Anal. Calcd for $C_{22}H_{23}NO_5$ (381.4): C, 69.27; H, 6.07; N, 3.67. Found: C, 68.96; H, 6.11; N, 3.68.

Acknowledgment. We thank the National Institute on Drug Abuse for financial support.

Registry No. 1, 78914-30-4; 4, 83967-59-3; 6, 103258-80-6.

Reaction of Benzeneselenenyl Halides with 3-Keto Steroids. A Novel Method for α-Bromination

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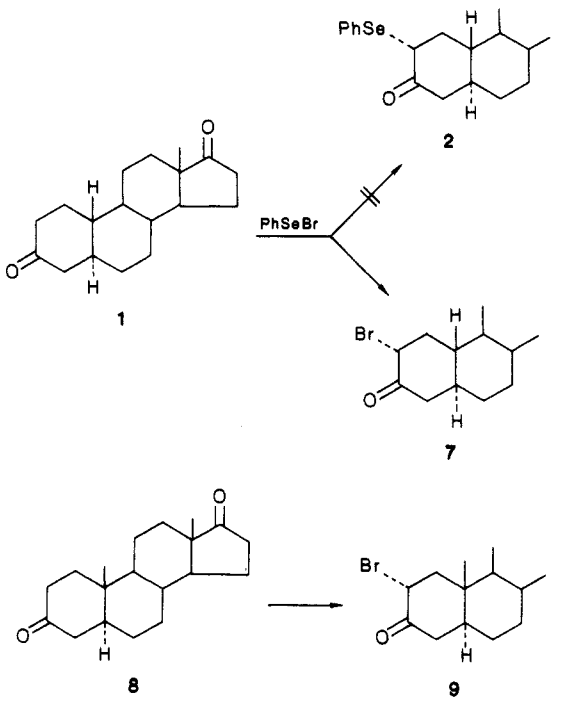
Received April 10, 1986

Recent studies on the introduction of the 1,2-double bond in 5α-estrane-3,17-dione (1) using benzeneselenenyl chloride[1] showed the formation of an unusual product which was identified as 2-chloro-5α-estr-1-ene-3,17-dione (5). It was proposed that compound 5 was formed by electrophilic attack of the chloro group in PhSeCl on 2-(phenylselenenyl)-5α-estrane-3,17-dione (2) to yield 2-chloro-2-(phenylselenenyl)-5α-estrane-3,17-dione (4) which undergoes 1,4-elimination following H_2O_2 oxidation as described by Sharpless et al.[2] It is interesting to note that the yield of 2-chloro-5α-estrenedione (5) is dependent on the amounts of PhSeCl used in the reaction mixture. Thus, as the molar ratio of PhSeCl increases the yield of compound 5 increases with a corresponding decrease in the formation of both 4-estrene-3,17-dione and 5α-estr-1-ene-3,17-dione (Table I).

To explore the reaction mechanism of formation of 2-chloro-5α-estrenedione (5), it was rationalized that compound 5 could be formed by either route a or route b as shown in Scheme I. When compounds 2 and 3 were reacted with PhSeCl, only compound 2 yielded 5, indicating that pathway a is involved in the formation of 5 from 1 using PhSeCl.

In an attempt to further extend these studies, it was presumed that reaction of 1 with PhSeBr would also follow the same reaction pathway leading to formation of 2-bromo-5α-estr-1-ene-3,17-dione (6). However, instead of introduction of the 1,2-double bond in 5α-estrane-3,17-dione (1), PhSeBr gave another compound which crystallized out of the reaction mixture and was shown by mass spectral analysis to be a monobromo estrane-3,17-dione. These observations led us to investigate the bromination of 3-keto 5α- and 5β-steroids by PhSeBr and to compare these products with bromo compounds obtained from brominations using bromine in acetic acid.

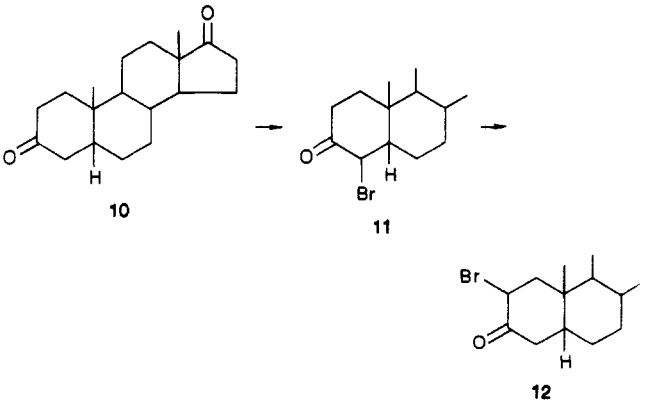
In a typical reaction, PhSeBr (404 mg) was added to 5α-estrane-3,17-dione (1) (390 mg) in ethyl acetate (15 mL), and the resulting solution was kept at room temperature for 1 h to afford, after purification by preparative thin-layer chromatography, compound 7 in yields ranging between 60% and 70%. This yield did not seem to increase even after a 96-h reaction time. Compound 7 was found to be identical with that obtained from bromination of 1 with Br_2/HOAc. Similarly, 5α-androstanedione (8) gave 2α-bromo-5α-androstane-3,17-dione (9) following reaction



of 8 with either PhSeBr or Br_2/HOAc.

It is interesting to note that in both the C-19 methyl and 19-nor 5α-series, the kinetically stable product is the 2α-bromo 5α-steroid, which suggests that steric hindrance due to the presence of the C-19 methyl group may be of secondary importance in determining the direction of attack by the brominium group as proposed by Corey[3,4] and later extended by Valls and Toromanoff.[5]

The above results on the bromination of 3-keto 5α-steroids are not unexpected since it is well documented that 3-keto 5α-steroids enolize primarily toward C-2.[6] However, in the case of 3-keto 5β-steroids, enolization toward C-4 predominates.[7] Thus, reaction of 5β-androstanedione (10) with Br_2/HOAc gave compound 11 which was found to be identical with an authentic sample of 4β-bromo-5β-androstanedione (11). Reaction of 10 with



PhSeBr for 1 h gave compound 11 in 65% yield, and its NMR spectrum showed a characteristic doublet centered at 4.94 ppm (J = 11.5 Hz), for C-4 proton and was identical with that of the product obtained from bromination of 10 with Br_2/HOAc. However, increasing the reaction time

(1) Abul-Hajj, Y. J. *J. Chem. Soc.* **1985**, 1479.
(2) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(3) Corey, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 175.
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(7) Turner, A. B.; Ringold, H. J. *J. Chem. Soc.* **1967**, 1720.

0022-3263/86/1951-3380$01.50/0

Scheme I

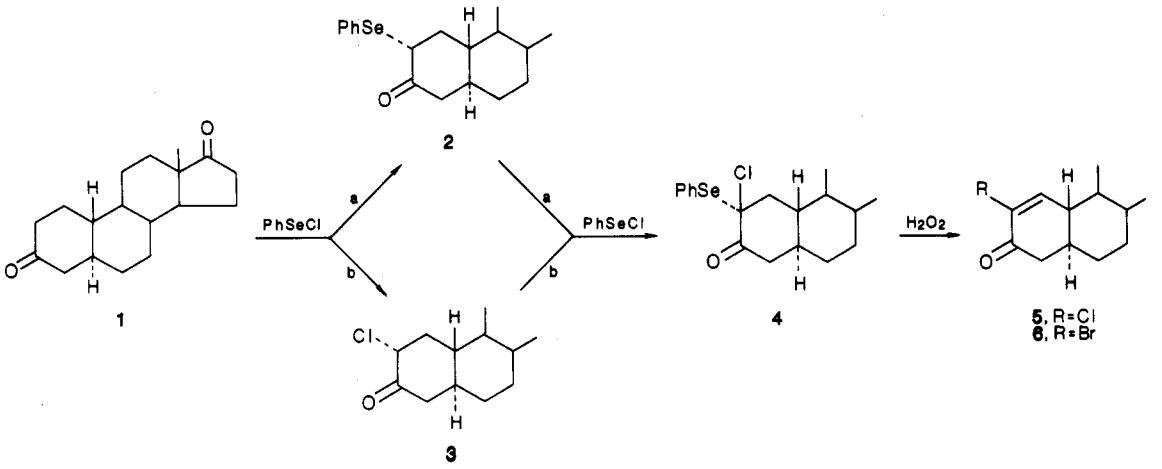


Table I. Effect of Increasing PhSeCl Molar Ratio on Product Formation

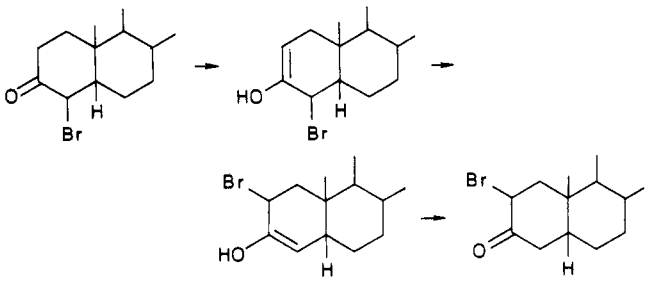
molar ratio of PhSeCl/5α-E-dione[a]	% yield		
	5α-E-1-dione	4-E-dione	2-chloro-5α-E-1-dione
1.0	55	24	15
1.5	42	20	30
2.0	20	15	50
4.0	0	10	65
10.0	0	5	70

[a] 5α-E-dione = 5α-estrane-3,17-dione. 5α-E-1-dione = 5α-estr-1-ene-3,17-dione. 4-E-dione = 4-estrene-3,17-dione. 2-chloro-5α-E-1-dione = 2-chloro-5α-estr-1-ene-3,17-dione

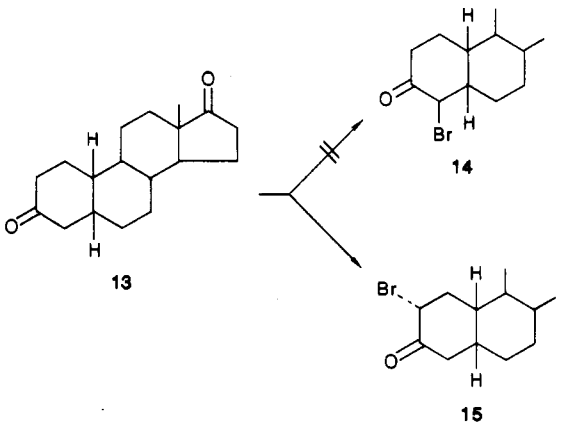
from 1 to 20, 44 and 96 h, which does not change significantly the overall yield of the product, results in a steady decrease in the C-4 proton peak and the appearance of and a simultaneous increase in a new proton peak appearing as a double doublet centered at 4.64 ppm with splitting constants of J = 14.07 and 5.72 Hz. While the exact stereochemistry of this new proton is not fully established, the initial studies obtained from IR and NMR data indicate that this compound is most likely 2β-bromo-5β-androstane-3,17-dione (**12**). The splitting constants for a 2α-proton and the shift of the C-19 methyl peak from 1.123 ppm in **11** to 1.089 ppm in **12** suggest that the reaction of compound **10** with PhSeBr leads to the formation of the kinetically controlled product **11**, which undergoes isomerization to the thermodynamically stable product **12**.

The equatorial bromine in **11** could arise from bromination of the half-boat conformation (a) by axial attack at the 4β-position followed by a conformational flip to the equatorial chair form as suggested by Liston,[8] (b) by axial attack of the chair conformation leading to the kinetically controlled 4α-bromo product followed by isomerization, through enol intermediate, to the thermodynamically stable 4β-bromo product as reported by this laboratory,[9] or (c) by direct equatorial attack as proposed by Villotti et al.[10] As to the exact mechanism for isomerization of **11** to **12**, the pathway proposed in Scheme II suggests an allylic rearrangement in the enolic form. This mechanism is essentially similar to that involving isomerization of 2,2-dibromocholestanone to 2α,4α-dibromocholestanone as shown by Warnoff.[11]

Scheme II



Earlier studies by Rapala and Farkas[12] reported that bromination of 5β-estrane-3,17-dione (**13**) using Br_2/HOAc results in the formation of 4β-bromo-5β-estranedione (**14**).



However, in a recent study in our laboratory,[13] it was found that the bromo product obtained from bromination of **13** with Br_2/HOAc was not **14** but the 2α-bromo product **15**. This was proven by NMR analysis and dehydrobromination studies.[13] This same product (**15**) was also obtained from reaction of **13** with PhSeBr. These studies indicate that enolization of 5β-estrane-3-ones is directed toward C-2. These results are contrary to those reported earlier by Rapala and Farkas[12] and are consistent with our recent results on studies involving introduction of 1,2-double bond in 5β-estrane dione using PhSeCl.[1] It is quite interesting to note that bromination of **13** leads to the formation of the axially oriented 2α-bromo compound **15**, which appears to be the kinetically and thermodynamically stable product even though the α-side of ring A is considerably hindered in 5β-steroids.

(8) Liston, A. J. *J. Org. Chem.* **1966**, *31*, 2105.
(9) Abul-Hajj, Y. J. *J. Labelled Cmpd.* **1970**, *7*, 261.
(10) Villotti, R.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 5693.
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(13) Abul-Hajj, Y. J. *J. Org. Chem.* **1986**, *51*, 3059.

In conclusion, the results obtained from these studies show that benzeneselenenyl halides react quite differently with 3-keto steroids in ethyl acetate and that PhSeBr is useful for the preparation of α-bromo 3-keto steroids.

Experimental Section

Melting points (uncorrected) were obtained on a Fisher-Johns apparatus. NMR spectra were determined with a JEOL-90Q spectrometer. Infrared spectra were recorded with a Perkin-Elmer 281 spectrophotometer. High-resolution mass spectra were taken on LKB-9000.

General Bromination Procedure Using Br_2/HOAc. To a solution of 3-keto steroid (350 mg, 13 mmol) in glacial acetic acid (6 mL) was added a solution (4 mL, 1 M) of bromine in glacial acetic acid, dropwise with stirring, at room temperature for 1 h. The bromo 3-keto 5α-steroids crystallized out and were purified by recrystallization from acetone–hexane. For the bromo 3-keto 5β-steroids, the reaction mixture was poured over water and extracted with $CHCl_3$. The chloroform fraction was dried ($MgSO_4$), filtered, and evaporated to give a residue from which pure α-bromo 3-keto steroids were purified by preparative thin-layer chromatography using benzene–ethyl acetate (3:1).

General Procedure for Bromination of 3-Keto Steroids Using PhSeBr. To a solution of 3-keto steroid (390 mg, 14.2 mmol) in ethyl acetate (15 mL) was added PhSeBr (404 mg, 17.2 mmol). The reaction mixture was kept at room temperature for 1 h. Bromo 3-keto 5α-steroids crystallized out of the reaction mixture and were purified by recrystallization from acetone–hexane. Bromo 3-keto 5β-steroids were applied directly to a preparative TLC as described above.

2α-(Phenylselenenyl)-5α-estrane-3,17-dione (2). To a solution of 1 (390 mg, 14.2 mL) in ethyl acetate (15 mL) was added PhSeCl (330 mg, 17.2 mmol). The resulting red orange solution was stirred at room temperature until it turned pale yellow. Chromatography over silica gel (hexane) gave 230 mg (60%) of 2 as colorless crystals. Recrystallization from acetone–hexane gave an analytical sample: mp 184–185 °C; ^{1}H NMR ($CDCl_3$) δ 0.912 (s, 3 H, C-18 CH_3), 4.13 (dd, 1 H, J = 13.68, 5.70 Hz, C-2 H), 7.23–7.30 (m, 3 H), 7.50–7.59 (m, 2 H).

2α-Chloro-5α-estrane-3,17-dione (3). To a solution of 1 (110 mg) in HOAc (1.5 mL) was added freshly prepared *tert*-butyl hypochlorite[14] (0.04 mL) and warmed to 65 °C for 1 h.[15] The reaction mixture was kept at room temperature overnight to yield white crystalline material. Crystals were filtered, washed with MeOH, and recrystallized from MeOH to yield 83 mg of 3 (73%): mp 242–244 °C; IR (KBr) 1740 (17-ketone), 1729 (3-ketone) cm^{-1}; ^{1}H NMR δ 0.90 (s, 3 H, C-18 CH_3), 4.48 (dd, 1 H, J = 13.58, 5.70 Hz, C-2 H); mass spectrum, calcd for $C_{18}H_{25}ClO_2$ m/e 308.85175, found m/e 308.84935.

2-Chloro-5α-estr-1-ene-3,17-dione (5). To a solution of 2 (80 mg) in ethyl acetate (3 mL) was added PhSeCl (65 mg) and the reaction mixture stirred for 1 h. The ethyl acetate solution was extracted with two 3-mL portions of H_2O and cooled to 10 °C, at which time 0.04 mL of 30% H_2O_2 is added. An additional 0.02 mL of 30% H_2O_2 was added after 10 min and again after 20 min. After the mixture was stirred for an additional 40 min, 5-mL of H_2O was added and the ethyl acetate layer separated, washed, dried over $MgSO_4$, and evaporated to dryness. The reaction mixture was resolved on preparative TLC as described above to yield 30 mg (37%) of 2-chloro-5α-estr-1-ene-3,17-dione (5), mp 177–179 °C. NMR and IR were identical with those of the previously synthesized compound.[1]

2α-Bromo-5α-estrane-3,17-dione (7): yield 75% from Br_2/HOAc reaction and 66% from PhSeBr reaction; mp 234–235 °C; IR (KBr) 1740 (17-ketone), 1725 (3-ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3 H, C-18 CH_3), 4.64 (dd, 1 H, J = 13.63, 5.71 Hz, C-2 H); mass spectrum, m/e (relative intensity) 354 (M^+ + 1, 44), 352 (M^+ - 1, 41), 273 (M^+ - Br, 69), 255 (43), 203 (37), 185 (43), 147 (100), 108 (59), 91 (59); mass spectrum, calcd for $C_{18}H_{25}BrO_2$ m/e 353.30775, found m/e 353.30695.

2α-Bromo-5α-androstane-3,17-dione (9): 87% and 73% yields from Br_2/HOAc and PhSeBr reactions, respectively; mp 206–207 °C; NMR and IR were identical with those of an authentic sample of 9.

4β-Bromo-5β-androstane-3,17-dione (11): 79% and 65% yields from Br_2/HOAc and PhSeBr reactions, respectively; mp 192–194 °C; IR (KBR) 1740 (17-ketone), 1726 (3-ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H, C-18 CH_3), 1.123 (s, 3 H, C-19 CH_3), 4.94 (d, 1 H, J = 11.5 Hz, C-4 H).

2β-Bromo-5β-androstane-3,17-dione (12). Reaction conditions were essentially similar to those used for bromination with PhSeBr described above except the time of reaction was increased from 1 to 96 h, which results in a mixture of 11 and 12 in a ratio of 1:5 based on NMR analysis. Recrystallization from acetone–hexane gave 45% yield of the analytical product: mp 198–199 °C; IR (KBr) 1740 (17-ketone) 1727 (3-ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H, C-18 CH_3), 1.089 (s, 3 H, C-19 CH_3), 4.69 (dd, 1 H, J = 14.07, 5.72 Hz, C-2 H); mass spectrum, m/e (relative intensity) 369 (M^+ + 1, 74), 367 (M^+ + 1, 73), 288 (M^+ - Br, 100), 270 (67), 231 (45), 218 (84), 200 (51), 161 (69), 122 (44); mass spectrum, calcd for $C_{19}H_{27}BrO_2$ m/e 367.55174, found m/e 367.55196.

2α-Bromo-5β-estrane-3,17-dione (15): 86% and 84% yields were obtained from Br_2/HOAc and PhSeBr reactions, respectively; mp 186–188 °C; ^{1}H NMR δ 0.90 (s, 3 H, C-18 CH_3), 4.64 (q, 1 H, J = 4.2 Hz, C-2 H).

Registry No. 1, 5696-58-2; 2, 103304-60-5; 3, 103304-61-6; 5, 101366-71-6; 7, 103304-62-7; 8, 846-46-8; 9, 28507-01-9; 10, 1229-12-5; 11, 4588-83-4; 12, 18000-82-3; 13, 5696-51-5; 15, 102922-53-2.

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Palladium-Mediated Diazo Insertions: Preparation of 3-Alkyl-2-carbomethoxycyclopentenones

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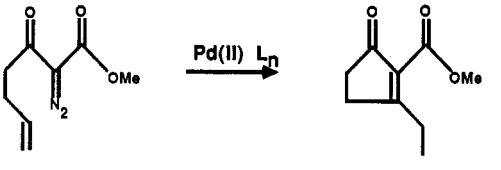
The development of new methods for carbocyclic ring formation is one of the abiding concerns of synthetic organic chemistry. We report a new method for the preparations of 3-alkyl-2-carbomethoxycyclopentenones, based on palladium(II)-mediated[3] cyclization of β-alkenyl α'-diazo ketones (1 → 2).[4,5]



1 2

We have briefly examined the scope of this reaction (Table I). While in general $PdCl_2$·$(PhCN)_2$[6] is effective

(1) Fellow of the Alfred P. Sloan Foundation, 1982–1987.
(2) Undergraduate research participant, University of Delaware.
(3) (a) Anciaux, A.; Hubert, A.; Noels, A.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695. (b) Casey, C. P.; Shusterman, A. J. *J. Mol. Cat.* **1980**, *8*, 1.
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(5) Lewis acid catalyzed rearrangement of β- and γ-alkenyl α'-diazo ketones to cyclopentenones has been reported. (a) Smith, A. B., III; Toder, B. H.; Branca, S. J.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 1996. (b) Doyle, M. P.; Trudell, M. L. *J. Org. Chem.* **1984**, *49*, 1196. Similar acid-mediated cyclization of the diazoesters in Table I was attempted but was not successful.
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