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Electrophilic Reactions of 4-Methyl-A-homo-4-azacholest-4a-en-3-one

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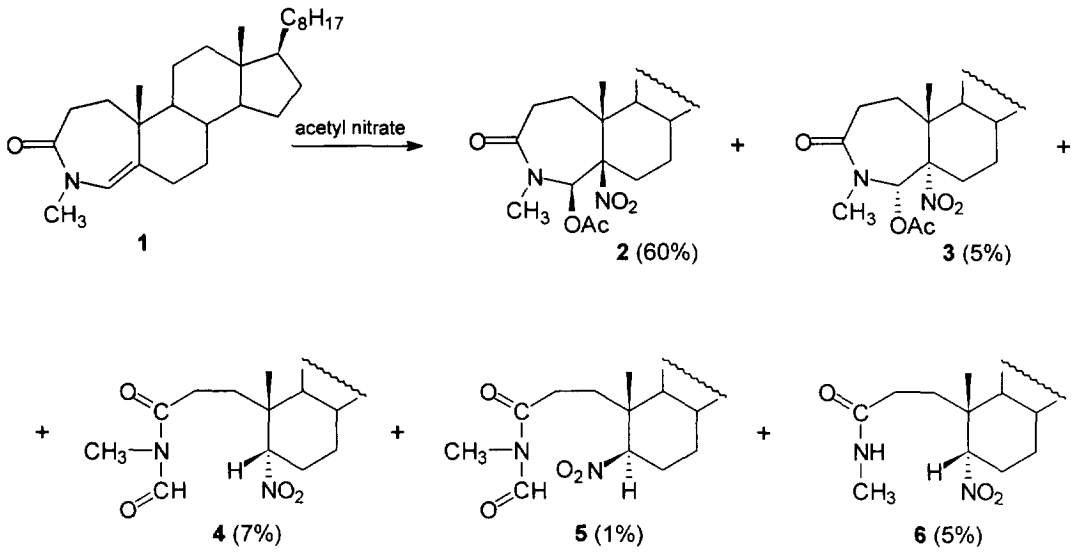
Abstract: Nitration, bromination and oxidation reactions of 4-methyl-A-homo-4-azacholest-4a-en-3-one (**1**) were studied. The reaction with acetyl nitrate gave products of *cis* addition to the double bond accompanied by the A-seco compounds. The results of bromination were dependant on the reaction conditions. After the initial electrophilic attack at C-5, further transformations involved the addition of a nucleophile, which was followed by isomerization to the A-seco compounds or rearrangement to the six-membered lactams or lactone promoted by $AgBF_4$. The CrO_3 oxidation yielded the product of a double bond cleavage.

We have recently described the reactions of 4-azacholest-5-en-3-one and 6-azacholest-4-en-7-one with electrophilic reagents.[1,2] The dominating process observed in these systems was the electrophilic substitution at the terminal carbon atom of the enamide double bond.[3,4] It was of interest to study the electrophilic reactions of an enamide disubstituted at this carbon atom. A readily available[5] 4-methyl-A-homo-4-azacholest-4a-en-3-one (**1**) was chosen as a model compound and its reactions (nitration, bromination and oxidation) were examined.

A mixture of acetic anhydride and nitric acid has been used for nitration for many years, and found to be particularly effective for nitration of compounds sensitive to strong acids.[6,7] It is known that acetic anhydride converts absolute nitric acid almost entirely to acetyl nitrate.[6,8] When excess acetic anhydride is present, the only nitrating agent detectable is acetyl nitrate. However, it is believed that dinitrogen pentoxide, a powerful nitrating agent, is also present in the mixture, although in a very low concentration. The reactions of olefins with acetyl nitrate typically afford β-nitro acetates as the major products accompanied by variable amounts of β-nitroalkenes and β-nitro nitrates. The latter compounds are formed in low yield due to the presence of dinitrogen pentoxide in the reaction mixture. In the case of the ene-lactams studied so far by us,[1,2] the β-nitro acetates were not detected as the reaction products. Nitration at the terminal carbon atom of the enamide double bond was frequently followed by consecutive reactions, such as allylic oxidation or Nef type reaction.

The reaction of 4-methyl-A-homo-4-azacholest-4a-en-3-one (**1**) with acetyl nitrate afforded 5β-nitro-4aβ-acetate **2** in 60% yield, accompanied by a number of by-products, which are - the α,α-stereoisomer of the nitro acetate **3**, two isomeric A-seco 5-nitro formimides (**4** and **5**) and the corresponding A-seco 5α-nitro amide



Scheme 1

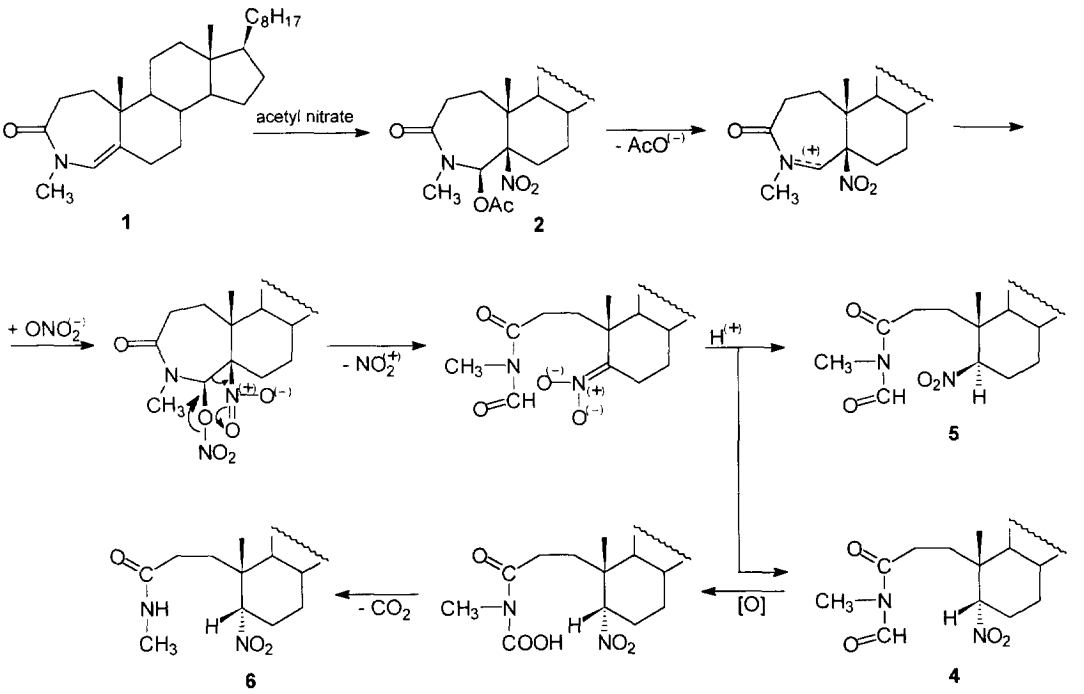
6. The formation of nitro acetates in the reaction of olefins with acetyl nitrate is known to be a stereospecific *cis* addition.[6] It is either a pure concerted addition or an asynchronous addition with carbonium ion formation, in which the collapse to *cis* adduct occurs more rapidly than the reaction with an external nucleophile. The transition states leading to the nitro acetates are very demanding sterically, and therefore these products were not observed in the reactions of the more hindered ene-lactams previously studied by us. The stereochemical outcome of the compound **1** reaction was rather unexpected and needs some comments. The inspection of the Dreiding stereomodels and the use of computer assisted molecular modeling showed that there are two low energy rigid conformations of **1** and in one of them, the upper side (β) of molecule is more accessible to the approaching reagent. This is probably the prevailing conformation in the polar solvent. The major reaction product, 5β-nitro 4aβ-acetate **2**, formed by addition of acetyl nitrate from the β-side, is a relatively high energy compound (see Table 1).

Table 1. The steric energies and the 4-H - 19-H distances calculated[9] for the 5-nitro 4a-acetate stereoisomers.

	5α,4aα	5α,4aβ	5β,4aα	5β,4aβ
steric energy (kcal/mol)	65.6	69.9	75.8	77.4
shortest 4-H - 19-H contact (Å)	2.06	3.92	4.90	4.78

The α,α-stereoisomer **3**, also isolated from the reaction mixture, is the most stable of the four isomeric nitro acetates. α-Configuration of substituents in this compound, was unequivocally proved by NOE measurements. Thus, in the soft pulse NOE difference spectroscopy (dpfgnoe) experiment, compound **3** showed upon

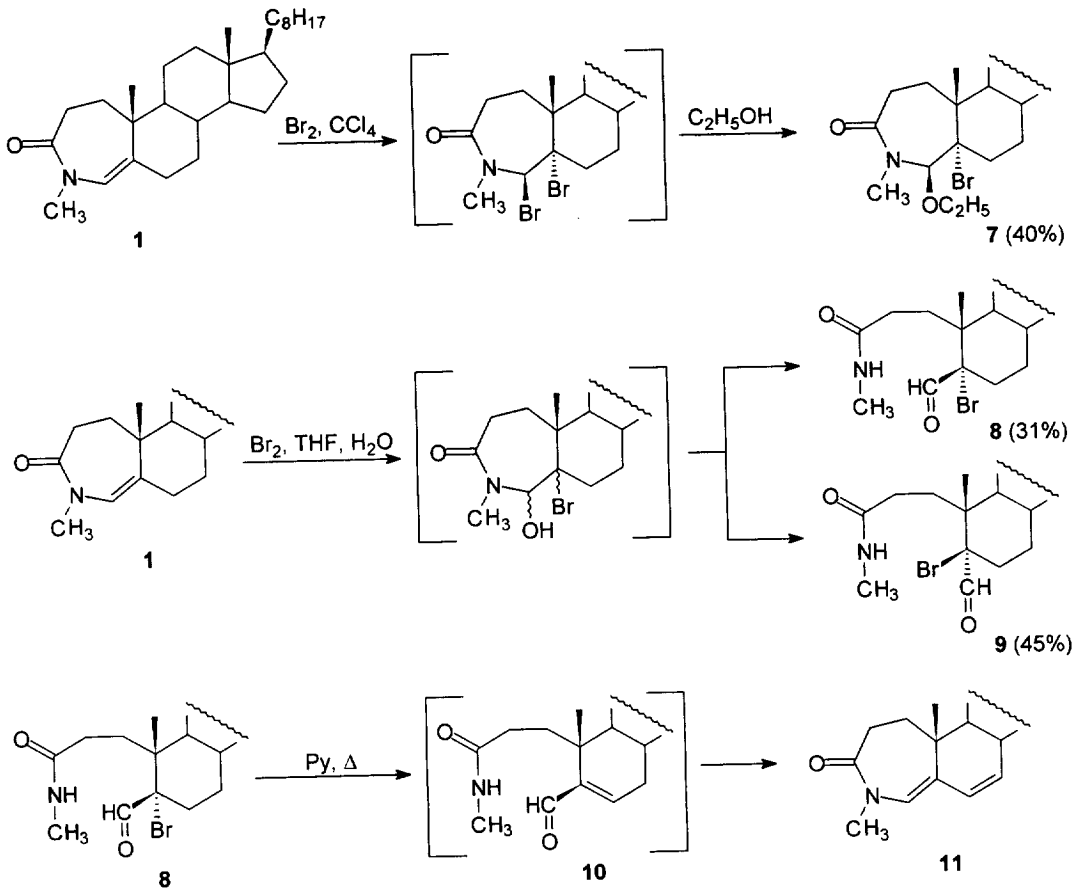
irradiation of the 4H signal at δ 7.45, a 6.5% enhancement of the signal at δ 1.07 corresponding to the 19-H protons. It must be added that the 5α-nitro 4aα-acetate **3** is the only stereoisomer in which the 4-H proton is in close proximity (~2.06 Å) to the 19-methyl protons (for the other three stereoisomers in their optimal conformations, the distance of 4-H proton from the methyl group protons is much longer). It is well known that α-acetoxy amides readily undergo heterolysis to afford N-acyliminium ions.[10,11] This highly reactive intermediate is probably responsible for the formation of the A-seco products. The 5β-nitro 4aβ-acetate **2**, the principal primary product of reaction, slowly disappears in time, and is not found among the products of reaction lasting 2 hours, whereas the concentration of its α,α-stereoisomer **3** in the reaction mixture, remains approximately constant in prolonging the reaction time.



Scheme 2

The N-acyliminium ion originated from 5β-nitro 4aβ-acetate **2**, probably reacts with nitrate to afford the unstable 4ξ-ONO_2 derivative, which undergoes the carbon-carbon bond cleavage. Since the reaction proceeds *via* an acid form of the nitro compound, an equilibrium mixture of both 5-epimers of A-seco 5-nitro formimides (**4** and **5**) is formed. It is likely that compound **4** is partially further transformed into the A-seco 5α-nitro amide **6** under the reaction conditions by oxidation to carbamic acid followed by decarboxylation. However, compound **6** may also be formed on a different route (for example, by cleavage of the N(4)-C(4a) bond first in the intermediate nitrate). The configuration at the chiral centre C-5, in the A-seco 5-nitro compounds was

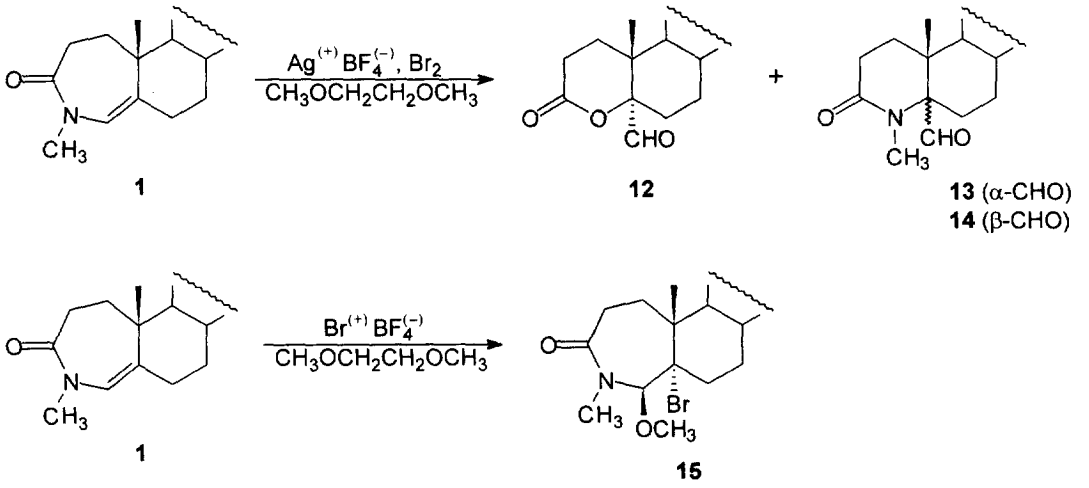
unequivocally assigned by the analysis of the 5-H signal in their ^{1}H NMR spectra. In all cases, this signal is doublet of doublets with greater coupling constants for axial proton at C-5 (5α-H).



Scheme 3

Another electrophilic reaction of 4-methyl-A-homo-4-azacholest-4a-en-3-one (**1**) studied by us, was bromination. The reaction performed with bromine in tetrachloromethane afforded a 5α-bromo 4aβ-ethoxy derivative **7** (40%) in addition to the isomeric A-seco 5-bromo aldehydes (**8** and **9**). The major reaction product was probably formed on the work-up of the reaction mixture (a commercial chloroform stabilized with 1% ethanol was used for extraction). The primary bromination product, 4aβ,5α-dibromide, undergoes heterolysis of the 4aβ-bromo substituent easily, to form an α-bromonium ion. Its *trans*-opening with ethanol gives the isolated 5α-bromo 4aβ-ethoxy amide.

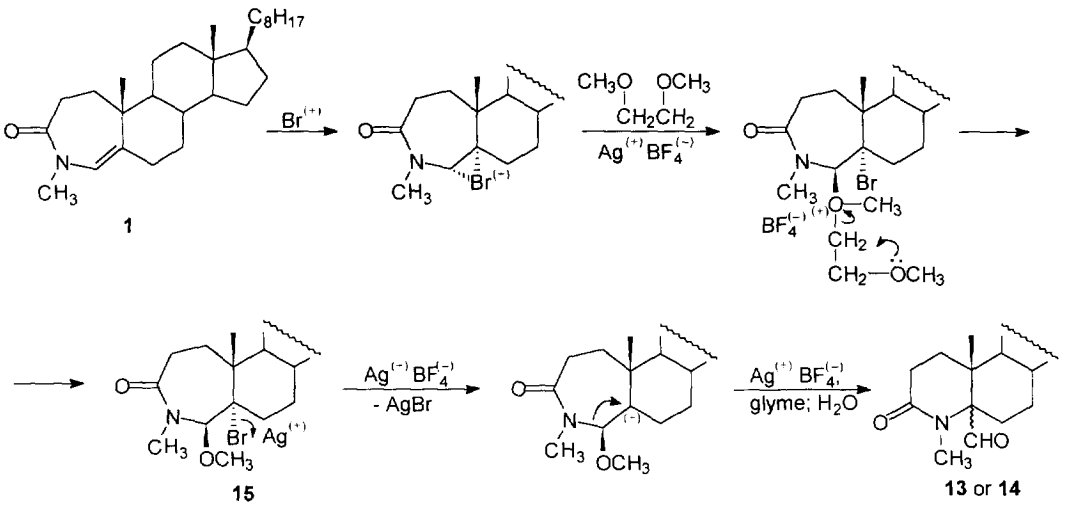
The reaction of compound **1** with bromine in aqueous THF, yielded a mixture of A-seco 5α-bromo (31%) and 5β-bromo (45%) aldehydes (**8** and **9**). These products are obviously formed from the corresponding bromohydrines. The equilibrium between bromohydrine and A-seco 5-bromo aldehyde lies far to the right in both (5α- or 5β-bromo compounds) cases. It has been shown, that the reaction between secondary amides and aldehydes can be a favourable process only if a five- or six-membered hydroxy lactam is formed.[10] The stereochemical outcome of the reaction was rather unexpected (the prevailing product stems from β-attack of bromine on ene-lactam **1**). This can be explained by assuming that the conformation dominating in a polar solvent is less hindered from the β-side (similarly, as in the case of nitration). The configuration of bromine in A-seco 5-bromo aldehydes, was proved by a chemical method. Both epimers were subjected to dehydrobromination by heating in pyridine at reflux. Only compound **8** with an axial 5α-bromo substituent underwent smooth elimination of HBr, which was followed by N-cyclization and dehydration to **11**. The primary elimination product **10**, was not isolated from the reaction mixture, but it was an intermediate in the process as proved by ^{1}H NMR.



Scheme 4

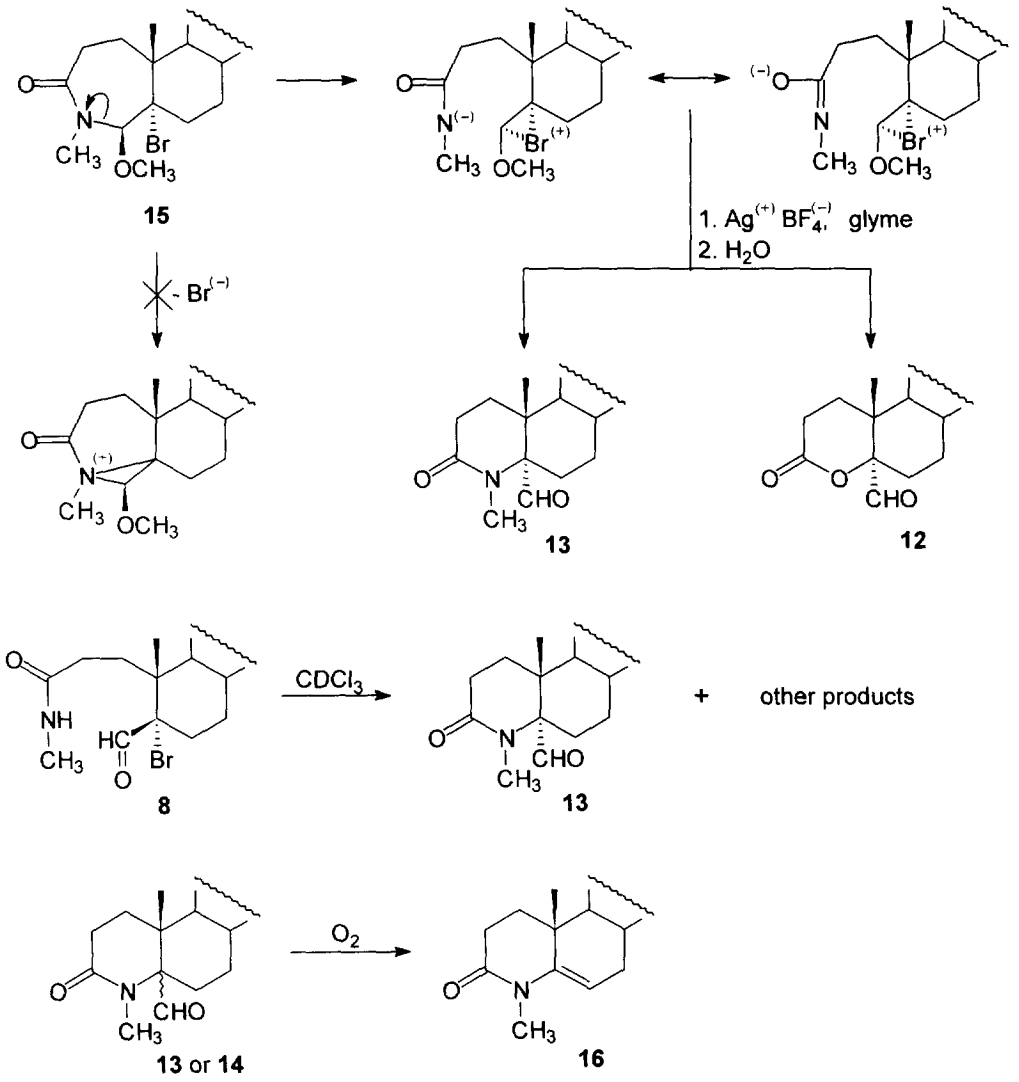
A number of experiments were performed with so called "positive bromine".[12,13] Ene-lactam **1**, dissolved in 1,2-dimethoxyethane (containing $AgBF_4$) and subjected to bromine afforded lactone **12** and lactams (**13** and **14**). A similar reaction with "bromonium tetrafluoroborate" (ene-lactam **1** was added to an equimolar mixture of $AgBF_4$ and bromine) yielded a 5α-bromo-4aβ-methoxy derivative **15** as a main product. This compound was formed by the methoxyl transfer from 1,2-dimethoxyethane to C-4a promoted by tetrafluoroborate, which stabilizes oxonium ions. In the former experiment, α-bromoether **15** reacted further with the halophilic $Ag^{(+)}$ cation, which presumably acts as a Lewis acid and facilitates rearrangement. The observed lack of

stereoselectivity in the rearrangement to the six-membered lactams suggests an S_N1-like mechanism, *via* the initial formation of a carbocation intermediate, followed by migration of the amide group.



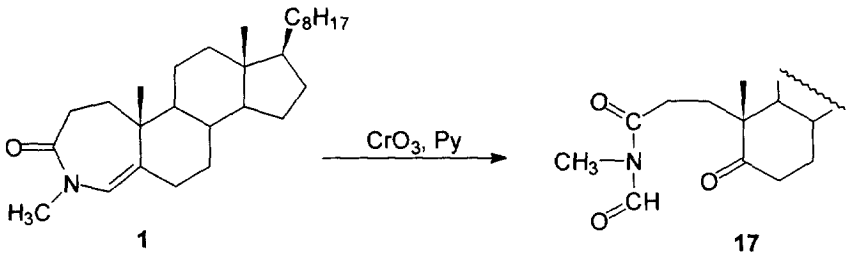
Scheme 5

A similar A-nor rearrangement of 3α-chloro- and 3β-chloro-5-azasteroid lactams described recently,[14] proceeded with complete stereospecificity *via* the formation of aziridinium ion intermediates. In the present case, the neighbouring nitrogen atom does not participate in the departure of the bromine atom from C-5. This is due to low nucleophilicity of the lactam nitrogen atom, the destabilizing effects of the carbonyl and methoxyl groups, and geometrical reasons. The bromine atom departure clearly precedes the amide group migration as the concerted process would also result in some degree of reaction stereoselectivity. Contrary to the six-membered lactams formation, the major reaction product, a six membered lactone, was obtained with complete stereoselectivity (only one epimer, presumably 5a-formyl lactone **12**, was detected in the reaction mixture). The tentative mechanism of lactone formation is shown in Scheme 6. It is assumed that heterolysis of the N(4)-C(4a) bond takes place prior to the leaving of the bromine atom. This heterolytic cleavage is relatively easy because both counter-ions are stabilized by delocalization. The formation of a bromonium ion in this process in essential to control the stereochemistry. The negative charge is located mostly on the amide oxygen atom. The nucleophilic attack of the oxygen atom on a bromonium ion from the opposite side, leads to a six-membered ring closure. The intermediate thus formed yielded 5α-formyl lactone **12** on aqueous work-up. In a similar way (a nitrogen atom attack on a bromonium ion) a 5α-formyl lactam **13** may also be produced. It must be added that the configuration at C-5 in lactone **12** could not be detected from its spectra and has been given tentatively on the basis of the above mechanism. In the case of 5-epimeric lactams **13** and **14**, the configuration at C-5 was chemically proved. When A-seco 5α-bromo aldehyde **8** was allowed to stand in a $CDCl_3$ solution in an NMR



Scheme 6

tube for a few days, it underwent partial decomposition, mainly to the more polar six-membered lactam **13**. Assuming that a nucleophilic attack of a nitrogen atom on C-5 took place on the side directly opposite to the leaving bromine atom, the configuration of a formyl group in the product must then be α. It is of interest that both six-membered lactams, when left standing in an open flask for several days, yielded the same ene-lactam **16** by the unknown radical mechanism (in the reaction oxygen from the air probably participates).



Scheme 7

4-Methyl-A-homo-4-azacholest-4a-en-3-one (**1**) was also subjected to oxidation with a CrO_3/Py complex in methylene chloride. The reaction proceeded smoothly and afforded an A-seco formimide **17** in 55% yield. The reaction is similar to other oxidations of enamides with the same reagent previously investigated by us.[1,2] In all cases, an oxidative cleavage of the double bond took place, and the corresponding carbonyl products were formed.

Azasteroids display diverse types of biological activity, and consequently their preparation and further transformations are of importance.[15,16] Many 4-azasteroids are potent 5α-reductase inhibitors, and some of them are being used for the benign prostatic hyperplasia treatment.[17-19] Other derivatives (*e.g.* 4-methyl-4-aza-5α-cholestane) show high antimicrobial activity against Gram-positive bacterie, yeasts, and molds.[20] Some compounds obtained through out this work are also expected to exhibit an interesting biological activity.

EXPERIMENTAL

Melting points were determined on a Köffler apparatus of the Boetius type and were uncorrected. NMR spectra were taken with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with TMS as the internal standard. Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer as chloroform solutions unless otherwise stated. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. Elemental analyses were performed at the Institute of Organic Chemistry, Polish Academy of Sciences. The reaction products were isolated by column chromatography performed on 70-230 or 230-400 mesh silica gel (Merck). Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use. 4-Methyl-A-homo-4-azacholest-4a-en-3-one (**1**) was prepared by rearrangement of cholest-4-en-3-one nitrone according to the known procedure.[4]

Nitration with acetyl nitrate

To a reagent prepared from 5 mL of acetic anhydride and 1 mL of nitric acid the steroidal ene-lactam **1** (200 mg; 0.5 mmol) was added. The reaction mixtures were magnetically stirred 40 min at room temperature,

quenched with water, and extracted with chloroform. The extract was washed with sodium bicarbonate solution, water, dried ($MgSO_4$), and was then evaporated *in vacuo*. The products were separated by silica gel column chromatography. The following compounds were consecutively eluted with benzene - ether mixtures (the percentage of ether was gradually increased up to 15%): the nitro formimides **5** (2.5 mg; 1%) and **4** (16 mg; 7%), the nitro acetates **3** (12.5 mg; 5%) and **2** (150 mg; 60%), and the nitro amide **6** (11 mg; 5%).

Compound **5**: mp 119-122°C (hexane - methylene chloride); IR, ν_{max} 1724 (weak), 1674, 1545 cm^{-1}; ^1H NMR, δ 9.31 (s, 1H, N-CHO), 4.45 (dd, J = 12.5 Hz, 3.8 Hz, 1H, 5α-H), 3.14 (s, 3H, N-CH_3), 1.04 (s, 3H, 19-H), 0.89 (d, J = 6.4 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.67 (s, 3H, 18-H); ^{13}C NMR, δ 174.1 (C), 162.5 (CH), 90.6 (CH), 56.1 (CH), 56.0 (CH), 46.7 (CH), 42.4 (C), 40.4 (C), 39.53 (CH_2), 39.47 (CH and CH_2), 36.1 (CH_2), 35.7 (CH), 34.4 (CH), 31.1 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 28.04 (CH_2), 27.99 (CH), 26.9 (CH_3), 25.8 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.0 (CH_2), 18.6 (CH_3), 16.4 (CH_3), 11.9 (CH_3); MS, m/z 477 (M^++1, <1), 458 (<1), 446 (10), 428 (58), 417 (32), 369 (86), 60 (100).

Compound **4**: mp 178-181°C (hexane - methylene chloride); IR, ν_{max} 1724 (weak), 1676, 1544 cm^{-1}; ^1H NMR, δ 9.22 (s, 1H, N-CHO), 4.60 (dd, J = 4.3 Hz, 2.3 Hz, 1H, 5β -H), 3.10 (s, 3H, N-CH_3), 1.05 (s, 3H, 19-H), 0.90 (d, J = 7 Hz, 3H, 21-H), 0.87 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.68 (s, 3H, 18-H); ^{13}C NMR, δ 174.2 (C), 162.3 (CH), 96.6 (CH), 56.1 (CH), 55.6 (CH), 44.1 (CH), 42.4 (C), 39.7 (CH_2), 39.5 (CH_2), 38.7 (C), 36.1 (CH_2), 35.7 (CH), 34.6 (CH), 32.2 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 28.0 (CH), 26.8 (CH_3), 26.1 (CH_2), 24.7 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.5 (CH_2), 18.62 (CH_3), 18.56 (CH_3), 12.0 (CH_3); MS, m/z 446 (11), 428 (23), 385 (59), 369 (100), 60 (96); anal. calcd for $C_{28}H_{48}N_2O_4$: C, 70.59; H, 10.08; N, 5.88; found: C, 70.75; H, 10.11; N, 5.93.

Compound **3**: mp 222-224°C (hexane - methylene chloride); IR, ν_{max} 1764, 1733, 1541, 1309, 1199 cm^{-1}; ^1H NMR, δ 7.45 (s, 1H, 4β-H), 3.22 (s, 3H, N-CH_3), 2.42-2.58 (m, 2H, 2-H), 2.16 (s, 3H, CH_3CO), 1.12 (s, 3H, 19-H), 0.90 (d, J = 6.5 Hz, 3H, 21-H), 0.86 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.66 (s, 3H, 18-H); ^{13}C NMR, δ 170.2 (C), 168.3 (C), 87.9 (C), 80.7 (CH), 56.0 (CH), 55.8 (CH), 42.2 (C), 42.1 (CH), 39.6 (CH_2), 39.5 (CH_2), 37.3 (C), 36.1 (CH_2), 35.7 (CH), 34.4 (CH_3), 34.0 (CH), 28.2 (CH_2), 28.1 (CH_2), 28.0 (CH), 26.1 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 20.3 (CH_3), 18.6 (CH_3), 17.2 (CH_3), 11.8 (CH_3); MS, m/z 475 (1), 459 (<1), 429 (9), 387 (100).

Compound **2**: mp 154-156°C (hexane); IR, ν_{max} 1766, 1736, 1547, 1305, 1197 cm^{-1}; ^1H NMR, δ 7.64 (s, 1H, 4α-H), 3.28 (s, 3H, N-CH_3), 2.56-2.68 (m, 2H, 2-H), 2.15 (s, 3H, CH_3CO), 1.17 (s, 3H, 19-H), 0.90 (d, J = 7 Hz, 3H, 21-H), 0.87 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.68 (s, 3H, 18-H); ^{13}C NMR, δ 170.8 (C), 167.7 (C), 87.5 (C), 81.5 (CH), 55.8 (CH), 55.3 (CH), 47.6 (CH), 42.8 (C), 39.5 (CH_2), 39.3 (CH_2), 38.7 (C), 36.0 (CH_2), 35.7 (CH), 34.4 (CH), 34.2 (CH_3), 30.2 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 28.1 (CH_2), 28.0 (CH), 25.5 (CH_2), 23.79 (CH_2), 23.76 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.6 (CH_2), 20.3 (CH_3), 18.6 (CH_3), 16.6 (CH_3), 12.2 (CH_3);

MS, m/z 475 (<1), 429 (6), 387 (100); anal. calcd for $C_{30}H_{50}N_2O_5$: C, 69.46; H, 9.72; N, 5.40; found: C, 69.67; H, 9.81; N, 5.43.

Compound **6**: mp 163-165°C (hexane - methylene chloride); IR, ν_{max} 3459, 1665, 1543 cm^{-1}; ^1H NMR, δ 5.60 (broad s, 1H, N-H), 4.48 (dd, J = 12.5 Hz, 3.8 Hz, 1H, 5α-H), 2.80 (d, J = 4.8 Hz, 3H, N-CH_3), 0.99 (s, 3H, 19-H), 0.89 (d, J = 6.2 Hz, 3H, 21-H), 0.86 (d, J = 6.4 Hz, 6H, 26-H, 27-H), 0.65 (s, 3H, 18-H); ^{13}C NMR, δ 173.3 (C), 90.6 (CH), 56.1 (CH), 55.9 (CH), 46.5 (CH), 42.4 (C), 40.5 (C), 39.51 (CH_2), 39.47 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.3 (CH), 33.1 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 28.0 (CH), 26.4 (CH_3), 25.8 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.8 (CH_2), 18.6 (CH_3), 16.2 (CH_3), 11.9 (CH_3); MS, m/z 418 (23), 400 (27), 287 (19), 86 (100); anal. calcd for $C_{27}H_{48}N_2O_3$: C, 72.28; H, 10.78; N, 6.24; found: C, 72.27; H, 10.85; N, 6.28.

It must be added that the reaction mixture composition varies with the reaction time. For example, the nitration reaction lasting 2 hours afforded the nitro formimides **5** (6%) and **4** (38%), the nitro acetate **3** (10%), and the nitro amide **6** (2%).

Bromination of 4-methyl-A-homo-4-azacholest-4a-en-3-one (1) with bromine in tetrachloromethane

A solution of compound **1** (400 mg; 1 mmol) in tetrachloromethane (3 mL) was treated with bromine (0.05 mL; 2 mmol) and magnetically stirred for 1 hour. The reaction mixture was then poured into water and extracted with chloroform (POCh Poland, reagent grade, stabilized with 0.6-1% ethanol). The extract was dried ($MgSO_4$), evaporated *in vacuo* and the residue was subjected to chromatografic separation. Bromo ether **7** (206 mg; 40%) was eluted with benzene - ethyl acetate (92:8). Further elution with 10% ethyl acetate in benzene afforded bromo aldehydes **9** (20 mg; 4%) and **8** (85 mg; 17%).

Compound **7**: mp 144-146°C (hexane); IR, ν_{max} 1637, 1084 cm^{-1}; ^1H NMR, δ 4.49 (s, 1H, 4-H), 3.70 and 3.36 (2 x dq, J_{AB} = 8.9 Hz, J_{AX} = J_{BX} = 7.0 Hz, 2 x 1H, an ABX_3 system, O-CH_2-), 3.11 (s, 3H, N-CH_3), 2.98 (m, 1H, 2-H?), 1.36 (s, 3H, 19-H), 1.22 (t, J = 7.0 Hz, 3H, CH_3-CH_2O-), 0.90 (d, J = 6.5 Hz, 3H, 21-H), 0.86 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.65 (s, 3H, 18-H); ^{13}C NMR, δ 174.6 (C), 101.4 (CH), 90.4 (C), 65.6 (CH_2), 56.1 (CH), 56.0 (CH), 49.4 (CH), 44.2 (C), 42.4 (C), 40.5 (CH_3), 39.7 (CH_2), 39.5 (CH_2), 36.8 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.3 (CH), 32.0 (CH_2), 31.6 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 18.6 (CH_3), 17.4 (CH_3), 15.0 (CH_3), 12.1 (CH_3); MS, m/z 539 and 537 (M^+, <1), 491 and 489 (4), 413 (79), 398 (37), 125 (100); exact mass calcd for $C_{30}H_{52}NO_2Br$: 539.3161 and 537.3181; found: 539.3169 and 537.3184.

Compound **9**: an oil; IR, ν_{max} 3461, 1716, 1665, 1525 cm^{-1}; ^1H NMR, δ 9.60 (s, 1H, CHO), 5.72 (m, 1H, N-H), 2,80 (d, J = 4.8 Hz, 3H, N-CH_3), 1.25 (s, 3H, 19-H), 0.88 (d, J = 6.4 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.65 (s, 3H, 18-H); ^{13}C NMR, δ 192.9 (C), 173.4 (CH), 84.9 (C), 56.0 (CH), 55.7 (CH), 50.7 (CH), 43.5 (C), 42.1 (C), 39.8 (CH_2), 39.5 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.5 (CH), 33.9 (CH_2), 33.6 (CH_2),

33.2 (CH_2), 30.7 (CH_2), 28.1 (CH_2), 28.0 (CH), 26.5 (CH_3), 24.1 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 18.5 (CH_3), 17.3 (CH_3), 11.9 (CH_3); MS, m/z 492 and 490 (2), 413 and 411 (51), 400 (71), 398 (31), 125 (100).

Compound **8**: an oil; IR, ν_{max} 3461, 1716, 1666, 1525 cm^{-1}; ^1H NMR, δ 9.76 (s, 1H, CHO), 5.44 (m, 1H, N-H), 2.80 (d, J = 4.8 Hz, 3H, N-CH_3), 1.04 (s, 3H, 19-H), 0.90 (d, J = 6.5 Hz, 3H, 21-H), 0.86 (d, J = 6.9 Hz, 6H, 26-H, 27-H), 0.66 (s, 3H, 18-H); ^{13}C NMR, δ 194.9 (CH), 173.2 (C), 85.4 (C), 56.1 (CH), 55.7 (CH), 48.1 (CH), 42.4 (C), 42.2 (C), 39.7 (CH_2), 39.4 (CH_2), 36.0 (CH_2), 35.6 (CH), 34.9 (CH_2), 34.5 (CH), 33.4 (CH_2), 31.5 (CH_2), 28.1 (CH_2), 27.9 (CH), 26.8 (CH_2), 26.2 (CH_3), 24.0 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 21.5 (CH_2), 18.5 (CH_3), 15.9 (CH_3), 11.9 (CH_3); MS, m/z 492 and 490 (17), 413 (57), 411 (23), 400 (31), 398 (33), 125 (100).

Bromination of 4-methyl-A-homo-4-azacholest-4a-en-3-one (1) with bromine in aqueous THF

A warm solution (about 40°C) of compound **1** (200 mg; 0.5 mmol) in aqueous THF (4 mL) was treated with bromine (0.5 mL) and magnetically stirred 40 min. The reaction was quenched by pouring into a diluted solution of sodium sulfite and extracted with chloroform. The solvent was removed from the dried ($MgSO_4$) extract under the reduced pressure. Column chromatography of the residue (elution with benzene - ether 9:1) afforded previously described bromo aldehydes **9** (111 mg; 45%) and **8** (76 mg; 31%).

Bromo aldehyde **8** (20 mg; 0.125 mmol) was dissolved in pyridine (3 mL) and heated under reflux for 4 hours. The reaction mixture was cooled, poured into water and extracted with chloroform. The extract was washed with diluted sulfuric acid, water, dried ($MgSO_4$) and was then evaporated *in vacuo*. The crude product was purified by the column chromatography (elution with petroleum ether - ethyl acetate 85:15) and crystallized from hexane to afford compound **11** (9 mg; 45%); mp 98-101°C (hexane); IR, ν_{max} 1646, 1638, 1273, 1105 cm^{-1}; ^1H NMR, δ 5.91 (dd, J = 9.8 Hz, 2.5 Hz, 1H, 7-H), 5.67 (s, 1H, 4a-H), 5.57 (dd, J = 9.8 Hz, 1.9 Hz, 1H, 6-H), 3.04 (s, 3H, N-CH_3), 1.02 (s, 3H, 19-H), 0.90 (d, J = 7 Hz, 3H, 21-H), 0.87 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.71 (s, 3H, 18-H); ^{13}C NMR, δ 174.6 (C), 132.8 (C), 129.3 (CH), 128.6 (CH), 126.7 (CH), 56.0 (CH), 54.4 (CH), 49.4 (CH), 43.1 (C), 39.8 (CH_2), 39.5 (CH_2), 39.3 (CH), 36.7 (CH), 36.1 (CH_2), 36.0 (C), 35.8 (CH), 35.6 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 28.0 (CH), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.2 (CH_2), 20.6 (CH_3), 18.6 (CH_3), 12.0 (CH_3); MS, m/z 411 (M^+, 48), 396 (4), 356 (6), 57 (100); exact mass calcd for $C_{28}H_{45}NO$: 411.3501; found: 411.3496.

Bromo aldehyde **9** did not undergo dehydrobromination under similar conditions.

Bromination of 4-methyl-A-homo-4-azacholest-4a-en-3-one (1) with "positive" bromine

(a) A solution of $AgBF_4$ (200 mg; 1.0 mmol) in 5 mL of 1,2-dimethoxyethane was treated with bromine (0.05 mL; 2 mmol). The reaction mixture was magnetically stirred 15 min before steroid **1** (200 mg; 0.5 mmol) was

added. After 0.5 h the reaction mixture was quenched with aqueous sodium sulfite solution and extracted with chloroform. The solvent was evaporated *in vacuo* and the oily residue was subjected to the silica gel column chromatography. With benzene-ether mixtures (from 5% to 10% of ether) bromo ether **15** (92 mg; 36%), bromo aldehydes **9** (11 mg; 4.6%) and **8** (8 mg; 3.2%), were consecutively eluted.

Compound **15**: IR, ν_{max} 1637, 1084 cm^{-1}; ^1H NMR, δ 4.40 (s, 1H, 4-H), 3.36 (s, 3H, O-CH_3), 3.14 (s, 3H, N-CH_3), 1.32 (s, 3H, 19-H), 0.90 (d, J = 6.5 Hz, 3H, 21-H), 0.86 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.65 (s, 3H, 18-H); ^{13}C NMR, δ 174.6 (C), 103.1 (CH), 90.3 (C), 57.3 (CH_3), 56.1 (CH), 56.0 (CH), 49.5 (CH), 44.3 (C), 42.4 (C), 40.7 (CH_3), 39.7 (CH_2), 39.5 (CH_2), 36.9 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.3 (CH), 31.9 (CH_2), 31.6 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.6 (CH_2), 18.6 (CH_3), 17.2 (CH_3), 12.1 (CH_3).

(b) To a stirred solution of steroid **1** (200 mg; 0.5 mmol) and $AgBF_4$ (200 mg; 1.0 mmol) in 5 mL of 1,2-dimethoxyethane bromine (0.05 mL; 2 mmol) dissolved in 1 mL of the same solvent was dropwise added. After 0.5 h the reaction mixture was quenched with sodium sulfite solution and extracted with chloroform. Evaporation of the solvent *in vacuo* from the dried ($MgSO_4$) extract yielded an oily residue which was subjected to the silica gel chromatography. Benzene-ether mixtures (from 10% to 20% of ether) eluted lactone **12** (44 mg; 21%) followed by lactams **14** (35 mg; 18%) and **13** (13 mg; 6.5%).

Compound **12**: mp 157-160°C (hexane); IR, ν_{max} 1737, 1269, 1171 cm^{-1}; ^1H NMR, δ 9.69 (s, 1H, CHO), 1.14 (s, 3H, 19-H), 0.90 (d, J = 6.9 Hz, 3H, 21-H), 0.87 (d, J = 6.9 Hz, 6H, 26-H, 27-H), 0.69 (s, 3H, 18-H); ^{13}C NMR, δ 200.6 (CH), 170.8 (C), 90.8 (C), 56.1 (CH), 55.7 (CH), 42.4 (C), 41.4 (CH), 39.5 (CH_2), 39.4 (CH_2), 36.4 (CH_2), 36.0 (C), 35.7 (CH), 34.2 (CH), 28.2 (CH_2), 28.0 (CH), 27.6 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 19.7 (CH_2), 18.6 (CH_3), 17.6 (CH_3), 11.9 (CH_3); MS, m/z 387 (M^+ - CHO; 100), 261 (21); exact mass calcd for $C_{26}H_{43}O_2$: 387.3263; found: 387.3276.

Compound **14**: IR, ν_{max} 1727, 1630 cm^{-1}; ^1H NMR, δ 9.66 (s, 1H, CHO), 2.81 (s, 3H, N-CH_3), 1.06 (s, 3H, 19-H), 0.89 (d, J = 6.6 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.67 (s, 3H, 18-H); ^{13}C NMR, δ 202.2 (CH), 171.9 (C), 72.8 (C), 56.1 (CH), 55.8 (CH), 42.4 (C), 41.9 (CH), 39.6 (CH_2), 39.4 (CH_2), 37.9 (C), 36.1 (CH_2), 35.7 (CH), 34.4 (CH), 28.9 (CH_3), 28.2 (CH_2), 28.1 (CH_2), 28.0 (CH), 27.6 (CH_2), 25.9 (CH_2), 24.5 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 19.8 (CH_2), 18.6 (CH_3), 18.5 (CH_3), 11.9 (CH_3); MS, m/z 428 (M^+ - H; 3), 400 (100), 124 (50); exact mass calcd for $C_{28}H_{46}NO_2$: 428.3529; found: 428.3528.

Compound **13**: IR, ν_{max} 1721, 1632 cm^{-1}; ^1H NMR, δ 9.80 (s, 1H, CHO), 2.82 (s, 3H, N-CH_3), 1.06 (s, 3H, 19-H), 0.90 (d, J = 6.6 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.68 (s, 3H, 18-H); ^{13}C NMR, δ 198.1 (CH), 173.1 (C), 70.3 (C), 56.1 (CH), 55.9 (CH), 48.4 (CH), 42.5 (C), 42.3 (C), 39.5 (CH_2), 39.1 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.9 (CH_2), 33.7 (CH), 28.2 (CH_2), 28.0 (CH), 27.4 (CH_3), 27.1 (CH_2), 26.3 (CH_2), 25.4

(CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.3 (CH_2), 18.6 (CH_3), 15.4 (CH_3), 12.0 (CH_3); MS, m/z 428 (M^+-H; <1), 400 (100), 124 (44); exact mass calcd for $C_{28}H_{46}NO_2$: 428.3529; found: 428.3528.

When aldehyde **14** was allowed to stand at room temperature in an open flask for a few days, it underwent complete transformation into the known ene-lactam **16**. The analogous reaction was also observed in the case of the isomeric aldehyde **13**.

Oxidation with CrO_3 - pyridine complex

A stirred solution of pyridine (2.6 g; 0.032 mol) in 33 mL of methylene chloride was treated with P_2O_5 (3.3 g; 0.024 mol) and cooled to 4°C. Then, anhydrous CrO_3 (1.6 g; 0.016 mol) was portionwise added. The reagent was stirred until the complete dissolution of CrO_3 (about 1h), and then a solution of ene-lactam **1** (200 mg; 0.5 mmol) in 3 mL of methylene chloride was added. The reaction mixture was heated under reflux 1h, quenched by pouring into water, and extracted with chloroform. The solvent was removed *in vacuo* from the dried ($MgSO_4$) extract and the product was purified by silica gel column chromatography. A-Seco formimide **17** (118 mg; 55%) was eluted with benzene - ether (5%) mixture, mp 98-100°C (methanol - acetone); IR, ν_{max} 1722, 1697, 1670, 1298 cm^{-1}; ^1H NMR, δ 9.41 (s, 1H, N-CHO), 3.12 (s, 3H, N-CH_3), 1.15 (s, 3H, 19-H), 0.91 (d, J = 6.5 Hz, 3H, 21-H), 0.87 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.74 (s, 3H, 18-H); ^{13}C NMR, δ 215.4 (C), 175.1 (C), 163.3 (CH), 56.0 (CH), 55.7 (CH), 50.4 (C), 48.3 (CH), 42.5 (C), 39.5 (CH_2), 39.3 (CH_2), 38.1 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.9 (CH), 31.6 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 28.04 (CH_2), 27.98 (CH), 26.5 (CH_3), 24.2 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.4 (CH_2), 20.2 (CH_3), 18.6 (CH_3), 12.0 (CH_3); MS, m/z 445 (M^+, 1), 427 (2), 418 (2), 399 (99), 384 (54), 332 (100); exact mass calcd for $C_{28}H_{47}NO_3$: 445.3556; found: 445.3552.

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