Tetrahedron Letters No. 1, pp 85 - 88, 1975. Pergamon Press. Printed in Great Britain.

STEREOCHEMISTRY OF THE FUNCTIONALIZATION OF C-26 IN THE BIOSYNTHESIS OF NEOTIGOGENIN

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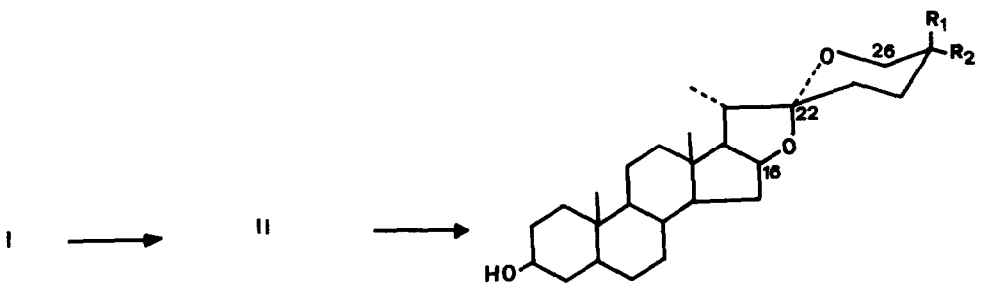
(Received in UK 13 November 1974; accepted for publication 26 November 1974)

THE biosynthesis of steroidal sapogenins involves[1] the conversion of a Δ^{24} intermediate like lanosterol or cycloartenol (I) into a side chain saturated sterol like cholesterol (II), which is in turn oxidized in positions 16, 22 and 26 to give the spiroketal system (scheme 1) of sapogenins (III,IV).



III $R_1 = H$ $R_2 = CH_3$

IV $R_1 = CH_3$ $R_2 = H$

SCHEME 1

Tamm et al.[2] showed that in tigogenin (III), a 25 R sapogenin, the equatorial methyl group derives from C-2 of mevalonic acid (MVA): this means that the saturation at C-25 of the Δ^{24} intermediate, the geometry[3] of which is shown in fig.1, occurred from the 24-si,25-si face.

We report now the results of a research on the stereochemistry of the reduction at C-25 of the Δ^{24} intermediate during the biosynthesis of neotigogenin (IV),

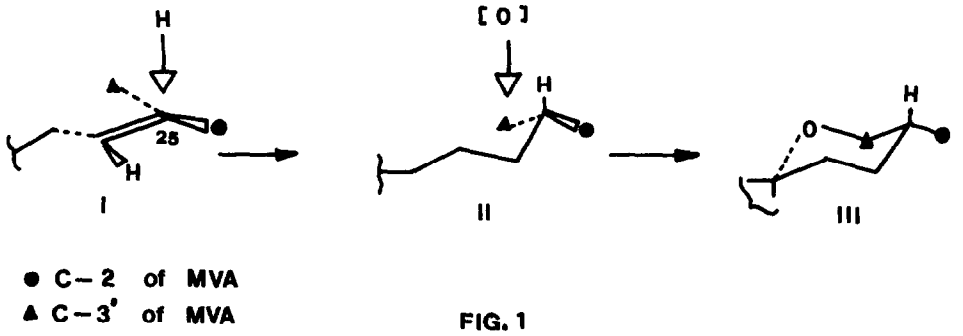


FIG. 1

the 25 S isomer of tigogenin.

The formation of a 25 S sapogenin involves the introduction of an oxygen function on the pro-R methyl of the terminal isopropyl group of the side chain of cholesterol. This pro-R methyl group will derive from C-2 of mevalonic acid in the case of saturation of C-25 of the Δ^{24} intermediate from the 24-si,25-si face (fig. 2a), whereas saturation at C-25 of the Δ^{24} intermediate from the 24-re,25-re face should result in assumption of the pro-R position by the methyl group deriving from C-3' of mevalonic acid (fig.2b).

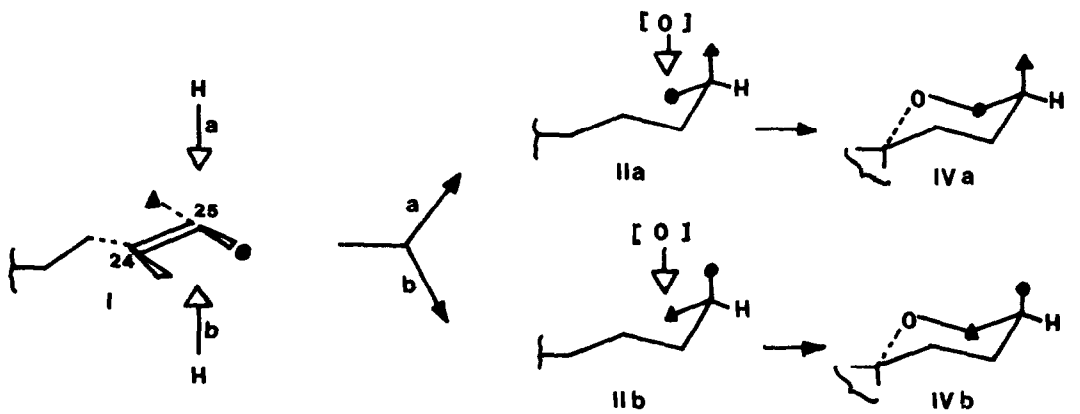
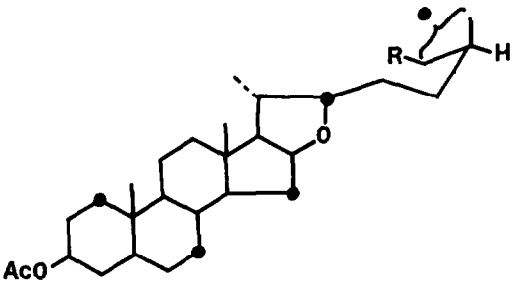


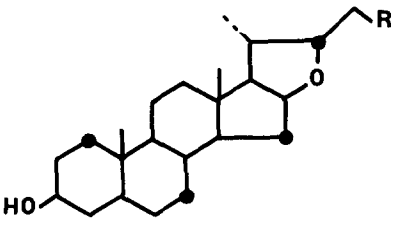
FIG. 2

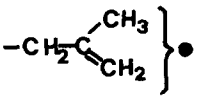
We administered 2-^{14}C MVA (0.2 mCi) to young plants of Lycopersicon pimpinellifolium and, after four weeks, we obtained from neutral extracts of the plants, radioactive neotigogenin (2.04 x 10^5 dpm) with label in positions 1,7,15,22,26 (or 27). The labelled neotigogenin was acetylated, purified by preparative TLC and diluted with carrier material. Hydrogenation on Pt in AcOH yielded dihydroneotigogenin acetate (V) which was transformed into the 27-iodide (VI) by tosylation followed by treatment with NaI in methyl ethyl ketone. Treatment of the iodide (VI) with methanolic KOH afforded the olefin (VII) which was converted with OsO_4 into the diol (VIII) (8.03 x 10^5 dpm/mM).

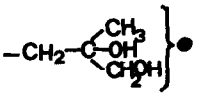


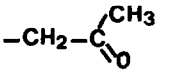
V R = OAc

VI R = I



VII R = 

VIII R = 

IX R = 

Oxidation of the diol (VIII) with $NaIO_4$ yielded the ketone (IX) and formaldehyde isolated as dimedone derivative), corresponding to C-26 of neotigogenin. The radioactivities of the ketone (IX) and of formaldehyde corresponded, respectively to 77.3% (6.21 x 10^5 dpm/mM) and to 18.2% (1.46 x 10^5 dpm/mM) of the total radioactivity, close to the calculated values of 80% and 20%.

The above results indicate that the C-26 of neotigogenin derives from C-2 of MVA and that the introduction of hydrogen at C-25 of the Δ^{24} intermediate occurs, as for tigogenin, from the 24-si,25-si face (fig. 2a).

A similar experiment[4] revealed that the same process occurs during the biosynthesis of the 25 S steroidal alkaloid tomatidine.

Aknowledgements- We thank Prof. Luigi Canonica for his interest in this work and Simes s.p.A. for growing the plants.

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