Synthesis of Chondrillasterol and Spinasterol [(22*E*,24*R*)- and (22*E*,24*S*)-5α-Stigmasta-7,22-dien-3β-ol]

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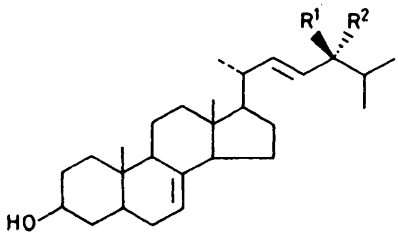
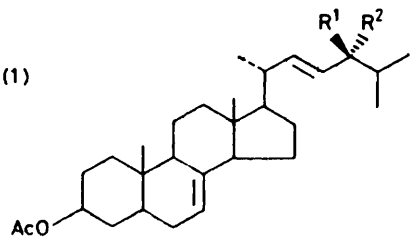
Spinastesterol (1a) and chrondrillasterol (1b) have been synthesized from the ethyl (22*E*,24*S*)- and (22*E*,24*R*)-3β-acetoxy-5α-stigmasta-7,22-dien-29-oates, (2c) and (2d), respectively.

SPINASTEROL (1a) and chondrillasterol (1b) are C-24 stereoisomers which were first isolated from *Spinacea oleracea* and *Chondrilla nucula*, respectively.[1,2] With the advent of more sophisticated instrumentation and chromatographic methods compounds (1a) and (1b) have been isolated from a number of other sources.[3]



(1)



(2)

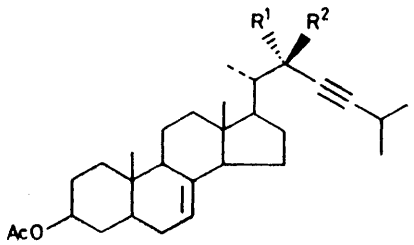
	R¹	R²
a;	Et	H
b;	H	Et
c;	CH_2CHO	H
d;	H	CH_2CHO

Ts = tosyl

	R¹	R²
a;	Et	H
b;	H	Et
c;	CH_2CO_2Et	H
d;	H	CH_2CO_2Et
e;	CH_2CHO	H
f;	H	CH_2CHO
g;	CH_2CH_2OH	H
h;	CH_2CH_2OTs	H
i;	H	CH_2CH_2OH
j;	H	CH_2CH_2OTs

Although spinasterol (1a) was first synthesised in 1949,[4] chondrillasterol was not synthesized until 1976 [5] and, despite the potential of these sterols in studies of phytosterol biosynthesis,[3] only one alternative synthesis of compound (1a) has been available.[6] As part of an investigation of phytosterols, we have devised an improved route to compounds (1a) and (1b).

In previous work on the synthesis of two side-chain models of oogoniols [7] the ethyl (22*E*,24*S*)- and (22*E*,24*R*)-3β-acetoxy-5α-stigmasta-7,22-dien-29-oates, (2c) and (2d), were obtained in a stereospecific manner from the (22*S*)- and (22*R*)-3β-acetoxy-5a-cholest-7-en-23-yne-3,22-diols, (3a) and (3b), respectively.† Compounds (2c) and (2d) have now been transformed into spinasterol (1a) and chondrillasterol (1b), respectively. Di-isobutylaluminium hydride reduction [8] of compound (2c) at −78 °C afforded the C-29-aldehyde (1c) in good yield which, after acetylation of the 3β-hydroxy-group, was reduced with sodium borohydride to give the alcohol (2g). Reaction of the latter with pyridine and toluene-*p*-sulphonyl chloride and then sodium iodide and zinc powder in glyme [9] gave spinasterol acetate (2a). The chemicophysical properties of the acetate (2a), as well as those of the alcohol (1a), were identical with those reported for synthetic and natural compounds.[5,10]



(3)

	R¹	R²
a;	OH	H
b;	H	OH

Similar treatment of the epimeric ester (2d) gave chondrillasterol (1b) with properties identical with those reported for the synthetic product.[5]

This simple reaction sequence to compounds (1a) and (1b) is suitable for the stepwise labelling of hydrogen atoms at C-29.

EXPERIMENTAL

All m.p.s are uncorrected. I.r. spectra were recorded for solutions in chloroform or for Nujol mulls. Optical rotations were measured for solutions in chloroform.

^1H N.m.r. spectra were recorded on a Varian XL-100 spectrometer in [^2H]chloroform solutions with Me_4Si as internal standard. Mass spectra where recorded on a Varian 112 S mass spectrometer (direct inlet).

(22E,24S)- and (22E,24R)-3β-*Hydroxy*-5α-*stigmasta*-7,22-*dien*-29-*one* (1c) *and* (1d).—The ester (2c) [7] (420 mg) in toluene (15 ml) was cooled to −70 °C and di-isobutyl aluminium hydride (235 mg in 2.5 ml of toluene) was added under dry nitrogen. The solution was kept at −70 °C for 2 h before ethyl acetate (0.5 ml) was added. The solution was allowed to warm to room temperature and then poured

† The C-22 configuration of the diols (3a) and (3b) was first assigned by analogy (ref. 7), but has now been confirmed chemically (M. Anastasia and A. Fiecchi, *J. Org. Chem.*, 1981, in the press).

into saturated ammonium chloride solution. Work-up followed by flash chromatography [11] (20% ethyl acetate–hexane) afforded the *aldehyde* (1c) (340 mg), m.p. 152—153 °C (from methanol); $\nu_{max.}$ 3 335, 2 720, 1 720, and 970 cm^{-1}; δ 0.55 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 2.3 (3 H, m, 24- and 28-H), 3.3—3.8 (2 H, m, 3α-H and OH), 5.17—5.45 (3 H, m, 7-, 22- and 23-H), and 9.75 (1 H, m, CHO); *m/e* 426 (Found: C, 81.6; H, 10.9. $C_{29}H_{46}O_2$ requires C, 81.7; H, 10.9).

The ester (3b), after similar treatment, gave the *aldehyde* (1d) (350 mg), m.p. 145—146 °C (from methanol), $[\alpha]_D^{20}$ +2.5°; $\nu_{max.}$ 3 335, 2 720, 1 720, and 970 cm^{-1}; δ 0.55 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 2.35 (3 H, m, 24- and 28-H), 3.3—3.8 (2 H, m, 3α-H and OH), 5.17—5.45 (3 H, m, 7-, 22-, and 23-H), and 9.75 (1 H, m, CHO); *m/e* 426 (Found: C, 81.7; H, 11.0. $C_{29}H_{46}O_2$ requires C, 81.7; H, 10.9).

Conversion of the (22E,24S)- *and* (22E,24R)-*Aldehydes* (1c) *and* (1d) *into Spinasterol* (1a) *and Chondrillasterol* (1b).—The aldehyde (250 mg) was acetylated with acetic anhydride to afford the acetoxy-aldehyde (2e) (250 mg), m.p. 169—170 °C [δ 0.52 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 2.35 (3 H, m, 24- and 28-H), 4.72 (1 H, m, 3α-H), 5.15—5.43 (3 H, m, 7-, 22-, and 23-H), and 9.73 (1 H, m, CHO); *m/e* 468] which was dissolved in methanol (5 ml) and treated with sodium borohydride (35 mg) at 0 °C for 10 min to afford, after work-up, the alcohol (2 g) (180 mg), m.p. 150—151 °C (from ethyl acetate), $[\alpha]_D^{21}$ −1°. A portion of the alcohol (2g) (100 mg) was dissolved in pyridine (1.5 ml) at 0 °C and treated with toluene-*p*-sulphonyl chloride (110 mg); the mixture was then allowed to warm to 23 °C and was stirred for a further 21 h. Work-up afforded the tosylate (2 h) (85 mg), m.p. 125—126 °C (from methanol); *m/e* 624. A mixture of the tosylate (2h) (75 mg), sodium iodide (150 mg), zinc powder (130 mg), and glyme (2 ml) was refluxed for 2 h while being stirred. The reaction mixture was filtered and work-up afforded the acetoxy-compound (2a) (45 mg); m.p. 187—188 °C (from ethanol–benzene), $[\alpha]_D^{22}$ −4.9 (lit.,[1,2] m.p. 187—189 °C, $[\alpha]_D$ −5.2°); δ 0.55 (3 H, s, 18-H), 0.82 (3 H, s, 19-H), 4.7 (1 H, m, 3α-H), and 3.50 (3 H, overlapping, 7-, 22-, and 23-H); *m/e* 454 (Found: C, 81.9; H, 11.2. $C_{31}H_{50}O_2$ requires C, 81.9; H, 11.0). Saponification of compound (2a) afforded spinasterol (1a), m.p. 171—173 °C (from ethanol–benzene), $[\alpha]_D^{22}$ −2.5° (identical in all respects with the compound obtained previously [4,5]).

A similar sequence of reactions starting from the aldehyde (1d) afforded the acetoxy-aldehyde (2f), m.p. 152—153 °C (from methanol); the alcohol (2c), m.p. 164—166 °C (from methanol), $[\alpha]_D^{22}$ +4°; the tosylate (2j), m.p. 120—121 °C (from hexane); the acetoxy-compound (2b), m.p. 182—183 °C (from chloroform–methanol); and finally chondrillasterol (1b), m.p. 172—173 °C (from acetone–methanol), $[\alpha]_D^{20}$ −2° (identical with the compound previously synthesized[5]).

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