HIGHLY STEREOSELECTIVE CYCLIZATION OF EPOXYKETONE PROMOTED BY ACID

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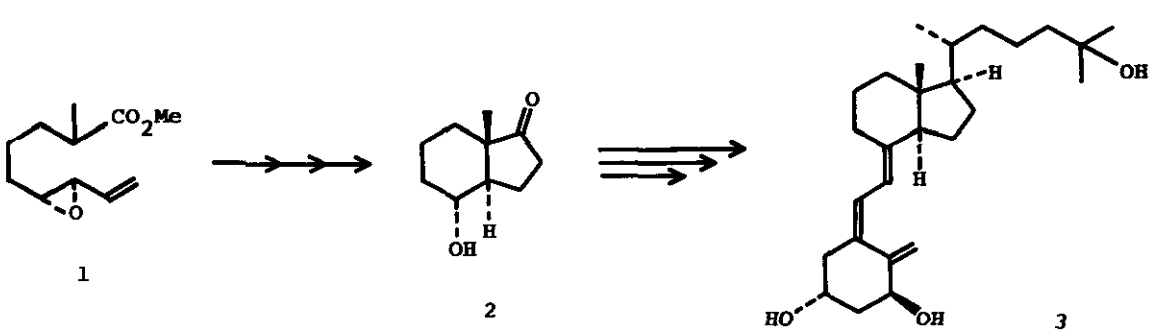
Abstract ——— Epoxidation of the protected allyl alcohol (**8**) with m-chloroperbenzoic acid provided the unexpected 1-oxa-bicyclo[3.2.0^{3,6}]heptane (**11**) along with the corresponding epoxyketone (**10**) which was easily converted to (**11**) by acid.

Intramolecular ring opening of epoxides by carbanions is a well established method for the synthesis of functionalized cycloalkanes, particularly for three to six-membered ring.[1] Extensive studies on this reaction had been done by Stork and co-workers[2] and concluded that regioselectivity in the ring opening of the non-terminal epoxides with equal degree of substitution at the electrophilic carbons was generalized to yield always the smaller ring.

Stork also reported reverse ring opening of the epoxides (1) by simply

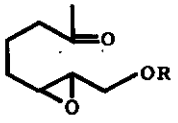


1 2 3

introduction of the double bond at the end of the oxirane ring to provide the highly substituted ring with excellent stereoselectivity and demonstrated its usefulness by the synthesis of angularly methylated hydroxy-trans-hydrindanone (**2**)[3] which had already converted to 1,25-dihydroxy-vitamin D_3 (**3**).[4]

In connection with this work, we have been interested in an intramolecular cyclization of the functionalized epoxyallylsilane (**5**) by Lewis acid. On this reason, we required a preparation of the epoxyketone (**4**) as a precursor of the compound (**5**).

Here we wish to report a facile and unexpected cyclization founded in a synthetic process of the compound (**4**).



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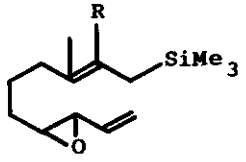

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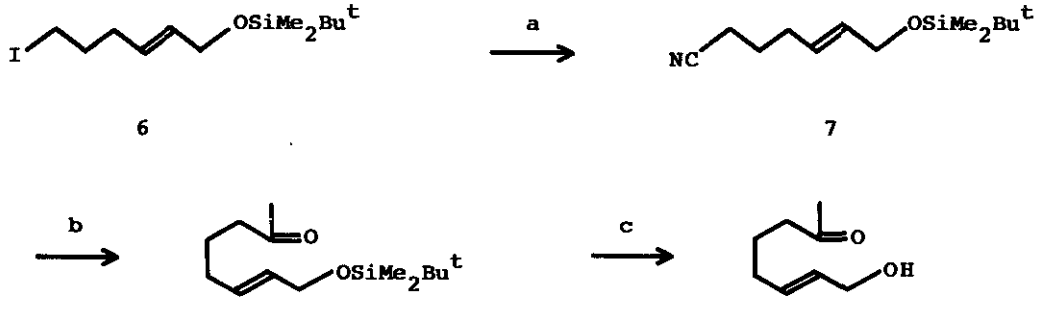
Thus, a treatment of the known iodide (**6**)[3] with sodium cyanide in dry dimethyl-sulfoxide at room temperature afforded the protected cyanoallyl alcohol (**7**) in 80.1% yield. Deprotection of the tertiary butyldimethylsilyl group of (**8**) obtained, in 75% yield, from Grignard reaction of (**7**) with methylmagnesium bromide in dry dimethoxyethane provided the allyl alcohol (**9**) in 80% yield.

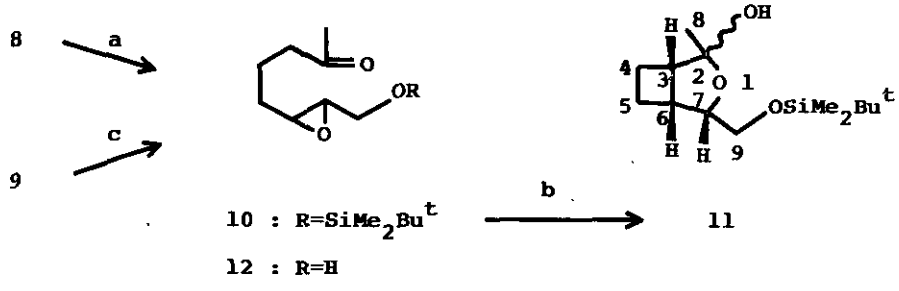


6 **7**

8 **9**

a) 1.2 eq. NaCN, dry DMSO, r.t., 3 h; b) 3 eq. MeMgBr, dry dimethoxyethane, 0° reflux; c) cat. p-TsOH, MeOH, r.t., 2.5 h

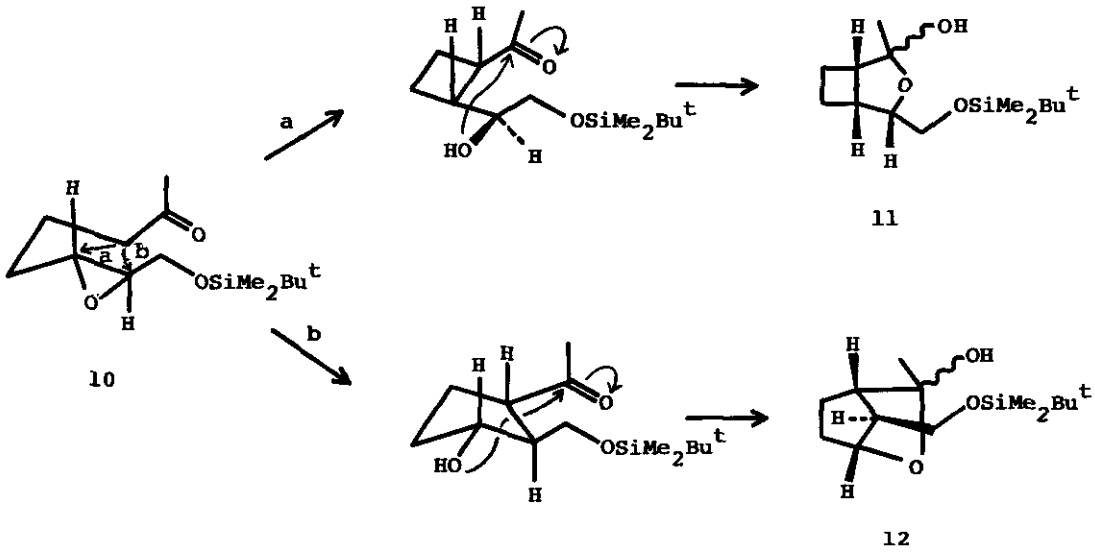
Epoxidation of the protected allyl alcohol (**8**) with m-chloroperbenzoic acid in the presence of sodium carbonate provided the unexpected compound (**11**)[5] which revealed a signal due to methyl group at 1.43 ppm in nmr spectrum and showed no carbonyl absorption in ir spectrum along with the corresponding epoxide (**10**) in 25.0 and 58.4% yield, respectively. At this stage, we assumed that an intramolecular ring closure promoted by acid of the epoxyketone (**10**) obtained in epoxidation would provide the compound (**11**). Thus, a reaction of the epoxide (**10**) with benzoic acid proceeded smoothly to afford the cyclized product (**11**) in 87.4% yield as we expected. On the other hand, epoxidation of the allyl alcohol (**9**) under almost the same condition as that in (**8**) gave only the corresponding epoxide (**12**) in 80.5% yield.



a) 2 eq. MCPBA, 1 eq. $NaHCO_3$, r.t., 18 h; b) 2 eq. benzoic acid, $CHCl_3$, r.t., 30 h; c) 2 eq. MCPBA, 1 eq. $NaHCO_3$, r.t., 2.5 h

The possible reaction mechanism of the formation of (**11**) is shown in the following scheme. Feasibility of the compound (**12**) which might be produced through path (**b**) could be easily excluded by the decoupling experiment of ^1H nmr in (**11**) where methine proton at C_7 coupled with methylene protons at C_9.

Thus, acid catalysed cyclization of the epoxyketone described herein is not only limited to producing 4-membered ring with excellent stereoselectivity, but also can be applicable to 5- or 6- membered ring with highly functionalized substituents. Based on this, a stereo and enantioselective synthesis of grandisol and prostaglandins is now under investigation in this laboratory.



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2. G. Stork, L. D. Cama, and D. R. Coulson, J. Am. Chem. Soc., 1974, **96**, 5268; G. Stork and J. F. Cohen, ibid., 1974, **96**, 5270.
3. G. Stork and T. Suzuki, 48th Synposium on Organic Synthesis, Nov., 1985, Tokyo, Abstracts p.39.
4. E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy, and M. R. Uskokovic, J. Am. Chem. Soc., 1982, **104**, 2945.
5. Ir($CHCl_3$) 3400-3466; ^1H nmr ($CDCl_3$, 400 MHz) 0.07 (6 H, s, $Si(CH_3)_2$), 0.89 (9 H, s, $Si(CH_3)_3$), 1.43 (3 H, s, $C(OH)CH_3$), 1.70-1.56 (4 H, m, CH_2CH_2), 1.90-1.77 (2 H, m, CHCH), 3.80 (1 H, dd, J = 10.3 and 8.1 Hz, CHHO), 3.98 (1 H, dd, J = 10.3 and 5.9 Hz, CHHO), 4.13 (1 H, ddd, J = 8.1, 5.9 and 3.1 Hz, CHO); MS Calcd for $C_{14}H_{28}O_3Si$, 272.1807 (M^+). Found 272.1802.

Received, 7th August, 1987