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Communication

Participation of the Allylsilane Group as a Terminator of Biomimetic Polyene Cyclizations to Form Steroid-Like Products[1]

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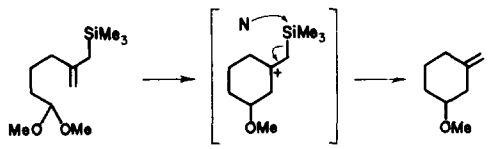
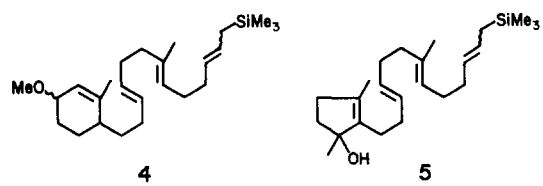
The considerable synthetic utility of the allylsilane group is well documented (*2*). In particular it is attacked regiospecifically by an electrophile at the γ-carbon atom with concomitant elimination of the silyl residue to form an allylically transposed olefinic bond at the α,β position. Only a few cases are on record in which carbon electrophiles are involved in an intramolecular process resulting in cyclizations to form carbocycles (*3*), the first being that of Fleming *et al.* (*3*a), who made the intriguing observation that acid-catalyzed cyclization of the acetal **1** gives olefin **3** via cation **2**.



1 **2** (N = nucleophile) **3**



4 **5**

As a part of our continuing interest in finding improved terminating groups for biomimetic polyene cyclizations, we undertook an investigation to ascertain whether the allylsilane group would serve as an effective terminator of such a cyclization process to form more than one ring, and, if so, whether it would participate so as to produce, with high stereoselectivity,[2] a *trans*-fused five-membered ring system having a steroid-like structure. These questions have now been answered in the affirmative through a study of the synthesis and cyclization of the substrates **4** and **5**, the subject of the present communication.

[1] For recent papers in this series on biomimetic polyene cyclizations, see Ref. (*1*).

[2] In contrast with acetylenic terminators, olefinic types appear to participate in cyclizations with very high stereoselectivity to give *trans*-fused rings characteristic of the C/D ring system of steroids (*1*).

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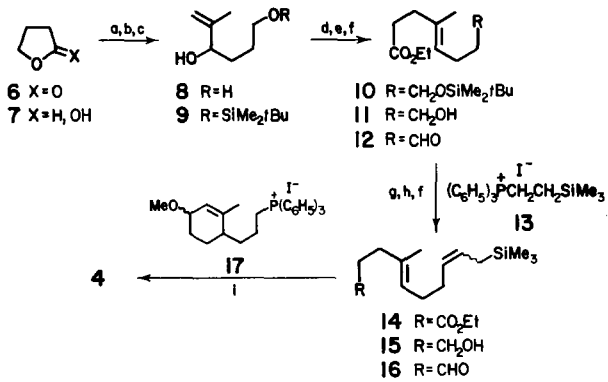


SCHEME 1. (a) 2 mol eq DIBAH, Et_2O–$C_6H_5CH_3$, −70°C, 5 hr; (b) 3 mol eq $CH_2{=}C(CH_3)MgBr$, THF, 5–25°C, 2 hr; (c) 1 mol eq t-$BuMe_2SiCl$, imidazole, DMF, −5°C, 0.5 hr; (d) $CH_3C(OEt)_3$, 0.1% $C_2H_5CO_2H$, 130°C, 1 hr; (e) 1 mol eq $Bu_4N^+F^-$, THF, 25°C, 15 hr; (f) 1.5–2 mol eq $CrO_3 \cdot C_5H_5N \cdot HCl$, CH_2Cl_2, 25°C, 4 hr; (g) **13** + BuLi, THF, 0°C, then +**12** at −70°C, 1 hr; (h) excess $LiAlH_4$, Et_2O, 25°C, 2 hr; (i) **17** + C_6H_5Li, THF, 0°C, 1 hr, then +**16** at −70°C, 1 hr, then +2.5 mol eq $C_6H_5Li \rightarrow$ 0°C, 2 hr, then +EtOH at −70°C.

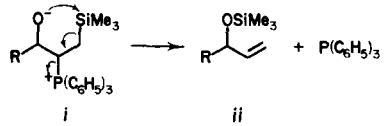
The cyclohexenyl substrate **4** was synthesized in a convergent manner as shown in Scheme 1, the key step being a Wittig reaction between the aldehyde **16** and the phosphorane derived from the phosphonium salt **17**. The synthesis of the aldehyde **16** began with the reduction of γ-butyrolactone (**6**) with diisobutylaluminum hydride (cf. (*4*)) to form 2-hydroxytetrahydrofuran (**7**).[3] Treatment of lactol **7** with excess of isopropenylmagnesium bromide gave the diol **8**[4d,5] (90%), which on reaction with 1 mol eq of t-butyldimethylsilyl chloride (*6*) afforded the monosilyl ether **9**[4d,5] (89%); this in turn underwent a smooth Claisen orthoester reaction (*7*) to give the ester **10**[4d,5] (89%, 97.5:2.5 (E)/(Z) mixture by vpc). Desilylation (*6*) of this product gave the ester alcohol **11**[4d,5] (85%), which was oxidized (*8*) to the corresponding ester aldehyde **12**[4d,5] (73%). Condensation of **12** with the phosphorane derived from the known phosphonium salt **13** (*9*) produced the allylsilane **14**[4a,d,5a] (88%).[6] The Wittig product **14**

[3] This product consisted of a 96:4 mixture of hemiketal and γ-hydroxyaldehyde tautomers in carbon tetrachloride (nmr); cf. (*5*).

[4] The product was purified by (a) chromatography on Florisil, (b) chromatography on alumina, (c) chromatography on silica gel, and (d) distillation at reduced pressure in a short path distillation apparatus or in a Kugelrohr using a Büchi Kugelrohrofen.

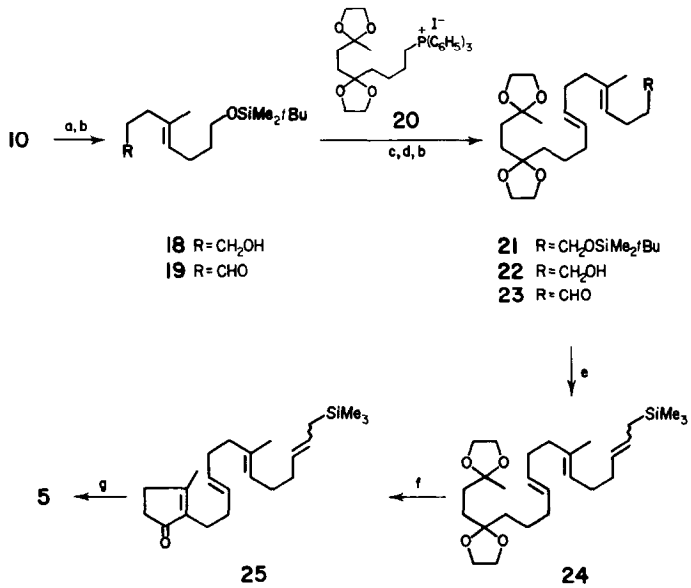
[5] (a) The nmr and ir spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for this compound.

[6] A contaminant in this product as well as in that from the analogous Wittig reaction with aldehyde **23** (to give **24**; see Scheme 2) was the silyl ether of type *ii* (**14**/*ii* = 5:1 and **24**/*ii* = 9:1, respectively, by vpc). The formation of silyl ether *ii* can be rationalized by an internal elimination in the intermediate betaine *i*. The proposed mechanism is supported by the detection of triphenylphosphine in the reaction mixture.



i *ii*

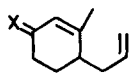
was converted to the key aldehyde **16**[4d,5a] (in 51% overall yield) by hydride reduction to give **15**[4a,5a] followed by oxidation (*8*). The aldehyde **16** was condensed with the phosphorane formed from the phosphonium salt **17** (*10*), (65:35 mixture of epimers),[7] using the Schlosser (*11*, *12*) modification of the Wittig reaction, to give in 64% yield the cyclization substrate **4**[4a,5a] ($\Delta^{\text{pro-C-8,9}} \geqslant 90\%$ (E) by vpc).



SCHEME 2. (a) Excess $LiAlH_4$, Et_2O, 5°C, 2 hr; (b) 6 mol eq $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 25°C, 0.5–4 hr; (c) **20** + C_6H_5Li, THF, 25°C, 0.3 hr, then +**19** at −70°C, 0.5 hr, then +2 mol eq $C_6H_5Li \rightarrow$ 0°C, 0.1 hr, then +MeOH at −70°C; (d) 2 mol eq $Bu_4N^+F^-$, THF, 25°C, 2 hr; (e) **13** + BuLi, THF, 0°C, 0.2 hr, then +**23** at −70°C, 1 hr, then 25°C, 1 hr; (f) 0.4% pTsOH, 5% H_2O–$(CH_3)_2CO$, 25°C, 48 hr; then 2% aqu. NaOH–EtOH–THF (4:2:5), 70°C, 5 hr; (g) excess MeLi, Et_2O, 0°C, 0.2 hr.

The synthesis of the cyclopentenyl substrate **5** (Scheme 2) followed similar lines except that the order of the two Wittig reactions was reversed. The aldehyde **19**[4d,5] was obtained in 92% yield from ester **10** by hydride reduction followed by oxidation (*13*) of the alcohol **18**.[4d,5] Condensation of aldehyde **19** with the phosphorane derived from the known phosphonium salt **20** (*14*) according to the Schlosser (*11*, *12*) modification of the Wittig reaction afforded bisketal **21**[4b,5] (77%) as a 98:2 (E)/(Z) mixture

[7] This substance was synthesized by a scheme similar to that used for the preparation of the known phosphonium salt **17** (–$S(CH_2)_2S$– instead of CH_3O–, H) (*11*), except that the thioketalization step of the intermediate *iii* (X = O) was replaced by reduction with lithium tetrahydridoaluminate (to give *iii*, X = OH,H) followed by etherification with iodomethane and sodium hydride (to give *iii*, X = CH_3O,H; 65:35 mixture of epimers by vpc).



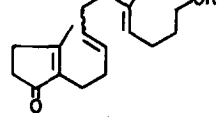
iii

(by vpc) about the newly formed disubstituted double bond.[8] Desilylation (*6*) gave the alcohol **22**[4a,5] (97%) which was oxidized (*13*) to aldehyde **23**[4d,5] (90%). Wittig reaction between this aldehyde and the phosphonium salt **13** (*9*) introduced the allylsilane residue to provide bisketal **24**[4b,5] in 87% yield.[6] Hydrolysis to the corresponding dione followed by base-catalyzed cyclodehydration gave the cyclopentenone **25**[4a,5] (87%). Treatment of this ketone with an excess of methyllithium produced the tetraenol **5**, which was subjected immediately to cyclization without purification.

The substrates **4** and **5** underwent smooth cyclizations upon addition to 0.5–2% solutions (v/v) of trifluoroacetic acid in dichloromethane maintained at −45 to −35°C[9] to give mainly nonpolar hydrocarbons (single spot by tlc) and some polymeric material. Thus cyclization of the cyclohexenyl substrate **4** afforded DL-5β-pregna-1,20-diene (**26**)[4c,5a] in 66% yield as a 1 : 1 mixture (by vpc) of the 17α and 17β epimers. Cyclization of the tetraenol **5** gave in 83% yield the diene **29**[4c,d,5] as a 47 : 53 mixture (by vpc) of the 17α and 17β epimers. Only small amounts of by-products ($\leqslant$10% of total of volatile products by vpc in the crude product mixture from cyclization of **4**, $\leqslant$5% in the cyclization of **5**) were formed, thus indicating a highly regio- and stereoselective course of the cyclization.[10] Lewis acids may also be used to induce cyclizations. Thus, addition of substrate **5** to a 2% solution of stannic chloride in dichloromethane at −45°C or to a 1% solution of stannic chloride in nitromethane–dichloromethane (4 : 1) at −30°C resulted in formation of **29**[4c,4d] (1 : 1, 17α/17β epimeric mixtures) in 56 and 67% yields, respectively. Similar treatment with a 2.5% solution of boron trifluoride etherate at −40°C afforded **29**[4c,d] (1 : 1 epimeric mixture) in 72% yield.

The structural assignment of the dienes **26** and **29** is based on their spectroscopic properties (ir, nmr)[11] and on their chemical interrelation with authentic specimens (Scheme 3). Hydrogenation of **26** over palladium gave DL-5β-pregnane (**27**)[5a] as a 17α/17β epimeric mixture. One of the epimers was shown to be identical (by vpc coinjection and nmr) with an authentic sample of 5β,17β-pregnane (17β-**27**) prepared

[8] In order to ascertain the (E)/(Z) ratio the bisketal **21** was converted to the cyclopentenone derivatives *iv* (R = H or $SiMe_3$) by acid-catalyzed deketalization (with simultaneous silyl ether cleavage) followed by base-catalyzed cyclodehydration and finally silylation with *N,O*-bis(trimethylsilyl)acetamide. Analyses by vpc showed *iv* (R = H or $SiMe_3$) to be 98 : 2 (E)/(Z) mixtures of the disubstituted double bond. For comparison and proof of the configurational assignment, a normal Wittig reaction between **19** and **20** was carried out and the resulting bisketal **21** converted to the derivatives *iv* (1 : 4 (E)/(Z) mixtures by vpc).

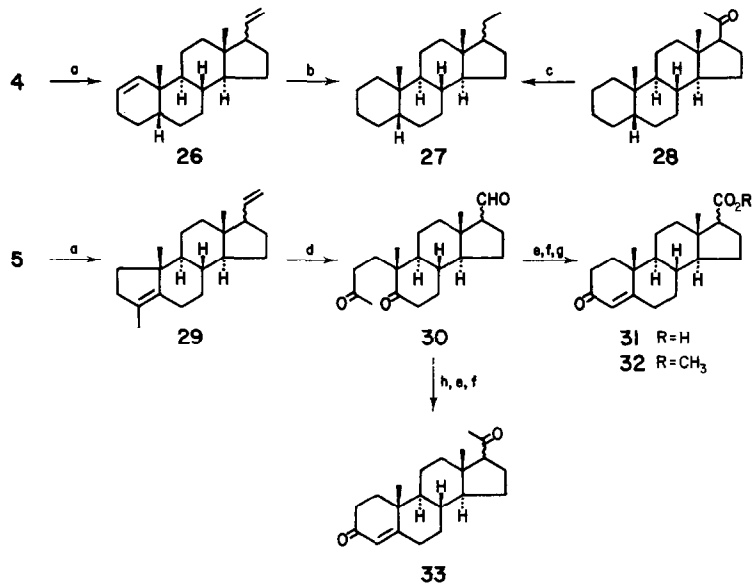


iv

[9] See Ref. (*1*a) for a more detailed procedure.

[10] The cyclization may indeed be completely regio- and stereoselective as the small amounts of by-products may have arisen from isomeric contaminants in the substrates **4** and **5**.

[11] The most characteristic spectroscopic properties are the absorptions of the terminal vinyl groups (ir (film), 3080, 1635, 1000, and 915 cm^{-1}; ^{1}H-nmr (100 MHz, $CDCl_3$), 4.65–5.0 ppm (**26**) and 4.75–5.1 ppm (**29**), terminal vinyl protons) and the ^{1}H-nmr singlet absorptions of the methyl groups (**26**, 0.94 ppm (3H–C(19)); 0.72 and 0.52 ppm (3H–C(18) from 17α and 17β epimers); **29**, 1.57 ppm (vinylic methyl group); 0.90 (3H–C(19)), 0.81 and 0.61 ppm (3H–C(18) from 17α and 17β epimers).



SCHEME 3. (a) 0.5–2% CF_3CO_2H, CH_2Cl_2, −45 to −35°C, then NaOH–CH_3OH; (b) H_2, 10% Pd/C, CH_3CO_2Et, 25°C, 24 hr; (c) HS–$(CH_2)_2$–SH, CH_3CO_2H, $BF_3 \cdot Et_2O$, 25°C, 1 hr, then Raney–Ni, EtOH, 78°C, 1 hr; (d) O_3, 1% C_5H_5N–CH_2Cl_2, −70°C, then Zn, CH_3CO_2H, 25°C, 0.5 hr; (e) $CrO_3 \cdot H_2SO_4$, $(CH_3)_2CO$, 0°C, 0.25 hr; (f) 2% aqu. NaOH–EtOH–THF (4:2:5), 70°C, 4 hr; (g) CH_2N_2, CH_2Cl_2–Et_2O, 0°C, 0.2 hr; (h) 2 mol eq Me_2CuLi, Et_2O, −20°C, 0.1 hr.

by Raney nickel desulfuration of the ethylene thioketal of ketone **28** (*15*). Ozonolysis of diene **29** (reductive processing) afforded crude diketoaldehyde **30**[5a] in 90% yield. Oxidation (*16*) of the aldehyde function and subsequent base-catalyzed cyclodehydration of the diketone moiety produced the carboxylic acid **31**[5a] (95%, 1:1 epimeric mixture by nmr), which was further converted with diazomethane into the methyl ester **32**[5a] (1:1 epimeric mixture by vpc and nmr). The epimer with the longer vpc retention time was shown to be identical (by vpc-coinjection and nmr) with an authentic sample of ester 17β-**32** prepared from naturally derived acid (+)-17β-**31**. The structural assignment for the 17α epimer was confirmed by calculations of ^{1}H-nmr chemical shifts according to Zürcher (*17*).[12] Moreover this epimer was shown to have identical vpc behavior (coinjection) with the minor component of a 5:95 mixture of 17α- and 17β-**32**, which was obtained by partial epimerization of the authentic acid (+)-17β-**31** (in refluxing acetic anhydride-pyridine) and subsequent esterification. Alternatively the diketoaldehyde **30** was converted in 44% overall yield into DL-progesterone (**33**)[4a,5a] (3:7, 17α/17β epimeric mixture) by a sequence of selective addition of lithium dimethylcuprate to the aldehyde group (*18*), oxidation (*16*) of the resulting secondary alcohol and finally base-catalyzed cyclodehydration of the unaltered diketone moiety. A vpc and nmr comparison of this synthetic material with a 2:8 mixture of 17α- and 17β-progesterone obtained by base-catalyzed equilibration of an authentic sample of progesterone revealed their identity.

[12] The calculated chemical shifts for the angular methyl groups of **32** were in excellent agreement with the observed absorptions (3H–C(18), calc. 0.925 and 0.717 ppm, obs. 0.92 and 0.71 ppm for 17α- and 17β-**32**; 3H–C(19), calc. 1.192 and 1.201 ppm, obs. 1.19 ppm).

ACKNOWLEDGMENTS

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