A Caveat Concerning the Use of *N*-(Phenylseleno)phthalimide and Tri-*n*-butylphosphine for the Conversion of Alcohols to Selenides. Formation of 3-Phthalimido Derivatives from an Allylic 3-Sterol[1a]

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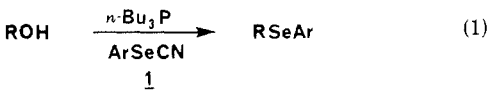
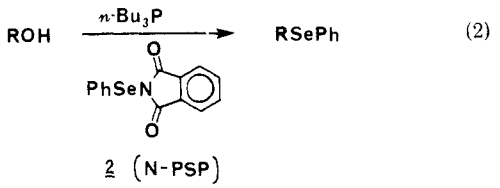
Several years ago, Grieco and co-workers[2] reported an effective and convenient method for the one-step transformation of primary or secondary alcohols to selenides with aryl selenocyanates **1** and tri-*n*-butylphosphine (eq 1). More recently *N*-(phenylseleno)phthalimide (N-PSP,



(1)



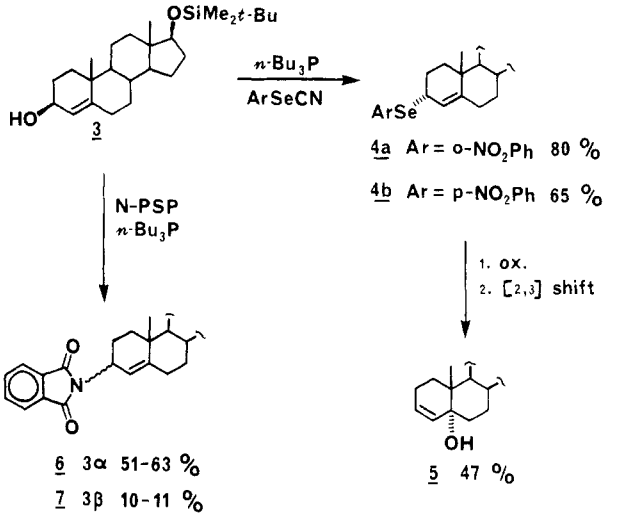
(2)

2) has been employed instead of the selenocyantes **1**, with equally impressive results[3,4] (eq 2). In the case of the latter reagent, excess N-PSP (1.5–2.0 equiv) and phosphine (2.0 equiv) are typically required, and reported examples to date have been confined to primary alcohols.[3,6]

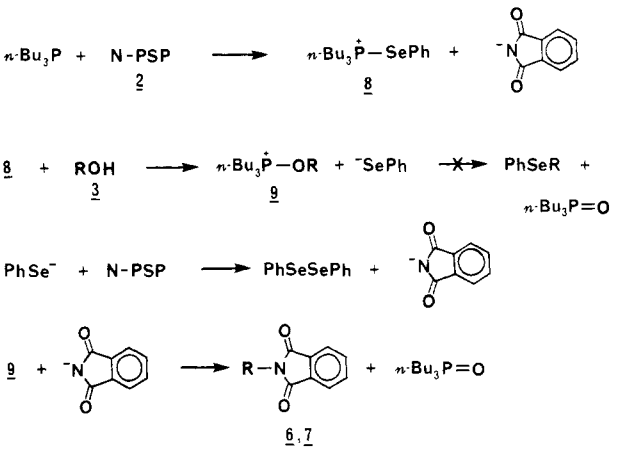
We recently required a convenient source of the Δ^3-5-sterol **5** and endeavored to prepare it from the readily available[7] Δ^4-3-hydroxy isomer **3** by means of a 1,3-allylic alcohol transposition such as previously described by Clive et al.[8] with various primary allylic alcohols. This procedure requires the conversion of the sterol **3** to the selenide **4**, followed by [2,3]-sigmatropic rearrangement of the corresponding selenoxide to the desired **5** (Scheme I).

The preparation of **4** (Ar = Ph) was first attempted with excess N-PSP and tri-*n*-butylphosphine in THF at 0 °C, as this would simultaneously test whether the method[3] is effective for secondary as well as for primary alcohols. However, instead of the expected selenide, the principal products proved to be the 3α- and 3β-phthalimido steroids

Scheme I



Scheme II



6 and **7**, obtained in yields of 51% and 10%, respectively (Scheme I). These yields were slightly enhanced (**6**, 63%; **7**, 11%) when the phosphine was introduced via slow addition.

The stereochemical assignment of **6** and **7** as the 3α and 3β epimers, respectively, is based on the observation that the major isomer **6** has ^{1}H NMR signals from both the proton at C-3 and those of the angular methyl group C-19 further upfield than its counterpart **7**. Moreover, the vinylic proton at C-4 is found further downfield in **6** than in **7**. These findings are consistent with similar trends reported for the chemical shifts of other Δ^4-3α and -3β substituted steroids, including the somewhat related 3-acetamido derivatives.[9]

Neither the use of only a stoichiometric amount of N-PSP nor its slow addition to the reaction mixture produced any significant amounts of the selenide **4**. Diphenyl diselenide was a major byproduct in all of these reactions.

The first steps in the mechanism of this process appear to resemble those proposed by Grieco et al.[2] for the variation employing aryl selenocyanates and entail the successive formation of phosphonium intermediates **8** and **9** (Scheme II). When **9** is derived from a primary alcohol, the displacement of the phosphine oxide by the selenolate anion is facile and gives the usual selenide product. In the present instance, however, where **9** is obtained from a secondary allylic alcohol,[10] attack by the selenolate must

(1) (a) We gratefully acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada and from the Alberta Heritage Foundation for Medical Research. (b) Recipient of an AHFMR Postgraduate Studentship.

(2) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(3) Grieco, P. A.; Jaw, J. Y.; Claremon, D. A.; Nicolaou, K. C. *J. Org. Chem.* **1981**, *46*, 1215.

(4) Both reagents **1** and **2** have also been employed for the conversion of carboxylic acids to their seleno esters in a related process.[3,5]

(5) Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283.

(6) (a) Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1001. (b) Ley, S. V.; Neuhaus, D.; Simpkins, N. S.; Whittle, A. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2157. (c) Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 503.

(7) Hosoda, H.; Yamashita, K.; Sagae, H.; Nambara, T. *Chem. Pharm. Bull.* **1975**, *23*, 2118.

(8) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 770.

(9) Ortar, G.; Paradisi, M. P.; Morera, E.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 4.

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instead occur preferentially upon a second molecule of N-PSP, particulary if the reagent is present in large excess. This results in the formation of the diselenide and phthalimide anion, which reacts further with **9** to afford the observed products **6** and **7**. It is not clear whether the product-forming step involves an S_N1 or S_N2 process as both are expected to favor the major stereoisomer **6**. A predominantly S_N2 displacement would result in inversion of configuration at C-3 from β to α, while an S_N1 step would produce an allyl cation which is known to undergo preferential nucleophilic attack from the α-face in the cholestane series.[9]

In contrast to the above results, sterol **3** was smoothly converted to selenides **4a** and **4b** with selenocyanates **1a** and **1b** in yields of 80% and 65%, respectively. Evidently the selenocyanates are less effective than N-PSP in competing with the alkoxyphosphonium ion **9** for available selenolate. Product **4a** was transformed to the rearranged alcohol **5** in 47% yield with *m*-chloroperbenzoic acid;[11] **4b** provided a slightly lower yield.[12] These experiments suggest that selenocyanates are a more prudent choice than N-PSP for the conversion of secondary alcohols to selenides.

Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 467 instrument while NMR spectra were obtained on a Varian XL200 spectrometer at 200 MHz in $CDCl_3$ solution with tetramethylsilane as the internal standard. A Varian MAT CH5 instrument was employed in recording mass spectra and optical rotations were measured on a Rudolph Autopol III polarimeter in $CHCl_3$ solution. Elemental analyses were performed by Dr. W. S. Lin (University of Calgary). Preparative TLC was carried out on Analtech 20 × 20 cm glass plates coated with 1 mm of silica gel GF. Sterol **3** was prepared by a variation of a literature method,[7] via the reduction of the corresponding enone with diisobutylaluminum hydride. Selenocyanates **1a** and **1b**,[14] as well as N-PSP,[15] were obtained by previously reported procedures. Tri-*n*-butylphosphine and *m*-chloroperbenzoic acid were purchased from the Aldrich Chemical Co. and used without further purification.

Reaction of 3β,17β-Dihydroxy-4-androstene 17-(*tert*-Butyldimethylsilyl Ether) (3) with N-PSP and Tri-*n*-butylphosphine. Sterol **3** (203 mg, 0.50 mmol) and N-PSP (302 mg, 1.00 mmol) were dissolved in 3 mL of dry, degassed THF at 0 °C under nitrogen. The phosphine (0.25 mL, 1.0 mmol) was introduced via syringe and the solution was stirred at 0 °C for 2 h. The mixture was then concentrated and filtered through a short column of silica gel with ethyl acetate as the solvent to remove polar byproducts (tri-*n*-butylphosphine oxide, phthalimide), and the remaining products were separated by preparative TLC in 15% ethyl acetate–hexane to afford three principal bands: (A) Diphenyl diselenide: 110 mg (71%); R_f 0.72; identified by comparison with an authentic sample (TLC, mp, NMR). (B) 17β-Hydroxy-3α-phthalimido-4-androstene *tert*-butyldimethylsilyl ether (**6**): 137 mg (51%); R_f 0.52; mp 152–155 °C (from dichloromethane–methanol); $[\alpha]_D$ +155°; IR (Nujol) 1760, 1715, 1608 cm^{-1}; ^1H NMR 7.9–7.7 (m, 4 H), 5.19 (d, J = 2.4 Hz, 1 H), 4.78 (m, 1 H), 3.56 (t, J = 8 Hz, 1 H), 1.04 (s, 3 H), 0.87 (s, 9 H), 0.73 (s, 3 H); mass spectrum, m/e (relative intensity) 533 (M^+, <1), 476 ($M^+ - C_4H_9$, 25). Anal. Calcd for $C_{33}H_{47}NO_3Si$: C, 74.25; H, 8.88; N, 2.62. Found: C, 74.65; H, 8.88; N, 2.44. (C) The 3β-epimer **7**: 28 mg (10%); R_f 0.46; mp 226–227 °C (from dichloromethane–methanol); $[\alpha]_D$ −25°; IR ($CHCl_3$) 1768, 1707, 1609 cm^{-1}; ^1H NMR 7.9–7.7 (m, 4 H), 5.11 (d, J = 1.5 Hz, 1 H), 4.84 (m, 1 H), 3.56 (t, J = 8 Hz, 1 H) 1.21 (s, 3 H), 0.88 (s, 9 H), 0.74 (s, 3 H); mass spectrum, m/e (relative intensity) 533 (M^+, 2), 476 ($M^+ - C_4H_9$, 61). Anal. Calcd for $C_{33}H_{47}NO_3Si$: C, 74.25; H, 8.88; N, 2.62. Found: C, 74.22; H, 8.86; N, 2.61.

In a separate experiment the phosphine in 2 mL of THF was added over 1.5 h to the other reactants via a mechanically driven syringe. After workup as above, the yields of **6** and **7** were 168 mg (63%) and 30 mg (11%), respectively.

17β-Hydroxy-3α-[(2-nitrophenyl)seleno]-4-androstene *tert*-Butyldimethylsilyl Ether (4a). Sterol **3** (2.03 g, 5.00 mmol) and *o*-nitrophenyl selenocyanate (**1a**, 1.25 g, 5.50 mmol) were dissolved in 40 mL of dry THF under nitrogen. Tri-*n*-butylphosphine (1.5 mL, 6.0 mmol) was injected via syringe. After 1.5 h at room temperature, the mixture was concentrated and chromatographed over 80 g of silica gel. Elution with 30% benzene–hexane afforded 2.35 g (80%) of the title compound as a bright yellow solid: mp 129–130° (from ether–isopropyl alcohol); $[\alpha]_D$ +194°; IR (Nujol) 1593, 1585, 1565, 1515 cm^{-1}; ^1H NMR 8.3–7.25 (m, 4 H), 5.45 (d, J = 5 Hz, 1 H), 4.18 (m, 1 H), 3.56 (t, J = 8 Hz, 1 H), 1.05 (s, 3 H), 0.88 (s, 9 H), 0.72 (s, 3 H); mass spectrum, m/e (relative intensity) 387 ($M^+ - o$-NO_2PhSe, 28). Anal. Calcd for $C_{31}H_{47}NO_3SeSi$: C, 63.24; H, 8.05; N, 2.38. Found: C, 63.55; H, 8.31; N, 2.37.

17β-Hydroxy-3α-[(4-nitrophenyl)seleno]-4-androstene *tert*-Butyldimethylsilyl Ether (4b). The title compound was prepared in 65% yield from sterol **3**, selenocyanate **1b**, and tri-*n*-butylphosphine by the same procedure as **4a**, as a pale yellow solid: mp 143–145 °C (from hexane); $[\alpha]_D$ +108°; IR (Nujol) 1595, 1515 cm^{-1}; ^1H NMR 8.08 (d, J = 9 Hz, 2 H), 7.57 (d, J = 9 Hz, 2 H), 5.49 (d, J = 5 Hz, 1 H), 4.22 (m, 1 H), 3.56 (t, J = 8 Hz, 1 H), 1.03 (s, 3 H), 0.89 (s, 9 H), 0.72 (s, 3 H); mass spectrum, m/e (relative intensity) 387 ($M^+ - p$-NO_2PhSe, 28). Anal. Calcd for $C_{31}H_{47}NO_3SeSi$: C, 63.24; H, 8.05; N, 2.38. Found: C, 63.01; H, 8.17; N, 2.18.

5α,17β-Dihydroxy-3-androstene 17-*tert*-Butyldimethylsilyl Ether (5). Selenide **4a** (230 mg, 0.39 mmol) was dissolved in 5 mL of THF at 0 °C. *m*-Chloroperbenzoic acid (0.2 g of ca. 85% purity, 1 mmol) was added and the yellow color rapidly faded. After 10 min the solution was diluted with ether, washed 3 times with aqueous K_2CO_3, dried over anhydrous $MgSO_4$, and purified by preparative TLC (15% ethyl acetate–hexane) to afford 75 mg (47%) of the title compound; R_f 0.51, mp 96–97 °C (from methanol); $[\alpha]_D$ −26°; IR ($CHCl_3$) 3600, 3470 cm^{-1}; ^1H NMR 5.73 (dt, J = 10, 3 Hz, 1 H), 5.60 (dt, J = 10, 2 Hz, 1 H), 3.56 (t, J = 8 Hz, 1 H), 0.91 (s, 3 H), 0.87 (s, 9 H), 0.70 (s, 3 H); mass spectrum, m/e (relative intensity) 404 (M^+, <1), 386 ($M^+ - H_2O$, 6). Anal. Calcd for $C_{25}H_{44}O_2Si$: C, 74.19; H, 10.96. Found: C, 73.85; H, 11.17.

Registry No. **1a**, 51694-22-5; **1b**, 19188-18-2; **2**, 71098-88-9; **3**, 57711-52-1; **4a**, 91384-94-0; **4b**, 91384-95-1; **5**, 91384-96-2; **6**, 91384-97-3; **7**, 91384-98-4; *n*-Bu_3P, 998-40-3; PhSeSePh, 1666-13-3.

(10) It is interesting to note that geraniol, a primary allylic alcohol, affords the corresponding selenide in 82% yield under similar conditions.[3] This suggests that steric factors are important in determining the course of the reaction.

(11) The use of other oxidants such as hydrogen peroxide and ozone under various conditions failed to provide better yields of **5**.

(12) The stereochemistry of **4a,b** is assumed to be 3α since the conversion of alcohols to selenides with PhSeCN–*n*-Bu_3P is known[13] to proceed with inversion of configuration. This in turn results in the 5α-hydroxy stereoisomer **5** upon [2,3]-sigmatropic rearrangement.

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(14) Bauer, H. *Ber.* **1913**, *46*, 92.

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Two-Bond Cleavage in the Oxidation of Acyclic Tertiary 1,4-Diols with *N*-Iodosuccinimide

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Recently, we found that 1,2-diols[1] and α-hydroxy carboxylic acids[2] were easily cleaved with *N*-iodosuccinimide

(1) Beebe, T. R.; Hii, P.; Reinking, P. *J. Org. Chem.* **1981**, *46*, 1927.

0022-3263/84/1949-3843$01.50/0