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BIOMIMETIC POLYENE CYCLIZATIONS.[1] PARTICIPATION OF THE TRIMETHYLSILYLACETYLENIC GROUP AS A TERMINATOR AND THE TOTAL SYNTHESIS OF A D-HOMOSTEROID

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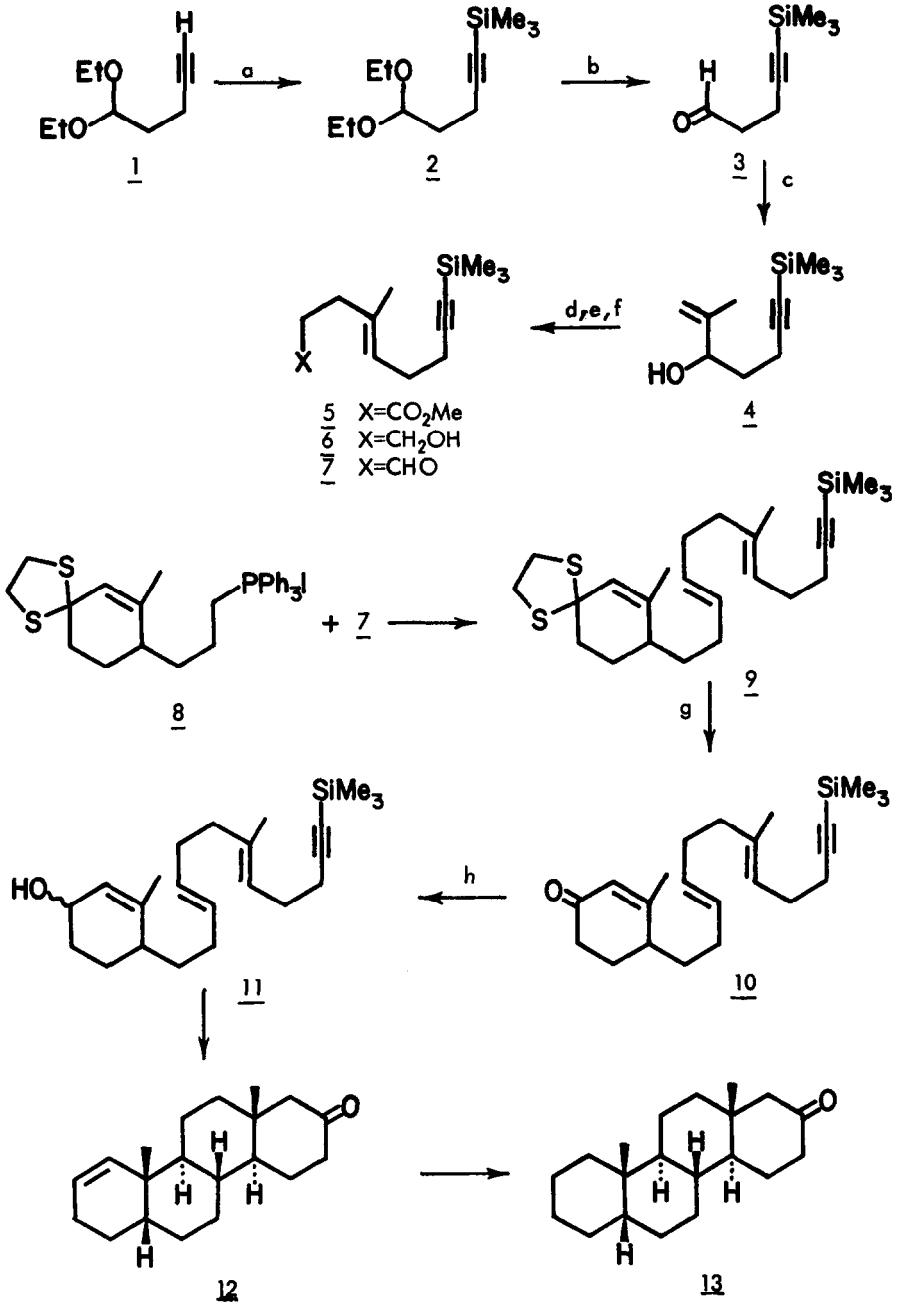
In view of the recent report by Heathcock, et al.,[2] we wish to disclose some of our results, already briefly summarized,[3] relating to the participation of the trimethylsilylacetylenic group in biomimetic polyene cyclizations, namely the conversion of substance 11 into 5β-D-homoandrost-1-en-17-one (12).[4] This behavior is to be compared with that, e.g., the conversion 14 → 15,[5] involving participation of the methylacetylenic end group which induces formation of the five- instead of six-membered D ring.

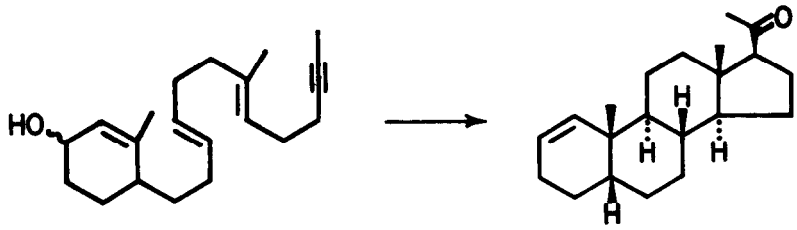
The cyclization substrate 11 was prepared by a convergent synthesis, the key step being the Wittig condensation of the phosphonium salt 8 with the aldehyde 7. The latter was prepared by the sequence shown in the accompanying flow sheet. Thus the known diethoxypentyne 1,[6] on silylation gave a 68% yield of distilled (60°/0.3 mm)[7] product 2.[8] Hydrolysis followed by distillation[7] at 125°/35 mm afforded the aldehyde 3[8] in 89% yield, which, on treatment with isopropenylmagnesium bromide was converted into the allylic alcohol 4, 98% yield after distillation[7] at 70°/0.1 mm. The orthoacetate Claisen reaction[9] with 4 afforded in 95% yield after distillation[7] at 70°/0.3 mm, the ester 5[8] which was reduced to the alcohol 6[8] (100% yield after distillation[7] at 120°/0.1 mm), then oxidized with Collins reagent[10] to the aldehyde 7[8a] (98% yield after distillation[7] at 80°/0.75 mm).

The aforementioned aldehyde 7 was allowed to interact with the phosphorane from the known phosphonium salt 8[11] under conditions for the Schlosser modification[12,11] of the Wittig condensation. The product 9[8] after hydrolysis of the thioketal residue[11] was converted into the enone 10[8] in 58% yield after chromatography (Florisil) and distillation[7] at 155°/7 μ. Analysis of 9 by VPC indicated that the trans/cis ratio of isomers about the newly formed olefinic bond was 95/5. Hydride reduction of the enone afforded the cyclization substrate 11[8] in 95% yield after distillation[7] at 140°/7 μ.

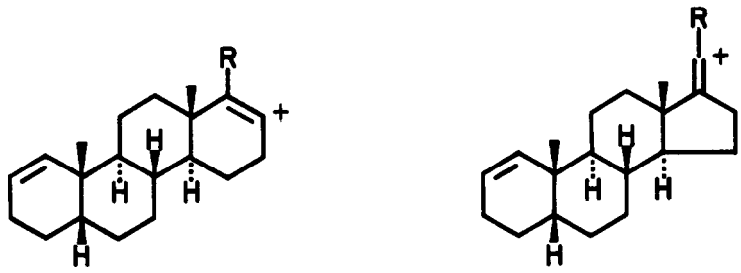


[a] n-BuLi, -78°, $(CH_3)_3SiCl$; [b] 1:5 5% HCl:THF, 3 hrs., 25°; [c] 1.5 mol equiv $CH_2=C(CH_3)MgBr$, THF; [d] (to form 5) 3 mol equiv $HC(OCH_3)_3$ containing ca. 12% HOAc, 110°, 12 hrs.; [e] (to form 6) $LiAlH_4$, Et_2O; [f] (to form 7) 6 mol equiv $CrO_3 \cdot 2$ py, CH_2Cl_2, 0.5 hrs., 25°; [g] 4:1 $CH_3CN:H_2O$, 26 mol equiv CH_3I, 40°, 19 hrs.; [h] $LiAlH_4$, Et_2O, -20°.

A solution of 11 in 1,2-dichloroethane containing 3 mol equiv of ethylene carbonate, was treated with 4.7 mol equiv of trifluoroacetic acid at -20° for 3 hrs.; then the reaction was quenched by the addition of excess aqueous sodium bicarbonate. Preparative TLC followed by two crystallizations from pentane-methanol gave a 52% yield of colorless needles, mp 107-110°C.[8] The constitution of this product was established by hydrogenation over 10% palladium-on-carbon in ethyl acetate which gave, after crystallization from methanol, a 96% yield of colorless plates, mp 98-101°C. This material was shown to be the racemic form of 5β-D-homoandrostan-17-one (13). The NMR and solution IR spectra were identical with the corresponding spectra of authentic (naturally derived) 5β-D-homoandrostan-17-one,[13] and the two samples gave identical response on VPC coinjection experiments.



14 15



A B

The implication of these results is that the cyclization of 11 proceeds so as to form the cation A (R = $(CH_3)_3Si$) rather than B (R = $(CH_3)_3Si$); whereas in the cyclization of 14, formation of the cation B (R = CH_3) is favored over A (R = CH_3). The preference observed when R = CH_3 has been rationalized on the basis of a transition state preference for formation of a linear (B) rather than a bent (A) vinyl cation[1] and/or a steric destabilization of A relative to B due to larger non-bonded interactions between the methylene groups at C-7 and C-15 in the transition state leading to A rather than B.[14] When R = $(CH_3)_3Si$ these effects appear to be overridden by other factors such as, perhaps, the tendency for stabilization of a positive charge in the β rather than the α position to a silicon atom,[15] and a likely steric preference to electrophilic attack of an acetylenic bond at that carbon carrying the bulkier substituent because of the probable angle of approach of reagents to the sp^1 bond.[16]

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References and Notes

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(3) See pp. 90-91, ref. 1.

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(7) The product was submitted to short-path (evaporative) distillation using a Buchi Kugelrohroffen.

(8) (a) The product was of adequate purity for proceeding to the next step and the NMR and IR were consistent with the indicated structure; (b) Satisfactory C,H analyses were obtained on specimens which usually were purified further by chromatography and/or redistillation (ref. 7).

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(15) See inter alia A. W. P. Jarvie, Organometal. Chem. Rev. A, 6, 153-207 (1970); T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton and R. S. Brown, J. Am. Chem. Soc., 93, 5715 (1971); M. A. Cook, C. Eaborn and D. R. M. Walton, J. Organometal. Chem., 29, 389 (1971).

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TERREIN, AN OPTICALLY ACTIVE PROSTAGLANDIN SYNTHON OF FUNGAL ORIGIN. II.[1] CHEMICAL CONVERSION TO 4(R)-ACETOXY-2-CYCLOPENTENONE.

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Synthetic approaches to the prostaglandins are still of high interest because natural sources are unable to supply the projected needs. Recent efforts in several laboratories have been devoted to chiral processes in an effort to avoid wasteful resolution steps. The recent establishment of 4(R)-acetoxy-2-cyclopentenone, 1, by Kurozumi, et al. (Table I) as a prostaglandin synthon by use of a combined chemical-microbiological process is a case in point.[2] Stork, et al. had previously published a prostaglandin synthesis based upon a similarly substituted but racemic intermediate.[3] We wish to report a convenient preparation of the optically active Kurozumi synthon from terrein, 2, a metabolite of Aspergillus fischerii[4-8] which has the correct absolute configuration for prostaglandin synthesis.

Terrein, 2, was converted selectively to its crystalline 5-acetyl derivative, 3, in 75% yield, by warming at 65° for 48 hr. in a THF, acetic anhydride (1 equivalent), sodium acetate (1.5 equivalents) slurry [mp 96.5-97°, $\lambda_{max}^{CHCl_3}$ 278 nm (ε=28,600), m/e 196 (M^+)]. Reduction of 3, in acetone with chromous chloride solution[10,11] afforded 4 as a clear yellow oil in 99% yield [$\lambda_{max}^{CHCl_3}$ 270 nm (ε=17,600); m/e 138 (M^+); pmr_{CDCl_3} 2.3δ(dd, J = 2,20 Hz, 1H, H···C-C=O), 2.8δ(dd, J = 5,20 Hz, 1H, H▶C-C=O), and 5.2δ(dd, J = 5,2 Hz, H▶C-CH_2-C=O)]. Analogous reduction of diacetylterrein tended to remove both acetoxy functions.