The synthesis of 16-dehydropregnenolone acetate (DPA) from potato glycoalkaloids

Patrick J.E. Vronen[a], Nadeshda Koval[b], and Aede de Groot[a]*

[a] *Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands, and*
[b] *Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220141, Minsk, Belarus*
E-mail: Aede.deGroot@wur.nl

Dedicated to Professor Binne Zwanenburg on his 70th birthday
(received 18 Sep 03; dedicated 18 Nov 03; published on the web 21 Nov 03)

Abstract

The use of solanidine as starting material for the synthesis of steroid hormones was strongly stimulated by the possibility to isolate large amounts (ton scale) of potato glycoalkaloids from a waste stream of the potato starch production. A procedure is available to isolate these glycoalkaloids from the potato protein fraction and after hydrolysis solanidine is set free and can be made available as alternative for diosgenine as starting material for the production of dehydropregnenolon acetate (DPA). The conversion of solanidine to DPA was first tried by reinvestigation of several known methods like oxidation with $Hg(OAc)_2$, the Cope reaction and the Polonovski reaction but none of these approaches were successful. The best option was to open the E,F-ring system using the Von Braun reaction. Besides the desired major E-ring opened compound also the minor F-ring opened compound was isolated. Alternatives for the hazardous Von Braun reagent BrCN were investigated but not found. Further degradation using the Hofmann reaction was successful in a Δ^{16} derivative, which led to the desired triene intermediate.

Finally DPA could be obtained starting from solanidine in 9 reaction steps in 30% overall yield using the known conversion to spirosolane compounds followed by conversion to DPA. Extensive research has been performed on finding shortcuts in this route but despite all our efforts, further shortening of the route from 3-acetoxysolanidine via tomatidenol to DPA could not be accomplished.

Keywords: Solanidine, dehydropregnenolon acetate, Von Braun reaction, Hofmann degradation

Introduction

Since the first structure elucidation of solanidine (**1**) about 70 years ago, research has been carried out to convert this aglycon to an intermediate for the synthesis of steroids. Renewed interest in this conversion was stimulated by the possibility to isolate large amounts (ton scale) of potato glycoalkaloids from a waste stream of the potato starch production. During the starch refining process the proteins together with the glycoalkaloids are separated from the starch. This protein fraction is then subjected to a number of refining steps in which the proteins are separated from the glycoalkaloids. The glycoalkaloids together with free amino acids, peptides and minerals end up in the so-called protamylasse fraction. The amount of glycoalkaloids present in this fraction varies from 200-2000 ppm dependent on the potatoes processed per campaign. Potato glycoalkaloids consist for more than 95% of α-chaconine and α-solanine, which both have the steroid-like solanidine (**1**) as aglycon, thus a large potential of starting material may become available for conversion to steroid hormones.

During the last 50 years diosgenine is used as the main starting material in the industrial synthesis of progestagens, androgens, estrogens, norsteroids, and a diuretic spironolactone. Uncertain external factors have often influenced the guaranteed supply of diosgenine and in the course of time many alternatives have been investigated. These alternatives should have in common that they can be implemented in existing production facilities for economic and pharmaceutical reasons. Solanidine (**1**) could be such an alternative on condition that it can be converted in an industrially attractive way to DPA (**6**), which is a key intermediate in the industrial syntheses of progesterone and cortisone derivatives. We here like to report on our results in this field.

Results and Discussion

Isolation and hydrolysis of potato glycoalkaloids

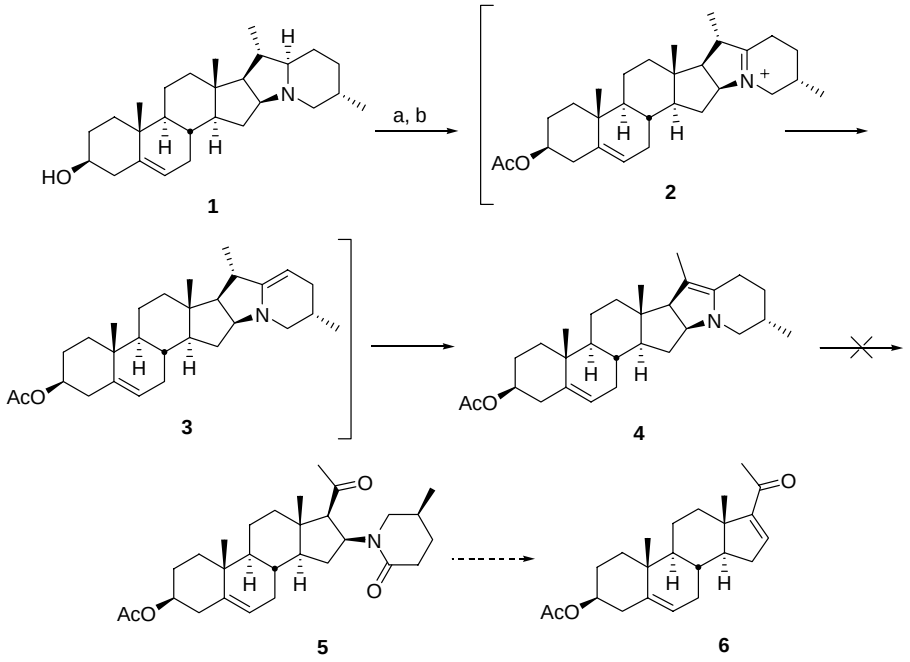
To obtain the starting material for our research, an improved simple and effective method has been developed for the isolation of the potato glycoalkaloids, α-chaconine and α-solanine, from the spray dried protamylasse fraction, which was obtained from AVEBE[1]. When this crude fraction was directly subjected to hydrolysis a complex product mixture was formed. Therefore a modified method of Friedman *et al.*[2] was used for the extraction of the potato glycoalkaloids from the protamylasse fraction. A crude mixture of α-chaconine and α-solanine was obtained by using aqueous ethanol for this extraction, and recrystallization from ethanol gave a clean mixture of both glycoalkaloids. In this way 221.1 g of spray-dried protamylasse yielded 10.8 g of glycoalkaloids, which is 85% yield based on a 5.7% glycoalkaloid content in the spray-dried protamylasse as determined by HPLC. Chemical hydrolysis was performed with acid and

solanidine (**1**) was isolated from the acidic ethanol in an almost quantitative yield after precipitation with NH_4OH.

Because both the isolation and hydrolysis of the glycoalkaloids can be performed on a large scale, attempts were made to combine both procedures. Since the protamylasse fraction has a pH of 5-6 it could be dissolved in water without addition of acid. After the aqueous solution was made basic with NH_4OH and stored overnight at 4ºC, the slurry was centrifuged and the supernatant discarded. The pellet was again directly subjected to hydrolysis but also in this case a complex product mixture was formed, and extraction with ethanol proved to be necessary prior to hydrolysis. Thus the pellets were transferred to a Soxhlett apparatus and extracted with ethanol for 24 hours. After concentration of the extract, a crude glycoalkaloid fraction was obtained. This fraction was hydrolyzed in acidic ethanol for 2.5 hours, and the alkaloids were precipitated with NH_4OH. The crude precipitate was filtered and recrystalized from ethanol to give pure solanidine (**1**). The hydrolysis of the glycoalkaloids is accompanied by the formation of solanidiene in 9% yield, but lowering the amount of acid in the hydrolysis step from 2M to 1M HCl in ethanol reduced the formation of solanidiene to a negligible amount.

The conversion of solanidine to DPA

The conversion of solanidine (**1**) to DPA (**6**) was first tried by the recently published method using $Hg(OAc)_2$ as oxidation reagent.[3] Electrochemical[4,5] oxidations of solanidanes have shown that the $\Delta^{22(N)}$-iminium salt is exclusively formed in acetone, while the $\Delta^{16(N)}$-iminium salt is the sole product in CH_2Cl_2, in both cases pyridine is added as base. Chemical[6,7] oxidation of solanidine with $Hg(OAc)_2$ in acetone or CH_2Cl_2 showed the same preference in formation of the $\Delta^{16(N)}$-iminium and $\Delta^{22(N)}$-iminium salts.



Scheme 1. a. Ac_2O, pyridine, 98%. b. $Hg(OAc)_2$, acetone, 97%.

In 1997 Gaši *et al.*[3] reported the conversion of solanidine (**1**) to DPA (6) via iminium ion **2** and the enamine intermediates **3** and **4** (Scheme 1). Enamine **4** is oxidized with $NaIO_4$, NaI, and $NaHCO_3$ in a mixture of water and *t*-BuOH to ketolactam **5**, and elimination of the lactam moiety in **5** gives DPA (**6**) in an overall yield of 28%. Before reinvestigation of the degradation of solanidine (**1**), it was converted to its acetate prior to oxidation with $Hg(OAc)_2$. Because the $Hg(OAc)_2$ contained some acetic acid[7], enamine **4** was directly formed in 90% yield, which made the separate isomerization step superfluous. However, oxidation of enamine **4** according to the procedure of Gaši *et al.*[3] was unsuccessful in our hands and the starting material was recovered almost quantitatively. Many other oxidation reagents were tried (ozone,[8] O_2/CuCl,[9] MnO_2,[10,11] $KMnO_4$,[12] $KMnO_4/Al_2O_3$,[13] CrO_3/HOAc,[14-16] CrO_3/pyridine,[17] H_2O_2,[18] MMPP[19]), but in all cases no oxidation product could be obtained. To rule out a possible involvement of the $\Delta^{5,6}$ double bond during the oxidation,[20] **1** was transformed into solanidan-4-en-3-one (**7**) by treatment of **1** with Al(*i*-PrO)$_3$ in toluene in the presence of cyclohexanone (Scheme 2). Oxidation of enone (**7**) with $Hg(OAc)_2$ again showed the exclusive formation of the corresponding $\Delta^{20,22}$-enamine, which was subjected again to a range of oxidation reactions,[3,8,10-16,18,19,21] but all failed in our hands.

According to Gaši and co-workers[3] the modest yield of the oxidation of enamine **4** was due to its instability. However, Mopac[22] PM3 calculations[23,24] showed that enamine **4** (ΔH_f = -76.57 kcal) is more stable than enamine **3** (ΔH_f = -68.86 kcal).The energy difference is large enough to make isomerization during the oxidation reaction unlikely and the difficulties in the oxidation reaction can not only be imputed to the instability of enamine **4**. These calculations also show that enamine **4** is not really an enamine but more an isolated double bond and a separate amino group. The bond order of the C-N bond is 1.03, which indicates that there is nearly a single bond between C22 and N. The $\Delta^{20,22}$ double bond forces the five membered E-ring to be completely flat, and as a consequence the D-ring is bent in such a way that C18 and the six membered ring shield its top and bottom side, respectively (Figure 1). The methyl group (C21) lies in the plane of the $\Delta^{20,22}$ double bond making it even more difficult to approach. In our opinion, steric hindrance is the main reason for the low reactivity of this $\Delta^{20,22}$ double bond.

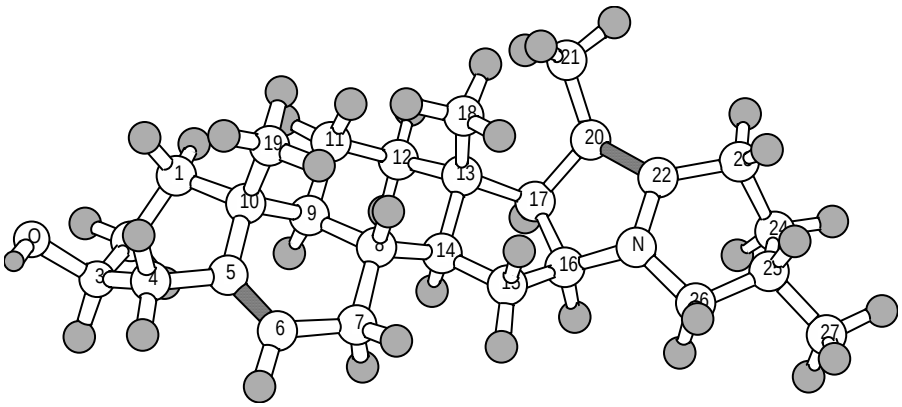
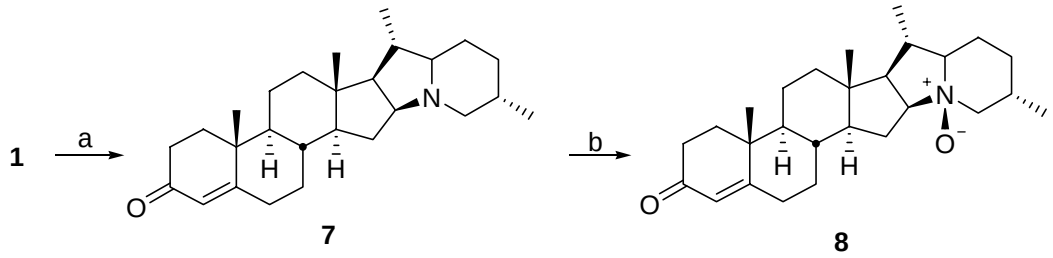


Figure 1. Enamine 4.

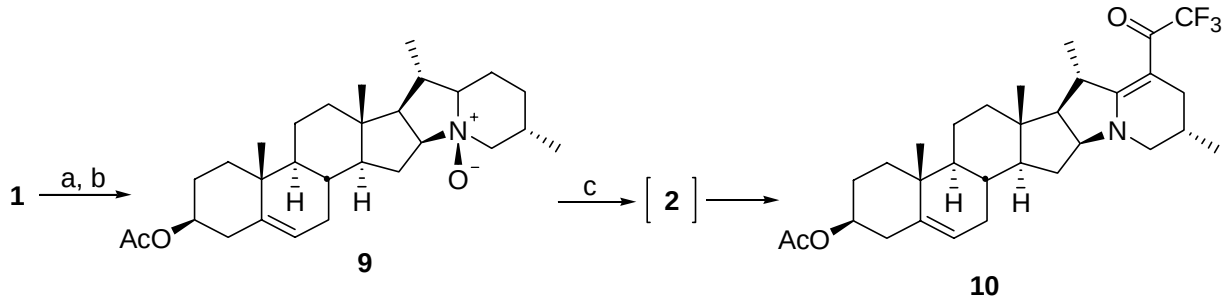
The Cope and Polonovski reactions

In the second attempt to convert solanidine (**1**) to DPA (**6**) the Cope and Polonovski reactions were studied and to do so it was necessary to synthesize a solanidine *N*-oxide first. To avoid epoxidation problems solanidine (**1**) was converted to solanidi-4-en-3-one (**7**), which could be oxidized with MMPP to the corresponding solanidi-4-en-3-one *N*-oxide (**8**) in good yield (Scheme 2). It turned out that the Cope reaction did not give the desired results because a 5-membered planar transition state, necessary for the Cope reaction, is not possible in this molecule. In such cases deoxygenation, being a competitive process, takes over and indeed, solanidi-4-en-3-one (**7**) was recovered in all attempts.

The Polonovski reaction can be carried out with Ac_2O or $(CF_3CO)_2O$ under rather extreme conditions. With Ac_2O no reaction was observed for solanidine *N*-oxide (**8**) or 3-acetoxysolanidine *N*-oxide (**9**). Treatment of **9** with $(CF_3CO)_2O$ yielded compound **10** as the result of elimination, isomerization of iminium ion **2** and trifluoroacylation (Scheme 3). This is a new result, but no further attempts have been undertaken to convert compound **10** in DPA (**6**).



Scheme 2. a. Al(*i*-PrO)$_3$, toluene, cyclohexanone, Δ, 72%. b. MMPP, CH_2Cl_2, H_2O, RT, 12 h, 53%.



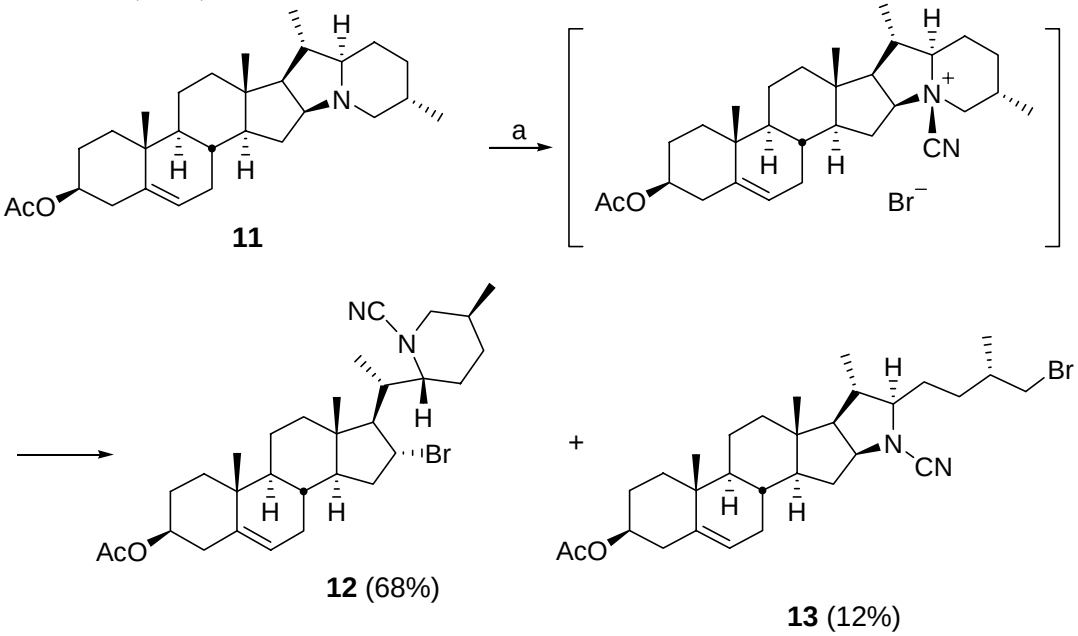
Scheme 3. a. Ac_2O, pyridine, 97%. b. *m*CPBA, CH_2Cl_2, RT, 2 hours, 90%. c. $(CF_3CO)_2O$, THF, *t*-BuOK, *t*-BuOH, RT, 6 h, 41%.

The Von Braun reaction

The third option was to open the E,F-ring system using the Von Braun reaction, which was performed on 3-acetoxysolanidine (**11**) according to the method of Beisler and Sato.[25,26] Next to a 68% yield of **12**, the F-ring opened side-product **13** was isolated in 10% yield, which must be the result of bromide attack at C26 (Scheme 4). Although not described in the literature, it is

most likely that this product is always formed in the Von Braun reaction but it has never been mentioned before.

Because the use of BrCN in industry requires special safety measures, less toxic alternatives such as acetyl chloride,[27,28] ethyl chloroformate,[29-35] trichloroethyl chloroformate,[36] benzoylchloride,[37] and benzyl chloride[38] have been investigated. Although these reagents give good results with common tertiary amines, no reaction was observed with 3-acetoxysolanidine (**11**). Other attempts with Ac_2O and $(CF_3CO)_2O$,[39] trichlorotriazine, chlorodimethoyxytriazine[40-42] and TMSCl, NaI, Ac_2O[43] were also unsuccessful.



Scheme 4. a. BrCN, $CHCl_3$, 24 h.

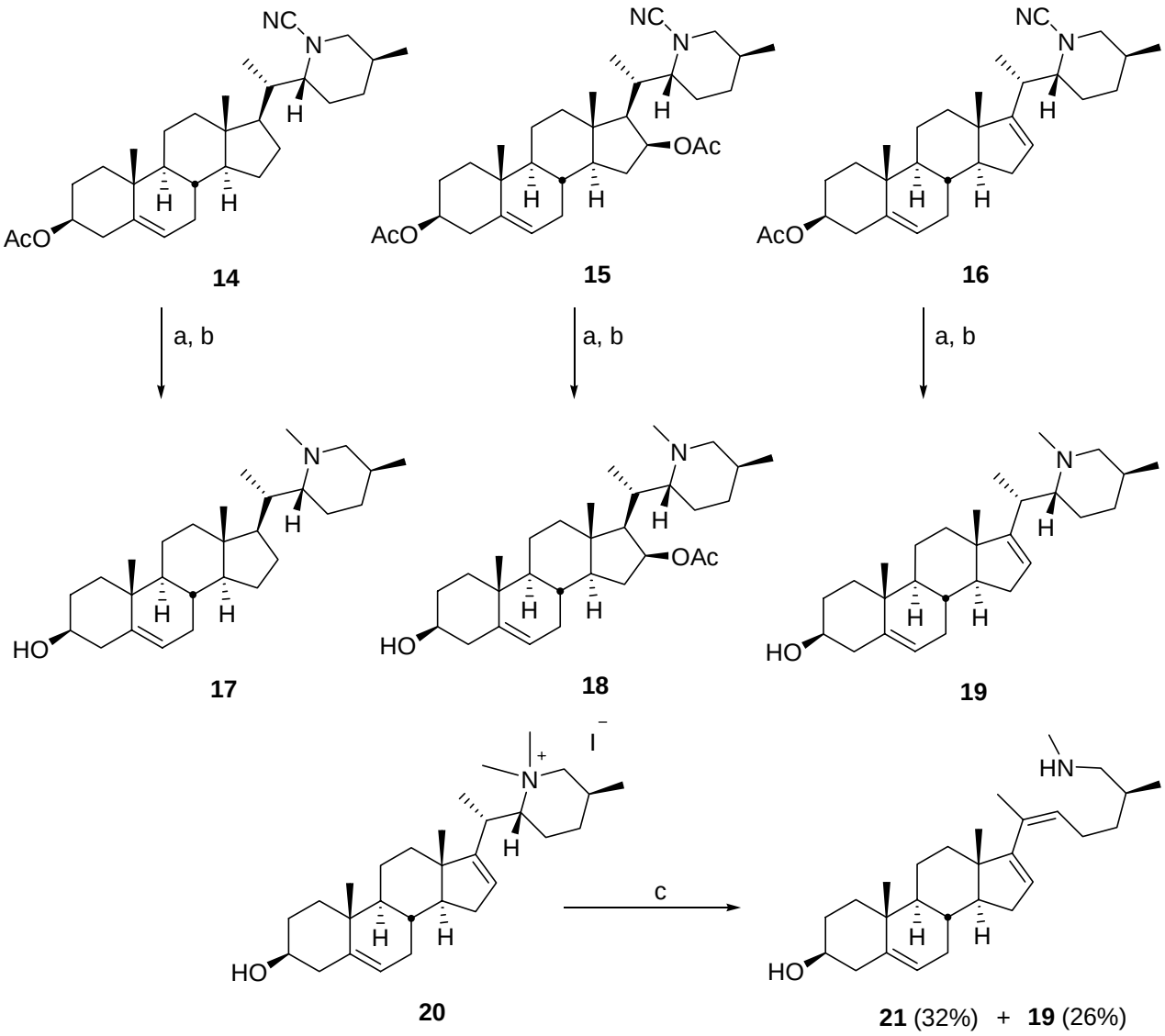
The fact that ringopening can only be achieved with BrCN can be explained by the unique electronic and steric properties of this reagent. Besides, a striking difference between an N-atom bearing a nitrile group, and an acylated N-atom is the formal positive charge of the N-atom as shown by MOPAC PM3 calculations. The N-atom of the intermediate *N*-nitrilium ion possesses a formal charge of +0.75 while the N-atom of the corresponding *N*-acylium ion has a charge of only +0.38. This makes the neighboring C-atoms in the *N*-nitrilium ion much more susceptible to nucleophilic attack than in the *N*-acylium ions.

Despite all attempts, BrCN remains the only reagent until now, capable to open the indolizidine ring system of 3-acetoxysolanidine (**11**). Although the objectives against large-scale industrial application of BrCN remain, the reaction itself gives a good yield of **12**, which has possibilities for further transformation to DPA (**6**).

The Hofmann degradation

One of the possibilities for further transformation of the ringopened product **12** is the Hofmann degradation. To avoid disturbing side reactions under the basic reaction conditions, the bromide

was removed, replaced by an acetate or eliminated. Treatment of **12** with Bu_3SnH and AIBN in benzene at reflux temperature, gave **14** in 94% yield. Treatment of **12** with KOAc in DMF at 90ºC gave the acetate **15** in 83% yield[26] and introduction of the $\Delta^{16,17}$ double bond was achieved by treatment of **12** with *s*-collidine to afford **16** in 98% yield.[7] Direct methylation of these nitriles was unsuccessful as expected, so the nitrile was removed by reduction with Red-Al to give the corresponding secondary amines.

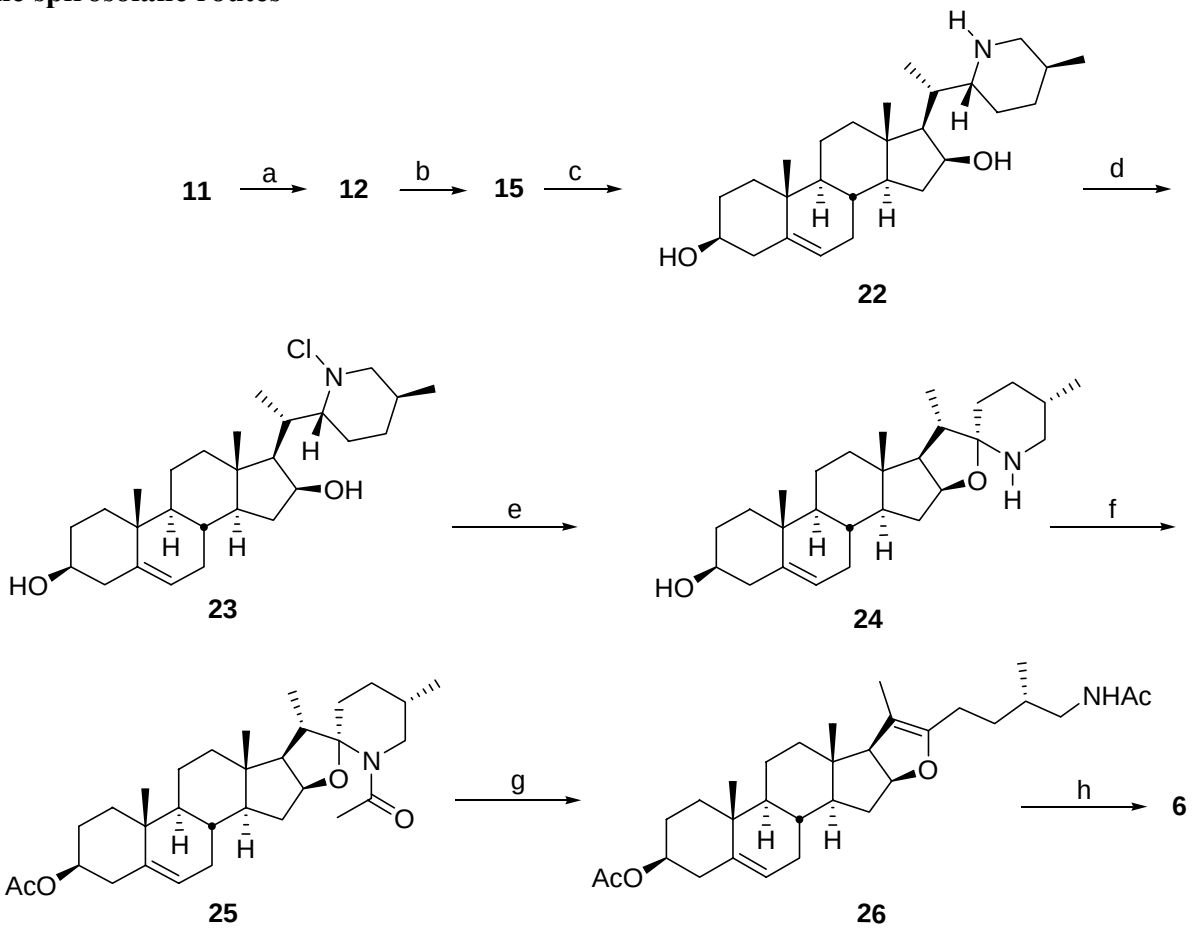


Scheme 5. a. Red-Al, toluene, Δ. b. Na_2CO_3, MeI, then KOH, MeOH, Δ̃ c. LDA, THF, -78ºC, 32% (**20**), 26% (**19**).

Methylation with MeI and Na_2CO_3 in water proceeded smoothly and gave the ammonium salts in high yields, which were subjected to treatment with base without further purification. This resulted in formation of the demethylated products **17** and **18** in 76% and 32% yield,

respectively. Treatment of the unsaturated ammonium salt **20** with KOH,[44] *t*-BuOK,[45,46] NaOH,[47,48] NaOMe,[49] or Et_3N,[50] gave products which immediately decomposed during the isolation process. Only when **20** was treated with LDA the desired product **21** together with the *N*-monomethylated product **19** could be isolated in 32% and 26% yield, respectively (Scheme 5). The formation of demethylated products can be explained by difficulties in the proton abstraction, which is necessary for ringopening. In these cases the competitive nucleophilic substitution resulting in demethylation is strongly favored over the Hofmann degradation. LDA is a small and strong enough base to abstract the proton from C20, but only in the case of **20** compound **21** was formed. The presence of the $\Delta^{16,17}$ double bond makes H20 to an allylic proton, which is more prone to abstraction. The further degradation of **21** to DPA (**6**) requires several protection and deprotection steps as shown by Maitra and Breslow,[51] which are not very attractive for industrial application. Besides the use of several hazardous reagents is another reason to look for alternatives.

The spirosolane routes



Scheme 6. a. BrCN, $CHCl_3$, Δ, 24 h, 68%. b. KOAc, DMF, 83%. c. Red-Al, toluene, Δ, 93%. d. NCS, CH_2Cl_2, RT, 2 h, 95%. e. NaOMe, MeOH, Δ, 95%. f. Ac_2O, pyridine, 98%. g. HOAc, Δ, 85%. h. CrO_3, HOAc, Δ, 76%.

A better industrially applicable alternative may be found in the conversion of solanidine (**1**) to spirosolanes. In 1971 Schramm and Riedl[26] already mentioned that the degradation of solanidine (**1**) to DPA (**6**) can be accomplished via the tomatidine series but up to now the complete procedure has never been published.

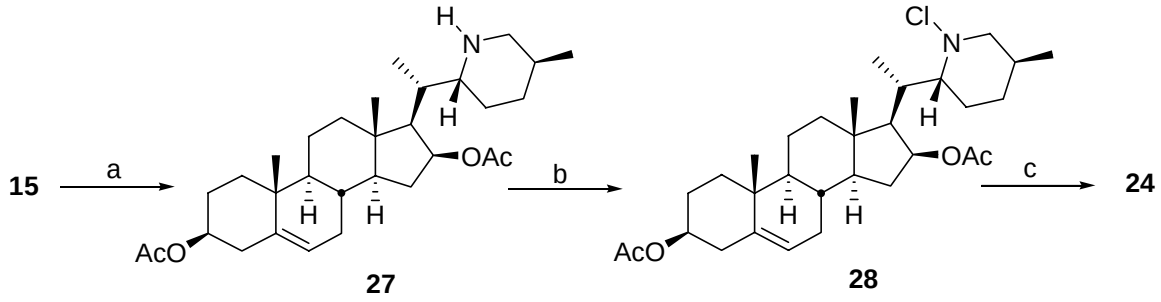
Therefore 3-acetoxysolanidine (**11**) was first submitted to the Von Braun reaction, which gave **12** in 68% yield[25] (Scheme 6). Substitution of the bromide at C16 with KOAc yielded acetate **15** in 83%.[26] Subsequent reduction of **15** with Red-Al then gave **22** in 93% yield[52]. Chlorination of **22** with NCS afforded **23** in 95% yield and elimination of HCl with NaOMe resulted in ringclosure to give tomatidenol (**24**) in 95% yield.[53-58] Acetylation of tomatidenol with Ac_2O in pyridine gave **25** in 98% yield. Treatment of **25** with HOAc at reflux temperature gave compound **26** in 85% yield. Subsequent oxidation with CrO_3 in HOAc and elimination of the resulting C16-ester gave DPA (**6**) in 76% yield. The overall yield starting from 3-acetoxysolanidine (**11**) to DPA (**6**) over 9 steps was 30%.

An alternative procedure for the conversion of tomatiedol (**24**) in DPA consists of nitrosation of tomatidenol followed by decomposition of the nitroso compound, oxidation and elimination[59].

Shortcuts to tomatidenol (24) starting from 3-acetoxysolanidine (11)

To compete with existing industrial processes this route should be shortened and expensive reagents should be avoided. Shortcuts were attempted to convert compounds from the first part of the route (**11→24**) to compounds from the second part of the route (**24→6**).

A first improvement was found in the replacement of Red-Al by activated Zn in HOAc[60] in the reduction of **15**, which was already mentioned in a patent (Scheme 7). Best results were obtained by using freshly prepared activated Zn[61] and the acetate **27** was obtained in a yield of 90%. $LiAlH_4$[62] also reduces nitrile **15** to **22** but the yield (64%) is lower than in the cases of Red-Al or Zn/HOAc.[52] Chlorination of **27** with NCS leads to chloride **28**[63] in 95% yield and subsequent treatment of **28** with NaOMe in MeOH gives tomatidenol (**24**) in 95% yield[53-58,64,65].

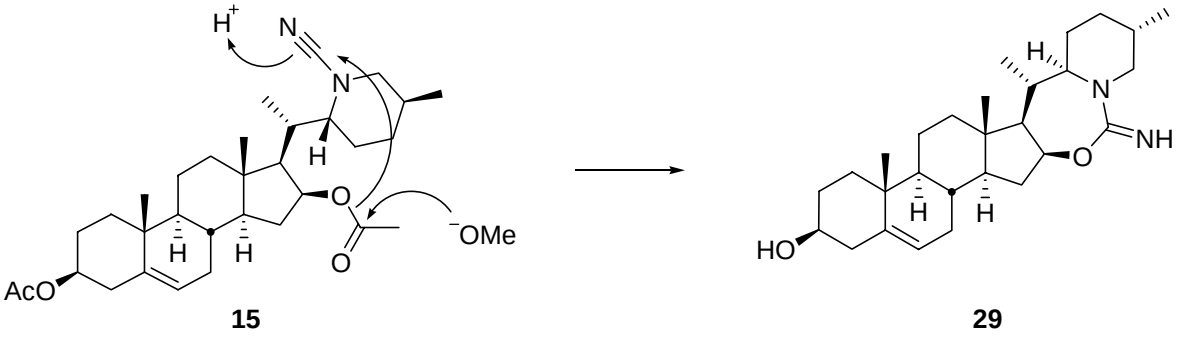


Scheme 7. a. Zn, HOAc, H_2O, 90%. b. NCS, CH_2Cl_2, RT, 2 h, 95%. c. NaOMe, MeOH, Δ, 2 h, 95%.

The chlorination/dehydrochlorination process is an economically unfavorable two-step process and direct introduction of the $\Delta^{22,N}$ double bond would be more efficient. This has been

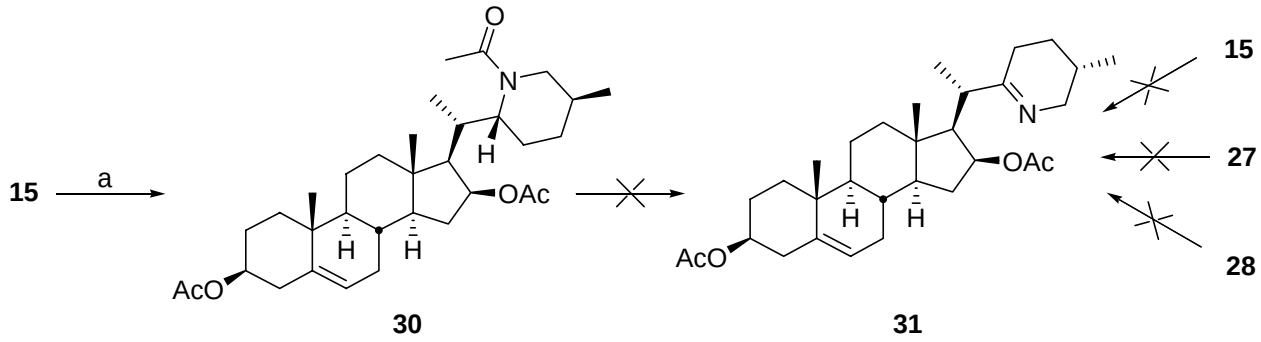
tried i) by elimination of HCN from **15** (Scheme 8), ii) by oxidation of amide **30** (Scheme 9), iii) by elimination of chlorine from **28**, and iv) by oxidation of amine **27**.

Direct elimination of the nitrile group from **15** has been tried by treatment with NaOMe, which led to a single product that was identified as **29**. A mechanistic explanation for the formation of **28** is depicted in Scheme 8.[66]



Scheme 8

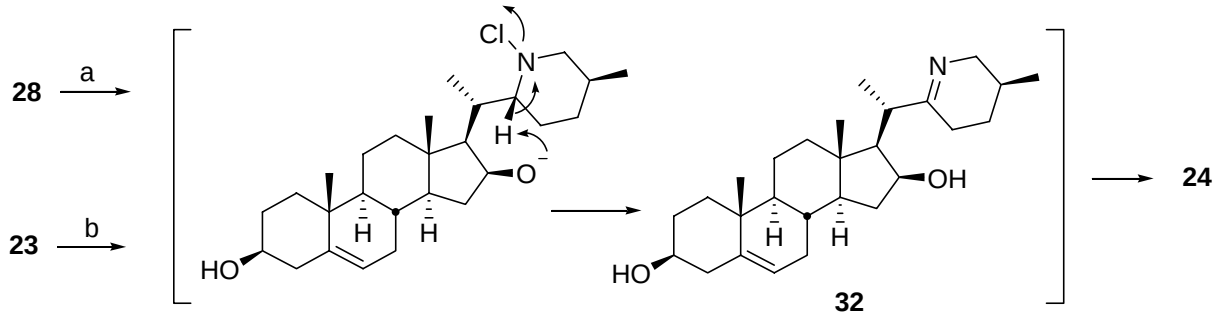
The amide **30** could be obtained in 95% yield by treatment of nitrile **15** with Zn in anhydrous HOAc.[26,67] The introduction of the double bond in **30** was attempted with CAN[68], MnO_2,[10,11] and HCl(aq.)[69] but unfortunately without success.



Scheme 9. a. HAc, Zn, 95%.

These results indicate that an imine can only be formed by chlorination and subsequent dehydrochlorination of **28** with NaOMe, but under these circumstances the acetates are saponified also, and a further reaction to tomatidenol (**24**) can not be avoided. To achieve formation of the $\Delta^{22(N)}$ bond and to prevent further reaction to tomatidenol, it will be necessary to maintain the acetate group at C16. Therefore **28** was treated with several bases (NaOAc/EtOH[70], K_2CO_3/DMF,[71] LiBr/Li_2CO_3/DMF,[71] NaOMe/toluene, t-BuOK,[72] Et_3N,[73] Et_2Nli,[74] KHMDS,[74,75] NaH/DMSO[76]) but all attempts were unsuccessful. It proved to be impossible to eliminate HCl from **28**, when an acetate group at C16 is present[65]. On the other hand, elimination of HCl

proved to be relatively easy if a free hydroxyl group is present at C16 as was demonstrated by the conversion of **23** to tomatidenol (**24**) in 73% yield with DBU.[77] An intramolecualr elimination as depicted in Scheme 10[53,54,56,58,78] can explain these results.



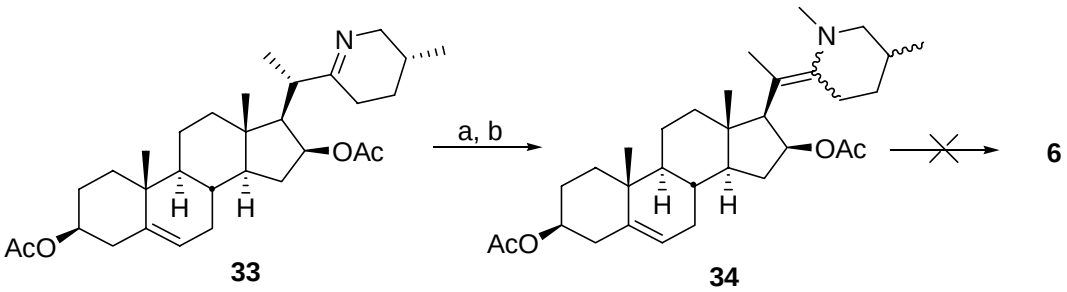
Scheme 10. a. NaOMe, MeOH, Δ, 2 h, 95%. b. DBU.

Direct oxidation of **27** with CrO_3/pyridine,[79] $KMnO_4$,[12] CAN,[68] or $KMnO_4/Al_2O_3$[68] was in all cases unsuccessful and only the starting material was recovered. Adam and Huong[80] described several successful spirosolane formations (tomatidine (**24**), solasodine, soladulcidine, and solasodenone) through oxidation of the secondary amine with MnO_2[81] followed by stereospecific cyclization.[54,82] However, several attempts with differently activated MnO_2[80,83] failed to give any of the desired imine **31** and only with MnO_2 freshly prepared according to the method of Attenburrow et al.[81] some imine **31** could be detected in the reaction mixture but the major product was still the starting material **27**.

Although the diacetylated imine **31** could not be obtained from nitrile **15**, amide **30**, chloride **28**, or amine **27**, it can become available from tomatidenol (**24**) by treatment with $ZnCl_2$ and Ac_2O in HOAc.[84] The availability of **31** gives the possibility to investigate two alternative degradation routes toward DPA (**6**). However, the limited amount of solanidine (**1**), available from the spray-dried protamylasse fraction, and the fact that tomatidenol (**24**) is not commercially available gave severe problems for further research. On the other hand, solasodine, which differs from tomatidenol only in the configuration at C25, is commercially available and can be considered as an acceptable model compound to investigate two alternative degradation routes toward DPA (**6**). Any successful results could then be repeated with tomatidenol (**24**) itself. Treatment of solasodine with $ZnCl_2$ in Ac_2O and HOAc in the same manner as previously described for tomatidenol (**24**) gave imine **33** in 96% yield[85] (Scheme 11).

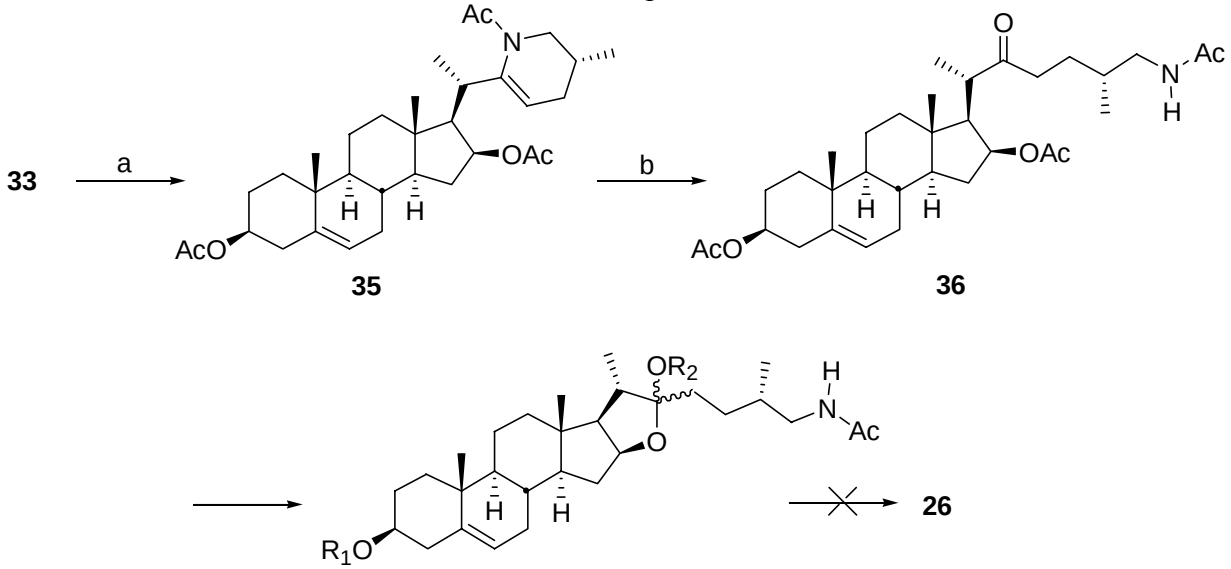
In the first route, isomerization of the endocyclic $\Delta^{22(N)}$ double bond to the exocyclic $\Delta^{20,22}$ position was achieved after methylation of **33** followed by treatment with aqueous $NaHCO_3$ in acetone[85] to **34** in 80% overall yield (Scheme 11). Oxidation of **34** was attempted with CrO_3/HOAc,[86] $KMnO_4/Al_2O_3$,[13] ozone,[87] and O_2/CuCl[88] but all attempts were unsuccessful. Hydrolysis of **34** with HCl or HBr in HOAc was tried but failed as well. The reasons for these failures are probably the same as for the oxidation of 3-acetoxysolanidi-5,20-ene (**4**), namely the

steric hindrance around the $\Delta^{20,22}$ double bond. Mopac calculations on **37** indicate that it becomes difficult for other reagents to approach the $\Delta^{20,22}$ double bond due to C18, the F-ring itself, and the *N*-methyl. Similar negative results were found by Sato and Ikekawa in their attempt to oxidize a compound similar to **34** with an acetyl instead of a methyl group attached to the nitrogen.[89]



Scheme 11. a. MeI, benzene, acetone, Δ, 3 h, 82%. b. $NaHCO_3$, acetone, 97%.

Treatment of **33** with Ac_2O and pyridine acetylates the nitrogen and simultaneously shifts the $\Delta^{22(N)}$ double bond to the $\Delta^{22,23}$ position yielding the thermodynamic compound **35** quantitatively[89,90] (Scheme 12). Mild hydrolysis of **35** with aqueous HCl and HOAc gives **36** in quantitative yield.[89,90] Deprotection of the C16 acetate with methanolic K_2CO_3 followed by addition of HOAc gave a 82% yield of **37** instead of the expected **26.**[89] A renewed attempt to eliminate MeOH from **37** with HOAc at reflux temperature also failed.



Scheme 12. a. Ac_2O, pyridine, RT, 4 days, 99%. b. HCl, HOAc, 99%. c_i. K_2CO_3, MeOH, 82% (**40**). c_{ii}. K_2CO_3, EtOH, 78% (**40**). c_{iii}. NaOH, dioxane, 78% (**40**).

Treatment of **36** with K_2CO_3 in a mixture of water and EtOH overnight gave hemiacetal **38** in 78% yield. The formation of **38** in about the same yield was also achieved upon treatment of **36** with NaOH in dioxane. In this case the elimination of water from **38** with HOAc at reflux temperature[89] also failed. This result is in agreement with that of Cambie *et al.,*[91] who was not able to dehydrate compound **39**. However a similar dehydration could be achieved by Sato and Ikekawa.[89] It thus turned out that properties of imine **33** as an intermediate in the synthesis of DPA (**6**) were not redeemed. Despite all our efforts, shortening of the route from 3-acetoxysolanidine (**11**) via tomatidenol (**24**) to DPA (**6**) as depicted in Scheme 6, could not be accomplished.

Experimental Section

General Procedures. Dry reactions were performed under a steady stream of dry nitrogen or argon with glassware dried at 140ºC. All ^1H and ^{13}C NMR spectra were measured with a Bruker AC-E 200 spectrometer. 400 MHz ^1H and 100 MHz ^{13}C NMR were measured with a DPX 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). MS and HRMS data were obtained with a Finnigan Mat 95 spectrometer. FT-IR spectra were measured with a BIO-RAD FTS-7 infra-red spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with the concentrations denoted in units of g/100 ml. Analytical data were obtained using a Carlo Erba Elemental Analyzer 7206. Melting points are uncorrected. Solvents were freshly distilled by common practice. Product solutions were dried over Na_2SO_4 prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. For flash chromatography, Merck Kieselgel silica 60 (230-400 Mesh) or Baker Alumina was used. Reactions were monitored with TLC using Merck silica gel 60F254 plastic sheets. Compounds were visualized on TLC by UV detection and by spraying with acid and subsequent heating.

Isolation of α-chaconine (6) and α-solanine (7) according to Friedman *et al* [2]

Spray-dried protamylasse (39.4 g) was dissolved in diluted acetic acid (120 ml, 1%) and stirred for 10 minutes at room temperature. The solution was made basic with NH_4OH to pH 9~10, heated at 70ºC for 30 minutes, and stored overnight at 4ºC. The mixture was then centrifuged (3161 rpm) for 50 minutes and the supernatant was discarded. The solid pellet was washed with cold aqueous NH_4OH (2%) and recentrifuged (3161 rpm) for 30 minutes. The pellet was taken up in a mixture of EtOAc/EtOH/NH_4OH (5%)(250 ml, 80/16/4) and filtered. The remaining filter cake was extracted twice with EtOAc/EtOH/NH_4OH (5%)(250 ml, 80/16/4). The combined filtrates were evaporated under reduced pressure to afford a yellow solid (3.0 g). Crystallization from ethanol (80%) gave 2.16 g of a mixture of **6** and **7**.

MS *m/z* (r.i.) 870.4 (MH^++2, α-solanine), 869.5 (MH^++1, α-solanine), 868.5 (MH^+, α-solanine), 854.5 (MH^++2, α-chaconine), 853.5 (MH^++1, α-chaconine), 852.5 (MH^+, α-chaconine), 723.5 (MH^++1, β_2-solanine), 722.5 (MH^+, β_2-solanine), 707.5 (MH^++1, β-chaconine), 706.5 (MH^+, β-chaconine), 561.5 (MH^+, γ-chaconine), 560.5 (MH^+, γ-chaconine), 399.6 (MH^++1, solanidine), 398.5 (MH^+, solanidine)

Isolation of solanidine (1) and solanida-3,5-diene

The spray-dried potato protein (225 g) was dissolved in water (700 ml), made basic with NH_4OH (35%) to pH 10-12, and stored overnight at 4ºC. The solution was then centrifuged (6000 rpm) for 30 minutes and the supernatant was discarded. The crude glycoalkaloid mixture was transferred to a Soxhlett apparatus and extracted with ethanol for 24 hours. After evaporation, the resulting brown solid was dissolved in ethanol (350 ml) and hydrolyzed with aqueous HCl (37%, 40 ml) at reflux temperature for 3 hours. The solution was cooled to room temperature and made basic with NH_4OH (35%). The solvent was evaporated to yield a brown solid, which was taken up in H_2O (250 ml) and $CHCl_3$ (250 ml). The water layer was extracted three times with $CHCl_3$ (200 ml) and the combined organic extracts were dried and flash chromatographed (Al_2O_3, $CHCl_3$/MeOH 9/1) to give a crude mixture of **1** and solanida-3,5-diene. Crystallization from the eluent gave **1** (2.47 g). After concentration of the mother liquor, crystallization of the remaining residue from EtOH (96%) provided solanid-3,5-diene (0.51 g).

NMR and mass spectral data of solanidine[92] and solanid-3,5-diene[93] are in accordance with literature data.

3β-Acetoxysolanidine (11). The NMR spectral data for **11** were identical to those reported in literature.[92]

3β-Acetoxy-5,20(22)-solanidiene (4). *The ^1H NMR spectral data of **4** were identical to those reported in literature.*[5]

Solanid-4-en-3-one (7). A solution of **1** (0.51 g, 1.27 mmol) in toluene (150 ml) and cyclohexanone (25 ml) was stirred. Then Al(*i*-OPr)$_3$ (0.54 g, 2.67 mmol) was added and the mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried, and evaporated to give a brown oil (0.54 g). The brown oil was flash chromatographed ($CHCl_3$/MeOH 9/1) to give **7** (0.36 g, 72%) as a white solid. M.p. 218ºC (lit. 218ºC[94]); ^1H NMR δ 0.74 (s, 3H), 0.79 (d, 3H, *J*= 6.4 Hz), 0.85 (d, 3H, *J*= 5.7 Hz), 1.14 (s, 3H), 5.67 (d, 1H, *J*= 1.5 Hz); ^{13}C NMR δ 16.92 (q), 17.41 (q), 18.26 (q), 19.54 (q), 20.84 (t), 29.25 (t), 31.04 (d), 31.16 (t), 32.14 (t), 32.93 (t), 33.30 (t), 33.97 (t), 35.41 (d), 35.70 (t), 36.62 (d), 38.66 (s), 39.77 (t), 40.37 (s), 53.90 (d), 56.71 (d), 60.14 (t), 62.87 (d), 68.86 (d), 75.55 (d), 123.76 (d), 171.51 (s), 199.56 (s); MS *m/z* (r.i.) 395 (50), 380 (9), 204 (25), 150 (100); HRMS calculated for $C_{27}H_{41}NO$ (M^+) 395.3188, found 395.3181.

Solanidan-4-en-3-one *N*-oxide (8). To a solution of **89** (130.1 mg, 0.33 mmol) in CH_2Cl_2 (5 ml) was added a solution of MMPP (223.2 mg, 0.45 mmol) in CH_2Cl_2/H_2O 1/1 (11 ml). After 12 hours in the dark, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried and the solvent evaporated *in vacuo*. The remaining residue was flash chromatographed (EtOAc/MeOH 9/1) yielding **98** (69.0 mg, 53%) as a white solid. M.p. 197-200ºC; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 0.86 (d, 1H, *J*= 6.1 Hz) 0.96 (d, 3H, *J*= 6.6 Hz), 1.13 (s, 3H), 1.19 (s, 3H), 2.74 (dt, 1H, *J*= 10.3 and 2.3 Hz), 3.35 (d, 1H, *J*= 6.9 Hz), 3.73 (m, 1H), 5.71 (d, 1H, *J*= 0.9 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 14.65 (q), 16.29 (q), 17.29 (q), 18.32 (q), 20.90 (t), 21.92 (t), 23.61 (t), 26.30 (d), 31.56 (t), 23.12 (t), 32.68 (t), 33.82 (d), 33.89 (t), 34.74 (d), 35.60 (t), 38.61 (s), 39.91 (s), 40.08 (t), 53.70 (d), 56.24 (d), 61.32 (d), 71.21 (t), 81.25 (d), 83.49 (d), 123.76 (d), 171.11 (s), 199.52 (s).

3β-Acetoxysolanidine *N*-oxide (9) and 3β-acetate-5,6α-epoxy-solanidine *N*-oxide. To a solution of **11** (4.89 g, 11.14 mmol) in CH_2Cl_2/MeOH 2/1 (750 ml) was added a suspension of 70-75% *m*CPBA (5.45 g, 22.11 mmol) in CH_2Cl_2 (200 ml). After 18 hours in the dark, the reaction mixture was concentrated, washed with a dilute solution of $NaHCO_3$, dried, and evaporated *in vacuo*. Repeated flash chromatography ($CHCl_3$/MeOH 9/1) of the amorphous residue yielded **9** (1.82 g, 36%) and 3β-Acetate-5,6α-epoxy-solanidine *N*-oxide (1.82 g, 36%), both as white solids.

9. ^{1}H NMR δ 0.65 (d, 3H, *J*= 6.2 Hz), 0.73 (d, 3H, *J*= 6.6 Hz), 0.78 (s, 3H), 0.80 (s, 3H), 1.78 (s, 3H), 3.14 (d, 1H, *J*= 9.6 Hz), 3.47 (1H), 4.32 (m, 1H), 5.12 (br d, 1H, *J*= 3.8 Hz); ^{13}C NMR δ 14.56 (q), 16.38 (q), 18.38 (q), 19.27 (q), 20.96 (t), 21.43 (q), 21.93 (t), 23.69 (t), 26.29 (d), 27.68 (t), 31.04 (d), 31.66 (t), 31.91 (t), 32.03 (t), 33.82 (d), 36.69 (s), 36.93 (t), 38.03 (t), 39.84 (s), 40.28 (t), 49.94 (d), 57.11 (d), 61.51 (d), 71.25 (t), 73.83 (d), 81.45 (d), 83.56 (d), 122.21 (d), 139.70 (s), 170.57 (s).

3β-Acetate-5,6α-epoxy-solanidine *N*-oxide. ^{1}H NMR δ 0.80 (d, 3H, *J*= 6.5 Hz), 0.86 (d, 3H, *J*= 6.6 Hz), 0.90 (s, 3H), 0.98 (s, 3H), 1.92 (s, 3H), 3.68 (m, 1H), 4.92 (m, 1H); ^{13}C NMR δ 14.46 (q), 15.95 (q), 17.81 (q), 20.73 (2q), 21.14 (d), 21.48 (q), 23.44 (t), 26.11 (d), 26.31 (t), 29.32 (t), 31.08 (d), 32.04 (t), 33.57 (d), 35.36 (t), 37.26 (t), 38.91 (s), 40.02 (t+s), 44.67 (t), 49.99 (d), 55.38 (d), 61.06 (d), 63.45 (d), 70.43 (t), 71.59 (t), 75.23 (s), 81.44 (d), 83.53 (d), 171.76 (s).

(3β)-Acetoxy-23-trifluoroacetylsolanid-5,22-diene (10). To a solution of **7** (100.3 mg, 0.22 mmol) in THF (2 ml) was added $(CF_3CO)_2O$ (35 μl, 0.24 mmol) under argon atmosphere. The solution colored immediately yellow and then slowly to orange. After 30 minutes, *t*-BuOK (60.6 mg, 0.51 mmol) was added and the solution was stirred for 16 hours. The reaction mixture was diluted with H_2O, and extracted three times with $CHCl_3$ (50 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried, and evaporated *in vacuo*. Flash chromatography of the remaining residue (EtOAc/PE 9/1) yielded **10** (45.9 mg, 41%) as an orange oil. ^{1}H NMR (main peaks) δ 0.60 (s, 3H), 1.03 (s, 3H), 1.03 (d, 3H, *J*= 6.4 Hz), 1.19 (d, 3H, *J*= 6.9 Hz), 2.05 (s, 3H), 2.29 (br d, 1H, *J*= 15.0 Hz), 2.78 (dd, 1H, *J*= 8.2 and 12.9 Hz), 3.31 (dd, 1H, *J*= 4.3 and 12.9 Hz), 3.90 (q, 1H, *J*= 6.9 Hz), 4.21 (ddd, 1H, *J*= 5.6, 7.9, and 7.9 Hz),

4.61 (m, 1H), 5.38 (br d, 1H, *J*= 5.2 Hz); ^{13}C NMR δ 13.81 (q), 18.67 (q), 19.73 (q), 20.16 (q), 20.74 (t), 21.82 (q), 26.59 (d), 28.10 (t), 29.05 (t), 31.41 (t), 31.76 (d), 32.32 (t), 37.07 (s), 37.35 (t), 38.47 (2t), 39.61 (d), 42.13 (s), 49.81 (t), 50.43 (d), 55.38 (d), 60.07 (d), 67.36 (d), 74.17 (d), 90.93 (s), 116.21 (q, *J*= 285 Hz), 122.23 (d), 140.42 (s), 170.98 (s), 172.32 (s). The chemical shift of the quartet signal for the C=O group of the trifluoroacetyl moiety could not be determined because its intensity was too low. MS *m/z* (r.i.) 534 (M^++1, 35), 533 (M^+, 100), 465 (28), 464 (M^+-HCF_3, 89), 404 (17), 258 (22), 195 (9), 69 (11), 43 (9); HRMS calculated for $C_{31}H_{42}F_3NO_3$ (M^+) 533.3117, found 533.3120.

(3β,16*α*,20*S*)-16-Bromo-20-[(2*R*,5*S*)-1-cyano-5-methylpiperidinyl]pregn-5-en-3-yl acetate (12)[95] **and (2*S*,4a*R*,4b*S*,6a*S*,6b*R*,7*S*,9a*S*,10a*S*,10b*S*)-8-[(3*R*)-4-bromo-3-methylbutyl]-9-cyano-4a,6a,7-trimethyl-1,2,3,4,4a,4b,5,6,6a,6b,7,8,9,9a,10,10a,10b,11-octadecahydronaphtho- [2',1':4,5]indeno[2,1-*b*]pyrrol-2-yl acetate (13).** A solution of **11** (0.9 g, 2.05 mmol) in $CHCl_3$ (20 ml) was treated with a 3M solution of BrCN (5 ml, 15.00 mmol) in $CHCl_3$. After heating at reflux temperature for 24 hours under nitrogen atmosphere, the solvent was removed *in vacuo* and the remaining gum crystallized from PE/EA 1/1 to give **12** (0.5 g, 45%). The mother liquor was purified by column chromatography (PE/EA 5/1) to give additional **12** (0.255 g, 23%) and the F-ring opened product **13** (0.135 g, 12%).

12. M.p. 250-260ºC (EtOH) (lit. 245-260ºC[95]); IR[95] ν_{max} (neat) 1717, 2199, 2841, 2911, 2932 cm^{-1}; ^{1}H NMR δ 0.72 (s, 3H), 0.85 (d, 3H, *J*= 6.5 Hz), 0.96 (d, 3H, *J*= 7.7 Hz), 0.98 (s, 3H), 2.00 (s, 3H), 2.29 (d, 2H, *J*= 7.5 Hz), 2,72 (t, 1H, *J*= 11.0 Hz), 3.17 (d, 1H, *J*= 11.0 Hz), 3.38 (dd, 1H, *J*= 3.3 and 10.9 Hz), 4.04 (t, 1H, *J*= 6.2 Hz), 4.57 (m, 1H), 5.34 (d, 1H, *J*= 4.1 Hz); ^{13}C NMR δ 12.50 (q), 13.98 (q), 18.63 (q), 19.23 (q), 20.72 (t), 21.40 (q), 23.76 (t), 27.63 (t), 30.54 (2d), 31.58 (t), 31.68 (t), 36.46 (s), 36.82 (t), 37.08 (d), 37.97 (t), 39.51 (t), 39.67 (t), 45.16 (s), 49.47 (d), 53.15 (d), 54.16 (d), 58.25 (t), 60.08 (d), 63.77 (d), 73.72 (d), 117.08 (s), 121.97 (d), 139.64 (s), 170.48 (s)); MS *m/z* (r.i.) 425 (8), 410 (7), 124 (14), 112 (100), 98 (31), 58 (71); HRMS calculated for $C_{28}H_{41}N_2Br$ ([M-HOAc]$^+$) 484.2453, found 484.2454. The ^{1}H NMR data were in accordance with the literature data[2,5]

13. ^{1}H NMR δ 0.77 (s, 3H), 0.98 (2s, 6H), 0.99 (d, 3H, *J*= 6.4 Hz), 1.97 (s, 3H), 3.32 (d, 2H, *J*= 5.4 Hz), 3.87 (m, 1H), 4.53 (m, 1H), 5.31 (d, 1H, *J*= 4.3 Hz); ^{13}C NMR d 16.09 (q), 18.54 (q), 19.13 (q), 20.11 (q), 20.32 (t), 21.28 (q), 27.53 (t), 28.18 (t), 29.63 (t), 31.10 (t), 31.26 (d), 31.64 (t), 35.00 (d), 35.42 (d), 36.47 (s), 36.78 (t), 37.87 (t), 38.83 (t), 40.71 (t), 41.28 (s), 49.63 (d), 56.95 (d), 61.18 (d), 65.21 (d), 72.12 (d), 73.56 (d), 116.19 (s), 121.93 (d), 139.52 (s), 170.30 (s)); MS *m/z* (r.i.) 484 (18), 439 (5), 405 (5), 150 (21), 123 (100); HRMS calculated for $C_{28}H_{41}N_2Br$ ([M-HOAc]$^+$) 484.2453, found 484.2441.

(3β,20*S*)-20-[(2*R*,5*S*)-1-Cyano-5-methylpiperidinyl]pregn-5-en-3-yl acetate (14). A solution of **12** (0.20 g, 0.37 mmol), Bu_3SnH (0.15 ml, 0.56 mmol), and AIBN (cat. amount) in benzene (5 ml) was heated at reflux temperature for 7.5 hours under a nitrogen atmosphere.[96] After cooling and concentration of the mixture *in vacuo*, ether (25 ml) and saturated aqueous KF (25 ml) were added and the mixture was stirred overnight at room temperature. The layers were

separated and the aqueous phase was extracted three times with chloroform (25 ml). The combined organic phases were washed with brine, dried, and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EA 9/1) gave **14** (0.11 g, 64%) as a white solid. ^{1}H NMR δ 0.66 (s, 3H), 0.80 (d, 3H, *J*= 6.6 Hz), 0.92 (d, 3H, *J*= 6.7 Hz), 0.95 (s, 3H), 1.97 (s, 3H), 2.25 (d, 2H, *J*= 7.9 Hz), 2.62 (t, 1H, *J*= 11.6 Hz), 2.76 (d, 1H, *J*= 8.9 Hz), 3.32 (dd, 1H, *J*= 2.4 and 11.7 Hz), 4.50 (m, 1H), 5.30 (d, 1H, *J*= 4.3 Hz); ^{13}C NMR δ 11.81 (q), 13.65 (q), 18.72 (q), 19.32 (q), 21.00 (t), 21.47 (q), 23.33 (t), 24.23 (2t), 27.56 (t), 27.74 (t), 30.64 (d), 31.83 (d), 32.34 (t), 36.56 (s), 36.98 (t), 37.34 (d), 38.09 (t), 39.69 (t), 42.69 (s), 49.98(d), 52.68 (d), 56.44 (d), 58.17 (t), 60.40 (d), 73.92 (d), 117.29 (s), 122.42 (d), 139,73 (s), 170.59 (s).

(3β,16β,20*S*)-16-(Acetyloxy)-20-[(2*R*,5*S*)-1-cyano-5-methylpiperidinyl]pregn-5-en-3-yl acetate (15). To a solution of **12** (0.4 g, 0.73 mmol) in DMF (40 ml) was added an aqueous KOAc solution (40%, 1.33 ml). The reaction mixture was heated at 90°C for 2 hours and then poured into water. The water layer was extracted three times with ether (15 ml). The combined organic layers were washed with water, dried and evaporated *in vacuo* yielding a white solid. Flash chromatography (PE/EA 5/1) yielded **15** (0.32 g, 83%) as a white solid. M.p. 163-167ºC (160-167ºC[52]); ^{1}H NMR δ 0.79 (d, 3H, *J*= 6.5 Hz), 0.86 (s, 3H), 0.95 (d, 3H, *J*= 5.0 Hz), 1.98 (s, 3H), 2.06 (s, 3H), 2.25 (d, 2H, *J*= 7.6 Hz), 2.55 (t, *J*= 11.5 Hz), 3.30 (dd, 1H, *J*= 2.4 and 11.7 Hz), 4.57 (m, 1H), 5.08 (m, 1H), 5,29 (d, 1H, *J*= 4.1 Hz); ^{13}C NMR δ 12.42 (q), 13.05 (q), 18.61 (q), 19.29 (q), 20.64 (t), 21.47 (2q), 23.84 (t), 27.69 (t), 30.61 (d), 31.32 (d), 31.58 (t), 31.90 (d), 32.16 (t), 34.76 (t), 36.53 (s), 36.90 (t), 38.04 (t), 39.47 (t), 42.72 (s), 49.86 (d), 54.63 (d), 55.63 (d), 58.35 (t), 59.64 (d), 73.80 (d), 73.88 (d), 116.97 (s), 122.10 (d), 139.78 (s), 170.56 (s), 171.04 (s). MS *m/z* (r.i.) 524 (1), 509 (7), 464 (26), 449 (19), 151 (100), 123 (100); HRMS calculated for $C_{32}H_{48}N_2O_4$ ($[M]^+$) 524.3614, found 524.3614.

(3β,20*S*)-20-[(2*R*,5*S*)-1-Cyano-5-methylpiperidinyl]pregna-5,16-dien-3-yl acetate (16). Compound 12 (0.1 g, 0.18 mmol) was dissolved in *s*-collidine (2 ml) and heated at reflux temperature for 16 hours. After cooling, the reaction mixture was diluted with EA, washed with aqueous HCl (10%) and water, and dried. Evaporation of the solvent *in vacuo* yielded 16 (0.083 g, 98%) as a white crystalline product. M.p.170-175ºC (173ºC[Schramm, 1970 #3725]); ^{1}H NMR δ 0.81 (d, 1H, *J*= 5.8 Hz), 0.82 (s, 3H), 0.99 (s, 3H), 0.99 (d, 3H, *J*= 6.8 Hz), 1.97 (s, 3H), 2.26 (d, 2H, *J*= 7.4 Hz), 2.55 (t, 1H, *J*= 11.9 Hz), 2.77 (m, 1H), 3.30 (m, 1H), 4.55 (m, 1H), 5.32 (d, 1H, *J*= 4.3 Hz), 5.40 (m, 1H); ^{13}C NMR δ 15.67 (q), 17.03 (q), 18.43 (q), 19.17 (q), 20.60 (t), 21.41 (q), 25.30 (t), 27.68 (t), 29.91 (d), 30.33 (d), 31.09 (t), 31.43 (t), 32.59 (t), 34.92 (t), 35.24 (d), 36.73 (s), 36.85 (t), 38.07 (t), 46.83 (s), 50.37 (d), 57.77 (d), 58.47 (t), 61.14 (d), 73.84 (d), 117.08 (s), 122.37 (d), 124.90 (d), 139.88 (s), 156.02 (s), 170.48 (s).

(3β,20*S*)-20-[(2*R*,5*S*)-1,5-Dimethylpiperidinyl]pregn-5-en-3-ol (17). (3β,20*S*)-20-[(2*R*,5*S*)-5-Methylpiperidinyl]pregn-5-en-3-ol was prepared as described in the literature, the NMR data were in accordance with the literature data.[97-100] A suspension of this compound (0.07 g, 0.175 mmol), Na_2CO_3 (0.035 g), and MeI (0.07 ml, 1.12 mmol) in water was heated at reflux temperature for 7 hours. After cooling, the white precipitate was filtered and washed with water.

The crude material was suspended in methanolic KOH (3.5 M, 5 ml) and heated under reflux for 3 hours. After cooling, the alkaline mixture was concentrated and water was added. The mixture was extracted three times with ether (5 ml) and dried. Evaporation of the solvent *in vacuo* yielded an amorphous material (0.065 g) which was flash chromatographed ($CHCl_3$/MeOH 9/1) yielding **17** (0.055 g, 76%) as a white solid. M.p. 296-301ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 0.51 (s, 3H), 0.73 (d, 3H, *J*= 6.6 Hz), 0.77 (s, 3H), 0.88 (d, 3H, *J*= 6.7 Hz), 2.03 (m, 2H), 2.34 (t, 1H, *J*= 12.0 Hz), 2.51 (s, 3H), 3.20 (m, 1H), 5.11 (d, 1H, *J*= 4.3 Hz); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 11.44 (q), 12.25 (q), 17.94 (q), 18.98 (q), 20.72 (t), 22.38 (t), 23.79 (t), 27.18 (t), 29.22 (d), 30.79 (t), 31.04 (t), 31.45 (t), 31.61 (d), 34.21 (d), 36.17 (s), 36.95 (t), 39.45 (t), 40.35 (q), 41.47 (t), 42.52 (s), 49.69 (d), 52.15 (d), 56.08 (d), 63.46 (t), 69.24 (d), 70.84 (d), 120.87 (d), 140.70 (s); MS *m/z* (r.i.) 412 (2), 112 (100); HRMS calculated for $C_{28}H_{46}NO$ ($[M-H]^+$) 412.3579, found 412.3579.

(3β,16β,20*S*)-20-[(2*R*,5*S*)-1,5-Dimethylpiperidinyl]pregn-5-ene-3,16-diol (18). (3β,16β,20*S*)-20-[(2*R*,5*S*)-5-Methylpiperidinyl]pregn-5-ene-3,16-diol was prepared as described in the literature, the NMR and mass data were in accordance with the literature data[101]. A suspension of this compound (0.04 g, 0.096 mmol), Na_2CO_3 (0.02 g), and MeI (0.04 ml, 0.64 mmol) in water was heated at reflux temperature for 7 hours. After cooling, the white precipitate was filtered and washed with water. Drying on air gave the ammonium salt (0.04 g, 99%) as a white solid. ^{1}H NMR ($CDCl_3$+CD_3OD) δ 0.52 (s, 3H), 0.52 (d, 3H, *J*= 6.7 Hz), 0.58 (s, 3H), 0.66 (d, 1H, *J*= 6.8 Hz), 2.64 (s, 3H), 2.82 (s, 3H), 3.83 (m, 1H), 4.89 (d, 1H, *J*= 4.6 Hz); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 11.83 (q), 14.26 (q), 16.91 (q), 18.25 (q), 20.02 (t), 20.39 (t), 26.06 (d), 28.27 (d), 30.26 (d), 30.43 (s), 30.89 (2t), 35.70 (s), 36.40 (2t), 39.41 (t), 40.97 (2t), 42.05 (q), 44.30 (d), 46.21 (q), 49.27 (d), 53.56 (q), 53.84 (d), 57.98 (d), 68.93 (d), 70.36 (t), 72.80 (t), 73.63 (d), 120.27 (d), 140.25 (s).

A suspension of this salt in 3.5 M methanolic KOH (3 ml, 10.5 mmol) was heated at reflux temperature for 3 hours. After cooling, the reaction mixture was filtered and washed with water. Flash chromatography ($CHCl_3$/MeOH 1/1) gave **18** (0.013 g, 32%) as a white solid. M.p. 199-202ºC (196.5-198.5ºC[99]); ^{1}H NMR δ 0.76 (s, 3H), 0.85 (d, 3H, *J*= 7.0 Hz), 0.92 (d, 6H, *J*= 6.6 Hz), 0.96 (s, 3H), 2.32 (s, 3H), 3.46 (m, 1H), 3.94 (m, 1H), 4.43 (q, 1H, *J*= 7.2 Hz), 5.29 (d, 1H, *J*= 4.9 Hz); ^{13}C NMR δ 14.75 (q), 16.27 (q), 18.34 (q), 19.44 (q), 20.74 (t), 27.37 (t), 30.41 (d), 30.98 (d), 31.61 (t), 32.04 (s), 32.11 (t), 33.46 (t), 35.45 (d), 36.67 (t), 37.21 (t), 39.67 (t), 40.92 (s), 42.27 (t), 45.11 (q), 50.14 (d), 55.55 (d), 64.31 (d), 66.08 (t), 71.68 (d), 81.63 (d), 84.11 (d), 121.40 (d), 140.82 (s). The NMR spectral data were in accordance with the literature data.[99,102]

(3β,20*S*)-20-[(2*R*,5*S*)-1,1,5-Trimethylpiperidiniumyl]pregna-5,16-dien-3-ol iodide (20). (3β,20*S*)-20-[(2*R*,5*S*)-5-Methylpiperidinyl]pregna-5,16-dien-3-ol was prepared as described in the literature, the NMR data are identical with those obtained from the reduction with Red-Al.

A suspension of this compound (0.048 g, 0.13 mmol), Na_2CO_3 (0.025 g), and MeI (0.05 ml, 0.8 mmol) in water (4 ml) was heated under reflux for 7 hours. After cooling, the white precipitate was filtered and washed with water. Drying on air gave 20 (0.065 g, 97%) as a rather

unstable compound through which further purification failed. ^{1}H NMR (DMSO) δ 0.83 (s, 6H), 0.83 (d, 3H, *J*= 6.8 Hz), 0.97 (s, 3H), 0.99 (d, 3H, *J*= 7.0 Hz), 2.99 (s, 3H), 3.14 (s, 3H), 4.62 (d, 1H, *J*= 4.4 Hz), 5.27 (d, 1H), 5.50 (m, 1H).

(3β,25*S*)-26-(Dimethylamino)cholesta-5,16,20(22)-trien-3-ol (21) and (3β,20*R*)-20-[(2*R*,5*S*)-1,5-dimethylpiperidinyl]pregna-5,16-dien-3-ol (19). To a solution of isopropylamine (0.85 ml, 10 mmol) in THF (2.9 ml) was added 1.6 M *n*-BuLi (6.25 ml, 10 mmol) in hexane at -20ºC. The reaction mixture was cooled to -60ºC and stirring was continued for 30 minutes. To a suspension of 20 (0.29 g, 0.49 mmol) in THF (3 ml) was added freshly prepared 1 M LDA (1.6 ml, 1.60 mmol) at -78ºC. The reaction mixture was allowed to warm to room temperature, stirred for 4 hours, and then quenched with an aqueous saturated NH_4Cl solution. The reaction mixture was extracted three times with CH_2Cl_2 (15 ml). The combined organic layers were washed with saturated brine, dried, and evaporated *in vacuo*. The residue was purified by flash chromatography ($CHCl_3$/MeOH 9/1) to afford 21 (0.070 g, 32%) and 19 (0.055 g, 26%), both as white solids.

21. M.p. 164-165ºC (MeOH); IR ν_{max} (neat): 3224, 1457, 1375, 1063 cm^{-1}. ^{1}H NMR δ 0.90 (d, 3H, *J*= 6.5 Hz), 0.94 (s, 3H), 1.00 (s, 3H), 1.62 (s, 3H), 2.19 (s, 6H), 3.50 (m, 1H), 5.34-5.59 (m, 3H); ^{13}C NMR ($CDCl_3$) 15.3 (q), 16.2 (q), 18.1 (q), 19.3 (q), 21.0 (t), 25.8 (t), 30.3 (d), 30.6 (d), 30.9 (t), 31.5 (t), 31.6 (t), 35.0 (t), 36.1 (t), 36.6 (s), 37.1 (t), 42.3 (t), 45.8 (2q), 46.7 (s), 50.3 (d), 57.6 (d), 67.0 (t), 71.7 (d), 121.5 (d), 124.8 (d), 126.6 (d), 130.5 (s), 141.0 (s), 156.4 (s); MS *m/z* (r.i.) 410 (2), 397 (4), 382 (1), 204 (2), 150 (8), 112 (100); HRMS calculated for $C_{29}H_{46}NO$ ([M-H]$^+$) 425.3658, found 425.3658.

19. M.p. 148-151ºC; IR ν_{max} (neat): 3382, 1455, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 0.73 (s, 3H), 0.81 (d, 3H, *J*= 6.4 Hz), 0.90 (s, 3H), 1.04 (d, 3H, *J*= 6.9 Hz), 2.59 (s, 3H), 3.25 (m, 1H), 5.29 (m, 1H), 5.45 (m, 1H); ^{13}C NMR ($CDCl_3$) 12.7 (q), 17.0 (q), 19.0 (q), 19.3 (q), 20.5 (t), 23.6 (t), 30.2 (d), 31.0 (t), 31.4 (t), 31.5 (t), 32.2 (t), 32 .5 (d), 34.5 (t), 36.6 (t), 37.1 (s), 41.8 (q), 42.2 (t), 46.3 (s), 50.4 (d), 58.6 (d), 65.3 (t), 66.9 (d), 71.5 (d), 121.3 (d), 126.5 (d), 141.0 (s), 155.9 (s); MS *m/z* (r.i.) 425 (8), 410 (7), 124 (14), 112 (100), 98 (31), 58 (71); HRMS calculated for $C_{28}H_{44}NO$ ([M-H]$^+$) 410.3421, found 410.3423.

(3β,16β,20*S*)-20-[(2*R*,5*S*)-1-Chloro-5-methylpiperidinyl]pregn-5-ene-3,16-diol (23). This compound was prepared as described in the literature, the NMR and mass data were in accordance with literature data.[100]

(3β,22*α*,25*α*)-Spirosol-5-en-3-ol (Tomatidenol) (24). This compound was prepared as described in the literature, M.p. 236-238ºC (234-238ºC)[103]

Method B. To a solution of **23** (150.2 mg, 0.33 mmol) in dry CH_2Cl_2 (3 ml) and dry Et_2O (2 ml) was added DBU (21 μl, 0.14 mmol) at -10ºC. After 2 hours, the reaction mixture was allowed to warm to room temperature, evaporated *in vacuo*, and crystallized from acetone to yield **24** (100.8 mg, 73%) as a white solid. M.p. 235-238ºC (234-238ºC[103]). The NMR and mass data are identical to those mentioned in the literature.[104]

(3β,22α,25α)-28-Acetylspirosol-5-en-3-yl acetate (25). Tomatidenol (**24**) (174.1 mg, 0.42 mmol) was dissolved in a mixture of Ac_2O (2 ml) and pyridine (10 ml). After 24 hours, the reaction mixture was poured into ice-water. The suspension was filtered, and the filter cake was washed with water and recrystallized from acetone/H_2O to yield **25** (205.5 mg, 98%) as a white solid. M.p. 161-163ºC (163-165ºC[103]); ^{1}H NMR δ 0.81 (s, 3H), 0.84 (d, 3H, *J*= 5.4 Hz), 1.00 (s, 3H), 1.19 (d, 3H, *J*= 6.9 Hz), 2.01 (s, 3H), 2.08 (s, 3H), 4.17 (q, 1H, *J*= 6.6 Hz), 4.57 (m, 1H), 5.35 (d, 1H, *J*= 4.4 Hz); ^{13}C NMR δ 16.00 (q), 17.78 (q), 19.02 (q), 19.34 (q), 20.70 (q), 21.46 (t), 24.75 (q), 27.73 (t), 28.13 (t), 28.36 (t), 31.50 (d), 31.73 (d), 32.03 (t), 32.75 (t), 36.71 (s), 36.96 (t), 38.09 (t), 38.52 (d), 39.43 (t), 41.13 (s), 50.00 (d), 52.12 (t,), 56.40 (d), 64.47 (d), 73.89 (d), 78.84 (d), 101.03 (s), 122.29 (d), 139.81 (s), 170.41 (s), 170.59 (s). MS *m/z* (r.i.) 497 (72, M), 482 (100), 454 (15), 428 (37), 155 (31), 114 (15), 43 (9); HRMS calculated for $C_{31}H_{47}NO_4$ 497.3505, found 497.3508.

(3β,25*S*)-26-(Acetylamino)furosta-5,20(22)-dien-3-yl acetate (26). This compound was prepared from **25** as described in the literature, the NMR and mass data were in accordance with literature data.[91]

(3β)-3-Acetoxypregna-5,16-dien-20-one (dehydropregnenolone acetate, DPA) (6). This compound was prepared as described in the literature, the NMR data were in accordance with literature data.[105]

(3β,16β)-16-(Acetyloxy)-20-[(2*R*,5*S*)-5-methylpiperidinyl]pregn-5-en-3-yl acetate (27). Zn powder was activated as follows[61]: To a vigorously stirred suspension of Zn (2 g, 16 mmol) in HOAc (10 ml) was added a solution of HCl (2M, 10 ml), followed by an aqueous solution of $CuSO_4$ (5%, 0.4 ml). After about 1 minute, the reaction mixture was decanted and the Zn washed several times with HOAc.

To a suspension of freshly activated Zn (210.7 mg) in HOAc (1.3 ml) and H_2O (3.0 ml) was added **15** (107.6 mg, 0.21 mmol) and the reaction mixture was heated at reflux temperature. After 2 hours, the reaction mixture was filtered through Hyflow and evaporated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with aqueous NaOH (0.05 M) and brine, dried, and evaporated *in vacuo* to obtain a white amorphous solid. Purification by column chromatography with $CHCl_3$/MeOH 9/1 followed by crystallization from EtOAc gave **27** (92.0 mg, 90%) as a white solid. M.p. 170-173ºC (172-173ºC[100]); ^{1}H NMR ($CDCl_3$+CD_3OD) δ 0.77 (d, 3H, *J*= 6.5 Hz), 0.83 (s, 3H), 0.91 (d, 3H, *J*= 5.6 Hz), 0.93 (s,3H), 1.93 (s, 3H), 2.02 (s, 3H), 3.27 (dd, 1H, *J*= 2.7 and 11.7 Hz), 3.50 (s,1H, NH), 4.48 (m, 1H), 5.04 (td, 1H, *J*= 3.8 and 7.6 Hz), 5.25 (d, 1H, *J*= 4.4 Hz); ^{13}C NMR δ 12.23 (q), 12.89 (q), 18.42 (q), 19.14 (q), 20.53 (t), 21.25 (2q), 23.73 (t), 27.56 (t), 30.50 (d), 31.23 (d), 31.46 (t), 31.83 (d), 32.00 (t), 34.63 (t), 36.43 (s), 36.77 (t), 37.89 (t), 39.34 (t), 42.62 (s), 49.74 (d), 54.50 (d), 10.46 (d), 58.14 (t), 59.57 (d), 73.99 (d), 74.06 (d), 122.04 (d), 139.63 (s), 171.02 (s), 171.26 (s). The NMR data are in accordance with literature data.[100]

(3β,16β)-16-(Acetyloxy)-20-[(2*R*,5*S*)-1-chloro-5-methylpiperidinyl]pregn-5-en-3-yl acetate (28). This compound was prepared from **27** as described for the synthesis of **23**, the NMR and mass data were in accordance with literature data.[100]

(3β,22α,25α)-Spirosol-5-en-3-ol (Tomatidenol) (24). To a solution of Na (120.1 mg) in MeOH (60 ml) was added a solution of **27** (34.5 mg, 0.65 μmol) in MeOH (5 ml). After reflux for 1 hour, the reaction mixture was concentrated *in vacuo*, and the remaining residue was taken up in H_2O (10 ml). The mixture was extracted three times with $CHCl_3$ (25 ml), dried, and evaporated *in vacuo* to yield **4** (27.5 mg, 85%) as a white solid. M.p. 234-238ºC (134-138ºC[103]). The NMR and mass data are identical with those obtained in method A as previously described for the synthesis of tomatidenol (**28**).

(3*S*,6a*S*,6b*S*,7a*S*,12*S*,14a*R*,15a*R*,15b*S*,17a*S*,17b*R*)-9-imino-12,15,15b,17b-tetramethyl-2,3,4,6,6a,6b,7,7a,11,12,13,14,14a,15,15a,15b,16,17,17a,17b-icosahydro-1*H*-naphtho[2',1':4,5]indeno [1,2-*f*]pyrido[1,2-*c*][1,3]oxazepin-3-ol (29). To a solution of Na (250.3 mg) in MeOH (120 ml) was added a solution of **15** (121.3 mg, 0.23 mmol) in MeOH (10 ml). After reflux for 1 hour, the reaction mixture was concentrated *in vacuo*, and the remaining residue was taken up in H_2O (10 ml). The mixture was extracted three times with $CHCl_3$ (25 ml), dried, and evaporated *in vacuo* to yield **29** (101.3 g, 81%) as a brown solid. ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 3H, *J*= 6.1 Hz), 0.78 (s, 3H), 0.95 (s, 3H), 0.95 (d, 3H, *J*= 6.5 Hz), 4.63 (q, 1H, *J*= 7.6 Hz), 5.27 (d, 1H, *J*= 4.9 Hz); ^{13}C NMR δ 13.02 (q), 17.87 (q), 18.92 (q), 19.35 (q), 20.82 (t), 27.62 (d), 30.15 (t), 30.96 (d), 31.52 (t), 31.89 (t), 33.21 (t), 34.44 (t), 34.81 (d), 36.45 (s), 37.12 (t), 40.22 (t), 42.18 (t), 42.60 (s), 49.83 (d), 53.01 (d), 57.55 (t), 57.86 (d), 65.92 (d), 71.58 (d), 80.56 (d), 121.19 (d), 140.83 (s), 163.53 (s); MS *m/z* (r.i.) 440 (15, M), 422 (7), 397 (27), 393 (15), 322 (34), 204 (11), 150 (47), 123 (34), 98 (100); HRMS calculated for $C_{28}H_{44}N_2O_2$ 440.3403, found 440.3400.

(3β,16β)-16-(Acetyloxy)-20-[(5*R*)-5-methyl-3,4,5,6-tetrahydro-2-pyridinyl]pregn-5-en-3-yl acetate (33). This compound was prepared from solasodine as described in the literature[85,100], the NMR and mass data were in accordance with literature data.[100]

(3β,16β)-16-(Acetyloxy)-20-[(5*R*)-1,5-dimethylpiperidinylidene]pregn-5-en-3-yl acetate (34). To a solution of **33** (1.07 g, 2.15 mmol) in benzene (50 ml) and acetone (100 ml) was added MeI (10 ml, mmol). After 3 hours reflux, the mixture was concentrated *in vacuo* and the remaining residue was dissolved in acetone. Precipitation with *n*-hexane and air-drying gave (3β,16β)-3,16-Bis(acetyloxy)-20-[(5*R*)-1,5-dimethyl-3,4,5,6-tetrahydro-2-pyridiniumyl]pregn-5-ene iodide (1.12 g, 82%) as a white solid. M.p. 266-268ºC (268-270ºC[85]); ^{1}H NMR δ 0.94 (s, 3H), 1.00 (s, 3H), 1.08 (d, 3H, *J*= 4.5 Hz), 1.59 (d, 3H, *J*= 6.8 Hz), 2.00 (s, 3H), 2.06 (s, 3H), 3.32 (q, 1H, *J*= 5.4 Hz), 3.78 (s, 3H), 4.33 (m, 1H), 4.56 (m, 1H), 5.13 (m, 1H), 5.32 (d, 1H, *J*= 4.4 Hz); ^{13}C NMR δ13.30 (q), 17.88 (q), 18.01 (q), 19.29 (q), 20.70 (t), 21.45 (q), 21.87 (q), 24.47 (t), 27.10 (d), 27.64 (t), 29.05 (t), 31.20 (d), 31.51 (t), 34.96 (t), 36.51 (s), 36.83 (t), 37.07 (d), 37.99 (t), 39.66 (t), 43.47 (s), 45.52 (q), 49.10 (d), 53.61 (d), 54.89 (d), 62.87 (t), 73.68 (d), 74.54 (d), 121.76 (d), 139.84 (s), 169.85 (s), 170.57 (s), 192.26 (s).

To a solution of this compound (695.3 mg, 1.09 mmol) in acetone (150 ml) was added an aqueous solution of $NaHCO_3$ (100 ml, 1 M). The resulting white suspension was filtered, washed with water, and air-dried yielding **34** (536.8 mg, 97%) as a white solid. M.p. 194-196ºC (194-197ºC[85]); ^{1}H NMR (C_6D_6) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.21 (d, 3H, *J*= 6.8 Hz), 1.80 (s, 3H), 1.84 (s, 3H), 1.93 (br s), 2.53 (s, 3H), 4.54 (d, 1H, *J*= 2.8 Hz), 4.88 (quintet, 1H, *J*= 5.3 Hz), 5.35 (d, 1H, *J*= 4.4 Hz), 5.53 (q, 1H, *J*= 6.2 Hz); ^{13}C NMR (C_6D_6) δ 12.62 (q), 19.11 (q), 19.33 (q), 20.80 (t), 20.80 (2q), 21.60 (q), 26.51 (d), 27.96 (2t), 31.34 (d), 31.68 (t), 34.52 (t), 36.48 (s), 36.90 (t), 38.37 (2t), 39.21 (q), 39.76 (t), 42.09 (s), 49.88 (d), 54.22 (d), 58.96(d), 59.99 (t), 73.58 (d), 74.22 (d), 95.80 (s), 122.49 (d), 139.48 (s), 150.06 (s), 168.96 (s), 169.35 (s); MS *m/z* (r.i.) 512 (33), 511 (67), 468 (40), 452 (100), 127 (54), 126 (83), 98 (70); HRMS calculated for $C_{32}H_{49}NO_4$ 511.3662, found 511.3664. The NMR and mass spectra were compared to literature data of comparable compounds.[90]

(3β,16β)-20-[(5*R*)-1-Acetyl-5-methyl-1,4,5,6-tetrahydro-2-pyridinyl]-16-(acetyloxy)pregn-5-en-3-yl acetate (35). This compound was prepared from **33** as described in the literature,[89] the NMR and mass data were in accordance with literature data.[90]

(3β,16β,25*R*)-26-(Acetylamino)-16-(acetyloxy)-22-oxocholest-5-en-3-yl acetate (36). Compound **35** (1.09 g, 2.02 mmol) was added to a mixture of aqueous HCl (5 ml, 5M) and HOAc (20 ml). After 1.5 hours, the reaction mixture was diluted with water (200 ml) and neutralized with solid $NaHCO_3$. The mixture was extracted three times with $CHCl_3$ (150 ml), dried, and evaporated *in vacuo* to obtain a yellow oil. Crystallization from acetone/hexane gave **36** (1.12 g, 99%) as white crystals. M.p. 176-179ºC (175-178ºC[89]); ^{1}H NMR δ 0.84 (s, 3H), 0.86 (d, 3H, *J*= 7.5 Hz), 1.00 (s, 3H), 1.11 (d, 3H, *J*= 7.1 Hz), 1.93 (s, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 3.06 (t, 1H, *J*= 5.9 Hz), 4.57 (m, 1H), 4.95 (m, 1H), 5.33 (d, 1H, *J*= 4.4 Hz), 5.96 (m, 1H, N*H*); ^{13}C NMR δ 13.18 (q), 16.76 (q), 17.73 (q), 19.24 (q), 20.65 (t), 21.12 (q), 21.39 (q), 23.30 (q), 27.03 (t), 27.64 (t), 31.19 (d), 31.54 (t), 32.80 (d), 34.73 (t), 36.49 (s), 36.89 (t), 37.97 (t), 38.04 (t), 39.32 (t), 41.84 (s), 43.52 (d), 44.94 (t), 49.69 (d), 53.87 (d), 60.02 (d), 73.78 (d), 75.58 (d), 122.24 (d), 139.58 (s), 169.88 (s), 170.36 (s), 170.51 (s), 213.45 (s); MS *m/z* (r.i.) 107 (11), 497 (7), 437 (6), 422 (14), 252 (84), 114 (100), 43 (10); HRMS calculated for $C_{33}H_{51}NO_6$ 107.3716, found 107.3720. The NMR and mass spectra were compared to literature data of comparable compounds.[90]

(25*R*)-26-(Acetylamino)-22-methoxyfurost-5-en-3-yl acetate (37). To a solution of **36** (249.5 mg, 0.44 mmol) in MeOH (10 ml) was added an aqueous solution of K_2CO_3 (2 ml, 0.3 M). The reaction mixture was refluxed for 3 hours, cooled to room temperature, and then mixed with aqueous HOAc (1.5 ml, 20%). After 1 hour, the reaction mixture was neutralized by addition of aqueous $NaHCO_3$, extracted three times with $CHCl_3$ (25 ml), dried, and evaporated *in vacuo*. The remaining residue was crystallized from aqueous methanol to yield **37** (190.9 mg, 82%) as a white solid. M.p. 138-140ºC (138-140C°[91]); ^{1}H NMR ($CDCl_3$+CD_3OD) δ 0.71 (s, 3H), 0.81 (d, 3H, *J*= 6.4 Hz), 0.92 (d, 3H, *J*= 5.0 Hz), 0.94 (s, 3H), 1.87 (s, 3H), 3.30 (s, 3H), 3.33 (m, 1H), 4.50 (q, 1H, *J*= 7.2 Hz), 5.23 (d, 1H, *J*= 3.8 Hz), 7.23 (m, 1H, N*H*); ^{13}C NMR δ 15.17 (q), 16.07 (q), 17.36 (q), 17.73 (q), 19.16 (q), 20.63 (t), 22.38 (q), 27.58 (t), 30.97 (d), 31.23 (t),

31.63 (t), 31.85 (t), 33.14 (d), 35.36 (t), 36.46 (s), 37.07 (t), 39.49 (t), 39.69 (d), 40.44 (s), 41.69 (t), 44.74 (t), 49.51 (q), 49.90 (d), 56.21 (d), 62.25 (d), 71.00 (d), 81.00 (d), 110.41 (s), 120.96 (d), 140.82 (s), 171.55 (s), 171.64 (s) . The NMR spectra were compared to literature data of comparable compounds.[91]

***N*-[(3β,25*R*)-3,22-dihydroxyfurost-5-en-26-yl]acetamide (38). Method A.** To a solution of **36** (128.5 mg, 0.23 mmol) in EtOH (10 ml) was added an aqueous solution of K_2CO_3 (1 ml, 1.5 M). After heating for 3 hours at reflux temperature, the reaction mixture was poured onto ice, allowed to come to room temperature overnight, extracted three times with $CHCl_3$ (50 ml), dried, and evaporated *in vacuo* to yield **38** as a colorless glass. Crystallization from acetone/hexane gave **38** (100.0 mg, 78%) as a white solid. M.p. 120-122ºC (119-122ºC[89]); ^{1}H NMR δ 0.73 (s, 3H), 0.84 (d, 3H, *J*= 6.6 Hz), 0.95 (s, 3H), 0.96 (d, 3H, *J*= 6.7 Hz), 1.91 (s, 3H), 3.44 (m, 1H), 4.53 (q, 1H, *J*= 7.2 Hz), 5.27 (d, 1H, *J*= 4.4 Hz), 5.87 (t, 1H, *J*= 5.9 Hz, N*H*); ^{13}C NMR δ 15.54 (q), 16.30 (q), 17.72 (q), 19.42 (q), 20.81 (t), 23.35 (q), 27.66 (t), 31.42 (d), 31.55 (t), 31.87 (t), 32.03 (t), 33.38 (d), 35.68 (t), 36.63 (s), 37.23 (t), 39.66 (t), 40.13 (d), 40.60 (s), 42.23 (t), 44.82 (t), 50.03 (d), 56.42 (d), 62.57 (d), 71.60 (d), 81.29 (d), 110.43 (s), 121.27 (d), 140.88 (s), 170.54 (s). The NMR spectra were compared to literature data of comparable compounds[91].

Method B. To a solution of **36** (249.5 mg, 0.44 mmol) in dioxane (10 ml) was added an aqueous solution of K_2CO_3 (6 ml, 0.3 M). After heating for 3 hours at reflux temperature, an aqueous solution of NaOH (1.5 ml, 2 M) was added and reflux was continued for 2 hours. After 16 hours at room temperature, the reaction mixture was concentrated *in vacuo*, dissolved in $CHCl_3$/H_2O 1/1 (50 ml), extracted three times with $CHCl_3$ (25 ml), dried, and evaporated *in vacuo* to yield a yellow foam. Recrystallization from acetone/hexane gave **38** (190.4 mg, 76%) as a white solid. The NMR data are identical to those obtained with method A.

References

1. AVEBE, Postbus 15, 9640 AA VEENDAM.
2. Friedman, M.; McDonald, G.; Haddon, W. F. *J. Ag. Food Chem.* **1993**, *41*, 1397.
3. Gaši, K. T. M. P.; Djurendic, E. A.; Colic, D. R.; Sakac, M. N.; Arcson, O. N.; Mejacevic, L. M.; Miljkovic, D. A. *J. Serb. Chem. Soc.* **1997**, *62*, 451.
4. Gaši, K. M.; Miljkovic, D. A. *J. Serb. Chem. Soc.* **1988**, *53*, 165.
5. Gunic, E.; Tabakovic, I.; Gaši, K. M.; Miljkovic, D.; Juranic, I. *J. Org. Chem.* **1994**, *59*, 1264.
6. Gasi, K. M. P.; Kolic, D. R.; Arcson, O. N.; Sakac, Z. O.; Djurendic, E. A.; Sakac, M. N.; Medic, L.; Miljkovic, D. A. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1655.
7. Schramm, G.; Österreichische Stickstoffwerke A.-G.: Austrian, 1970, p 8.
8. Herr, M. E.; The Upjohn Company: US, 1956; p 7.
9. van Rheenen, V. *J. Chem. Soc. D* **1969**, 314.

10. Fatiadi, A. J. *Synthesis* **1976**, *2*, 65.
11. Fatiadi, A. J. *Synthesis* **1976**, *3*, 133.
12. Misztal, S.; Marek, C. *Synthesis* **1985**, *12*, 1134.
13. Harris, C. E.; Chrisman, W.; Bickford, S. A.; Lee, L. Y.; Torreblanca, A. E.; Singaram, B. *Tet. Lett.* **1997**, *38*, 981.
14. Holysz, R. P.; The Upjohn Company: Bundesrepublik Deutschland, 1955; p 5.
15. Holysz, R. P.; The Upjohn Company: US, 1956; p 6.
16. Meystre, C.; Frey, H.; Neher, R.; Wettstein, A.; Miescher, K. *Helv. Chim. Acta* **1946**, *29*, 627.
17. Morzycki, J. W.; Wilczewska, A. Z. *Tetrahedron* **1996**, *52*, 14057.
18. Schreiber, K.; Horstmann, C. *Chem. Ber.* **1966**, *99*, 3183.
19. Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heany, H.; Thompson, N. *Synthesis* **1987**, *11*, 1015.
20. Kim, H.-S. K., In-Chul; Lee, Sang-Ok *Tetrahedron* **1997**, *53*, 8129.
21. Carlsen, P. H. J. K., Tsutomu; Martin, Victor S.; Sharpless, K. Barry *J. Org. Chem.* **1981**, *46*, 3936.
22. Stewart, J. J. "MOPAC manual. Sixth edition. A general molecular orbital package," Frank J. Seiler Res. Lab.,U.S. Air Force Acad., 1990.
23. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
24. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
25. Beisler, J. A.; Sato, Y. *Chemical Communications* **1968**, *16*, 963.
26. Schramm, G.; Riedl, H.; Lentia G.m.b.H.: Germany, 1971; p 16.
27. Clarke, R. L.; Mooradian, A.; Lucas, P.; Slauson, T. *J. Am. Chem. Soc.* **1949**, *71*, 2821.
28. Staedel, W. *Chem. Ber.* **1886**, *19*, 1947.
29. Bai, D. X., Rui; Chu, Guohua; Zhu, Xingzu *J. Org. Chem.* **1996**, *61*, 4600.
30. August, R. A. K., Jeffrey A.; Moody, Claire M.; Young, Douglas W. *J. Chem. Soc., Perkin I* **1996**, *6*, 507.
31. Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc.* **1967**, 2015.
32. Hanaoka, M. K., Nobuyuki; Shimada, Ken-ichi; Mukai, Chisato *J. Chem. Soc., Perkin I* **1987**, 677.
33. Hanaoka, M.; Nagami, K.; Imanishi, T. *Heterocycles* **1979**, *12*, 497.
34. Hanaoka, M.; Nagami, K.; Imanishi, T. *Chem. Pharm. Bull.* **1979**, *27*, 1947.
35. Zhang, C.; Gyermek, L.; Trudell, M. L. *Tet. Lett.* **1997**, *38*, 5619.
36. Olofson, R. A.; Abbott, D. E. *J. Org. Chem.* **1984**, *49*, 2795.
37. Dietzsch, K. *Chem. Chem. Zeit.* **1965**, *27*, 34.
38. Wentland, M. P. K., Rudolph K.; Tham, Fook S. *J. Org. Chem.* **1991**, *56*, 4701.
39. Ouannes, C.; Thal, C. *Tet. Lett.* **1981**, *22*, 951.
40. Kaminski, Z. J. P., P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248.

41. Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159.
42. Kunishima, M. K., Chiho; Iwasaki, Fumiaki; Terao, Keiji; Tani, Shohei *Tet. Lett.* **1999**, *40*, 5327.
43. Rönsch, H. *Zeit. fur Chem.* **1979**, *19*, 447.
44. Marion, L.; Lemay, L.; Portelance, V. *J. Org. Chem.* **1950**, *15*, 216.
45. Morelli, J.-F.; Pouilhes, A.; Langlois, Y. *Tetrahedron* **1997**, *53*, 5195.
46. Smith, S.; Elango, V.; Shamma, M. *J. Org. Chem.* **1984**, *49*, 581.
47. Doshi, H.; Cardis, A. B.; Crelling, J. K.; Miller, S. I.; Dalton, D. R.; Zacharias, D. E.; Glusker, J. P. *J. Org. Chem.* **1987**, *52*, 2604.
48. Blasko, G.; Elango, V.; Sener, B.; Freyer, A. J.; Shamma, M. *J. Org. Chem.* **1982**, *47*, 880.
49. Cospito, G. C.; Illuminati, G.; Lillocci, C.; Petride, H. *J. Org. Chem.* **1981**, *46*, 2944.
50. Shamma, M.; Rothenberg, A. S.; Jayatilake, G. S.; Hussain, S. F. *Tetrahedron* **1978**, *34*, 635.
51. Maitra, U.; Breslow, R. *Tet. Lett.* **1986**, *27*, 3087.
52. Schramm, G.; Österreichische Stickstoffwercke A-G.: Austria, 1971, p 8.
53. Schreiber, K.; Adam, G. *Experientia* **1961**, *17*, 13.
54. Schreiber, K.; Adam, G. *Liebigs Ann. Chem.* **1963**, *666*, 176.
55. Schreiber, K.; Roensch, H. *Tetrahedron Lett.* **1963**, *34*, 329.
56. Schreiber, K.; Rönsch, H. *Liebigs Ann. Chem.* **1965**, *681*, 196.
57. Quyen, L. T.; Ripperger, H.; Adam, G.; Schreiber, K. *Liebigs Ann. Chem.* **1993**, 167.
58. Schreiber, K.; Adam, G. *Tetrahedron* **1964**, *20*, 1707.
59. Bakker, C. C.; Vrijhof, P. *Tetrahdron Lett.* **1978**, *19*, 4699.
60. A-G, Ö. S.; Österreichische Stickstoffwerke A-G.: Republique Francais, 1970; p 16.
61. Gunda, T. E. *Liebigs Ann. Chem.* **1990**, 311.
62. Brown, E. J. *Austral. J. Chem.* **1985**, *38*, 765.
63. A possible alternative for a shorter route from 28 to DPA (6) could have been the degradation via irradiation of a halogenated pregnane derivate, but the presence of the ?5,6 bond is prohibitive for this approach.
64. Quyen, L. T.; Ripperger, H.; Schreiber, K. *Liebigs Ann. Chem.* **1990**, 519.
65. Quyen, L. T.; Ripperger, H.; Schreiber, K. *Liebigs Ann. Chem.* **1991**, 143.
66. Kusano, G.; Aimi, N.; Sato, Y. *J. Org. Chem.* **1970**, *35*, 2624.
67. Vona, M. L. D.; Luchetti, L.; Rosnati, V. *Tetrahedron* **1994**, *50*, 8203.
68. Li, W.-R.; Hsu, N.-M.; Chou, H.-H.; Lin, S. T.; Lin, Y.-S. *Chem. Commun.* **2000**, *5*, 401.
69. Chiou, C.-M.; Kang, J.-J.; Lee, S.-S. *J. Nat. Prod.* **1998**, *61*, 46.
70. Krishnamurthi, K.; Vijayan, B.; Ramarajan, K. *J. Indian Chem. Soc.* **1992**, *69*, 373.
71. Cardona, L.; Garcia, B.; Pedro, J. R.; Ruiz, D. *Tetrahedron* **1994**, *50*, 5527.
72. Fischer, G.; Fritz, H.; Rihs, G.; Hunkler, D.; Exner, K.; Knothe, L.; Prinzbach, H. *Eur. J. Org. Chem.* **2000**, 743.

73. Czombos, J.; Aelterman, W.; Tkachev, A.; Martins, J. C.; Tourwe, D.; Peter, A.; Toth, G.; Fulop, F.; Kimpe de, N. *J. Org. Chem.* **2000**, *65*, 5469.
74. Wright, J. M.; Jones, G. B. *Tetrahedron Lett.* **1999**, *40*, 7605.
75. Wenglovsky, S.; Hegedus, L. S. *J. Am. Chem. Soc.* **1998**, *120*, 12468.
76. Kochetkov, N. K.; Torgov, V. I.; Malysheva, N. N.; Shashkov, A. S.; Klimov, E. M. *Tetrahedron* **1980**, *36*, 1227.
77. Pihko, P. M. K., Ari M. P. *J. Org. Chem.* **1998**, *63*, 92.
78. Adam, G.; Voigt, D.; Schreiber, K. *Tetrahedron* **1971**, *27*, 2181.
79. Wiesner, K.; Armstrong, R.; Bartlett, M. F.; Edwards, J. A. *J. Am. Chem. Soc.* **1954**, *76*, 6068.
80. Adam, G.; Huong, H. T. *Tet. Lett.* **1980**, *21*, 1931.
81. Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
82. Adam, G.; Schreiber, K. *Tetrahedron* **1966**, *22*, 3581.
83. Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shiori, T. *Synlett* **1998**, *2*, 212.
84. Hohne, E.; Seidel, I.; Reck, G.; Ripperger, H.; Schreiber, K. *Tetrahedron* **1973**, *29*, 3065.
85. Sato, Y.; Latham, G.; Mossetig, E. *J. Org. Chem.* **1957**, *22*, 1496.
86. Sato, Y.; Ikekawa, N.; Mossetig, E. *J. Org. Chem.* **1960**, *25*, 783.
87. Engel, C. R.; Lachance, P.; Capitaine, J.; Zee, J.; Mukherjee, D.; Merand, Y. *J. Org. Chem.* **1983**, *48*, 1954.
88. Rousselet, G.; Capdevielle, P.; Maumy, M. L. *Tet. Lett.* **1995**, *36*, 4999.
89. Sato, Y.; Ikekawa, N. *J. Org. Chem.* **1960**, *25*, 786.
90. Bird, G. J.; Collins, D. J.; Eastwood, F. W.; Swan, J. M. *Austral. J. Chem.* **1979**, *32*, 597.
91. Cambie, R. C.; Potter, G. J.; Read, R. W.; Rutledge, P. S.; Woodgate, P. D. *Austral. J. Chem.* **1981**, *34*, 599.
92. Lawson, D. R.; Green, T. P.; Haynes, L. W.; Miller, A. R. *J. Ag. Food Chem.* **1997**, *45*, 4122.
93. Bird, G. J.; Collins, D. J.; Eastwood, F. W.; Exner, R. H.; Romanelli, M. L.; Small, D. D. *Austral. J. Chem.* **1979**, *32*, 783.
94. Schöpf, H.; Herrmann, R. *Chem. Ber.* **1933**, *66*, 298.
95. Beisler, J. A.; Sato, Y. *J. Chem. Soc.* **1971**, 149.
96. Kraus, G. A.; Landgrebe, K. *Tetrahedon Lett.* **1984**, *25*, 3939.
97. Kadota, S.; Chen, A. Z.; Li, J. X.; Xu, G. J.; Namba, T. *Phytochemistry* **1995**, *38*, 777.
98. Vassova, A.; Voticky, Z.; Tomko, J. *Coll. Czech. Chem. Comm.* **1977**, *42*, 3643.
99. Kaneko, K.; Nakaoka, U.; Tanaka, M. W.; Yoshida, N.; Mitsuhashi, H. *Tet. Lett.* **1978**, *24*, 2099.
100. Bird, G. J.; Collins, D. J.; Eastwood, F. W.; Exner, R. H. *Austral. J. Chem.* **1979**, *32*, 797.
101. Ripperger, H.; Porzel, A. *Phytochemistry* **1992**, *31*, 1837.

102. Qian, Z. Z.; Nohara, T. *Phytochemistry* **1995**, *40*, 979.
103. Schreiber, K.; Roensch, H. *Liebigs Ann. Chem.* **1965**, *681*, 187.
104. Wanyonyi, A. W.; Chhabra, S. C.; Mkoji, G.; Eilert, U.; Njue, W. M. *Phytochemistry* **2002**, *59*, 79.
105. Szendi, Z.; Forgo, P.; Sweet, F. *Steroids* **1995**, *60*, 442.