Synthesis and Biological Activity of Unsymmetrical Bis-Steroidal Pyrazines Related to the Cytotoxic Marine Natural Product Cephalostatin 1

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A mild, high-yielding synthesis of symmetrical steroidal pyrazines was achieved from the dimerization of 2-amino-3-ketosteroids, which were produced *in situ* from the triphenylphosphine–water reduction of the corresponding α-azido ketone. 2-Azidocholestan-3-one gave the dimeric steroidal pyrazine very cleanly, and two known dimeric pyrazines based on androstanone were also made using this methodology. Both C_2-symmetric geometric isomers of the dimeric steroidal pyrazine derived from cholestane were prepared by reaction of 2,3-diaminocholestane with cholestane-2,3-dione. A route to unsymmetrical bis-steroidal pyrazines was based on the observation that α-acetoxy ketones react with α-amino oximes directly with no need for oxidation of intermediate dihydropyrazines. Heating either 2β,17β-dihydroxyandrostan-3-one diacetate or 2β,17β-dihydroxyhecogenin-3-one diacetate with 2-amino-3-methoxyiminocholestane in toluene at 145 °C gave the corresponding unsymmetrical pyrazine in moderate yield. Five of the steroidal pyrazines were evaluated in the National Cancer Institute's new *in vitro*, disease-oriented antitumor screen, but none showed sufficient activity to warrant *in vivo* investigation.

Introduction and Background

The cephalostatins are a group of complex steroidal pyrazines that have recently been isolated from the Indian Ocean marine worm, *Cephalodiscus gilchristi*.[2] This series of compounds are among the most potent cytotoxins ever screened by the National Cancer Institute, although *in vivo* tests have not been possible because of limited availability of the natural materials.[3]

The structure of cephalostatin 1 (**1**) was confirmed by single crystal X-ray diffraction.[1a] Cephalostatins 2–9 (**2**–**11**) were subsequently shown to possess a common steroidal component (Figure 1). The other steroidal half of each cephalostatin is different, but in nearly all cases this does not seem to affect the powerful cytotoxic activity shown by the series. Exceptions are cephalostatins 5 and 6, which have markedly diminished potency.[1d] More recently, cephalostatins 7–11 have been shown to exhibit potent growth inhibition and cytotoxicity against diverse human solid tumors in the National Cancer Institute's new *in vitro*, disease-oriented antitumor screen.[1e]

The novel structures and exceptional activities of the cephalostatins led to our interest in the synthesis of these compounds. An obvious place to start was the development of a method for the synthesis of unsymmetrical bis-steroidal pyrazines.[4]

Results and Discussion

Since one of our primary objectives was the synthesis of unsymmetrical steroidal pyrazines it was decided initially to investigate the Beirut reaction, cycloaddition of an enamine with a benzofuroxan to obtain the corresponding quinoxaline di-*N*-oxide.[5] If this process could be extended to simple furoxans, it would provide convenient access to the required unsymmetrical steroidal pyrazines.

Treatment of cholestanone (**12**) with potassium *tert*-butoxide and oxygen afforded the 2,3-dione **13**, which was converted into the bis-oxime **13** by reaction with hydroxylamine in refluxing ethanol. Oxidation of **13** with sodium hypochlorite gave a 1:1 mixture of the two furoxan regioisomers **15** and **16** (Scheme 1). Although it has been reported that one isomer can be obtained in low yield by fractional crystallization,[6] it was decided to carry out initial investigations on the chromatographically inseparable mixture.

Steroidal furoxans **15** and **16** were inert under conditions that normally suffice to bring about the Beirut reaction (e.g., cyclohexanone enamines; refluxing toluene; neat from room temperature to 120 °C; in the presence of $TiCl_4$ in CH_2Cl_2). Thus, it would seem that the extra driving force provided by rearomatization of the benzene ring (in the case of a benzofuroxan) is essential for the success of the Beirut reaction.

Having been thwarted in our initial approach to unsymmetrical pyrazines, we examined possible dimerization routes with the hope that we might find a way to accomplish an "unsymmetrical" dimerization. Several

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(1) Present Address: ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, England.

(2) (a) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N. D.; Niven, M. L.; Herald, D. L. *J. Chem. Soc., Chem. Commun.* **1988**, 865. (c) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N. D.; Niven, M. L.; Herald, D. L. *J. Chem. Soc., Chem. Commun.* **1988**, 1440. (d) Pettit, G. R.; Kamano, Y.; Dufresne, C.; Inoue, M.; Christie, N.; Schmidt, J. M.; Doubek, D. L. *Can J. Chem.* **1989**, *67*, 1509. (e) Pettit, G. R.; Kamano, Y.; Inoue, M.; Dufresne, C.; Boyd, M. R.; Herald, C. L.; Schmidt, J. M.; Doubek, D. L.; Christie, N. D. *J. Org. Chem.* **1992**, *57*, 429. (f) Pettit, G. R.; Xu, J.-P.; Williams, M. D.; Christie, N. D.; Doubek, D. L.; Schmidt, J. M.; Boyd, M. R. *J. Nat. Prod.* **1994**, *57*, 52.

(3) Suffness, M. National Cancer Institute, personal communication.

(4) For comprehensive reviews on the preparation and chemistry of pyrazines, see: (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*, 1st ed.; Pergamon Press: Oxford, 1984, pp 157–197. (b) Barlin, G. B. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; John Wiley: New York, 1982; Vol. 41, The Pyrazines.

(5) (a) Issidorides, C. H.; Haddadin, M. J. *Tetrahedron Lett.* **1965**, *6*, 3253. (b) Issidorides, C. H.; Haddadin, M. J. *J. Org. Chem.* **1966**, *31*, 4067.

(6) Chadwick, D. J.; Cottrell, W. R. T.; Meakins, G. D. *J. Chem. Soc., Perkin Trands. 1*, **1972**, 655.

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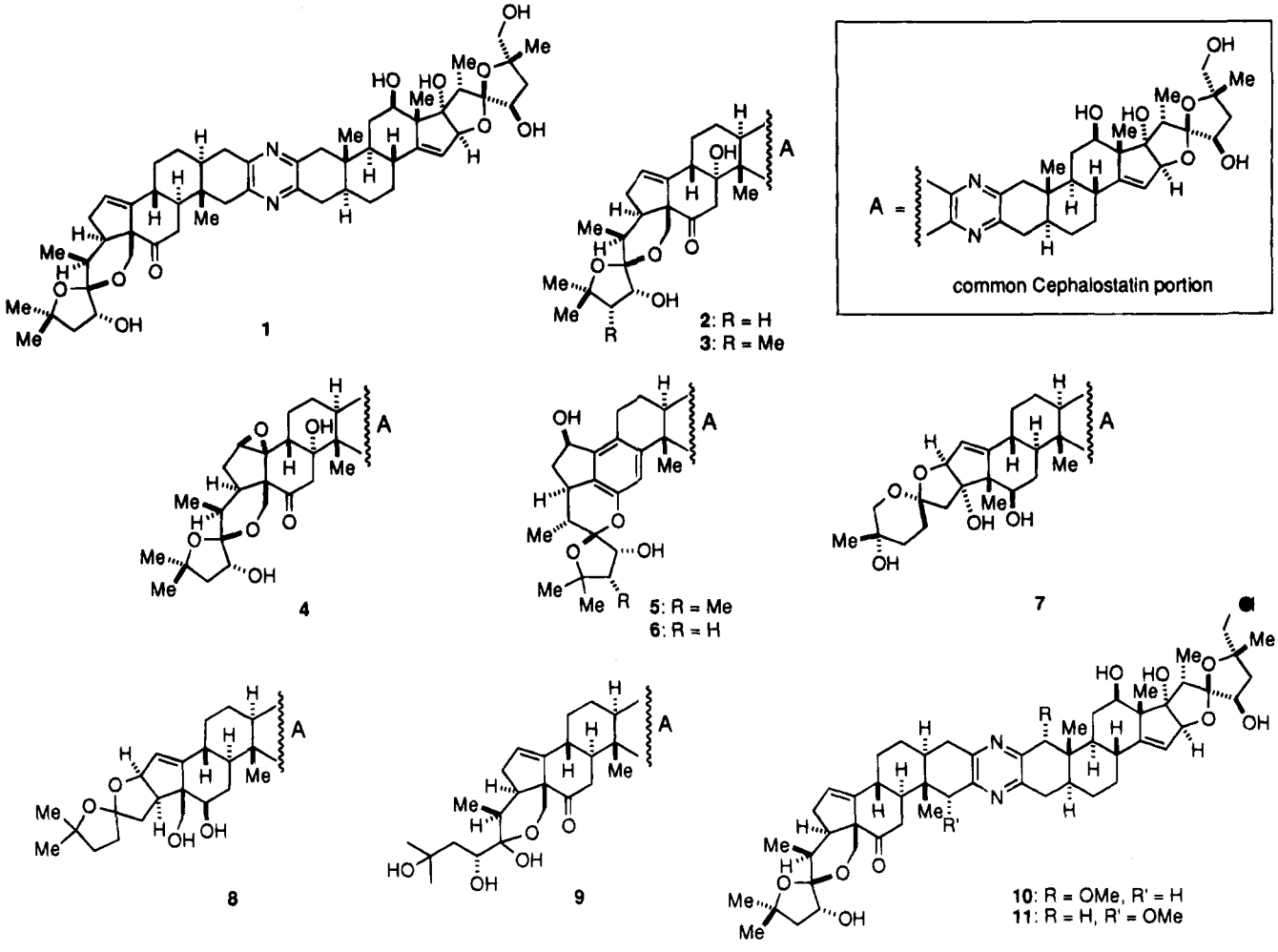
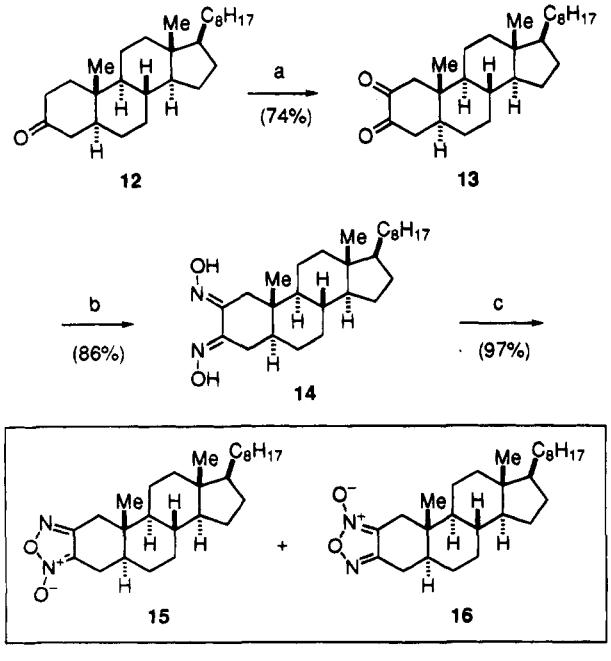


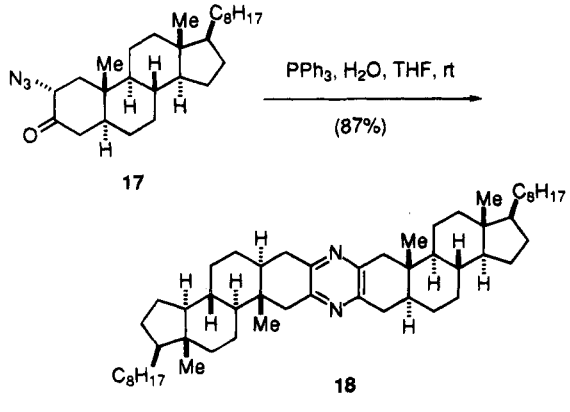
Figure 1. Cephalostatins 1–11 (**1**–**11**, respectively).

Scheme 1[a]



[a] Key: (a) *t*-BuOK, *t*-BuOH, rt; (b) $HONH_2$·HCl, NaOAc, EtOH, reflux; (c) NaOCl, NaOH, MeOH, H_2O 0 °C.

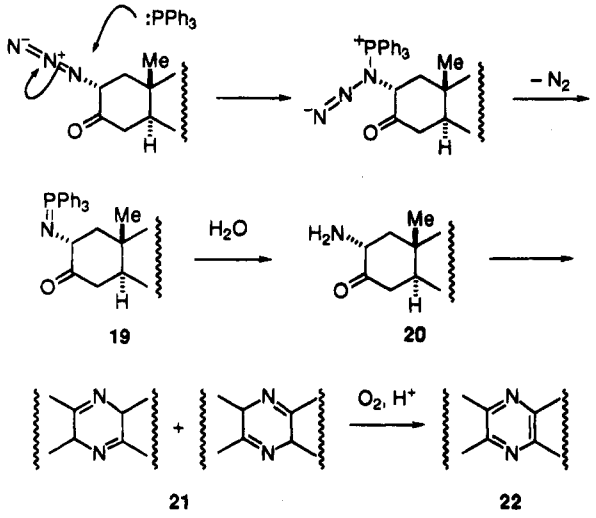
Scheme 2



symmetrical steroidal pyrazines had been known for some time.[7] Hydrogenation of 2-oximinocholestan-3-one in the presence of HCl is reported to give the corresponding amino ketone hydrochloride, which affords the corresponding symmetrical pyrazine upon basification with sodium hydroxide and concurrent air oxidation.[7a] A similar pyrazine was prepared by the same approach in 26% yield from the corresponding 2-oximino 3-one in the androstane series.[7b] A more convenient preparation of a dimeric steroidal pyrazine is outlined in Scheme 2. Treatment of the known azido ketone **17**[8] with aqueous triphenylphosphine in THF[9] gave a mixture of dihydropyrazine intermediates that were suspended in absolute

(7) (a) Ohta, G.; Koshi, K.; Obata, K. *Chem. Pharm. Bull.* **1986**, *16*, 1497. (b) Smith, H. E.; Hicks, A. A. *J. Org. Chem.* **1971**, *36*, 3659.

Scheme 3

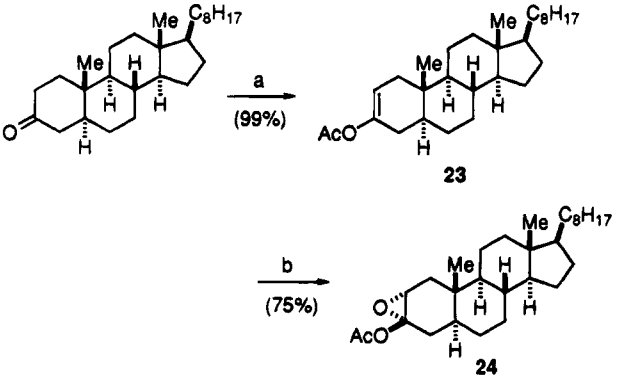


ethanol containing a catalytic amount of *p*-toluenesulfonic acid and stirred in air to obtain the crystalline pyrazine **18**, which is conveniently isolated by simple filtration.

The proposed mechanism for the formation of pyrazine **18** is given in Scheme 2. Initial attack by triphenylphosphine on the azido group gives the imino phosphorane **19** with loss of nitrogen. Although such ylides have been used in double bond forming reactions,[10] dimerization in this case was shown to occur by way of the amino ketone (**20**), rather than by reaction of ylide **19** with a ketone, by carrying out the reaction under anhydrous conditions (Scheme 3). The NMR spectrum of the crude product revealed the stable intermediate **19**, which gave dihydropyrazines **21**, and eventually pyrazine **22**, upon addition of water. The high yield of this dimerization reaction and the relatively slow rate of phosphorane hydrolysis (several hours) led to the suggestion that if a more hindered amino ketone were present, it might not dimerize with itself, but could trap the more reactive **20** as it formed.

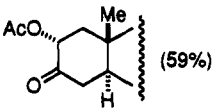
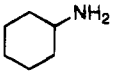
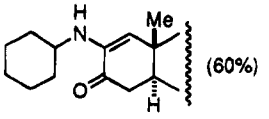
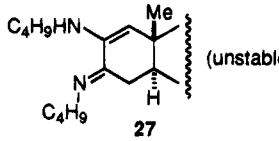
2-Amino-3-keto steroids have been prepared by the reaction of 2α,3α-epoxy-3β-acetates with neat amines.[11] Attempted substitution reactions on the corresponding α-bromo ketones reportedly led to problems with elimination products. To investigate the use of a 2α,3α-epoxy-3β-acetate for preparation of a 2-amino-3-keto steroid, enol acetate **23** was prepared by treatment of cholestan-3-one with acetic anhydride and catalytic perchloric acid (Scheme 4).[12] Compound **23** was oxidized to epoxy acetate **24** with dimethyldioxirane,[13] a method that is superior to the published method involving perbenzoic acid because simple evaporation of the solvent provides a solid that can be crystallized from ether to give the desired epoxy acetate, without the need for aqueous workup and removal of byproducts.

Scheme 4[a]



[a] Key: (a) Ac_2O, $HClO_4$, EtOAc, rt; (b) dimethyloxirane, acetone, rt.

Table 1. Reactions of Epoxy Acetate 24 with Amines

Amine and conditions	Product(s)
 neat, 105 °C, 72 h	 (59%) **25**
 neat, 105 °C, 4 h	 (60%) **26**
$C_4H_9NH_2$ neat, rt, 12 h	 (unstable) **27**

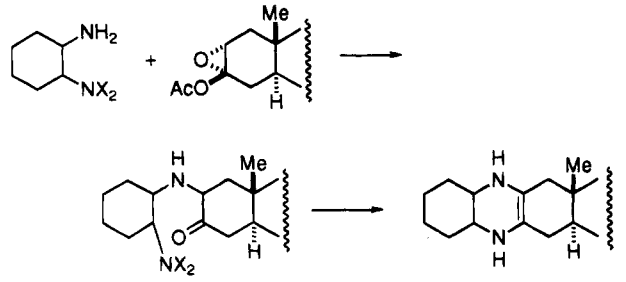
The reactions of epoxy acetate **24** with several amines are summarized in Table 1. Not surprisingly, epoxide opening was more facile with less hindered amines. In the case of *tert*-butylamine, the epoxy acetate rearranged thermally to α-acetoxy ketone **25**.[14] A more successful reaction occurred with cyclohexylamine, although the product underwent air oxidation and isomerization to the α-amino enone **26** upon silica gel chromatography. Epoxy acetate **24** undergoes epoxide opening at room temperature when treated with *n*-butylamine, but the resulting ketone also forms an unstable imine (**27**). This partially decomposed to an unsaturated ketone similar to **26**.

Despite the apparent overall lack of success, formation of **26** was promising in that, with another nitrogen group present in the amine, it might be possible to cyclize onto the ketone to give a pyrazine (Scheme 5). An amino oxime was the first choice since the difference in reactivity of the two nitrogen groups should allow control of regioselectivity.[15]

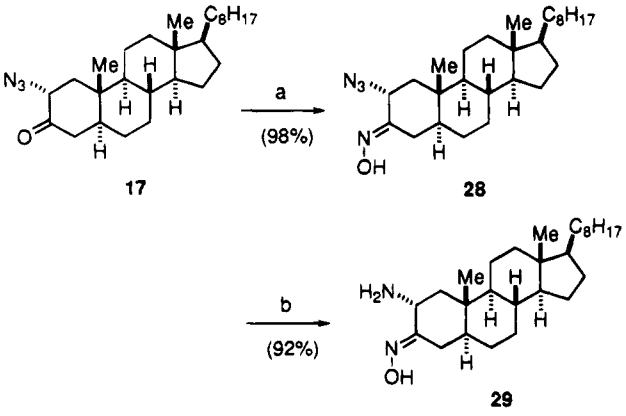
Amino oxime **29** was obtained in 91% overall yield from azido ketone (**17**; Scheme 6) by formation of the oxime (**28**) and reduction of the azido group with triphenylphosphine in aqueous THF. Only one oxime geometric isomer

(8) Schönecker, V. B.; Ponsold, K. *J. Für Praktische Chem. Bond* **1971**, *313*, 817.
(9) (a) Zbiral, E.; Stroh, J. *Liebigs Ann. Chem.* **1969**, *727*, 231. (b) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5044.
(10) Taylor, E. C.; Patel, M. *J. Heterocycl. Chem.* **1991**, *28*, 1857.
(11) Hassner, A.; Catsoulacas, P. *J. Org. Chem.* **1967**, *32*, 549.
(12) Edwards, B. E.; Rao, P. N. *J. Org. Chem.* **1966**, *31*, 324.
(13) For a review of dioxirane chemistry, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Gurci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. Preparation: (c) Murray, R. W.; Jeyarama, R. *J. Org. Chem.* **1985**, *50*, 2847. For a large scale preparation see: (d) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.
(14) Williamson, K. L.; Johnson, W. S. *J. Org. Chem.* **1961**, *26*, 4563.
(15) For reactions of simple α-amino oximes with aldehydes, see: Gnichtel, H. *Chem. Ber.* **1970**, *103*, 2411 and 3442.

Scheme 5



Scheme 6[a]



[a] Key: (a) $HONH_2$·HCl, pyridine, rt, 30 min; (b) Ph_3P, H_2O, THF, rt, 24 h.

was observed, and it is assigned the *anti* configuration based on literature precedent.[16]

When **29** was heated with epoxy acetate **24** in toluene at 85 °C, several products were obtained, including pyrazine **18** as an inseparable mixture with *N*-oxide **30** and the keto acetate **31** (Scheme 7). The expected "cis" product **32** was not observed (although analysis of similar reactions at a later stage indicated that it *was* being formed to a certain extent).

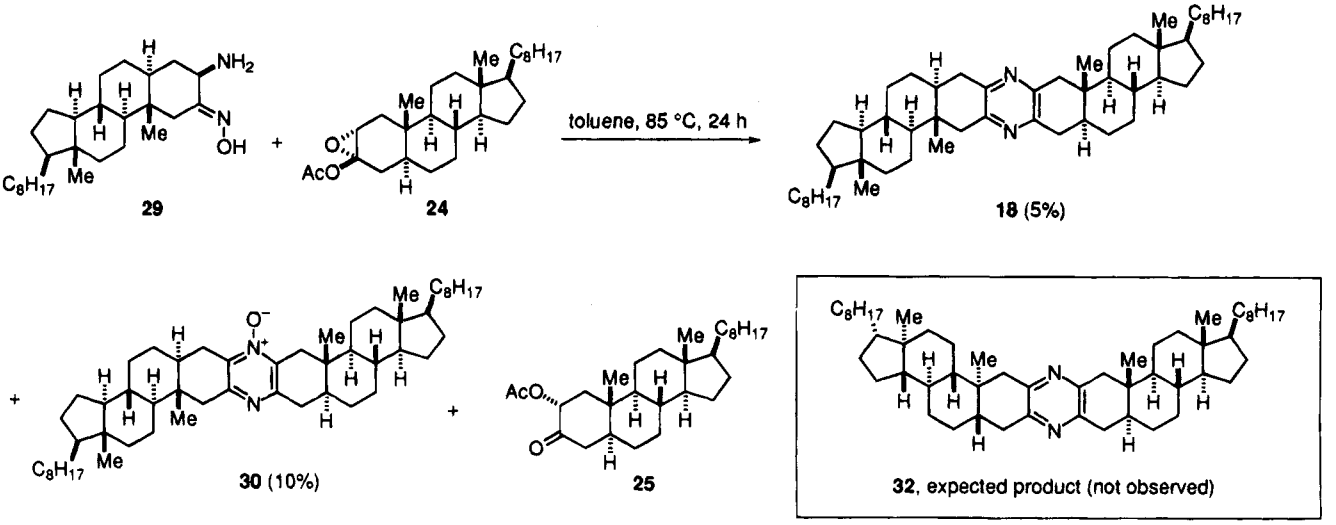
Several control reactions gave a clearer picture as to how the unexpected products **18**, **30**, and **31** arose (Scheme 8). First, heating a solution of the amino oxime **29** in toluene to 85 °C gave the dimeric "trans" pyrazine **18** along with a trace of the *N*-oxide. Second, epoxy acetate **24** was found to slowly rearrange at 85 °C to give the acetoxy ketone **33**, which epimerized under the reaction conditions to equatorial acetate **25**. When amino oxime **29** and acetoxy ketone **33** were heated together, not only was the dimer **18** observed, but the major product was the inseparable *N*-oxide **30**. The ratio of *N*-oxide to pyrazine was greater at higher initial concentrations of **33**. The latter reaction was very interesting, as coupling a steroidal keto acetate with an amino oxime based on a dissimilar steroid would provide a route to unsymmetrical steroidal pyrazines.

Proof of the structure of the *N*-oxide **30**, which is not C-2 symmetric, came from *m*-CPBA oxidation of the pyrazine **18** to the di-*N*-oxide **34** (Scheme 9). The oxidation was unselective with 1 equiv of *m*-CPBA, but the ^1H NMR spectrum of the crude product showed the presence of *N*-oxide **30**, along with the C_2-symmetric di-*N*-oxide **34** and starting material. Mass spectral analysis of the pyrazine/*N*-oxide **18/30** mixture showed the highest mass peak at 781, corresponding to MH^+ of **30**.

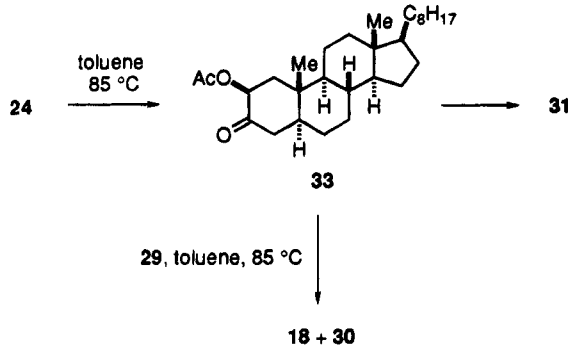
To make use of this reaction, it was necessary to find a new amino component that does not dimerize so easily. Attempts to make the *N,N*-dimethylhydrazone failed, but the *O*-methyloxime **36** was synthesized in an analogous fashion to **29** by way of the azido oxime **35** (Scheme 10). *O*-Methyloxime **36** is thermally much more stable than **29**, undergoing complete dimerization only after being heated to 140 °C. This reaction proved to be a very clean way of making pyrazine **18**.

Heating a toluene solution of amino oxime **36** with the keto acetate **37** at 85 °C gave **18** in only 3.5% yield after 24 h. Compound **18** was accompanied in this experiment by unidentified compounds, possibly intermediates in the formation of **18**. Heating this mixture for an additional 72 h at 85 °C provided an additional 7% yield of **18**; no amino oxime **36** remained after this period of time. Prolonging the reaction time to 14 days increased the yield to 23%. These investigations suggest that amino oxime **36** condenses with acetoxy ketone **37** at 85 °C but that the unidentified intermediate products require high temperature or long reaction time for efficient conversion into **18**. Because our goal is to prepare unsymmetrical pyrazines, we obviously do not want **36** to undergo self-condensation. For this reason, our subsequent cyclizations always involved heating at 85–90 °C for an initial

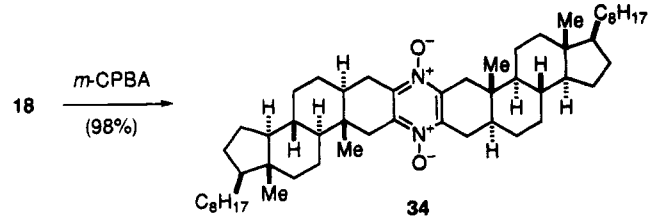
Scheme 7



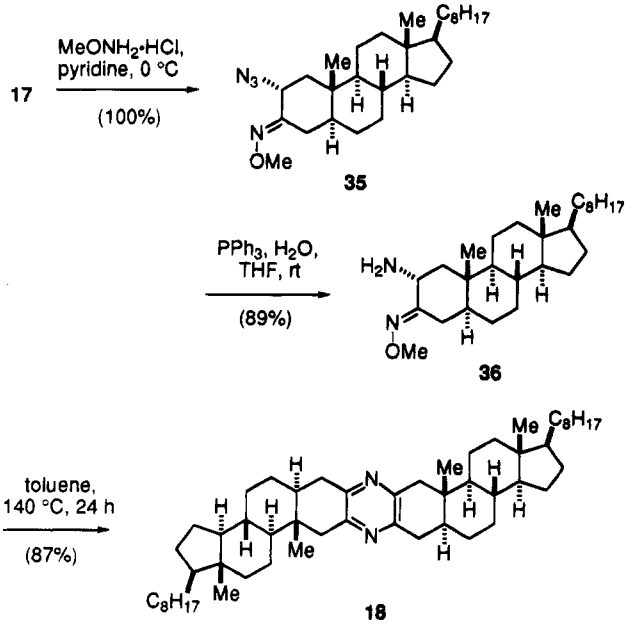
Scheme 8



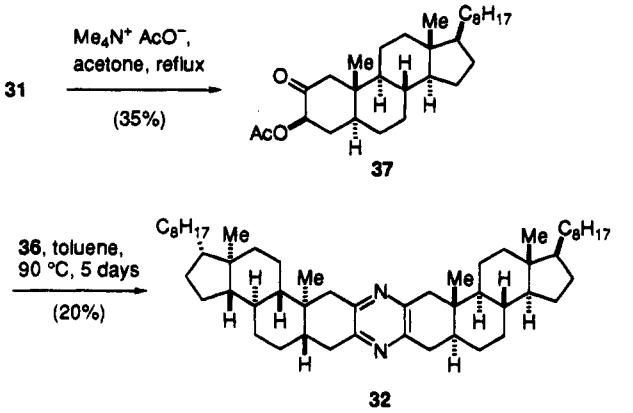
Scheme 9



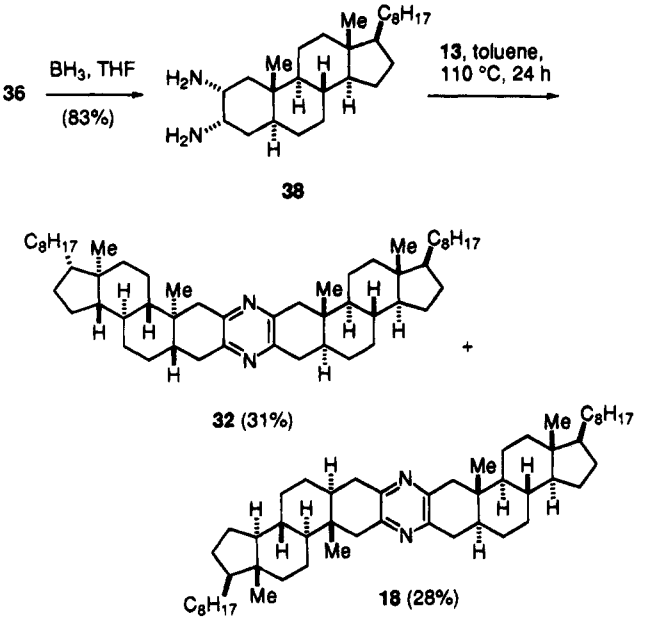
Scheme 10



Scheme 11



Scheme 12



period, followed by completion of the reaction by heating at a higher temperature.

It also proved possible to make the "cis" steroidal pyrazine **32**. Isomerization of 2α-acetoxy 3-ketone **31** to the 3β-acetoxy 2-ketone **36** using tetramethylammonium acetate in acetone gave a 1:1 mixture of the two regioisomers, from which **36** was selectively crystallized. This compound seemed less reactive than the regioisomer **31**, and to avoid dimerization of unreacted amine **36** at higher temperatures, the reaction mixture was kept at 90 °C for 5 days to give the *"cis"* pyrazine **32** in 20% yield (Scheme 11).

Both **18** and **32** are C_2-symmetric, and the ^1H NMR spectra are nearly identical (Figure 2). The only noticeable difference is a small shift in the resonance at 2.76 ppm (dd, J = 17.7, 5.2 Hz) in the *trans*-pyrazine to 2.77 ppm (dd, J = 18.0, 5.2) in the *cis*-pyrazine. The ^{13}C spectra are also identical except for a slight shift in the aromatic carbon resonances (trans: 148.53, 148.96; cis: 148.39, 149.11 ppm). Furthermore, the optical rotations for the two compounds are identical ($[\alpha]_D$ = +82). However, the solubilities are strikingly different, and this difference in physical properties permits a clean separation of a mixture of the two isomers. By trituration of the mixture with ethanol, the trans isomer can be obtained by filtration; evaporation of the filtrate provides the crude cis isomer.

Using this separation procedure, we were able to obtain both pyrazine products in pure form from the reaction of diketone **13** with diamine **38**, which was prepared by borane–THF reduction of the *O*-methyloxime **36** (Scheme 12).[17] The relative configuration of **38** was tentatively assigned based on the coupling constants of the protons α to the amino groups.

Androstanone (**39**) was converted into both C-2 acetoxy epimers for coupling studies as shown in Scheme 13. Protection of the C-17 hydroxy as the *tert*-butyldimethylsilyl ether **40** followed by reaction with acetic anhydride and catalytic perchloric acid gave enol acetate **41**. It was immediately obvious that the silyl ether had been removed and replaced with acetate under these conditions.

(16) Discussion of oxime geometry: (a) Gnichtel, H.; Töpper, B. *Liebigs Ann. Chem.* **1989**, 1071. (b) Danilewicz, J. C. *J. Chem. Soc.* C **1970**, 1049.

(17) Mohamed, M.S.; Potoghese, P. S. *J. Org. Chem.* **1986**, *51*, 105.

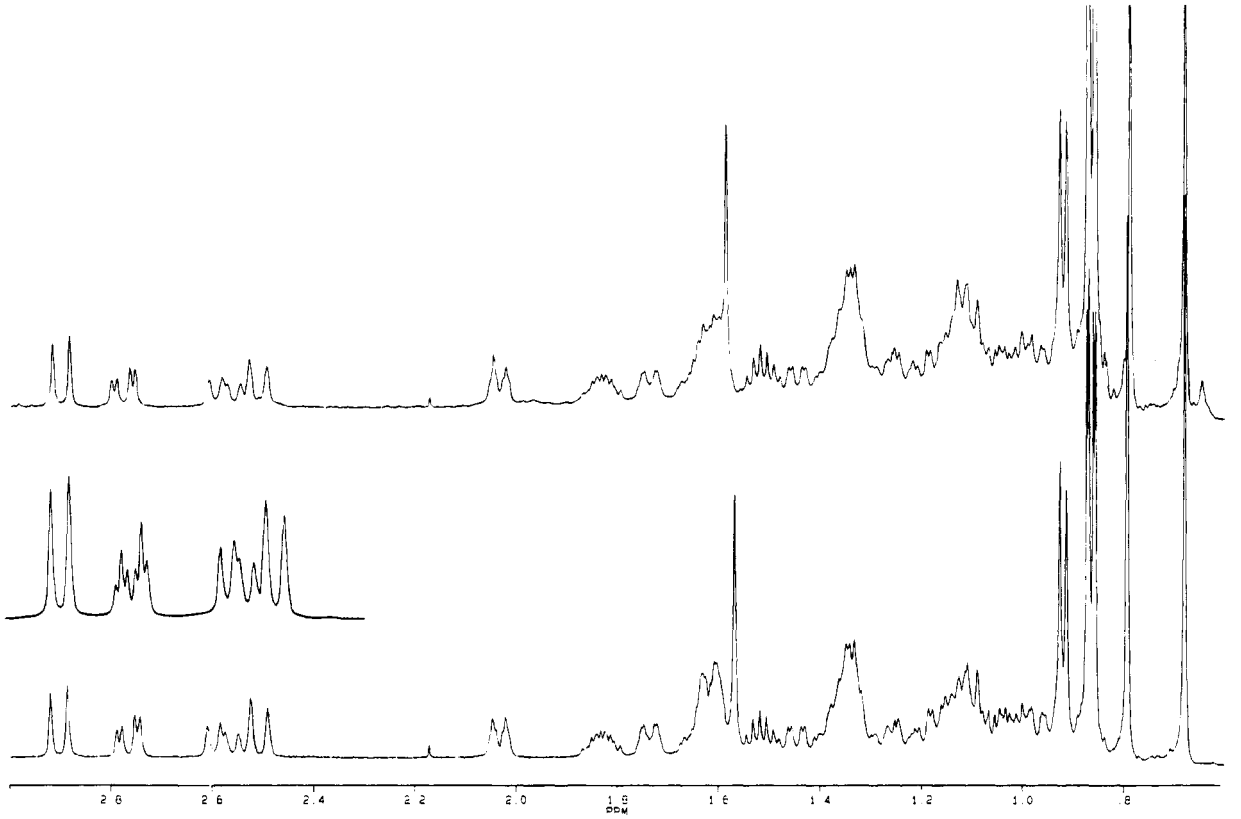
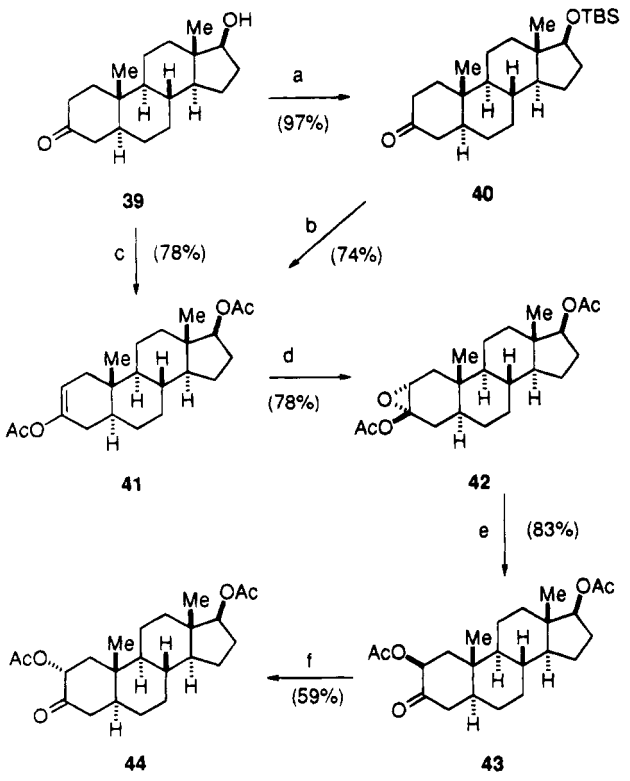


Figure 2. ^{1}H NMR spectra of compounds **18** (top) and **32** (bottom). The middle trace is a 1:1 mixture of the two compounds.

Scheme 13[a]



[a] Key: (a) *t*-BuMe$_2$SiCl, imidazole, DMF, rt; (b) Ac_2O, $HClO_4$, EtOAc, rt; (c) Ac_2O, $HClO_4$, EtOAc, rt; (d) dimethyloxirane, acetone, 0 °C → rt; (e) toluene, 10% pyridine, reflux; (f) HBr (cat.), HOAc, rt.

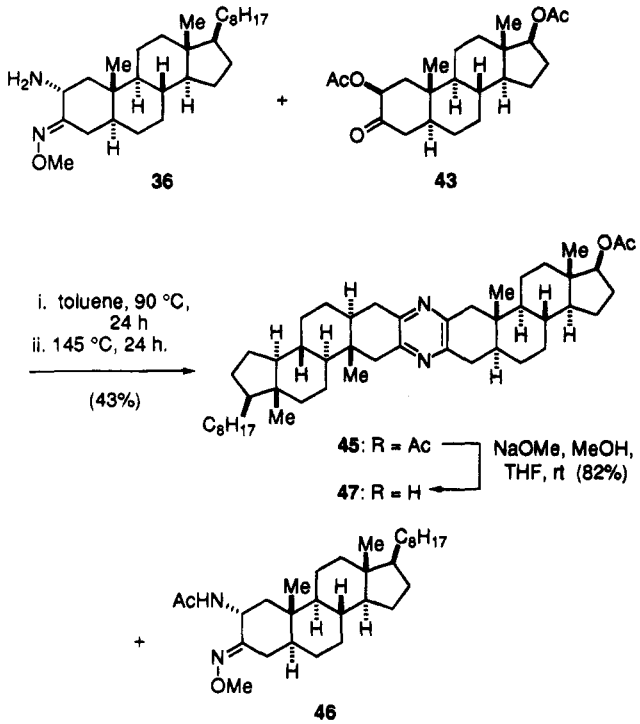
Alternatively, androstanone could be transformed directly into the C17-acetoxy enol acetate **41**. Oxidation with dimethyldioxirane gave a single isomer (**42**) upon crystallization. Compound **42** rearranged cleanly to the acetoxy ketone **43** in refluxing toluene containing 10% pyridine. Treatment of **43** with a catalytic amount of HBr in acetic acid caused epimerization to the more stable equatorial acetoxy isomer **44**. As in the oxidation of **23**, dimethyldioxirane proved to be the best oxidant for **41**.

Coupling of the amino-*O*-methyloxime **36** with keto acetate **43** by heating a degassed toluene solution of the two in a sealed tube to 90 °C for 24 h, followed by 24 h at 145 °C, gave the unsymmetrical bis-steroidal pyrazine **45** (Scheme 14). A byproduct, the *N*-acetoxy compound **46**, was obtained in about 10% yield. Saponification of the acetate gave the corresponding alcohol **47**, which is more soluble and convenient to handle. The thermal coupling of **36** and **43** has a temperature ceiling of 145 °C, above which no further increases in yield were obtained. The α- and β-acetates gave similar yields, although only the α-isomer was recovered in either case, so it is not clear which is the more reactive of the two.

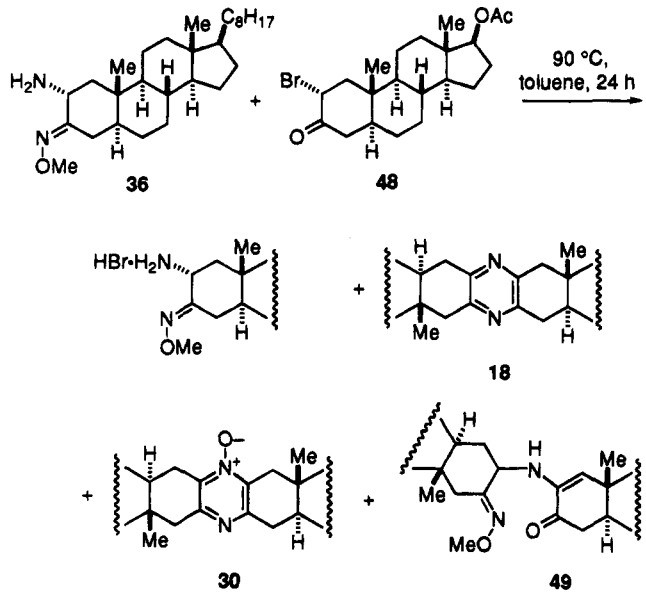
α-Bromo ketones such as **48** gave very messy reactions as exemplified by the products in Scheme 15, including the HBr salt of the amine starting material **49** (as a 1:3 mixture with **48**), the product of substitution at C-2 and subsequent air oxidation, characterized by the distinctive olefinic proton NMR resonance at 5.72 ppm and comparison with the similar enone **26**, pyrazine **18**, and the *N*-oxide **30**. The latter two products probably result from HBr-promoted demethylation of the *O*-methyloxime and subsequent self-condensation.

A preliminary investigation of the effects of solvents other than toluene in the coupling reaction indicated that

Scheme 14



Scheme 15

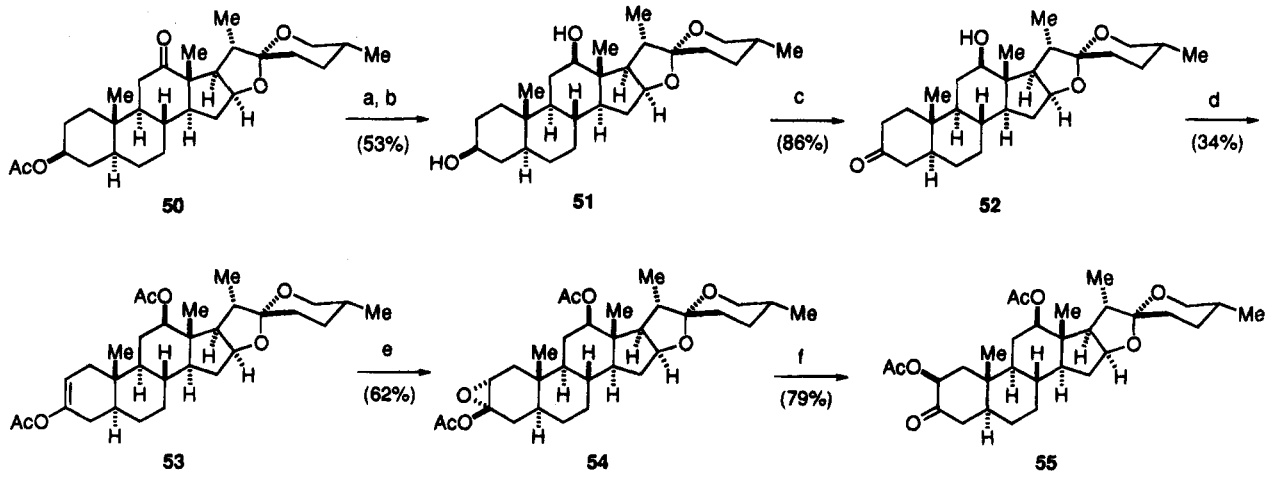


temperature is probably more important than the solvent. One specific problem occurred with ethanol as solvent, where it was noticed in the NMR spectrum of the crude product that the acetoxy ketone **43** had partially isomerized to the regioisomeric 3-acetoxy-2-ketone (as in Scheme 11). This rearrangement obviously ruins the regioselective nature of the pyrazine formation.

Several reactions of the amino *O*-methyloxime **36** with epoxy acetate substrates such as **4** were attempted, where it was hoped that the epoxy acetate would rearrange under the reaction conditions, generating the acetoxy ketone **43** *in situ*. However, both *cis*- and *trans*-pyrazines were formed in these reactions in a ratio of approximately 1:1. The cis compound must arise from direct reaction of the amino oxime with the epoxy acetate, justifying our earlier proposal of this novel pyrazine-forming reaction (Scheme 5).

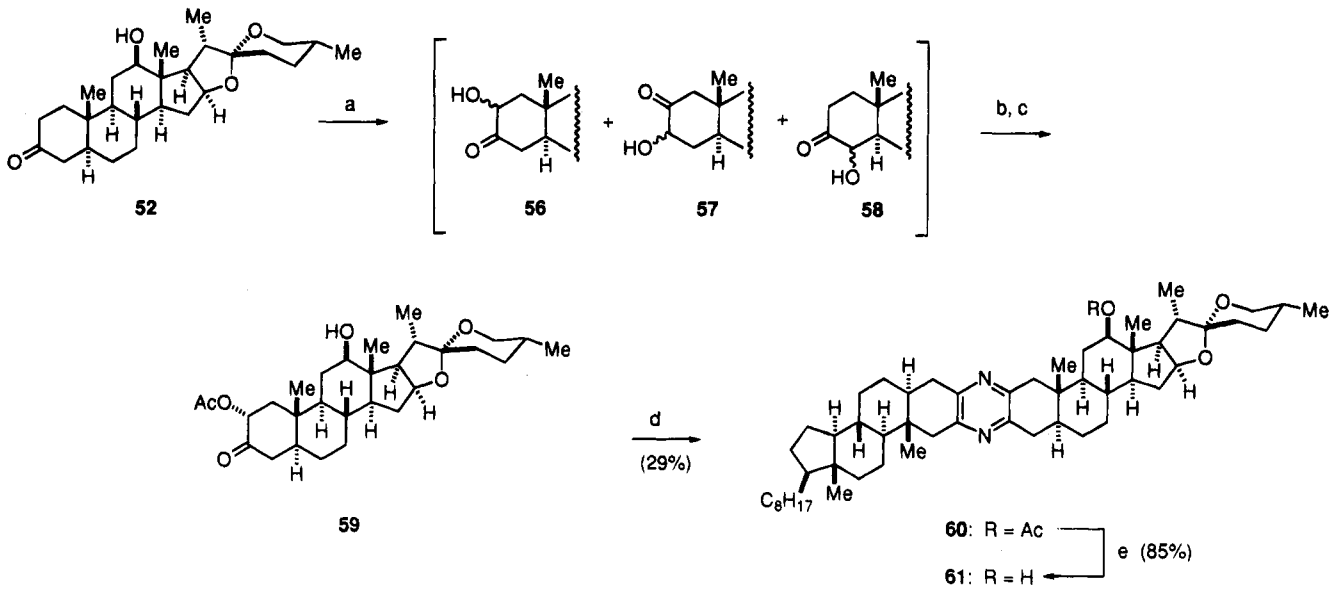
Because the cephalostatins all contain at least one spiroacetal, the next logical step was to prepare a steroidal pyrazine also containing this structural feature. As shown in Scheme 16, hecogenin acetate (**50**) was reduced with sodium borohydride and the resulting diol monoacetate saponified to obtain diol **51** (also known as "rockogenin")[18] on a multigram scale. Selective oxidation at the C-3 position was best achieved with oxygen and a platinum catalyst.[19] Formation of the enol acetate using acetic anhydride and catalytic perchloric acid proved to be inconsistent, probably because of sensitivity of the spiroacetal under the acidic reaction conditions. In addition, even after recrystallization, compound **53** still contained at least one impurity (~10%), probably the Δ^3 regioisomer. Epoxidation of **53** with dimethyldioxirane proceeded relatively cleanly to give the sensitive epoxy acetate **54**. However, the resulting solid product was difficult to crystallize. It was not possible to use heat because the epoxy acetate would undergo thermal rearrangement. It was eventually discovered that the epoxy product **54** crystallized from the reaction mixture in

Scheme 16[a]



[a] Key: (a) $NaBH_4$, MeOH, THF, 0 °C → rt; (b) K_2CO_3, MeOH, rt; (c) O_2, Pt, EtOAc; (d) Ac_2O, $HClO_4$, EtOH, rt; (e) dimethyldioxirane, acetone, CH_2Cl_2, rt; (f) toluene, 10% pyridine, reflux.

Scheme 17[a]



[a] Key: (a) (i) LDA, THF, −78 °C; (ii) MoOPD, −40 °C → rt; (b) Ac_2O, DMAP, CH_2Cl_2, 0 °C; (c) recrystallize from EtOH; (d) (i) **36**, toluene 90 °C, 24 h; (ii) 145 °C, 24 h; (e) NaOMe, MeOH, THF, rt.

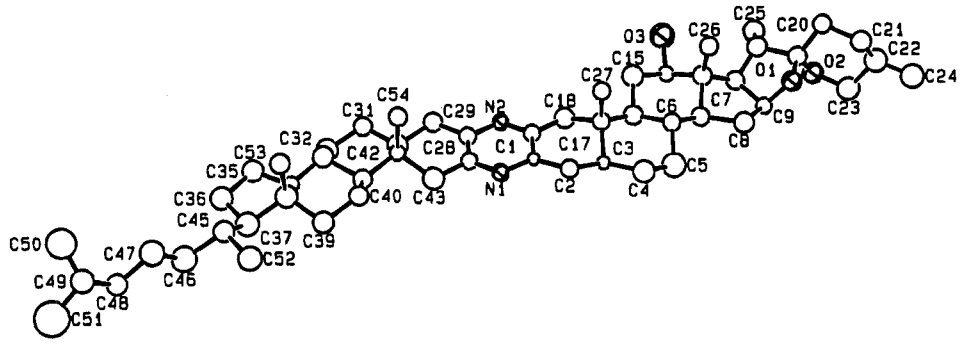


Figure 3. ORTEP representation of pyrazine **61**.

>90% purity if a combination of CH_2Cl_2 and acetone is used as solvent for the oxidation. Thermal rearrangement in refluxing toluene gave the acetoxy ketone **55**, albeit on a fairly small scale (<20 mg).

A more convenient synthesis of the 2α-acetoxy compound **59** is outlined in Scheme 17. Oxidation of the dianion of hydroxy ketone **52** with oxodiperoxomolybdenum−pyridine−DMPU complex[20] gave a mixture of the two regioisomeric hydroxy ketones **56** and **57** along with a small amount of the 3-hydroxy-2-ketosteroid **58**. Acetylation of the crude product mixture gave a chromatographically inseparable 4:1:1 mixture of the three isomers. All were isolated as the most stable epimer, although it is possible that epimerization occurred during acetylation. The required regioisomer **59** was the major component and it was possible to recrystallize it to purity from absolute ethanol.

Amino oxime **36** reacted with the keto acetate **59** under the usual conditions to give the unsymmetrical bis-steroidal pyrazine **60**. The acetate was saponified with sodium methoxide to provide a more crystalline derivative, **61**. The structure of compound **61** was verified by single-crystal X-ray analysis; an ORTEP representation of the structure is shown in Figure 3.[21]

Pyrazines **18**, **45**, **47**, **60**, and **61** were submitted for testing by the National Cancer Institute in their new *in vitro*, disease-oriented antitumor screen. None of the compounds showed sufficient activity to warrant *in vivo* studies. Subsequent investigations have shown that the ring-D double bonds are essential for activity in this series.[22]

After this work was completed, several other reports of synthetic investigations aimed at the cephalostatins have appeared. Fuchs and co-workers have reported the synthesis and pharmacological evaluation of a number of symmetrical pyrazines related to cephalostatin,[23] and Winterfeldt and co-workers have reported the synthesis and desymmetrization of a compound similar to **61** (but containing double bonds in the steroid D rings).[24]

(18) Sanne, C.; Lapin, H. *Bull. Soc. Chim. Fr.* **1952**, 1080.
(19) For numerous examples of steroid oxidations, see: Djerassi, C. *Steroid Reactions, An Outline for Organic Chemists;* Holden-Day: San Francisco, 1963; pp 99−134.
(20) Anderson, J. C.; Smith, S. C. *Synlett* **1990**, 107.
(21) Crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre.
(22) Winterfeldt, E. Private communication.
(23) (a) Pan, Y.; Merriman, R. L.; Tanzer, L. R.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 967. (b) Jeong, J. U.; Fuchs, P. L. *J. Am. Chem. Soc.* **1994**, *116*, 773. (c) Jeong, J. U.; Fuchs, P. L. *J. Am. Chem. Soc.* **1994**, *116*, 773.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Diethyl ether and THF were distilled under nitrogen from sodium/benzophenone immediately prior to use. Dichloromethane and toluene were distilled under nitrogen from CaH_2. Organic extracts were concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 230–400-mesh silica gel. Reactions and chromatography fractions were analyzed using Analtech 250-μm silica gel GF plates. All reactions involving air- or moisture-sensitive reagents were conducted under an atmosphere of nitrogen in septum-stoppered flasks. Transfer of reagents was accomplished by standard syringe techniques. Infrared spectra were recorded as thin films or as solutions. NMR spectra were measured at 500 MHz for ^1H and 125 MHz for ^{13}C. J values are given in Hz. Unless otherwise indicated NMR samples were dissolved in $CDCl_3$. Improved procedures for the preparation of a number of known compounds are included in the supplementary material.

Di(Cholestano[2,3-*b*:2′,3′-*e*])pyrazine (18). Tetrahydrofuran (2 mL) was added by syringe to an intimate mixture of azide **17**[8] (100 mg, 0.234 mmol) and triphenylphosphine (184 mg, 0.702 mmol, 3 equiv) under N_2. Gas was observed evolving from the solution. Water (0.10 mL, 5.6 mmol) was added by syringe, and the resulting pale yellow solution was stirred at rt for 24 h, during which time a precipitate formed. The reaction mixture was concentrated and the yellow residue azeotroped with toluene to remove water. Absolute EtOH (8 mL) and TsOH (5 mg, catalytic amount) were added. The orange mixture was stirred vigorously at rt open to the atmosphere for 16 h. The fine solid was filtered over a pad of Celite and the filtrate discarded. The solid was purified by dissolving in $CHCl_3$ (20 mL), adding absolute EtOH (5 mL), and concentrating until 3–4 mL of solvent remained. The resulting suspension was filtered over Celite, and the solid was dissolved in $CHCl_3$ and concentrated to give the pure dimeric pyrazine **18** (78.6 mg, 87%) as an amorphous colorless solid. Crystallization from hot toluene gave fine plates, mp > 265 °C. $[\alpha]_D$: +82.9 (c = 0.38, $CHCl_3$). ^1H NMR (500 MHz): δ 0.68 (s, 6), 0.79 (s, 6), 0.86 (d, 6, J = 6.6), 0.87 (d, 6, J = 6.5), 0.85–1.38 (m, 32), 0.92 (d, 6, J = 6.5), 1.43 (dq, 2, J = 3.6, 13.1), 1.52 (hept, 2, J = 6.6), 1.58–1.67 (m, 8), 1.72–1.75 (dm, 2, J = 12.8), 1.79–1.85 (m, 2), 2.03 (dm, 2, J = 12.9), 2.50 (d, 2, J = 16.5), 2.58 (dd, 2, J = 17.6, 13.2), 2.76 (dd, 2, J = 17.7, 5.2), 2.90 (d, 2, J = 16.5). ^{13}C NMR (125 MHz): δ 11.97, 18.69, 21.22, 22.56, 22.81, 23.86, 24.25, 28.01, 28.24, 28.47, 31.62, 35.36, 35.56, 35.59, 35.81, 36.18, 39.52, 39.94, 41.77, 42.49, 46.01, 53.70, 56.31, 56.36, 148.53, 148.96. MS (EI): 764 (M^+), 749, 624, 609, 450, 302, 281, 229. Anal. Calcd for $C_{54}H_{88}N_2$: C, 84.75; H, 11.59; N, 3.66. Found: C, 85.17; H, 11.52; N, 3.50.

2α-Azido-3-(hydroxyimino)cholestane (28). Hydroxylamine hydrochloride (143 mg, 2.05 mmol) was added to a solution of azido ketone **17**[8] (87.7 mg, 0.205 mmol) in pyridine (8 mL). The solution was stirred at rt for 30 min and filtered through a pad of silica (3 cm × 3 cm diameter), washing with EtOAc (150 mL). The filtrate was evaporated to give oxime **28** (91 mg, quantitative) as pale yellow microcrystals, mp 68–72 °C dec. R_f (25:75 EtOAc–hexanes): 0.33. ^1H NMR (500 MHz): δ 0.66 (s, 3), 0.72–0.77 (m, 1), 0.86 (d, 3, J = 6.6), 0.865 (d, 3, J = 6.6), 0.90 (d, 3, J = 6.5), 0.93 (s, 3), 0.96–1.37 (m, 19), 1.43–1.58 (m, 4), 1.64–1.70 (m, 2), 1.78–1.84 (m, 1), 2.00 (dt, 1, J = 12.7, 3.2), 2.21 (dd, 1, J = 12.5, 5.5), 3.12 (dd, 1, J = 15.1, 3.0), 4.02 (dd, 1, J = 12.3, 5.4). ^{13}C NMR (125 MHz): δ 12.05, 12.40, 18.64, 21.26, 22.54, 22.80, 23.80, 24.15, 26.86, 27.99, 28.12, 28.18, 31.54, 34.88, 35.75, 36.11, 36.63, 39.49, 39.75, 42.53, 44.81, 45.02, 53.82, 56.18, 58.36, 156.66. MS (FAB, NBA matrix): 443 (MH^+), 427, 415, 400, 382, 356. Anal. Calcd for $C_{27}H_{46}N_4O$: C, 73.25; H, 10.47; N, 12.65. Found: C, 73.60; H, 10.56; N, 12.39.

2α-Amino-3-(hydroxyimino)cholestane (29). THF (1 mL) was added by syringe to 2α-azido-3-(hydroxyimino)-cholestane (**28**; 91 mg, 0.205 mmol) and triphenylphosphine (161 mg, 0.615 mmol, 3 equiv) under N_2. Water (80 mL) was added by syringe, and the resulting pale yellow solution was stirred at rt for 24 h. The reaction mixture was concentrated and the orange residue azeotroped with toluene to remove water. The amorphous solid was purified by flash chromatography on silica, eluting with 10:90:0.5 MeOH–CH_2Cl_2–NH_4OH (aq), to give amino oxime **29** (78.6 mg, 92%) as a glass. This material crystallized from THF to give colorless microcrystals that decomposed on heating. R_f (20:80:1 MeOH–CH_2Cl_2–NH_4OH (aq)): 0.40. ^1H NMR (500 MHz): δ 0.66 (s, 3), 0.68–0.71 (m, 1), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 0.89 (d, 3, J = 6.6), 0.93 (s, 3), 0.95–1.69 (m, 27), 1.77–1.83 (m, 1), 1.97 (dt, 1, J = 12.7, 3.3), 2.17 (dd, 1, J = 12.5, 5.1), 3.07 (dd, 1, J = 15.1, 2.4), 3.53 (dd, 1, J = 12.3, 5.1). ^{13}C NMR (125 MHz): δ 12.06, 12.46, 18.69, 21.30, 22.53, 22.77, 23.84, 24.15, 26.83, 27.97, 28.20, 28.29, 31.73, 34.92, 35.75, 36.14, 36.53, 39.48, 39.89, 42.56, 45.93, 48.30, 49.59, 54.03, 56.29, 110.10, 160.79. MS (FAB, NBA matrix): 417 (MH^+), 400 ($M - NH_2$)$^+$, 382. HRMS (MH^+): 417.3847, $C_{27}H_{49}N_2O$ requires 417.3845.

Di(Cholestano[2,3-*b*:2′,3′-*e*])pyrazine Bis-*N*-oxide (34). A mixture of the pyrazine **18** (43.1 mg, 56.4 mmol), *m*-CPBA (61 mg, ~80% by weight, ~5 equiv) and $NaHCO_3$ (200 mg) in $CDCl_3$ (5 mL) was stirred at rt for 24 h. ^1H NMR analysis of an aliquot from the crude reaction mixture showed no starting material and complete formation of the bis-*N*-oxide. The solid was removed by filtration, and absolute EtOH (5 mL) was added to the filtrate. Upon concentration to half volume a precipitate appeared. This was collected by filtration through Celite, washing through with $CHCl_3$, and evaporation. Repeating this precipitation from $CHCl_3$/EtOH gave the pure pyrazine bis-*N*-oxide (**34**; 44.0 mg, 98%) as a colorless amorphous solid. ^1H NMR (500 MHz): δ 0.68 (s, 6), 0.75 (s, 6), 0.85 (d, 6, J = 6.6), 0.87 (d, 6, J = 6.6), 0.91 (d, 6, J = 6.5), 0.91–1.62 (m, 40), 1.70–1.86 (m, 8), 2.04 (dm, 2, J = 12.8), 2.28 (d, 2, J = 18.3), 2.40 (dd, 2, J = 19.0, 11.9), 3.04 (dd, 2, J = 19.1, 5.1), 3.22 (d, 2, J = 18.2). ^{13}C NMR (125 MHz): δ 11.99, 12.18, 18.67, 21.33, 22.55, 22.80, 23.81, 24.17, 27.89, 28.00, 28.28, 28.36, 31.28, 34.56, 35.27, 35.78, 36.15, 38.10, 39.50, 39.70, 40.21, 42.44, 53.53, 56.18, 56.22, 142.30, 142.55. MS (FAB, NBA matrix): 797 (MH^+), 781 ($M - OH$)$^+$, 423. HRMS (MH^+): 797.6914, $C_{54}H_{89}N_2O_2$ requires 797.6924.

2α-Azido-3-(methoxyimino)cholestane (35). *O*-Methylhydroxylamine (3.51 g, 42.0 mmol, 3 equiv) was added in one portion to a stirring solution of the known azido ketone **17**[8] (6.00 g, 14.0 mmol) in pyridine (300 mL) at 0 °C. After 3.5 h a fine suspension had appeared. Ethyl acetate (300 mL) was added and the mixture filtered through a pad of silica (5 cm deep by 10 cm), washing with EtOAc (500 mL). The filtrate was evaporated to give the *O*-methyloxime **35** (6.39 g, 100%) as colorless microcrystals, mp 132–135 °C. R_f (25:75 EtOAc–hexanes): 0.72. ^1H NMR (500 MHz): δ 0.66 (s, 3), 0.71–0.76 (m, 1), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 0.90 (d, 3, J = 6.2 overlapping s, 3), 0.95–1.52 (m, 22), 1.58–1.69 (m, 2), 1.78–1.83 (m, 1), 1.98 (dt, 1, J = 12.9, 3.1), 2.18 (dd, 1, J = 12.5, 5.5), 3.00 (dd, 1, J = 15.2, 3.5), 3.91 (s, 3), 3.98 (dd, 1, J = 12.0, 5.5). ^{13}C NMR (125 MHz): δ 12.04, 12.40, 18.63, 21.23, 22.53, 22.78, 23.78, 24.14, 27.49, 27.98, 28.12, 28.17, 31.53, 34.88, 35.74, 36.11, 36.50, 39.48, 39.75, 42.52, 44.93, 53.84, 56.17, 57.83, 61.87, 155.68. MS (FAB, NBA matrix): 457 (MH^+), 429 ($MH - N_2$)$^+$, 414 ($M - N_3$)$^+$, 399, 382. Anal. Calcd for $C_{28}H_{48}N_4O$: C, 73.63; H, 10.59; N, 12.29. Found: C, 73.80; H, 10.56; N, 11.97.

2-Amino-3-(methoxyimino)cholestane (36). Tetrahydrofuran (30 mL) was added by syringe to 2α-azido-3-(methoxyimino)cholestane (**35**; 1.07 g, 2.34 mmol) and triphenylphosphine (1.84 g, 7.02 mmol, 3 equiv) under N_2. Gas was observed evolving from the solution. Water (0.90 mL, 50 mmol) was added by syringe, and the resulting pale yellow solution was stirred at rt for 48 h. The reaction mixture was concentrated and the orange residue azeotroped with toluene to remove water. The amorphous solid was purified by flash chromatography on silica, eluting first with EtOAc (to remove triphenylphosphine and triphenylphosphine oxide) and then a gradient of 10:90–30:70 MeOH–EtOAc to give the amino compound (**36**; 900 mg, 89%) as colorless microcrystals, mp 113–115 °C.

(24) Kramer, A.; Ullmann, U.; Winterfeldt, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2865.

R_f (20:80:1 MeOH–CH_2Cl_2–NH_4OH (aq)): 0.48. ^1H NMR (500 MHz): δ 0.65–0.70 (s, 3, overlapping m, 1), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 0.89 (d, 3, J = 6.5), 0.91 (s, 3), 0.92–1.68 (24, m), 1.77–1.83 (m, 1), 1.97 (dt, 1, J = 12.6, 3.4), 2.16 (dd, 1, J = 12.5, 5.2), 2.35 (br s, 2), 2.95 (dd, 1, J = 15.0, 3.3), 3.47 (dd, 1, J = 12.2, 5.0), 3.84 (s, 3). ^{13}C NMR (125 MHz): δ 12.06, 12.49, 18.65, 21.24, 22.54, 22.79, 23.80, 24.17, 27.42, 28.00, 28.21, 28.27, 31.71, 34.93, 35.76, 36.15, 36.45, 39.50, 39.88, 42.57, 45.90, 48.74, 49.64, 53.96, 56.22, 56.27, 61.44, 160.65. MS (FAB, NBA matrix): 431 (MH^+), 414 ($M - NH_2$)$^+$, 399 (M^+ – MeOH). Anal. Calcd for $C_{28}H_{50}N_2O$: C, 78.08; H, 11.70; N, 6.51. Found: C, 78.07; H, 11.67; N, 6.56.

Di(Cholestano[2,3-*b*:3′,2′-*e*])pyrazine (32). A degassed solution of the acetoxy ketone (**37**) (105 mg, 0.236 mmol, 1.5 equiv) and the amino oxime (**36**) in toluene (0.5 mL) was heated to 90 °C for 5 days. After cooling, the mixture was preadsorbed on silica and placed on the top of a silica column. Elution with 5:95 EtOAc–CH_2Cl_2 gave the pyrazine (**32**; 24 mg, 20%) as pale tan microcrystals, initial mp 152 °C, residue melts at 202 °C. R_f (CH_2Cl_2): 0.67. $[\alpha]_D$: +82.5 (c = 0.28, $CHCl_3$). ^1H NMR (500 MHz): δ 0.68 (s, 6), 0.79 (s, 6), 0.85 (d, 6, J = 6.6), 0.86 (d, 6, J = 6.5), 0.92 (d, 6, J = 6.5), 0.96–1.40 (m, 28), 1.44 (dq, 2, J = 3.6, 13.0), 1.51 (hept, 2, J = 6.6), 1.57–1.68 (m, 12), 1.72–1.79 (m, 2), 1.80–1.85 (m, 2), 2.03 (dt, 2, J = 12.8, 3.3), 2.50 (d, 2, J = 16.9), 2.57 (dd, 2, J = 18.0, 12.7), 2.77 (dd, 2, J = 18.0, 5.2), 2.89 (d, 2, J = 16.9). ^{13}C NMR (125 MHz): δ 11.94, 11.97, 18.70, 21.23, 22.55, 22.79, 23.86, 24.25, 28.01, 28.23, 28.49, 31.36, 35.38, 35.59, 35.80, 36.20, 39.53, 39.97, 41.82, 42.50, 46.03, 53.72, 56.33, 56.36, 148.39, 149.11. MS (FAB, NBA matrix): 765 (MH^+), 749, 651, 611, 487. Anal. Calcd for $C_{54}H_{88}N_2$: C, 84.75; H, 11.59; N, 3.66. Found: C, 85.40; H, 11.39; N, 3.48.

2α,3α-Diaminocholestane (38). Borane–THF complex (4.25 mL of a 1.0 M solution in THF, 4.25 mmol) was added dropwise to a solution of the *O*-methyloxime (**36**; 64.6 mg, 0.15 mmol) in THF (3 mL) at −5 °C. The colorless solution was allowed to warm to rt and stirred for 1 h 50 min before heating to reflux for 2 h. After the solution was cooled to 0 °C, water (250 mL) followed by 20% KOH (aqueous; 250 mL) were added very cautiously and the mixture heated to reflux for 90 min. Upon cooling, further water (20 mL) was added and the mixture extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried (Na_2SO_4) and evaporated and the residue purified by flash chromatography, eluting with 40:60 MeOH–CH_2Cl_2 (containing 2% NH_4OH (aqueous)) to give the diamine (**37**; 50.0 mg, 82%) as an amorphous solid. R_f (1:1:0.1 MeOH–CH_2Cl_2–NH_4OH (aqueous)): 0.29. ^1H NMR (500 MHz): δ 0.66 (s, 3), 0.80 (s, 3), 0.86 (2d, 6, J = 6.6, 6.6), 0.89 (d, 3, J = 6.4), 0.73–1.68 (m, 27), 1.76–1.81 (m, 1), 1.96 (br d, 1, J = 12.4), 2.22 (v br s, 4), 2.99 (br dt, 1, J = 12.2, 3.5), 3.07 (v br s, 1). ^{13}C NMR (125 MHz): δ 12.05, 12.53, 18.64, 20.85, 22.53, 22.79, 23.80, 24.14, 27.97, 28.20, 31.89, 34.98, 35.63, 35.76, 36.14, 36.82, 38.50, 39.48, 39.93, 41.20, 42.56, 48.88, 50.47, 54.33, 56.19, 56.40. MS (FAB, NBA matrix): 403 (MH^+), 386 ($M - NH_2$)$^+$. HRMS (MH^+): 403.4048, $C_{27}H_{51}N_2$ requires 403.4053.

Condensation of Diamine 38 with Diketone 13. A degassed solution of diamine **38** (76.0 mg, 0.189 mmol) and diketone **13** (83.2 mg, 0.208 mmol) in toluene (1.5 mL) was heated in a sealed tube to 110 °C for 24 h. After cooling, the solvent was evaporated and the residue taken up in EtOH, stirring open to the air for 3 h. Evaporation of the EtOH gave a solid that was dissolved in $CHCl_3$ (3 mL). EtOH (3 mL) was added and the solvent evaporated to half volume, precipitating the *trans*-pyrazine **18**, which could be collected by filtration. Repeating the $CHCl_3$/EtOH precipitation gave pure *trans*-pyrazine (40.0 mg, 28%). The combined filtrates were evaporated and the residue purified by flash chromatography, eluting with 5:95 EtOAc–CH_2Cl_2, to give the pure cis isomer **32** (44.2 mg, 31%).

2α,3α-Epoxyandrostane-3β,17β-diol Diacetate (42). A freshly prepared cold (0 °C) solution of dimethyldioxirane (180 mL of a 0.041 M solution in acetone, 7.38 mmol, 1.2 equiv) was added by syringe to enol acetate **40** (2.30 g, 6.14 mmol) under N_2. The solution was allowed to warm to rt and stirred for 4 h, whereupon a further quantity of dimethyldioxirane solution (40 mL, 1.64 mmol) was added and stirring was continued for 2 h. Dimethyldioxirane solution (20 mL, 0.82 mmol) was again added, and the solution was refrigerated for 12 h. The solvent was evaporated and the residue crystallized by dissolving in ether at rt and concentrating to 5 mL to give epoxy acetate **41** (2.16 g, 90%) as colorless microcrystals, mp 142–144 °C. R_f (25:75 EtOAc–hexanes): 0.38. ^1H NMR (500 MHz): δ 0.62 (dt, 1, J = 6.3, 12.2), 0.76 (s, 3), 0.81 (dq, 1, J = 4.2, 13.0), 0.95–1.00 (m, 1, overlapping 0.95, s, 3), 1.03 (1H, m) 1.11 (dt, 1, J = 4.3, 12.9), 1.19–1.33 (m, 6), 1.37 (dm, 1, J = 14.8), 1.41–1.50 (m, 2), 1.57–1.66 (m, 2), 1.71 (dt, 1, J = 12.5, 3.3), 1.91 (dd, 1, J = 14.2, 11.6), 2.00 (s, 3, overlapping dd, 1, J = 15.4, 5.7), 2.04 (s, 3), 2.07 (dd, 1, J = 14.2, 4.4), 2.10–2.16 (m, 1), 3.30 (d, 1, J = 5.6), 4.56 (dd, 1, J = 8.0, 7.0). ^{13}C NMR (125 MHz): δ 11.97, 12.76, 20.50, 21.11, 21.13, 23.44, 27.44, 27.89, 30.71, 31.04, 34.43, 35.25, 36.75, 38.71, 38.75, 42.40, 50.49, 53.34, 58.27, 82.68, 82.97, 169.41, 171.13. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.33; H, 8.82.

2β,17β-Dihydroxyandrostan-3-one Diacetate (43). A solution of epoxy acetate **41** (2.16 g, 5.53 mmol) in toluene (100 mL) containing pyridine (10 mL) was heated to reflux for 24 h. After the solution was cooled to rt the solvent was evaporated and the residue recrystallized from ether to give the 2β-acetoxy ketone **43** (1.79 g, 83%) as colorless microcrystals, mp 169–171 °C. R_f (25:75 EtOAc–hexanes): 0.24. ^1H NMR (500 MHz): δ 0.76 (s, 3), 0.83 (s, 3), 0.83–1.90 (m, 15), 1.95–2.02 (m, 1, overlapping 2.00, s, 3), 2.10 (s, 3), 2.09–2.16 (m, 2), 2.20 (dd, 1, J = 17.8, 12.2), 2.36 (dd, 1, J = 17.8, 6.2), 4.56 (t, 1, J = 8.9), 5.34 (dd, 1, J = 10.1, 7.1). ^{13}C NMR (125 MHz): δ 11.99, 14.26, 20.74, 20.90, 21.05, 23.34, 27.40, 28.07, 30.72, 34.94, 36.05, 36.70, 41.64, 42.07, 42.56, 43.40, 50.36, 54.60, 74.20, 82.48, 169.81, 171.03, 206.68. MS (EI): 390 (M^+), 348, 330 (M^+ – HOAc), 288, 270. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.54; H, 8.66.

2α,17β-Dihydroxyandrostan-3-one Diacetate (44). HBr (5 drops of a 48% aqueous solution) was added to a solution of the 2β-acetoxy ketone **43** (270 mg, 0.691 mmol) in acetic acid (20 mL). The resulting solution was stirred at rt for 24 h during which time it turned several colors. The solvent was evaporated, azeotroping with toluene to remove the last acetic acid and water. Column chromatography, eluting with 20:80 EtOAc–hexanes, gave a pale yellow residue that was crystallized from ether to give the 2α-acetoxy ketone **43** (160 mg, 59%) as colorless microcrystals, mp 189–193 °C. R_f (25:75 EtOAc–hexanes): 0.28. ^1H NMR (500 MHz): δ 0.76–0.82 (m, 1, overlapping 0.79, s, 3), 0.91 (m, 1), 1.12 (s, 3), 1.15 (dt, 1, J = 4.1, 12.9), 1.27–1.57 (m, 10), 1.70–1.75 (m, 2), 2.02 (s, 3), 2.13 (s, 3, overlapping m, 1), 2.19 (dd, 1, J = 14.1, 3.6), 2.25 (dd, 1, J = 12.4, 6.7), 2.41 (t, 1, J = 14.3), 4.57 (dd, 1, J = 9.1, 7.9), 5.27 (dd, 1, J = 12.9, 6.7). ^{13}C NMR (125 MHz): δ 12.06, 12.69, 20.70, 21.04, 21.09, 23.42, 27.44, 28.15, 31.03, 34.46, 36.65, 37.20, 42.58, 43.44, 44.73, 47.70, 50.37, 53.68, 74.27, 82.51, 170.05, 171.08, 203.90. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.51; H, 8.48.

(17β-Acetoxyandrostano[2,3-*b*])cholestano[2,3-*e*]pyrazine (45). A solution of acetoxy ketone **43** (70.3 mg, 0.18 mmol) and amino oxime **36** (64.6 mg, 0.15 mmol) in toluene (1 mL) was degassed by cooling to −78 °C, evacuating, and allowing to warm to rt before introducing N_2. This freeze/thaw procedure was repeated twice to remove traces of O_2, leaving the solution under N_2. The reaction mixture was heated in a sealed tube for 24 h at 90 °C and then for 24 h at 145 °C. Slow cooling to rt resulted in a precipitate. The slurry was removed from the reaction vessel by dissolving in $CHCl_3$. Concentration gave a pale yellow residue that was suspended in absolute EtOH (6 mL), and filtered over Celite and the filtrate discarded. The solid was washed through with $CHCl_3$, and EtOH (3 mL) was added. Concentration to a volume of 2 mL gave a fine precipitate of pyrazine **45** (45.9 mg, 43%) as a colorless, amorphous solid, mp > 260 °C. R_f (25:75 EtOAc–hexanes): 0.39. $[\alpha]_D$: +77.3 (c = 0.55, $CHCl_3$). ^1H NMR (500 MHz): δ 0.67 (s, 3), 0.78 (s, 3), 0.80 (2s, 6), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.5), 0.91 (d, 3, J = 6.4), 0.85–1.85 (m, 39), 2.01–2.09 (m, 1, overlapping 2.03, s, 3), 2.12–2.20 (m,1), 2.50 (dd, 2, J = 16.9, 6.0), 2.53–2.60 (m, 2), 2.76 (dt, 2, J = 18.4, 6.3), 2.89 (d,

2, J = 16.9), 4.61 (t, 1, J = 8.5). ^{13}C NMR (125 MHz): δ 11.95, 12.01, 18.67, 20.66, 21.15, 21.20, 22.54, 22.79, 23.51, 23.84, 24.22, 27.46, 27.99, 28.22, 28.25, 28.43, 31.12, 31.58, 35.11, 35.33, 35.47, 35.52, 35.56, 35.64, 35.79, 36.15, 36.87, 39.49, 39.91, 41.72, 42.46, 42.52, 45.93, 45.97, 50.60, 53.60, 53.66, 56.27, 56.33, 82.74, 148.32, 148.61, 148.69, 149.04, 171.19. MS (FAB, NBA matrix): 711 (MH^+), 651 $(M - OAc)^+$. $C_{30}H_{52}N_2O_2$ requires 472.4026. Anal. Calcd for $C_{48}H_{74}N_2O_2$: C, 81.07; H, 10.49; N, 3.94. Found: C, 81.07; H, 10.51; N, 3.80.

Chromatography of the residue on silica, eluting with 60:40 EtOAc–hexanes, gave some recovered **36**, several unidentified compounds, and the *N*-acetyl byproduct **46** (7 mg, 10%) as an amorphous solid. ^{1}H NMR (500 MHz): δ 0.64–0.67 (m, 1, overlapping s, 3), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 0.88 (d, 3, J = 6.5), 1.00 (s, 3), 0.91–1.68 (m, 24), 1.78–1.81 (m, 1), 1.94 (dt, 1, J = 12.7, 3.0), 2.00 (s, 3), 2.46 (dd, 1, J = 12.3, 5.1), 2.99 (dd, 1, J = 14.1, 2.9), 3.83 (s, 3), 4.53 (dt, 1, J = 12.9, 5.4), 6.36 (d, 1, J = 6.7). MS (EI): 472 (M^+), 441 $(M - OMe)^+$, 424, 399, 382. Accurate mass measured for M^+: 472.4029, found 472.4026

(17β-Hydroxyandrostano[2,3-*b*])cholestano[2,3-*e*]pyrazine (47). Sodium methoxide (2.5 mL of a 0.36 M solution in MeOH, 0.92 mmol, 5 equiv; prepared by dissolving sodium (167 mg, 7.26 mmol) in MeOH (20 mL) at 0 °C) was added by syringe to a suspension of acetate **45** (130 mg, 0.183 mmol) in THF (10 mL) at rt. The first two drops gave an initial yellow color which did not darken. After 24 h, most of the remaining solid had dissolved. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Combined organic phases were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica, using a gradient elution of 25:75–60:40 EtOAc–hexanes to give diol **47** (101 mg, 82%) as a colorless, amorphous solid, mp > 270 °C. R_f (25:75 EtOAc–hexanes): 0.07. $[\alpha]_D$: +90.6 (c = 0.33, $CHCl_3$). ^{1}H NMR (500 MHz): δ 0.69 (s, 3), 0.76 (s, 3), 0.78 (s, 3), 0.80 (s, 3), 0.84 (d, 3, J = 6.6), 0.85 (d, 3, J = 6.6), 0.91 (d, 3, J = 6.4), 0.80–1.86 (m, 40), 2.01–2.06 (m, 2), 2.49 (dd, 2, J = 16.8, 6.9), 2.54–2.60 (m, 2), 2.75 (dt, 2, J = 17.9, 4.9), 2.89 (dd, 2, J = 17.0, 7.1), 3.64 (br t, 1, J = 8.4). ^{13}C NMR (125 MHz): δ 11.05, 11.95, 11.98, 18.67, 20.80, 21.20, 22.54, 22.79, 23.38, 23.85, 24.22, 27.99, 28.22, 28.28, 28.43, 30.46, 31.15, 31.58, 35.32, 35.38, 35.50, 35.55, 35.67, 35.79, 36.16, 36.71, 39.49, 39.91, 41.73, 41.81, 42.46, 42.87, 45.96, 50.91, 53.67, 53.82, 56.29, 56.33, 81.82, 148.35, 148.59, 148.73, 149.02. Anal. Calcd for $C_{46}H_{72}N_2O$: C, 82.58; H, 10.85; N, 4.19 Found C, 82.15; H, 10.73; N, 3.95.

Hydroxy Ketone 52. Platinum dioxide (1.00 g, 4.40 mmol, 0.7 equiv) was suspended in a solution of diol **51** (2.72 g, 6.29 mmol) in EtOAc (60 mL). The mixture was degassed under aspirator vacuum and refilled with N_2 five times, and hydrogen was introduced by degassing and refilling with hydrogen from a balloon three times. The mixture was hydrogenated at 1 atm for 30 min, whereupon the fine brown PtO_2 became black and granular platinum. Degassing and refilling three times with N_2 was followed by further degassing and refilling three times with oxygen. The platinum became a fine black dispersion, and the reaction mixture was left stirring under oxygen at 1 atm for 30 h. The catalyst was removed by filtration through Celite, washing with copious quantities of EtOAc (1.5 L) and acetone (0.5 L) to remove all of the product. Concentration of the filtrate and flash chromatography of the resulting residue, using a gradient elution of 30:70–40:60 EtOAc–hexanes, gave ketone **52** (2.32 g, 86%) as colorless microcrystals, mp 239–241 °C. R_f (EtOAc): 0.65. ^{1}H NMR (500 MHz): δ 0.77 (s, 3, overlapping d, 3, J = 6.1), 0.80–0.91 (m, 2), 1.01 (d, 3, J = 6.8), 1.02 (s, 3), 1.00–1.08 (m, 2), 1.29–1.72 (m, 14), 1.81–1.90 (m, 2), 1.95–2.03 (m, 2), 2.08 (ddd, 1, J = 15.1, 3.8, 2.2), 2.21–2.31 (m, 1, overlapping 2.24, t, 1, J = 14.3), 2.36 (dt, 1, J = 6.6, 15.5), 3.31–3.37 (m, 1, overlapping t, 1, J = 10.9, 3.34), 3.45 (ddd, 1, J = 10.8, 4.3, 2.0), 4.39 (dd, 1, J = 15.0, 7.5). ^{13}C NMR (125 MHz): δ 10.45, 11.41, 13.91, 17.10, 28.74, 28.77, 30.24, 30.59, 31.26, 31.37, 31.46, 33.91, 35.69, 38.02, 38.38, 42.10, 44.51, 45.98, 46.51, 52.71, 54.52, 61.75, 66.85, 79.58, 80.61, 109.43, 211.49. Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.22; H, 9.91.

Enol Diacetate 52. An acetylation solution was freshly prepared, consisting of EtOAc (250 mL), 70% $HClO_4$ (aqueous; 0.25 mL), and Ac_2O (25 mL). This solution was added to hydroxy ketone **52** (310 mg, 0.720 mmol) and the resulting solution stirred at rt for 2 h. The reaction was quenched by addition to saturated $NaHCO_3$ (aqueous; 25 mL). The organic phase was separated, washed with saturated $NaHCO_3$ (aqueous; 3 × 25 mL), and dried (Na_2SO_4). MEtOH (1 mL) and pyridine (1 mL) were added to remove traces of Ac_2O and the solvent was evaporated. Column chromatography of the residue, eluting with a gradient of 10:90–20:80 EtOAc–hexanes, gave enol diacetate **53** (220 mg, 59%) as a colorless solid. Further purification was achieved by recrystallization from ether to give colorless microcrystals (125 mg, 34%), mp 175–177 °C. R_f (25:75 EtOAc–hexanes): 0.50. ^{1}H NMR (500 MHz): δ 0.77 (d, 3, J = 6.4), 0.83 (s, 3), 0.85 (s, 3), 0.89 (d, 3, J = 6.7), 0.87–0.96 (m, 2), 1.12–1.70 (m, 12), 1.76 (dt, 1, J = 12.7, 4.4), 1.80–1.90 (m, 4), 1.93–1.97 (m, 3), 2.03 (s, 3), 2.00–2.05 (m, 1), 2.08 (s, 3), 3.33 (t, 1, J = 11.0), 3.43–3.46 (m, 1), 4.39 (dd, 1, J = 14.8, 7.5), 4.53 (dd, 1, J = 11.2, 4.7), 5.22 (d, 1, J = 4.3). ^{13}C NMR (125 MHz): δ 11.51, 11.66, 13.64, 17.09, 20.98, 21.52, 26.70, 28.17, 28.75, 30.21, 31.15, 31.22, 21.28, 31.36, 34.09, 34.68, 37.79, 41.63, 42.18, 44.46, 52.08, 54.72, 61.21, 66.80, 80.44, 81.59, 109.25, 112.30, 146.88, 169.50, 170.44. Anal. Calcd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.22; H, 8.92.

2α,3α-Epoxy Diacetate 54. A cold (0 °C) solution of dimethyldioxirane (8.25 mL of a 0.045 M solution in acetone, 0.35 mmol, 1.5 equiv) was added by syringe to enol acetate **53** (120 mg, 0.233 mmol), and the resulting suspension was allowed to warm to rt. After 10 min CH_2Cl_2 (4 mL) was added to aid solubility, and the solution was stirred for 7 h. The resulting precipitate was collected by filtration after half the solvent was evaporated. Washing with a little cold acetone gave epoxy acetate **54** (75.4 mg, 61%) as fine, colorless needles, mp 182–183 °C. R_f (25:75 EtOAc–hexanes): 0.32. ^{1}H NMR (500 MHz): δ 0.75 (d, 3, J = 6.3) 0.78–0.85 (m, 2), 0.81 (s, 3), 0.87 (d, 3, J = 6.7), 0.95 (s, 3, overlapping m, 1), 1.09 (dt, 1, J = 5.5, 9.5), 1.18–2.08 (m, 25), 3.27 (d, 1, J = 5.7), 3.30 (t, 1, J = 11.0), 3.42 (br dd, 1, J = 10.9, 3.8), 4.36 (q, 1, J = 7.5), 4.48 (dd, 1, J = 11.1, 4.6). ^{13}C NMR (125 MHz): δ 11.45, 12.71, 13.60, 17.05, 21.07, 21.47, 26.49, 27.79, 28.70, 30.14, 30.56, 31.05, 31.15, 31.29, 34.02, 34.43, 38.49, 28.53, 42.06, 44.33, 51.88, 54.53, 58.00, 61.10, 66.74, 80.33, 81.36, 82.78, 109.20, 169.41, 170.37. Anal. Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 69.97; H, 8.74.

Keto Diol Diacetate 55. A solution of epoxy acetate **54** (24.0 mg, 45.2 mmol) in toluene (5 mL) containing pyridine (0.5 mL) was heated at reflux for 24 h. Evaporation of the solvent and flash chromatography, eluting with a gradient of 20:80–30:70 EtOAc–hexanes, gave a colorless residue that was crystallized from ether–hexane to give compound **55** (19.0 mg, 79%) as fine colorless needles, mp 183–189 °C. R_f (EtOAc): 0.66. ^{1}H NMR (500 MHz): δ 0.78 (d, 3, J = 6.3), 0.85 (s, 6), 0.90 (d, 3, J = 6.8, overlapping m, 1), 1.13–1.90 (m, 18), 2.03 (s, 3, overlapping m, 1), 2.11 (s, 3), 2.16 (dd, 1, J = 13.7, 3.4), 2.22 (dd, 1, J = 17.9, 5.7), 2.41 (dd, 1, J = 17.9, 6.2), 3.33 (t, 1, J = 11.0), 3.44 (br dd, 1, J = 10.7, 2.5), 4.40 (q, 1, J = 7.4), 4.52 (dd, 1, J = 11.1, 4.5), 5.36 (dd, 1, J = 10.3, 7.1). ^{13}C NMR (125 MHz): δ 11.55, 13.64, 14.28, 17.08, 20.75, 21.45, 26.87, 28.10, 28.74, 30.19, 30.95, 31.07, 31.34, 33.88, 36.10, 41.45, 42.01, 42.12, 43.15, 44.58, 53.11, 54.51, 61.23, 66.82, 73.97, 80.34, 81.24, 109.27, 169.83, 170.43, 206.52. Anal. Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 70.08; H, 8.67.

Keto Diol Monoacetate 59. A solution of LDA was prepared at −20 °C by adding ^{n}BuLi (5.0 mL of a 2.0 M solution in hexanes, 10.0 mmol, 2.1 equiv) to diisopropylamine (1.40 mL, 10.0 mmol, 2.1 equiv) in THF (40 mL). After being stirred for 20 min, the solution was cooled to −78 °C, and ketone **52** (2.05 g, 4.76 mmol) was added in THF (40 mL + 5 mL washing) by cannula. After 30 min at −78 °C, the solution was warmed to −40 °C, and oxodiperoxomolybdenum–pyridine–dimethylpyrrolidinone[20] (2.74 g, 7.14 mmol, 1.5 equiv) was added in one portion. After 20 min at −40 °C, a thick slurry had formed and the color had darkened from yellow to

pale orange. The mixture was allowed to warm to rt and stirred for 1 h, during which time the color dissipated. Saturated sodium thiosulfate (aqueous; 5 mL) and ether (20 mL) were added and the mixture stirred vigorously for 10 min. The aqueous layer was separated and re-extracted with ether. The combined organic extracts were washed with water (3 × 20 mL) and brine (20 mL), dried ($Na_2S_2O_4$), and evaporated. Flash chromatography on silica, eluting with 40:60 EtOAc–hexanes, gave an inseparable mixture of hydroxy ketones **55**, **56**, and **57** (1.18g, 55%) as a colorless gum. This was dissolved in CH_2Cl_2 (50 mL) with DMAP (30 mg, catalytic amount) and cooled to 0 °C. Triethylamine (3.68 mL, 26.4 mmol) and acetic anhydride (1.25 mL, 13.2 mmol) were added sequentially by syringe, and the resulting solution was stirred for 5 h at 0 °C. The solution was poured into saturated $NaHCO_3$ (aqueous; 50 mL). The organic phase was dried (Na_2SO_4) and evaporated and the residue purified by flash chromatography, eluting with a gradient of 30:70–40:60 EtOAc–hexanes, to give a mixture of acetoxy ketones (1.35 g, 96%). The major component (**59**) was purified by three crystallizations from absolute EtOH to give colorless needles (530 mg, 38%), mp 219–222 °C. ^{1}H NMR (500 MHz; shows the presence of 0.5 equiv of EtOH): δ 0.78 (d, 3, J = 6.3), 0.88 (s. 3), 0.90 (d, 3, J = 6.7), 0.92–1.03 (m, 2), 1.14 (s, 3), 1.14–1.22 (m, 2), 1.33–1.76 (m, 12), 1.83–1.90 (m, 3), 2.04 (s, 3, overlapping m, 1), 2.14 (s, 3), 2.19 (dd, 1, J = 12.5, 5.8), 2.23 (dd, 1, J = 14.3, 3.5), 3.40 (t, 1, J = 14.2), 3.34 (t, 1, J = 11.0), 3.45–3.47 (m, 1), 4.40 (dd, 1, J = 14.6, 7.5), 4.52 (dd, 1, J = 11.1, 4.6), 5.27 (dd, 1, J = 12.8, 6.6). ^{13}C NMR (125 MHz): d 11.55, 12.60, 13.59, 17.04, 20.66, 21.39, 26.96, 28.08, 28.72, 30.15, 31.10, 31.17, 31.32, 33.35, 37.17, 42.10, 43.30, 44.51, 47.42, 52.16, 54.35, 61.23, 66.78, 74.01, 80.30, 81.15, 109.21, 170.04, 170.36, 203.47. Anal. Calcd for $C_{31}H_{46}O_7$·1/2EtOH: C, 69.41; H, 8.92. Found: C, 69.38; H, 8.86.

Pyrazine 60. A degassed solution of acetoxy ketone **59** (502 mg, 0.946 mmol) and *O*-methyloxime **36** (340 mg, 0.788 mmol) in toluene (5 mL) was heated at 90 °C for 24 h and then at 145 °C for a further 24 h. After cooling, the solvent was removed and the residue was suspended in absolute EtOH. Filtration of the fine suspension through Celite gave the pure pyrazine **60** as a colorless solid (169 mg, 25%). Partial purification of the filtrate by flash chromatography, eluting with 25:75 EtOAc–hexanes, and then precipitation of this product from $CHCl_3$–EtOH gave a bit more of the pyrazine (combined yield 197 mg, 29%) as a colorless solid, mp 228 °C dec. R_f (25:75 EtOAc:hexanes): 0.22. $[\alpha]_D$: +13.0 (c = 0.94, $CHCl_3$). ^{1}H NMR (500 MHz): δ 0.67 (s, 3), 0.78 (br s, 6), 0.81 (s, 3), 0.85 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 0.88 (s, 3), 0.91 (2d, 6, J = 6.5 and 6.8), 0.70–1.91 (m, 45), 1.95 (dt, 1, J = 12.5, 4.3), 2.04 (s, 3), 2.01–2.59 (m, 2), 2.76 (t, 1, J = 17.7), 2.77 (t, 1, J = 17.7), 2.82 (d, 1, J = 16.8), 2.89 (d, 1, J = 16.8), 3.34 (t, 1, J = 11.0), 3.44 (m, 1), 4.41 (q, 1, J = 7.6), 4.57 (dd, 1, J = 11.2, 4.7). ^{13}C NMR (125 MHz): δ 11.54, 11.95, 13.64, 17.09, 18.67, 21.21, 21.39, 22.54, 22.78, 23.84, 24.22, 26.75, 27.99, 28.20, 28.43, 28.78, 30.22, 31.16, 31.31, 31.39, 31.59, 33.93, 35.34, 35.47, 35.57, 35.65, 35.79, 36.16, 39.49, 39.92, 41.65, 41.72, 42.16, 42.47, 44.47, 45.76, 45.98, 52.21, 53.67, 54.77, 56.29, 56.34, 61.23, 66.82, 80.45, 81.42, 109.27, 148.04, 148.33, 148.77, 149.13, 170.17. MS (FAB, NBA matrix): 851 (M^+), 835, 791, 765, 677. HRMS (MH^+): 851.6669, $C_{56}H_{87}N_2O_4$ requires 851.6666. Anal. Calcd for $C_{56}H_{86}N_2O_4$: C, 79.01; H, 10.18; N, 3.29. Found C, 78.70; H, 10.13; N, 3.36.

Pyrazine 61. Sodium methoxide (670 mL of a 0.51 M solution in MeOH) was added by syringe to a solution of diacetate **60** (58.0 mg, 68.1 mL) in THF (5 mL) at rt. After 16 h, the mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (5 x 20 mL), and the combined extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography, eluting with 40:60 EtOAc–hexanes, gave diol **61** (47.0 mg, 85%) as a colorless solid, mp > 270 °C dec. $[\alpha]_D$: +35.0 (c = 0.56, $CHCl_3$). ^{1}H NMR (500 MHz): δ 0.68 (s, 3), 0.79 (br s, 9), 0.82 (s, 3), 0.86 (2d, 6, J = 6.6, 6.6), 0.91 (d, 3, J = 6.5), 1.04 (d, 3, J = 6.8), 0.80–1.89 (m, 44), 1.92 (dd, 1, J = 8.3, 7.7), 2.02–2.08 (m, 2), 2.51 (2d, 2, J = 17.0 and 16.8), 2.57 (dd, 1, J = 17.3, 12.5), 2.77 (ddd, 2, J = 16.9, 11.0, 5.0), 2.89 (2d, 2, J = 17.0, 16.9), 3.37 (t, 1, J = 10.9, overlapping m, 1), 3.46–3.48 (m, 1), 4.42 (q, 1, J = 7.3). ^{13}C NMR (125 MHz): δ 10.42, 11.98, 13.85, 17.13, 18.70, 21.24, 22.56, 22.81, 23.86, 24.25, 28.02, 28.24, 28.29, 28.46, 28.81, 20.28, 30.63, 31.29, 31.42, 31.62, 33.87, 35.37, 35.41, 35.59, 35.66, 35.81, 36.19, 39.52, 39.95, 41.72, 41.78, 42.17, 42.50, 45.87, 46.02, 52.72, 53.71, 54.69, 56.32, 56.37, 61.81, 66.88, 79.58, 80.66, 109.49, 148.24, 148.43, 148.75, 149.19. Anal. Calcd for $C_{54}H_{84}N_2O_3$: C, 80.14; H, 10.14; N, 3.46. Found: C, 79.91; H, 10.30; N, 3.80.

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Supplementary Material Available: Procedures for the preparation of several known compounds: cholestan-3-one (**12**), di(17β-acetoxyandrostano[2,3-b:3′,2′-e])pyrazine, di(17β-hydroxyandrostano[2,3-b:3′,2′-e])pyrazine, 2-azidocholestan-3-one (**17**), 3β-acetoxy-2α,3α-epoxycholestane (**24**), 2α-acetoxycholestan-3-one (**31**), 3β-acetoxycholestan-2-one (**37**), 17β-(*tert*-butyldimethylsiloxy)androstan-3–one (**40**), Δ^2-androstene-3β,17β-diol diacetate (**41**), and 17β-dihydrohecogenin (**51**) (6 pages). This material is found in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.