Total Synthesis of (±)-Androst-4-en-3-one-17-carboxylic Acid

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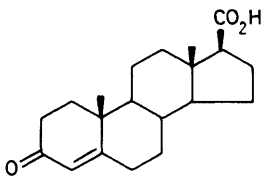
The synthesis of the title compound (**1**) has been accomplished *via* the polycyclization of epoxide (**7d**) having an enol acetate as a terminator.

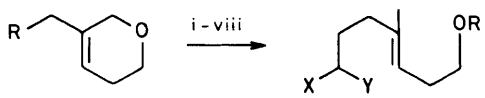
The β-keto ester[1] and its enol acetate[2] function as efficient terminators in the non-enzymatic cyclization process. Use of these terminators in non-enzymatic polyolefin cyclization to steroidal systems eliminates the need for external trapping reagents.‡ We report here a novel synthesis of (±)-androst-4-en-3-one-17-carboxylic acid (**1**). The cyclization precursor, the epoxy enol acetate polyene (**7d**), was prepared *via* a highly stereoselective method for making *E*-trisubstituted olefins.

(**7d**)



(**1**)

The C,D-ring precursor was synthesized (Scheme 1) from 5,6-dihydro-2*H*-pyran-3-methanol (**2a**) (Aldrich). Conversion§ of bromide (**2b**) into the ester (**2c**) followed by ester hydrolysis gave crystalline acid (**2d**). Ring opening[4] of (**2d**) gave *trans*-hydroxy acid (**3a**) in 76% isolated yield using lithium in ethylamine at −78 °C. Protective silylation of (**3a**)



(**2**) (**3**)

a; R = OH
b; R = Br
c; R = CH_2CO_2Et
d; R = CH_2CO_2H

a; X = O, Y = OH, R = H
b; X = O, Y = OH, R = $SiBu^tMe_2$
c; X = OH, Y = H, R = $SiBu^tMe_2$
d; X = O, Y = H, R = $SiBu^tMe_2$

Scheme 1. i, PBr_3, Et_2O, 0 °C, 93%; ii, $CH_2(CO_2Et)_2$, Na, EtOH, room temp.; iii, KOH–EtOH (1.1 M), 18-crown-6, room temp. → reflux, (86% overall for ii, iii); iv, 10% NaOH (aq.), reflux, 100%; v, Li, $EtNH_2$, −78 °C, 10 h, 76%; vi, Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF), room temp., 53%; vii, $LiAlH_4$, tetrahydrofuran (THF), room temp., 66%; viii, Collins reagent, 89%.

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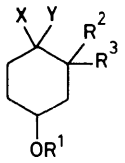
‡ The combination of a methyl acetylene terminator and a cyclohexene oxide initiator gives the best overall yield so far of isolated, pure, single, nonaromatic sterol for any overall nonenzymatic polycyclization process, including subsequent molecular adjustments (ref. 3). For the highest yield to date for the nonenzymatic polycyclization step *per se*, see ref. 11. However, the medium includes a cationic trapping reagent, ethylene carbonate, required for the cyclization step.

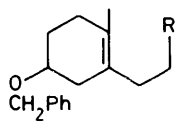
§ Attempts to prepare (**2c**) from (**2b**) *via* the S_N2 displacement of bromide ion by the anion derived from ethyl acetate were unsuccessful, as were attempts to achieve the direct synthesis of (**2d**) *via* the reaction of (**2b**) with the dianion derived from acetic acid.



(4)

a; X,Y = OCH_2CH_2O; R^1,R^2,R^3 = H
b; X,Y = OCH_2CH_2O; R^1 = CH_2Ph; R^2,R^3 = H
c; X,Y = O; R^1 = CH_2Ph; R^2,R^3 = H
d; X,Y = O; R^2 = CH_2NMe_2; R^3 = H; R^1 = CH_2Ph
e; X,Y = O; R^2 = CH_2NMe_3I; R^3 = H; R^1 = CH_2Ph
f; X,Y = O; R^1 = CH_2Ph; R^2,R^3 = CH_2
g; X = Me; Y = OH; R^1 = CH_2Ph; R^2,R^3 = CH_2
h; X = Me; Y = $OCH{=}CH_2$; R^1 = CH_2Ph; R^2,R^3 = CH_2

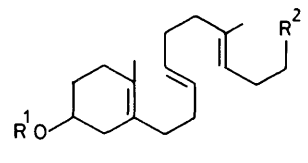
i-xi



(5)

a; R = CHO
b; R = CH_2OH
c; R = $CH_2OO_2SC_6H_4Me$-*p*
d; R = CH_2I
e; R = CH_2PPh_3I

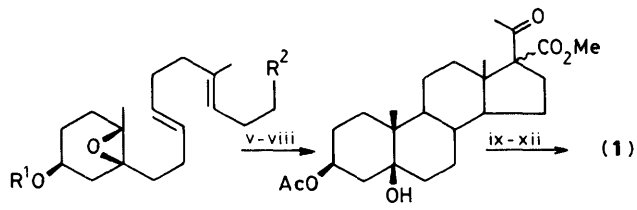
Scheme 2. i, NaH, THF, $PhCH_2Br$, reflux, 93%; ii, 2 M H_2SO_4 (aq.), acetone, reflux, 75%; iii, Me_2NH_2Cl, $(CH_2O)_n$, EtOH, HCl (catalyst), reflux, 98%; iv, MeI, Et_2O, room temp., 85%; v, DBU, THF, −5 °C, 4 h; vi, MeLi, Et_2O, −78 °C (95% overall for v, vi); vii, $Hg(OAc)_2$, n-butyl vinyl ether, reflux, 62%; viii, $LiAlH_4$, THF, 92%; ix, *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, 85%; x, NaI, Me_2CO, room temp., 88%; xi, Ph_3P, PhH, 84 °C, 84%.



(6)

a; R^1 = CH_2Ph, R^2 = $OSiBu^tMe_2$
b; R^1 = H, R^2 = OH
c; R^1 = H, R^2 = $OO_2SC_6H_4Me$-*p*

i-iv



(7) (8)

a; R^1 = H, R^2 = $OO_2SC_6H_4Me$-*p*
b; R^1 = H, R^2 = Br
c; R^1 = H, R^2 = $CH_2(COMe)CO_2Me$
d; R^1 = COMe, R^2 = $C(CO_2Me){=}CMeOAc$

Scheme 3. i, Bu^n_4NF, THF, room temp., 96%; ii, Li, NH_3, THF, −40 °C, 100%; iii, *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, 50%; iv, Bu^tO_2H, MoO_2(acetylacetonate)$_2$, 0 °C, 75%; v, LiBr, THF, room temp., 98%; vi, LiH, $MeCOCH_2CO_2Me$, DMF, 80 °C, 65%; vii, MeCOCl, NEt_3, hexamethylphosphoramide, room temp., 64 h, 65%; viii, $SnCl_4$, CH_2Cl_2, 0 °C → room temp., 24 h; ix, methanolic KOH; x, pyridinium chlorochromate–CH_2Cl_2; xi, KOH(aq.)–THF; xii, 10% HCl (aq.).

followed by reduction and oxidation gave aldehyde (**3d**).¶ This reductive cleavage provides a methodology for generating *E*-trisubstituted olefins in high stereochemical purity [>98% *E* by capillary g.c. of (**3c**)].

Acetalization of 4-methoxycyclohex-3-en-1-ol[6] [$(CH_2OH)_2$, *p*-$MeC_6H_4SO_2OH$, benzene, reflux, 90%] to give (**4a**) was the starting point for obtaining the A,B-ring precursor (Scheme 2). Alcohol protection at C-4 followed by acetal removal gave (**4c**) *via* (**4b**). Following the Mannich reaction to give (**4d**), the Mannich salt (**4e**) was deaminated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[7] to give unstable enone (**4f**), which was immediately allowed to react with methyl-lithium to give allylic alcohol (**4g**). The conversion of (**4g**) into (**5e**) included the Claisen rearrangement, $LiAlH_4$ reduction, tosylation, iodide formation, and conversion into the phosphonium iodide.

The Wittig–Schlosser reaction[8] of (**5e**) with (**3d**) (2 equiv. of PhLi, THF–diethyl ether, −78 → −30 °C, 80%) gave all *trans*-triene (**6a**). Successive deprotection of silyl and benzyl ethers gave diol (**6b**) which was selectively tosylated to furnish (**6c**) (Scheme 3). Epoxidation of the *pro*-A-ring olefin[9] and conversion of the epoxy methyl toluene-*p*-sulphonate (**7a**) into the bromide gave (**7b**). Alkylation of (**7b**) with the lithium salt of methyl acetoacetate gave (**7c**). The epoxy enol acetate polyene (**7d**) resulted from acetate formation at C-3 and conversion of the β-keto ester into the enol acetate in one step.[10]

In line with previous experiences,[2] a Lewis acid induces cyclization of (**7d**) under homogeneous conditions to give product (**8**), convertible by traditional methodology (deacetylation,[2] oxidation at C-3, saponification, and dehydration) into the desired (±)-androst-4-en-3-one-17-carboxylic acid (**1**) [11% from (**7d**) after h.p.l.c. (Whatman Partisil psx 10/25, 40% diethyl ether–hexane)].[11]

¶ The aldehyde (**3d**) was also prepared from homogeraniol (ref. 5). The terminal olefin of the t-butyldimethylsilyl-protected ether of homogeraniol (t-butyldimethylsilyl chloride, imidazole–DMF, 42 °C, 16 h, 91%) was cleaved as the epoxide (*via* the bromohydrin: *N*-bromosuccinimide–THF–H_2O, 5 °C, 3 h, 66%; bromohydrin to epoxide: K_2CO_3–MeOH, 90%) following treatment by periodic acid–diethyl ether (30 min, room temp., 88%).

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