks CIBA-GEIGY foundation and Iwaki foundation for generous financial support.

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