Monatshefte für Chemie 127, 1189–1196 (1996)

Monatshefte für Chemie
Chemical Monthly

Steroids, LIII: New Routes to Aminosteroids [1]

Z. Szendi[1,*], **G. Dombi**[2], and **I. Vincze**[1]

[1] Department of Organic Chemistry, Attila József University, H-6720 Szeged, Hungary
[2] Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical School, H-6720 Szeged, Hungary

Summary. Steroid ketoximes were reduced with sodium tetrahydroborate in the presence of nickel chloride or molybdenum trioxide. These processes yielded 17α- and 20α- aminosteroids (**1c–5c**) in higher yields than common reduction methods.

Keywords. Steroids; Aminosteroids; Reduction of ketoximes; $NiCl_2/NaBH_4$ and $MoO_3/NaBH_4$-reagents.

Steroide, 53. Mitt.: Neue Wege zu Aminosteroiden

Zusammenfassung. Oxime von Ketosteroiden wurden mit $NaBH_4$ in Gegenwart von $NiCl_2$ und MoO_3 reduziert. Dieses Verfahren lieferte 17α- und 20α-Aminosteroide (**1c–5c**) in größeren Ausbeuten als übliche Methoden.

Introduction

Aminosteroids are potential anti-inflammatory [2], fungicidal [3], and antibacterial [4] agents. They have also been used recently for the synthesis of N-alkyl or N-peptidyl derivatives that influence the immune response *in vitro* experiments [5].

The simplest synthetic pathways for aminosteroids apply reductive amination of the corresponding ketosteroids: either the iminosteroids are reduced by means of $LiAlH_4$ [4], or the benzyl iminosteroids are hydrogenated followed by hydrogenolysis of the benzyl group [6–8]. There are several methods for the transformation of steroid ketoximes, including catalytic [9] and lithium aluminum hydride reduction [7, 10, 11]. They can also be reduced with nascent hydrogen produced in the reaction mixture from sodium and propanol [12].

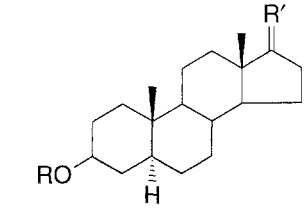
In comparison with the above mentioned methods, using hydrogen gas, sodium metal, and lithium aluminum hydride, the potential hazard of fire or explosion is minimized if $NaBH_4$ is used in the presence of transition metal salts or oxides. These milder conditions are also advantageous in cases when the minor (α) isomer is needed.

Results and Discussion

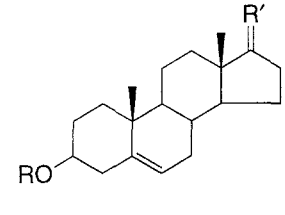
Sodium tetrahydroborate does not reduce oximes by itself; however, in the presence of certain transition metal oxides or salts it becomes an effective reducing agent. The use of molybdenum trioxide or nickel chloride has been demonstrated to result in the formation of the corresponding amine in 87–95% yield [13].

Concerning the mechanism of the reduction, it has been shown that metal borides are formed in this reaction [14] which in the transformation of nitriles have been demonstrated to catalyze the reduction only by hydride but not by hydrogen. The subsequent rate-determining step is hydride addition [15]. The reduction of oximes may follow a similar mechanism.

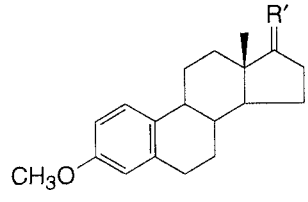
We prepared 17-amino-5α-androstan-3β-ol (**1c**) [8, 16–18], 17-aminoandrost-5-en-3β-ol (**2c**) [16, 19, 20], 17-amino-3-methoxyestra-1,3,5(10)-triene (**3c**) [21, 22], 20-aminopregn-5-en-3β-ol (**4c**) [11, 12, 23–26], and 20-aminopregna-5,16-dien-3β-ol (**5c**) starting from the corresponding ketoximes **1b**–**5b** [11, 16, 17, 19, 21, 22, 27] and using sodium tetrahydroborate in the presence of nickel chloride or molybdenum trioxide (Scheme 1). ^{1}H NMR and TLC analyses showed that both methods yield a mixture of the epimeric amines.



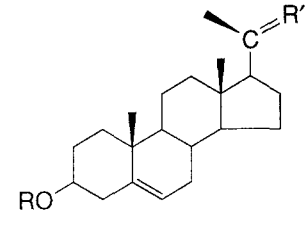
1a–d



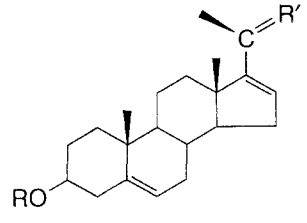
2a–e



3a–d



4b–d



5b–d

	R	*R′*
a	H	=N—CH$_2$—⬡
b	H	=N—OH
c	H	NH$_2$ / H
d	Ac	H / NHAc
e	H	NHFMOC / H

Scheme 1

In order to compare synthetic processes suitable for the production of such aminosteroids, we prepared several of the amines by various reduction methods. Thus, the steroidal ketoximes were reduced by means of lithium aluminum hydride in boiling tetrahydrofuran (**5b**) and in propanol with sodium (**1b–5b**). 17-Benzyliminosteroids (**1a–3a**) were reduced in two steps: to avoid special conditions sometimes needed for the catalytic saturation of the imino group [28], this reaction was carried out using sodium tetrahydroborate. Then the benzyl group was split off by catalytic hydrogenation.

To evaluate the stereochemical results of the reductions, ^{1}H NMR spectra of the crude reduction products were recorded. In the ^{1}H NMR spectrum of 17α,β-aminoandrost-5-en-3β-ol (**2c**), the signals related to the individual isomers appear at different chemical shifts. It has already been reported that the 17α (*quasi*-axial) hydrogen is found at higher field than the 17β (*quasi*-equatorial) hydrogen [20]. Furthermore, these signals exhibit also different couplings. The 17α-hydrogen in 17β–**2c** appears as a triplet, indicating couplings with both hydrogens at position 16, whereas the 17β-hydrogen in the isomeric 17α–**2c** is coupled only with the 16β-hydrogen (doublet).

To achieve better solubility, the crude reduction products were acetylated and these derivatives (**1d–5d**) [8, 16, 22, 24, 29] were investigated without purification to preserve the original ratio of the isomers. The multiplicity of the ^{1}H NMR signals of hydrogen atoms geminal to the nitrogen changed upon acetylation: the doublet of the 17β-hydrogen in 17α–**2c** became a triplet in 17α–**2d**, whereas the triplet of the 17α-hydrogen in 17β–**2c** turned into a quartet in 17β–**2d**. These changes point to an additional coupling, probably with the hydrogen atom of the amide group. This was proved experimentally by adding D_2O to the $CDCl_3$ solution of 17β–**2d**. The amide hydrogen exchanged slowly (4 days at room temperature). The spectrum then no longer contained the doublet of NH at 5.28 ppm, and at the same time the multiplicity of the 17α-H signal changed from a quartet into a triplet. Irradiation at 5.28 ppm resulted in the same change in the spectrum.

The ratio of the integrals of the corresponding signals gives the quantitative ratio of the isomers.

Pure stereoisomers can be obtained from benzylimine derivatives and from 17-ketoxime **1b** with lithium aluminum hydride. Reduction of oximes by any other method affords a mixture of isomers. The reductions with $NaBH_4/NiCl_2$ or $NaBH_4/MoO_3$ are superior to other methods not only because of their simplicity, but also when 17α- and 20α-amines are desired. The $NaBH_4/MoO_3$ reduction is mainly advantageous from this latter point of view, though the yields are not high enough.

Our studies based on direct analysis of the isomer mixtures indicate that the isomer ratios in the $LiAlH_4$ and Na/propanol reduction of **4b** and **5b** differ significantly from the literature data [11, 22]. We believe that the cause of the difference lies in the difference in analytical methods involving purification steps. The separation of the stereoisomers in literature involves silica gel column chromatography [24, 26] for 20α,β-amino-5α-pregnanes and -5-pregnenes. Separation of 17-amine isomers with very close polarity cannot be solved in this manner with a satisfactory result. A good separation of their N-acetyl derivatives was achieved by preparative HPLC (experimental details will be published elsewhere).

Table 1. Yields[a] and ratio of isomers[b]

	Reduction of benzylimines with H_2/Pd/C		$LiAlH_4$/THF		Reduction of oximes by means of Na/PrOH		$NaBH_4/NiCl_2$		$NaBH_4/MoO_3$	
	yield	ratio of isomers (%)	yield	ratio of isomers (%)	yield	ratio of isomers (%)	yield	ratio of isomers (%)	yield	ratio of isomers (%)
1d	97	100β			98	77β:23α	50	70β:30α	70	39β:61α
2d	98	100β			98	89β:11α	97	67β:33α	70	55β:45α
3d	71	100β			100	81β:19α	47	65β:35α	40	39β:61α
4d					92	50β:50α	81	50β:50α	97	39β:61α
5d			92	35β:65α	98	50β:50α	100	36β:64α	95	50β:50α

[a] Calculated from oxime or benzyl imine for N-acetyl, or N,O-diacetyl amin; [b] calculated from the 1H NMR spectra

We successfully applied the N-9′-fluorenylmethoxycarbonyl (F*moc*) derivatives used in peptide chemistry for acid resistant protection of amino groups [30]. As reagent, 9-fluorenylmethylsuccinimidyl carbonate was used [31]. The strong UV activity of this protecting group permits a fine UV controlled HPLC separation of the isomers. A further advantage of the F*moc* derivatives is the ready decomposition of their urethane bond by means of inorganic or *sec*-amine bases [30] or with potassium fluoride in the presence of a crown ether, as reported recently [32].

Experimental

For TLC, DC Alufolien Kieselgel 60 F_{254} 0.2 mm (Art. 5554) or 0.25 mm (Art. 5715) or Kieselgel HF_{254} 2 mm (Art. 5717) (Merck) were used. Solvent systems: A: methanol:benzene = 3:7; B: chloroform:methanol:NH_4OH_{conc} = 132:12:1. The spots were visualized by spraying the plates with 50% aqueous H_3PO_4 or conc. H_2SO_4 and heating for 10 min. at 120 °C. Elemental analyses were carried out in a KOVO (Czech Republic) C,H,N apparatus. Experimental data were in accordance with the calculated ones. ^{1}H NMR spectra were obtained with Bruker 250 MHz and Bruker AM 400 MHz spectrometers in $CDCl_3$ or in *DMSO*-d_6 solutions, or in a mixture of these solvents.

Preparation of amines by reduction of oximes

Molybdenum trioxide/sodium tetrahydroborate reduction of oximes

Hydroximinosteroids **1b**–**5b** (0.01 mol) were dissolved in 400–500 ml methanol. Molybdenum trioxide (0.07 mol) and 0.3 mol sodium tetrahydroborate were added in portions to the solution within 30 minutes at room temperature. Next, 5 g potassium hydroxide dissolved in 20 ml water were added, and the suspension was left to stand at 20 °C overnight. After filtration, the precipitate was washed with methanol, and the combined mother liquor and washings were evaporated. Ice water (150–200 ml) was added to the residue until amine crystals started to separate. They were filtered off, washed with water until neutral, and dried. Yields were between 70 and 97% (**1c**–**5c**); **3c** could only be isolated in 40% yield.

Nickel chloride/sodium tetrahydroborate reduction of oximes

Hydroximinosteroids **1b**–**5b** (0.002 mol) were dissolved in 40–50 ml methanol, and 0.004 mol nickel chloride hexahydrate was added. Solid sodium tetrahydroborate (0.02 mol) was added in small aliquots to the solution within 30 minutes at 22 °C during stirring. The black suspension was left to stand overnight at 22 °C, and the inorganic precipitate was filtered off. The clear brown solution was concentrated to 10 ml and acidified to *pH* 5 with dry ethanolic hydrogen chloride (8.3% w/w). The precipitated white crystalline amine hydrochloride was filtered off after allowing to stand the mixture overnight at 5 °C. The bases **1c**–**5c** were obtained from the methanolic solution of the crude hydrochloride by adjusting the *pH* to 9 with 2 *M* sodium hydroxide solution and adding ice water until turbidity occured. After standing overnight at 5 °C, the precipitate was filtered off, washed with water until neutral, and dried at 90 °C. Yields were between 47% and 100%.

17α,β-Aminoandrost-5-en-3β-ol (**2c**)

The mixture of 17α–**2c** and 17β–**2c** prepared by the $NaBH_4/NiCl_2$ method is an amorphous solid. Yield: 67%; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 0.66$ (s, 3H, 18-H_3 in 17β–**2c**), 0.71 (s, 3H, 18-H_3 in17α–**2c**), 1.02 (s, 3H, 19-H_3), 2.66 (t, 1H, 17α-H in 17β–**2c**), 2.93 (d, 1H, 17β-H in 17α–**2c**), 3.52 (m, 1H, 3α-H), 5.35 (m, 1H, 6-H) ppm; ratio of 17α–**2c**:17β–**2c** = 35:65. The other aminosteroids were not analyzed directly by ^{1}H NMR; instead, their acetylated crude derivatives were used.

Reduction of oximes with nascent hydrogen

Hydroximinosteroids **1b**–**5b** (0.01 mol) were dissolved in 200 ml propanol, and 9.2 g sodium in pieces (0.4 atom equivalents) were added to the refluxing solution within 45 min. After the vigorous evolution of hydrogen had ceased, the suspension was heated until all the sodium was dissolved (about 2 h). The dense suspension was poured into 21 ice water and left to stand overnight. The precipitate was filtered off, washed neutral, and dried. Yields of **1c**–**5c** are above 90%.

Lithium aluminum hydride reduction of oxim **5b**

The hydroximinosteroid **5b** (0.016 mol) was dissolved in 100 ml of dry tetrahydrofuran, and a suspension of 3 g lithium aluminum hydride in 100 ml tetrahydrofuran was dropped into the solution during cooling and stirring. After the addition, the solution was left to warm to 22 °C, and the reduction was completed by refluxing the solution for 2 h. After standing overnight, the excess of lithium aluminum hydride was decomposed with 150 ml saturated aqueous ammonium chloride solution. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 × 75 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated to dryness to afford **5c** as amorphous solid in 92% yield.

Preparation of amines by reduction of benzyliminosteroids with nascent hydrogen

Preparation and reduction of benzyliminosteroids

Steroid ketones (0.01 mole) were boiled in an excess of benzylamine (8–10 ml) until TLC did not show any residual starting material (2–6 h). The benzylamine was removed by steam distillation, and the remaining benzylimino compound (**1a**, **2a**, or **3a**) was dried at 80 °C for 3 hours. The amorphous solid was then dissolved in 50–70 ml methanol, and 2 g sodium tetrahydroborate was added in portions to the solution. After 2 h, 200–250 ml ice water was added to the reduction mixture, and the precipitate was separated by filtration and washed with water until neutral. After drying, the white powder was dissolved in dry ethanol; 0.2 g 5% Pd/c were added, and the suspension was shaken in a hydrogen atmosphere. After 10–12 h, the catalyst was filtered off and the solution was evaporated to dryness. Yields of the crude aminosteroids **1c**–**3c** were between 70 and 98%.

Derivatives of amines

Acetamido-steroids by acetylation of **1c**–**5c**

Aminosteroids (**1c**–**5c** (0.003 mol) were dissolved in 5 ml of pyridine, and 5 ml acetic anhydride were added. After standing overnight at 22 °C, the solution was poured into 300 ml ice water and acidified with conc. HCl to *pH* 5. The precipitate was filtered off, washed until neutral, and dried. Yields were between 96 and 100%.

Data of compounds **1c**–**5c** *(prepared by Na/n-propanol from* **1b**–**5b** *followed by acetylation):*

17-Acetamido-5α-androsztan-3β-ol acetate (**1d**; $C_{23}H_{37}NO_3$)

$R_f = 0.76$ (A); ^{1}H NMR ($CDCl_3$): $\delta = 0.67$ (s, 3H, 18-H_3 in 17β–**1d**), 0.79 (s, 3H, 18-H_3 in 17α–**1d**), 0.82 (s, 3H, 19-H_3), 1.98 (s, 3H, O-Ac CH_3), 2.02 (s, 3H, N-Ac CH_3), 3.85 (q, 1H, 17α-H in 17β–**1d**, $J_{17\alpha,16\beta} = 9.2$ Hz, $J_{17\alpha,16\beta} = 9.2$ Hz, $J_{17\alpha,NH} = 9.2$ Hz), 3.97 (t, 1H, 17-βH in 17α–**1d**, $J_{17\beta,16\beta} = 8.1$ Hz, $J_{17\beta,NH} = 8.1$ Hz), 4.68 (m, 1H, 3-H), 5.46 (b, 1H, NH) ppm.

17-Acetamido-androst-5-en-3β-ol acetate (**2d**; $C_{22}H_{35}NO_3$)

$R_f = 0.80$ (A); ^{1}H NMR ($CDCl_3$): $\delta = 0.70$ (s, 3H, 18-H_3 in 17β–**2d**), 0.82 (s, 3H, 18-H_3 in 17α–**2d**), 1.02 (s, 3H, 19-H_3), 1.99 (s, 3H, O-Ac CH_3), 2.03 (s, 3H, N-Ac CH_3), 3.90 (q, 1H, 17-αH in 17β–**2d**,

$J_{17\alpha,16\alpha} = 8.9$ Hz, $J_{17\alpha,16\beta} = 8.9$ Hz, $J_{17\alpha,NH} = 8.9$ Hz), 4.01 (t, 1H, 17-βH in 17α–**2d**, $J_{17\beta,16\beta} = 7.8$ Hz, $J_{17\beta,NH} = 7.8$ Hz), 4.58 (m, 1H, 3-H), 5.39 (m, 1H, 6-H), 5.30 (b, 1H, NH) ppm.

3-Methoxy-estra-1,3,5(10)-trienyl-17-amine acetate (**3d**; $C_{21}H_{29}NO_2$)

$R_f = 0.73$ (A); ^{1}H NMR ($CDCl_3$): $\delta = 0.72$ (s, 3H, 18-H_3 in 17β–**3d**), 0.84 (s, 3H, 18-H_3 in 17α–**3d**), 2.00 (s, 3H, N-Ac CH_3), 3.97 (q, 1H, 17-αH in 17β–**3d**, $J_{17\alpha,16\alpha} = 9.0$ Hz, $J_{17\alpha,16\beta} = 9.0$ Hz, $J_{17\alpha,NH} = 9.0$ Hz), 4.06 (t, 1H, 17β-H in 17α–**3d**, $J_{17\beta,16\beta} = 8.0$ Hz, $J_{17\beta,NH} = 8.0$ Hz), 3.77 (s, 3H, OMe), 5.32 (b, 1H, NH in 17β–**3d**), 5.37 (b, 1H, NH in 17α–**3d**), aromatic hydrogens: 6.63 (d, 1H, 4-H), 6.72 (dd, 1H, 2-H), 7.19 (d, 1H, 1-H) ppm.

20-Acetamido-pregn-5-en-3β-ol acetate (**4d**; $C_{25}H_{39}NO_3$)

$R_f = 0.83$ (A); ^{1}H NMR ($CDCl_3$): $\delta = 0.74$ (s, 3H, 18-H_3 in 20β–**4d**), 0.71 (s, 3H, 18-H_3 in **20**α–**4d**), 1.02 (s, 3H, 19-H_3), 1.94 (s, 3H, O-Ac CH_3), 2.04 (s, 3H, N-Ac CH_3), 1.07 (d, 3H, 21-H_3 in 20β–**4d**), 1.16 (d, 3H, 21-H_3 in 20α–**4d**), 3.98 (m, 1H, 20-H), 4.60 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 5.27 (b, 1H, NH in 17β–**4d**), 5.23 (b, 1H, NH in 20α–**4d**) ppm.

20-Acetamido-pregn-5,16-dien-3β-ol acetate (**5d**; $C_{25}H_{37}NO_3$)

$R_f = 0.83$ (A); ^{1}H NMR ($CDCl_3$): $\delta = 0.73$ (s, 3H, 18-H_3 in 20β–**5d**), 0.70 (s, 3H, 18-H_3 in 20α–**5d**), 1.02 (s, 3H, 19-H_3), 1.96 (s, 3H, O-Ac CH_3), 2.04 (s, 3H, N-Ac CH_3), 1.10 (d, 3H, 21-H_3 in 20β–**5d**), 1.16 (d, 3H, 21-H_3 in 20α–**5d**), 3.96 (m, 1H, 20-H), 4.62 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 5.62 (m, 1H, 16-H), 5.24 (b, 1H, NH in 17β–**5d**), 5.17 (b, 1H, NH in 20α–**5d**) ppm.

Some samples of **1c**–**5c** and **1d**–**5d** prepared by $NaBH_4/NiCl_2$ or MoO_3 reduction contained some inorganic impurities.

Fluorenylmethyloxycarbamoylation of **2c**

17α,β(9′-fluorenylmethyloxycarbamoyl)-androst-5-ene-3β-ol (**2e**)

To 30 ml of a *THF* solution of 0.29 g **2c** (1 mmol), 0.92 g sodium hydrocarbonate (1.1 mmol), 0.37 g 9-fluorenylmethylsuccinimidyl carbonate (1.1 mmol), and 2 ml water were added and the solution was stirred at 25 °C. After 1 h, TLC (B) showed complete transformation to a less polar product. Water (20 ml) was added to the solution, and the mixture was extracted with 3 × 15 ml diethyl ether. The combined organic phases were dried over Na_2SO_4 and evaporated in vacuum. The remaining yellowish foam (0.36 g, 70.4%) was analyzed without purification. ^{1}H NMR ($CDCl_3$/DMSO-d_6): $\delta = 0.69$ (s, 3H, 18-H_3 in 17β–**2e**), 0.80 (s, 3H, 18-H_3 in 17α–**2e**), 1.02 (s, 3H, 19-H_3), 3.62 (q, 1H, 17α-H in 17β–**2e**), 3.73 (t, 1H, 17β-H in 17α–**2e**), 3.52 (m, 1H, 3α-H), 5.35 (m, 1H, 6-H) ppm; ratio of integrals: 17α–**2e**:17β–**2e** = 35:65. Preparative HPLC separation of the mixture (0.25 g) on a BST RP10-C^{18} column (details will be published separately) afforded the pure stereoisomers (17β–**2e**, 0.17 g; 17α–**2e**, 0.06 g).

Acknowledgements

We thank *G. Bozóki-Bartók* for the elemental analyses and *M. Rózsa-Tarjáni* for recording NMR spectra and for helpful discussions. This work was supported by Grant OTKA No. T020938.

References

[1] Part 52: Tietze LF, Wölfling J, Schneider Gy, Noltemeyer M (1994) Steroids **59**: 305
[2] Griggs SC, King JA (1978) *J Pharm Sci* **67**: 1215

[3] Babcock JC (to Upjon Co.) (1991) US Patent 3,009.925 Chem Abstr **56**: 10233i; Herzog HL, Payne CC, Herschberg EB (1955) J Am Chem Soc **77**: 5324
[4] Holysz RP (to Upjohn Co.) (1959) US Patent 2,886,564 (Continuation in part of US Patent 2,752,368 Chem Abstr **51**: 5852b) Chem Abstr **53**: 18106c
[5] Deraedt R, Torelli V, Benzoni J (Roussel-Uclaf) (1982) Ger Offen DE 3,146,117 Chem Abstr **97**: 110287j
[6] Schmitt J, Panouse JJ, Hallot A, Pluchet H, Comoy P, Cornu P-J (1962) Bull Soc Chim France Ser **28**: 1846
[7] Schmitt J, Panouse JJ, Hallot A, Cornu P-J, Pluchet H, Comoy P (1962) Bull Soc Chim France 5e Ser **28**: 1855
[8] Schmitt J, Panouse JJ (Clin-Byla) (1966) Fr Patent 1,459.719; Chem Abstr **67**: 117112n
[9] Glaser R, Gabbay EJ (1970) J Org Chem **35**: 2907
[10] Cowell DB, Davis AK, Mathieson DW, Nicklin PD (1974) J Chem Soc Perkin I, 1505
[11] Tzikas A, Tamm C, Boller A, Fürst A (1976) Helv Chim Acta **59**: 1850
[12] Davis M, Parnell EW, Rosenbaum J (1972) J Chem Soc (C): 1420
[13] Ipaktschi J (1984) Chem Ber **117**: 856
[14] Heinzman SW, Ganem B (1982) J Am Chem Soc **1-4**: 6801
[15] Osby JO, Heinzman SW, Ganem B (1986) J Am Chem Soc **108**: 67
[16] Schmidt-Thomé J (1955) Chem Ber **88**: 895
[17] Pettit GR, Gupta AKD, Smith RL (1966) Canad J Chem **44**: 2023
[18] Davis M, Parnell EW, Warburton D (1966) J Chem Soc (C): 1698
[19] Ruzicka L, Goldberg MW (1936) Helv Chim Acta **19**: 107
[20] Robinson CH, Ermann C, Hollis DP (1965) Steroids **6**: 509
[21] Ivanenko TI, Kolomin LV, Golubovskaja LE, Pivnickij KK (1982) Khim Pharm Zh **16**: 1192; Chem Abstr (1983) **98**: 119856x
[22] Nambara T, Shibata T, Nimura M, Hosoda H (1971) Chem Pharm Bull **19**: 954
[23] Lucas RA, Dickel DF, Dziemian RL, Ceglowski MJ, Hensle BL, MacPhillamy HB (1960) J Am Chem Soc **82**: 5688
[24] Van De Woude G, Van Hove L (1967) Bull Soc Chim Belges **76**: 566
[25] Janot M-M, Monseur X, Coureur C, Goutarel R (1962) N^0 54 Bull Soc Chim France: 285
[26] Goutarel R, Mahler HR, Green G, Khuong-Huu Q, Cavé A, Conreur C, Jarreau FX, Hannart J (1967) Bull Soc Chim France **12**: 4575
[27] Butenandt A, Schmidt-Thomé I (1939) Chem Ber **72**: 182
[28] Ye YH, Huang YS, Wang ZQ, Chen SM, Tian Y (1993) Steroids **58**: 35
[29] de Ruggieri P, Ferrari C, Gandolfi C (1961) Gazz Chim Ital **91**: 655
[30] Carpino LA, Han GY (1970) J Am Chem Soc 92: 5748
[31] Paquet A (1982) Canad J Chem **60**: 976
[32] Jiang J-J, Li W-R, Joullié MM (1994) Synth Comm **24**: 187

Received May 2, 1996. Accepted (revised) June 4, 1996