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THE CARBOALKOXYALLYLSILANE TERMINATOR FOR BIOMIMETIC POLYENE CYCLIZATIONS. A ROUTE TO 21-HYDROXYPROGESTERONE TYPES

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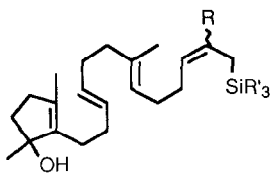
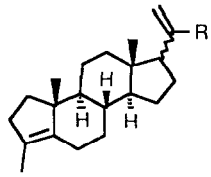
Abstract. *Polyene **3** containing a carboalkoxyallylsilane terminator was cyclized to give pro-steroid **6** in 68-75% yield. Unequivocal proof for the structure of **6** was obtained by conversion to the racemic form of the natural cortical hormone 17-desoxycorticosterone (**15**).*

The allylsilane group has proved to be an effective terminator of polyene cyclizations.[1] Thus the substrate **1** afforded the pro-steroid product **4** in 83% yield [1a] with the highly selective formation of the *trans*-fused, five-membered D-ring. The vinyl substituent in **4**, however, does not lend itself particularly well to the development of useful functionality at C-17, and therefore the possibility of employing substituted allylsilane terminators is being explored. An attempt to prepare the substrate **2** with the methallylsilane terminator, having the potential of leading (via ozonolysis of **5**) to the progesterone side-chain, was defeated by premature protodesilylation of this acid-sensitive function.[2] We predicted that this difficulty would be obviated with the carboalkoxyallylsilane terminator, e.g., **3**, since the electron-withdrawing ester group would stabilize the conjugated olefinic bond toward protonation. Moreover, this group promised to afford a facile means of developing the important 21-hydroxyprogesterone side-chain. This communication discloses the preparation and cyclization of substrate **3** to give **6** and conversion of the latter to the racemic form of the adrenal hormone, 17-desoxycorticosterone (**15**).





1 (R = H, R' = Me)

2 (R = R' = Me)

3 (R = $CO_2{}^iPr$, R' = Et)

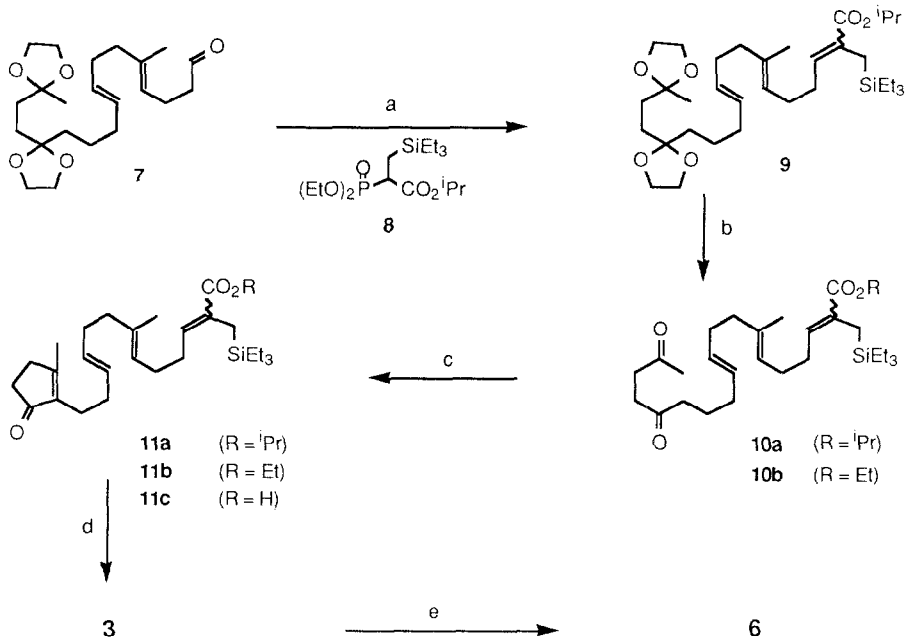
4 (R = H)

5 (R = Me)

6 (R = $CO_2{}^iPr$)

Introduction of the terminator function by Horner-Emmons reaction with the known aldehyde **7**[1] required the preparation of phosphonate **8**,[3] available from isopropyl (diethylphosphono)acetate[4] and triethylsilylmethyl triflate.[5] The triene ester **9**,[3] produced in 76% yield as a 1:2 of mixture E and Z isomers, was converted to carbinol **3**[3] by established methodology (Scheme 1).[6] The choice of the carboisopropoxy substituent was directed by two factors. Firstly, the ethyl analog **10b**[3] proved vulnerable to hydrolysis during cyclodehydration, giving 21% of the carboxylic acid **11c**;[3] secondly, the ester **11b**[3] was shown to react with excess methyllithium[7] at -78°C whereas the isopropyl ester **11a**[3] was completely stable to these conditions. Treatment of **3** with 10% TFA in dichloromethane at -20°C for 3.5 h gave **6**[3] in 68-75% yield as the only detectable product, consisting of a 1:1 mixture of C-17 epimers. The constitution of this product was established unequivocally by its conversion to a natural product of known configuration (see below).

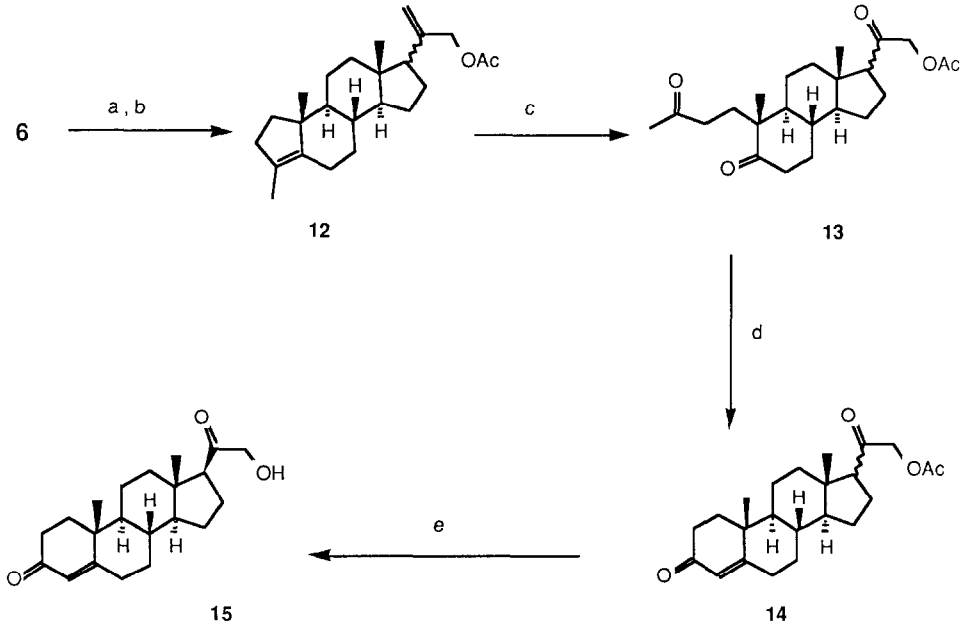
Scheme 1



[a] **8**, BuLi (1.1 equiv.), DME, -23-24°C, 2 h then **7**, 0-24°C, 4 h, 76%; [b] $pyH^+ TsO^-$, acetone, H_2O, reflux, 15 h, 99%; [c] 2:1:3 2% NaOH: CH_3OH: THF, reflux, 2.5 h, 87%; [d] MeLi (6 equiv.), -78°C, 1 h then repeat, 100%; [e] 10% TFA in CH_2Cl_2, -20°C, 3.5 h, 68-75%.

Reduction of the pro-steroid **6** with DIBAL and acetylation of the resulting allylic alcohol gave **12**[3] (Scheme 2). Ozonolysis of **12** afforded triketone **13** which, without purification, was subjected to cyclodehydration,[8] producing enone **14**[3] in 47% yield from **12**. Separation of epimers by hplc[9] followed by saponification of the C-21 acetate gave *dl*-17-desoxycorticosterone (**15**) in 20% yield overall from **6**. This material and the epimerically pure acetate were identical by vpc,[10] nmr and ir to the authentic optically active compounds. It seems reasonable to expect that ways may be found for converting the 17α-isomer into the more stable 17β-epimer,[11] thus rendering the whole process stereoselective.

Scheme 2



[a] DIBAL (3.0 equiv.), CH_2Cl_2, -78°C, 95%; [b] Ac_2O (2.5 equiv.)/pyridine, 25°C, 20 h, 100%; [c] O_3, CH_2Cl_2, -78°C, then Zn/AcOH, -78-26°C; [d] 40: 4: 1 AcOH: aq HCl: H_2O, dark, 26°C, 48 h; [e] 0.1N K_2CO_3 in 80% CH_3OH/H_2O, 26°C, 5 min, 88%.

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References and Notes

1. a. Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorganic Chem.*, **1979**, *8*, 513: b. Johnson, W. S.; Chen, Y.- Q.; Kellogg, M. S. *J. Am. Chem. Soc.*, **1983**, *105*, 6653.
2. Johnson, W. S.; Schmid, R. unpublished observations.
3. Products were purified by low pressure column chromatography using Merck 60H silica gel. The vpc and tlc showed no indication of extraneous components and the ^{1}H nmr and ir spectra were consistent with the assigned structure. A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound except in the case of **10b**, **11b** and **11c** for which mass spectra were obtained.
4. Prepared according to an adaption of a procedure described by Erickson, K. L; Markstein, J.; Kim, K. *J. Org. Chem.*, **1971**, *36*, 1024.
5. Prepared according to an adaption of a procedure described by Ambasht, S.; Chiu, S. K.; Peterson, P. E.; Queen, J. *Synthesis*, **1980**, 318.
6. Johnson, W. S. *Bioorganic Chem.*, **1976**, *5*, 51.
7. Excess methyllithium was observed to minimize enolization and give high conversion to the carbinol **3**.
8. Johnson, W. S.; Dumas, D. J.; Berner, D. *J. Am. Chem. Soc.*, **1982**, *104*, 3510.
9. DuPont Zorbax SIL normal phase column eluted with 30:70 ethyl acetate:hexanes.
10. SE-54, 15m column with hydrogen as carrier gas.
11. For example the 17α : 17β equilibrium of 3: 7 in the pregnenolone series, Fieser, L. F. and Fieser, M. "Steroids"; Reinhold Publishing Corporation: New York, 1959; p 566.

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