Indole Diterpene Synthetic Studies. 2. First-Generation Total Synthesis of (-)-Paspaline

Richard E. Mewshaw, Michael D. Taylor, and Amos B. Smith, III*

Department of Chemistry, The Laboratory for Research on the Structure of Matter, and The Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

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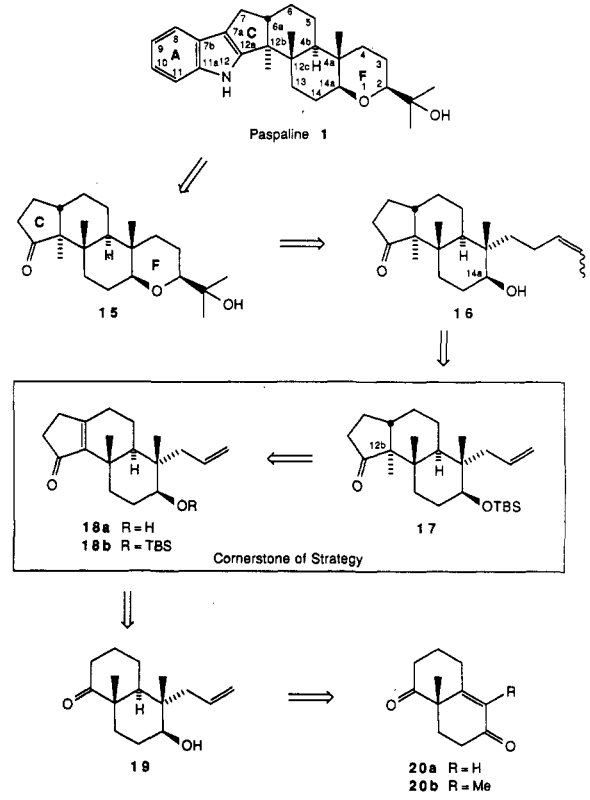
We record here a full account of the first total synthesis of (-)-paspaline (1), the simplest member of a rapidly growing class of architecturally complex diterpene indole alkaloids, many of which possess potent tremorgenic activity. In terms of sequential annulation, the strategy involves the following operations: DE → CDE → CDEF → ABCDEF. Proceeding in 23 steps from Wieland-Miescher ketone, the synthesis afforded (-)-paspaline (1) in high enantiomeric purity.

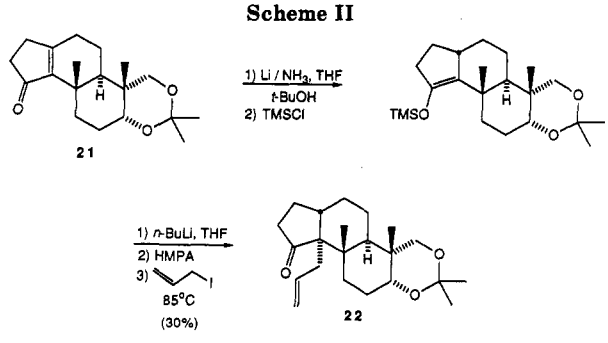
Paspaline (1)[1,2] and paspalicine (2),[1,2] the simplest members of a rapidly growing class of tremorgenic indole diterpenes, which now includes paspalinine (3),[3] paxilline (4),[4] aflatrem (5),[5] the paspalitrems A–C (6–8),[3a,6] and the penitrems A–F (9–14),[7] were first isolated by Arigoni and co-workers in 1966 from the ergot fungus *Claviceps paspali*[1] (Chart I). Seven years later, Gysi, a student in the Arigoni laboratory, proposed the relative and absolute configurations of five of the seven stereogenic centers in paspaline (1), on the basis of a combination of chemical degradation, spectral analysis, and biosynthetic rationale. The complete structure, however, remained unknown until 1980. In that year Springer and Clardy reported an X-ray crystallographic study of both paspaline (1) and paspalicine (2).[2]

As a class, these fungal metabolites hold considerable interest not only because of their novel architecture but also because they constitute significant environmental hazards, given their potent tremorgenic activity.[2,3a,5b] Moreover, the fungi that produce these toxins are often associated with important agricultural feedstocks, such as silage, maize, and other forages.[8] Livestock, the principal victims, upon ingesting the infected food experience a variety of neurological syndromes, including Dallis grass poisoning[3a] and ryegrass staggers.[9] The resultant symptoms, not unlike a number of human disorders (e.g., Wilson's disease),[10] are characterized by sustained tremors, discoordination, limb weakness, and convulsions, which if severe can lead to death. Interestingly, the simplest members, paspaline (1) and paspalicine (2), do not possess tremorgenic activity. Cole attributes this lack of activity to the absence of an axial hydroxyl group at C(4b).[2,6] Despite their structural novelty and potent tremorgenic activity, there were no reported efforts toward the synthesis of members of this class prior to our work.[11]

Scheme I



Scheme II



(1) (a) Fehr, T.; Acklin, W. *Helv. Chim. Acta* **1966**, *49*, 1907. (b) Gysi, R. R. Dissertation No. 4990, Eidgenossische Technische Hochschule, Zurich, Switzerland, 1973. (c) Leutwiler, A. Dissertation No. 5163, Eidgenossische Technische Hochschule, Zurich, Switzerland, 1973.

(2) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, 231.

(3) (a) Cole, R. J.; Dorner, J. W.; Landsen, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicholson, S. S.; Bedell, D. M. *J. Agric. Food Chem.* **1977**, *25*, 1197 and references therein. (b) Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *Ibid.* **1981**, *29*, 293. (c) Gallagher, R. T.; Finer, J.; Clardy, J.; Leutwiler, A.; Weible, F.; Acklin, W.; Arigoni, D. *Tetrahedron Lett. 1980*, 235. (d) Weible, F. Dissertation No. 6314, Eidgenossische Technische Hochschule, Zurich, Switzerland, 1979.

(4) (a) Cole, R. J.; Kirksey, J. W.; Wells, J. M. *Can. J. Microbiol.* **1974**, *20*, 1159. (b) Springer, J. P.; Clardy, J.; Wells, J. M.; Cole, R. J.; Kirksey, J. W. *Tetrahedron Lett.* **1975**, 2531.

(5) (a) Wilson, B. J.; Wilson, C. H. *Science* **1964**, *144*, 177. (b) Gallagher, R. T.; Clardy, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, 239.

(6) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069.

(7) (a) DeJesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289. (b) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77. (c) Hou, C. T.; Ciegler, A.; Hesseltine, C. W. *Can. J. Microbiol.* **1971**, *17*, 599.

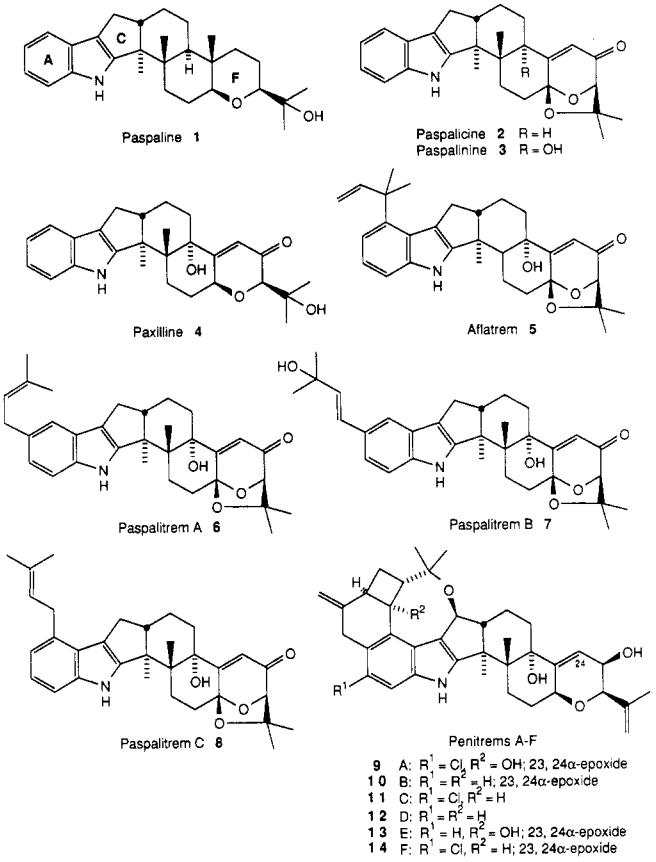
(8) Steyn, P. S.; Vleggaar, R. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1985; Vol. 48, p 1.

(9) Mantle, P. G.; Mortimer, P. H.; White, E. P. *Res. Vet. Sci.* **1977**, *24*, 49. diMenna, M. E.; Mantle, P. B. *Ibid.* **1977**, *24*, 347. Mantle, P. G.; Day, J. B.; Haigh, C. R.; Penny, H. C. *Vet. Rec.* **1978**, *103*, 403.

(10) Brimblecombe, R. W.; Pinder, R. M. *Tremors and Tremorgenic Agents, Scientechnia*; Bristol, U. K., 1972; pp 14–15.

0022-3263/89/1954-3449$01.50/0

Chart I



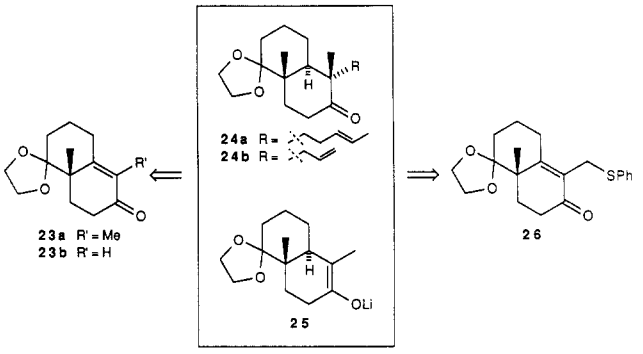
Synthetic Strategy for Construction of (-)-Paspaline (1)

From the retrosynthetic perspective, paspaline (1) possesses a number of intriguing structural elements, not the least of which are the vicinal quaternary centers at C(12b) and C(12c), juxtaposed with the trans C/D-ring fusion. Orchestration of these structural features would clearly be the central thrust of any successful synthetic strategy.

Our solution to this problem, outlined in Scheme I, began with the retrosynthetic removal of the indole ring system to afford tetracyclic intermediate **15**. In the synthetic direction, execution of a Fischer[12] or related indole annulation would constitute the ultimate operation. The tetracyclic intermediate in turn was anticipated to arise from tricyclic ketone **16**, assuming the viability of an acid-promoted oxidative cyclization involving the pendant olefin and the equatorial hydroxyl group at C(14a).[13] Refunctionalization of the resultant C(2) side chain would complete the diterpene unit.

Continuing with this analysis, the cornerstone of our strategy was envisioned to involve the reductive alkylation of enone **18** to **17**. Excellent precedent for this critical operation could be found in Trost's aphidicolin synthesis.[14] In particular, Trost reported that the reductive alkylation of the structurally quite similar enone **21**, employing allyl iodide as the electrophile, selectively furnished **22**, wherein

Scheme III



the allyl and methyl groups were disposed trans (Scheme II).

The requisite enone for paspaline (i.e., **18**) was expected to derive from ketone **19** via a cyclopentenone annulation.[15] Finally, we anticipated that **19** would be readily available in enantiomerically pure form from (+)-Wieland-Miescher ketone **20a**[16] or the corresponding homologue **20b**.

In this, a full account, we record a first-generation synthesis of (-)-paspaline. We note in advance that considerable difficulty was experienced in introducing the vicinal quaternary centers at C(12b) and C(12c). Furthermore, the synthetic approach did not appear amenable to other members of the paspaline family. Elsewhere we will describe a second-generation approach, which not only addresses the problem posed by the vicinal quaternary centers but also presents a unified synthetic strategy for this class of tremorgens.

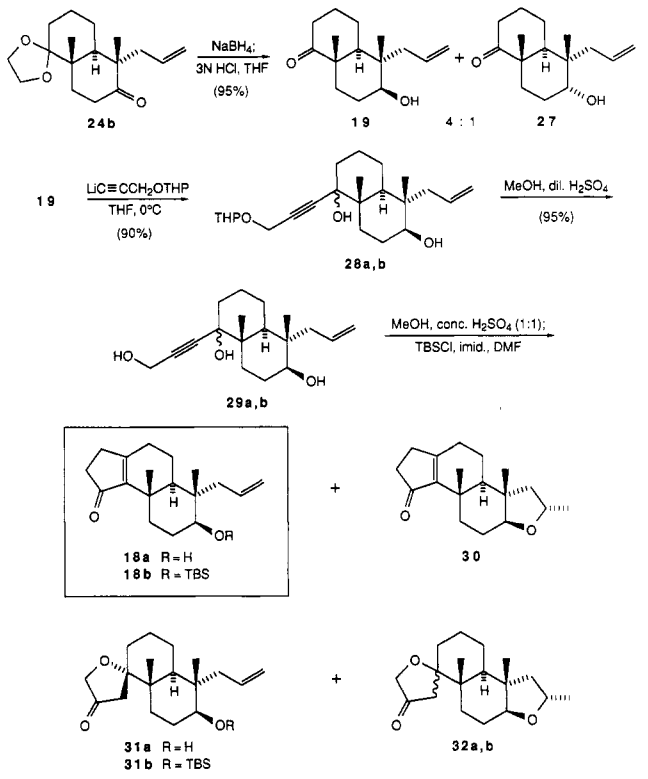
Results and Discussion

1. Construction of Cyclopentenone 18b: Our Initial Synthetic Target. At the outset of this venture, we planned to prepare *trans*-decalone **24a** (R = $CH_2CH_2CH{=}CHCH_3$) via reductive alkylation of enone **23a** (Scheme III). Although **23a** is a well-known intermediate,[17] a convenient method for its preparation both in high yield and high enantiomeric purity was not available. We therefore developed a synthetic equivalent of **23a** [i.e., (+)-phenylthio enone **26**], which upon reduction with lithium in liquid ammonia furnished enolate **25**.[18] Importantly, this enolate could be captured with reactive electrophiles to produce a variety of chiral, nonracemic *trans*-decalones in high yield.[18] However, all attempts to exploit this procedure for the preparation of ketone **24a**, employing *trans*-1-iodo-3-pentene as the electrophile, proved unsuccessful. Presumably this difficulty reflected the facile elimination of HI from the homoallylic iodide.

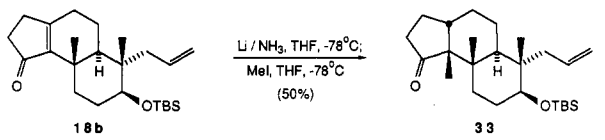
To circumvent this obstacle, we turned to **24b** (R = $CH_2CH{=}CH_2$), readily available from **26** via reductive

(11) Smith, A. B., III; Mewshaw, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 1769.
(12) For reviews, see: (a) Robinson, B. *Chem. Rev.* **1962**, *62*, 373. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. Also see: (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley Interscience: New York, 1982.
(13) Fukuyama, T.; Wang, C. L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260 and references therein.
(14) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328.
(15) (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 43. (b) Dev, S.; Rai, C. *J. Indian Chem. Soc.* **1957**, *34*, 266. (c) Jacob, T. M.; Dev, S. *J. Indian Chem. Soc.* **1959**, *36*, 429. (d) Paquette, L. A.; Wyvratt, M. J.; Schallner, D. F.; Begley, W. J.; Glankenship, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 6744. (e) Eaton, P. E.; Muller, R. H.; Carlson, G. R.; Cullison, D. A.; Cooper, G. F.; Chou, T.-H.; Krebs, E.-P. *J. Am. Chem. Soc.* **1977**, *99*, 2751. (f) Jacobson, R. M.; Lahm, G. M. *J. Org. Chem.* **1979**, *44*, 462. (g) Ellison, R. A. *Synthesis* **1973**, 397.
(16) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew.* Chem. **1971**, *83*, 492; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Gutzwiller, J.; Buchschacher, P.; Furst, A. *Synthesis* **1977**, 167. (d) Buchschacher, P.; Furst, A. *Org. Synth.* **1984**, *63*, 37.
(17) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1103.
(18) Smith, A. B., III; Mewshaw, R. E. *J. Org. Chem.* **1984**, *49*, 3685. For an earlier report on **24b**, see: Ardon-Jimenez, A.; Halsall, T. G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1461.

Scheme IV



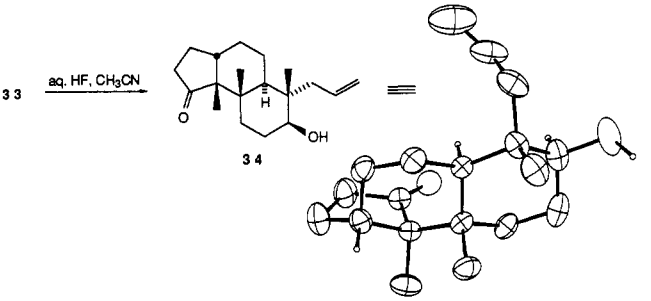
Scheme V



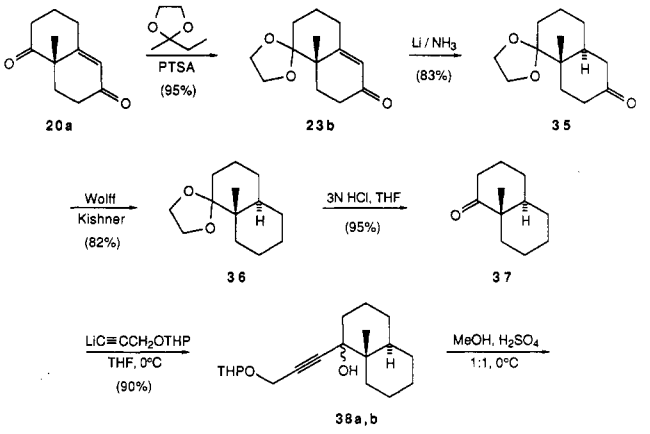
alkylation with allyl bromide.[18] The intent was to transform the allyl group to the corresponding pentenyl appendage after construction of the cyclopentanone ring system. Toward this end, stereoselective reduction of ketone **24b** with $NaBH_4$,[19] followed by deketalization, afforded a 4:1 mixture of alcohols **19** and **27**, which were readily separable by flash chromatography (Scheme IV).[20]

The equatorial major isomer **19** was next converted to cyclopentenone **18b** via a four-step sequence. First, treatment of keto alcohol **19** with the lithium anion derived from the THP ether of propargyl alcohol (2.2 equiv)[21] provided a 6:1 mixture of diols **28a,b** in 90% yield. The THP protecting group was then removed with mild acid, and the resultant triols **29a,b** were briefly exposed to a 1:1 mixture of concentrated H_2SO_4 and MeOH,[21d] followed by reaction of the product mixture with *tert*-butyldimethylsilyl chloride and imidazole.[22] This afforded enone **18b** in conjunction with minor amounts of **30**, **31b**, and **32a,b**; the yields were respectively 25, 6, 14, and 14%. Elucidation of these structures entailed a combination of spectroscopic and X-ray crystallographic techniques (see Experimental Section).[23]

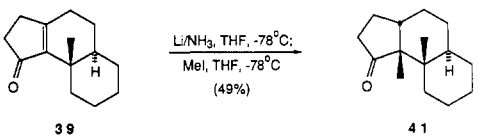
Scheme VI



Scheme VII



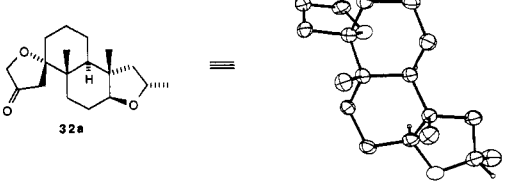
Scheme VIII



2. Reductive Alkylation of Enone 18b: A Most Surprising Result. Having secured rapid access to our initial target (i.e., **18b**), we turned to the reductive alkylation sequence, the cornerstone of our synthetic strategy. Treatment of cyclopentenone **18b** with lithium in liquid ammonia (0.25 M),[24] employing water (0.9 equiv) as the proton source, was followed sequentially by removal of the ammonia, addition of THF, and alkylation with excess methyl iodide, to furnish a single product in 50%

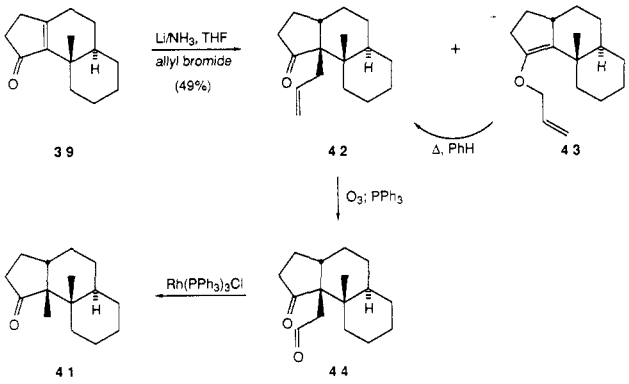
(19) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2112.
(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(21) (a) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1953**, 2247. (b) Baumann, M.; Hoffman, W.; Muller, N. *Tetrahedron Lett.* **1976**, 3585. (c) Hiyama, T.; Shinoda, M.; Saimoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2747. (d) MacAlpine, G. A.; Paphael, R. A.; Shaw, A.; Taylor, A. W.; Wild, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 410.
(22) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6109.

(23) An ORTEP plot of a single-crystal X-ray analysis is shown below of **32a**.



(24) For best results, the concentration of the substrate in the lithium–ammonia solution should be 0.25 M or greater, in order that the radical anion can compete effectively for the limited amount of water.

Scheme IX

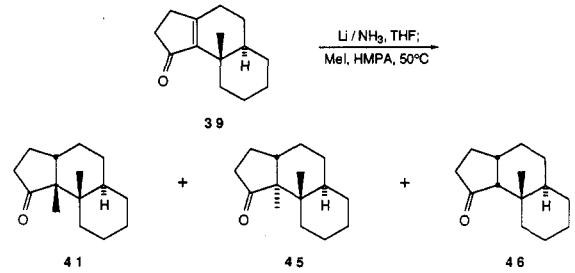


yield (Scheme V). The spectroscopic properties of this material were completely consistent with structure **17**, the expected product on the basis of the Trost precedent. We therefore proceeded with the synthetic venture. However, upon completion of our proposed paspaline sequence (vide infra), direct comparison indicated that the synthetic material differed significantly from natural (−)-paspaline. Careful reflection suggested that the reductive alkylation of **18b** might have instead afforded **33**, in which the C(12b) methyl had been introduced cis to the C(12c) methyl. Confirmation of this surmise came through the aegis of a single-crystal X-ray analysis of alcohol **34**, prepared from **33** by removal of the TBS group (Scheme VI).[25] Needless to say, formation of the cis alkylation product is in marked contrast to Trost's observation.

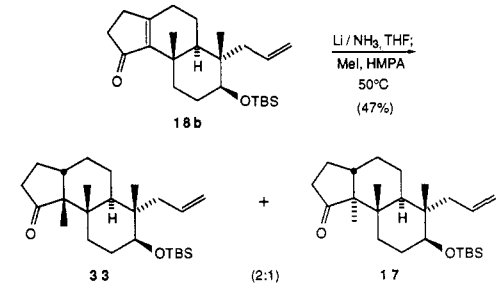
3. Reductive Alkylation Model Studies. Given this discrepancy, we felt compelled to explore further the reductive alkylation. Selection of a less precious substrate seemed prudent, and to this end enone **39** was prepared in six steps from (+)-Wieland–Miescher ketone **20a** (Scheme VII).

The same reductive alkylation was then performed with **39**. Again the methyl group was introduced cis to the angular methyl substituent to afford **41** (Scheme VIII). At this point, it occurred to us that Trost's "trans-alkylation" might in fact have followed a different reaction pathway. One possibility would be O-alkylation of the initially derived enolate, followed by a Claisen rearrangement of the enol allyl ether.[26] Some support for this scenario could be found in the somewhat unusual alkylation conditions employed by Trost, namely, inverse addition of the enolate to a 1:1 mixture of the electrophile and HMPA *held at 85 °C*.[27] Intrigued by this possibility, we performed the reductive alkylation of **39** with allyl bromide; two products were obtained (Scheme IX). C-Alkylation once again furnished a *cis*-hydrindan derivative (i.e., **42**), confirmed by degradation to **41**. The second product arose by O-alkylation (**43**) which, upon heating in benzene at reflux overnight, readily underwent the proposed Claisen rearrangement. However, the product proved to be identical with the *cis*-cyclopentanone **42**. Thus, O-alkylation followed by Claisen rearrangement is a viable pathway, but the observed β-facial selectivity provides circumstantial evidence that Trost's trans reductive alkylation does not arise in this manner. The mystery remains!

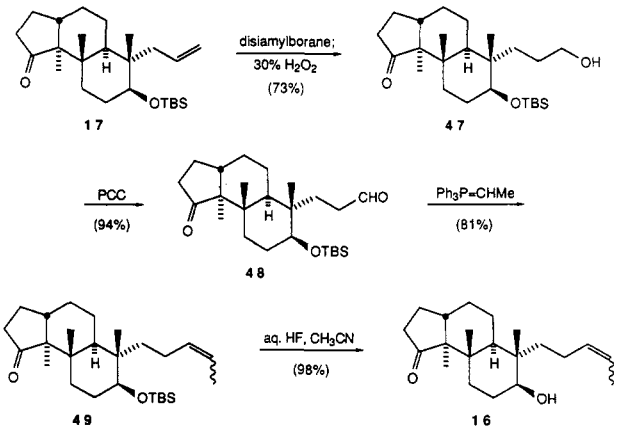
Scheme X



Scheme XI



Scheme XII



Undaunted, we again focused on the reductive alkylation of enone **39**, attempting to reproduce the precise conditions reported by Trost. Specifically, reduction with lithium in liquid ammonia (0.25 M,[24] 0.9 equiv of H_2O) was followed by inverse addition of the derived enolate to a warm solution of MeI–HMPA. Under these conditions, a mixture of **41** and **45** (2.1:1; 50%), together with a small amount (10–15%) of the unalkylated material (**46**), resulted (Scheme X).

Equally important, analogous reductive alkylation of the advanced paspaline substrate (**18b**) also afforded a 2:1 mixture of the cis- and trans-fused cyclopentanones **33** and **17** (Scheme XI). The isolated yields were 32 and 15%, respectively. Unfortunately, all attempts to improve the isomer ratio and yield of this crucial reductive alkylation went unrewarded.

4. Elaboration of the Pyranyl Ring: Completion of the Diterpene Unit. Notwithstanding the low yield, sufficient **17** was prepared to continue the synthesis. By this time, as noted earlier, we had the great advantage of an unanticipated model study, namely, the completed synthesis of epipaspaline wherein the major reductive alkylation product (**33**) was employed.

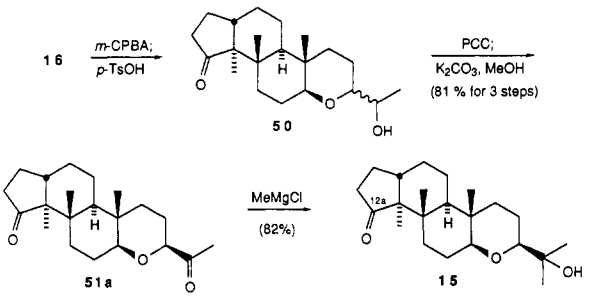
Turning first to the construction of the pyranyl ring system, we achieved a two-carbon chain extension of the allyl group in four steps (Scheme XII). Specifically, hydroboration–oxidation gave alcohol **47**. Further oxidation

(25) Unpublished results of P. Carroll, University of Pennsylvania X-ray Crystallographic Facility.

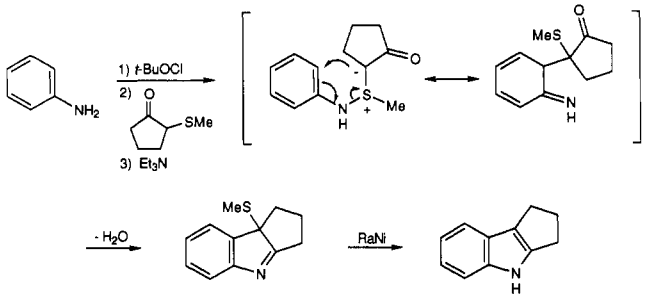
(26) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. Also see: Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983 and 6984.

(27) For a general review on the structure and reactivity of enolates, see: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737 and references cited therein.

Scheme XIII



Scheme XIV

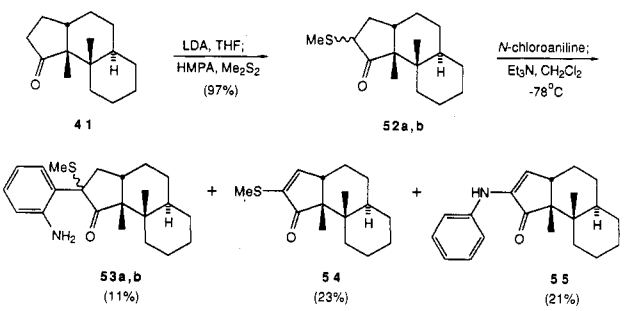


with PCC[28] and Wittig olefination ($CH_3CH{=}PPh_3$)[29] of the derived aldehyde then led to keto olefin **49**. Finally, deprotection with aqueous HF afforded alcohol **16** as an 85:15 *E*–*Z* mixture. The overall yield was 54%.

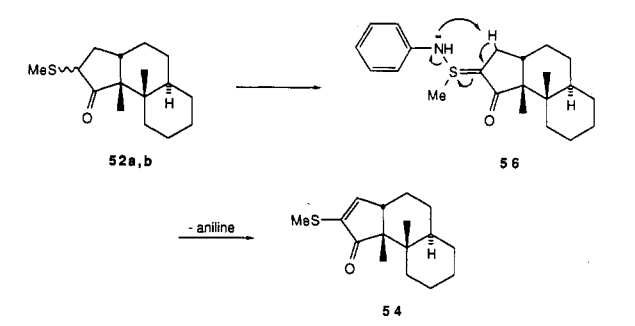
Formation of the pyranyl ring was then accomplished (Scheme XIII) via treatment of alcohol **16** with an unbuffered solution of *m*-CPBA in dichloromethane, followed by addition of a catalytic amount of a sulfonic acid (*p*-TsOH or CSA).[30] Without separation, alcohols **50a,b** were oxidized with PCC[28] to afford a 2.2:1 mixture of diketones **51a,b**, which upon equilibration with K_2CO_3 in MeOH provided an 85:15 mixture (**51a**:**51b**) in 81% yield. Further improvement of this ratio to 95:5 was achieved by recrystallization from hexane–ether. Methylation with methylmagnesium chloride then completed the diterpene portion of paspaline (**1**). Interestingly, the latter reaction proceeded with very high chemoselectivity, affording ketone **15** in 82% yield; no addition to the cyclopentanone carbonyl could be detected. We attribute this selectivity to the considerable steric hindrance at the C(12a) carbonyl group (paspaline numbering).

5. Introduction of the Indole Ring: A Nontrivial Operation. Although there exist numerous methods for construction of indoles, the obvious first choice here appeared to be the classical Fischer approach.[12] However, in our hands this method proved singularly unsuccessful with a variety of sterically hindered model ketones. Anticipating similar difficulties with any procedure that would involve initial attack on the carbonyl carbon in **15**, we looked for an alternative approach. Particularly attractive in this regard appeared to be the Gassman indole synthesis,[30] wherein the first bond of the indole ring is constructed via a [2,3]-sigmatropic rearrangement of an intermediate sulfur ylide, derived from *N*-chloroaniline and the requisite α-alkylthio ketone (Scheme XIV). Dehydration followed by reductive desulfurization then completes the indole synthesis. Importantly, this process

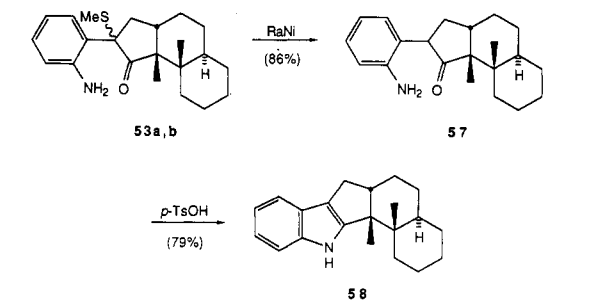
Scheme XV



Scheme XVI



Scheme XVII



defers carbonyl attack until the aniline and substrate ketone have been coupled. In the case of a severely hindered carbonyl, the difficult closure of the indole ring thus enjoys the considerable advantage of intramolecularity.[31]

In view of the precious nature of our advanced intermediate **15**, we decided to test this approach with a model system. The previously prepared cyclopentanones **41** and **45** appeared ideal. Because we were working in the epipaspaline series at the time, we will describe our model work with **41** first.

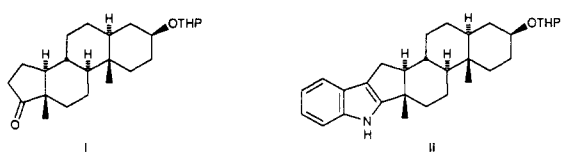
In preparation for the Gassman procedure, the α-methylthio group was introduced by using the conditions of Trost[32] (Scheme XV). Exposure of the sulfide to *N*-chloroaniline followed by triethylamine afforded the coupling products **53a,b**, albeit accompanied by two major side products **54** and **55**. Enone **55** (23%) was quickly recognized to result from a Stevens [2,3]-sigmatropic rearrangement (Scheme XVI); similar competing reactions

(28) Herscovici, J.; Egron, M.-J.; Antonakis, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1962.

(29) For an excellent review, see: *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979.

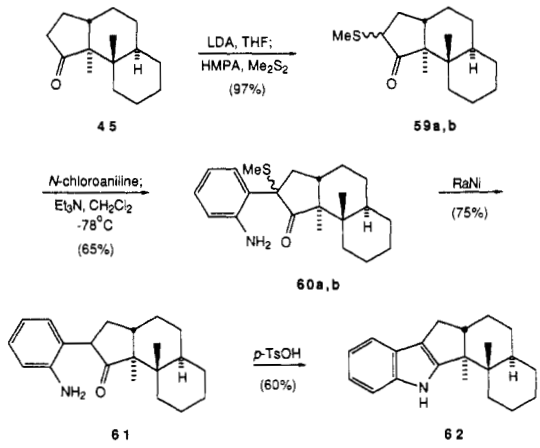
(30) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495 and references therein.

(31) A preliminary model study using readily available steroid i afforded indole ii in 70% overall yield using the Gassman protocol.[30] See Experimental Section for details.

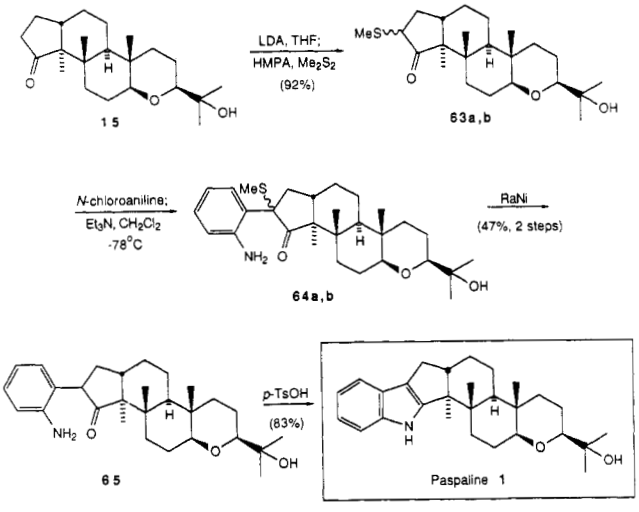


(32) Trost, B. M.; Salzmann, T. N.; Hiro, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

Scheme XVIII



Scheme XIX



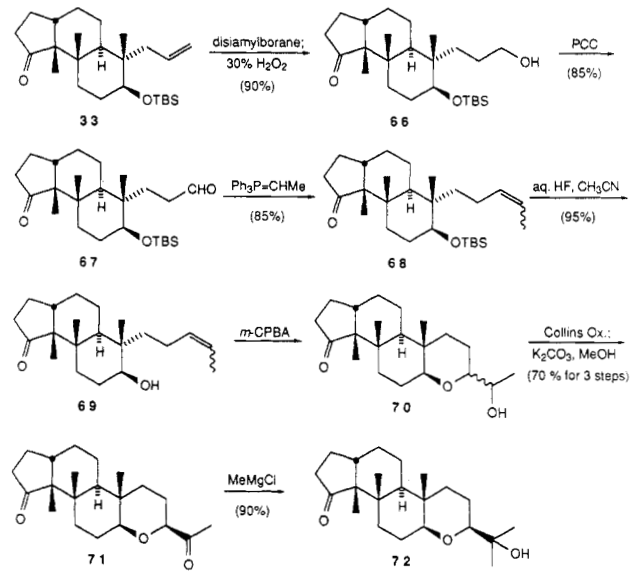
have been observed by Gassman.[30] The formation of enone **54**, on the other hand, appears unprecedented. Mechanistically, it can be rationalized via an intramolecular elimination of aniline from intermediate **56**. The predominance of these alternate reaction pathways presumably reflects the considerable steric hindrance of the cyclopentanone carbonyl group.

Reduction with Raney nickel in ethanol then led to aminophenyl ketone **57**, a single isomer as determined by ^{1}H NMR (Scheme XVII). Finally, acid-induced cyclization of **57** was effected with *p*-TsOH, affording indole **58**. The overall yield for these two steps was 68%. Interestingly, both **57** and its immediate precursor **53a,b** preferred to exist in the keto aniline form, rather than undergo spontaneous dehydration as most often observed by Gassman. Presumably this is another manifestation of the steric hindrance at the carbonyl carbon.

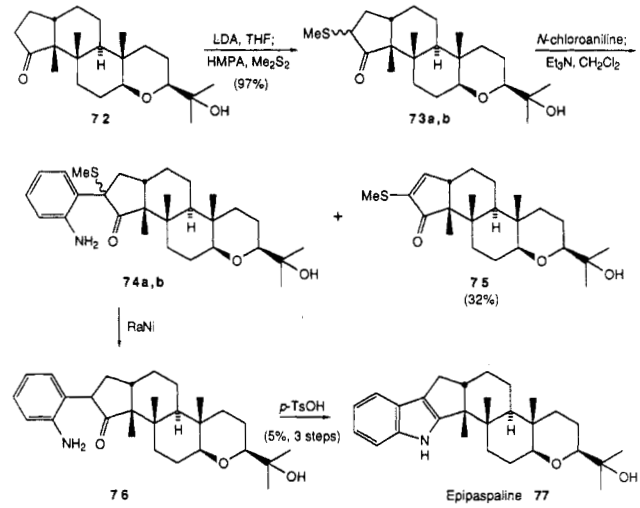
In the case of *trans*-cyclopentanone **45**, the Gassman protocol afforded model indole **62** in 28% overall yield for the four steps (Scheme XVIII). In this instance, the critical [2,3]-sigmatropic rearrangement (i.e., **59** → **60**) proceeded uneventfully. The contrasting results obtained with cyclopentanones **41** and **45** suggest that the [2,3]-sigmatropic rearrangement is quite sensitive to the inherent structural subtleties of the substrate.[30]

6. Preparation of (−)-Paspaline. Having successfully constructed model indole **62**, we focused on appending the indole ring to our advanced tetracyclic intermediate **15** (Scheme XIX). As with our model system, sulfenylation of cyclopentanone **15** with dimethyl disulfide led to a 1:1 mixture of methylthio ketones **63a,b**. Execution of the Gassman procedure then gave a 1.6:1 mixture of epimeric methylthio keto anilines **64a,b**, which in turn were reduced with Raney nickel to furnish **65** in 47% yield from **63a,b**. The latter was again shown to be a single compound by ^{1}H NMR. Acid-induced cyclization completed the paspaline synthesis in 83% yield. That in fact (−)-paspaline (**1**) was now in hand derived from careful comparison of the physical and spectral properties with those of an authentic sample, kindly provided by Professor Arigoni.[33]

Scheme XX



Scheme XXI



7. Synthesis of C(12b)-Epipaspaline (77). As noted earlier, we had the misfortune of preparing C(12b)-epipaspaline (**77**) during the course of this synthetic program. We present here a summary of this work; for complete details see the Experimental Section.

Beginning with the major reductive alkylation product **33**, the pyranyl ring system was appended as previously described for paspaline. The sequence proved quite workable, affording alcohol **72** in 39% overall yield (Scheme XX).

Application of the Gassman protocol to **72** then gave C(12b)-epipaspaline (**77**) (Scheme XXI). The overall yield

(33) We thank Professor D. Arigoni of the Eidgenossische Technische Hochschule, Zurich, for providing a very generous sample of (−)-paspaline.

for the final three steps, however, was only 5%. As in the model work, the steric encumbrance of the cis-fused system is believed to be the culprit vis-à-vis the [2,3]-sigmatropic rearrangement (i.e., **73** → **74a,b**), the major side product being enone **75**.

8. Summary. The first total synthesis of (-)-paspaline (**1**) and C(12b)-epipaspaline (**77**) has been achieved. The synthesis proceeded in 23 steps from (+)-Wieland-Miescher ketone and afforded (-)-paspaline in high enantiomeric purity. Elsewhere we will present a synthetic strategy that not only permits completion of a highly stereocontrolled second-generation paspaline synthesis but may also prove effective for other members of the indole diterpene family of tremorgenic alkaloids.[35]

Experimental Section[34]

***trans*-3-Penten-1-ol.** A 250-mL three-necked flask equipped with a dry-ice condenser was charged with 100 mL of ammonia and 4.5 g (0.196 mol) of sodium. After the sodium dissolved, 5.0 g (0.059 mol) of 3-pentyn-1-ol was added over 15 min. The reaction mixture then was stirred for 1.5 h, followed by the cautious addition of solid ammonium chloride. The ammonia was allowed to evaporate, and the residue was partitioned between methylene chloride (150 mL) and water (100 mL). The aqueous layer was extracted with two 60-mL portions of methylene chloride, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. Distillation (short path, bp 130–138 °C) afforded 4.1 g (80%) of *trans*-3-penten-1-ol: ^{1}H NMR (CCl_4, 60 MHz) δ 1.60 (3 H, br d), 1.90–2.38 (2 H, m), 3.30–3.60 (1 H, m), 3.42 (2 H, t, J = 6.0 Hz), 5.30 (2 H, m).

***trans*-1-Iodo-3-pentene.** In a 100-mL round-bottomed flask, triethylamine (5.98 g, 0.059 mol) and *trans*-3-penten-1-ol (3.9 g, 0.045 mol) were dissolved in methylene chloride (50 mL), and methanesulfonyl chloride (5.92 g, 0.052 mol) was added. The solution was stirred for 1 h and then was poured onto 50 mL of cold 10% hydrochloric acid. The aqueous phase was extracted with methylene chloride (100 mL), and the organic layers were dried over magnesium sulfate and concentrated. Mesylate: ^{1}H NMR (CCl_4, 60 MHz) δ 1.62 (3 H, br d, J = 5 Hz), 2.40 (2 H, m), 2.92 (3 H, s), 4.10 (2 H, t, J = 6 Hz), 5.40 (2 H, m).

The mesylate was added to a solution of sodium iodide (1.5 equiv) in 100 mL of acetone. After being stirred for 3 days, the solution was evaporated and the residue was partitioned between 10% aqueous $NaHSO_3$ (50 mL) and ether (100 mL). The organic phases were dried over magnesium sulfate and concentrated, and the crude material was distilled (bp 110 °C, 80 mmHg), affording 6.19 g (70%) of the iodide: IR ($CHCl_3$) 3000, 2970, 2940, 2920, 1580, 1460, 1285, 1175, 980 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.64 (3 H, d, J = 5 Hz), 2.40–2.80 (2 H, m) 3.05–3.30 (2 H, m), 5.34–5.55 (2 H, m).

(+)-Phenylthio Enone 26. A solution of enone **23b**[17] (2.65 g, 11.9 mmol), freshly distilled thiophenol (17.9 mmol, 1.5 equiv), 37% aqueous formaldehyde (19.4 mmol, 1.63 equiv), and triethylamine (15 mmol, 1.26 equiv) in ethanol (10 mL) was heated at reflux under nitrogen for 4 days. The solution was cooled and partitioned between 5% potassium hydroxide (50 mL) and ether (100 mL). The organic layer was washed with 5% aqueous potassium hydroxide (25 mL), and the combined aqueous phases were extracted with ether (100 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. Evaporation of solvent afforded a crystalline product, which was washed with cold ether (10–20 mL). The washings were concentrated and chromatographed (ethyl acetate–hexane, 1:4) to give a total of 3.58 g (87%) of **26**: mp 89–91 °C (ether); $[\alpha]^{28}_D$ +147.4° (c 1.0, benzene); IR (CCl_4) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.45 (10 H, m), 3.75 (1 H, d, J = 11.6 Hz), 3.85–4.00 (5 H, m), 7.22–7.40 (5 H, m); high-resolution mass spectrum, m/z 344.1442 (M$^+$, calcd for $C_{20}H_{24}O_3S$ 344.1446).

Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 6.97. Found: C, 69.66; H, 6.99.

(4′a*S*,5′*S*,8′a*S*)-5′-Allylhexahydro-5′,8′a-dimethylspiro-[1,3-dioxolane-2,1′(2′*H*)-naphthalen]-6′(5′*H*)-one (24b).[18b] A solution of enone **26** (4.2 g, 11.9 mmol) and water (0.42 g, 23.3 mmol) in tetrahydrofuran (20 mL) was added dropwise over 30 min to a stirred solution of lithium (0.51 g, 73 mmol) in ammonia (300 mL). After being stirred for another 45 min, the solution was diluted with 70 mL of tetrahydrofuran, followed by rapid addition of allyl bromide (15 equiv) dissolved in tetrahydrofuran (20 mL). The solution was stirred for 30 min, and then the ammonia was evaporated. The residue was diluted with ether and washed with water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The resulting oily yellow residue was chromatographed (ethyl acetate–hexane, 1:20), furnishing 2.78 g (84%) of **24b**: $[\alpha]^{25}_D$ +26.8° (c 1.4, $CHCl_3$); IR (CCl_4) 3065, 1695, 1635, and 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (3 H, s), 1.21 (3 H, s), 1.32–2.63 (13 H, m), 3.80–3.96 (4 H, m), 4.94–5.04 (2 H, m), 5.58–5.74 (1 H, m); high-resolution mass spectrum, m/z 278.1895 (M$^+$, calcd for $C_{17}H_{26}O_3$ 278.1882).

5α-Allyl-6β-hydroxy-5β,9β-dimethyl-*trans*-decalin-1-one (19) and the 6α-Epimer 27. Sodium borohydride (10.0 mmol) was added in several portions over 4 h to a solution of ketone **24b** (2.79 g, 10.0 mmol) in absolute ethanol (25 mL at 0 °C). The reaction mixture was allowed to warm to room temperature and stirred overnight. After evaporation of solvent, the residue was worked up with ether and water and the organic phase was dried over magnesium sulfate and concentrated, furnishing 2.70 g (95%) of crude product. ^{1}H NMR (250 MHz) analysis revealed the formation of a 4:1 mixture of epimeric 6β- and 6α-hydroxy compounds.

The mixture of alcohols was dissolved in tetrahydrofuran (30 mL) containing water (5 mL) and 3 N hydrochloric acid (5 mL), and the mixture was stirred for 4 h. The reaction mixture then was partitioned between ether (150 mL) and water (50 mL). The aqueous layer was extracted with ether (75 mL), and the combined organic solutions were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:9) afforded 1.73 g (76%) of **19** and 432 mg (19%) of **27**. **19**: mp 98–100 °C (ether); $[\alpha]^{25}_D$ -28.9° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3650–3170, 3065, 1695, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, s), 1.17 (3 H, s), 1.23–2.28 (12 H, comp), 2.37 (1 H, dd, J = 14.0, 7.0 Hz), 2.55 (1 H, dt, J = 14.0, 7.0 Hz), 3.45 (1 H, m), 5.04 (1 H, d, J = 3.8 Hz), 5.10 (1 H, s), 5.78 (1 H, m); high-resolution mass spectrum, m/z 236.1780 (M$^+$, calcd for $C_{15}H_{24}O_2$ 236.1777). **27**: mp 118–120 °C (ether); $[\alpha]^{25}_D$ -50.2° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3625–3350, 3065, 1695, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, s), 1.18 (3 H, s), 1.33–2.30 (13 H, comp), 2.59 (1 H, m), 3.55 (1 H, m), 5.09 (1 H, s), 5.15 (1 H, d, J = 5.6 Hz), 5.98 (1 H, m); high-resolution mass spectrum, m/z 236.1778 (M$^+$, calcd for $C_{15}H_{24}O_2$ 236.1776).

Acetylenic Diols 28a and 28b. To a stirred solution of 3-(tetrahydropyran-2-yloxy)propyne (5.69 g, 40.6 mmol) in dry tetrahydrofuran (40 mL) at -78 °C was added 2.0 M *n*-butyllithium (18.5 mL, 37 mmol). After being stirred at -78 °C for 1.5 h, the reaction mixture was warmed to 0 °C and stirred for 0.5 h further. The solution was cooled to -78 °C, and a solution of ketone **19** (2.91 g, 12.3 mmol) in tetrahydrofuran (25 mL) was added. The reaction mixture was allowed to warm to room temperature while being stirred for another hour. The solution then was partitioned between ether (200 mL) and water (100 mL). The aqueous phase was extracted with ether (100 mL), and the combined organic layers were washed with brine, dried over

(34) **Materials and Methods.** Melting points were obtained on a Thomas-Hoover instrument and are corrected. All solvents used were reagent grade. Ether and THF were distilled from sodium and benzophenone. Precoated silica gel plates (250 μm) with a fluorescent indicator (Merck) were used for analytical thin-layer chromatography (TLC). Visualization was achieved with ultraviolet light or ethanolic 12-molybdophosphoric acid [7% (w/v)]. Silica gel 60 (particle size 0.043–0.63 mm) supplied by Merck was used for flash chromatography. *n*-Butyllithium was standardized by titration with diphenylacetic acid. ^{1}H and ^{13}C NMR spectra were obtained in deuteriochloroform solutions on either a Varian T-60A (60 MHz) or a Bruker WP250 FT (250 MHz) spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. All infrared spectra were recorded on either a Perkin-Elmer Model 337 or Model 283B spectrophotometer. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter. Microanalyses were determined by the Rockefeller University Microanalytical Laboratories under the direction of S. T. Bella. High-resolution mass spectra were obtained from the University of Pennsylvania Mass Spectrometer Service Center on a Hitachi Perkin-Elmer RMH-2 or VG 70-70 Micromass double-focusing spectrometer interfaced with a Kratos DS-50-s system.

(35) Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761–5768.

magnesium sulfate, and concentrated. The residue was quickly purified by flash chromatography (ethyl acetate–hexane, 1:3) to give 4.20 g (90%) of diols **28a** and **28b**. A 250-MHz ^{1}H NMR spectrum indicated that the ratio of diols **28a** and **28b** was 5.7:1. A small sample was chromatographed (ethyl acetate–hexane, 1:4) to separate the stereoisomers for characterization.

28b: $[\alpha]^{27}_D$ +14.2° (*c* 1.73, $CHCl_3$); IR ($CHCl_3$) 3615–3275, 3065, 1116, 1072, 1015, 965, 925, 893, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s), 1.12 (3 H, s), 1.20–2.20 (20 H, comp), 2.30 (1 H, dd, *J* = 14.0, 7.2 Hz), 2.48 (2 H, m), 2.84 (1 H, m), 4.28 (2 H, s), 4.81 (1 H, s), 5.12 (2 H, m), 5.88 (1 H, m); high-resolution mass spectrum, *m/z* 376.2676 (M$^+$, calcd for $C_{23}H_{36}O_4$ 376.2691).

28a: $[\alpha]^{25}_D$ +29.22° (*c* 3.58, $CHCl_3$); IR ($CHCl_3$) 3635–3200, 3065, 1115, 1015, 945, 905, 895, 863 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s), 1.01 (3 H, s), 1.20–1.92 (18 H, comp), 1.99 (1 H, dd, *J* = 14.8, 6.5 Hz), 2.28 (2 H, m), 2.50 (2 H, m), 3.84 (1 H, m), 4.33 (2 H, s), 4.60 (1 H, d, *J* = 3.0 Hz), 5.08 (2 H, m), 5.82 (1 H, m); high-resolution mass spectrum, *m/z* 376.2690 (M$^+$, calcd for $C_{23}H_{36}O_4$ 376.2691).

Triols 29a and 29b. Diols **28a** and **28b** (3.1 g, 8.24 mmol) were dissolved in methanol (100 mL) containing a few drops of concentrated sulfuric acid. The solution was stirred for 4 h, whereupon solid sodium bicarbonate was added and the mixture was stirred for another hour. The solids were filtered, and the methanol was evaporated. The resulting solid was dissolved in ether and filtered through Celite, furnishing 2.29 g (95%) of triols **29a** and **29b**. A small sample was flash chromatographed (ethyl acetate–hexane, 1:2) to separate the stereoisomers for characterization.

29b: mp 120.5–121.5 °C (hexane–ether); $[\alpha]^{27}_D$ +14.1° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3625–3125, 3050, 1055, 1028, 965, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s), 1.11 (3 H, s), 1.15–2.05 (13 H, comp), 2.29 (1 H, dd, *J* = 14.2, 7.3 Hz), 2.48 (1 H, m), 2.98 (1 H, m), 3.45 (1 H, m), 4.26 (2 H, s), 5.10 (2 H, m), 5.88 (1 H, m); high-resolution mass spectrum, *m/z* 292.2093 (M$^+$, calcd for $C_{18}H_{28}O_3$ 292.2117).

29a: mp 191–192.5 °C (acetone); $[\alpha]^{27}_D$ +6.93° (*c* 1.0, MeOH); ^{1}H NMR ($(CD_3)_2CO$) δ 0.81 (3 H, s), 1.01 (3 H, s), 1.08–1.75 (13 H, comp), 1.95 (1 H, dd, *J* = 14.1, 7.1 Hz), 2.37 (1 H, dd, *J* = 14.0, 7.2 Hz), 3.40 (2 H, m), 4.25 (2 H, s), 5.05 (2 H, m), 5.85 (1 H, m); high-resolution mass spectrum, *m/z* 292.2130 (M$^+$, calcd for $C_{18}H_{28}O_3$ 292.2117).

5α-(*tert*-Butyldimethylsiloxy)-8-methyl-3,5-seco-*A*,18-dinor-8α,9β,10α-androsta-2,13-dien-15-one (18b). Concentrated sulfuric acid (12 mL) was added over 30 min to a solution of triols **29a** and **29b** (1.2 g, 4.11 mmol) in methanol (12 mL) at 0 °C. The solution was stirred at 0 °C for an additional 20 min. The mixture then was diluted with ether (100 mL) and neutralized by the cautious addition of saturated sodium bicarbonate. The aqueous phase was extracted with ether (150 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was quickly chromatographed (ethyl acetate–hexane, 1:9), affording a mixture of **18a**, **30**, **31a**, and **32a,b**. A small sample was rechromatographed to provide pure enone **18a**: $[\alpha]^{24}_D$ + 46.1° (*c* 1.6, $CHCl_3$); mp 123–124 °C (hexane); IR (CCl_4) 3635–3195, 3065, 1680, 1625, 1045, 1025, 1003, 980, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, s), 1.11 (3 H, s), 1.15–2.50 (15 H, comp), 2.68 (1 H, dt, *J* = 13.7, 3.4 Hz), 3.52 (1 H, dd, *J* = 10.4, 6.0 Hz), 5.06 (1 H, s), 5.12 (1 H, d, *J* = 3.7 Hz), 5.80 (1 H, m); high-resolution mass spectrum, *m/z* 274.2008 (M$^+$, calcd for $C_{18}H_{26}O_2$ 274.2011).

The mixture was dissolved in dry DMF (10 mL) containing excess *tert*-butyldimethylsilyl chloride and imidazole, as well as a catalytic amount of DMAP. After being stirred at 45 °C for 6 h, the solution was partitioned between ether (100 mL) and water (75 mL). The aqueous phase was extracted with ether (75 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed (ethyl acetate–hexanes, 1:20) to afford 234 mg of **31b** (14%), 400 mg of **18b** (25%), 168 mg of **32a,b** (14%), and 68 mg of **30** (6%).

31b: IR ($CHCl_3$) 2945, 2935, 1757, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.045 (3 H, s), 0.054 (3 H, s), 0.78 (3 H, s), 0.88 (9 H, s), 0.94 (3 H, s), 1.20–2.00 (13 H, comp), 2.32 (1 H, dd, *J* = 8.9, 6.5 Hz), 2.56 (1 H, d, *J* = 18.2 Hz), 3.49 (1 H, dd, *J* = 8.9, 6.5 Hz), 3.92 and 4.07 (2 H, AB, *J* = 17.7 Hz), 5.05 (2 H, m), 5.80 (1 H, m); high-resolution mass spectrum, *m/z* 406.2916 (M$^+$, calcd for $C_{24}H_{42}O_3Si$ 406.2929).

18b: mp 103–104 °C (hexane); $[\alpha]^{25}_D$ +68.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3070, 1695, 1630, 1100, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.039 (3 H, s), 0.059 (3 H, s), 0.82 (3 H, s), 0.89 (9 H, s), 1.10 (3 H, s), 1.12–2.42 (14 H, comp), 2.63 (1 H, dt, *J* = 13.8, 3.5 Hz), 3.51 (1 H, dd, *J* = 10.3, 5.8 Hz), 5.02 (1 H, br s), 5.07 (1 H, br s), 5.72 (1 H, m); high-resolution mass spectrum, *m/z* 388.2885 (M$^+$, calcd for $C_{24}H_{40}O_2Si$ 388.2876).

Anal. Calcd for $C_{24}H_{40}O_2Si$: C, 74.23; H, 10.31. Found: C, 74.26; H, 10.54.

32a,b: IR (CCl_4) 2950, 2875, 1765, 1650, 1475, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84, 0.86, 0.97, 1.14 (4 s, 6 H, diastereomers), 1.235, 1.244 (d, d, *J* = 6.2, 6.2 Hz, 3 H, diastereomers), 1.05–1.82 (13 H, comp), 2.02, 2.33, 2.58, 2.72 (4 d, *J* = 18.0, 18.7, 18.0, 18.7 Hz, 2 H, diastereomers), 3.10, 3.25 (dd, dd, *J* = 12.0, 3.0 Hz, *J* = 12.0, 3.0 Hz, 1 H, diastereomers), 3.91–4.30 (3 H, comp); high-resolution mass spectrum, *m/z* 292.2027 (M$^+$, calcd for $C_{18}H_{28}O_3$ 292.2039). A sample of racemic **32a,b** was recrystallized to afford pure **32a**: mp 157–158.5 °C (ether–hexanes); ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, s), 0.97 (3 H, s), 1.24 (3 H, d, *J* = 6.2 Hz), 1.05–1.82 (13 H, comp), 2.02 (1 H, d, *J* = 18.0 Hz), 2.58 (1 H, d, *J* = 18.0 Hz), 3.25 (1 H, dd, *J* = 12.0, 3.0 Hz), 3.95 (1 H, d, *J* = 17.6 Hz), 4.10 (1 H, d, *J* = 17.6 Hz), 4.24 (1 H, m).

30: $[\alpha]^{24}_D$ +0.44° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 2940, 2870, 1685, 1625, 1380, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, s), 1.09 (3 H, s), 1.25 (3 H, d, *J* = 6.2 Hz), 1.30–1.95 (9 H, comp), 2.25–2.42 (5 H, m), 2.80 (1 H, dt, *J* = 13.9, 3.3 Hz), 3.20 (1 H, dd, *J* = 12.2, 3.6 Hz), 4.28 (1 H, m); high-resolution mass spectrum, *m/z* 274.1937 (M$^+$ calcd for $C_{18}H_{26}O_2$ 274.1932).

5α-(*tert*-Butyldimethylsiloxy)-8,14-dimethyl-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14α-androst-2-enone (33) (Method A). A solution of enone **18b** (200 mg, 0.52 mmol) in tetrahydrofuran (2 mL) containing water (8.8 mg, 0.95 equiv) was added to a solution of lithium (38 mg, 5.5 mmol) in ammonia (8 mL) at −78 °C over 15 min. After stirring for an additional 10 min, the excess lithium was destroyed with isoprene. The ammonia and tetrahydrofuran were allowed to evaporate over 1.5 h, the enolate was dissolved in tetrahydrofuran (2 mL), and HMPA (1.5 mL) was added. This solution was cooled to −78 °C, and methyl iodide (10 equiv) was added rapidly. The reaction mixture was stirred for 30 min and then partitioned between ether (100 mL) and water (25 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:99) afforded 105 mg (50%) of **33** and 18 mg (9%) of **18s**, the saturated analogue of **18b**.

33: mp 78–80 °C (hexanes); $[\alpha]^{22}_D$ +32.5° (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 2955, 2925, 2850, 1710, 1630, 1460, 1410, 1385, 1360, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.040 (3 H, s), 0.057 (3 H, s), 0.80 (3 H, s), 0.88 (9 H, s), 0.95 (3 H, s), 0.99 (3 H, s), 1.22–2.40 (15 H, comp), 2.75 (1 H, m), 3.54 (1 H, dd, *J* = 8.9, 6.7 Hz), 4.95 (2 H, m), 5.74 (1 H, m); high-resolution mass spectrum, *m/z* 404.3177 (M$^+$, calcd for $C_{25}H_{44}O_2Si$ 404.3188).

18s: $[\alpha]^{23}_D$ −42.7° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2965, 2940, 2860, 1730, 1460, 1385, 1310, 1250, 1100, 1080, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.033 (3 H, s), 0.050 (3 H, s), 0.76 (3 H, s), 0.88 (9 H, s), 0.91 (3 H, s), 0.95–2.52 (17 H, comp), 3.47 (1 H, dd, *J* = 10.5, 5.6 Hz), 4.95–5.06 (2 H, m), 4.60–4.82 (1 H, m); high-resolution mass spectrum, *m/z* 390.2932 (M$^+$, calcd for $C_{24}H_{42}O_2Si$ 390.2954).

5α-Hydroxy-8,14-dimethyl-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14α-androst-2-en-15-one (34). Ketone **33** (80 mg, 0.20 mmol) was dissolved in acetonitrile (5 mL) containing ca. 3 drops of 49% aqueous HF. The solution was stirred for 2 h and then partitioned between ether (80 mL) and water (20 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:10) afforded 53.6 mg (92%) of **34**: mp 113.5–114.5 °C; $[\alpha]^{23}_D$ +15.5° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3625–3200, 2955, 1730, 1630, 1445, 1385, 1040, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, s), 0.96 (3 H, s), 1.00 (3 H, s), 1.20–2.42 (16 H, comp), 2.80 (1 H, td, *J* = 13.0, 4.7 Hz), 3.57 (1 H, m), 4.95–5.10 (2 H, m), 5.72–5.95 (1 H, m); high-resolution mass spectrum, *m/z* 291.2315 (M$^+$, calcd for $C_{19}H_{30}O_2$ 291.2324).

1,1-Ethylenedioxy-9β-methyl-*trans*-decalin-6-one (35). Ammonia (500 mL) was condensed in a three-necked round-bottomed flask equipped with a dry-ice condenser. Lithium wire

(0.78 g, 0.11 mmol) was added and allowed to dissolve over 30 min. Then a solution of enone **23b** (10 g, 0.045 mol) in tetrahydrofuran (20 mL) containing *tert*-butyl alcohol (3.3 g, 1 equiv) was slowly added over 10 min. After stirring for another 30 min, the reaction was quenched by the addition of solid ammonium chloride (1 g). The ammonia was allowed to evaporate, and the residue was partitioned between ether (200 mL) and water (70 mL). The aqueous layer was extracted again with ether, and the combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of solvent followed by flash chromatography (ethyl acetate–hexane, 1:20) afforded 8.4 g (83%) of ketone **35**: IR ($CHCl_3$) 2950, 2890, 1710, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.21–2.45 (13 H, comp), 2.82–3.95 (4 H, m).

1,1-Ethylenedioxy-9β-methyl-*trans*-decalin (36). A solution of ketone **35** (7.0 g, 0.031 mol) in triethylene glycol (100 mL) was treated with hydrazine (25 mL) and heated at 110 °C for 1.5 h. After cooling to room temperature, potassium hydroxide (11 g) was added and the excess hydrazine and water were distilled off. The reaction mixture then was heated at 200 °C for 3 h and allowed to cool to room temperature. The solution was partitioned between ether (250 mL) and water (150 mL). The aqueous phase was extracted with two 100-mL portions of ether, and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:20) gave 5.4 g (82%) of **36**: IR ($CHCl_3$) 2940, 1450, 1175, 1120, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, s), 1.10–1.80 (15 H, comp) 3.83–3.95 (4 H, m); high-resolution mass spectrum, m/z 210.1622 (M^+, calcd for $C_{13}H_{22}O_2$ 210.1620).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.30; H, 10.47. Found: C, 74.16; H, 10.53.

1-Oxo-9β-methyl-*trans*-decalin (37). Ketal **36** (6.0 g, 0.029 mol) was dissolved in tetrahydrofuran (60 mL), and 3 N hydrochloric acid (6 mL) was added. After stirring for 10 h, TLC analysis indicated that the reaction was complete. The solution then was partitioned between ether (150 mL) and water (50 mL). The aqueous phase was extracted with ether (60 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:20) furnished 4.5 g (95%) of ketone **37**: IR ($CHCl_3$) 2935, 2865, 1705, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3 H, s), 1.15–2.28 (14 H, comp), 2.58–2.75 (1 H, m); high-resolution mass spectrum, m/z 166.1364 (M^+, calcd for $C_{11}H_{18}O$ 166.1358).

(1α,4aβ,8aα)-Decahydro-8a-methyl-1-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl]-1-naphthalenol (38a) and the 1β-Isomer 38b. To a stirred solution of 3-[(tetrahydropyran-2-yl)oxy]propyne (3.1 g, 22 mmol, 1.2 equiv) in dry tetrahydrofuran (60 mL) at 0 °C was slowly added 2.2 M *n*-butyllithium (9.95 mL, 22 mmol). After being stirred for 1 h, the reaction mixture was cooled to −78 °C and a solution of ketone **37** (3.0 g, 18.3 mmol) in tetrahydrofuran (15 mL) was added over 5 min. The mixture was allowed to warm to room temperature and then was partitioned between ether (200 mL) and water (80 mL). The aqueous phase was extracted with ether (80 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was quickly purified by flash chromatography (ethyl acetate–hexane, 1:4), affording 5.0 g (90%) of alcohols **38a** and **38b**. The 250-MHz ^1H NMR spectrum indicated that the ratio of epimeric alcohols **38a** and **38b** was 6.2:1. A small sample was flash chromatographed (ethyl acetate–hexane, 1:10) to separate the stereoisomers for characterization. **38b**: IR ($CHCl_3$) 2948, 2868, 1448, 1345, 1120, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3 H, s), 1.04–2.08 (22 H, comp), 3.52 (1 H, m), 3.84 (1 H, m), 4.28 (2 H, s), 4.84 (1 H, br s); high-resolution mass spectrum, m/z 306.2196 (M^+, calcd for $C_{19}H_{30}O_3$ 306.2195).

38a: IR ($CHCl_3$) 2950, 2870, 1450, 1360, 1340, 1330, 1120, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.08–1.92 (21 H, comp), 1.98 (1 H, s), 3.52 (1 H, m), 3.75 (1 H, m), 4.34 (2 H, s), 4.88 (1 H, br s); high-resolution mass spectrum, m/z 306.2183 (M^+, calcd for $C_{19}H_{30}O_3$ 306.2195).

(5a-*trans*)-2,3,4,5,5a,6,7,8,9,9a-Decahydro-9a-methyl-1*H*-benz[*e*]inden-1-one (39). Concentrated sulfuric acid (10 mL) was slowly added to a solution of **38a,b** (4.8 g, 15.7 mmol) in methanol (10 mL) at 0 °C. After being stirred for 15 min, the mixture was diluted with ether (150 mL) and neutralized by slow addition of aqueous sodium bicarbonate. The aqueous phase was extracted with two 100-mL portions of ether, and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The black residue was chromatographed (ethyl acetate–hexane, 1:2) to furnish 356 mg (10%) of **40a,b** followed by 1.06 g (33%) of enone **39**.

40a,b: IR ($CHCl_3$) 2930, 2860, 1760, 1450, 1435, 1400, 1380, 1195 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78, 0.85 (s, s, 3 H, diastereomers), 1.05–1.90 (15 H, comp), 1.96, 2.31, 2.59, 2.80 (4 d, J = 18.1, 18.5, 18.1, 18.5 Hz, 2 H, diastereomers), 3.75, 3.87, 3.96, 4.07 (4 d, J = 9.5, 9.5, 17.7, 17.7 Hz, 2 H, diastereomers); high-resolution mass spectrum, m/z 222.1621 (M^+, calcd for $C_{14}H_{22}O_2$ 222.1620).

39: IR ($CHCl_3$) 2940, 2870, 1690, 1630, 1385, 1305, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.05–1.78 (11 H, comp), 2.28–2.45 (5 H, comp), 2.60 (1 H, d, J = 13.1 Hz); high-resolution mass spectrum, m/z 204.1514 (M^+, calcd for $C_{14}H_{20}O$ 204.1514).

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a,9b-dimethyl-1-oxo-9b*H*-benz[*e*]indene (41) (Method A). A solution of enone **39** (190 mg, 0.93 mmol) and water (15 mg, 0.83 mmol) in tetrahydrofuran (3 mL) was slowly added to a solution of lithium (36 mg) in 8 mL of ammonia at −78 °C. After stirring for 10 min, the excess lithium was destroyed with isoprene and the ammonia was evaporated under argon. The enolate then was dissolved in tetrahydrofuran (2 mL), followed by the addition of HMPA (1.5 mL). The solution was cooled to −78 °C, and excess methyl iodide was added. The reaction mixture was stirred for 30 min and then was partitioned between ether (100 mL) and water (25 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography afforded 100 mg (49%) of **41** and 13 mg (7%) of **39s**, the saturated analogue of **39**.

41: IR ($CHCl_3$) 2975, 2935, 2870, 1735, 1460, 1450, 1385, 1375, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, s), 0.98 (3 H, s), 1.05–1.75 (12 H, comp), 1.93–2.62 (6 H, comp); high-resolution mass spectrum, m/z 220.1828 (M^+, calcd for $C_{15}H_{24}O$ 220.1827).

39s: IR ($CHCl_3$) 2940, 2860, 1730, 1450, 1408, 1383, 1270, 1210, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.90–2.02 (17 H, comp), 2.15–2.47 (2 H, m); high-resolution mass spectrum, m/z 207.1742 (M^+, calcd for $C_{14}H_{22}O$ 207.1749).

(3aα,5aβ,9aα,9bβ)-Dodecahydro-9a-methyl-9b-(2-propenyl)-1-oxo-9b*H*-benz[*e*]indene (42) and (3aα,5aβ,9aα)-3,3a,4,5,5a,6,7,8,9,9a-Decahydro-9a-methyl-1-(2-propenyloxy)-2*H*-benz[*e*]indene (43). To a lithium–ammonia solution (19 mg of lithium in 4 mL of ammonia) at −78 °C was added over 5 min a solution of **39** (107 mg, 0.52 mmol) and water (9 mg, 0.50 mmol) in tetrahydrofuran (1.5 mL). After 10 min, the excess lithium was destroyed with isoprene, and the ammonia was evaporated and replaced by HMPA (1 mL). The reaction mixture was cooled to −20 °C, and allyl bromide (0.3 mL) was added. After being stirred for 30 min, the mixture was diluted with ether (30 mL) and washed with aqueous sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was quickly purified by flash chromatography (ethyl acetate–hexane, 1:50), affording 26 mg (20%) of **43**, 23 mg (18%) of **42**, and 32 mg (30%) of **39s**.

43: ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s), 0.85–2.40 (18 H, comp), 2.58 (1 H, m), 4.28 (1 H, dd, J = 5.0, 2.0 Hz), 5.16 (1 H, dd, J = 10.0, 2.0 Hz), 5.30 (1 H, dd, J = 17.0, 2.0 Hz), 5.94 (1 H, m).

42: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.00–2.68 (20 H, comp), 4.95–5.09 (2 H, m), 5.82 (1 H, m); high-resolution mass spectrum, m/z 246.1978 (M^+, calcd for $C_{17}H_{26}O$ 246.1984).

39s: IR ($CHCl_3$) 2940, 2860, 1730, 1450, 1410, 1385, 1280, 1210, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.90–1.50 (12 H, comp), 1.65 (1 H, m), 1.75–2.05 (4 H, m), 2.22 (1 H, m), 2.42 (1 H, br d, J = 13.0 Hz); high-resolution mass spectrum, m/z 207.1742 (MH^+, calcd for $C_{14}H_{23}O$ 207.1749).

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a-methyl-1-oxo-9b*H*-benz[*e*]indene-9b-acetaldehyde (44). Ketone **42** (12 mg, 0.049 mmol) was dissolved in methylene chloride (15 mL) and treatd with ozone at −78 °C. Triphenylphosphine (2.0 equiv) was added, and the reaction mixture was allowed to warm to room temperature and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:30) afforded 10 mg (83%) of aldehyde **44**: ^1H NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.10–1.70 (11 H, comp), 1.76

(1 H, m), 2.08 (1 H, m), 2.30–2.70 (6 H, m), 9.74 (1 H, apparent t, J = 2.8 Hz).

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a,9b-dimethyl-1-oxo-9b*H*-benz[*e*]indene (41). Aldehyde **44** (10 mg, 0.040 mmol) was dissolved in benzene (10 mL), Wilkinson's catalyst (2 equiv) was added, and the mixture was heated at reflux for 6 h. After filtration, the organic layer was concentrated. Flash chromatography (ethyl acetate–hexanes, 1:10) then afforded 2 mg (23%) of a product whose IR, ^{1}H NMR, and high-resolution mass spectra were identical with those of ketone **41**.

Claisen Rearrangement of 43. A solution of **43** (20 mg, 0.081 mmol) in dry benzene (10 mL) was heated to reflux overnight. The reaction mixture then was poured into water (5 mL), and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated. A 250-MHz ^{1}H NMR spectrum of the material revealed the formation of two predominant products (ca. 1:1). A methyl singlet at δ 0.84 was indicative of ketone **39s**, arising via hydrolysis, whereas a methyl singlet at δ 0.94 corresponded to ketone **42**, resulting from a Claisen rearrangement.

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a,9b-dimethyl-1-oxo-9b*H*-benz[*e*]indene (41) and the 9bβ-Isomer 45 (Method B). A solution of enone **39** (190 mg, 0.93 mmol) and water (15 mg, 0.83 mmol) in tetrahydrofuran (3 mL) was slowly added to a solution of lithium (36 mg) in ammonia (8 mL) at −78 °C. After stirring for 10 min, the excess lithium was destroyed with isoprene and the ammonia was evaporated under argon. The enolate was dissolved in tetrahydrofuran (2 mL), followed by the addition of HMPA (1.5 mL). The latter solution then was added by syringe over 5 min to a solution of methyl iodide (2 mL) and HMPA (2 mL) maintained at 50 °C. The reaction mixture was stirred for 30 min and then was poured into water (25 mL) and extracted with two 35-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude material was dissolved in methanol (20 mL) at 0 °C, and small portions of $NaBH_4$ were added until GC analysis indicated the complete reduction of any unalkylated ketone. Excess $NaBH_4$ then was destroyed by the cautious addition of water. The methanol was evaporated and the residue partitioned between ether (50 mL) and water (20 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:99) afforded 69.6 mg (34%) of **41** and 33 mg (16%) of **45**.

41: IR ($CHCl_3$) 2975, 2935, 2870, 1735, 1460, 1450, 1385, 1375, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, s), 0.98 (3 H, s), 1.05–1.75 (12 H, comp), 1.93–2.62 (6 H, comp); high-resolution mass spectrum, m/z 220.1828 (M^+, calcd for $C_{15}H_{24}O$ 220.1827).

45: IR ($CHCl_3$) 2940, 2860, 1738, 1435, 1370, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (3 H, s), 0.95 (3 H, s), 1.05–2.40 (18 H, comp); high-resolution mass spectrum, m/z 221.1900 (MH^+, calcd for $C_{15}H_{25}O$ 221.1905).

5α-(*tert*-Butyldimethylsiloxy)-8,14-dimethyl-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14α-androst-2-en-15-one (33) and the 14β-Stereoisomer 17 (Method B). A solution of **18b** (200 mg, 0.52 mmol) and water (8.8 mg, 0.95 equiv) in tetrahydrofuran (2 mL) was added to a solution of lithium (38 mg, 5.5 mmol) in ammonia (8 mL) at −78 °C over 15 min. After stirring for an additional 10 min, the excess lithium was destroyed with isoprene. The ammonia and tetrahydrofuran were allowed to evaporate over 1.5 h. The enolate was dissolved in tetrahydrofuran (2 mL), and HMPA (1.5 mL) was added. The latter solution then was added by syringe over 5 min to a solution of methyl iodide n(2 mL) in HMPA (2 mL), maintained at 50 °C. The reaction mixture was poured into water (25 mL) and extracted with two 40-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude material was dissolved in methanol (15 mL) at 0 °C, and small portions of $NaBH_4$ were added until GC analysis revealed only the presence of the two epimeric monoalkylated products. Excess $NaBH_4$ then was destroyed by the cautious addition of water. The methanol was evaporated and the residue partitioned between ether (40 mL) and water (15 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:30) afforded 66.8 mg (32%) of **33** and 30.6 mg (15%) of **17**.

33: mp 78–80 °C (hexanes); $[\alpha]^{22}_D$ +32.5° (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 2955, 2925, 2850, 1710, 1630, 1460, 1410, 1385, 1360, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.040 (3 H, s), 0.057 (3 H, s), 0.80 (3 H, s), 0.88 (9 H, s), 0.95 (3 H, s), 0.99 (3 H, s), 1.22–2.40 (15 H, comp), 2.75 (1 H, m), 3.54 (1 H, dd, J = 8.9, 6.7 Hz), 4.95 (2 H, m), 5.74 (1 H, m); high-resolution mass spectrum, m/z 404.3177 (M^+, calcd for $C_{25}H_{44}O_2Si$ 404.3188).

17: $[\alpha]^{22}_D$ −29.6° (*c* 0.67, $CHCl_3$); IR ($CHCl_3$) 2965, 2865, 1737, 1650, 1475, 1415, 1395, 1375, 1260, 1097, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.040 (3 H, s), 0.054 (3 H, s), 0.76 (3 H, s), 0.877 (3 H, s), 0.883 (9 H, s), 0.99 (3 H, s), 1.05–2.40 (16 H, comp), 3.43 (1 H, dd, J = 10.6, 5.1 Hz), 5.05 (2 H, m), 5.78 (1 H, m); high-resolution mass spectrum, m/z 404.3095 (M^+, calcd for $C_{25}H_{44}O_2Si$ 404.3080).

5α-(*tert*-Butyldimethylsiloxy)-3-hydroxy-8,14-dimethyl-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14β-androstan-15-one (47). 2-Methyl-2-butene (0.36 mL, 3.4 mmol) was dissolved in tetrahydrofuran (5 mL), 1.0 M borane–THF complex (1.8 mL, 1.8 mmol) was added, and the solution was stirred for 2.5 h at 0 °C. A solution of **17** (315 mg, 0.78 mmol) in tetrahydrofuran (3 mL) then was added. After being stirred for 1 h, the solution was treated with 3 N NaOH (1.5 mL) followed by 30% aqueous H_2O_2 (1.5 mL). The reaction mixture was stirred for 1.5 h and then partitioned between ether (80 mL) and 10% aqueous sodium bisulfite (20 mL). The aqueous phase was extracted with ether (50 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:4) afforded 58 mg (18%) of recovered starting material followed by 240 mg (73%) of alcohol **47**: mp 161–162 °C (hexane); $[\alpha]^{23}_D$ −36.4° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3620, 3550, 2950, 2860, 1730, 1475, 1465, 1405, 1390, 1360, 1255, 1110, 1090, 1075, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.018 (3 H, s), 0.044 (3 H, s), 0.76 (3 H, s), 0.86 (9 H, s), 0.90 (3 H, s), 0.99 (3 H, s), 1.05–2.32 (19 H, comp), 3.40 (1 H, dd, J = 10.7, 4.9 Hz), 3.55 (2 H, m); high-resolution mass spectrum, m/z 422.3208 (M^+, calcd for $C_{25}H_{46}O_3Si$ 422.3200).

Anal. Calcd for $C_{25}H_{46}O_3Si$: C, 71.10; H, 10.89. Found: C, 71.04; H, 10.95.

5α-(*tert*-Butyldimethylsiloxy)-8,14-dimethyl-15-oxo-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14β-androstan-3-al (48). To a solution of alcohol **47** (49 mg, 0.116 mmol) in methylene chloride (3 mL) were added pyridinium chlorochromate (90 mg, 0.42 mmol, 3.6 equiv) and 4-Å molecular sieves (0.2 g). The reaction mixture was stirred for 1 h, whereupon the mixture was diluted with ether and filtered through florisil. Evaporation of solvent afforded 46 mg (94%) of aldehyde **48**: $[\alpha]^{23}_D$ −41.2° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 2950, 2850, 1725, 1460, 1405, 1385, 1360, 1252, 1110, 1090, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.003 (3 H, s), 0.048 (3 H, s), 0.82 (3 H, s), 0.86 (9 H, s), 0.90 (3 H, s), 1.00 (3 H, s), 1.10–2.50 (18 H, comp), 3.32 (1 H, dd, J = 10.7, 5.1 Hz), 9.72 (1 H, t, J = 2.0 Hz); high-resolution mass spectrum, m/z 420.3077 (M^+, calcd for $C_{25}H_{44}O_3Si$ 420.3094).

5α-(*tert*-Butyldimethylsiloxy)-4,8,14-trimethyl-4,5-seco-18-nor-8α,9β,13α,14β-androst-3-en-15-one (49). A suspension of (ethyl)triphenylphosphonium bromide (371 mg, 1.0 mmol) in tetrahydrofuran (10 mL) was treated at 0 °C with *n*-butyllithium (1.0 mmol), and the reaction mixture was stirred for 10 min. Then a solution of aldehyde **48** (211 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added. After being stirred for 20 min, the reaction mixture was diluted with ether (60 mL) and washed with water (25 mL). The aqueous phase was extracted with ether (40 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:10) gave 175 mg (81%) of **49**; the 250-MHz ^{1}H NMR spectrum revealed an *E*:*Z* ratio of 85:15. **49**: IR ($CHCl_3$) 2945, 2850, 1725, 1455, 1400, 1382, 1355, 1250, 1110, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.025 (3 H, s), 0.048 (3 H, s), 0.74, 0.75 (s, s, 3 H, diastereomers), 0.87 (9 H, s), 0.90, 0.93 (s, s, 3 H, diastereomers), 0.99, 1.00 (s, s, 3 H, diastereomers), 1.61 (3 H, d, J = 5.4 Hz), 1.05–2.38 (18 H, comp), 3.45 (1 H, dd, J = 10.7, 5.0 Hz), 5.37 (2 H, m); high-resolution mass spectrum, m/z 432.3429 (M^+, calcd for $C_{27}H_{48}O_2Si$ 432.3435).

5α-Hydroxy-4,8,14-trimethyl-4,5-seco-18-nor-8α,9β,13α,14β-androst-3-en-15-one (16). Olefin **49** (156 mg, 0.36 mmol) was dissolved in acetonitrile and THF (1:1, 4 mL), aqueous HF (50%, 0.5 mL) was added, and the solution was stirred for 4 h. The reaction mixture then was partitioned between ether (60 mL) and water (15 mL). The aqueous phase was extracted

with ether (30 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:4) afforded 113 mg (98%) of **16**: IR ($CHCl_3$) 3600, 3450, 3000, 2940, 2860, 1730, 1450, 1405, 1388, 1235, 1025, 968, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.772, 0.780 (s, s, 3 H, diastereomers), 0.903, 0.923 (s, s, 3 H, diastereomers), 0.987, 0.997 (s, s, 3 H, diastereomers), 1.61 (3 H, d, J = 5.5 Hz), 1.15–2.40 (19 H, comp), 3.48 (1 H, m), 5.42 (2 H, m); high-resolution mass spectrum, m/z 318.2561 (M^+, calcd for $C_{21}H_{34}O_2$ 318.2563).

3aα-Acetyl-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,10α,-13α,14β-androstan-15-one (51a). A solution of **16** (104 mg, 0.33 mmol) in methylene chloride (10 mL) was treated with *m*-chloroperbenzoic acid (1.5 equiv) and stirred until TLC analysis indicated the complete consumption of **16**. A catalytic amount of camphorsulfonic or *p*-toluenesulfonic acid then was added, and the reaction mixture was stirred until TLC revealed the disappearance of the intermediate epoxides. The mixture was partitioned between ether (80 mL) and saturated sodium bisulfite (20 mL). The aqueous phase was extracted with ether (40 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude material was filtered through a small column of silica, and any residual water was removed azeotropically with benzene. The mixture of alcohols **50a,b** then was dissolved in methylene chloride (3.0 mL), and PCC (1.3 mmol) and 4-Å molecular sieves (0.5 g) were added. After being stirred for 1.5 h, the reaction mixture was diluted with ether and filtered through Florisil, furnishing 117 mg of ketones **51a,b**. Gas chromatographic analysis revealed a 2.17:1 ratio of equatorial and axial epimers.

The mixture of ketones was dissolved in methanol (10 mL) containing solid K_2CO_3. Gas chromatographic analysis indicated that equilibrium was reached after stirring for 1 h, affording a 5.6:1 mixture of **51a** and **51b**. The solvent was evaporated and the residue partitioned between ether (70 mL) and water (25 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography gave 88 mg (81%) of an 85:15 mixture of diketones. Crystallization from hexanes then furnished 53 mg (60%) of a 95:5 mixture of **51a** and **51b**: mp 150–153.5 °C (hexanes); $[\alpha]^{21}_D$ −151° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 2950, 1725, 1450, 1405, 1385, 1375, 1355, 1100, 1060, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s), 0.92 (3 H, s), 1.03 (3 H, s), 2.20 (3 H, s), 1.08–2.40 (18 H, comp), 2.94 (1 H, dd, J = 11.2, 3.8 Hz), 3.81 (1 H, dd, J = 11.1, 4.4 Hz); high-resolution mass spectrum, m/z 332.2366 (M^+, calcd for $C_{21}H_{32}O_3$ 332.2381).

3α-(1-Hydroxy-1-methylethyl)-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,10α,13α,14β-androstan-15-one (15). A solution of diketones **51a,b** (95:5 mixture, 36 mg, 0.11 mmol) in tetrahydrofuran (5 mL) was treated at −78 °C with methylmagnesium chloride (1.2 equiv). After an extraction workup, the combined organic layers were dried over magnesium sulfate and concentrated. Flash chromatography afforded 31 mg (82%) of **15**. For characterization, a sample of **15** was recrystallized: mp 149–150.5 °C (hexanes); $[\alpha]^{21}_D$ −94.5° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 3550, 2950, 1730, 1455, 1385, 1375, 1325, 1232, 1155, 1085, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.92 (3 H, s), 1.02 (3 H, s), 1.14 (3 H, s), 1.16 (3 H, s), 1.20–2.40 (18 H, comp), 2.65 (1 H, br s), 2.94 (1 H, m), 3.16 (1 H, dd, J = 11.7, 3.0 Hz); high-resolution mass spectrum, m/z 348.2673 (M^+, calcd for $C_{22}H_{36}O_3$ 348.2682).

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a,9b-dimethyl-12-(methylthio)-1*H*-benz[*e*]inden-1-one (52a) and the 2-Epimer 52b. Diisopropylamine (82 mg, 0.81 mmol, 2.4 equiv) was dissolved in tetrahydrofuran (1.5 mL), and 2.1 M *n*-butyllithium (0.38 mL, 0.80 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min, and a solution of ketone **41** (73 mg, 0.34 mmol) in tetrahydrofuran (1.5 mL) was added. After stirring for 5 min, a solution of dimethyl disulfide (0.09 mL, 1.0 mmol) in hexamethylphosphoramide (2 mL) was introduced rapidly. The reaction mixture was stirred for 15 min and then partitioned between ether (30 mL) and water (10 mL). The aqueous phase was extracted with ether (20 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:9) afforded 88 mg (97%) of a mixture of methylthio ketones **52a,b**. A 250-MHz ^1H NMR spectrum revealed a 4:1 ratio of epimers **52a** and **52b**. For characterization, ketones **52a** and **52b** were separated by chromatography (ethyl acetate–hexane, 1:99).

52a (less polar): IR ($CHCl_3$) 2930, 2875, 1725, 1445, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, s), 1.12 (3 H, s), 2.33 (3 H, s), 1.05–2.68 (16 H, comp), 3.10 (1 H, apparent t, J = 9.7 Hz); high-resolution mass spectrum, m/z 267.1723 (MH^+, calcd for $C_{16}H_{27}SO$ 267.1782).

52b: IR ($CHCl_3$) 2930, 2870, 1730, 1450, 1380, 1370, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s), 1.07 (3 H, s), 1.01–1.75 (11 H, comp), 1.90–2.12 (2 H, m), 2.15 (1 H, d, J = 4.2 Hz), 2.38 (3 H, s), 2.45–2.68 (2 H, m), 3.35 (1 H, dd, J = 11.0, 2.4 Hz); high-resolution mass spectrum, m/z 267.1722 (MH^+, calcd for $C_{16}H_{27}SO$ 267.1782).

2-(2-Aminophenyl)dodecahydro-9a,9b-dimethyl-2-(methylthio)-1*H*-benz[*e*]inden-1-one (53a,b), (3aα,5aβ,9aα,9bα)-3a,4,5,5a,6,7,8,9,9a,9b-Decahydro-9a,9b-dimethyl-2-(methylthio)-1*H*-benz[*e*]inden-1-one (54), and (3aα,5aβ,9aα,9bα)-3a,4,5,5a,6,7,8,9,9a,9b-Decahydro-9a,9b-dimethyl-2-(phenylamino)-1*H*-benz[*e*]inden-1-one (55). A solution of aniline (19 mg, 0.20 mmol) in methylene chloride (1 mL) was treated at −78 °C with a solution of *tert*-butyl hypochlorite (22 mg, 0.20 mmol) in methylene chloride (1 mL), and the reaction mixture was stirred for 5 min. A solution of **52a,b** (47 mg, 0.18 mmol) in methylene chloride (1.5 mL) was added and the reaction mixture stirred for 4 h at −78 °C. After the introduction of triethylamine (0.40 mmol), the reaction mixture was allowed to warm to room temperature, poured into water (15 mL), and extracted with two 30-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by preparative thin-layer chromatography afforded 11.6 mg (21%) of **55** (R_f = 0.5, ethyl acetate–hexane, 1:10), 10.6 mg (23%) of **54** (R_f = 0.38, ethyl acetate–hexane, 1:10), and 7.2 mg (11%) of **53a,b** (R_f = 0.34, ethyl acetate–hexane, 1:10). The ^1H NMR spectrum of **53a,b** indicated the formation of a 7:1 mixture of diastereomers.

55: IR ($CHCl_3$) 3375, 3015, 2935, 2865, 1690, 1645, 1525, 1495, 1445, 1385, 1310, 1285, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (3 H, s), 1.15 (3 H, s), 1.05–1.87 (12 H, comp), 2.15 (1 H, m), 2.64 (1 H, m), 6.22 (1 H, br s), 6.56 (1 H, d, J = 3.3 Hz), 6.92 (1 H, t, J = 7.6 Hz), 7.02–7.32 (4 H, m); high-resolution mass spectrum, m/z 310.2168 (MH^+, calcd for $C_{21}H_{28}ON$ 310.2171).

54: mp 53–55 °C (hexanes); IR ($CHCl_3$) 3010, 2985, 2930, 2870, 1690, 1585, 1450, 1380, 1280, 1230, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3 H, s), 1.12 (3 H, s), 1.02–2.68 (11 H, comp), 1.83 (1 H, m), 2.19 (1 H, m), 2.33 (3 H, s), 2.61 (1 H, m), 6.88 (1 H, d, J = 3.1 Hz); high-resolution mass spectrum, m/z 265.1537 (MH^+, calcd for $C_{16}H_{25}OS$ 265.1627).

Anal. Calcd for $C_{16}H_{24}OS$: C, 72.73; H, 9.08. Found: C, 72.73; H, 9.33.

53a,b: IR ($CHCl_3$) 3440, 3330, 2930, 2860, 1722, 1615, 1490, 1450, 1385, 1220, 1200, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72, 0.87, 0.89, 0.95 (4 s, 6 H, diastereomers), 1.08–2.10 (14 H, comp), 1.95, 2.12 (s, s, 3 H, diastereomers), 2.75 (2 H, m), 4.42, 4.59 (br s, s, 2 H, diastereomers), 6.42–7.14 (4 H, comp); high-resolution mass spectrum, m/z 358.2164 (MH^+, calcd for $C_{22}H_{32}OSN$ 358.2205).

(3aα,5aβ,9aα,9bα)-Dodecahydro-9a,9b-dimethyl-2-(phenylamino)-1*H*-benz[*e*]inden-1-one (57). Raney nickel (ca. 50 mg) was added to a solution of **53a,b** (8.9 mg, 0.025 mmol) in ethanol (2 mL), and the reaction mixture was stirred for 15 min. The mixture was filtered through Florisil and the solvent evaporated. Flash chromatography (ethyl acetate–hexanes, 1:4) afforded 6.7 mg (86%) of **57**: IR ($CHCl_3$) 3430, 3340, 3005, 2970, 2930, 2860, 1720, 1625, 1495, 1452, 1380, 1240, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.01 (3 H, s), 1.12–2.08 (13 H, comp), 2.26 (1 H, m), 2.54 (2 H, m), 3.88 (1 H, t, J = 10.0 Hz), 6.76 (2 H, br s), 7.00–7.15 (4 H, comp).

(4aα,6aβ,12bβ,12β)-1,2,3,4,4a,5,6,6a,7,12,12b,12c-Dodecahydro-12b,12c-dimethylbenz[6,7]indeno[1,2-*b*]indole (58). A solution of **57** (6.7 mg, 0.022 mmol) in chloroform (2 mL) was treated with *p*-toluenesulfonic acid (ca. 2 mg), and the reaction mixture was stirred for 2 h. The mixture was poured into water (10 mL) and extracted with two 20-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexanes, 1:4) gave 5.0 mg (79%) of **58**: IR ($CHCl_3$) 3490, 3005, 2975, 2935, 2865, 1455, 1380, 1365, 1305, 1275, 1225, 1120, 1090, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97

(3 H, s), 1.08 (3 H, s), 1.10–1.86 (12 H, comp), 2.01 (1 H, m), 2.23 (1 H, d, J = 13.8 Hz), 2.50 (1 H, m), 2.84 (1 H, dd, J = 13.8, 5.7 Hz), 7.01–7.42 (4 H, m), 7.90 (1 H, br s); high-resolution mass spectrum, m/z 294.2170 (MH^+, calcd for $C_{21}H_{28}N$ 294.2222).

(3aα,5aβ,9aα,9bβ)-Dodecahydro-9a,9b-dimethyl-2-(methylthio)-1*H*-benz[*e*]inden-1-one (59a,b). Ketone **45** was deprotonated with lithium diisopropylamide and sulfenylated with dimethyl disulfide, as in the preparation of methylthio ketones **58a** and **58b**, affording 72 mg (97%) of **59a,b**. Analysis by 250-MHz ^1H NMR revealed that the epimeric ratio was 1.4:1: IR ($CHCl_3$) 2930, 2860, 1725, 1445, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, s), 1.00, 1.04 (s, s, 3 H, diastereomers), 1.06–2.60 (16 H, comp), 2.23, 2.24 (s, s, 3 H, diastereomers), 2.94, 3.13 (dd, br d, J = 10.0, 8.2 Hz, J = 7.7 Hz, 1 H, diastereomers); high-resolution mass spectrum, m/z 266.1687 (M^+, calcd for $C_{16}H_{26}OS$ 266.1670).

2-(2-Aminophenyl)dodecahydro-9a,9b-dimethyl-2-(methylthio)-1*H*-benz[*e*]inden-1-one (60c) and the 2-Epimer 60b. A solution of aniline (21 mg, 0.23 mmol) in dry methylene chloride (1 mL) was treated at −78 °C with a solution of *tert*-butyl hypochlorite (25 mg, 0.23 mmol) in methylene chloride (0.5 mL). After stirring for 15 min, a solution of **59a,b** (55 mg, 0.21 mmol) in methylene chloride (1 mL) was added. The reaction mixture was stirred for 30 min, whereupon dry triethylamine (25 mg, 0.25 mmol) was added. The reaction mixture was allowed to warm to room temperature and then was poured into water (10 mL) and extracted with two 25-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:50) afforded 31 mg (41%) of **60a** followed by 18 mg (24%) of **60b**. **60a**: IR ($CHCl_3$) 3440, 3330, 2930, 2860, 1725, 1615, 1492, 1450, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (3 H, s), 1.34 (3 H, s), 1.05–1.91 (13 H, comp), 1.93 (3 H, s), 2.17 (2 H, m), 2.79 (1 H, dd, J = 12.6, 5.8 Hz), 4.66 (2 H, br s), 6.66 (2 H, m), 7.06 (2 H, m); high-resolution mass spectrum, m/z 357.2104 (M^+ calcd for $C_{22}H_{31}OSN$ 357.2082).

60b: IR ($CHCl_3$) 3440, 3330, 2935, 2865, 1720, 1615, 1495, 1450, 1375, 1305, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.12 (3 H, s), 1.15–1.75 (12 H, comp), 1.90 (3 H, s), 1.92–2.25 (2 H, m), 2.53 (2 H, m), 4.57 (2 H, br s), 6.62–6.68 (2 H, m), 7.04–7.13 (2 H, m); high-resolution mass spectrum, m/z 357.2100 (M^+, calcd for $C_{22}H_{31}SON$ 357.2083).

(3aα,5aβ,9aα,9bβ)-Dodecahydro-9a,9b-dimethyl-2-(phenylamino)-1*H*-benz[*e*]inden-1-one (61). Raney nickel (50 mg) was added to a solution of **60a,b** (20 mg, 0.06 mmol) in ethanol (1.5 mL), and the reaction mixture was stirred until TLC analysis indicated that the starting material had disappeared (ca. 15 min). The mixture was filtered through Florisil and concentrated, and the crude product was purified by flash chromatography (ethyl acetate–hexane, 1:10), furnishing 13 mg (75%) of **61**: IR ($CHCl_3$) 2940, 2870, 1728, 1630, 1500, 1460, 1380, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.01 (3 H, s), 1.05–1.75 (14 H, comp), 1.95–2.14 (2 H, comp), 2.38 (1 H, m), 4.26 (2 H, br s), 6.74–6.80 (2 H, m), 7.02–7.11 (2 H, m); high-resolution mass spectrum, m/z 311.2233 (M^+, calcd for $C_{21}H_{29}ON$ 311.2217).

(4aα,6aβ,12bα,12cβ)-1,2,3,4,4a,5,6,6a,7,12,12b,12c-Dodecahydro-12b,12c-dimethylbenz[6,7]indeno[1,2-*b*]indole (62). *p*-Toluenesulfonic acid (10 mg) was added to a solution of **61** (9 mg, 0.03 mmol) in methylene chloride (2.0 mL). After being stirred for 22 h, the reaction mixture was partitioned between ether and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by preparative TLC afforded 5 mg (60%) of **62**: IR ($CHCl_3$) 3470, 2930, 2850, 1450, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (3 H, s), 1.03 (3 H, s), 1.10–1.85 (14 H, comp), 2.37 (1 H, dd, J = 13.2, 10.7 Hz), 2.66 (1 H, dd, J = 13.2, 6.4 Hz), 7.04–7.45 (4 H, comp), 7.77 (1 H, br s); high-resolution mass spectrum, m/z 293.2133 (M^+ calcd for $C_{21}H_{27}N$ 293.2122).

16χ-(Methylthio)-3α-(1-hydroxy-1-methylethyl)-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,13α,14β-androstan-15-one (63ab). A solution of keto alcohol **15** (24 mg, 0.070 mmol) in tetrahydrofuran (0.2 mL) was added to a 0.25 M solution of lithium diisopropylamide in tetrahydrofuran (5 equiv, 1.4 mL) at 0 °C. The reaction mixture was stirred for 10 min, and then HMPA (1 mL) was added, followed by the addition of dimethyl disulfide (39 mg, 0.42 mmol). After being stirred for 15 min, the reaction mixture was poured into water (10 mL) and extracted with two 30-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:8) afforded 25.3 mg (92%) of **63a,b**. NMR analysis revealed the formation of a 1:1 mixture of epimers. **63a,b**: IR ($CHCl_3$) 3550, 2950, 2870, 1728, 1452, 1388, 1375, 1325, 1240, 1082, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 0.84 (s, s, 3 H, diastereomers), 0.97, 1.006, 1.014, 1.12 (4 s, 6 H, diastereomers), 1.05–2.20 (21 H, comp), 2.22, 2.24 (s, s, 3 H, diastereomers), 2.47 (1 H, m), 2.62, 2.64 (br s, br s, 1 H, diastereomers), 2.90–3.22 (3 H, m); high-resolution mass spectrum, m/z 394.2544 (M^+, calcd for $C_{23}H_{38}O_3$ 394.2549).

16χ-(2-Aminophenyl)-3α-(1-hydroxy-1-methylethyl)-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,10α,13α,14β-androstan-15-one (65). A solution of aniline (0.27 mL, 0.25 M in methylene chloride, 0.061 mmol) was treated at −78 °C with *tert*-butyl hypochlorite (0.27 mL of a 0.25 M solution in methylene chloride), and the reaction mixture was stirred for 15 min. A solution of **63a,b** (24 mg, 0.0607 mmol) in methylene chloride (0.3 mL) then was added, and the mixture was stirred for 1 h, followed by the addition of triethylamine (3 equiv). The reaction mixture was allowed to warm to room temperature, poured into water (10 mL), and extracted with two 25-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexanes, 1:4) then furnished 28 mg of product. Analysis by 250-MHz ^1H NMR revealed that the product mixture contained ca. 72% of the epimeric methylthio keto anilines **64a,b** (1.6:1), along with 28% starting material.

The mixture was dissolved in ethanol (2 mL), and Raney nickel (ca. 100 mg) was added. After being stirred for 30 min, the reaction mixture was filtered through Florisil and the solvent was evaporated. Purification by flash chromatography (ethyl acetate–hexanes, 1:2) afforded 2.2 mg of keto alcohol **15**, followed by 12.5 mg (47%) of keto aniline **65**: mp 214–216 °C (ether); $[\alpha]^{24}_D$ +122.1° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 3550, 3420, 3330, 2950, 2870, 1725, 1650, 1495, 1455, 1395, 1375, 1150, 1090, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s), 0.98 (3 H, s), 1.11 (3 H, s), 1.15 (3 H, s), 1.17 (3 H, s), 1.20–2.19 (19 H, comp), 2.36 (1 H, m), 2.63 (1 H, br s), 2.94 (1 H, m), 3.16 (1 H, dd, J = 11.2, 2.0 Hz), 3.53 (1 H, apparent t, J = 9.5 Hz), 4.20 (2 H, br s); high-resolution mass spectrum, m/z 439.3087 (M^+, calcd for $C_{28}H_{41}O_3N$ 439.3088).

(−)-Paspaline (1). To a solution of **65** (8.0 mg, 0.018 mmol) in methylene chloride (2 mL) was added *p*-toluenesulfonic acid (1 mg). After being heated to reflux for 18 h, the solution was poured into water (10 mL) and extracted with two 20-mL portions of ether. The organic layer was dried over magnesium sulfate and concentrated. Flash chromatography (ethyl acetate–hexane, 1:4) furnished 6.3 mg (83%) of (−)-paspaline (**1**) as a white solid, followed by 1.0 mg (12.1%) of recovered starting material. Synthetic (−)-paspaline: mp 238–240 °C (hexanes–ether); $[\alpha]^{21}_D$ −42.2° (*c* 0.64, benzene); IR ($CHCl_3$) 3550, 3470, 3320, 2980, 2950, 2850, 1450, 1385, 1375, 1330, 1300, 1260, 1240, 1160, 1090, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s), 1.02 (3 H, s), 1.13 (3 H, s), 1.17 (3 H, s), 1.19 (3 H, s), 1.25–2.04 (13 H, comp), 2.32 (1 H, dd, J = 12.7, 10.4 Hz), 2.62–2.85 (3 H, comp), 3.03 (1 H, dd, J = 11.3, 4.2 Hz), 3.21 (1 H, dd, J = 11.8, 3.0 Hz), 7.06–7.09 (2 H, m), 7.26–7.31 (1 H, m), 7.40–7.44 (1 H, m), 7.74 (1 H, br s); high-resolution mass spectrum, m/z 421.2997 (M^+, calcd for $C_{28}H_{39}O_2N$ 421.3013).

5α-(*tert*-Butyldimethylsiloxy)-3-hydroxy-8,14-dimethyl-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14α-androstan-15-one (66). 2-Methyl-2-butene (4.2 mmol) was dissolved in dry tetrahydrofuran (2 mL) at 0 °C, a solution of borane–THF (2.1 mmol) was added, and the reaction mixture was stirred for 2 h. A solution of **33** (1.05 mmol) in tetrahydrofuran (2 mL) then was introduced. After stirring for 1 h, 3 N NaOH (1.4 mL) was added slowly, followed by 30% aqueous H_2O_2 (1.4 mL). The reaction mixture was stirred for 0.5 h and then was partitioned between ether and aqueous sodium bisulfite (10%). The ether layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was chromatographed (ethyl acetate–hexane, 1:2), furnishing 399 mg (90%) of alcohol **66**: mp 140–141 °C (hexanes); $[\alpha]^{24}_D$ +5.56° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3625, 1725, 1462, 1387, 1265, 1108, 1095, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.009 (3 H, s), 0.037 (3 H, s), 0.78 (3 H, s), 0.85 (9 H, s), 0.95 (3 H, s), 0.98 (3 H, s), 1.22–2.40 (18 H, comp), 2.74 (1 H, m), 4.50–6.80 (3 H, comp).

Anal. Calcd for $C_{25}H_{46}O_3Si$: C, 71.10; H, 10.89. Found: C, 71.10; H, 11.04.

5α-(*tert*-Butyldimethylsiloxy)-8,14-dimethyl-15-oxo-3,5-seco-*A*,18-dinor-8α,9β,10α,13α,14α-androstan-3-al (67). A mixture of methylene chloride (10 mL), chromium trioxide (6.0 mmol), and dry pyridine (12.0 mmol) was stirred under argon for 0.5 h. A solution of alcohol **66** (423 mg, 1.0 mmol) in methylene chloride (2 mL) then was added in one portion, and the reaction mixture was stirred for 1 h. The dark suspension was diluted with ether (40 mL) and washed successively with 5% aqueous NaOH (w/v), 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Drying over magnesium sulfate, evaporation of solvent, and purification via flash chromatography (ethyl acetate–hexane, 1:10) gave 357 mg (85%) of aldehyde **67**: $[\alpha]^{24}_D$ −6.18° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2950, 2925, 2850, 1725, 1450, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.002 (3 H, s), 0.048 (3 H, s), 0.84 (3 H, s) 0.86 (9 H, s), 0.96 (3 H, s), 0.99 (3 H, s), 1.05–2.41 (17 H, comp), 2.68 (1 H, m), 3.43 (1 H, apparent t, *J* = 8.0 Hz), 9.70 (1 H, br s); high-resolution mass spectrum, *m/z* 420.3150 (M^+, calcd for $C_{25}H_{44}O_3Si$ 420.3138).

5α-(*tert*-Butyldimethylsiloxy)-4,8,14-trimethyl-4,5-seco-18-nor-8α,9β,13α,14α-androst-3-en-15-one (68). A suspension of (ethyl)triphenylphosphonium bromide (707 mg, 1.9 mmol) in tetrahydrofuran (10 mL) was treated at 0 °C with *n*-butyllithium (0.76 mL, 1.9 mmol, 2.5 M). The resultant orange mixture was stirred for 15 min, and a solution of keto aldehyde **67** (400 mg, 0.95 mmol) in tetrahydrofuran (4 mL) was added. The mixture was stirred for 15 min and then was diluted with ether (80 mL) and washed with water (20 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate–hexane, 1:50) afforded 349 mg (85%) of keto olefin **68**: IR ($CHCl_3$) 2925, 1725, 1450, 1380, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.025 (3 H, s), 0.048 (3 H, s), 0.77, 0.78 (s, s, 3 H, diastereomers), 0.86 (9 H, s), 0.95, 0.96 (s, s, 3 H, diastereomers), 0.99 (3 H, s), 1.05–2.42 (20 H, comp), 2.75 (1 H, m), 3.55 (1 H, apparent t, *J* = 8.0 Hz), 5.32 (2 H, m); high-resolution mass spectrum, *m/z* 432.3510 (M^+, calcd for $C_{27}H_{48}O_2Si$ 432.3518).

5α-Hydroxy-4,8,14-trimethyl-4,5-seco-18-nor-8α,9β,13α,14α-androst-3-en-15-one (69). Silyl alcohol **68** (267 mg, 0.62 mmol) was dissolved in acetonitrile (10 mL), and 49% (v/v) aqueous hydrogen fluoride (0.5 mL) was added. After being stirred for 1 h, the solution was diluted with ether (60 mL) and washed with water. The aqueous phase was extracted with ether (40 mL), and the organic layers were combined, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. Flash chromatography (ethyl acetate-hexane, 1:4) furnished 187 mg (95%) of **69**: IR ($CHCl_3$) 2925, 1725, 1450, 1380, 1050, 1040, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.98 (3 H, s), 1.01 (3 H, s), 1.20–2.45 (21 H, comp), 2.84 (1 H, apparent dt, *J* = 12.0, 5.0 Hz), 3.61 (1 H, dd, *J* = 10.8, 5.1 Hz), 5.38 (2 H, m); high-resolution mass spectrum, *m/z* 318.2623 (M^+, calcd for $C_{21}H_{34}O_2$ 318.2637).

3aα-Acetyl-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,10α,13α,14α-androstan-15-one (71). A solution of keto alcohol **69** (187 mg, 0.59 mmol) in methylene chloride (12 mL) was treated with *m*-chloroperbenzoic acid (122 mg, 0.7 mmol, 12.2 equiv). After stirring for 1.5 h, a catalytic amount of *p*-toluenesulfonic acid was added and the solution was stirred for an additional 30 min. The reaction mixture then was diluted with ether, washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the crude product was filtered through a short column of silica. The solvent was again removed, and the reaction products **70a,b** were dissolved in methylene chloride (3 mL). The solution was added in one portion to a solution of CrO_3·2Pyr (6 equiv) in methylene chloride (6 mL), and the reaction mixture was stirred for 1 h. The resultant dark suspension was diluted with ether (30 mL), washed successively with 5% aqueous NaOH, 5% HCl, $NaHCO_3$, and brine, and dried over magnesium sulfate. After removal of solvent, analysis by TLC and ^1H NMR revealed the presence of two epimeric diketones **71** (α:β ratio = 1.5:1). The mixture was treated with K_2CO_3 in methanol (15 mL) for 2 h. The solvent was removed and the product mixture filtered through a plug of silica, affording 137 mg (70%) of diketone **71**: $[\alpha]^{24}_D$ −97° (*c* 1.0, benzene); IR ($CHCl_3$) 2950, 1730, 1720, 1460, 1395, 1365, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, s), 0.98 (3 H, s), 1.04 (3 H, s), 2.21 (3 H, s), 1.05–2.60 (17 H, comp), 2.87 (1 H, m), 3.10 (1 H, dd, *J* = 10.2, 5.3 Hz), 3.83 (1 H, dd, *J* = 11.2, 4.3 Hz); high-resolution mass spectrum, *m/z* 332.2462 (M^+, calcd for $C_{21}H_{32}O_3$ 332.2429).

3α-(1-Hydroxy-1-methylethyl)-8,14-dimethyl-18-nor-4-oxa-5α,8α,9β,10α,13α,14α-androstan-15-one (72). A solution of diketone **71** (120 mg, 0.36 mmol) in dry tetrahydrofuran (5 mL) was treated at 0 °C with 2.8 M methylmagnesium chloride (0.14 mL, 1.1 equiv). After being stirred for 10 min, the reaction mixture was quenched with water (5 mL) and extracted with two 25-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:2) gave 113 mg (90%) of keto alcohol **72**: $[\alpha]^{24}_D$ −36.9° (*c* 1.5, benzene); IR ($CHCl_3$) 3550, 1725, 1450, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s), 0.98 (3 H, s), 1.03 (3 H, s), 1.14 (3 H, s), 1.17 (3 H, s), 1.23–2.46 (17 H, comp), 2.65 (1 H, s), 2.85 (1 H, m), 3.08 (1 H, dd, *J* = 9.0, 6.4 Hz), 3.18 (1 H, dd, *J* = 11.7, 3.0 Hz); high-resolution mass spectrum, *m/z* 348.2632 (M^+, calcd for $C_{22}H_{36}O_3$ 348.2664).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.87; H, 10.34. Found: C, 75.92; H, 10.53.

16χ-(Methylthio)-3α-(1-hydroxy-1-methylethyl)-8,14-dimethyl-18-nor-4-oxa-5β,8α,9β,10α,13α,14α-androstan-15-one (73). Diisopropylamine (0.137 mL, 0.98 mmol) was dissolved in dry tetrahydrofuran (1 mL), and 2.5 M *n*-butyllithium (0.39 mL, 0.98 mmol) was added at 0 °C. The reaction mixture was stirred for 15 min, whereupon a solution of keto alcohol **72** (85 mg, 0.24 mmol) in tetrahydrofuran (2.5 mL) was introduced. After stirring for 10 min, dry HMPA (2 mL) was added, followed by rapid addition of dimethyl disulfide (1.22 mmol, 5 equiv). The mixture then was stirred for 15 min, poured into water (15 mL), and extracted with two 30-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexane, 1:4) gave 93 mg (97%) of **73** as an inseparable mixture of isomers. ^1H NMR analysis indicated that the isomer ratio was 4.3:1: IR ($CHCl_3$) 2980, 2950, 1725, 1450, 1385, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, s), 0.99 (3 H, s), 1.08 (3 H, s), 1.11 (3 H, s), 1.14 (3 H, s), 1.15–2.10 (15 H, comp), 2.310, 2.314 (s, s, 3 H, diastereomers), 2.61 (1 H, s), 2.70–3.38 (4 H, comp); high-resolution mass spectrum, *m/z* 395.2606 (MH^+, calcd for $C_{23}H_{39}O_3S$ 395.2620).

C(12b)-Epipaspaline (77). A solution of aniline (11 mg, 0.11 mmol) in dry methylene chloride (1.0 mL) was treated at −78 °C with *tert*-butyl hypochlorite (12 mg, 0.11 mmol), and the reaction mixture was stirred for 15 min. A solution of methylthio ketone **73** (45 mg, 0.11 mmol) in dry methylene chloride (0.5 mL) was added, and the solution was stirred for 1.5 h. After the introduction of triethylamine (17 mg, 0.17 mmol), the solution was stirred for 30 min and then allowed to warm to room temperature. The mixture was poured into ether (30 mL) and washed with water (10 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography afforded 11 mg (32%) of pure enone **75**: $[\alpha]^{23}_D$ −50° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1690, 1450, 1385, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.10 (3 H, s), 1.12 (3 H, s), 1.136 (3 H, s), 1.138 (3 H, s), 1.15 (3 H, s), 1.20–1.63 (8 H, comp), 2.15 (1 H, m), 2.33 (3 H, s), 2.60–2.70 (3 H, comp), 2.90 (1 H, apparent t, *J* = 6.5 Hz), 3.12 (1 H, dd, *J* = 11.4, 2.9 Hz), 6.85 (1 H, d, *J* = 3.4 Hz); high-resolution mass spectrum, *m/z* 392.2392 (M^+, calcd for $C_{23}H_{36}O_3S$ 392.2399).

The remaining product mixture containing **74a,b** was then dissolved in ethanol, and Raney nickel (ca. 150 mg) was added. The reaction was complete after 15 min, as indicated by TLC. The mixture was filtered through Florisil, the solvents were evaporated, and the resultant material was quickly purified by flash chromatography (ethyl acetate–hexane, 1:4), furnishing 4 mg (8.3%) of keto aniline **76**. The latter was immediately exposed to a catalytic amount of *p*-toluenesulfonic acid in ethanol (5 mL) for 5 h. The reaction mixture was partitioned between water (10 mL) and ether (20 mL). Concentration of the organic layer and flash chromatography (ethyl acetate-hexane, 1:4) gave 2.2 mg (5%) of epipaspaline (**77**): $[\alpha]^{23}_D$ −67° (*c* 0.13, benzene); IR ($CHCl_3$) 3485, 3015, 2945, 2865, 1455, 1385, 1375, 1225, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, s), 1.09 (3 H, s), 1.15 (3 H, s), 1.16 (3 H, s), 1.17 (3 H, s), 1.20–2.10 (13 H, comp), 2.25 (1 H, d, *J* = 14.0 Hz),

2.50 (1 H, m), 2.64 (1 H, s), 2.83 (1 H, dd, J = 14.0, 5.5 Hz), 3.01 (1 H, m), 3.15 (1 H, dd, J = 11.7, 3.0 Hz), 7.05–7.15 (2 H, m), 7.30–7.50 (2 H, m), 7.87 (1 H, br s); high-resolution mass spectrum, m/z 422.3047 (MH^+, calcd for $C_{28}H_{40}O_2N$ 422.3058).

3β-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-5α-androstan-17-one (i). To a solution of dihydropyran (162 mg, 1.92 mmol) in methylene chloride (8 mL) was added epiandrosterone (400 mg, 1.4 mmol, Aldrich), followed by a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred for 30 min and quenched with triethylamine (0.5 mL). The solution was partitioned between water (20 mL) and ether (30 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (ethyl acetate–hexanes, 1:4) afforded 474 mg (92%) of i: IR ($CHCl_3$) 2940, 2845, 1730, 1450, 1130, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.85 (3 H, s), 0.60–2.48 (28 H, comp), 3.40–3.62 (2 H, m), 3.88 (1 H, m), 4.70 (1 H, br s).

16χ-(Methylthio)-3β-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5α-androstan-17-one (iii). At 0 °C a solution of diisopropylamine (138 mg, 3 equiv) in tetrahydrofuran (2 mL) was treated with *n*-butyllithium (3 equiv), and the reaction mixture was stirred for 15 min. A solution of ketone i (170 mg, 0.45 mmol) in tetrahydrofuran (1.5 mL) was added, followed by the addition of HMPA (2 mL). Dimethyl disulfide (210 mg, 5 equiv) was immediately introduced, and after being stirred for 15 min, the reaction mixture was poured into ether (20 mL). The solution was washed with two 5-mL portions of water, washed with brine, and dried over magnesium sulfate. Concentration and flash chromatography (ethyl acetate–hexanes, 1:4) gave 187 mg (98%) of iii. The 250-MHz ^1H NMR spectrum revealed an epimer ratio of 2:1. iii: IR ($CHCl_3$) 2915, 2860, 1730, 1455, 1445, 1370, 1350, 1130, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81, 0.88, 0.97 (3 s, 6 H, diastereomers), 0.70–1.92 (26 H, comp), 2.23, 2.26 (s, s, 3 H, diastereomers), 2.98, 3.35 (apparent t, d, J = 9 Hz, J = 8.4 Hz, 1 H, diastereomers), 3.40–3.62 (2 H, m), 3.88 (1 H, m), 4.70 (1 H, br s); high-resolution mass spectrum, m/z 420.2707 (M^+, calcd for $C_{25}H_{40}O_3S$ 420.2698).

(3β,5α)-16-(Methylthio)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-3′*H*-androstano[17,16-*b*]indole (iv-a) and Its 16-Epimer iv-b. To a solution of aniline (42.5 mg, 0.46 mmol) in methylene chloride (1 mL) at −78 °C was added 1.8 mL of a 0.25 M solution of *tert*-butyl hypochlorite (0.45 mmol) in methylene chloride. After stirring for 10 min, a solution of iii (160 mg, 0.38 mmol) in methylene chloride (2 mL) was added. The reaction mixture was stirred for 1 h, triethylamine (54 mg, 0.53 mmol) was introduced, and the solution was allowed to warm to room temperature. The reaction mixture then was partitioned between water (15 mL) and ether (20 mL). The aqueous phase was extracted with ether (10 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash chromatography (1:4 ethyl acetate–hexane) afforded 158 mg (84%) of iv-a,b. The 250-MHz ^1H NMR spectrum revealed an epimer ratio of 1.9:1. iv-a,b: IR ($CHCl_3$) 2995, 2940, 2845, 1605, 1485, 1470, 1450, 1125, 1070, 1020, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60, 0.77, 0.80, 0.98 (4 s, 6 H, diastereomers), 0.70–2.20 (28 H, comp), 3.40–3.65 (2 H, m), 3.90 (1 H, m), 4.12 (1 H, m), 4.70 (1 H, br s), 6.45–7.40 (4 H, m); high-resolution mass spectrum, m/z 493.3004 (M^+, calcd for $C_{31}H_{43}O_2NS$ 493.3014).

(3β,5α)-3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-1′*H*-androst-16-eno[17,16-*b*]indole (ii). Raney nickel (ca. 10 mg) was added to a solution of methylthio imines iv-a,b (15 mg, 0.03 mmol) in methanol (1 mL). After being stirred for 10 min, the mixture was diluted with ether and filtered through a short plug of Florisil. Concentration and flash chromatography afforded 9.5 mg (70%) of indole ii: IR ($CHCl_3$) 3475, 2960, 2940, 1470, 1450, 1300, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, s), 0.98 (3 H, s), 0.78–1.95 (23 H, comp), 2.04 (1 H, m), 2.31 (1 H, dd, J = 13.4, 10.8 Hz), 2.72 (1 H, dd, J = 13.4, 6.2 Hz), 3.46–3.60 (2 H, m), 3.92 (1 H, m), 4.72 (1 H, br s), 7.00–7.10 (2 H, m), 7.30 (1 H, m), 7.45 (1 H, m), 7.85 (1 H, br s); high-resolution mass spectrum, m/z 447.3151 (M^+, calcd for $C_{30}H_{41}O_2N$ 447.3137).

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