Studies of Enamidic Δ^5-4-Azasteroidal Selenoxides: Preparation, Pummerer Reactions, Configurational Stability, and Conversion to Carbinol Amides[1]

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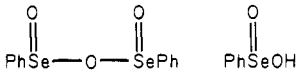
Enamidic 4-azasteroids **5a,b** were oxidized by benzeneseleninic anhydride (1) to afford carbinol amides **6a,b**, 7α- and 7β-hydroxy-6-phenylseleno derivatives **7a,b** and **8a,b**, and selenides **9a,b**. Selenoxide intermediates **12a,b** are initially formed in this process and generate the observed products through Pummerer reactions. Selenoxide **12a** was prepared independently in excellent yield by the sequential treatment of enamide **5a** with benzeneselenenyl chloride and 1 equiv of *m*-chloroperbenzoic acid. A 2:1 mixture of selenoxide diastereomers was obtained, from which the major isomer could be separated by equilibration and precipitation from aqueous potassium carbonate solution. The selenoxide is thermally stable but racemizes via an achiral selenoxide hydrate. The further oxidation of **12a,b** with *m*-chloroperbenzoic acid produced carbinol amides **6a,b** in yields of 72% and 62%, respectively. Compound **6a** underwent facile hydroxyl exchange in acidic methanol. The oxidation of enamide **5a** with the peracid in the presence of methanol produced the 6-hydroxy carbinol amide methyl ether **18**, which readily eliminated methanol to give the 6-keto lactam **19**.

The preparation of new azasteroid derivatives[2] has long been stimulated by frequent reports of their biological activity.[3] Our interest in such compounds[4] recently led us to examine the oxidation of a Δ^5-4-azasteroidal enamide with benzeneseleninic anhydride (1).[5] We observed that products with new oxygen functions at C-5, C-6, and C-7 were formed from the Pummerer reaction of a C-6 selenoxide intermediate. Our continuing efforts in this area as described in the present paper were prompted by the following considerations. First, the above enamide oxidation comprises a novel extension of the known chemistry of the versatile reagent 1 and of the related seleninic acid



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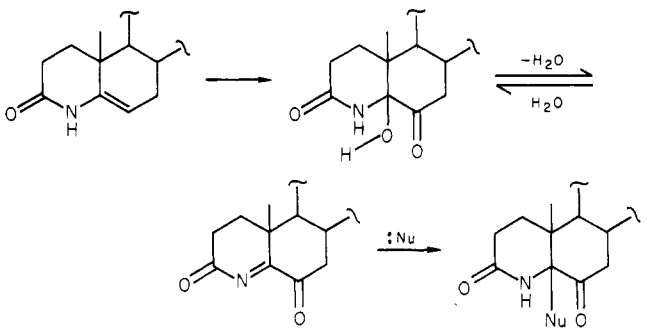
2.[6] Second, although selenoxides have been thoroughly studied in recent years,[7] only a few examples where they undergo Pummerer reactions have been previously reported.[8]

Scheme I



Furthermore, one diastereomer of the selenoxide implicated in the above process can be isolated in a high state of purity. To our knowledge, it is the only selenoxide reported to date which is both optically pure and chemically inert under ambient conditions. These properties make it a convenient subject for studies of the configurational stability of the selenoxide moiety.

Finally, we desired to convert readily available azasteroid enamides to 6-keto carbinol amide derivatives. These products are of special interest as they are expected to alkylate nucleophiles by hydroxyl exchange (Scheme I). Such interactions with nucleophilic groups in steroid receptor proteins might result in interesting biological properties.[9] For instance, if the carbinol amides display high binding affinities for steroid receptors, they could find application in affinity labeling studies[10] or as antineoplastic agents for tumors of receptor-rich organs or tissues.[11] We now report a new, simple procedure for preparing the desired carbinol amides from their enamide counterparts via selenoxide intermediates.

(1) We gratefully acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada.

(2) (a) Huisman, H. O. in "MTP International Reviews of Science: Organic Chemistry"; Hey, D. H., Johns, W. F., Eds.; Butterworths: London, 1973; Series 1, Vol. 8, Chapter 9. (b) Huisman, H. O.; Speckamp, W. N. *Ibid.*, 1976, Series 2, Vol. 8, Chapter 8.

(3) For examples see: (a) Chiu, W. H.; Klein, T. H.; Wolff, M. E., *J. Med. Chem.* **1979**, *22*, 119. (b) Singh, H.; Bhardwaj, T. R.; Ahuja, N. K.; Paul, D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 305. (c) Rulin, V. A.; Shner, V. F.; Lisitsa, L. I.; Terekhina, A. I.; Suvorov, N. N. *Zh. Org. Khim.* **1975**, *11*, 1763. (d) Solomons, W. E.; Doorenbos, N. J. *J. Pharm. Sci.* **1974**, *63*, 19. (e) Doorenbos, N. J.; Solomons, W. E. *Ibid.* **1973**, *62*, 638. (f) Doorenbos, N. J.; Scott, J.; Vaidya, S. S. *Ibid.* **1971**, *60*, 1236.

(4) Back, T. G. *J. Org. Chem.* **1981**, *46*, 1442.

(5) Preliminary communication: Back, T. G.; Ibrahim, N. *Tetrahedron Lett.* **1979**, 4931.

(6) For leading references see: (a) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1981**, *46*, 1564. (b) Back, T. G. *J. Chem. Soc., Chem. Commun.* **1981**, 530. (c) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473. (d) Yamakawa, K.; Satoh, T.; Ohba, N.; Sakaguchi, R.; Takita, S.; Tamura, N. *Tetrahedron* **1981**, *37*, 473.

(7) For reviews see: (a) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (c) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9.

(8) (a) Norcross, B. E.; Lansinger, J. M.; Martin, R. L., *J. Org. Chem.*, **1977**, *42*, 369. (b) Reich, H. J.; Shah, S. K. *Ibid.* **1977**, *42*, 1773. (c) Sharpless, K. B.; Gordon, K. M. *J. Am. Chem. Soc.* **1976**, *98*, 300. (d) Reich, H. J.; Renga, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5434. (e) Okamoto, Y.; Chellappa, K. L.; Homsany, R. *J. Org. Chem.* **1973**, *38*, 3172.

(9) For recent examples of steroidal and related alkylating agents see: (a) Katzenellenbogen, J. A.; McGorrin, R. J.; Tattee, T.; Kempton, R. J.; Carlson, K. E.; Kinder, D. H. *J. Med. Chem.* **1981**, *24*, 435. (b) Catsoulacos, P.; Politis, D. *Eur. J. Med. Chem.—Chim. Ther.* **1981**, *16*, 181. (c) Catsoulacos, P.; Politis, D.; Boutis, L.; Papageorgiou, A. *Ibid.* **1980**, *15*, 473. (d) Simons, S. S., Jr.; Pons, M.; Johnson, D. F. *J. Org. Chem.* **1980**, *45*, 3084.

(10) Dence, J. B. In "Steroids and Peptides"; Wiley: New York, 1980; Chapter 3.

(11) Other steroidal alkylating agents have been investigated in this context. For instance, nitrogen mustard derivatives of estrogens (estramustines) have been studied in the treatment of breast and prostatic carcinomas, with favorable results being obtained in the latter case. Leclercq, G.; Heuson, J. C. *Curr. Probl. Cancer* **1976**, *1*, 1.

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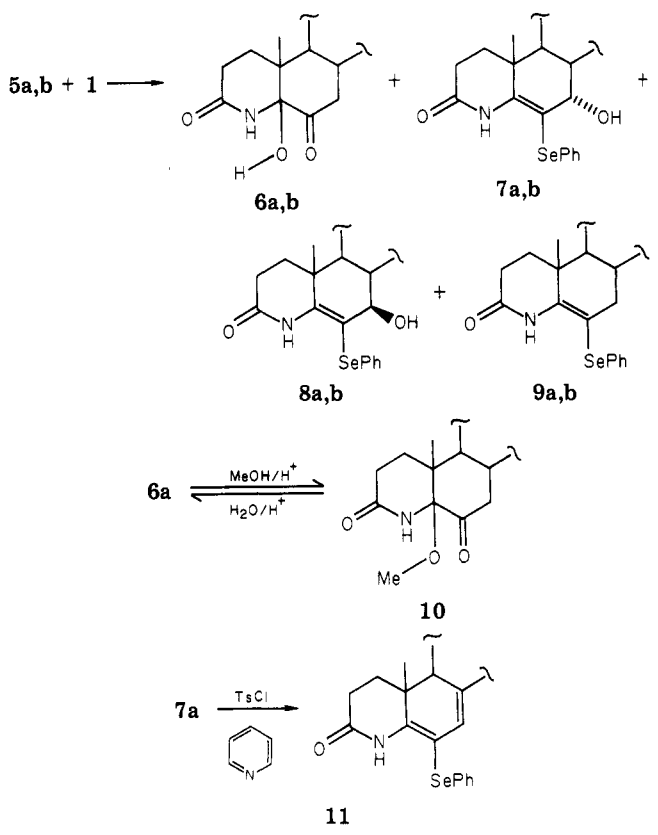
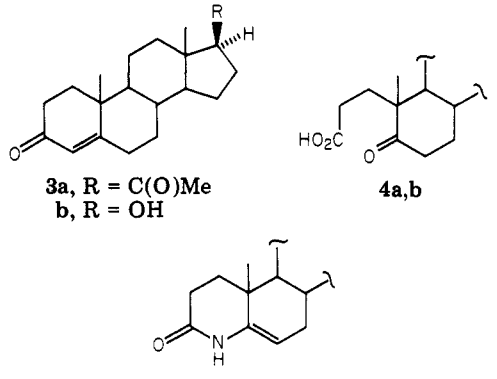
Scheme II



Results and Discussion

Progesterone (**3a**) and testosterone (**3b**) were converted to the corresponding enamides **5a,b** via the seco acids **4a,b**



by standard procedures.[12,13] The oxidation of 4-aza-5-pregnene-3,20-dione (**5a**) with **1** in dichloromethane proceeded readily at room temperature to afford, after aqueous workup, the carbinol amide **6a**, the 7α- and 7β-hydroxy enamidic selenides **7a** and **8a**, and the selenide **9a** in respective yields of 40%, 28%, 12%, and 16%. The products were identified from spectroscopic and analytical data as well as from the following experiments. The presence of the carbinol amide moiety in **6a** was demonstrated by the facile exchange of the hydroxyl group in slightly acidic methanol. This observation also confirms the potential of such azasteroid carbinol amides to alkylate nucleophiles. The resulting 5-methoxy derivative **10** could be reconverted to **6a** by aqueous acid. Compound **7a** underwent elimination to give the diene **11** as the chief product when treated with *p*-toluenesulfonyl chloride–pyridine. The stereochemical assignments of **7a** and **8a** were derived from their ^{1}H NMR spectra. The 7α-hydroxy epimer, where H-7 and H-8 are cis oriented, is expected to show a smaller coupling constant $J_{7,8}$ than its 7β counterpart where these protons are trans diaxial.[14] Since the major and minor isomers **7a** and **8a** have $J_{7,8} < 2$ Hz and $J_{7,8} = 7.5$ Hz, respectively, we assign the 7α-hydroxy structure to the former compound and the 7β-hydroxy structure to the latter. When 4-aza-17β-hydroxy-5-androsten-3-one (**5b**) was similarly oxidized, the corresponding products **6b–9b** were obtained in yields of 9%, 30%, 9%, and 18%, respectively. These processes are summarized in Scheme II.

The transformations in Scheme II are consistent with a mechanism involving Pummerer reactions of the corresponding C-6 selenoxides. In Scheme III, seleninylation of **5a,b** with **1** affords selenoxides **12a,b** and seleninic acid **2** in the initial step. The acidity of the latter compound ($pK_a = 4.79$[15]) enables it to catalyze the conversion of **12a,b** to the Pummerer intermediates **13a,b**.[16] Further reactions of these species by either of two pathways is envisaged. In the first process, hydrolysis of **13a,b** at C-6 and hydration of the *N*-acyl imine moiety leads directly to products **6a,b**, with simultaneous formation of benzeneselenol. It is also possible that intermediates such as **14a,b** are first formed from **13a,b** and seleninic acid **2** and are subsequently hydrolyzed to carbinol amides **6a,b**.

The second process involves proton abstraction from C-7 of intermediates **13a,b** by benzeneseleninate anion.[17] A 1,4-hydration of the resulting conjugated *N*-acyl imines **15a,b** during aqueous workup then provides products **7a,b** and **8a,b**. Again, hydrolytically labile[18] seleninic esters **16a,b** may actually be the immediate precursors of the final products.[19]

The formation of the remaining products **9a,b** also follows readily from Scheme III. Selenols are known to reduce selenoxides to selenides.[8d] Hence, the benzeneselenol produced during the hydrolysis of **13a,b** or **14a,b** could similarly reduce selenoxides **12a,b**. Alternatively, oxidation of the selenol with **1** or **2** and comproportionation of the resulting diphenyl diselenide with **2** would generate benzeneselenenic acid (PhSeOH) and related selenenic electrophiles[20] (eq 1). The additions of such species to

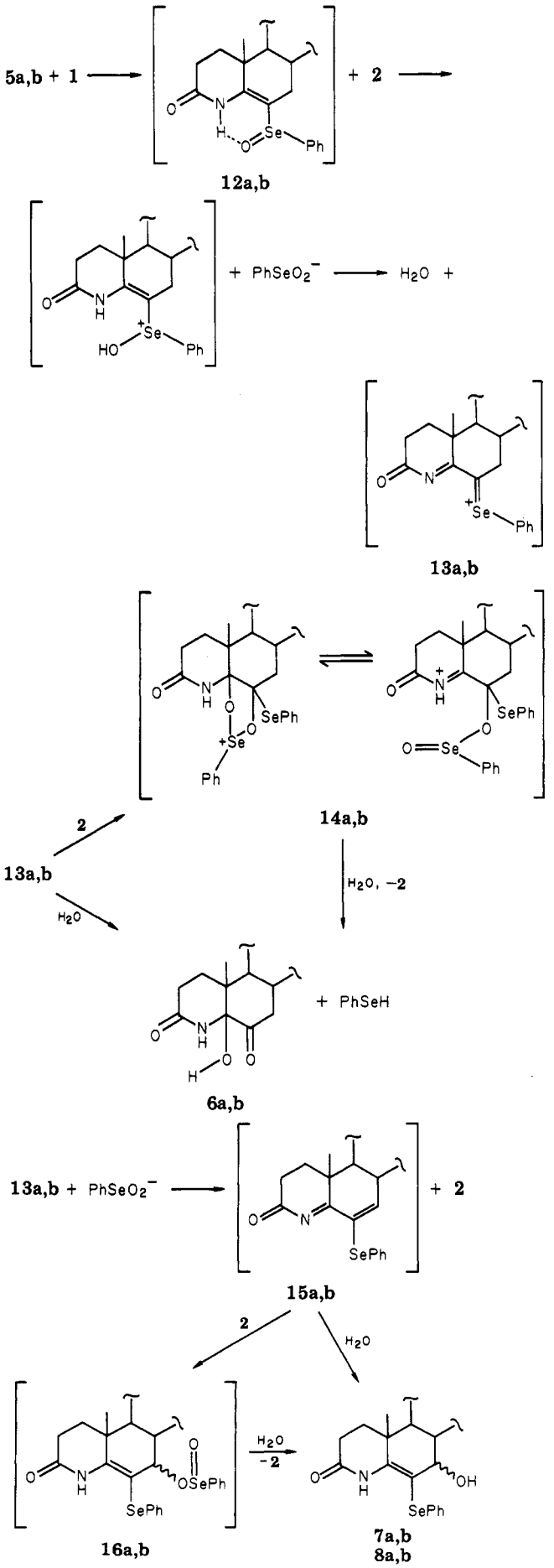
$$\mathrm{PhSeSePh} + \mathrm{PhSeO_2H} + \mathrm{H_2O} \rightleftharpoons 3\mathrm{PhSeOH} \quad (1)$$

$$\mathbf{5a,b} + \mathrm{PhSeOH} \rightarrow \mathbf{9a,b} + \mathrm{H_2O} \quad (2)$$

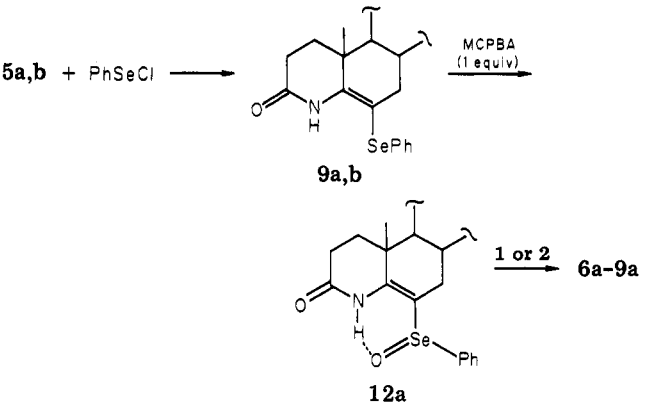
unactivated olefins have been well established,[6a,20,21] and their capture by the more nucleophilic enamides **5a,b** is

(12) Edward, J. T.; Holder, D.; Lunn, W. H.; Puskas, I. *Can. J. Chem.* **1961**, *39*, 599.
(13) Doorenbos, N. J.; Huang, C. L.; Tamorria, C. R.; Wu, M. T. *J. Org. Chem.* **1961**, *26*, 2546.
(14) Jackman, L. M.; Sternhell, S. In "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969, Chapter 4; Section 2.
(15) McCullough, J. D.; Gould, E. S. *J. Am. Chem. Soc.* **1949**, *71*, 674.
(16) Pummerer reactions of selenoxides have been observed in the presence of acetic acid,[8a] an acid of comparable strength to **2**.
(17) The free acid itself might be sufficiently basic for this purpose. The amphoteric nature of seleninic acids has long been recognized. Klayman, D. L. In "Organic Selenium Compounds: Their Chemistry and Biology"; Klayman, D. L., Günther, W. H. H., Eds.; Wiley: London, 1973; Chapter 4, p 124.
(18) Klayman, D. L. "Organic Selenium Compounds: Their Chemistry and Biology"; Klayman, D. L., Günther, W. H. H., Eds.; Wiley: London, 1973; Chapter 4, p 134.
(19) The reaction of **2** with *N*-acyl imines to form seleninic esters has been observed in previous work. At higher temperatures, the esters reacted via five-centered eliminations to generate carbonyl functions.[4]
(20) (a) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *Ibid.* **1978**, *43*, 1697.
(21) Labar, D.; Krief, A.; Hevesi, L. *Tetrahedron Lett.* **1978**, 3967.

Scheme III



Scheme IV



therefore expected to be even more facile (eq 2). Either process would account for the formation of selenides **9a,b**.

In order to confirm the Pummerer mechanism in Scheme III, we attempted to establish the intermediacy of selenoxide **12a** in the oxidation of **5a** with **1**. Unfortunately, **12a** could not be isolated from the reaction mixture. Instead, we prepared an authentic sample of **12a** by an independent method and subjected it to the conditions of the previous reaction in order to observe whether the same products **6a–9a** would again be formed. Thus, treatment of **5a** or **5b** with benzeneselenenyl chloride afforded selenides **9a** and **9b** in yields of 99% and 92%, respectively (Scheme IV). Oxidation of **9a** with 1 equiv of *m*-chloroperbenzoic acid (MCPBA) gave the required selenoxide **12a** in 99% yield. Although the product was stable in solution at room temperature, the addition of seleninic acid **2** caused rapid decomposition to afford the same products **6a–9a** as obtained previously. Catalysis with seleninic anhydride **1** gave similar results.[22] These experiments confirm the ability of selenoxide **12a** to act as an intermediate in the oxidation of enamide **5a** with **1** and lend strong support to the Pummerer mechanism depicted in Scheme III.

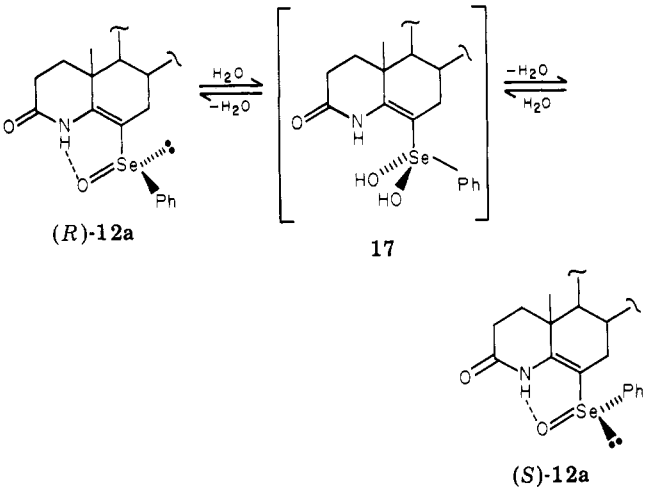
In a separate experiment, the reaction of selenoxide **12a** with **2** was quenched after 2 h by washing with sodium bicarbonate solution. The starting material was almost completely consumed. Since the oxidation of enamide **5a** with seleninic anhydride **1** required the longer reaction time of 18 h, it is evident that the initial seleninylation of **5a** in Scheme III is slower than the subsequent transformation of the selenoxide to the products.

The oxidation of **9a** creates a new chiral center at the selenium atom and so produces a pair of diastereomeric selenoxides. NMR analysis of product **12a** confirms the formation of two isomers by the presence of two sets of signals attributed to the NH protons as well as to the angular methyl groups. Integration of these signals indicates that the two diastereomers are formed in the ratio of ca. 2:1. When this mixture was stirred during one week in 5% aqueous potassium carbonate solution, equilibration of the two stereoisomers occurred, and the major isomer precipitated in a high state of purity. This result is of special interest as only a few stereochemically pure selenoxides have heretofore been reported. Cinquini et al.[23] separated meso and racemic forms of a bisselenoxide by fractional crystallization, while Jones[24] and Salmond[25] and

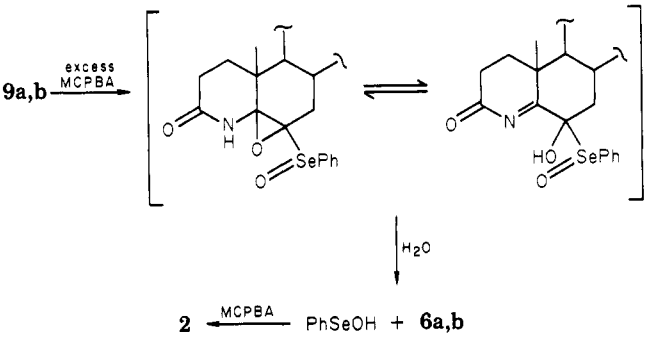
(22) By analogy, Pummerer reactions of sulfoxides may be catalyzed by a variety of electrophiles such as acetic anhydride. Durst, T. In "Advances in Organic Chemistry"; Taylor, E. C., Wynberg, H., Eds.; Wiley: New York, 1969; Vol. 6, p 356.

(23) Cinquini, M.; Colonna, S.; Landini, D. *Boll. Sci. Fac. Chim. Ind. Bologna* **1969**, *27*, 207.

Scheme V



Scheme VI



their co-workers independently prepared diastereomeric pairs of unstable steroidal selenoxides, which decomposed at or below room temperature by syn elimination or by [2,3] sigmatropic rearrangement. Separation of a selenoxide pair was achieved in only one case by chromatography at −50 °C.[24] The major diastereomer of **12a** is thus unique in being both optically pure and stable under ambient conditions.

When the mixture of selenoxide stereoisomers was equilibrated in aqueous (D_2O) potassium carbonate under homogeneous conditions with acetone-d_6 as a cosolvent, the NMR spectrum revealed that the original ratio of 2:1 remained unchanged after 1 week. Furthermore, when the pure, major diastereomer was similarly treated, it racemized to the same 2:1 mixture within 3 h. We therefore conclude that the 2:1 ratio reflects the relative thermodynamic stabilities of the two diastereomers and that the formation of the major isomer in the absence of acetone is fortuitously driven toward completion by its lower solubility and consequent precipitation from aqueous potassium carbonate solution.

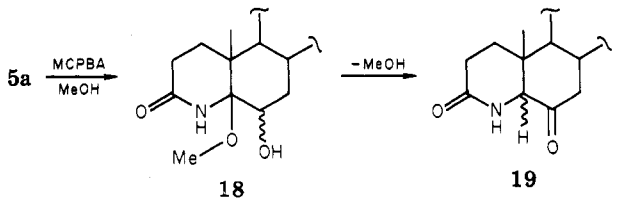
Interconversion of the diastereomers of **12a** requires an intermediate which is achiral at selenium, such as the selenoxide hydrate **17** (Scheme V). The formation of similar hydrates has been previously invoked to explain the configurational instability of other selenoxides.[26] Although the diastereomeric selenoxide pair reported by Jones and co-workers[24] did not interconvert in the presence of water, this may be attributed to the milder exposures presumably necessitated by the sensitive nature of the substrates in that experiment. Further evidence for racemization via hydrate formation in the present system stems from the failure of this process to occur under anhydrous conditions. We also observed that base catalysis is not required for the racemization of **12a**, as this process proceeded in D_2O–acetone-d_6 at comparable rates in the presence or absence of potassium carbonate. The effects of acid catalysis were not studied because of the competing Pummerer reaction.[27] The major diastereomer of **12a** was heated to 80 °C in perchloroethene solution. The NMR spectrum showed no noticeable conversion to the minor isomer under these conditions. Higher temperatures or prolonged heating resulted in decomposition to unidentified products. Apparently racemization via pyramidal inversion is less facile than thermal decomposition for this selenoxide.

The presence of strong intramolecular hydrogen bonds between the selenoxide oxygens and the enamidic hydrogen atoms in the stereoisomers of **12a** is revealed by the abnormally low field of the NMR signals of these protons. Their resonances are observed at δ 11.80 and 11.55 for the major and minor diastereomers, respectively, as compared to δ ca. 8.3 for enamides **7a–9a**. Moreover, the NH absorption at 3370 cm^{-1} in the IR spectrum of **12a** is independent of concentration, thus confirming the intramolecular nature of the hydrogen bond. The ORD spectrum of the major diastereomer of **12a** showed a positive Cotton effect with a maximum absorption at 300 nm. This spectrum strongly resembles that of (*R*)-6β-(phenylseleninyl)cholestane[24] and suggests that the present compound also possesses the *R* configuration at selenium. However, the validity of making such a comparison is uncertain, and the unequivocal assignment of absolute configuration to the present selenoxide awaits the outcome of an X-ray crystallographic study.

Only a few azasteroid carbinol amides have previously been reported.[13,28] These were prone to dehydration when heated or when treated with an acid catalyst, giving the more stable enamides instead of *N*-acyl imines.[13] It is therefore doubtful whether such compounds would be of use in the alkylation of nucleophiles. However, the presence of the 6-keto function in carbinol amides **6a,b** prevents enamide formation and makes these compounds more suitable as alkylating agents via Scheme I. Unfortunately, these products are obtained in poor yield from the oxidation of enamides **5a,b** with **1** (Scheme II). An alternative procedure involving the photooxidation of a 4-azasteroidal enamide has also been recently described but again affords only the modest yield of 41% of the corresponding 6-keto carbinol amide.[29] We consequently endeavored to find a more efficient preparation of these compounds. It occurred to us that further oxidation of selenoxides **12a,b** might result in the formation of the desired products according to Scheme VI. Since the selenoxides are themselves obtained by oxidation of the corresponding readily available selenides **9a,b**, a one-step procedure for converting the selenides directly to carbinol amides was foreseen. Thus, the reaction of **9a,b** with ex-

(24) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86.
(25) Salmond, W. G.; Barta, M. A.; Cain, A. M.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1683.
(26) (a) Trend, J. E. Ph.D. Thesis, University of Wisconsin (Madison), 1976; *Diss. Abstr. Int. B* **1976**, *37*, 2867. (b) Oki, M.; Iwamura, H. *Tetrahedron Lett.* **1966**, 2917. (c) Burlant, W. J.; Gould, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 5775.
(27) NMR studies of the degenerate isomerization at selenium of 3,3-dimethylselenolane 1-oxide have revealed the coexistence of several mechanisms. The process is acid but not base catalyzed.[26a]
(28) Uskokovič, M.; Gut, M. *Helv. Chim. Acta* **1959**, *42*, 2258.
(29) (a) Abelló, F.; Boix, J.; Gomez, J.; Morell, J.; Bonet, J. J. *Helv. Chim. Acta* **1975**, *58*, 2549. (b) A related Δ^1 derivative has also been reported: Vallet, J. A.; Cánovas, A.; Boix, J.; Bonet, J. J. *Ibid.* **1978**, *61*, 1165.

Scheme VII



cess MCPBA in chloroform, followed by workup with aqueous base, provided carbinol amides **6a,b** in the improved yields of 72% and 62%, respectively.

The direct conversion of enamide **5a** to the carbinol amide methyl ether **18** was also attempted. By analogy, previous model studies of the "eastern zone" of maytansine had demonstrated that an enamide precursor could be converted in good yield to the corresponding carbinol amide methyl ether by oxidation with MCPBA in methanol.[30] Similar treatment of **5a** afforded **18** in only 42% yield. The product readily eliminated methanol to furnish the corresponding ketone **19** (Scheme VII). The instability and poor yield of **18** make it less attractive than carbinol amides **6a,b** for use as a steroidal alkylating agent. Further studies of the exchange reactions of the latter compounds with nucleophiles are currently in progress in this laboratory.

Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus or in sealed capillaries on a Gallenkamp block. UV spectra were recorded on a Cary 15 or on a Varian-Cary 219 spectrometer. A Perkin-Elmer 467 instrument was used to obtain IR spectra. NMR spectra were obtained on a Hitachi Perkin-Elmer R24B, a Varian XL200, or a Bruker WH-90 instrument. All NMR spectra were taken in $CDCl_3$ solution unless otherwise noted and are reported in parts per million downfield from tetramethylsilane as the internal standard. Only selected signals are reported for ^{13}C NMR spectra. Mass spectra were recorded on a Varian MAT CH5 spectrometer by Dr. R. Yamdagni. The high-resolution mass spectrum of compound **8a** was provided by Dr. A. Hogg (University of Alberta). Optical rotations and the ORD spectrum of compound **12a** were obtained on a JASCO ORD-UV5 instrument with the assistance of Dr. R. S. Roche. Elemental analyses were performed by Mr. L. Malek or by Guelph Chemical Laboratories. Preparative TLC was carried out on Analtech 20 × 20 cm glass plates coated with 1 mm of silica gel GF. All solvents were reagent grade; dichloromethane and chloroform were predried over molecular sieves. Progesterone and testosterone were purchased from the Aldrich Chemical Co. Benzeneseleninic acid and anhydride were either purchased from the latter source or were prepared by a literature procedure;[31] MCPBA (Aldrich Chemical Co.) was purified by treatment with a pH 7.5 phosphate buffer and was assumed to be 100% pure.[32] All other reagents were commercially available and were used without further purification.

5,20-Dioxo-3,5-seco-4-norpregnan-3-oic Acid (4a) and 17β-Hydroxy-5-oxo-3,5-seco-4-norandrostan-3-oic Acid (4b). The title compounds were prepared from progesterone (**3a**) and testosterone (**3b**) in yields of 60% and 80%, respectively, by the method described by Edward et al.[12] for the analogous oxidative cleavage of 4-cholesten-3-one.

4-Aza-5-pregnene-3,20-dione (5a). The title compound was prepared from **4a** by the method of Doorenbos et al.[13]

4-Aza-17β-hydroxy-5-androsten-3-one (5b). The title compound was prepared by the preceding procedure in 77% yield. Purification of the crude product was effected by vacuum sublimation at ca. 150 °C (0.1 mm): mp 315 °C (sealed capillary; lit.[28] mp 292–296 °C); IR ($CHCl_3$) 3600 (OH), 3390 (NH), 1680 (C=C), 1658 (C=O) cm^{-1}.

Oxidation of Enamide 5a with 1. Azasteroid **5a** (188 mg, 0.60 mmol) and seleninic anhydride **1** (238 mg, 0.66 mmol) were stirred 18 h in 15 mL of dichloromethane. The reaction mixture was then diluted with dichloromethane until clear, washed with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was separated by preparative TLC in chloroform–ethyl acetate–benzene–methanol (60:20:10:2.5)[33] to afford, in increasing order of mobility, the following bands.

(A) 4-Aza-5-hydroxypregnane-3,6,20-trione (**6a**): 82 mg (40%); mp 232–234 °C (from dichloromethane–ether); IR ($CHCl_3$) 3630 (OH), 3380 (NH), 1725 (C=O, C-6), 1700 (C=O, C-20), 1660 (C=O, C-3) cm^{-1}; ^1H NMR (90 MHz) 7.00 (br s, exchanged, 1 H, NH), 3.80 (br s, exchanged, 1 H, OH), 2.8–1.0 (complex, s at 2.14, total 21 H), 0.80 (s, 3 H, Me), 0.64 (s, 3 H, Me); ^{13}C NMR (Me_2SO-d_6) 208.3 (C-20), 205.2 (C-6), 170.5 (C-3), 84.8 (C-5); mass spectrum *m/e* (relative intensity) 347 (<5, M^+), 329 (7, $M^+ - H_2O$). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 68.94; H, 8.45; N, 4.10.

(B) 4-Aza-7α-hydroxy-6-(phenylseleno)-5-pregnene-3,20-dione (**7a**): 81 mg (28%); solid foam; $[\alpha]_D$ −132° (*c* 0.47, $CHCl_3$); UV (MeOH) 249 nm (ε 15 400); IR ($CHCl_3$) 3580 (OH), 3310 (NH), 1696 (C=O, C-20), 1672 (C=O, C-3), 1626 (C=C), 1578 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.25 (br s, exchanged, 1 H, NH), 7.27 (s, 5 H, Ph), 4.05 (br s, 1 H, H-7), 2.6–1.0 (complex, s at 2.13 and 1.21, total 23 H), 0.66 (s, 3 H, Me); ^{13}C NMR 209.2 (C-20), 169.7 (C-3), 148.6, 130.1, 129.7, 127.1 (Ph and C-5; a fifth signal near 130 ppm could be resolved in acetone-d_6), 106.8 (C-6), 70.3 (C-7); mass spectrum, *m/e* 487 (M^+, ^{80}Se), 485 (M^+, ^{78}Se). Anal. Calcd for $C_{26}H_{33}NO_3Se$: C, 64.22; H, 6.78; N, 2.88. Found: C, 64.05; H, 7.13; N, 2.77.

(C) 4-Aza-7β-hydroxy-6-(phenylseleno)-5-pregnene-3,20-dione (**8a**): 34 mg (12%); solid foam; $[\alpha]_D$ +46° (*c* 0.17, $CHCl_3$); UV (MeOH) 247 nm (ε 17 300); IR ($CHCl_3$) 3550 (OH), 3310 (NH), 1696 (C=O, C-20), 1675 (C=O, C-3), 1629 (C=C), 1578 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.26 (br s, exchanged, 1 H, NH), 7.27 (s, 5 H, Ph), 3.93 (dd, J = 7.5, 3.0 Hz, collapsed to d, J = 7.5 Hz upon exchange, 1 H, H-7), 2.6–1.2 (complex, s at 2.13, 1.27, total 23 H), 0.71 (s, 3 H, Me); ^{13}C NMR 209.3 (C-20), 169.5 (C-3), 148.5, 129.7, 129.4, 126.9 (Ph and C-5; the remaining signal was not resolved), 106.8 (C-6), 74.7 (C-7); high-resolution mass spectrum calcd for $C_{26}H_{33}NO_3{}^{80}Se$ *m/e* 487.1626, found *m/e* 487.1630.

(D) 4-Aza-6-(phenylseleno)-5-pregnene-3,20-dione (**9a**): 45 mg (16%); identical (TLC, IR, NMR) with an authentic sample (vide infra).

(E) A yellow band near the solvent front afforded diphenyl diselenide (16 mg) identical with an authentic sample (TLC, melting point).

Hydroxyl Exchange in Carbinol Amide 6a. Compound **6a** (25 mg) was suspended in 2 mL of methanol. One drop of methanol saturated with anhydrous HCL was added, and the solid rapidly dissolved. After 30 min, the solvent was removed in vacuo. The residue was redissolved in chloroform and reevaporated four times to ensure the removal of traces of methanol. The product was dried at 60 °C (0.1 mm) to give the 5-methoxy derivative **10** as a wide-melting solid (mp <130 °C) of higher TLC mobility than **6a**: IR ($CHCl_3$) 3380 (NH), 1724 (C=O, C-6), 1700 (C=O, C-20), 1670 (C=O, C-3) cm^{-1}; ^1H NMR (60 MHz) 6.95 (br s, 1 H, NH), 3.07 (s, 3 H, OMe), 2.7–1.0 (complex, s at 2.13, 0.80, total 24 H), 0.64 (s, 3 H, Me).

The above product was dissolved in 5 mL of acetone and 1 mL of 5% aqueous HCl. After 1 h, the mixture was diluted with dichloromethane, washed with water, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The resulting white solid was identical with authentic **6a** (melting point, IR, NMR).

4-Aza-6-(phenylseleno)-5,7-pregnadiene-3,20-dione (11). Azasteroid **7a** (52 mg, 0.11 mmol), *p*-toluenesulfonyl chloride (20 mg, 0.11 mmol), and pyridine (8 mg, 0.10 mmol) were dissolved in 2 mL of dichloromethane. After 24 h at room temperature followed by 4 h at reflux, the reaction mixture was concentrated and separated by preparative TLC in chloroform–ethyl acetate–benzene–methanol (60:20:10:2.5) to furnish 40.5 mg (80%) of diene

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(33) The use of this solvent in separating azasteroid mixtures has been previously reported.[29a] The system alumina GF–ether is also suitable.

11, contaminated with a small amount of an unidentified impurity from which it could not be separated: UV (MeOH) 243 nm (ε 13 200), 315 (8900); IR ($CHCl_3$) 3320 (NH), 1700 (C=O, C-20), 1670 (C=O, C-3), 1629, 1587 (diene), 1579 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.33 (br s, exchanged, 1 H, NH), 7.24 (m, 5 H, Ph), 5.70 (t, J = 2.7 Hz, 1 H, vinylic), 2.7–1.1 (complex, s at 2.15, 1.18, total 21 H), 0.62 (s, 3 H, Me), signals from impurity at δ 2.12, 1.21, 0.66; high-resolution mass spectrum calcd for $C_{26}H_{31}NO_2{}^{80}Se$ m/e 469.1520, found m/e 469.1478.

Oxidation of Enamide 5b with 1. Azasteroid **5b** (147 mg, 0.51 mmol) and seleninic anhydride 1 (200 mg, 0.56 mmol) were stirred 18 h in 5 mL of dichloromethane. The reaction was worked up as in the case of **5a**, and the products were separated by preparative TLC in ethyl acetate to afford, in increasing order of mobility, the following bands.

(A) 4-Aza-5,17β-dihydroxyandrostane-3,6-dione (**6b**): 15 mg (9%); mp 235–240 °C (from methanol–ether); IR spectrum identical with that of an authentic sample (vide infra).

(B) 4-Aza-7α,17β-dihydroxy-6-(phenylseleno)-5-androsten-3-one (**7b**): 70 mg (30%); solid foam; $[\alpha]_D$ −184° (c 1.0, $CHCl_3$); IR (Nujol) 3500–3200 (br, NH and OH), 1600 (C=O), 1630 (C=C), 1576 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.24 (br s, exchanged, 1 H, NH), 7.26 (s, 5 H, Ph), 4.02 (m, collapsed to d, J = 3.6 Hz upon exchange, 1 H, H-7), 3.72 (t, J = 8.3 Hz, 1 H, H-17), 2.6–1.0 (complex, s at 1.22, total 20 H), 0.78 (s, 3 H, Me); mass spectrum, m/e 461 (M^+, ^{80}Se), 459 (M^+, ^{78}Se). Anal. Calcd for $C_{24}H_{31}NO_3Se$: C, 62.60; H, 6.79; N, 3.04. Found: C, 61.80; H, 7.10; N, 3.08.

(C) 4-Aza-7β,17β-dihydroxy-6-(phenylseleno)-5-androsten-3-one (**8b**): 20 mg (9%); solid foam; $[\alpha]_D$ −25° (c 0.9, $CHCl_3$); IR (Nujol) 3500–3250 (br, NH and OH), 1663 (C=O), 1626 (C=C), 1576 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.26 (br s, exchanged, 1 H, NH), 7.24 (s, 5 H, Ph), 3.91 (d, J = 7.5 Hz, 1 H, H-7), 3.62 (t, J = 8.5 Hz, 1 H, H-17), 2.6–1.0 (complex, s at 1.27, total 20 H), 0.82 (s, 3 H, Me); mass spectrum, m/e (relative intensity) 461 (<5, M^+, ^{80}Se), 459 (<5, M^+, ^{78}Se), 443 (17, $M^+ - H_2O$, ^{80}Se), 441 (11, $M^+ - H_2O$, ^{78}Se). Anal. Calcd for $C_{24}H_{31}NO_3Se$: C, 62.60; H, 6.79; N, 3.04. Found: C, 62.82; H, 6.78; N, 3.04.

(D) 4-Aza-17β-hydroxy-6-(phenylseleno)-5-androsten-3-one (**9b**): 41 mg (18%); identical (TLC, IR, NMR) with an authentic sample (vide infra).

(E) A yellow band near the solvent front afforded diphenyl diselenide (13 mg) identical with an authentic sample (TLC, melting point).

4-Aza-6-(phenylseleno)-5-pregnene-3,20-dione (9a). Benzeneselenenyl chloride (383 mg, 2.00 mmol) in 2 mL of dichloromethane was added dropwise to a solution of enamide **5a** (630 mg, 2.00 mmol) in 10 mL of dichloromethane. After 30 min, the solution was washed twice with 5% K_2CO_3 solution and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo furnished 930 mg (99%) of **9a** as a pale yellow solid foam with IR and NMR spectra identical with those of an analytical sample. The latter was prepared by preparative TLC in chloroform–methanol (95:5): $[\alpha]_D$ −107° (c 0.6, $CHCl_3$); UV (Et_2O) 252 nm (ε 17 000); IR ($CHCl_3$) 3320 (NH), 1699 (C=O, C-20), 1667 (C=O, C-3), 1580 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.28 (br s, exchanged, 1 H, NH), 7.23 (s, 5 H, Ph), 2.6–1.1 (complex, s at 2.12, 1.21, total 24 H), 0.66 (s, 3 H, Me); ^{13}C NMR 209.0 (C-20), 169.2 (C-3), 144.9, 130.9, 128.5, 128.1, 125.6 (Ph and C-5), 102.7 (C-6); mass spectrum, m/e 471 (M^+, ^{80}Se), 469 (M^+, ^{78}Se). Anal. Calcd for $C_{26}H_{33}NO_2Se$: C, 66.35; H, 7.07; N, 2.98. Found: C, 66.31; H, 7.18; N, 2.87.

4-Aza-17β-hydroxy-6-(phenylseleno)-5-androsten-3-one (9b). Benzeneselenenyl chloride (96 mg, 0.50 mmol) and enamide **5b** (145 mg, 0.50 mmol) were allowed to react as in the previous procedure. The crude product was purified by preparative TLC in ethyl acetate to give 205 mg (92%) of **9b**: mp 152–154 °C (from chloroform–hexane); $[\alpha]_D$ −150° (c 1.1, $CHCl_3$); IR (Nujol) 3400 (OH), 3320 (NH), 1660 (C=O), 1633 (shoulder, C=C), 1575 (Ph) cm^{-1}; ^1H NMR (200 MHz) 8.29 (br s, exchanged, 1 H, NH), 7.23 (s, 5 H, Ph), 3.64 (t, J = 8.1 Hz, 1 H, H-17), 2.6–0.7 (complex, s at 1.22, 0.78, total 24 H); mass spectrum, m/e 445 (M^+, ^{80}Se), 443 (M^+, ^{78}Se). Anal. Calcd for $C_{24}H_{31}NO_2Se$: C, 64.85; H, 7.03; N, 3.05. Found: C, 64.39; H, 7.10; N, 2.94.

4-Aza-6-(phenylseleno)-5-pregnene-3,20-dione *Se*-Oxide (12a). A solution of MCPBA (172 mg, 1.00 mmol) in 5 mL of dichloromethane was added dropwise over 5 min to selenide **9a** (471 mg, 1.00 mmol) in 10 mL of dichloromethane. The reaction mixture was promptly washed three times with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated in vacuo to afford 483 mg (99%) of selenoxide **12a** as a mixture of two diastereomers of sufficient purity for further use. The mixture had the following: IR ($CHCl_3$) 3660 (trace of H_2O), 3370 (NH), 1699 (C=O, C-20), 1668 (C=O, C-3) cm^{-1}; ^1H NMR (200 MHz) showed all of the signals observed for the major diastereomer (vide infra) superimposed on those of the minor isomer at δ 11.50 (br s, exchanged, NH), 1.13 (s, Me), and 0.60 (s, Me). The integrated intensities of the respective NH and Me signals indicated that the ratio of the two stereoisomers was 2:1. An analytical sample was prepared by preparative TLC[34] in chloroform–methanol (95:5) followed by drying for 3 h at 65 °C (0.1 mm). Anal. Calcd for $C_{26}H_{33}NO_3Se$: C, 64.17; H, 6.84; N, 2.88. Found: C, 64.05; H, 7.01; N, 2.86.

A sample of the above mixture of diastereomers (80 mg) was stirred vigorously in 5 mL of 5% K_2CO_3 solution for 1 week. During this time, the initial gummy residue was transformed into a clean, white powder. The product was filtered, washed with water, and dried in vacuo to afford 61 mg of the major diastereomer containing a trace (<5%) of the minor one. The filtrate was acidified with HCl, promptly extracted with chloroform, and dried over anhydrous $MgSO_4$ to furnish 13 mg of a residue containing the two selenoxide diastereomers in the ratio of 2:1 along with small amounts of unidentified impurities. The filtered solid was recrystallized twice from chloroform–ether: mp[35] 182–184 °C; $[\alpha]_D$ +131°; $[\Phi]_{300}$ +23 300°, $[\Phi]_{276}$ 0° (c 0.2, MeCN); UV (MeOH) 220 nm (ε 13 100), 252 (14 100); IR ($CHCl_3$) 3370 cm^{-1} (NH, unaffected by 10-fold dilution); ^1H NMR (200 MHz) 11.84 (br s, exchanged, 1 H, NH), 7.8–7.5 (m, 5 H, Ph), 2.6–1.0 (complex, s at 2.11, 1.20, total 24 H), 0.67 (s, 3 H, Me); ^{13}C NMR 208.8 (C-20), 168.3 (C-3), 150.8, 131.5, 130.0, 126.9, 126.3 (Ph and C-5), 106.3 (C-6); mass spectrum, m/e (relative intensity) 487 (<5, M^+, ^{80}Se), 485 (<5, M^+, ^{78}Se), 471 (41, $M^+ - O$, ^{80}Se) 469 (48, $M^+ - O$, ^{78}Se).

Reaction of Selenoxide 12a with 1 or 2. The major diastereomer of selenoxide **12a** (52 mg, 0.103 mmol) and seleninic acid **2** (24 mg, 0.13 mmol) were stirred 20 h in 5 mL of dichloromethane. The reaction mixture was then worked up as in the oxidation of **5a** with **1** to afford 8.4 mg (24%) of **6a**, 24.7 mg (49%) of **7a**, 8.5 mg (17%) of **8a**, and 4.0 mg (8%) of **9a**. The products were identified by comparison with authentic samples (TLC, IR, NMR). Similar results were obtained when the mixture of diastereomers was treated with **2** or when the major diastereomer reacted with **1**.

In a separate experiment, the mixture of diastereomers of **12a** was allowed to react with **2** in dichloromethane for 2 h. The solution was then washed with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated in vacuo. NMR analysis of the product revealed the presence of only a small amount of starting material (ca. 10%) while new signals at δ 8.3–8.2 (NH), 7.3–7.2 (Ph), and 4.1–3.9 (H-7) indicated nearly complete conversion to the usual products.

Stability of Selenoxide 12a. The mixture of diastereomers of **12a** could be stored in the solid state at −10 °C for at least 1 year with no noticeable decomposition. A deuteriochloroform solution of **12a** remained unchanged (NMR) after 54 h at room temperature. The addition of 1 drop of acetic acid resulted in extensive decomposition after a further 19 h. The products were not investigated.

The pure major diastereomer of **12a** could be stored in the solid state at −10 °C in a desiccator for at least 1 year with only slight (ca. 15%) racemization.

A 2:1 mixture of the two diastereomers (50 mg) was dissolved in 1 mL of acetone-d_6 containing 0.4 mL of 5% K_2CO_3 in D_2O. After 8 days at room temperature, NMR analysis indicated that the ratio of stereoisomers was unchanged and that no new products had formed. When the major diastereomer (10 mg) was dissolved in 0.3 mL of acetone-d_6 containing 0.2 mL of 5% K_2CO_3 in D_2O, a mixture of both diastereomers in the usual ratio of 2:1 formed

(34) TLC in a variety of solvents failed to separate the two diastereomers, possibly because of equilibration on the adsorbent. Prolonged exposure to silica gel resulted in partial decomposition.

(35) The values of the melting point and optical rotation are different from those originally reported.[5] It is likely that the previous sample had undergone partial racemization.

after 3 h. Similar results were obtained when the latter experiment was repeated without the presence of K_2CO_3.

A solution of the major diastereomer in perchloroethene was heated to 80 °C. No change was observed in the NMR spectrum. At higher temperatures, decomposition to unidentified products occurred.

4-Aza-5-hydroxypregnane-3,6,20-trione (6a). MCPBA (480 mg, 2.79 mmol) was added to a solution of **9a** (376 mg, 0.80 mmol) in 5 mL of chloroform. After 20 min, the reaction mixture was diluted to 20 mL and washed several times with 5% K_2CO_3 solution, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Crystallization of the residue from chloroform–methanol afforded 201 mg (72%) of carbinol amide **6a** (mp 234–236 °C), having an IR spectrum identical with that of the authentic sample obtained from the oxidation of **5a** with 1.

4-Aza-5,17β-dihydroxyandrostane-3,6-dione (6b). MCPBA (258 mg, 1.50 mmol) was added to a solution of **9b** (208 mg, 0.47 mmol) in 10 mL of chloroform. Workup as in the preceding procedure, followed by crystallization from acetone–hexane, furnished 94 mg (62%) of carbinol amide **6b**: mp 239–242 °C; IR (Nujol) 3440 (OH), 3280 (NH), 1735 (C=O, C-6), 1640 (C=O, C-3) cm^{-1}; ^1H NMR (pyridine-d_5) 3.92 (t, J = 8.4 Hz, 1 H, H-17), 3.0–0.8 (complex, s at 0.96, 0.88, total 24 H); mass spectrum, m/e (relative intensity) 321 (<1, M^+), 303 (13, $M^+ - H_2O$). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.40; H, 8.65; N, 4.28.

4-Aza-6-hydroxy-5-methoxypregnane-3,20-dione (18). A solution of MCPBA (189 mg, 1.10 mmol) in 10 mL of dichloromethane was added over 30 min to enamide **5a** (315 mg, 1.00 mmol) in 5 mL of dichloromethane and 5 mL of methanol. The reaction mixture was washed three times with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated in vacuo. Crystallization of the product from dichloromethane–ether afforded 152 mg (42%) of **18**, mp 170–172 °C; IR ($CHCl_3$) 3560 (OH), 3380 (NH), 1699 (C=O, C-20), 1668 (C=O, C-3) cm^{-1}; ^1H NMR (200 MHz) 7.00 (br s, exchanged, 1 H, NH), 3.85 (m, 1 H, H-6), 3.26 (s, 3 H, OMe), 2.6–1.0 (complex, s at 2.12, 1.16, total 25 H), 0.64 (s, 3 H, Me); ^{13}C NMR 209.3 (C-20), 174.4 (C-3), 87.4 (C-5), 68.1 (C-6); mass spectrum, m/e (relative intensity) 363 (<1, M^+), 332 (100, $M^+ - OMe$). Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 68.58; H, 9.08; N, 3.96. Attempts at further purification resulted in decomposition.

4-Azapregnane-3,6,20-trione (19). The preceding reaction was repeated with 95 mg (0.55 mmol) of MCPBA and 158 mg (0.50 mmol) of **5a**. The reaction mixture was allowed to stand for 24 h prior to workup in the previous manner. Crystallization of the product from dichloromethane–ether provided 93 mg (56%) of **19**: mp 185–210 °C; IR ($CHCl_3$) 3390 (NH), 1720 (C=O, C-6), 1700 (C=O, C-20), 1663 (C=O, C-3) cm^{-1}; ^1H NMR (200 MHz) 6.43 (br s, exchanged, 1 H, NH), 3.85 (s, 1 H, H-5), 2.7–1.0 (complex, s at 2.14, total 21 H), 0.82 (s, 3 H, Me), 0.66 (s, 3 H, Me);[36] ^{13}C NMR 208.8 (C-20), 203.5 (C-6), 170.7 (C-3), 67.5 (C-5); mass spectrum, m/e 331 (M^+). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.19; H, 8.61; N, 4.36.

Registry No. 1, 17697-12-0; 2, 6996-92-5; **3a**, 57-83-0; **3b**, 58-22-0; **4a**, 3510-20-1; **4b**, 1759-35-9; **5a**, 20283-95-8; **5b**, 82093-09-2; **6a**, 74214-10-1; **6b**, 82093-10-5; **7a**, 74214-11-2; **7b**, 82093-11-6; **8a**, 74214-12-3; **8b**, 82093-12-7; **9a**, 74214-13-4; **9b**, 82093-13-8; **10**, 82093-14-9; 11, 82093-15-0; **12a** (isomer 1), 74214-14-5; 12a (isomer 2), 74214-15-6; **18**, 82093-16-1; **19**, 82093-17-2.

(36) Signals at δ 0.80 and 0.63 (<10% of those at δ 0.82 and 0.66) suggest the presence of an impurity. It is possible that **19** is formed as a mixture of 5α and 5β isomers. This would also account for the broad melting point which was not improved by repeated recrystallization.

Synthesis of Enantiomerically Pure Forms of *N*-Acyl Derivatives of *C*-Methyl Analogues of the Aminodeoxy Sugar L-Acosamine from Noncarbohydrate Precursors

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The 2*S*,3*R* diol **2a** and the 3*R* α-ketol **5b**, prepared in fermenting baker's yeast from cinnamaldehyde and α-methylcinnamaldehyde, are converted into the chiral *N*-trifluoroacetyl deoxy *C*-methyl-branched amino sugars **15b,c** and **19b**. Key intermediates in the synthesis are the C_4 and C_5 chiral aldehydes **9a** and **17a** and the α,β-unsaturated carbonyl compounds **11a** and **18**, which upon threo stereoselective addition of ammonia, eventually give **15b,c** and **19b**. The stereochemistry and the conformations of the aminodeoxy sugar derivatives and of the intermediate lactones are deduced by NMR studies.

A current approach[1] to the synthesis of enantiomerically pure forms of natural products and drugs is based on the use as starting materials of components of the collection of inexpensive, readily available, optically active compounds produced by nature, called the "pool of chirality", which includes, among others, carbohydrates, amino acids, hydroxy acids like tartaric, malic, lactic, and citramalic, alcohols like D-mannitol, and a few terpenes. Chemists are, however, not fully satisfied with the present composition of the "pool of chirality", since most of the compounds are available in only one enantiomeric form, a circumstance which dictates, when the absolute configuration of the target molecule is opposite the one of the chosen starting material, chemical manipulation of the chiral center(s), usually through multistep, low-yield sequences. This is the case of the synthesis of the 2,3,6-trideoxy-3-aminohexoses of the L series present in the therapeutically important anthracycline glycosides daunomycin (**26a**), adriamycin (**26b**), and their 4′-epimers (**26c** and **26d**),[2]

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