Tetrahedron Vol. 31, pp. 2363 to 2367. Pergamon Press 1975. Printed in Great Britain

TOTAL SYNTHESIS OF THE 6-SILASTEROID RING SYSTEM

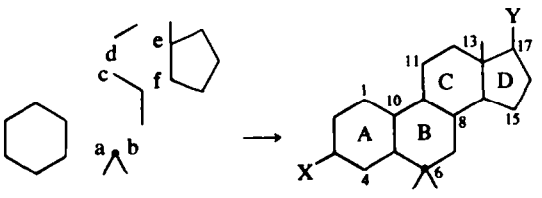
S. BARCZA* and C. W. HOFFMAN
Chemistry Research Department, Sandoz Inc., East Hanover, NJ 07936, U.S.A.

(*Received in USA* 14 *February* 1975; *Received in UK for publication* 13 *May* 1975)

Abstract—The total synthesis of the first[1] silasteroid ring system is described. A bidirectional construction was employed, starting from precursors of rings A and D. Metal-organic substitutions on dimethyldichlorosilane gave the allyl-m-methoxyphenyl derivative **2**, as elements of rings AB. Hydroboration-oxidations led to the arylsilylpropionic acid **5**. Activation and cyclization gave the key intermediate, 4,4 - dimethyl - 4 - sila - 6 - methoxy - 1 - tetralone, **7**. Attachment of ring D and closure of ring C followed the Torgov-Smith outline, but required important differences in implementation, to give D,L-6, 6 - dimethyl - 6 - sila - 3 - methoxy - estra - 1,3,5(10),8,14 - pentaene - 17 - one, **11**. Extensive physical data are presented.

The construction of a biologically important ring system with silicon as a ring member was a challenging novel idea. It had been known, that there is no toxicity associated with silicon, *the element* in organosilicon compounds,[3] yet also that there exist biologically active organosilicon structures,[4] and that silicon analogs of organic compounds, in which silicon occurs in a nonreactive molecular environment, will often give rise to qualitatively similar activities.[5]

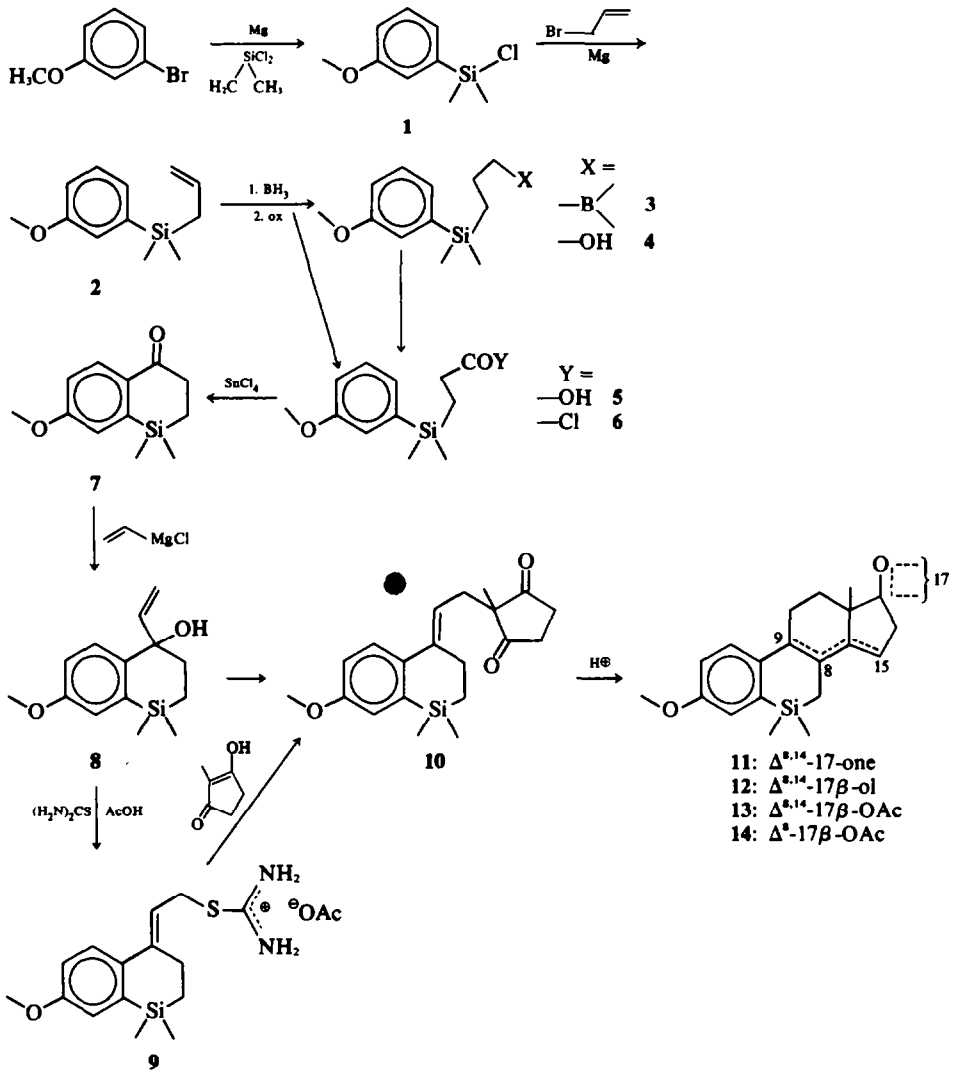
The presence of an SiH_n unit occurred as *a priori* undesirable because of its reactivity towards oxidation, and therefore we adopted the $Si(CH_3)_n$ unit as an element; specifically, we undertook the synthesis of the 6,6-dimethyl-6-silasteroid skeleton. This ring system appeared as one of those synthetically most accessible, furthermore, the steroid 6-hydroxylation pathway would be blocked in such structures, and the aromatization of ring B would be made impossible. As a general principle, the placement of silicon in the middle of a polycondensed ring structure prevents the eventual formation of polycondensed aromaticity avoiding possible carcinogenic effects. The presence of the two Me groups would certainly make the molecules more lypophilic, displacing the compounds in the Hansch π-parameter space.[6] A mild lipid-depot effect may arise from this, with a lower (and delayed) peak but longer duration of activity. The effect of the gem-dimethyl substitution on receptor fit could not be predicted. 6,6-Dimethyl-6-carbasteroids only recently became known.[7]



Scheme 1. Strategy of construction of the 6-silasteroid ring system, sequence of bond connections (a→f) and labeling scheme.

We initially investigated the partial synthesis of silasteroids by oxidative removal of carbon(s) six (and seven) and organometallic attachment of a dimethylsilicon unit in that place, but soon were attracted by the total synthesis approach. In particular, a strategy employing bidirectional construction from two major terminal fragments, rather than a linear buildup was appealing. Such is the Torgov-Smith approach,[8] which throughout the years has been used in several heterosteroid syntheses.[9]

The key intermediate silatetralone **7** had to be constructed. The Grignard reagent from *m*-bromoanisole was reacted with an excess of dimethyldichlorosilane to give **1**. No disubstitution was detected in this transformation. After removal of the excess of the dichlorosilane and without isolation of the product, the allyl group was attached via Grignard reaction to give **2**, *m*-anisyl-allyldimethylsilane as a stable liquid. The allyl group was reacted with borane, and the organoborane intermediate **3** was oxidized to yield the terminal, primary alcohol[10] **4** cleanly, as a stable oil. No silicon-carbon cleavage accompanied the oxidative boron-carbon cleavage. Cr^{VI} oxidation,[11] or basic permanganate oxidation and acidification yielded the acid **5**. This acid was also obtained by the shorter pathway of direct oxidation of the organoborane **3** by Jones reagent. One attempt was made to produce an acetal side chain, by employing β-chloropropionaldehyde diethylacetal instead of allyl bromide in the Grignard step, with inferior results. Direct[12] cyclization[11] of the acid was investigated: the use of stannic chloride left starting material, whereas polyphosphoric acid apparently caused protodesilylation of the aromatic ring. The desired cyclization was achieved in two steps but "one pot" by preparing the acid chloride under very mild conditions and immediately following with the Friedel Crafts cyclization, employing stannic chloride.[12] There was no evidence that any of the cyclization occurred *ortho* to the OMe group (steric hindrance); NMR would have diagnosed that very sensitively. Cyclization was also investigated at the earlier oxidation state of the allyl group. Lewis acid (BF_3) apparently led to allyl-silicon, and other acids to aryl-silicon cleavage. Throughout our work utmost protection against protodesilylation[13] had to be exercised by minimizing the presence of acidity, nucleophilicity and temperature. Particular care is needed in the Jones oxidations (cooling, speed), cyclization to tetralone (absence of moisture; cooling, speed, pH at quenching) and TsOH-catalyzed reactions (dry medium, minimum heating). When such care was exercised, the overall yield of tetralone **7** from *m*-bromoanisole was 50–55%.



Scheme 2. Total synthesis of the 6,6-dimethyl-6-silasteroid ring system.

The properties, especially spectral, of tetralone **7** were subjected to considerable scrutiny (Experimental), because of the importance of this key intermediate. The data, besides leaving no doubt about the structure, showed that the features of this tetralone are closest to those of the corresponding 7-membered[14] carbocyclic ketone. The CO group has appreciable back strain on it to open the $C_{1a}C_1C_2$ angle. It does not appear twisted out of conjugation with the benzene ring. The tetrahydro ring seems to be inverting easily at room temperature. Fragmentation under electron impact includes the formation of doubly charged ions, and, in general favors the formation of arylsilicon cation species, i.e. preservation of the aryl-Si bond.

Further transformations, from silatetralone **7**, followed the Torgov-Smith scheme.[8,9] However, conditions were not directly transferable; important differences exist in the pH- and solvent profile of the near-optimized reactions (Experimental). Vinylation of the tetralone appeared to be accompanied by enolate formation and had to be repeated in order to maximize the conversion to vinyl carbinol **8**. From the latter secosteroid **10** was formed directly, but yields were considerably better when the intermediacy of the isothiuroniumsalt **9** was employed. Secosteroid **10**, just as the natural steroid[15] precursor, exists in the E configuration of the styrene type double bond. Cyclization of **10** under acid catalyzed azeotroping conditions, with careful minimization of water content led to the silasteroid **11**. A few more highly reduced derivatives were prepared (i.e. Experimental) and were found to be weakly estrogenic.

With the pentaenone **11** the first asymmetry of natural steroids appeared at C^{13}, causing in principle nonequivalence of all geminal groups. Physical data on **11** were carefully studied. Chemical nonequivalence in the ^1H NMR spectrum was found within the $C^{16}HH'$, $C^{12}HH'$, $C^{11}HH'$ and C^7HH' groups. To our surprise, none was found within the SiMeMe' function. This might be ascribed at first sight to enough time averaged flattening of ring B to render the aromatic ring A a bisector and therefore an equal deshielder of the two Me groups. This is apparently not the case because an as remote change as reduction of the 17-keto group to the 17β-OH produces distinct shifts for those Me functions. Evidently, the accidental degeneracy within the 6,6-MeMe' Si group is a result of cancellation of the nearby anisotropy of the aryl

and the remote effect of the 17-CO group. The mass spectrum of **11** showed a great tendency to form peaks that most likely contain an aromatized ring C.

EXPERIMENTAL

M.ps are uncorrected. The following instruments were used: NMR, 60 MHz, Varian A-60; IR, Perkin-Elmer 137 and 237; UV, Cary-14; MS, CEC 21-103C, low resolution. Unless otherwise indicated, all concentrations were done *in vacuo* from a bath at 40°. Drying agent was Na_2SO_4. THF was rendered absolute and peroxide-free by distillation from LAH, benzene and acetone were dried with molecular sieves. All reactions were carried out under dry N_2. Spectra, in general were taken in, and are reported as: NMR, $CDCl_3$, δ, ppm downfield from internal TMS, J or apparent J (splittings) in Hz; MS, prominent and/or significant peaks; IR, $CHCl_3$ or thin film, cm^{-1}, prominent peaks; UV, MeCN, λ_{max}, nm/ϵ between 207 and 400 nm. Product purity was checked by TLC, some GLC, spectra and microanalysis. Solid samples for microanalysis were dried generally overnight at high vacuum *ca.* 20° below their m.p. Extensive thinlayer and some spectral monitoring was employed to test for disappearance of starting material and/or maximum development of product, where applicable.

Allyl-dimethyl-m-methoxyphenylsilane (2)

In a dry flask Mg turnings (9·36 g; $3 \times 0{\cdot}128 = 0{\cdot}385$ mol), mercuric chloride (20 mg) and I_2 (5 mg) were placed under N_2. THF (90 ml, abs) and dichlorodimethylsilane (76·4 ml = 81·5 g; $5 \times 0{\cdot}128 = 0{\cdot}642$ mol) were added at once, followed by up to one third of *m*-bromoanisole (24·0 g; 0·128 mol) to start the Grignard reagent formation and its reaction. The rest of the *m*-bromoanisole was added gradually, while maintaining the temp at 40°. Stirring at 40° was continued for 15 min more, Gilman test of a sample was negative. The solvent and the excess of dichlorodimethylsilane were removed at 14 mm and a bath at 40°, continually ensuring anhydrous conditions. A chaser of 20 ml additional THF was used. The sticky crystalline residue containing **1** with Mg was stirred with 100 ml of fresh THF, while allyl bromide (22·35 ml = 31·2 g; $2 \times 0{\cdot}128 = 0{\cdot}257$ mol) was gradually (~1 hr) added. The temp was maintained around 40° during the addition and at 50° overnight. After cooling, the mixture was poured into stirred, cold 250 ml of nearly saturated aqueous ammonium chloride soln and 100 ml benzene. With one additional benzene wash, the organic layer was dried and concentrated to yield **2** (27·3 g; expected 26·5 g) as an oily product. A small amount of diallyl-dimethylsilane present does not interfere with subsequent conversions. An analytical sample was obtained by fractional distillation of a portion (12·6 g): main cut taken (8·26 g) b.p. 58–60° (0·06 mm); NMR, ($CDCl_3$) δ 0·27 (s, 6, Si $(CH_3)_2$), 1·75 (br d, 2, J = 7·5 Hz, $SiCH_2C$=), 3·80 (s, 3, OCH_3), 4·8 (m, 2, $C{=}CH_2$), 5·65 (m, 1, -CH=C) 6·7–7·4 (m, 4, arom); IR (neat) 2955, 1630, 1570, 1480, 1410, 1245, 1045, 820; UV (acetonitrile), λ_{max}/ϵ, sh 270/1160, 278/1794, 285/1590. (Found: C, 69·4, 69·9; H, 8·9, 8·9. Calcd for $C_{12}H_{18}OSi$: C, 69·8; H, 8·8%).

Dimethyl - m - methoxyphenyl - 3 - hydroxypropyl - silane (3)

Method A. Compound **2** (1 g; 4·85 mmol) was dissolved in 30 ml abs THF. The soln was cooled to 0°, and 1 M borane soln in THF (5·34 ml; 5·34 mmol) was added. The mixture was kept at 0° for 1 hr and at 25° for 15 min. A 10% sample was removed. 3 N NaOH aq was prepared from 181 mg of NaOH and cooled to 0°. This was mixed with 30% H_2O_2 (1·65 ml) precooled to 0°. The cold basic peroxide was gradually added to the organoborane soln at 0°, stirring was continued overnight at room temp. Dilution with water, removal of THF *in vacuo*, extraction with benzene (two NaCl soln washes), drying and concentration gave 944·5 mg of the oily product.

Method B. From **2** (1·003 g; 4·85 mmol) and 1 M borane (2·42 ml) in THF the soln of the organoborane intermediate was obtained after 3 hr at 25°. At 0°, an ice-cold mixture of Et_3N (1 ml) and 90% t-butyl hydroperoxide (1 ml) was gradually added. The resultant soln was kept at 25° for 18 hr. It was then diluted with benzene, extracted with water, 3 portions of 5% aqueous tartaric acid, twice with water, dried and concentrated yielding 1·143 g of colorless oil. A sample was evaporatively distilled (93–108°/0·12 mm) for physical and analytical measurements and GLC.

The alcohols obtained by the two methods were found identical; NMR ($CDCl_3$) δ 0·24 (s, 6, Me_2Si), 0·72 (m, 2, $SiCH_2$), 1·56 (wide m, 2, $C{-}CH_2{-}C$), 3·54 (t, 2, J = 6·6, OCH_2), 6·72–7·44 (m, 4, arom), variable (s, 1, OH); IR (neat), 3300, 2890, 1560, 1465, 1390, 1270, 1235, 1040, 830. (Found: C, 64·5; H, 9·0. Calcd for $C_{12}H_{20}O_2Si$: C, 64·2; H, 9·0%).

3 - (*Dimethyl* - m - *methoxyphenyl silyl*) - *propionic acid* (5)

1. *Directly from the allyl compound* (2). Unpurified **2**, (26·4 g; 0·128 mol) in 300 ml of abs THF was reacted with 63·7 ml 1 M borane in THF ($0{\cdot}5 \times 0{\cdot}128$ mol = $1{\cdot}5 \times 0{\cdot}128$ equiv) in the manner described for the preparation of the alcohol. To the THF soln of the organoborane intermediate 50 ml acetone was added at 0° to react with excess BH bonds. The soln was concentrated under anhydrous conditions. Another (100 ml) portion of acetone was added, and the concentration was repeated to drive off THF, which could consume oxidant subsequently. The residue was taken up in 800 ml acetone. (Dry acetone was used throughout.) The soln, as well as 224 ml Jones' reagent (8 M, $2 \times 7 \times 0{\cdot}128 = 1{\cdot}79$ ox. equiv) were precooled to 0°. The oxidant was added to the substrate with vigorous stirring and cooling (bath below 0°) to keep the temp. at 0–10°, preferably 0–5°. Stirring was continued for 15 min more at 0–10° after the addition, then cooling was renewed and 68·4 ml (53·7 g, 0·895 mol, 1·79 equiv) iso-propanol was added under the same conditions as with the oxidant, to consume excess oxidant. The thus quenched redox slurry was stirred 5 min more, and was concentrated to one third volume at 0–10°, using a dry-ice cooled receiver. First benzene then water was added to the concentrate, two liquid phases resulted. Three benzene washes of the aqueous phase were used. The combined organic phase was washed with two portions of sat Na_2SO_4 aq and with five 50 ml portions of 2 N K_2CO_3, dried and concentrated (neutral by-product). Benzene was layered over the combined carbonate extracts and with stirring and cooling, enough tartaric acid (45–85 g, 0·3–0·56 mol) was added to reach pH = 4. (Foaming controlled with ether). Three additional benzene extractions, one water wash, drying and concentration gave the acid **5**, 21·1 g, 69% suitable for the cyclization step if kept dry. The ensuring of proper cooling is crucial for the outcome of this reaction.

2. *From the alcohol* **4**. The alcohol (6·5 g, 29 mmol) in 647 ml of dry acetone at 0° was oxidized with 59·8 ml Jones' reagent (excess) as described above. The excess of oxidant was consumed by adding an excess of isopropanol. Workup was effected as described above to yield 4·183 g of acidic fraction as an oil. Proper cooling whenever oxidant or sulfuric acid is present is crucial.

The oxidation of the alcohol **4** to acid **5** was also performed with CrO_3 in AcOH or in acetone-AcOH, and with $KMnO_4$ in NaOH aq.

A sample of the crude acid was evaporatively distilled at 108° and 15 mm. It crystallized to a low-melting solid upon cooling (m.p. ~30°). NMR ($CDCl_3$) δ 0·29 (s, 6, Me_2Si) 1·10 and 2·32 (m, 2 each, $SiCH_2$ and CH_2CO, symmetrical AA'BB' pattern, $J_{AB} + J_{AB'} = 17$ Hz), 3·82 (s, 3, OCH_3) 6·7–7·48 (m, 4, arom) 10·6 (s, 1, COOH); IR ($CHCl_3$) 3500–2500, 2900, 1700, 1570, 1390, 1200, 1110, 1035, 910, 832. (Found: C, 60·7; H, 7·7. Calcd for $C_{12}H_{18}O_3Si$: C, 60·5; H, 7·6%).

4,4 - *Dimethyl* - 6 - *methoxy* - 4 - *silatetralone* - 1 (7).

Under anhydrous conditions until quenching and under N_2, PCl_5 (18·2 g; $1{\cdot}2 \times 72{\cdot}5$ mmol) was suspended in 50 ml benzene (dry benzene used until quenching). The suspension was cooled to 5°, and **5** (17·25 g; 72·5 mmol, crude, but well dried) was added in 80 ml benzene over a period of 25 min with stirring at 0–10°, preferably 0–5°. Nearly all solids dissolved by the end of the addition. The mixture at this point contained the acid chloride **6** which was not isolated. To it was added $SnCl_4$ (18·1 ml; 40·4 g, $2{\cdot}14 \times 72{\cdot}5$ mmol) in 70 ml benzene over a period of 10 min at 0–5°. After additional 5 min of stirring in an ice bath, the mixture was

added in a thin stream to a vigorously stirred ice-cold emulsion of sodium-potassium tartrate tetrahydrate (410 g; 20 × 72·5 mmol) in 1 l. water and 200 ml benzene. The mixture was stirred for 5 min more after quenching, allowed to settle, and the organic phase was decanted. The remainder was filtered. Cake and mother liquor were extracted (resuspending) twice with benzene, the combined organic layer was washed with water, dried and concentrated, to give oily 7 (12·5 g; 78·4%), suitable for the next step if kept dry. It should be stored in the cold.

A sample of the oil was evaporatively distilled at 87° and 0·05 mm to give a colorless low-melting solid after cooling (m.p. ~30°). NMR ($CDCl_3$) δ 0·34 (s, 6, Me_2Si), 1·17 and 2·88 (m, m, 2, 2, $SiCH_2CH_2CO$, excellent fit obtained when analyzed as AA'XX': $J_{AX} = 3·34$, $J_{AX'} = 7·18$, $J_{AA'} = -17·6$, $J_{XX'} = -18·5$ Hz (insensitive to J_{gem})), 3·87 (s, 3, CH_3O), 6·95, 7·02 and 8·08 (q, d, d, 1, 1, 1, Ar 7, 5 and 8 resp., $J_{7,8} = 9$, $J_{5,7} = 2·5$, $J_{5,8} = \sim 0$ Hz); MS (heated inlet) 220 (P), 205 (P–CH_3), 192 (P–(CO or C_2H_4)), 177 (P–(CO or $C_2H_4 + CH_3$)), 164 (P–$COCH_2CH_2$) 149 (P–$COCH_2CH_2$–CH_3), 134 ($C_6H_5Si(CH_3)_2$ or $CH_3OC_6H_3CO$), 119 ($C_6H_4SiCH_3$), 105 (C_6H_5Si), doubly charged ions: 102·5 (P–CH_3), 96·5 (P–CO or C_2H_4) + H), 88·5 (P–(CO or C_2H_4)–CH_3), many others, metastable transitions: ~168·5 (P→P–(CO or C_2H_4)), ~140·5 (P–(CO or C_2H_4)→P–(CO + C_2H_4)), ~110 (P–CH_3→P–CH_3–CH_2CH_2CO); IR (neat) 2945, 1668, 1582, 1478, 1315, 1245, 1130, 825, 778 cm^{-1}; UV (CH_3CN) (λ_{max} nm/ϵ) 224/14700, 273/14000. (Found: C, 65·2; H, 7·5. Calcd for $C_{12}H_{16}O_2Si$: C, 65·4; H, 7·3%).

For comparison, 7 - methoxy - benzo - cycloheptanone - 1 (homotetralone), NMR ($CDCl_3$) 2·8 (m, 4, $ArCH_2 + COCH_2$); IR ($CHCl_3$) 1665 cm^{-1}, UV (CH_3CN) 221/13500, Sh 226, 268/13200; 6-methoxy-tetralone-1, UV (EtOH) 276/16600; 4,4 - diphenyl - 4 - sila - 1 - tetralone,[11] IR: 1680 cm^{-1}.

1,1 - *Dimethyl* - 1 - *sila* - 4 - *vinyl* - 4 - *hydroxy* - 7 - *methoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**8**)

To a soln of 2 M vinylmagnesium chloride (156 ml; 0·312 mol), THF in 450 ml of further THF, 7 (34·5 g; 0·157 mol) in 150 ml THF was added over a period of 30 min at 5–10° reaction temp. The mixture was allowed to warm to room temp over *ca.* 45 min, then further stirred at 25° for 30 min. It was recooled by an ice bath and added to vigorously stirred and cooled sat NH_4Cl aq (1 l.). Stirring was continued for 1 hr in the cold. The aqueous layer was washed with one small portion of benzene, the combined organic phase with three small portions of sat NaCl aq. It was then dried and concentrated: 43·1 g. This oil showed residual C=O absorption in the IR, which may typically arise through enolate ion formation. For complete conversion, the above vinylation procedure was immediately repeated on the oil, using one half of all the above ingredients; 42·8 g oil, (NoC=O). The product **8** is heat- and extremely acid-sensitive. It should be used immediately in the next step or stored at −20°. NMR ($CDCl_3$ δ 0·21 and 0·25 (s, s, 3, 3, SiMeMe'), 0·7–1·3 (m, ~3, SiHH'C, OH), 2·1 (m, 2, C–CHH'COVi), 3·78 (s, 3, OCH_3), 4·71–5·22 (m, 2, $=CH_2$), 6·07 (q, 1. J = 16·5 and 10·5 Hz, –CH=), 6·6–7·6 (m, 3, arom); IR ($CHCl_3$) 3400, 2900, 1580, 1550, 1465, 1220, 1030, 820, 777.

S - [2' - (1,1 - *Dimethyl* - 1 - *sila* - 7 - *methoxy* - 1,2,3,4 - *tetrahydronapht* - 4 - *ylidene*) - *ethyl*] *isothiuronium acetate*, **9**

Thiourea (15·5 g, 0·204 mol) was homogenized with 350 ml AcOH, and was added at room temp to 42·8 g (containing max. 39·0 g, 0·157 mol of the desired compound) vinyl carbinol **8** from the previous step. The soln was allowed to stand under N_2 at 25° for 2 days. AcOH was removed, using a bath at 35°. The residual oil was stirred with five 50 ml portions of pentane. The pentane-insoluble portion was pumped at high vacuum to obtain 180·7 g (excess weight, contains AcOH) of a brown oil which partly crystallized. Attempts failed to purify this material without decomposition. It should be used as such for the next step or stored at −20°. NMR ($CDCl_3$ + DMSO-d_6, broad throughout) δ 0·3 (s, 6, Me_2Si), 1·05 (m, 2, $SiCH_2$), 2·0 (s, excess, AcO), 2·63 (m, 2, $SiCH_2\underline{CH_2}C$=), 3·84 overlapping 3·96 (s, m, 3, 2, OCH_3, =C–CH_2–S), 5·75 (m, 1, =CH–), 6·6–7·7 (m, 3, arom) 9·36 (s, excess (>4), NH, HOOC).

1,1 - *Dimethyl* - 1 - *sila* - 4 - [2' - (1",3" - *dioxo* - 2" - *methyl* - *cyclopenta* - 2" - *yl*)*ethylidene*] - 7 - *methoxy* - 1,2,3,4 - *tetrahydronaphthalene*, 10, ("*Secosteroid*")

From the isothiuronium salt **9**. The isothiuronium salt (180·7 g, max. 0·157 mol), 900 ml of t-BuOH, 150 ml water and 68·1 g 1-methylcyclopentane-2,5-dione (3·88 × 0·157 = 0·61 mol) were combined and refluxed for 19 hr. After cooling the BuOH was stripped off *in vacuo*. The aqueous residue was combined with 700 ml benzene, and the excess solid dione reagent was filtered off. It was washed well with benzene. The combined organic phases were thoroughly washed with six portions of 2 N Na_2CO_3, then with three portions of sat NaCl aq, dried and concentrated, to give 46·9 g of brown oil. This was dissolved in benzene and filtered through silicagel, to obtain, after concentration of the effluent with rinses, 40·2 g of the "secosteroid" (74·9% from the tetralone **7**).

From the vinyl carbinol **8**. For convenience (but not for highest yield), the secosteroid may be prepared directly from the vinyl carbinol. A mixture of 1·2 mg (catalytic amount, $8·68 \times 10^{-3}$ mmol) K_2CO_3, 486 mg (4·34 mmol) of 1 - methyl - cyclopentane - 2,5 - dione, 215·5 mg (0·868 mmol) of the vinyl carbinol **8** and 5 ml of t-BuOH was refluxed for 21 hr. After standing at room temp for 68 hr, the excess, separated dione was filtered off and washed with benzene. The combined organic liquids were extracted with four portions of 2 N Na_2CO_3, once with NaCl aq, dried and concentrated: 209·5 mg of oil (85% by weight, UV implies 85% of desired component). The conversion can also be accomplished using Triton B as catalyst.

Material which had been purified using silicagel, was used for physical measurements and analysis. Attempted distillation led to partial cyclization. NMR ($CDCl_3$) δ (assignments using steroid numbering) 0·22 (s, 6, Me_2Si), 0·94 (m, 2, $SiCH_2$). 1·17 (s, 3, C^{13}–CH_3), 2·52 overlapping 2·56 (m, d, 2, 2, J = 8 Hz, $SiCH_2\underline{CH_2}$ and $C^{12}\underline{H_2}$–C^{11}H=resp), 2·71 (s, 4, $OCCH_2CH_2CO$, accidentally degenerate), 3·81 (s, 3, CH_3O), 5·43 (t, 1, J = 8 Hz, $=C^{11}\underline{H}$–$C^{12}H_2$), 6·7–7·4 (m, 3, arom); ms, (heated inlet) (assignments using steroid nomenclature) 342 (P), 286 (P–$C^{13}H_2$–$C^{16}H_2$–C^{17}=O), 271 (286–CH_3), 259 (P–OC–CH_2–CH_2–CO), 231 (vinyl + rings AB), 215 (231–CH_3–H), 203 (rings AB), 189 (rings AB–CH_3), 175 (rings AB-2CH_3), 112 (ring D with $C^{18}H_3$); IR (neat), 2950, 1735, 1600, 1480, 1280, 1230, 1040, 825; UV (CH_3CN) λ = 260, ϵ = 12,400. (Found: C, 69·6; H, 8·0. Calcd for $C_{20}H_{26}O_3Si$: C, 70·1; H, 7·7%).

DL - 6,6 - *Dimethyl* - 6 - *sila* - 3 - *methoxyestra* - 1,3,5(10),8,14 - *pentaene* - 17 - *one*, **11**

Moisture was azeotropically removed by separately gently distilling off *ca.* 10% of the solvent from a soln of the "secosteroid" **10** (40·2 g) in 100 ml benzene, and by refluxing 1·4 g (catalytic amount) of *p*-toluenesulfonic acid hydrate in 500 ml benzene, employing a Dean-Stark water trap. The soln of the secosteroid was then added to the refluxing benzene-acid over a period of 1 hr. Refluxing was continued until the optical density of samples, removed periodically, stopped increasing at 308 nm (in CH_3CN), which took 22 hr. The mixture was cooled and washed with three portions of sat $NaHCO_3$ aq and with three portions of water. The extractions should be done with minimum simultaneous exposure to base and oxygen (colored by-product formation, probably fully conjugated 16,17-semidione). The base- and acid-free benzene soln was dried and concentrated to give 36·5 g of oil. This crude product was crystallized from 95% EtOH to give 20·3 g of pure silasteroid **11**, m.p. 92–101°. The mother liquor on chromatography yielded further product of good quality. Total yield from silatetralone **7**: 40%.

An analytically pure sample was prepared by additional crystallization from ether-pentane (−50°), 95% EtOH with charcoal treatment, m.p. 106–109·5°; NMR ($CDCl_3$, 60 MHz, with decoupling between 15 and 16 and 11 and 12, and 100 MHz, courtesy JEOL Co, Mr. R. Martin) δ 0·24 (s, 6, Me_2Si, accidental degeneracy), 1·15 (s, 3, $C^{18}H_3$), *ca.* 1·65, 1·75 and 2·0 (m, m, m, 4, SiCHH', $C^{12}\alpha$H, $C^{12}\beta$H), 2·7 (m, 2, C^{11}HH'), 2·94, 3·29, 5·93 (split d, brd, apparent t, 1, 1, 1, $C^{16}\beta$H, $C^{16}\alpha$H, C^{15}H, $J_{16\alpha,16\beta} = (-)23$, $J_{15,16\alpha} = 2$, $J_{15,16\beta} = 3$ Hz), 3·82 (s, 3, OCH_3), 6·87, 7·03, 7·43 (q, d, d, 1, 1, 1, arom C^2H, C^4H, C^1H, $J_{1,2} = 8·5$, $J_{1,4} = \sim 0$, $J_{2,4} = 2·5$ Hz); MS (direct inlet) 324 (P), 309 (P–CH_3), 296 (P–CO), 281 (P–$OCCH_2$–H), 267 (P–$OCCH_2CH_2$–H), 251 (Rings ABC; in

fragments 281, 267, 251 *et sequ.* ring C is probably aromatized (migration of Δ^{14} into C)), 237 (rings ABC-CH_3), 223 (rings ABC-2CH_3), 209 (rings ABC-3 CH_3), 191, 189, 178, 165, 148, 133 (Me_2SiCH_2 + ring C + C^{18} + C^{15} + C^{16} with gradual losses of appended carbons and at various unsaturations of ring C), 165 (also likely: ring A + H + $SiMe_2$); IR ($CHCl_3$) 2950, 1745, 1595, 1465, 1290, 1040, 845; UV (CH_3CN) sh 216/14180, 236/13700, sh 242/12200, 308/22300. (Found: C, 74·0; H, 7·3. Calcd for $C_{20}H_{24}O_2Si$: C, 74·0; H, 7·5%).

For comparison, the corresponding 6-CH_2-steroid:[16] UV (EtOH) 313 nm/ϵ = 35,100.

DL - 6,6 - *Dimethyl* - 6 - *sila* - 3 - *methoxy* - 17β - *hydroxyestra* - 1,3,5(10),8,14 - *pentaene*, **12**

An amount of **11** (53·3 g; 164·5 mmol) was dissolved in a mixture of 250 ml each of toluene and MeOH. The soln was cooled to −60°, and with stirring, $NaBH_4$ (6·21 g; 164·5 mmol) was added. The mixture was allowed to warm to −20° over a period of 45 min, was stirred for 30 min at −20°, then during 1·5 hr was allowed to warm to 25°. It was recooled to near 0° and cautiously acidified with *ca.* 50 ml (slight excess) of AcOH. After 15 min of additional stirring, the mixture was concentrated to an oil. The oil in benzene soln was extracted with water and three small portions of brine, the organic soln was dried ($MgSO_4$) and concentrated: 62·7 g of oily product (contains solvent, but suitable for the next step). An analytical sample of the monohydrate was obtained by crystallization sequentially with pentane, ether-pentane 2 × methanol, isopropanol-water, DMF-water, ether-pentane and iPrOH-water: m.p. 67–73°, NMR ($CDCl_3$) δ 0·18, 0·24 (s, s, 3, 3, SiMeMe'), 0·98 (s, 3, $C^{18}H_3$), 1·2–2·9, incl 2·1 (m, s, ~11, 4 CHH' incl OH), 3·82 (s, 3, OCH_3), 4·08 (q, 1, J_{app} = 7·5, J'_{app} = 9·5 Hz, 17αH), 5·56 (t, 1, J_{app} = 2 Hz, $C^{15}H$), 6·86, 7·0, 7·41 (q, d, d, 1, 1, 1, arom at C^2, C^4, C^1, $J_{1,2}$ = 8·5, $J_{2,4}$ = 2·5 Hz; IR ($CHCl_3$) 3675, 3600, br 3450, 2925, 1582, 1462, 1400, 1285, 1070, 835; UV (CH_3CN) sh 217/13000, 237/11520, sh 245/10000, 308/21815. (Found: C, 69·8; H, 8·2. Calcd for $C_{20}H_{26}O_2Si{\cdot}H_2O$: C, 69·7; H, 8·15%). A sample dried over P_4O_{10}, 64 hr, 25°, 0·1 mm: (Found: C, 72·3; H, 8·5. Calcd for $C_{20}H_{26}O_2Si$: C, 73·6; H, 8·0%).

DL - 6,6 - *Dimethyl* - 6 - *sila* - 3 - *methoxy* - 17β - *acetoxyestra* - 1,3,5(10),8,14 - *pentaene*, **13**

The 17β-hydroxy compound **12** (62·7 g, max. 164·5 mmol) was dissolved in 360 ml Ac_2O, and 1·8 ml pyridine was added. After 16 hr additional 1·8 ml pyridine was added. The soln was kept at 25° for a total of 3·5 days by which time it largely crystallized. The slurry was added to and stirred with 150 ml MeOH at 0°. Filtration gave 32·4 g of first crop, m.p. (120)–123–134°. The filtrate upon concentration and MeOH-crystallization gave 15 g of second crop m.p. (123)-131–133°. Combined yield 49·2 g, 81% from the ketone **11**. Material for analysis was obtained by two recrystallizations from MeOH: m.p. 134–136·5°; NMR ($CDCl_3$) δ 0·19, 0·24 (s, s, 3, 3, SiMeMe'), 1·02 (s, 3, $C^{18}H_3$) 1·2–3·0 (m, 8, 4 CHH'), 2·10 (s, 3, AcO), 3·82 (s, 3, OCH_3), 5·04 (t, 1, J_{app} = 8·5 Hz, 17αH), 5·57 (t, 1, J_{app} = 2·7 Hz, $C^{15}H$), 6·87, 7·03, 7·43 (q, d, d, 1, 1, 1, $J_{1,2}$ = 8·5, $J_{2,4}$ = 2·5 Hz, arom C^2H, C^4H, C^1H); IR ($CHCl_3$) 2950, 1730, 1590. 1440, 1380, 1250, 1035, 840; UV (CH_3CN) sh 220/17800, 237/14600, sh 245/12300, 262/4250, 308/23653. (Found: C, 71·6; H, 8·1, 8·0. Calcd for $C_{22}H_{28}O_3Si$: C, 71·7; H, 7·7%).

DL - 6,6 - *Dimethyl* - 6 - *sila* - 3 - *methoxy* - 17β - *acetoxyestra* - 1,3,5(10), 8-*tetraene*, **14**

5% Pd on $CaCO_3$ (10 g) was thoroughly prehydrogenated in 350 ml abs EtOH. At once **13** (5 g; 13·6 mmol) was added, and the mixture was vigorously stirred. In 3 min 338 ml (~13·52 mmol) of H_2 was taken up. Stirring was promptly stopped and the catalyst was immediately filtered off. Concentration gave 5·36 g of oil. Treatment with 95% EtOH yielded 1·45 g crystalline single isomer, assigned 14α on grounds of steric approach control and analogies,[16,14] m.p. 87–90°. The mother liquor contained more of this and its minor epimer. A sample for analysis was additionally recrystallized from heptane and from MeOH, m.p. 92–93°, NMR ($CDCl_3$) δ 0·22 (s, 6, SiMeMe', accidental degeneracy), 0·85 (s, 3, $C^{18}H_3$), 1·2–2·9 (m, ~11, aliph. envelope), 2·05 (s, 3, AcO), 3·81 (s, 3, OCH_3), 4·77 (t, 1, J_{app} = 8 Hz, 17αH), 6·67–7·07 and 7·32 (m, d, 2, 1, C^2H + C^4H, C^1H, $J_{1,2}$ = 8·5 Hz); IR (CS_2) 2925, 1730, 1385, 1282, 1230, 1035, 830 cm^{-1}; UV (CH_3CN) 280/14500 (Found: C, 70·9; H, 8·3. Calcd for $C_{22}H_{30}O_3Si$: C, 71·3; H, 8·2%).

Acknowledgements—We wish to thank Mr. U. Stoeckli for physical, Mr. W. J. Bonkoski for microanalytical and Mr. L. E. Janaskie for separation services, and to Dr. A. J. Frey for encouragement to pursue this work. Biological tests on the end product(s) were performed by Dr. R. E. Elton *et al.* We thank the JEOL Co. and Mr. R. Martin for a 100 MHz NMR spectrum.

REFERENCES

[1]S. Barcza and C. W. Hoffman, *2nd Intern. Symp. on Organosilicon Chemistry, Abstracts* (II^e Symposium International sur la Chimie des Composes Organiques du Silicium, Resumes des Communications) pp. 12–13, Bordeaux, France (1968). See also, S. Barcza, *U.S. Pat* 3,637,782 (25 Jan. 1972) and 3,529,005 (15 Sept. 1970). Substantial continuation of this work occurred by Pitt *et al.*[2]

[2]C. G. Pitt, A. E. Freidman, D. Rector and M. C. Wani, in press. We thank Dr. Pitt for sending us a manuscript before publication.

[3]C. A. Burkhard, E. G. Rochow, H. S. Booth and J. Hartt, *Chem. Rev.* **41**, 97 (1947).

[4]R. J. Fessenden and J. S. Fessenden, *Adv. in Drug Research* **4**, 92 (1967); L. R. Garson and L. K. Kirchner, *J. Pharm. Sci.* **60**, 1113 (1971); E. Bien, *Die Pharmazie*, **26**. 577 (1971); *Silicon and Life. Biochemistry, Toxicology and Pharmacology of Silicon Compounds* (*Kremnii i Zhizn*....) by M. G. Voronkov, G. I. Zelchan and E. Ya. Lukevits (Zinatne Riga, Latvian SSR) 1971, 327 pp. German translation/publication in progress.

[5]R. J. Fessenden and M. D. Coon, *J. Med. Chem.* **8**, 604 (1965).

[6]C. Hansch, *Accounts Chem. Res.* **2**, 232 (1969).

[7]R. Nakayama and M. Masuoka, *J. Pharm. Soc. Jap.* **94**, 238 (1974).

[8]S. N. Ananchenko and I. V. Torgov, *Tetrahedron Letters* 1553 (1963); J. Weill-Raynal, *Bull. Soc. Chim. Fr.* 4566 (1969).

[9]H. O. Huisman, *Angew. Chem.* Intnat. Edn. **10**, 450 (1971).

[10]For a general application of this sequence to allylsilanes see S. Barcza and M. G. Hidalgo, *Third Internat. Symp. on Organosilicon Chem.* Abstracts of Papers, p. 20. Madison, Wisc., U.S.A. (1972).

[11]D. Wittenberg, P. B. Talukdar and H. Gilman, *J. Am. Chem. Soc.* **82**, 3608 (1960), 4,4 - diphenyl - 4 - sila - 1 - tetralone; their conditions were not applicable to our case.

[12]W. S. Johnson, *Org. Reactions* **2**, 144 (1944).

[13]C. Eaborn, DRM. Walton and M. Chan, *J. Organometal. Chem.* **9**, 251 (1967).

[14]E. Galantay and H. P. Weber, *Experientia* **25**, 571 (1969); and unpublished information.

[15]D. P. Strike, T. Y. Jen, G.A. Hughes, G. H. Douglas and H. Smith, *Steroids* **8**, 309 (1966).

[16]G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.* 5072 (1963), *Ibid.* 4472 (1964).