Michael addition of 5-nitro-2-methylpentanol-1 acetate to cis-5,17(20)-pregnadien-3β-ol-16-one:

Kohler, Connor and McClellan and more recently Kloetzel have studied the Michael addition of nitroalkanes to α, β-unsaturated ketones under a variety of conditions. In the present study, addition of 5-nitro-2-methylpentanol-1 acetate (XXVI) to cis-5,17(20)-pregnadien-3β-ol-16-one (L) to obtain 26-acetoxy-22-nitro-5-cholesten-3β-ol-16-one (XXVII), the key intermediate discussed in the introductory chapter, was carried out in tertiary butyl alcohol in presence of potassium tertiary butoxide. The reaction mixture was analysed at various intervals by t.l.c.; little unsaturated ketone could be detected after allowing the reaction to proceed for 10 days at room temperature. Isomerisation of the starting ketone to a slight extent was observed in the initial stages. A portion of the nitro adduct which had crystallised out at the end of the reaction was collected as such. From mother liquor no other crystalline adduct could be isolated. The obtained solid adduct was crystallised twice to a constant melting compound which showed a single spot on t.l.c. in a number of solvent systems.
It seems that a single diastereomer, later found to have
R configuration at C-25, fortuitously crystallises out of
the reaction mixture. It may be pointed out that the
sharp melting point of this product and homogeneity on t.l.c.
are not conclusive evidence for its being a single compound.
This solid, because of its good crystalline nature, was
used for all further experiments. Its gross structure was
established on basis of I.R. spectrum and elemental analysis.
It is noteworthy that the acetyl group as shown by I.R.
absorption at 1262 cm⁻¹ was not lost during the reaction.

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\text{XXVI}
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\text{XXVII}
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Nef reaction on 26-acetoxy-22-nitro-5-cholesten-3β-ol-16-one:

Preparation of nitro ketone XXVII essentially established the feasibility of this route to steroidal sapogenins and solanum alkaloids. Some methods for its transformation to these were then explored. Nef reaction on XXVII furnished, after purification by thick layer chromatography and crystallisation, a solid melting at 186-188°. It showed two absorption peaks at 1714 and 1734 cm⁻¹ which are characteristic of kryptogenin, a ring-B-open sapogenin. Although melting point of its mixture with the natural material could not be taken, its subsequent elaboration to diosgenin confirms its identity. This constitutes first formal total synthesis of kryptogenin (LXVI). Direct conversion of this diketo sapogenin to solasodine, a typical spirostan, is known.

The C-16 keto group of LXVI was reduced selectively according to the procedure of Uhle. Crystallisation of the reaction product obtained after acidification afforded diosgenin. It showed no depression in melting point on
admixture with the natural sample and their I.R. spectra could be completely superimposed. The above synthesis of diosgenin is remarkably short and is stereoselective.

Stereochemistry of 26-acetoxy-22-nitro-5-cholesten-3β-ol-16-one:

Four new asymmetric centres are generated by Michael addition of XXVI to L. For synthesis of sapogenins, however, no difficulty was visualised on this account. Stereochemistry at C-25 could be controlled by employing resolved nitro addenda, whereas asymmetry at C-22 would be eliminated on Nef reaction. The adduct was expected to have thermodynamically more stable β-configuration at C-17, equilibration being possible because of the neighbouring C-16 carbonyl function. From known preference for backside attack in steroids, natural (α) configuration at C-20 could be expected on addition to cis-ketone L. Even if some complicating factors like prior isomerisation of substrate intervened, the C-16, C-22 dicarbonyl compounds, to be formed on Nef reaction, are known to isomerise to more stable 20α
For synthesis of solanum alkaloids, however, no isomerisation at C-20 could be expected and it was important to investigate if proper stereochemistry obtains at this centre on Michael addition. It was sought to gain some insight into the mode of this addition through reaction of nitromethane with L and LI. This simple nitro-alkane was chosen to avoid complications introduced by additional asymmetric centres at C-22 and C-25. Moreover, it seemed possible to correlate this adduct with bismorcholeenic acid.

Addition of nitromethane (excess) to cis-5,17(20)-pregnadien-3β-ol-16-one (L) was carried out in tertiary butyl alcohol in presence of potassium tertiary butoxide and progress of the reaction was followed by t.l.c. This addition is relatively fast. At 35° the reaction is complete in 1 hour when only one spot corresponding to the adduct could be detected. On interruption after 15 minutes, the reaction product was found to contain the adduct (LXVII, ca. 50%), the cis-ketone (L, ca. 40%) and a small amount of the trans-ketone (LI).

In contrast, when nitromethane was added to the trans-ketone (LI) under identical conditions, the reaction product after 15 minutes contained mostly the starting material. After 20 hours the reaction mixture consisted of a product (ca. 50%) having the same Rf value as that of cis-ketone adduct (LXVII), trans-ketone (ca. 40%) and a small amount of
a new product having Rf slightly lower than that of LXVII. It is assumed to be the isomeric adduct LXVIII. A little cis-ketone was also detected. The major adducts in the two cases seem to be identical, since the spots on t.l.c. were symmetrical and had the same Rf values in a number of solvent systems. Isolation of the addition products from the trans-ketone has not been attempted due to scarcity of this material.

Stereochemistry of the adduct LXVII was established through the following series of reactions which are expected to preserve stereochemical integrity. The adduct LXVII was
acetylated and the keto group was protected by conversion to thio-ketal LXX. This product (LXX) was reduced with lithium aluminium hydride, acetylated and desulphurised with Raney nickel. The resulting 20-aminomethyl-5-pregnen-3β-ol O,N-diacetate (LXXIII) was compared with the authentic sample obtained, as shown, from bisnorcholenic acid. No depression in melting point on admixture of the two was observed; specific rotations and Rf values were also identical. To avoid fractionation, purification was not attempted at any of the steps involved, except that the final product was crystallised once.
The above experiments established that the addition of nitromethane to the cis-ketone (L) is much faster than to the trans-ketone (LI). The major product of addition to the trans-ketone also seems to be the adduct LXVII. To explain these results it is suggested that the transition state, approaching LXXVI, corresponding to a backside nitromethane anion addition to L, is stabilised by a polar interaction between the negative charge on carbonyl oxygen and the positive charge on the nitrogen atom of the nitro group. Such stabilisation of the transition state approaching LXXVII, corresponding to a frontside attack on L, is obstructed by the interference between the methyl groups on C-13 and C-20,
as shown. This coupled with usual preference for backside attack observed in steroid reactions results in a highly stereospecific addition. This may be compared with the random 1,4-Grignard addition observed with a similar $\alpha,\beta$-unsaturated ketone system.

In case of addition to the trans-ketone, the two factors, i.e., tendency for backside attack and stabilisation by polar interaction, operate in opposite directions. The attack seems to be preferred from frontside, provided the product LXVII is being obtained directly from the trans-ketone. The earlier observed stereospecificity, however, is now reduced to stereoselectivity only.

An alternate explanation for the formation of LXVII from the trans-ketone (LI) can be that the reaction proceeds through isomerisation to cis-ketone which undergoes fast stereospecific addition. It may be that the adduct LXVII is being formed both through isomerisation to cis-ketone and by direct front-side addition to the trans-ketone. It should be pointed out that absence of substantial quantities of the cis-ketone (L)
at any stage of the reaction does not rule out isomerisation to it as this ketone is known to undergo rapid nitromethane addition. The small quantity of the isomeric adduct (LXVIII) is inferred to be arising directly by backside attack on the trans-ketone.

The observed rate of addition of nitro acetate XXVI to cis-ketone L is much lower than that of nitromethane, and isomerisation to trans-ketone LI is detected before substantial addition proceeds. Inference about the configuration of the adduct at C-20 cannot, therefore, be drawn by simple comparison with nitromethane addition to cis-ketone L. Yet, little adduct is expected to arise from addition of XXVI to trans-ketone LI because the rate of this addition will be much lower than both the rate of addition to cis-ketone L (by analogy with relative rates of nitromethane addition to L and LI) and the rate of cis-trans equilibration. Most of the adduct XXVII is, thus, expected to arise from backside addition to cis-ketone L, and to have desired S configuration.

Elucidation of stereochemistry at C-22 in adduct XXVII has not been attempted so far. When the resolved (S) nitro acetate becomes available, correlation of the adduct with solanidine, absolute stereochemistry of which is known, would settle this point.
A number of routes for conversion of the nitro adduct (XXVII) to solanidans can be visualised. Two methods which envisaged simultaneous formation of rings E and F were explored. Lavagnino and associates, and Heinenecke and Kray have observed cyclisation of amino alcohols by heating them with Raney nickel. It was proposed to use first this reaction, which is considered to proceed by an oxidation-reduction process, as it seemed to simulate a possible biosynthetic pathway. The nitro ketone (XXVII) was reduced with lithium aluminium hydride to amino triol LXXVIII, which melted over a range. Heating LXXVIII with Raney nickel in xylene for 30 hours furnished only a small amount of (ca. 5%) a tertiary amine, identified as O-acetate hydrochloride. This product was obtained in such a small quantity that its further characterisation could not be carried out.

* See appendix I
Cyclisation with iodine in xylene was also tried. The result, however, was not encouraging even in this case. It appears that the ring closures may have to be carried out in a stepwise fashion.