ethers.[22] We speculate that the $\pi$-electron cloud of the phenyl group associates with the catalyst or its activated charcoal support in an exothermic way to cause an apparent $\Delta H_h$ that is too large in magnitude by the amount of the heat of association.

To test this hypothesis, we ran "blanks", described in the Experimental Section, designed to detect heat effects other than those due to hydrogenation. These led to an enthalpy change of -0.63 J for injection of 65 $\mu$mol of phenylacetylene into the system in the absence of hydrogen. The spurious heat effect is 9.6 kJ mol$^{-1}$ or 2.3 kcal per mol of phenylacetylene but monotonically approaches zero after six to eight injections. A similar experiment was run on DPE with similar results. Subtracting the measured association blank from the $\Delta H_h$ referred to above yields -65.4 - (-2.3) = -63.1 kcal mol$^{-1}$, which is within the combined experimental uncertainties of the grand mean listed in Table I. These results are semiquantitative because neither the amount of Pd-C catalyst nor its homogeneity was precisely known. Nevertheless, the direction and approximate magnitude of the heat effect favors some kind of association mechanism involving the phenyl group and the catalyst or its support. Results for reactant and product are indistinguishable at this level of accuracy.

## Experimental Section

**Reagents.** Alkynes and allylbenzene were obtained from Wiley Organics and certified to be 99% pure or better by the manufacturer. This was verified by GLC. The monophenylalkynes were slightly yellow. Color was removed by distillation at reduced pressure. GLC revealed no measurable impurities in the distillate. Other reagent sources have been given.[14]

**Procedure.** The method of hydrogen calorimetry has been described.[14] These studies differed from our published work on linear alkynes[14] only in that the calorimetric standard was allylbenzene rather than hexene. This change was made to minimize the difference in reaction medium interactions for the reactant and for the standard and because the kinetics of hexene hydrogenation were progressively slowed by the presence of accumulated aromatic product in the calorimeter. This kinetic effect did not occur when allylbenzene was used as the thermochemical standard.

A 10% w/w standard solution of allylbenzene in hexane was injected into a 25-mL solution calorimeter, at 2 atm of pressure of $H_2$, containing a slurry of Pd catalyst on carbon support in an inert solvent (hexane) and being stirred magnetically. Following this injection, a 10% solution of alkyne in hexane solvent was injected into the same calorimeter, and the thermal response was compared for the two hydrogenation reactions. Taking the enthalpy of hydrogenation of a terminal, unconjugated double bond[14b] to be -30.25 kcal mol$^{-1}$, one can calculate $\Delta H_h$ of the alkyne from the ratio of the heats produced. After the first few runs were discarded data were collected. The enthalpy of hydrogenation approximates the standard state value if, as we suppose,[14a] the conditions given in the Discussion section are fulfilled.

After a series of experiments, the calorimeter fluid was subjected to GLC analysis using a 30-m SE 30 capillary column. No peaks that would indicate incomplete reaction or side reactions were found except as indicated in the attempt to measure $\Delta H_h$ for DPCP. Numerous experiments[16] have been carried out on samples of calorimeter fluid that were intentionally contaminated with reactant or an anticipated side product. These experiments lead us to believe that capillary GLC is sensitive to undesired products present at one part per thousand or less.

Attempts to measure the enthalpy of hydrogenation of DPCP directly were unsuccessful. Thermal response was slow, and no unequivocal $\Delta T$ could be obtained. GLC and MS analysis of the calorimeter fluid showed several reaction products. Under the conditions that we use, DPA is, however, quantitatively and rapidly hydrogenated to DPE.

**Blank Runs.** A calorimeter was prepared that is identical with the one used in the main set of experiments except that it is electrically calibrated. Injections of a solution of DPA in hexane were made into the new calorimeter containing hexane and a normal catalyst charge but no hydrogen. This was followed by injection of pure hexane as a thermal blank to correct for a small temperature mismatch between the injected solution and the calorimeter fluid. Subtraction of the thermal blank from the heat effect of the first injection yielded the heat effect due to DPA in the absence of hydrogen. This was compared with the recorder deflection for an electrical calibration pulse of 1.0 J, and the ratio yielded the magnitude of the heat effect. A similar experiment was run on DPE, the hydrogenation product.

**Acknowledgment.** We acknowledge support from the NIH Minority Access to Research Careers program, the Research Corporation, through a Cottrell College Science Grant, and Long Island University for released time. We thank Raymond R. Mandra for obtaining and interpreting GLC-MS data on DPCP and its hydrogenation products.

**Registry No.** Phenylacetylene, 536-74-3; 1-phenyl-1-propyne, 673-32-5; 1-phenyl-1-butyne, 622-76-4; 1-phenyl-1-hexyne, 1129-65-3; diphenylbutadiyne, 886-66-8; diphenylacetylene, 501-65-5.

(22) Allinger, N. L.; Glasser, J. A.; Davis, H. E.; Rogers, D. W. *J. Org. Chem.* **1981**, *46*, 685.

# Effects of 16-Heterosubstitution on the Regiochemistry of the *D*-Homo Rearrangement[1a]

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*Received January 29, 1985*

The 16$\beta$-phenylthio-, 16$\beta$-phenylseleno-, and 16$\beta$-dimethylphenylsilyl-substituted 3$\beta$,17$\alpha$-dihydroxy-5-pregnen-20-ones have been prepared by nucleophilic ring opening of 16$\alpha$,17$\alpha$-epoxysteroids in order to study the influence of the 16-substituent on the regiochemistry of the *D*-homo rearrangement. It was found that the phenylthio substituent redirected the course of the base-catalyzed ketol rearrangement, resulting in quantitative formation of the usually unobserved 17$\beta$-hydroxy-17a-keto-17$\alpha$-methyl-*D*-homo isomer, whereas phenylseleno or dimethylphenylsilyl substituents showed no influence. Thus, only S, but not Se or Si, seems capable of effectively stabilizing the negative charge in the $\alpha$ position in the transition state. On Lewis acid catalysis, however, neither S nor Se nor surprisingly Si had any effect on the regiochemistry of the rearrangements, resulting in the "normal" 17$\alpha$-hydroxy-17a-keto-17$\beta$-methyl-*D*-homo isomers.

The $\alpha$-ketol rearrangement of 17-hydroxy-20-keto-steroids, termed the *D*-homo rearrangement, was discovered in 1938[2] and has been the subject of investigation ever since.[3] Thus treatment of 17$\alpha$-hydroxy-20-keto steroids

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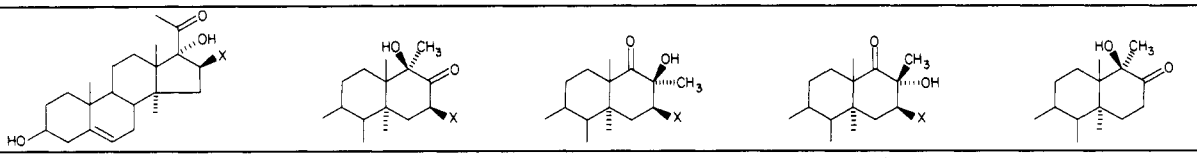
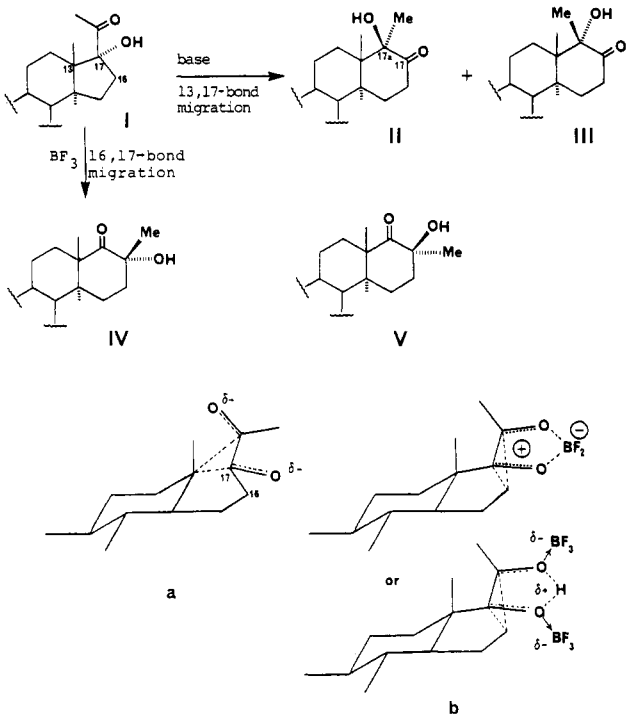
**Table I. Acid- and Base-Catalyzed Rearrangements**

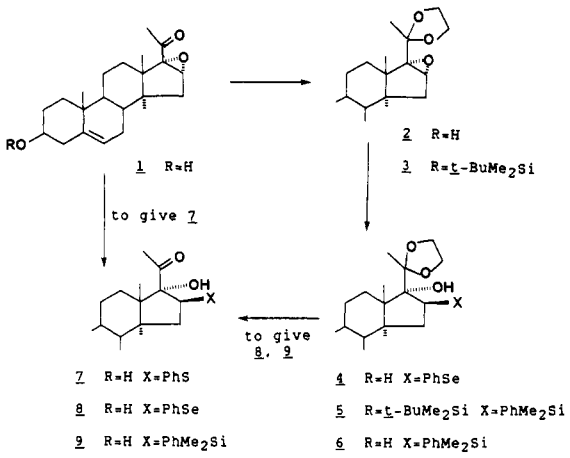


| | 10 | 14 | 16 | |
|---|---|---|---|---|
| 7, X = PhS | | | | |
| KOH/EtOH | 50% | 40% | 5% | |
| *t*-BuOK/$Me_2SO$ | | ~100% | | |
| $BF_3$ | | | ~100% | |
| 8, X = PhSe | 11 | | 17 | 13 |
| KOH/EtOH | 30% | | | 60% |
| *t*-BuOK/$Me_2SO$ | ~80% | | | |
| $BF_3$ | | | ~100% | |
| 9, X = $PhMe_2Si$ | 12 | | 18 | 13 |
| *t*-BuOK/$Me_2SO$ | 40% | | | 40% |
| $BF_3$ | | | ~100% | |

**Scheme I**




**Scheme II**




I with base yields 17-keto-17a$\alpha$-methyl-17a$\beta$-hydroxy-*D*-homosteroids II along with minor amounts of their epimers III, whereas on $BF_3$-catalyzed rearrangement the corresponding 17a-keto-17$\beta$-methyl-17$\alpha$-hydroxy isomers IV are obtained (Scheme I). The isomers V have either not been observed in these rearrangements or have been present in mixtures in low yield only.[4]

The stereoselectivity of these rearrangements has been accounted for on the basis of transition-state models.[5]

Charge–dipole repulsion in the base-catalyzed rearrangement brings about transition state a with trans alignment of the two oxygen functionalities, yielding isomer II with the hydroxy group in the $\beta$ position. In the $BF_3$-catalyzed rearrangement, however, the oxygen functionalities are forced into a cis orientation through complexation favoring transition state b, yielding the isomer with an $\alpha$ orientation of the hydroxy group as in IV. The factors controlling the regioselectivity of the *D*-homo rearrangement, i.e., the migration of the 16,17-bond on base catalysis vs. migration of the 13,17-bond on $BF_3$-treatment, however, are less well understood.

In a program directed toward the synthesis of natural products we became interested in regiospecific *D*-homo rearrangements and decided to study the influence of substituents at the 16-position on the course of this rearrangement. Phenylthio, phenylseleno, and dimethylphenylsilyl seemed suitable directing groups since they are known to stabilize anions in $\alpha$ positions and cations in $\beta$ positions. Moreover, these substituents would allow further transformations at the 15- and 16-positions of the *D*-homo products.

The required 16-substituted 3$\beta$,17$\alpha$-dihydroxy-5-pregnen-20-ones **7**, **8**, and **9** were prepared from the 16,17-epoxide **1** (Scheme II). The 16$\beta$-phenylthio ketol **7** was readily available by treatment of **1** with $PhSH/Na_2CO_3$ in acetone. The attempted analogous epoxide opening with phenyl selenide (prepared from $(PhSe)_2/NaBH_4$/ethanol), however, resulted in direct formation of the *D*-homo isomer **13**. Presumably, under the basic conditions, the initial product **8** undergoes *D*-homo rearrangement with subsequent reduction by $PhSe^-$ to give **13** (vide infra). The desired product **8** was obtained by nucleophilic epoxide

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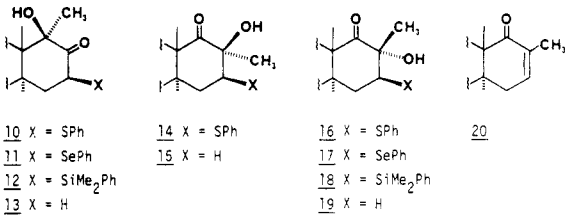
(2) Ruzicka, L.; Meldahl, H. F. *Helv. Chim. Acta* **1938**, *21*, 1760.

(3) For reviews, see: (a) Wendler, N. L. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1964; Vol. 2, pp 1114–1121. (b) Kirk, D. N.; Hartshorn, M. P. "Steroid Reaction Mechanisms"; Elsevier: Amsterdam, 1968; pp 294–313. (c) Boswell, G. A., Jr. In "Organic Reactions in Steroid Chemistry"; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. II, pp 382–386.

(4) See footnote 208b of ref 3a.

(5) (a) Turner, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 3484. (b) Kirk, D. N.; McHugh, C. R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 173 and ref 1–3 therein.

**Scheme III**



10 X = SPh
11 X = SePh
12 X = $SiMe_2Ph$
13 X = H

14 X = SPh
15 X = H

16 X = SPh
17 X = SePh
18 X = $SiMe_2Ph$
19 X = H

20

opening of the ketal **2** yielding **4** (PhSeNa/THF), which gave **8** after deprotection (*p*-TsOH/acetone). Likewise addition of $PhMe_2SiLi$ in THF to the 3-protected ketal **3** gave β-hydroxysilane **5** along with minor amounts of **6**. Compound **5** was O-desilylated (TBAF/THF) and subsequently deketalized (*p*-TsOH/acetone), furnishing ketol **9**.

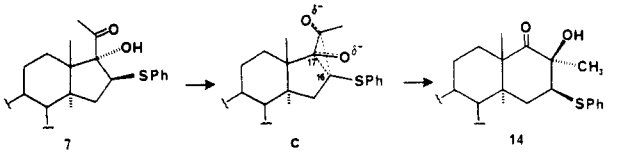
## Results and Discussion

The results of the base- and acid-catalyzed rearrangements are given in Table I.

Neither the dimethylphenylsilyl nor the phenylseleno substituent had any effect on the direction of the base-catalyzed *D*-homo rearrangement. Thus **8** yielded **11** and **9** yielded **12** (Scheme III), these being the "normal" rearrangement products of base catalysis.

In contrast, the phenylthio substituent shows a remarkable influence on the regiochemistry of the *D*-homo rearrangement. The ketol **7** on treatment with *t*-BuOK yields the isomer **14** resulting from C(16)–C(17) bond migration in near quantitative yields. Isomers of type **14** having a 17β-hydroxy group are usually not obtained from *D*-homo rearrangements or are present in trace amounts only.[4]

This result allows an interesting comparison between the anion stabilizing abilities of S, Se, and Si. It seems that only S is capable of effectively stabilizing negative charge in the α position in the transition state thereby causing the C(16)–C(17) bond to migrate (**7** → c → **14**). In contrast the Se- and Si-substituted compounds rearrange by C(13)–C(17) bond migration despite the presence of α-anion stabilizing heteroatoms. This agrees with the fact that sulfur compounds are generally more acidic[6] than Se compounds and indicates more efficient charge stabilization by sulfur.

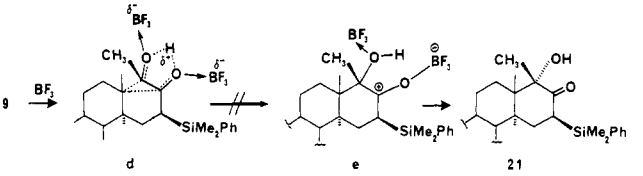


7 c 14

The base-catalyzed *D*-homo rearrangement of the phenylthio compound **7** also exhibits a remarkable solvent effect. With *t*-BuOK/$Me_2SO$ the single isomer **14** is obtained, whereas in EtOH/KOH the isomer **10** resulting from C(13)–C(17) bond migration is also formed along with minor amounts of **16**.[7] The isomer **10**, however, is not formed from **14** through equilibration, since the isomer **14** is practically stable to the EtOH/KOH conditions. Thus, the rearrangement in EtOH/KOH seems to favor the normal pathway relative to *t*-BuOK/$Me_2SO$.

These results also shed some light on the nature of the transition state in base-catalyzed *D*-homo rearrangements. The directive effect of the phenylthio substituent indicates a certain degree of charge separation in the transition state.

The acid-catalyzed rearrangement of **7**, **8**, and **9** with $BF_3$·$OEt_2$ leads uniformly to the products **16**, **17**, and **18** resulting from C(16)–C(17) bond migration, which is the normal mode of Lewis acid catalyzed rearrangement. This might seem surprising in the case of silyl-substituted compound **9**, since silicon is known to stabilize positive charge in the β-position, and hence rearrangement with migration of the C(13)–C(17) bond (**9** → d → e → **21**) might be anticipated.[8] Thus either the acid-catalyzed rearrangement does not proceed with a certain degree of charge separation to form a cationic transition state or silicon cannot effectively stabilize the positive charge by virtue of stereoelectronic or steric factors.



9 d e 21

The structure of the products in Table I can be largely deduced from their $^1H$ NMR spectra: the chemical shifts of the methyl groups of the phenylthio and phenylseleno compounds are very similar and follow the rules that have been established for *D*-homo rearrangement products.[9,10] The chemical shift of the H–C(16) allows a distinction between 17- and 17a-ketones: the signal is shifted downfield by ~1 ppm when the HC(16) is adjacent to the carbonyl group as in **10** and **11** relative to **14**, **16**, and **17**. The coupling constants between H–C(16) and $H_2C(15)$ are characteristic of one axial–axial and one axial–equatorial coupling as expected from the Karplus equation[11] and mandate a β (equatorial) orientation of the substituent X in the above compounds.

In order to unambiguously confirm their structures, compounds **14** and **16** were reduced with Raney Ni to yield **15** and **19**, respectively. Similarly the seleno compound **11** was reduced with $Bu_3SnH$ to yield **13**. (Some reduction occurred already during the base-catalyzed rearrangement (EtOH/KOH, see Table I) where **13** was formed in 60% yield.) The reduction products **13** and **19** were identical in their physical data with the literature values (see Experimental Section). The *D*-homo isomer **15** had not been isolated in pure form previously; however, the chemical shifts of the methyl groups in the $^1H$ NMR are in agreement with reported values[9a] determined from a mixture. These transformations confirm the orientation and location of the 17 or 17a methyl group; the stereochemistry of the 16-substituents follows from their β orientation in the starting materials and the distinctive coupling of H–C(16) in the products. The dimethylphenylsilyl compound **12**

(6) For a discussion of the acidity of protons in the α position to S vs. Se and leading references, see: Reich, H. J.; Willis, W. W., Jr. *J. Org. Chem.* **1980**, *45*, 5227.

(7) A similar solvent dependence of the *D*-homo rearrangement has been reported: Kirk, D. N.; Mudd, A. *J. Chem. Soc. C* **1970**, 2045.

(8) The cation stabilizing ability of Si has been successfully applied, e.g., in directed Baeyer–Villiger reactions: Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894.

(9) (a) Jankowski, K.; Berse, C. *Can. J. Chem.* **1969**, *47*, 751. (b) Cleve, G.; Schulz, G. *Tetrahedron* **1971**, *27*, 1415. (c) Knight, J. C. *Steroids* **1980**, *35*, 511. (d) Shoppee, C. W.; Hughes, N. W.; Newman, B. C. *J. Chem. Soc. C* **1970**, 558.

(10) It should be noted that the chemical shifts cited for the C(17a) methyl groups in ref 6a (Table III) are approximately 0.1 ppm too high (downfield), as has been pointed out by other authors.[6b] This error is particularly confusing since the chemical shifts for the *epimer* of **13** having a 17aβ-methyl group reported in this reference (B in Table III in ref 6a) coincide with the accepted values[6b,6d] for compound **13**. We have prepared compound **13** independently and shown the accepted chemical shifts to correspond to the reported melting point (see Experimental Section).

(11) Williams, D. H.; Fleming, I. "Spectroscopic Methods in Organic Chemistry", 2nd ed.; McGraw-Hill: London, 1973; p 101.

yielded the desilylated D-homo isomer **13** under basic conditions, and **18** was transformed to the enone **20** under acidic conditions, proving its structure.

The present results indicate that a phenylthio substituent in the 16-position of steroidal 17,20-ketols effectively influences the direction of the base-catalyzed D-homo rearrangement resulting in C(16)–C(17) bond migration. This effect might be applicable to natural products synthesis where the phenylthio substituent might serve to further functionalize the molecule in the 15- and/or 16-positions.

## Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were measured on a Sargent-Welch Model 3-200 IR spectrophotometer. The UV spectra were recorded with a Hewlett-Packard Model 8450 A UV–vis spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. The NMR spectra were obtained with a Bruker WM-300 spectrometer, and the chemical shifts are recorded as parts per million ($\delta$) from internal tetramethylsilane. The high-resolution mass spectra were obtained with a Finnigen MAT 311A mass spectrometer. Elemental analyses were performed by the Analytical Department of Syntex Research, Institute of Organic Chemistry, or Atlanta Laboratories. Compound **1** was a commercial sample but can be obtained from Sigma. The term "worked up" implies standard isolation procedures consisting of extraction with ether, drying ($MgSO_4$), and evaporation of the solvent.

**3β,17α-Dihydroxy-16β-(phenylthio)pregn-5-en-20-one (7).** A mixture of 16α,17-epoxypregnenolone **1**[12] (11.0 g; 33.3 mmol), thiophenol (10 mL; 97 mmol), and anhydrous $K_2CO_3$ (4.2 g; 30 mmol) in acetone (100 mL) was stirred under reflux for 2 days. The reaction mixture was filtered through $SiO_2$, the solvent evaporated, and the solid residue crystallized from ethyl acetate. After recrystallization of the mother liquor, a total of 12.6 g (28.8 mmol; 80%) of **7** was obtained: mp 178–180 °C; $\alpha^{25}_D$ −55° (*c* 2% in $CHCl_3$); IR ($CHCl_3$) 3590, 3440 br (OH), 1715, 1680 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 1.02 and 1.09 (2 s, 2 $CH_3$), 2.35 (s, $CH_3CO$), 3.48–3.58 (m, HC(3)), 3.72 (t, $J$ = 8.5 Hz, HC(16)), 5.35 (m, HC(6)), 7.1–7.2 (m, Ar H's). Anal. Calcd for $C_{27}H_{36}O_3S$ (440.65): C, 73.43; H, 8.45; S, 7.27. Found: C, 73.35; H, 8.24; S, 7.37.

**Attempted Preparation of 8 from 1.** To a solution of diphenyl diselenide (6.0 g; 19.2 mmol) in ethanol (100 mL) was added $NaBH_4$ (2.1 g; 54 mmol) portionwise, whereupon the yellow solution became colorless. After the addition of acetone (50 mL) and after the mixture was stirred for an additional 1 h, epoxypregnenolone **1** (11.1 g; 33.6 mmol) was added and the resulting mixture heated under reflux for 4 days. Workup and chromatography of the crude product ($SiO_2$; 1:2:2 hexane/$CH_2Cl_2$/ethyl acetate) yielded 6.27 g (56%) of **3β,17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one 13**: mp 182–186 °C (methanol), 185–187 °C (acetone) (lit.[3c,13] mp 180–182 °C from aqueous MeOH); $\alpha^{25}_D$ −96° (dioxane), −98° ($CHCl_3$) (lit.[3c,13] −104° ($CHCl_3$)); $^1H$ NMR $\delta$ 1.01, 1.12, and 1.43 (3 s, 3 $CH_3$). An authentic sample[6a] prepared by refluxing a solution of 3β,17α-dihydroxypregn-5-en-20-one[12] (270 mg; 0.81 mmol) in 5% KOH solution in MeOH (50 mL) overnight, quenching (dilute HCl), workup, and recrystallization from acetone (yield, 160 mg; 59%) had mp 181–183 °C, $\alpha^{25}_D$ −103° (*c* 3% in $CHCl_3$), and an identical $^1H$ NMR spectrum.

**20,20-(Ethylenedioxy)-3β,17α-dihydroxy-16β-phenylseleno-5-pregnene (4).** To a solution of diphenyl diselenide (900 mg; 2.88 mmol) in ethanol (50 mL) was added $NaBH_4$ (160 mg; 4.21 mmol) in small batches, whereupon the yellow solution became colorless. 16α,17-Epoxypregnenolone ethylene ketal **2**[14] was then added and the mixture refluxed overnight. Due to the low conversion of starting material the ethanol was distilled off and replaced by 1-butanol (50 mL), and reflux was continued for 4 days. Workup and subsequent chromatography ($SiO_2$; 2:1:1 hexane/$CH_2Cl_2$/ethyl acetate) yielded starting material (240 mg; 15%) and **4** (1.6 g; 56%, recrystallized from ethyl acetate): mp 185–187 °C; $\alpha^{25}_D$ 102° (*c* 3% in $CHCl_3$); IR (KBr) 3450 br (OH) $cm^{-1}$; $^1H$ NMR $\delta$ 1.00 and 1.09 (2 s, 2 $CH_3$), 1.46 (s, $H_3C(21)$), 2.50 (s, OH), 3.45–3.60 (m, HC(3), HC(16)), 3.95–4.33 (m, $OCH_2CH_2O$), 5.27 (m, HC(6)), 7.20–7.30 and 7.50–7.60 (m, Ar H's). Anal. Calcd for $C_{29}H_{40}O_4Se$ (531.60): C, 65.52; H, 7.58. Found: C, 65.50; H, 7.54.

**3β,17α-Dihydroxy-16β-(phenylseleno)pregn-5-en-20-one (8).** A solution of the ketal **4** (1.18 g; 2.2 mmol) in $CH_2Cl_2$ (50 mL) and acetone (20 mL) was stirred at room temperature with *p*-toluenesulfonic acid (50 mg) for 3 h. After workup 1.10 g (2.2 mmol) (~100%) of **8** were obtained: mp 168–170 °C; $\alpha^{25}_D$ 41° (*c* 3% in $CHCl_3$); IR (KBr) 3380 br (OH), 1700 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 0.99 and 1.02 (2 s, 2 $CH_3$), 2.32 (s, $CH_3CO$), 3.47–3.57 (m, HC(16), HC(3)), 5.32 (m, HC(6)), 7.22–7.27 and 7.48–7.51 (Ar H's). Anal. Calcd for $C_{27}H_{36}O_3Se$ (487.54): C, 66.52; H, 7.44. Found: C, 66.60; H, 7.41.

**3β-[(Dimethyl(1,1-dimethylethyl)silyl)oxy]-16α,17-epoxy-20,20-(ethylenedioxy)-5-pregnene (3).** A mixture of 16α,17-epoxypregnenolone **1** (10.34 g; 31.3 mmol), benzene (200 mL), and ethylene glycol (30 mL) was heated under reflux to remove traces of $H_2O$. Collidinium *p*-toluenesulfonate[15] (500 mg; 1.7 mmol) was added and the mixture refluxed with a Dean–Stark water separator for 10 days. The reaction was worked up and the crude reaction mixture dissolved in DMF (100 mL) and stirred with imidazole (5 g; 73.5 mmol) and *t*-$BuMe_2SiCl$ (7.8 g; 52 mmol) overnight. Workup and chromatography ($SiO_2$; 3:1:0.5 hexane/$CH_2Cl_2$/ether) yielded 7.20 g (47%) of **3** (recrystallized from ether): mp 170–172 °C; $\alpha^{25}_D$ −23° (*c* 3% in $CHCl_3$); IR (KBr) 3450 br (OH) $cm^{-1}$; $^1H$ NMR $\delta$ 0.00 (s, $(H_3C)_2Si$), 0.83 (*t*-Bu), 0.93, 0.96, and 1.38 (3 s, 3 $CH_3$), 3.32 (s, HC(16)), 3.35–3.49 (m, HC(3)), 3.80–3.95 (m, $OCH_2CH_2O$), 5.25 (m, HC(6)). Anal. Calcd for $C_{29}H_{48}O_4Si$ (488.78): C, 71.26; H, 9.90. Found: C, 71.46; H, 9.98.

**1,1,2,2-Tetramethyl-1,2-diphenyldisilane.**[16] A mixture of Li chips (410 mg, 57 mmol) and HMPA (10 mL; 55.9 mmol) in ether (20 mL) was stirred at room temperature for 15 min and cooled to 0 °C. Dimethylphenylsilyl chloride (10.1 g; 59.1 mmol) was then added slowly to the dark blue mixture, whereupon the color disappeared. After being stirred for an additional 2 h at room temperature, the reaction was quenched and worked up and the crude product chromatographed ($SiO_2$; 0:1 to 1:20 ether/hexane). Distillation [bp ~110 °C (0.5 mm)] yielded 1,1,2,2 tetramethyl-1,2-diphenyldisilane as a colorless liquid (2.32 g; 29%).

**Treatment of 3 with $PhMe_2SiLi$.** To a solution of the epoxide **3** (2.52 g; 5.15 mmol) in THF (20 mL) was added dropwise a solution of $PhMe_2SiLi$[17] in THF (12 mL, ~8.7 mmol). The resulting mixture was stirred overnight and worked up. Subsequent chromatography of the reaction mixture ($SiO_2$; 1:4 to 1:0 ether/hexane yielded **5** (2.15 g; 67%) and **6** (360 mg; 13%).

**3β-[(Dimethyl(1,1-dimethylethyl)silyl)oxy]-16β-(dimethylphenylsilyl)-20,20-(ethylenedioxy)-17α-hydroxy-5-pregnene (5)** (recrystallized from $CH_2Cl_2$/hexane): mp 169–173 °C; $\alpha^{25}_D$ −33° (*c* 3% in $CHCl_3$); IR (KBr) 3610, 3460 br (OH) $cm^{-1}$; $^1H$ NMR $\delta$ 0.05 (s, $(H_3C)_2SiO$), 0.23 and 0.38 (2 s, $(H_3C)_2Si$), 0.73, 0.99, and 1.07 (3 s, 3 $CH_3$), 0.88 (s, *t*-BuSi), 2.00 (s, OH), 3.30–3.38, 3.66–3.75, and 3.84–3.91 (m, $OCH_2CH_2O$), 3.42–3.53 (m, HC(3)), 5.30 (m, HC(6)), 7.20–7.30 and 7.51–7.56 (m, Ar H's). Anal. Calcd for $C_{37}H_{60}O_4Si_2$ (625.06): C, 71.10; H, 9.67. Found: C, 71.30; H, 9.64.

**3β,17α-Dihydroxy-16β-(dimethylphenylsilyl)-20,20-(ethylenedioxy)-5-pregnene (6)**: mp 101–103 °C; $\alpha^{25}_D$ −39° (*c* 3% in $CHCl_3$); IR (KBr) 3480 br (OH) $cm^{-1}$; $^1H$ NMR $\delta$ 0.23 and 0.38 (2 s, $(H_3C)_2Si$), 0.73, 1.00, and 1.06 (3 s, 3$CH_3$), 2.09 (s, OH),

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3.30–3.40, 3.67–3.76, and 3.84–3.93 (m, $OCH_2CH_2O$), 3.43–3.56 (m, HC(3)), 5.34 (m, HC(6)), 7.26–7.32 and 7.51–7.58 (m, Ar H's).

**3β,17α-Dihydroxy-16β-(dimethylphenylsilyl)pregn-5-en-20-one (9).** A solution of **5** (1.26 g; 2.17 mmol) in THF (20 mL) was refluxed with tetrabutylammonium fluoride (670 mg; 1 M solution in THF) overnight. The reaction mixture was worked up, the crude product was dissolved in acetone (20 mL), and after addition of *p*-toluenesulfonic acid (150 mg), the solution was allowed to stand overnight. After workup and chromatography 630 mg (62%) of **9** were obtained: mp 177–179 °C (recrystallized from ether/hexane); $\alpha^{25}_D$ 52° (*c* 4% in $CHCl_3$); IR (KBr) 3450 br (OH), 1710 (CO) $cm^{-1}$; $^1H$ NMR δ 0.35 (s, $(H_3C)_2Si$), 0.53 and 0.99 (2 s, 2 $CH_3$), 2.03 (s, OH), 2.07 (s, $CH_3CO$), 3.45–3.57 (m, HC(3)), 5.32 (m, HC(6)), 7.28–7.34 and 7.50–7.56 (m, Ar H's). Anal. Calcd for $C_{29}H_{42}O_3Si$ (466.74): C, 74.63; H, 9.07. Found: C, 74.57; H, 9.00.

***D*-Homo Rearrangements of 7. (a) With KOH/EtOH.** A solution of 5% KOH in 50% aqueous EtOH was refluxed under $N_2$ for 5 min. The ketol **7** (200 mg) was then added, and the mixture was refluxed for 20 min, quenched (concentrated HCl), and worked up. $^1H$ NMR of the crude mixture indicated the presence of **10** (50%), **14** (40%), and **16** (5%). When ketol **7** was treated under the same conditions and refluxed for only 5 min, $^1H$ NMR analysis revealed **10** (45%), **14** (35%), and **16** (5%), along with starting material **7** (15%). Chromatography ($SiO_2$; 2:2:1 $CH_2Cl_2$/hexane/ethyl acetate) yielded a fraction (30 mg) consisting of pure **10**.

**(b) With *t*-BuOK/$Me_2SO$.** To a solution of **7** (196 mg; 0.418 mmol) in dry $Me_2SO$ (2 mL) was added a solution of *t*-BuOK in $Me_2SO$ (2.6 mL; 0.035 M). After being stirred for 2.0 min at room temperature, the reaction mixture was quenched (concentrated HCl) and worked up. After removal of the solvent 200 mg of product were obtained, which was pure **14** according to $^1H$ NMR.

**(c) With $BF_3$·$OEt_2$.** To a solution of **7** (740 mg; 1.58 mmol) in THF (15 mL) was added $BF_3$·$OEt_2$ (2 mL; 16.2 mmol) at −78 °C, and the resulting solution was kept at 0 °C for 2 h. Quenching (saturated $NaHCO_3$ solution) and workup yielded pure **16** (730 mg; 99%) according to $^1H$ NMR.

**3β,17aβ-Dihydroxy-17aα-methyl-16β-(phenylthio)-*D*-homoandrost-5-en-17-one (10):** mp 154–157 °C; $\alpha^{25}_D$ −67° (*c* 5% in $CHCl_3$); IR (KBr) 3460 br (OH), 1720 (CO) $cm^{-1}$; $^1H$ NMR δ 0.71 and 0.97 (2 s, 2 $CH_3$), 1.37 (s, $CH_3C(17a)$), 3.45–3.58 (m, HC(3)), 3.83 (s, OH), 4.11 (d × d, $J_1$ = 6.7 Hz, $J_2$ = 12.1 Hz, HC(16)), 5.3 (m, HC(6)), 7.2–7.65 (m, Ar H's). Anal. Calcd for $C_{27}H_{36}O_3S$ (440.65): C, 73.60; H, 8.24; S, 7.27. Found: C, 73.55; H, 8.20; S, 7.30.

**3β,17β-Dihydroxy-17α-methyl-16β-(phenylthio)-*D*-homoandrost-5-en-17a-one (14)** (recrystallized from ether): mp 131–133 °C; $\alpha^{25}_D$ −92° (*c* 3% in $CHCl_3$); IR (KBr) 3450 br (OH), 1705 (CO) $cm^{-1}$; $^1H$ NMR δ 1.00, 1.30, and 1.44 (3 s, 3 $CH_3$), 2.67 (s, OH), 3.15 (d × d, $J_1$ = 5.1 Hz, $J_2$ = 12 Hz, HC(16)), 3.48–3.58 (m, HC(3)), 5.31 (m, HC(6)), 7.20–7.48 (m, Ar H's). Anal. Calcd for $C_{27}H_{36}O_3S$ (440.65): C, 73.43; H, 8.45; S, 7.27. Found: C, 73.33; H, 8.26; S, 7.39.

**3β,17α-Dihydroxy-17β-methyl-16β-(phenylthio)-*D*-homoandrost-5-en-17a-one (16)** (recrystallized from ethyl acetate): mp 171–175 °C; $\alpha^{25}_D$ −62° (*c* 3% in $CHCl_3$); IR (KBr) 3460 br (OH), 1704 (CO) $cm^{-1}$; $^1H$ NMR δ 0.99 and 1.14 (2 s, 2 $CH_3$), 1.52 (s, $CH_3C(17)$), 3.23 (d × d, $J$ = 4.5 Hz, $J_2$ = 12 Hz, HC(16), 3.43–3.56 (m, HC(3)), 5.29 (m, HC(5)), 7.2–7.55 (m, Ar H's). Anal. Calcd for $C_{27}H_{36}O_3S$ (440.65): C, 73.43; H, 8.45; S, 7.27. Found: C, 73.12; H, 8.00; S, 7.08.

***D*-Homo Rearrangements of 8. (a) With KOH/EtOH.** A solution of 5% KOH in 50% aqueous EtOH (5 mL) was refluxed for 5 min under $N_2$. The ketol **8** (40 mg; 0.08 mmol) was added and the mixture refluxed for 20 min. Quenching (concentrated HCl), workup, and $^1H$ NMR analysis revealed the crude mixture to consist of **11** (30%) and **13** (60%).

**(b) With *t*-BuOH/$Me_2SO$.** To a solution of **8** (42 mg; 0.09 mmol) in $Me_2SO$ (2 mL) was added a solution of *t*-BuOK in $Me_2SO$ (1 mL, ~0.2 M). After being stirred at room temperature for 3 min, the mixture was quenched (concentrated HCl) and worked up. $^1H$ NMR analysis of the crude product showed **11** (~80%) to be present besides some other nonidentified products. Chromatography ($SiO_2$; 1:1 to 3:1 ether/hexane) yielded pure **11** (28 mg).

**(c) With $BF_3$·$OEt_2$.** To a solution of **8** (80 mg; 0.16 mmol) in THF (5 mL) was added $BF_3$·$OEt_2$ (1 mL; 8.1 mmol) at −78 °C. The mixture was kept at 0 °C for 70 min, quenched (saturated $NaHCO_3$ solution), and worked up. $^1H$ NMR showed the crude product (80 mg) to be **17** along with some unreacted starting material (~10%). Chromatography ($SiO_2$; 1:2 to 2:1 ether/hexane) yielded pure **17** (50 mg).

**3β,17aβ-Dihydroxy-17aα-methyl-16β-(phenylseleno)-*D*-homoandrost-5-en-17-one (11):** mp 91–94 °C; $\alpha^{25}_D$ −12° (*c* 6% in $CHCl_3$); IR (Nujol) 3400 br (OH), 1700 (CO) $cm^{-1}$; $^1H$ NMR δ 0.71 and 0.96 (2 s, 2 $CH_3$), 1.36 ($CH_3C(17a)$), 3.45–3.58 (m, HC(3)), 3.80 (s, OH), 4.23 (d × d, $J_1$ = 7.6 Hz, $J_2$ = 12.6 Hz, HC(16)), 5.27 (m, HC(6)), 7.27–7.31 and 7.62–7.69 (m, Ar H's); mass spectrum, exact mass calcd for $C_{27}H_{36}O_3Se$ *m/e* 488.1829, found *m/e* 488.1823.

**3β,17α-Dihydroxy-17β-methyl-16β-(phenylseleno)-*D*-homoandrost-5-en-17a-one (17)** (recrystallized from $CH_2Cl_2$/hexane): mp 178–180 °C; $\alpha^{25}_D$ −76° (*c* 3% in $CHCl_3$); IR (KBr) 3440 br (OH), 1700 (CO) $cm^{-1}$; $^1H$ NMR δ 0.99, 1.13, and 1.52 (3 s, 3 $CH_3$), 3.27 (d × d, $J_1$ = 4.2 Hz, $J_2$ = 13.2 Hz, HC(16)), 3.43–3.57 (m, HC(3)), 4.31 (s, OH), 5.28 (m, HC(6)), 7.23–7.31 and 7.62–7.70 (m, Ar H's). Anal. Calcd for $C_{27}H_{36}O_3Se$ (487.54): C, 66.52; H, 7.44. Found: C, 66.70; H, 7.50.

***D*-Homo Rearrangements of 9. (a) With *t*-BuOK/$Me_2SO$.** To a solution of the ketol **9** (120 mg; 0.26 mmol) in $Me_2SO$ (2 mL) was added a solution of *t*-BuOK in $Me_2SO$ (2 mL; ~0.2 M). After the mixture was stirred for 2 min at room temperature, TLC (3:1 ether/hexane) showed the formation of **12** as the single product. Increasing reaction times furnished increasing amounts of **13**. The reaction mixture was quenched after 7 min (concentrated HCl) and worked up. $^1H$ NMR showed the mixture to consist of **12** (50%) and **13** (45%). Chromatography ($SiO_2$; 2:1 to 3:1 ether/hexane) yielded pure **12** (40 mg) and **13** (30 mg).

**(b) With $BF_3$·$OEt_2$.** To a solution of **9** (110 mg; 0.24 mmol) in THF (5 mL) was added $BF_3$·$OEt_2$ (1 mL; 9.5 mmol) at −78 °C. The reaction was stirred at 0 °C for 30 min, quenched ($NaHCO_3$ solution), and worked up. $^1H$ NMR of the crude product showed the presence of **18**. Longer reaction times and/or higher temperatures yielded increasing amounts of **20**.

**3β,17aβ-Dihydroxy-16β-(dimethylphenylsilyl)-17aα-methyl-*D*-homoandrost-5-en-17-one (12):** mp 70–75 °C; $\alpha^{25}_D$ 69° (*c* 3% in $CHCl_3$); IR (KBr) 3420 br (OH), 1728 (CO) $cm^{-1}$; $^1H$ NMR δ 0.38 and 0.44 (2 s, $(H_3C)_2Si$), 0.80 and 0.99 (2 s, 2 $CH_3$), 1.38 (s, $CH_3C(17a)$), 3.48–3.60 (m, HC(3)), 5.35 (m, HC(6)), 7.30–7.40 and 7.58–7.67 (m, Ar H's). Anal. Calcd for $C_{29}H_{42}O_3Si$ (466.74): C, 74.63; H, 9.07. Found: C, 74.53; H, 9.18.

**3β,17α-Dihydroxy-16β-(dimethylphenylsilyl)-17β-methyl-*D*-homoandrost-5-en-17a-one (18):** mp 128–130 °C; $\alpha^{25}_D$ −124° (*c* 2% in $CHCl_3$); IR (KBr) 3450 br (OH), 1692 (CO) $cm^{-1}$; $^1H$ NMR δ 0.41 and 0.47 (2 s, $(H_3C)_2Si$), 0.97 and 1.07 (2 s, 2 $CH_3$), 1.37 (s, $CH_3C(17)$), 3.40–3.56 (m, HC(3)), 4.26 (s, OH), 5.29 (m, HC(6)), 7.3–7.6 (m, Ar H's). Anal. Calcd for $C_{29}H_{42}O_3Si$ (466.74): C, 74.63; H, 9.07. Found: C, 74.04; H, 9.20.

**Raney Ni Reduction of 14.** A solution of **14** (560 mg, 1.19 mmol) in EtOH (10 mL) was refluxed with Raney Ni (~3 g) and boric acid[18] (500 mg; 8.1 mmol) for 7 days. Filtration throught Celite, workup of the filtrate, and chromatography ($SiO_2$; 2:1 to 3:1 ether/hexane) yielded starting material **14** (70 mg; 12%) and **3β,17β-dihydroxy-17α-methyl-*D*-homoandrost-5-en-17a-one (15)** (170 mg; 40%; recrystallized from acetone): mp 161–163 °C, $\alpha^{25}_D$ −65° (*c* 5% in $CHCl_3$); IR (KBr) 3420 br (OH), 1712 (CO) $cm^{-1}$; $^1H$ NMR δ 1.01, 1.18, and 1.32 (3 s, 3 $CH_3$), 3.01 (s, OH), 3.46–3.58 (m, HC(3)), 5.36 (s, HC(6)). (Reported chemical shifts for the methyl groups:[9a] δ 1.02, 1.19, 1.28.) Anal. Calcd for $C_{21}H_{32}O_3$ (332.5): C, 75.85; H, 9.71. Found: C, 76.01; H, 9.70.

**Raney Ni Reduction of 16.** Raney Ni (~2 g) was washed with $H_2O$ (3 × 10 mL) and ethanol (10 mL), and then **16** (230 mg; 0.49 mmol) and ethanol (5 mL) were added. The mixture was refluxed for 2 days and filtered through Celite and the crude product chromatographed ($SiO_2$; 1:1 to 3:1 ether/hexane), furnishing starting material **16** (50 mg; 22%) and 3β,17α-dihydroxy-17β-methyl-*D*-homoandrost-5-en-17a-one (**19**) (70 mg, 40%). The $^1H$

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NMR of 19 was in agreement with the literature values.[9a]

**$Bu_3SnH$ Reduction of 11.** A solution of 11 (20 mg; 0.042 mmol) and $Bu_3SnH$ (60 mg; 0.21 mmol) in benzene (3 mL) was refluxed for 1 day. Chromatography ($SiO_2$; 1:1 to 1:0 ether/hexane) yielded a fraction (10 mg; 66%), which was identified as 3β,17aβ-dihydroxy-17aα-methyl-*D*-homoandrost-5-en-17-one 13 by comparison of its $^1H$ NMR spectrum with that of the authentic sample.

**Conversion of 18 to 20.** A solution of 18 (30 mg; 0.06 mmol) in ether (10 mL) was refluxed with $BF_3{\cdot}OEt_2$ (0.5 mL; 4 mmol) for 1 h and allowed to stand overnight at room temperature. Workup and recrystallization of the crude product from ether afforded 18 mg (95%) of **3β-hydroxy-17-methyl-*D*-homoandrosta-5,16-dien-17a-one (20)** (recrystallized from ether): mp 205–207 °C; $\alpha^{25}_D$ −189° (*c* 3% in $CHCl_3$); UV (0.097 mg/mL EtOH) 236 nm (ε 7000); IR (KBr) 3500 (OH), 1660 (CO) $cm^{-1}$; $^1H$ NMR δ 1.01 (s, 2 $CH_3$), 1.76 (d, $J$ = 1 Hz, $H_3CC(17)$), 3.45–3.60 (m, HC(3)), 5.36 (m, HC(6)), 6.62 (m, HC(16)). Anal. Calcd for $C_{21}H_{30}O_2$ (314.47): C, 80.21; H, 9.62. Found: C, 80.20; H, 9.71.

**Acknowledgment.** We gratefully acknowledge valuable discussions with Dr. M. Maddox and thank members of the Syntex Analytical Department for their excellent analytical support.

**Registry No.** 1, 974-23-2; 2, 19454-86-5; 3, 97350-86-2; 4, 97373-99-4; 5, 97350-87-3; 6, 97374-00-0; 7, 97350-88-4; 8, 97374-01-1; 9, 97350-89-5; 10, 97350-90-8; 11, 97350-91-9; 12, 97350-92-0; 13, 2460-10-8; 14, 97350-93-1; 15, 21549-33-7; 16, 97374-02-2; 17, 97374-03-3; 18, 97350-94-2; 19, 1458-74-8; 20, 97350-95-3; $PhMe_2SiLi$, 3839-31-4; thiophenol, 108-98-5; diphenyl diselenide, 1666-13-3; 3β,17α-dihydroxypregn-5-en-20-one, 387-79-1; dimethylphenylsilyl chloride, 768-33-2; 1,1,2,2-tetramethyl-1,2-diphenyldisilane, 1145-98-8.

# *Notes*

## Fluorination with Cesium Fluoroxysulfate. Room-Temperature Fluorination of Benzene and Naphthalene Derivatives

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*Received December 20, 1984*

The introduction of fluorine into aromatic molecules is very important from the chemical and pharmaceutical point of view, but the problem differs considerably from those concerning other halogen atoms.[1] In the last two decades many efforts have been made to find a fluorinating agent which could introduce fluorine into organic molecules under mild conditions. Fluoroxytrifluoromethane was the most extensively studied reagent, with various success, in the introduction of a fluorine atom into aromatic molecules, while experimental conditions demanded safety precautions because of the high toxicity of the reagent and its high reactivity.[2] Recently, Rozen and co-workers have found that trifluoroacetyl hypofluorite[3] and acetyl hypofluorite[4,5] represent a new class of fluoroxy derivatives that could also be used for the introduction of fluorine into organic molecules, but reactions must usually be carried out at lower temperatures. The most easily handled fluorinating agent known up to now is xenon difluoride,[6-8] but its high price is a great disadvantage. The recent preparation and characterization of cesium and rubidium fluoroxysulfate,[9] and their oxidative properties and stability at room temperature, made them promising as mild fluorinating agents for organic substrates. Appelman and co-workers found that $CsSO_4F$ reacted with several benzene derivatives.[10] We ourselves found that various benzene and naphthalene derivatives reacted in the presence of boron trifluoride as a catalyst,[11] and detailed studies of the effect of various catalysts on the fluorination of toluene, nitrobenzene, and naphthalene have finally appeared.[12] We now report our investigations of boron trifluoride catalyzed room-temperature fluorinations of various benzene and naphthalene derivatives with cesium fluoroxysulfate.

### Results and Discussion

In 1979 Appelman and co-workers described the first synthesis of $CsSO_4F$, which was formed in the reaction of nitrogen diluted fluorine with $Cs_2SO_4$ in water.[9] During the synthesis of $CsSO_4F$ in our laboratory, we found that its instability in water reduced the isolation yield and thus, we only slightly modified the preparation procedures so that the precipitating $CsSO_4F$ was simultaneously removed from the reaction mixture every half hour. Finally, after a 5-h introduction of fluorine diluted with nitrogen, 65–75% of dry product was obtained, which can be stored in a polyethylene vessel at 0 °C for at least 14 days without a significant loss of activity. For our investigations we synthesized more than 200 g of the reagent. No explosion occurred, but any contact with a metallic spatula or any mechanical pressure must be avoided. In a typical experiment carried out in a glass vessel, to a stirred suspension of (0.5–5 mmol) $CsSO_4F$ in acetonitrile (3–15 mL) was added substituted benzene derivative (0.5–5 mmol in

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