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STRUCTURES OF THORNASTEROLS A AND B
(BIOLOGICALLY ACTIVE GLYCOSIDES FROM ASTEROIDIA, XI)

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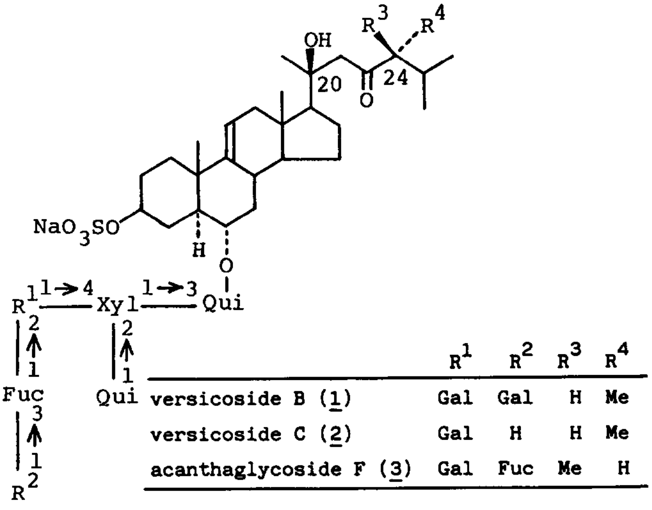
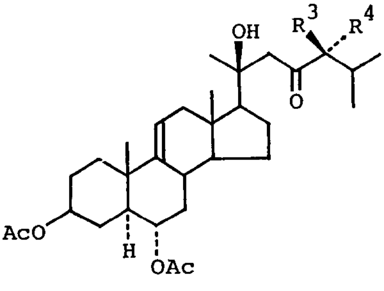
Summary: (20S)-thornasterol A, (20S,24R)-thornasterol B, (20S,24S)-thornasterol B, and (20S)-24-northornasterol A were stereoselectively prepared from (+)-asterone and were practically identical with the natural specimens. Consequently, the complete structures of versicosides B and C and acanthaglycoside F could be determined.

We have reported the isolation and structure of steroidal oligoglycoside sulfates from whole bodies of starfishes, Asterias amurensis [cf.] versicolor Sladen[1)] and Acanthaster planci L.[2)]. Versicosides B (1) and C (2)[1b)] and acanthaglycoside F (3)[2c)] contained thornasterol B[3)], 3β,6α,20ξ-trihydroxy-24ξ-methyl-5α-cholest-9(11)-en-23-one, as the steroidal component. However, they showed different negative Cotton maximums ($[\theta]_{284}$=-6028 for 1, $[\theta]_{287}$=-6884 for 2, but $[\theta]_{275}$=-685 for 3) in the CD spectrum[1b,2c)] and also different chemical shifts corresponding to C-24 and C-28 of their aglycones in the ^{13}C-NMR spectrum. These results were attributed to the presence of (20S,24R)-thornasterol B and (20S,24S)-thornasterol B. We have now determined the configurations of the C-24 position in thornasterol B's and of C-20 in thornasterols A, B and 24-northornasterol A. The former was determined by preparing two thornasterol B's and the latter by leading 20ξ-hydroxy-23-oxocholest-5-en-3β-yl p-bromobenzoate (13), which was prepared by the Mukaiyama's cross-aldol reaction, to 20β-hydroxycholesterol (15)[4)].

Diacetyl (20S,24R)-thornasterols B (4) and (20S,24S)-thornasterol B (5) were synthesized as follows. (E)-4-Methyl-2-pentenol (7) was epoxidized by the Katsuki-Sharpless reaction[5)],



	R^1	R^2	R^3	R^4
versicoside B (1)	Gal	Gal	H	Me
versicoside C (2)	Gal	H	H	Me
acanthaglycoside F (3)	Gal	Fuc	Me	H

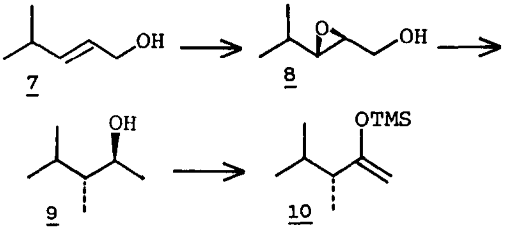


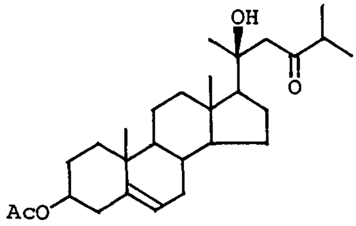
diacetyl (20S,24R)-thornasterol B (4): R^3= H, R^4=Me
diacetyl (20S,24S)-thornasterol B (5): R^3=Me, R^4= H
diacetyl (20S)-thornasterol A (6): R^3= H, R^4= H

using (+)-diethyl tartrate as a chiral element to an epoxy alcohol (8) (>90% e.e., ^{1}H-NMR of its MTPA ester) in a 64% yield. Treatment of 8 with trimethylaluminum in hexane at 0°C[7] afforded a 1,2-diol which was converted to an alcohol (9)[6] in a 48% yield from 8 by selective tosylation and subsequent LAH reduction. Swern oxidation of 9 to the corresponding ketone followed by enol etherification with trimethylchlorosilane gave (3R)-3,4-dimethyl-2-trimethylsilyloxy-1-pentene (10)[6] in a 56% yield from 9. 10 was treated with a mixture of diacetyl asterone[1a,2a] (11) and titanium tetrachloride in CH_2Cl_2 at RT for 1 hr[8] to give diacetyl (20S,24R)-thornasterol B (4)[6] in a 95% yield. The physical and spectroscopic properties of 4 were identical to those of the natural specimen[1] which was derived from versicoside B (1). Diacetyl (20S,24S)-thornasterol B (5) was prepared in a similar manner, except for the use of (-)-diisopropyl tartrate in the asymmetric epoxidation. The Mukaiyama's cross-aldol reaction of (3S)-3,4-dimethyl-2-trimethylsilyloxy-1-pentene (10')[6] with 11 gave 5[6] in excellent yield. The ^{13}C-NMR chemical shifts of C-12 to C-28 as well as the ^{1}H-NMR shifts of 5 were superimposable on those of the aglycone moiety of acanthaglycoside F (3)[2c]. The CD spectra of 3 and 5 showed the same Cotton effect as shown in Figures 1 and 2.

Diacetyl (20S)-thornasterol A (6)[1a,2b,2c,6] and diacetyl (20S)-24-northornasterol A (12)[6,9] could be prepared from the corresponding trimethylsilyl enol ether and 11 by means of the Mukaiyama's cross-aldol reaction[8]. 6 was identical to the natural specimen in every respect[1a,2b]. The ^{13}C-NMR chemical shifts of C-12 to C-27 of 12 and its characteristic ^{1}H-NMR peaks were in good agreement with those of the aglycone moiety of ophidianosides B and C[9].

In order to determine the C-20 configuration of thornasterols, 20ξ-hydroxy-23-oxocholest-5-en-3β-yl p-bromobenzoate (13)[6] and 20ξ-hydroxy-23-oxo-24-norcholest-5-en-3β-yl acetate (14)[6] were prepared from pregnenolone derivatives, in a similar manner. The conformation of the side chain, C-20 to C-27, of 13 and 14 were identical to that of 6 and 12, respectively, by comparison of the ^{13}C-NMR and ^{1}H-NMR chemical shifts of all the aldol products. In each case, the aldol reaction gave the single C-20 epimer having the 20-hydroxy-23-carbonyl moiety. These results could be well explained in terms of two factors, that the addition of organometallic reagents to the C-20 ketone of the steroid depends on the position and configuration of substituents near C-20 and the bulkiness of the reagent[10]. In the case of the reaction of pregnenolone acetate with a Grignard reagent, a 20S hydroxy compound is predominantly formed[4]. On the base of the above results and physical constants of thornasterols and their analogs, 13 and 14, the C-20 configuration was identical and apparently 20S. Conclusive evidence was obtained by chemical means. Sodium borohydride reduction of 13 led to a mixture of C-23 alcohols which were converted to acetates in a 71% yield from 13. The acetates were treated with lithium in $EtNH_2$ under reflux for 2 hr to give 20β-hydroxycholesterol (15)[6] in a 36% yield and 20β-hydroxycholest-5-ene (16)[6] in a 12% yield. 15 was acetylated to 17[6]. The physical constants of 15 and 17 were in excellent agreement with the values in the literature[4]. Consequently, it was revealed that thornasterols had the same 20S configuration and the structures of versicosides B (1) and C (2) and acanthaglycoside F (3) were considered to have (20S,24R)-thornasterols B (4) and (20S,24S)-thornasterol B (5) as the aglycone component, respectively.

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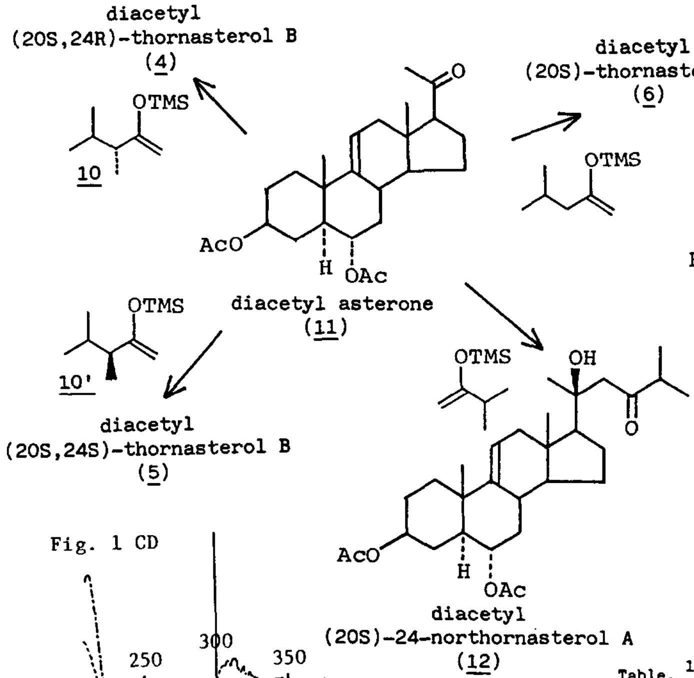

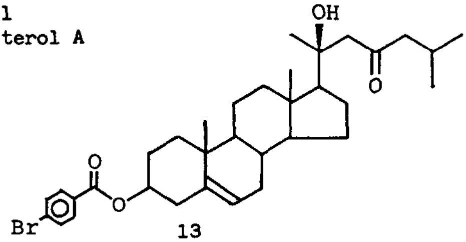

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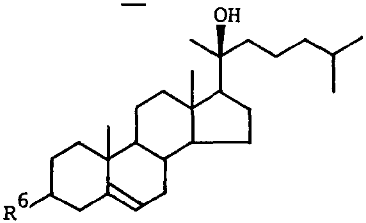

15: R^6=OH

16: R^6= H

17: R^6=AcO

Fig. 1 CD

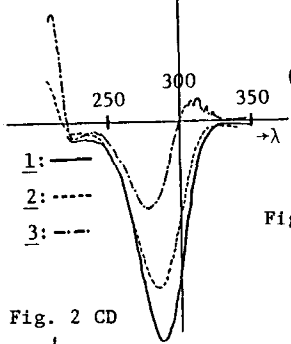

Fig. 2 CD

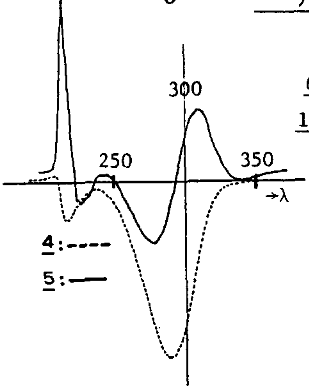

Fig. 3 CD

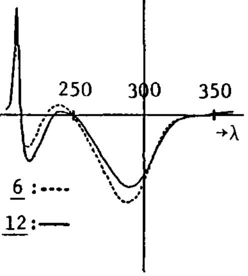

Table. ^{13}C-NMR chemical shifts (δ values, in C_5D_5N)

carbon number	1	4	3	5	6	13	12	14
1	35.8	35.3	36.0	35.4	35.2	37.2	35.5	37.2
2	29.4	29.0	29.4	29.2	29.2	28.1	29.2	28.1
3	77.7	73.1	77.7	73.2	73.3	75.2	73.2	74.1
4	30.8	27.4	30.8	27.5	27.5	38.4	27.5	38.5
5	49.3	46.9	49.3	47.0	47.0	140.0	47.0	140.0
6	80.3	72.0	80.4	72.1	72.1	122.8	72.1	122.8
7	41.6	38.4	41.6	38.6	38.6	32.1	38.6	32.1
8	35.3	35.0	35.3	35.2	35.2	31.5	35.2	31.5
9	145.5	144.4	145.4	144.6	144.6	50.2	144.6	50.2
10	38.8	38.4	38.3	38.6	38.6	36.9	38.6	36.8
11	116.7	117.7	116.7	117.7	117.7	21.2	117.7	21.2
12	42.5	42.3	42.5	42.5	42.4	40.4	42.4	40.4
13	41.6	41.5	41.6	41.7	41.7	43.1	41.7	43.0
14	54.1	53.8	54.1	53.9	53.9	57.1	53.9	57.1
15	23.3	23.1	23.2	23.2	23.3	23.3	23.3	23.2
16	25.1	24.9	25.2	25.0	25.0	24.2	25.0	24.2
17	59.2	59.0	59.1	59.0	59.4	59.5	59.3	59.3
18	13.5	13.5	13.6	13.6	13.6	13.8	13.6	13.8
19	19.2	18.9	19.2	19.0	19.0	19.4	19.0	19.4
20	73.8	73.7	73.8	73.7	73.7	74.0	73.8	74.1
21	27.0	27.0	27.1	27.3	27.2	27.4	27.2	27.4
22	53.7	53.8	53.8	53.7	55.0	55.1	52.2	52.3
23	215.9	215.8	216.0	215.9	211.6	211.7	215.9	215.9
24	53.7	53.8	54.1	54.2	54.0	54.1		
25	30.0	30.0	29.8	30.0	24.4	24.4	42.4	42.4
26	21.3	21.3	21.4	21.4	22.6	22.7	17.8	17.8
27	18.5	18.4	18.5	18.8	22.6	22.6	18.3	18.3
28	11.9	11.9	12.5	12.6				

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6) The following are physical constants of the products.
4: colorless needles, mp 140-141°C, CD(c=0.059,MeOH); $[\theta]^{25}$(nm)= 0(350), -5720 (288,valley), -223(238), -1250(216), ^{1}H-NMR(CDCl$_3$); δ=0.78(s,13-Me), 1.02(s,10-Me), 1.33(s,20-Me), 2.58(s,22-2H), 0.93(d,J=7.0Hz,26-or27-3H), 0.85(d,J=6.6Hz,26-or27-3H), 0.98(d,J=7.2Hz,24-Me).
5: colorless needles, mp 143-144°C, CD(c=0.077,MeOH); $[\theta]^{25}$(nm)= 0(338), +715(309), -631 (277,valley), +69(242), -215(226), ^{1}H-NMR(CDCl$_3$); δ=0.78(s,13-Me), 1.02(s,10-Me), 1.34(s,20-Me), 2.60(s,22-2H), 0.92(d,J=6.6Hz,26-or27-3H), 0.85(d,J=6.8Hz,26-or27-3H), 0.99(d,J=5.5Hz,24-Me).
6: colorless needles, mp 153-154.5°C, CD(c=0.066,MeOH); $[\theta]^{25}$(nm)= 0(340), -2450 (288,valley), +117(240), -1550(216), ^{1}H-NMR(CDCl$_3$); δ=0.77(s,13-Me), 1.02(s,10-Me), 1.33(s,20-Me), 2.54(s,22-2H), 0.92(d,J=6.3Hz,26-and27-3H).
9: bp 135-140°C, ^{1}H-NMR(CDCl$_3$); δ=1.15(d,J=6.3Hz,3H), 0.91(d,J=7.2Hz,3H), 0.83(d,J=6.6Hz,3H), 0.76(d,J=6.4Hz,3H), 1.30(m,1H), 1.87(m,1H), 3.72(m,1H).
10: bp 80°C/140mmHg, ^{1}H-NMR(CDCl$_3$); δ=0.20(s,9H), C.84(d,J=6.6Hz,3H), 0.89(d,J=6.6Hz,3H), 0.96(d,J=6.8Hz,3H), 3.97(s,2H), $[\alpha]^{20}_D$=-11°(c=2.0,EtOH).
10': $[\alpha]^{20}_D$=+11°(c=2.0,EtOH).
12: colorless needles, mp 158-159°C, CD(c=0.070,MeOH); $[\theta]^{25}$(nm)= 0(345), -2600 (287,valley), +311(239), -1040(216), $[\alpha]^{25}_D$=+21°(c=0.53,CHCl$_3$), IR(CCl$_4$); 3500, 1738, 1700cm^{-1}, ^{1}H-NMR(CDCl$_3$); δ=0.78(s,13-Me), 1.02(s,10-Me), 1.31(s,20-Me), 2.60(s,22-2H), 1.09(d,J=7.0Hz,26-and27-3H), ^{1}H-NMR(CD$_3$OD); δ=0.80(s,13-Me), 1.04(s,10-Me), 1.34(s,20-Me), 2.66(s,22-2H), 1.04(d,J=6.6Hz,26-or27-3H), 1.06(d,J=7.0Hz,26-or27-3H)[9], FD-MS; m/z= 502(M), 484(M - H$_2$O), 416(M - side chain).
13: colorless needles, mp 167-169°C, $[\alpha]^{20}_D$=-12°(c=2.1,CHCl$_3$), ^{1}H-NMR(CDCl$_3$); δ=0.87(s,13-Me), 1.06(s,10-Me), 1.34(s,20-Me), 2.55(s,22-2H), 0.92(d,J=6.4Hz,26-and27-3H), anal. calcd. for $C_{34}H_{47}O_4Br$; C68.10, H7.90, found; C68.11, H7.93.
14: ^{1}H-NMR(CDCl$_3$); δ=0.86(s,13-Me), 1.02(s,10-Me), 1.32(s,20-Me), 2.61(s,22-2H), 1.08(d,J=6.8Hz,26-and27-3H).
15: mp 134.5-135.5°C, ^{1}H-NMR(CDCl$_3$); δ=3.52(m,3-1H), 5.35 (d,J=4.8Hz,6-1H), 0.86(s,13-Me), 1.01(s,10-Me), 1.27(s,20-Me), 0.87(d,J=6.3Hz,26-and27-3H).
16: mp 43-44°C, ^{1}H-NMR(CDCl$_3$); δ=5.27(d,J=4.4Hz,6-1H), 0.86(s,13-Me), 1.00(s,10-Me), 1.27(s,20-Me), 0.87(d,J=6.3Hz,26-and27-3H), FD-MS; m/z=386(M), 301(M - side chain).
17: mp 157.5-159°C, $[\alpha]^{25}_D$=-58°(c=0.97,CHCl$_3$), ^{1}H-NMR(CDCl$_3$); δ=4.62(m,3-1H), 5.38 (d,J=3.9Hz,6-1H), 0.86(s,13-Me), 1.02(s,10-Me), 1.27(s,20-Me), 0.87(d,J=6.1Hz,26-and 27-3H).

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