Notes

A Concise Route to 19-Nor-10-azasteroids, a New Class of Steroid 5α-Reductase Inhibitors. 3.[1] Synthesis of (+)-19-Nor-10-azatestosterone and (+)-17*β*-(Acetyloxy)-(5*β*)-10-azaestr-1-en-3-one

Antonio Guarna,* Ernesto G. Occhiato, Fabrizio Machetti, and Dina Scarpi

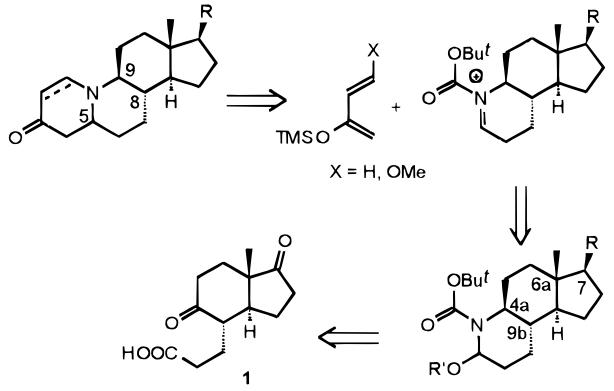
Dipartimento di Chimica Organica "U. Schiff" and Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, C.N.R., Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy

Received October 16, 1997

The enzyme steroid 5α-reductase (E. C. 1.3.99.5) is a system of two NADPH-dependent membrane bound isoenzymes (5αR-1 and 5αR-2) that catalyzes the conversion of testosterone (T) to dihydrotestosterone (DHT) in many androgen-sensitive cells.[2] DHT has an established role in the development of human benign prostatic hyperplasia (BPH),[3] whose incidence in the aging male population is very high. Male pattern baldness,[4] acne,[5] alopecia in man,[6] and hirsutism in woman[7] are also related to DHT formation. Thus, in the past decade, great efforts have been made toward the synthesis of 5α-reductase inhibitors, which by reducing the level of DHT in the target tissues, could be used as drugs for the pharmacological treatment of the above androgen-dependent disorders.[3b,8] This work has led to the discovery, among the others, of two classes of inhibitors based on the steroidal structure of testosterone modified through the introduction of a nitrogen atom in the A (4-azasteroids) or B ring (6-azasteroids).[3b,8,9]

Recently, we have reported on the synthesis and biological evaluation of a novel class of potent azasteroidal inhibitors (19-nor-10-azasteroids) having as a new feature a bridgehead nitrogen atom at position 10 of the steroidal skeleton.[1] We based the synthesis of these compounds on the sequential rearrangement-cyclization of isoxazoline-5-spirocyclopropanes, a methodology well established in our laboratory, which allows the incorporation of a 4-pyridone moiety in a polycyclic system.[1a,10] However, the preparation of the suitably functionalized isoxazolines required several synthetic steps, and moreover, the final thermal rearrangements always gave the azasteroids in low yield and in mixture with other products. Therefore, owing to the need of a more efficient procedure for the preparation of 10-azasteroids, we planned a new strategy based on the tandem *N*-(acyloxy)-iminium ion−Michael addition reaction, recently described by Pilli and co-workers for the synthesis of bicyclic *N*-bridgehead alkaloids,[11] which should provide the 19-nor-10-azasteroidal skeleton in only six steps from commercially available (+)-3-[(3a*S*)-(3aα,4α,7a*β*)-1,5-dioxo-7a-methyloctahydro-(1*H*)-inden-4-yl]propionic acid (**1**).[12] The key step of the retrosynthesis (Scheme 1) is the construction of the A ring of the azasteroid, which could be formed by reaction of the *N*-(acyloxy)iminium ion with a silyloxy diene in the presence of a Lewis acid. The use of Danishefsky's diene (X = OMe)[13] should directly lead to a compound having an unsaturation in the A ring.[14] The iminium ion can be generated in situ through the action of a Lewis acid on the *N*-*t*-Boc-3-alkoxy-substituted precursor. Acid **1**, which is obtained from the microbial degradation of sterols present in the soya bean, maintains

Scheme 1



1

* To whom correspondence should be addressed. Tel.: 0039-55-2757611. Fax: 0039-55-2476964. E-mail: guarna@chimorg.unifi.it.

(1) (a) Guarna, A.; Belle, C.; Machetti, F.; Occhiato, E. G.; Payne, H. P.; Cassiani, C.; Comerci, A.; Danza, G.; De Bellis, A.; Dini, S.; Marrucci, A.; Serio, M. *J. Med. Chem.* **1997**, *40*, 1112−1129. (b) Guarna, A.; Occhiato, E. G.; Machetti, F.; Marrucci, A.; Danza, G.; Serio, M.; Paoli, P. *J. Med. Chem.* **1997**, *40*, 3466−3477.

(2) (a) Russell, D. W.; Wilson, J. D. *Annu. Rev. Biochem.* **1994**, *63*, 25−61. (b) Wilson, J. D.; Griffin, J. E.; Russell, D. W. *Endocrine Rev.* **1993**, *14*, 577−593.

(3) (a) Geller, J. *J. Am. Geriatr. Soc.* **1991**, *39*, 1208−1266. (b) Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293−1314 and references therein.

(4) Dallob, A. L.; Sadick, N. S.; Unger, W.; Lipert, S.; Geissler, L. A.; Gregoire, S. L.; Nguyen, H. H.; Moore, E. C.; Tanaka, W. K. *J. Clin. Endocrinol. Metab.* **1994**, *79*, 703−706.

(5) Smith, L. S.; Tegler, J. J. *Annu. Rep. Med. Chem.* **1989**, *24*, 177−186.

(6) Gadwood, R. C.; Fiedler, V. C. *Annu. Rep. Med. Chem.* **1989**, *24*, 187−196.

(7) Brooks, J. R. *Clin. Endocrinol. Metabol.* **1986**, *15*, 391−405.

(8) (a) Holt, D. A.; Levy, M. A.; Metcalf, B. W. Inhibition of Steroid 5α-Reductase. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; JAI Press Inc: Greenwich, CT, 1993; Vol. 2, pp 1−29. (b) Abell, A. D.; Henderson, B. R. *Curr. Med. Chem.* **1995**, *2*, 583−597. (c) Li, X.; Chen, C.; Singh, S.; Labrie, F. *Steroids* **1995**, *60*, 430−441. (d) Frye, S. V. *Curr. Pharm. Des.* **1996**, *2*, 59−84.

(9) (a) Geller, J. *J. Clin. Endocrinol. Metab.* **1990**, *71*, 1552−1555. (b) Stoner E. *J. Steroid Biochem. Mol. Biol.* **1990**, *37*, 375−378.

(10) (a) Brandi, A.; Cordero, F. M.; De Sarlo; F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8. (b) Occhiato, E. G.; Guarna, A.; Brandi, A.; Goti, A.; De Sarlo, F. *J. Org. Chem.* **1992**, *57*, 4206−4211. (c) Belle, C.; Cardelli, A.; Guarna; A. *Tetrahedron Lett.* **1991**, *32*, 6395−6398.

(11) (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717−722. (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729−2732. (c) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213−2229.

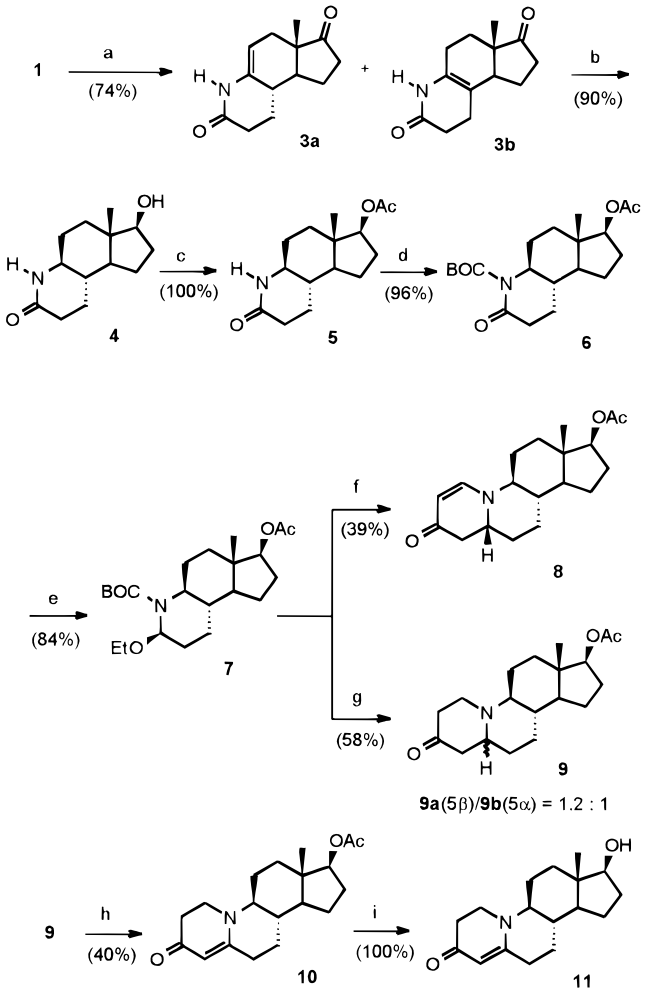
(12) Biggs, C. B.; Pyke, T. R.; Wovcha, M. G. (Upjohn Co.) U.S. Pat. 4 062 729, 1977; *Chem. Abstr.* **1978**, *88*, 188129t.

(13) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808.

(14) The conjugation between the N atom and the 3-oxo group through a double bond in the A ring is an essential feature for the biological activity of 19-nor-10-azasteroids (ref 1a).

S0022-3263(97)01917-8 CCC: $15.00
Published on Web 05/14/1998

Scheme 2[a]



[a]Key: (a) HCOOH, NH_4HCO_3, 120 °C, 1 h; **3a**:**3b** = 19:1; (b) $NaBH_3CN$, MeOH, pH 1.5−2, 48 h; (c) Ac_2O, pyridine, 25 °C, 48 h; (d) Boc_2O, Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, reflux, 13 h; (e) $LiEt_3BH$, THF, −78 °C, 15 min; then 2 N HCl, EtOH, −78 → 0 °C, 30 min; (f) 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene, Et_3N, TMSOTf, CH_2Cl_2, 0 → 25 °C, 45 min; then $NaHCO_3$, 25 °C, 36 h; (g) methyl vinyl ketone, TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 30 min; then **7**, TMSOTf, 0 → 25 °C, 45 min; then $NaHCO_3$, 25 °C, 36 h; (h) $Hg(OAc)_2$, EDTA tetrasodium salt, 20% AcOH, 90 °C, 2 h; (i) KOH, MeOH−H_2O, 25 °C, 5 h.

the steroidal configuration of the C and D rings, and therefore, it appeared to us as the ideal starting material for the preparation of the 3-alkoxy carbamate compound.

To ascertain if this strategy could represent a new general method for the preparation of 19-nor-10-azasteroids, we applied the above reaction sequence to the synthesis, reported herein, of enantiopure (+)-17β-hydroxy-10-azaestr-4-en-3-one [or (+)-19-nor-10-azatestosterone] (**11**)[15] and (+)-17β-(acetyloxy)-(5β)-10-azaestr-1-en-3-one (**8**) (Scheme 2).

The first step of the synthesis was a Leuckart reaction on keto acid **1**, which, in analogy to the results reported by Bertin et al.,[15] should provide as a main product saturated lactam **2a** (Figure 1), with the correct trans fusion of the C-4a, C-9b ring junction, in mixture with its 4aβ isomer **2b**. However, when compound **1** was

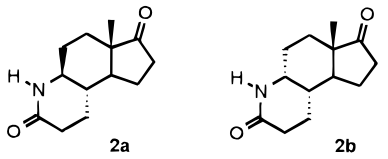


Figure 1.

heated at 120 °C in a mixture of NH_4HCO_3 and formic acid, only enelactam **3** (74%, as a 19:1 mixture of **3a** and **3b**, respectively) was obtained (Scheme 2) instead of the expected saturated compounds **2a**,**b**. This was probably due to the insolubility of **3** in hot formic acid, which prevented, even prolonging the reaction time, the subsequent reduction process to give **2**.

Since it has been observed that acidic hydride reduction of steroidal enelactams to lactams occurs with α selectivity,[16] the reduction of the double bond in **3a**, obtained in pure form by recrystallization from methanol, was performed by treating the enelactam with $NaBH_3$-CN in MeOH at pH 1.5−2. After 48 h, the reduction was complete, affording known alcohol **4**[15] having 4aα stereochemistry (Scheme 2). The same result was obtained using the 19:1 mixture of **3a** and **3b**, which therefore, can be used directly for the reduction step without separation of the isomers. Monitoring the reaction, the α reduction of the carbonyl group readily occurred, whereas the enelactam reduction was slower. The control of pH was crucial in this reaction, since a slight increase up to pH 3 reduced the reduction rate considerably.

Protection of the 7β-OH group in **4** as acetate was quantitatively achieved by treatment with Ac_2O in pyridine at room temperature, and following the strategy depicted in Scheme 1, protection of the N atom as *N*-*t*-Boc was accomplished by refluxing in CH_2Cl_2 a mixture of **5**, di-*tert*-butyl dicarbonate (Boc_2O), and Et_3N in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), providing after 13 h compound **6** in 96% yield.[17]

3-Ethoxy carbamate **7** was obtained as a single epimer in 84% yield by treatment of *N*-*t*-Boc-amide **6** with 2 equiv of $LiEt_3BH$ (Super-Hydride) in THF at −78 °C, followed by the addition of a 2 N HCl anhydrous solution in EtOH up to pH 4.[18] This procedure provided **7** in higher yield than that obtained by reduction of **6** with $NaBH_4$/HCl in cold ethanol[11] and, moreover, overreduction of the *N*-*t*-Boc amide did not take place. In the ^1H NMR spectrum of **7**, the proton on C-3 resonates at 5.41 ppm as a broad doublet (J = 9.0 Hz) reasonably due to a major trans diaxial coupling constant with one of the protons on C-2. The other vicinal J of 3-H is instead close to zero, suggesting an axial−equatorial relationship. These data are therefore consistent with the equatorial position of the ethoxy group.

The construction of the A ring was performed by the tandem *N*-(acyloxy)iminium ion−Michael reaction[11] of ethoxy derivative **7** with the appropriate silyloxy diene. For the synthesis of unsaturated compound **8** (Scheme 2), trimethylsilyl triflate (TMSOTf) was added to a

(15) Apart from the synthesis reported by us in ref 1a, only one synthesis of **11** has been reported so far: Bertin, D.; Perronet, J. *Bull. Soc. Chem. Fr.* **1969**, 117−122.

(16) Miller, R. A.; Humphrey, G. R.; Thompson, A. S. *Tetrahedron Lett.* **1995**, *36*, 7949−7952 and references therein.

(17) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

(18) Fischer, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447−1459.

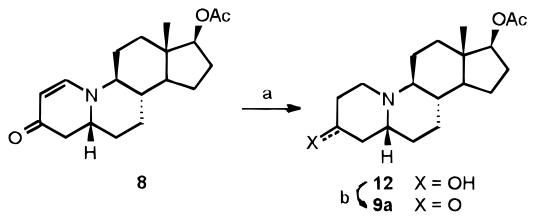
mixture of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene), Et_3N, and **7** at 0 °C in CH_2Cl_2, leading, after a 36 h $NaHCO_3$ treatment, to azasteroid **8** (39%)[19] as a single diastereoisomer. Since the enaminone moiety in the A ring of 19-nor-10-azasteroids is a planar system, with the N atom having a strong sp^2 character,[1b] the attribution of the α or β orientation to the proton on C-5 is the only stereochemical problem concerning compound **8**. The comparison of the ^1H and ^{13}C NMR spectra of **8** with those of the corresponding 17-oxo-substituted $\Delta^{1(2)}$-19-nor-10-azasteroid[1a] having 5α-H stereochemistry led to the observation that while 5-H in the latter compound resonates below 3.0 ppm and C-5 at 65.8 ppm, in compound **8** the same proton is found at 3.75 ppm and C-5 resonates at 53.1 ppm. These results can be explained only by assuming the opposite stereochemistry for 5-H in the two compounds. The 5β stereochemistry of **8** was definitively confirmed by a NOESY experiment, which did not show any correlation between 5-H and 9α-H.

For the synthesis of azasteroid **9**, 2-[(trimethylsilyl)oxy]-1,3-butadiene was generated in situ by treating methyl vinyl ketone with TMSOTf in CH_2Cl_2 and in the presence of Et_3N. Then, the addition of **7**, and a further amount of TMSOTf to promote the *N*-(acyloxy)iminium ion formation, followed by the usual $NaHCO_3$ treatment, completed the reaction. This provided azasteroid **9** (58% yield after chromatography) as a mixture of two diastereoisomers differing by the A/B ring fusion and in 1.2:1 ratio (the same ratio was measured by ^1H NMR in the crude reaction mixture).

The separation by chromatography of the two isomers was not possible. However, the major diastereoisomer **9a** was recovered in part unreacted after the next oxidative step of the mixture, and thus, homo- and heteronuclear correlation NMR experiments allowed the unambiguous assignments of the ^1H and ^{13}C NMR signals. The upfield shifted signal of the proton on C-9 (2.43 ppm), which has an established axial α orientation, can be accounted for by assuming a β orientation for the N lone pair.[20] Since the signal of 5-H is downfield shifted (3.36 ppm), this proton should be on the same side of the N lone pair,[20] consistent with the cis fusion of the A/B ring juncture in **9a**. This stereochemistry was confirmed by converting (5β)-10-azasteroid **8** into **9a** (Scheme 3). In fact, hydrogenation of the enone moiety over 5% Pd/C to give alcohol **12**, followed by Jones oxidation of the 3α-hydroxy group,[21] provided a 3-oxo compound having spectroscopic and analytical data identical to those of **9a**.

The stereochemistry of isomer **9b** was assigned by NMR analysis of the **9a** and **9b** mixture. The proton resonance at 3.56 ppm (the only one for **9b** in the 3−4 ppm region of the ^1H NMR spectrum) and the ^{13}C NMR

Scheme 3[a]



[a]Key: (a) H_2, 5% Pd/C, 25 °C, 24 h; (b) Jones oxidation, acetone, 0 °C.

signals at 68.4 (C-9) and 62.9 (C-5) ppm are indicative of the A/B ring trans fusion in **9b**, since 10-azasteroids (as, for example, the corresponding 17-keto derivative[1a]) that possess an established 5α stereochemistry display almost identical resonances.[1a] The stereochemistry of **9b** was definitively assigned preparing a pure sample of this isomer by hydrogenation of **10** followed by Jones oxidation of the 3-hydroxy derivative (not isolated from the crude reaction mixture), as described above. Since hydrogenation of the 4-en-3-one moiety in 10-azasteroids occurs with α facial selectivity,[1a] this sequence gave a 5α-H compound with NMR data identical to those of **9b** (from the mixture with **9a**) and melting point (78−79 °C) very close to that reported (81 °C) for the same compound prepared by a different strategy.[15]

Concerning the stereochemical outcome observed in the A ring construction of azasteroids **8** and **9**, although definitive mechanistic evidence is lacking, the reaction of 2-(silyloxy)-1,3-butadiene (X = H) with the *N*-(acyloxy)-iminium ion (Scheme 1) should occur through a tandem Mannich−Michael mechanism,[11] in which the nucleophilic attack of the diene on the activated C=N bond is almost equally probable on both the α and β face of the iminum ion. This leads, after N conjugate addition, to a mixture of cis- and trans-fused azasteroidal compounds (**9a** and **9b**). Instead, in the reaction of Danishefsky's diene (X = OMe) with the same *N*-(acyloxy)iminium ion leading to **8**, a hetero Diels−Alder reaction occurring with high α selectivity cannot be excluded, since the mechanism of Lewis acid-mediated reaction of imines with this electron-rich diene seems to vary with the structure of the heteroanalogous carbonyl compound employed.[22]

The oxidation of the **9a** and **9b** mixture by $Hg(OAc)_2$ and the tetrasodium salt of EDTA in 20% AcOH at 90 °C[1a,15,23] gave after chromatography 17β-*O*-acetyl (+)-19-nor-10-azatestosterone (**10**) (40%), whose spectroscopic and analytical data agree with those reported by Bertin et al.[15] As already mentioned, a small amount of pure **9a** (10%) was recovered unreacted after the oxidative step, whereas no traces of **9b** were detected in the crude reaction mixture or found in any of the chromatographic fractions. This result can be explained on the basis of the reported oxidative mechanism,[23] since, after coordination of the N atom to the Hg^{2+} cation, elimination of a trans proton adjacent to the N−Hg bond with formation of an iminium ion is favored. This should determine a lower reactivity of cis-fused compound **9a** with respect to trans-fused isomer **9b** and, therefore, the recovery of some unreacted **9a** after 2 h of heating under the above

(19) The crude reaction mixture contained a certain amount of unidentified decomposition products. Repeated purifications by chromatography were necessary to obtain pure **8**.

(20) It is known that, in cyclic systems, the protons adjacent to the nitrogen atom and on the same side of the N lone pair undergo a strong deshielding effect, whereas the protons on the opposite side are strongly shielded: (a) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109−126. (b) Wilson S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330−336. (c) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447−453. (d) Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *J. Heterocycl. Chem.* **1979**, *16*, 1041−1047. (e) Bohlmann, F.; Shumann, D. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, Chapter 5.

(21) The multiplet at 3.73 ppm for 3-H is consistent with its axial β orientation.

(22) (a) Waldmann, H. *Synthesis* **1994**, 535−551 and references therein. (b) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444−4451.

(23) Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439−444.

reaction conditions. Finally, the hydrolysis of the *O*-acetyl group in **10**, performed as reported,[15] afforded (+)-19-nor-10-azatestosterone (**11**)[1a,15] in quantitative yield.

In conclusion, we have described a new route for the synthesis of 19-nor-10-azasteroids, based on a tandem *N*-(acyloxy)iminium−Michael addition reaction for the construction of the A ring, which provided azasteroidal compounds in only six steps and in fair overall yields (21−31%). The present methodology is shorter and more efficient with respect to the other reported methods for the synthesis of 10-azasteroids:[1a,15,24] the yield in compound **11** is much higher (12%) than that obtained by Bertin et al. (0.1% after 11 steps)[15] or by us with the isoxazoline-5-spirocyclopropane rearrangement methodology (1% after 14 steps),[1a] while Huisman's short synthesis of 10-azasteroids furnishes racemic compounds.[24] Furthermore, our new route has the advantage that azasteroids with different A ring substitution patterns could be easily obtained by using 1-, 3-, or 4-substituted 2-(silyloxy)-1,3-butadienes for the tandem reaction. The synthesis of $\Delta^{1(2)}$ unsaturated compound **8** is a first example of such an application.

Experimental Section[1a]

(+)-3-[(3a*S*)-(3aα,4α,7a*β*)-1,5-dioxo-7a-methyloctahydro-(1*H*)-inden-4-yl]propionic acid (**1**)[12] was purchased from Pharmacia & Upjohn (Brussels, Belgium).

(+)-1,2,4,4,6,6a,7,8,9,9aα,9b*β*-Decahydro-6a*β*-methyl-(3*H*)-cyclopenta[f]quinoline-3,7-dione (3a). Acid **1** (30 g, 126 mmol) was added to a solution of NH_4HCO_3 (75 g, 0.95 mol) in HCOOH (60 mL, 1.59 mol) warmed at 100 °C and the resulting solution warmed at 120 °C for 1 h. After the solution was cooled to room temperature, the product was filtered and washed with MeOH, obtaining **3** as a 19:1 mixture of **3a** and **3b** (20.4 g, 74%). Recrystallization from MeOH afforded pure **3a** (16.2 g, 59%): mp 241−243 °C; $[\alpha]^{25}_D$ +294.0 (*c* 0.476, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.70 (br s, 1 H), 4.93 (m, 1 H), 2.62−2.34 (m, 3 H), 2.28−1.96 (m, 6 H), 1.80−1.35 (m, 3 H), 0.92 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 220.2 (s), 170.4 (s), 135.5 (s), 102.3 (d), 46.7 (s), 46.2 (d), 36.0 (t), 35.1 (d), 31.5 (t), 30.9 (t), 24.1 (t), 21.9 (t), 14.6 (q); MS *m*/*z* 219 (M^+, 89), 204 (93), 162 (77), 148 (78), 55 (100); IR ($CDCl_3$) 3393, 1735, 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.95; H, 7.92; N, 6.12. **3b** (main signals): ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, 1 H), 0.87 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 217.1 (s), 139.5 (s), 112.0 (s).

(+)-1,2,4,4aα,5,6,6a,7,8,9,9aα,9b*β*-Dodecahydro-7*β*-hydroxy-6a*β*-methyl-(3*H*)-cyclopenta[*f*]quinolin-3-one (4). Enelactam **3** (as the 19:1 mixture of **3a** and **3b**, 14.0 g, 63.9 mmol) was suspended in MeOH (700 mL), and 2 N HCl in MeOH was added until pH 1.5−2 was reached. $NaBH_3CN$ (15 g, 238.4 mmol) was slowly added, and the resulting solution was stirred 48 h at room temperature, maintaining the pH over the 1.5−2 range by adding 2 N HCl in MeOH. The mixture was poured into water (1 L), NaOH (satd) was added up to pH 10, and the product was extracted with CH_2Cl_2 (3 × 500 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated, obtaining **4** (12.8 g, 90%) as a white solid in sufficiently pure form to be used in the next step without purification: mp 248−249 °C (lit.[15] mp 249−250 °C); $[\alpha]^{25}_D$ +27.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.13 (br s, 1 H), 3.67 (t, *J* = 8.4 Hz, 1 H), 2.86 (ddd, *J* = 11.0, 9.5, 4.8 Hz, 1 H), 2.53−2.25 (m, 2 H), 2.16−2.05 (m, 1 H), 1.83−1.07 (m, 12 H), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2 (s), 81.0 (d), 58.7 (d), 47.4 (d), 43.9 (s), 38.3 (d), 34.4 (t), 31.3 (t), 30.6 (t), 28.8 (t), 25.1 (t), 22.4 (t), 11.3 (q); MS *m*/*z* 223 (M^+, 24), 164 (59), 123 (96), 110 (82), 55 (100); IR ($CDCl_3$) 3396, 2933, 1653 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.50; H, 9.49; N, 6.15.

(+)-1,2,4,4aα,5,6,6a,7,8,9,9aα,9b*β*-Dodecahydro-7*β*-(acetyloxy)-6a*β*-methyl-(3*H*)-cyclopenta[*f*]quinolin-3-one (5). To a solution of **4** (11.6 g, 52.1 mmol) in pyridine (60 mL), cooled at 0 °C, was slowly added Ac_2O (5.89 mL, 62.5 mmol), and the resulting solution was stirred at room temperature for 48 h. Water (50 mL) was added and the product extracted with CH_2Cl_2 (3 × 50 mL); the organic layer was washed with citric acid (solution at 5%), $NaHCO_3$ (satd), and brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **5** was obtained. This was purified by recrystallization (water), affording pure **5** (13.8 g, 100%): mp 202−204 °C; $[\alpha]^{25}_D$ +13.0 (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.60 (br s, 1 H), 4.61 (dd, *J* = 8.8, 7.3 Hz, 1 H), 2.87 (td, *J* = 9.1, 4.8 Hz, 1 H), 2.46−2.33 (m, 2 H), 2.32−2.08 (m, 1 H), 2.03 (s, 3 H), 1.86−1.06 (m, 12 H), 0.86 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.4 (s), 171.0 (s), 81.7 (d), 58.4 (d), 47.1 (d), 43.4 (s), 37.9 (d), 34.5 (t), 31.1 (t), 28.5 (t), 27.5 (t), 25.0 (t), 22.5 (t), 21.1 (q), 12.2 (q); MS *m*/*z* 265 (M^+, 10), 205 (12), 176 (12), 166 (20), 43 (100); IR ($CDCl_3$) 3395, 1727, 1655, 1250 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.73; N, 5.28. Found: C, 67.54; H, 8.72; N, 4.98.

(+)-1,2,4,4aα,5,6,6a,7,8,9,9aα,9b*β*-Dodecahydro-4-*N*-(*tert*-butoxycarbonyl)-7*β*-(acetyloxy)-6a*β*-methyl-(3*H*)-cyclopenta[*f*]quinolin-3-one (6). To a solution of **5** (13.8 g, 52.1 mmol) in CH_2Cl_2 (313 mL) were added Et_3N (8.0 mL, 57.3 mmol), Boc_2O (46.0 g, 208.4 mmol), and DMAP (637 mg, 5.21 mmol), and the resulting solution was heated at reflux for 13 h. Water (300 mL) was added, and after separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 1 M $KHSO_4$ (300 mL), $NaHCO_3$ (satd) (300 mL), and brine (300 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **6** was obtained. This was purified by chromatography, eluting first with CH_2Cl_2 and then with CH_2Cl_2−MeOH, 25:1 (R_f = 0.6), affording pure **6** (18.3 g, 96%): $[\alpha]^{25}_D$ +23.0 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.60 (dd, *J* = 8.8, 7.3 Hz, 1 H), 3.22 (td, *J* = 11.0, 4.0 Hz, 1 H), 2.64−2.30 (m, 2 H), 2.27−2.08 (m, 1 H), 2.00 (s, 3 H), 1.93−1.06 (m, 11 H), 1.49 (s, 9 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.0 (s), 170.5 (s), 153.8 (s), 83.8 (s), 81.7 (d), 62.5 (d), 47.5 (d), 43.0 (s), 37.7 (d), 34.7 (t), 33.2 (t), 27.7 (q, 3 C), 27.5 (t), 26.6 (t), 24.5 (t), 22.6 (t), 21.0 (q), 12.2 (q); MS *m*/*z* 310 (11), 309 (6), 266 (62), 206 (27), 57 (100); IR ($CDCl_3$) 1728, 1659, 1249, 1146 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.77; H, 8.80; N, 3.52.

(+)-1,2,4,4aα,5,6,6a,7,8,9,9aα,9b*β*-Dodecahydro-3*β*-ethoxy-4-*N*-(*tert*-butoxycarbonyl)-7*β*-(acetyloxy)-6a*β*-methyl-(3*H*)-cyclopenta[f]quinoline (7). A solution of amide **6** (1.5 g, 4.1 mmol) in THF (12 mL) was cooled to −78 °C, and a 1 M solution of $LiEt_3BH$ in THF (8.2 mL, 8.2 mmol) was slowly added. After 15 min of stirring at −78 °C, 2 N HCl in anhydrous EtOH was added dropwise until pH 3.5−4 was reached, immediately followed by the addition of 18 mL of EtOH. The mixture was allowed to warm to 0 °C and, after 30 min of stirring, was diluted with CH_2Cl_2 (120 mL); the organic layer was washed with water (120 mL), $NaHCO_3$ (satd) (120 mL), and brine (120 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **7** was obtained as an oil. This was purified by chromatography, eluting with petroleum ether−EtOAc, 6:1 (R_f = 0.42), affording pure **7** as a colorless oil (1.36 g, 84%): $[\alpha]^{25}_D$ +50.7 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.41 (br d, *J* = 9.0 Hz, 1 H), 4.59 (t, *J* = 7.7 Hz, 1 H), 3.64−3.27 (m, 2 H), 3.01 (m, 1 H), 2.33−2.05 (m, 2 H), 2.01 (s, 3 H), 2.00−1.43 (m, 8 H), 1.43 (s, 9 H), 1.43−1.17 (m, 4 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.9 (s), 155.2 (s), 82.0 (d), 80.7 (d), 79.6 (s), 61.6 (t), 61.1 (d), 49.2 (d), 43.4 (s), 35.3 (t), 33.6 (d), 29.0 (t), 28.4 (t), 28.3 (q, 3 C), 27.7 (t), 22.6 (t), 21.5 (t), 21.0 (q), 15.1 (q), 12.6 (q); MS *m*/*z* 350 (M^+-45, 7), 310 (43), 294 (100), 250 (58); IR ($CDCl_3$) 2974, 1722, 1664 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NO_5$: C, 66.81; H, 9.43; N, 3.54. Found: C, 67.15; H, 9.71; N, 3.30.

(+)-17*β*-(Acetyloxy)-(5*β*)-10-azaestr-1-en-3-one (8). To a solution of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (130 μL, 0.67 mmol), Et_3N (158 μL, 1.1 mmol), and **7** (220 mg, 0.56 mmol) in CH_2Cl_2 (4 mL) cooled at 0 °C was added TMSOTf (171 μL, 0.88 mmol) dropwise; the mixture was allowed to warm to room temperature and stirred for 45 min. Then $NaHCO_3$ (satd) (4 mL) was added and the resulting mixture stirred for 36 h at room temperature. After separation of the phases, the product was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and

(24) Wille, H. J.; Pandit, U. K.; Huisman, H. O. *Tetrahedron Lett.* **1970**, 4429−4432.

evaporation of the solvent, crude **8** was obtained. This was purified by repeated chromatographies, eluting with CH_2Cl_2−MeOH, 30:1 (R_f = 0.27), affording pure **8** (69 mg, 39%): yellowish oil; $[\alpha]^{25}_D$ +56.3 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20 (d, *J* = 7.4 Hz, 1 H), 4.91 (d, *J* = 7.4 Hz, 1 H), 4.58 (m, 1 H), 3.75 (m, 1 H), 3.19 (dt, *J* = 10.3, 4.8 Hz, 1 H), 2.50−2.03 (m, 3 H), 2.02 (s, 3 H), 1.90−1.00 (m, 13 H), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.3 (s), 173.0 (s), 149.6 (d), 96.7 (d), 81.6 (d), 59.7 (d), 53.1 (d), 50.2 (d), 42.5 (s), 42.4 (d), 35.3 (t), 34.8 (t), 29.6 (t), 27.8 (t), 25.6 (t), 23.6 (t), 22.6 (t), 21.1 (q), 12.1 (q); MS *m*/*z* 317 (M^+, 29), 302 (10), 274 (37), 258 (59), 84 (100); IR ($CDCl_3$) 1710, 1622, 1572, 1251 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.72; H, 8.64; N, 4.12.

(+)-17*β*-(Acetyloxy)-10-azaestran-3-one (9). To a solution of methyl vinyl ketone (256 μL, 3.03 mmol) in CH_2Cl_2 (6 mL) cooled at 0 °C were added Et_3N (778 μL, 5.54 mmol) and TMSOTf (826 μL, 4.58 mmol). After 30 min of stirring, a solution of **7** (1.0 g, 2.53 mmol) in CH_2Cl_2 (6 mL) was first added and then the remaining TMSOTf (469 μL, 2.59 mmol); the mixture was allowed to warm to room temperature and stirred for 45 min. Then $NaHCO_3$ (satd) (12 mL) was added and the resulting mixture stirred for 36 h at room temperature. After separation of the phases, the product was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **9** was obtained. This was purified by chromatography, eluting first with CH_2Cl_2−MeOH 25:1 (1% Et_3N) and then with CH_2Cl_2−MeOH 25:2 (1% Et_3N), affording **9** (469 mg, 58%) as a 1.2:1 mixture of **9a**/**9b** diastereoisomers (R_f = 0.44). A pure sample of **9a** was recovered in the next oxidative step: mp 133−135 °C; $[\alpha]^{25}_D$ +28.1 (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.60 (dd, *J* = 9.2, 7.4 Hz, 1 H), 3.64 (ddd, *J* = 14.3, 4.4, 2.4 Hz, 1 H), 3.36 (m, 1 H), 2.94−2.70 (m, 2 H), 2.43 (m, 1 H), 2.30−1.06 (m, 17 H), 2.02 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.7 (s), 171.2 (s), 82.3 (d), 58.7 (d), 56.3 (d), 48.7 (t), 48.3 (d), 42.8 (s), 41.3 (t), 40.3 (d), 36.0 (t), 35.6 (t), 29.3 (t), 27.7 (t), 25.8 (t), 23.7 (t), 22.8 (t), 21.1 (q), 12.0 (q); MS *m*/*z* 319 (M^+, 41), 260 (100), 177 (29), 151 (14); IR ($CDCl_3$) 2935, 1714, 1247 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.37; H, 9.42; N, 4.11.

(+)-17*β*-(Acetyloxy)-10-azaestr-4-en-3-one (10). Compound **9** (230 mg, 0.72 mmol) was dissolved in 3.6 mL of AcOH, and water was added dropwise until a final volume of 18 mL (corresponding to a 20% AcOH). EDTA tetrasodium salt (1.2 g, 2.88 mmol) and $Hg(OAc)_2$ (918 mg, 2.88 mmol) were added, and the resulting solution was heated for 2 h at 90−95 °C under vigorous stirring. After being cooled to room temperature, the solution was filtered on a Celite layer and Na_2CO_3 (satd) was added up to pH 8. The product was extracted with CH_2Cl_2 (5 × 25 mL) and the organic layer washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude material was purified by chromatography, eluting with acetone−petroleum ether, 1:1 (R_f = 0.2), affording pure **10** (91 mg, 40%) as a pale yellow solid. A fraction containing unreacted **9a** (22 mg, 10%) was also collected (R_f = 0.31). **10**: mp 142−143 °C (lit.[15] 144 °C mp); $[\alpha]^{25}_D$ +182.7 (*c* 0.10, $CHCl_3$) [lit.[15] $[\alpha]^{25}_D$ +155 (*c* 0.5, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 4.92 (s, 1 H), 4.62 (t, *J* = 7.3 Hz, 1 H), 3.69 (ddd, *J* = 10.0, 6.0, 3.2 Hz, 1 H), 3.16 (ddd, *J* = 15.6, 14.0, 5.2 Hz, 1 H), 2.65−2.05 (m, 5 H), 2.03 (s, 3 H), 1.85−1.14 (m, 12 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.5 (s), 171.1 (s), 164.3 (s), 100.5 (d), 81.7 (d), 64.4 (d), 48.2 (d), 45.7 (s), 42.8 (t), 39.0 (d), 36.1 (t), 35.2 (t), 30.9 (t), 29.7 (t), 27.1 (t), 24.1 (t), 22.6 (t), 21.1 (q), 12.2 (q); MS *m*/*z* 317 (M^+, 100), 258 (51), 175 (26), 149 (31); IR ($CDCl_3$) 1721, 1611, 1539, 1242 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.65; H, 8.72; N, 4.00.

(+)-17*β*-Hydroxy-10-azaestr-4-en-3-one (11). Compound **10** (40 mg, 0.13 mmol) dissolved in a MeOH−H_2O solution (1.2:1, 2 mL) was treated with KOH (11 mg, 0.195 mmol), and the resulting mixture was stirred at room temperature for 5 h. After neutralization with 5% HCl, the solution was in part concentrated and extracted with CH_2Cl_2 (3 × 5 mL), washed with brine, and dried over sodium sulfate. After evaporation of the solvent, **11** was obtained as a yellow solid (36 mg, 100%). Analytical and spectroscopic data of **11** are identical to those reported.[1a]

(+)-17*β*-(Acetyloxy)-(5*β*)-10-azaestran-3α-ol (12). The hydrogenation of compound **8** (50 mg, 0.16 mmol) was performed as reported for other 10-azasteroids.[1a] Chromatography of the crude reaction mixture (CH_2Cl_2−MeOH, 7:1) gave **12** (41 mg, 80%) as a colorless oil (R_f = 0.21) and **9a** (5 mg, 10%) as a solid (R_f = 0.60). **12**: $[\alpha]^{20}_D$ +23.2 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.58 (t, *J* = 7.3 Hz, 1 H), 3.73 (m, 1 H), 3.39 (m, 1 H), 3.00 (m, 1 H), 2.55 (td, *J* = 12.5, 3.3 Hz, 1 H), 2.38 (m, 1 H), 2.01 (s, 3 H), 2.20−1.00 (m, 20 H), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.1 (s), 82.5 (d), 70.4 (d), 56.3 (d), 56.1 (d), 48.3 (d), 47.1 (t), 42.8 (s), 40.7 (d), 35.7 (t), 32.7 (t), 30.1 (t), 27.8 (t), 27.5 (t), 25.4 (t), 24.3 (t), 22.9 (t), 21.1 (q), 12.0 (q); MS *m*/*z* 321 (M^+, 4), 262 (20), 179 (13), 153 (13), 86 (94), 84 (100); IR ($CDCl_3$) 3610, 1720, 1260 cm^{-1}. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.90; H, 9.56; N, 4.09.

Oxidation of 12. A solution prepared by dissolving CrO_3 (150 mg, 1.5 mmol) and 96% H_2SO_4 (0.28 mL) in water (2 mL) was added dropwise and under stirring to a cooled (0 °C) solution of **12** (40 mg, 0.12 mmol) in acetone (3 mL) until the color of the reaction mixture turned orange. After a further 1 h of stirring, the solution was diluted with water (5 mL) and, after addition of a 0.1 M NaOH solution up to pH 10, extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to give **9a** (34 mg, 89%).

Preparation of 9b from 10. Compound **10** (20 mg, 0.06 mmol) was submitted to hydrogenation as reported.[1a] After 18 h, the catalyst was filtered, the solvent evaporated, and the crude reaction mixture directly treated with the Jones reagent as described above. Chromatography (CH_2Cl_2−MeOH 10:1) gave pure **9b** (9 mg, 47%) as a yellowish solid (R_f 0.42): mp 78−79 °C (lit.[15] mp 81 °C); $[\alpha]^{20}_D$ +30.4 (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.58 (dd, *J* = 9.2, 7.4 Hz, 1 H), 3.56 (ddd, *J* = 11.3, 6.3, 2.4 Hz, 1 H), 2.65−2.45 (m, 1 H), 2.40−0.95 (m, 20 H), 2.01 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.8 (s), 171.2 (s), 82.3 (d), 68.4 (d), 62.9 (d), 50.8 (t), 48.7 (t), 48.6 (d), 42.5 (s), 41.3 (t), 39.6 (d), 35.7 (t), 33.6 (t), 28.4 (t), 27.7 (t), 26.0 (t), 22.9 (t), 21.1 (q), 12.0 (q); MS *m*/*z* 319 (M^+, 41), 260 (100), 177 (29), 151 (14); IR ($CDCl_3$) 2933, 2857, 2801, 1717, 1250 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.20; H, 9.37; N, 4.06.

Acknowledgment. The authors thank Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Consiglio Nazionale delle Ricerche (CNR), and the "Vigoni program" for financial support. E.G.O. thanks Università di Firenze for a two-year postdoctoral fellowship. Mrs. Brunella Innocenti and Mr. Sandro Papaleo are acknowledged for their technical assistance.

JO971917S