SYNTHESIS OF A-THIENOSTEROIDS AND RELATED COMPOUNDS

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The Grignard reaction of optically active 1,5-dioxo-7a-methyl-3aα,7aβ-hexahydroindan-4a-yl acetic acid with 2- and 3-thienyl magnesium bromide, followed by lactonization gave thienyl γ-lactones, 8a and 8b, respectively. Their configurations were established by the dipole moments. They were converted through multi-steps to a number of A-thienosteroids, namely modified steroids in which the ring A are displaced by fused thiophenes. A-thiolenone derivatives also were prepared from these A-thienosteroids.

An earlier paper of this series[1] reported that the irradiation of 17β-benzoyloxy-3-oxo-19-nor-5α-androstan-2α,5-episulphide 1 resulted in α-fission of the ketone with concomitant photofragmentation leading to 3-thia-A-norestra-1,5(10)-dien-17β-ol

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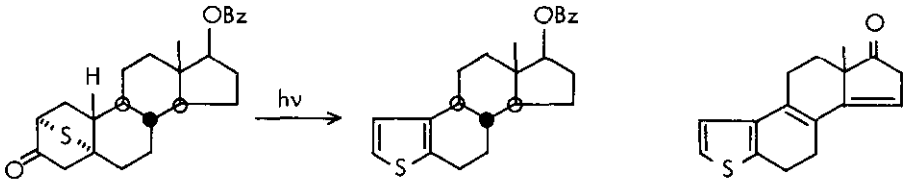
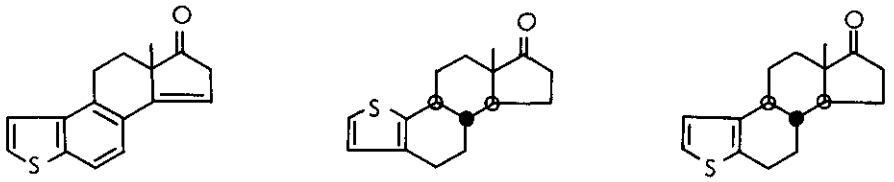
Dedicated to Professor Dr. A. Butenandt on the occasion of his 75th birthday.

benzoate 2c in a low yield. Recently, Trehan[2] and Ramadas[3] synthesized racemic A-thienoequilenine analogues 3 and 4 by a method similar to the Torgov Synthesis.



1 2c 3

Corvers[4] also synthesized racemic A-thienoestrones 5c and 6 by using the olefinic cyclization of thienyl 3(E)-hexenyl derivatives. We have been interested in a more efficient synthesis of A-thienosteroids having naturally occurring configuration. The

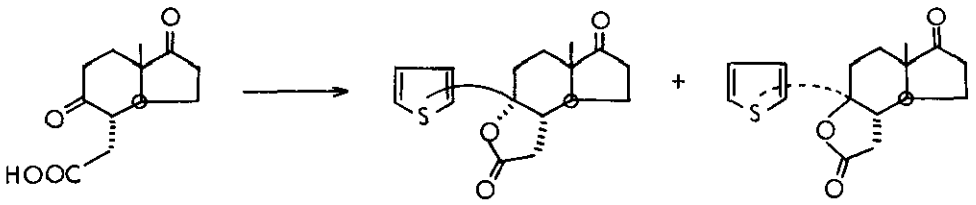


4 5c 6

present paper deals with the "CD-A-B" type of synthesis of the optically active compounds.

As the starting material, we chose optically active 1,5-dioxo-7a-methyl-3aα,7aβ-hexahydroindan-4a-yl acetic acid 7, mp 144-145° C, $[\alpha]_D$ +134°,[5] which is readily

obtainable from the corresponding propionic acid[6] by the Barbier-Wieland degradation[7] of its bisketal methyl ester. The selective Grignard reaction of 7 with an excess of 2-thienyl magnesium bromide at a low temperature gave an epimeric mixture of the 1 : 1 adducts retaining both the 1-oxo function in the 5-membered ring and the carboxyl moiety. The mixture on treatment with $HClO_4$-acetone afforded 2-thienyl cis γ-lactone 8a, mp 176-177° C, $[\alpha]_D$ +93°, in 75% yield. Similarly, the Grignard reaction of 7 with 3-thienyl magnesium bromide prepared from 3-thienyl lithium and $MgBr_2$,[8] followed



7 — 8a 2-Thienyl, 8b 3-Thienyl — 9a 2-Thienyl, 9b 3-Thienyl

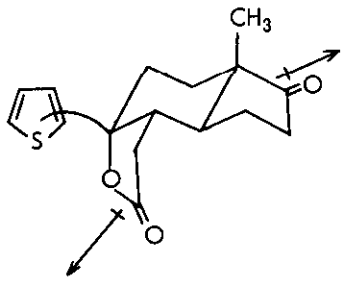
by treatment with $HClO_4$-acetone gave 3-thienyl cis γ-lactone 8b, mp 222-223.5° C, $[\alpha]_D$ +78°, in 75% yield. Instead of these acidic lactonizations, heating with Ac_2O in pyridine afforded 8a and 8b besides a considerable amount of thienyl trans γ-lactone 9a, mp 185-186° C, $[\alpha]_D$ +62°, and 9b, mp 175-177° C, $[\alpha]_D$ +36°, respectively. Treatment of 9a with $HClO_4$-acetone gave more stable cis γ-lactone 8a in a theoretical yield. These thienyl γ-lactones were characterized by their IR ($\nu_{C=O}$ 1770-1780, 1733-1741 cm^{-1}), UV (λ_{max} 233-235 nm) and MS ($C_4H_3S \cdot C{\equiv}O^+$: m/e 111). Configurational

assignment of the γ-lactones was confirmed finally by the determination of their dipole moments in benzene solutions, since their CD data are equivocal presumably due to the presence of the thiophene chromophore. (Table I)

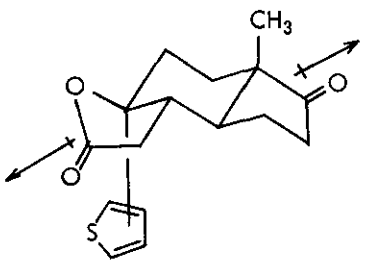
Table I. CD Data of thienyl lactones in MeOH

8a	$[\theta]_{205}$ -3440,	$[\theta]_{235}$ -2390,	$[\theta]_{298}$ +8035.
8b	$[\theta]_{230}$ -3950,	$[\theta]_{240}$ -4300,	$[\theta]_{295}$ +7890.
9a	$[\theta]_{214}$ -5740,	$[\theta]_{246}$ +7170,	$[\theta]_{296}$ +7005.
9b	$[\theta]_{210}$ -6040,	$[\theta]_{220}$ -12100,	$[\theta]_{295}$ +6830.

In their dipole moments, contribution of the thiophene seems to be relatively small because of its low value (0.54 D)[9] and of the rotation. The calculated values, therefore, were roughly estimated from the values of cyclopentanone (2.93 D), γ-butyrolactone (4.19 D)[10] and the angles between these dipole axes measured by using Dreiding models. As shown in Table II, the values are in full agreement with the observed values, supporting the validity of the above assignment.



8a, b

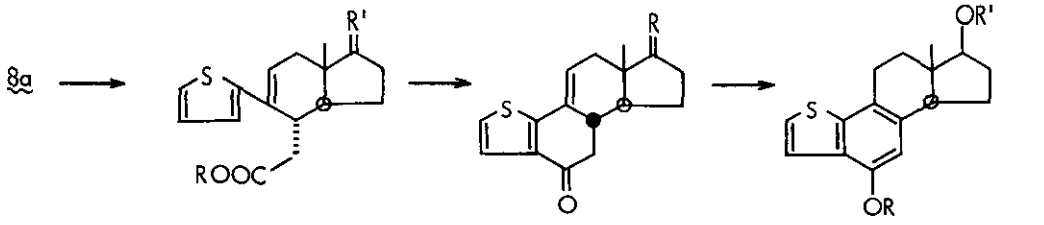


9a, b

Table II. Dipole moments of thienyl lactones in benzene (D)

	cis Lactone		trans Lactone	
	8a	8b	9a	9b
Obsd.	4.98	4.91	2.89	2.80
Calcd.	4.78		3.08	
	lactone	ketone	lactone	ketone
θ_x	71°	50°	81°	50°
θ_y	34°	202°	5°	195°
θ_z	56°	68°	85°	75°

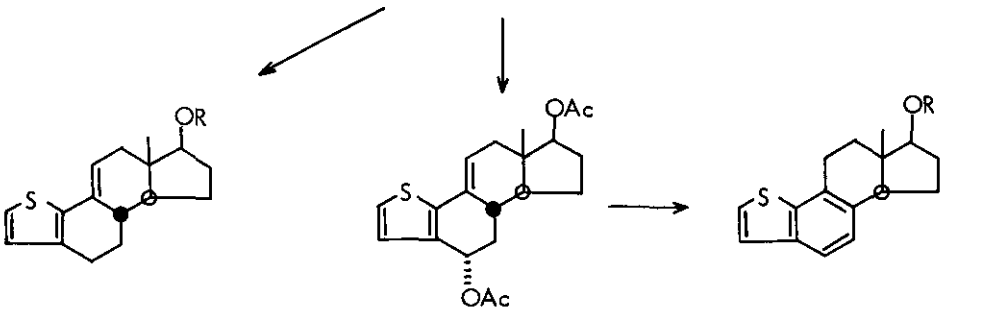
Alkaline hydrolysis of 2-thienyl cis γ-lactone 8a, followed by esterification with CH_2N_2 and usual dehydration with $SOCl_2$ in pyridine at 0° C gave vinylthiophene 10a, mp 75-76° C, $[\alpha]_D$ +105°, in 66% overall yield. Alternatively, one step conversion of 8a to 10a was achieved in 95% yield by refluxing in H_2SO_4-MeOH. The compound 10a was characterized by its UV (λ_{max} 259 nm) and PMR (vinyl-H: 6.04 δ, dt, J: 1.9, 4.2 Hz). The free acid 10b prepared by hydrolysis of 10a on treatment with $(CF_3CO)_2O$[11] in boiling benzene for 0.5 hr gave rise to cyclization to give 6-oxo-9-dehydro-A-thieno-steroid 11a, mp 214-216° C, $[\alpha]_D$ +303°, in 95% yield. Reduction of 10a with $NaBH_4$ in MeOH, followed by hydrolysis gave hydroxyvinylthiophene 10c, mp 168-170° C. The cyclization of 10c gave two products depending upon the conditions employed. Thus, treatment of 10c with $(CF_3CO)_2O$ in benzene at room temperature for 1 hr afforded the expected cyclization product 11b, mp 202-204° C, $[\alpha]_D$ +78°, Huang-Minlon reduction



10a: R=Me, R'=O
10b: R=H, R'=O
10c: R=H, R'=β-OH, α-H

11a: R=O
11b: R=β-OCOCF$_3$, α-H
11c: R=β-OH, α-H
11d: R=β-OAc, α-H

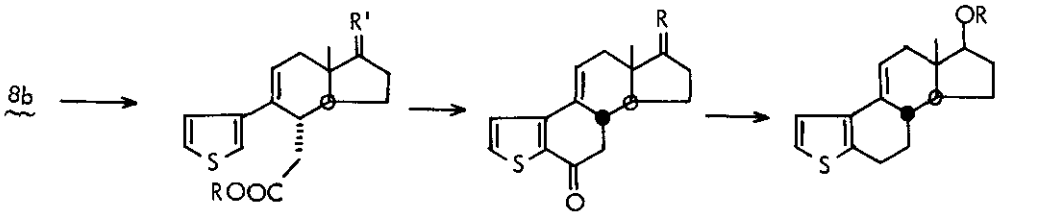
12a: R=R'=COCF$_3$
12b: R=R'=H
12c: R=R'=Ac
12d: R=Me, R'=H
12e: R=Me, R'=Ac



13a: R=H
13b: R=Ac

14

15a: R=Ac
15b: R=H



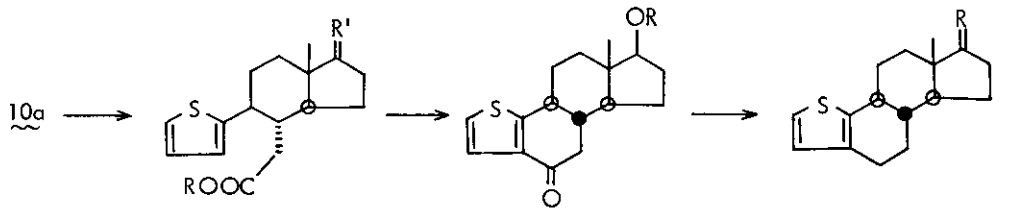
16a: R=Me, R'=O
16b: R=H, R'=O
16c: R=H, R'=β-OH, α-H

17a: R=O
17b: R=β-OCOCF$_3$, α-H
17c: R=β-OH, α-H
17d: R=β-OAc, α-H

18a: R=H
18b: R=Ac

of which gave 9-dehydro-A-thienosteroid 13a, mp 100-101° C, $[\alpha]_D$ +144°, in 97% yield from 10c. Refluxing 10c with $(CF_3CO)_2O$ in benzene gave another product 12a in addition to 11b and the refluxing for 24 hr gave an quantitative yield of 12a as an oily substance. The phenolic structure of its hydrolysis product 12b, mp 232-234° C, $[\alpha]_D$ +49°, was established by its PMR showing one aromatic proton signal at 6.93 δ together with two thienyl proton signals and by the chemical conversion to methyl ether 12d, mp 133-135° C, $[\alpha]_D$ +65°, with CH_3I and K_2CO_3 in acetone. The formation of 12a from 10c could be explained as an enol-acylation of the initially formed 11b with concomitant double bond migration resulting in the B-ring aromatization. A similar aromatization of the B-ring was also observed in the reaction of 6α-acetate 14, mp 182-184° C, $[\alpha]_D$ +39°, derived from 11c or 11d by $NaBH_4$ reduction and acetylation. In the case, heating 14 with p-TsOH·H_2O in benzene gave A-thienoequilenine 15a, mp 144-146° C, $[\alpha]_D$ -10°, in 88% yield. In a similar way, the stepwise reaction of 3-thienyl cis γ-lactone 8b afforded 6-oxo-9-dehydro-A-thienosteroids, 17a, mp 200-201° C, $[\alpha]_D$ +339°, 17b, mp 188-190° C, $[\alpha]_D$ +100°, and 9-dehydro-A-thienosteroid 18a, mp 104-106° C, $[\alpha]_D$ +137°, each step in a high yield.

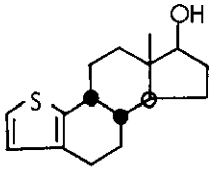
On the other hand, hydrogenation of vinylthiophene 10a in the presence of NEt_3 gave 19a, mp 74-75° C, $[\alpha]_D$ +108°. Reduction of 19a with $NaBH_4$ in MeOH, followed by hydrolysis and cyclization with $(CF_3CO)_2O$-benzene gave 6-oxo-A-thienosteroid 20a, mp 203-205° C, $[\alpha]_D$ -20°, which was converted to 17-alcohol 20b and 17-acetate 20c. Huang-Minlon reduction of 20a or 20c afforded 1-thia-A-norestra-2,5(10)-dien-17β-ol 5a, mp 137-139° C, $[\alpha]_D$ +91°, in 85% yield together with an oily isomer 21 in 5% yield. Velluz[12] reported that the sign of the Cotton effect due to benzene α-band at 280



19a: R = Me, R' = O
19b: R = H, R' = β-OH, α-H

20a: R = $COCF_3$
20b: R = H
20c: R = Ac

5a: R = β-OH, α-H
5b: R = β-OAc, α-H
5c: R = O
5d: R = β-OH, α-C≡CH
5e: R = β-OAc, α-C≡CH



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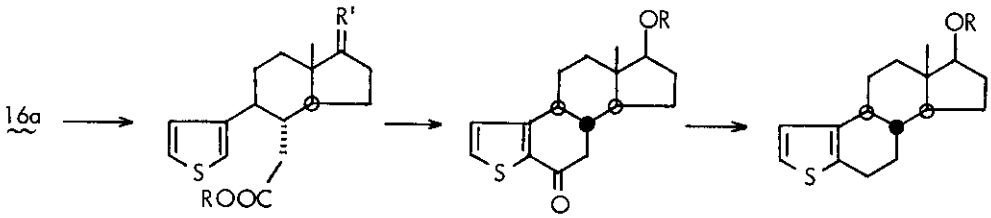


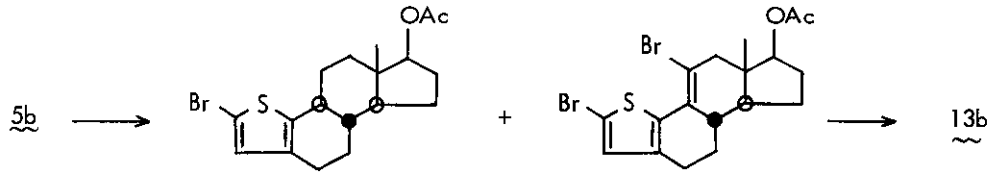
22a: R = Me, R' = O
22b: R = H, R' = β-OH, α-H

23a: R = $COCF_3$
23b: R = H
23c: R = Ac

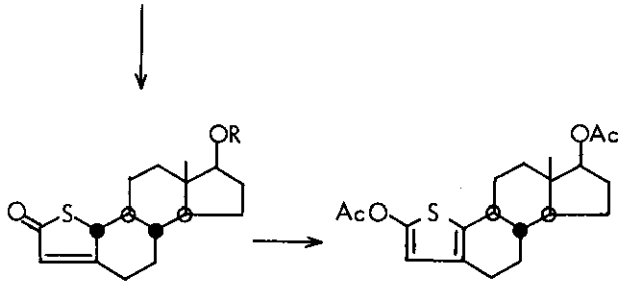
2a: R = H
2b: R = Ac
2c: R = Bz

nm is negative for 9α-estradiol which has a natural configuration and positive for 9β-isomer. The CD data of 5a and 21 at 250 nm are in accord with Velluz's data. Huang-Minlon reduction generally requires both high basicity and high reaction temperature. Therefore, the formation of 9β-isomer 21 may be reasonably understood. The conversion of 5a to ethynylcarbinol 5d, mp 98-99° C, $[\alpha]_D$ +20°, was carried out effectively by the usual ethynylation (HC≡CH, t-AmOK in THF) of 17-ketone 5c, mp 173-175° C, $[\alpha]_D$ +179°, prepared by Jones oxidation of 5a. Alternatively, hydrogenation of vinylthiophene 16a gave 22a, mp 64-65° C, $[\alpha]_D$ +96°, which on reduction with $NaBH_4$ followed by hydrolysis and cyclization with $(CF_3CO)_2O$ afforded 6-oxo-A-thienosteroid 23a, mp 213-215° C, $[\alpha]_D$ -32°. Huang-Minlon reduction of 23a gave 3-thia-A-norestra-1,5(10)-dien-17β-ol 2a, mp 154-156° C, $[\alpha]_D$ +76°, benzoylation of which furnished 2c identical with the photolysis product of the sulphur-bridged ketone 1. Thus, A-thienosteroids 5a and 2a were synthesized from 1,5-dioxo-7a-methyl-3aα,7aβ-hexahydroindan-4a-yl acetic acid 7 in about 50% overall yield.

Finally, 1-thia-A,19-bisnortestosterone and 3-thia analogue, thielenones, were synthesized from the acetates of A-thienosteroids 5a and 2a by using the general conversion of thiophene to thiolenone *via* thienyl borate.[13] Bromination of the acetate 5b with NBS in $CHCl_3$-AcOH (1 : 1) at room temperature[14] gave the expected 2-monobromide 24, mp 126-130° C, $[\alpha]_D$ +66°, in 86% yield accompanied by a 7% yield of dibromide 25, mp 155-158° C, $[\alpha]_D$ +36°. The PMR spectrum of 25 shows no protons on the carbon bearing the bromine atoms but one thienyl proton. In the usual dehydrobromination with Li_2CO_3-DMF, 25 was recovered unchanged. This observation excludes a 2,2-dibromide structure for 25. The MS spectrum of 25 indicates the presence of an additional double

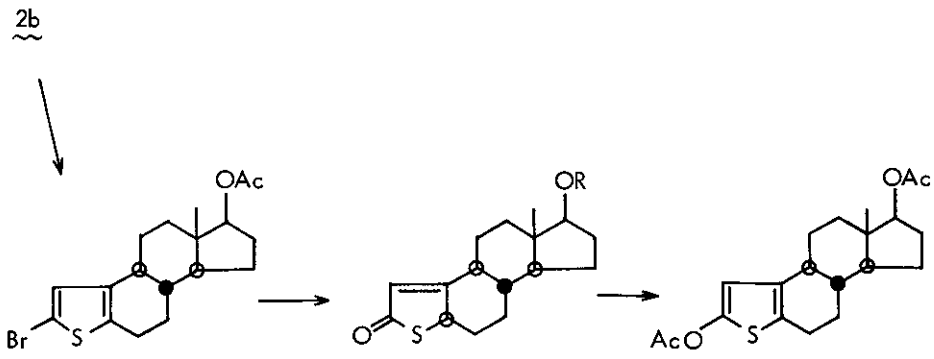


24 25



26a: R=H
26b: R=Ac

27



28

29a: R=H
29b: R=Ac

30

bond, and the reaction with Zn in boiling AcOH gave the 9-dehydro-A-thienosteroid 13b described above. From these results we assumed the structure 2,11-dibromo-9-dehydro-A-thienosteroid for 25. Halogen-metal interconversion reaction of the monobromide 24 with n-BuLi in THF at -70° C, and the subsequent substitution with $(n\text{-BuO})_3B$ followed by oxidation with 30% H_2O_2 gave 1-thia-A,19-bisnortestosterone 26a, mp 165-167° C, $[\alpha]_D$ +10°, in 54% yield and the acetate 26b, mp 170-172° C, $[\alpha]_D$ +1°, in 3.5% yield. The reaction of 26a with Ac_2O in hot pyridine for 1 hr afforded the acetate 26b in 61.4% yield and acetoxythiophene 27, mp 149-151° C, $[\alpha]_D$ +70°, in 21.6% yield.

Alternatively, bromination of 2b with NBS gave the monobromide 28, mp 135-137° C, $[\alpha]_D$ +53°, as a sole product in 88% yield. The conversion of 28 in a way similar to that described above gave thiolenone 29a, mp 210-212° C, $[\alpha]_D$ -165°, in 43% yield together with a 24.6% yield of the debrominated product 2a. Treatment of 29a with Ac_2O-AcOH in the presence of p-TsOH·H_2O at room temperature gave the thiolenone acetate 29b, mp 162-163° C, $[\alpha]_D$ -182°, in 86.5% yield and acetoxythiophene 30, mp 163-165° C, $[\alpha]_D$ +40°, in 12.9% yield. The structures of thus obtained thiolenones 26 and 29 were supported by their IR ($\nu_{C=O}$ 1622-1667 cm^{-1}) and UV (λ_{max} 232-233 and 263-265 nm) in accord with those reported by *Gronowitz*.[13]

Studies on the biological activities of thus synthesized A-thienosteroids and thiolenones are in progress.

Table III. Physicochemical properties - 1

	UV: λ_{max}^{EtOH} nm (ε)	PMR*: δ ppm. in $CDCl_3$ (J: Hz)
11c	249 (12360), 271 (9490), 279 (7830), 321 (9050).	0.83 (Me), 3.85 (17α-H), 6.32 (11-H), 7.04 (2-H) & 7.36 (3-H), J_{AB}: 5.4
12b	230 (32120), 265 (10350), 315 (6080), fine structure.	0.95 (Me), 4.13 (17α-H), 6.93 (7-H), 7.42 (2-H) & 7.93 (3-H), J_{AB}: 5.6
13a	285 (11550).	0.81 (Me), 3.80 (17α-H), 5.87 (11-H), 6.97 (2-H) & 6.73 (3-H), J_{AB}: 5.1
14	283 (12470).	0.84 (Me), 2.06 (17-OAc), 2.11 (6-OAc), 4.78 (17α-H), 5.92 (11-H), 6.00 (m, $W_{h/2}$: 17, 6β-H), 6.84 (3-H) & 7.04 (2-H), J_{AB}: 5.3
15b	227 (34640), 262 (7770), 301 (2010), fine structure.	0.67 (Me), 3.91 (17α-H), 7.26 (s, 2- & 3-H), 7.01 (7-H) & 7.57 (6-H), J_{AB}: 8.0
17c	235 (8560), 241^{sh} (7980), 297 (11210), 318 (9810).	0.83 (Me), 3.88 (17α-H), 6.39 (11-H), 7.23 (1-H) & 7.60 (2-H), J_{AB}: 5.2
18a	227 (15610), 233 (15130), 252 (12150), 260^{sh} (9740).	0.80 (Me), 3.82 (17α-H), 5.95 (11-H), 7.01 (1-H) & 7.09 (2-H), J_{AB}: 5.2
20b	220 (17150), 224 (17150), 256 (12070), 278^{sh} (4200).	0.82 (Me), 3.78 (17α-H), 7.07** (2-H) & 7.40 (3-H), J_{AB}: 5.3
5d	235 (5960), 245^{sh} (5050).	0.90 (Me), 2.57 (-C≡CH), 6.75 (3-H) & 7.04** (2-H), J_{AB}: 5.2
23b	277 (12170).	0.82 (Me), 3.77 (17α-H), 7.07 (1-H) & 7.64 (2-H), J_{AB}: 5.0

* TMS as Internal Standard. Thienyl proton signals in 6-oxo-A-thienosteroids are consistent with those in thienocyclohexanones reported by Cagniant, et al. D. Cagniant, P. Cagniant and G. Merle, Bull. Soc. Chim. France, 1968, 3816.

Table III. Physicochemical properties - 2

	UV	CD (MeOH)	PMR
5a	235 (5870) 245^{sh} (4910).	$[\theta]_{212}$ -6805, $[\theta]_{232}$ +11870, $[\theta]_{254}$ -930.	0.80 (Me), 3.74 (17α-H), 6.76 (3-H) & 7.05** (2-H), J_{AB}: 5.1
21	236 (2280), 245^{sh} (2140).	$[\theta]_{205}$ -6520, $[\theta]_{234}$ -1760, $[\theta]_{255}$ +725.	0.81 (Me), 3.54 (17α-H), 6.73 (3-H) & 7.04** (2-H), J_{AB}: 5.3
2a	237 (6140).	$[\theta]_{217}$ -10500, $[\theta]_{238}$ -4300, $[\theta]_{249}$ -6000.	0.78 (Me), 3.73 (17α-H), 6.85 (1-H) & 7.03 (2-H), J_{AB}: 5.2
26a	233 (10125), 264^{sh} (1850).	$[\theta]_{232}$ -20400, $[\theta]_{260}$ -3640, $[\theta]_{291}$ -9970.	0.84 (Me), 3.69 (17α-H), 3.97 (d, J: 10, 10β-H), 5.93 (t, J: 1.5, 3-H).
29a	232 (13040), 264^{sh} (2180).	$[\theta]_{234}$ -18300, $[\theta]_{253}$ -8000, $[\theta]_{287}$ -14300.	0.78 (Me), 3.69 (17α-H), 4.09 (m, $W_{h/2}$: 20, 5α-H), 5.88 (s, 1-H).
27	237 (5080), 258 (5150).	$[\theta]_{212}$ -2400, $[\theta]_{235}$ +10500, $[\theta]_{261}$ +2700.	0.85 (Me), 2.05 (17-OAc), 2.25 (2-OAc), 4.70 (17α-H), 6.32 (s, 3-H).
30	236 (5670), 258 (4960).	$[\theta]_{224}$ -4800, $[\theta]_{235}$ -2500, $[\theta]_{253}$ -5100.	0.84 (Me), 2.04 (17-OAc), 2.25 (2-OAc), 4.69 (17α-H), 6.41 (s, 1-H).

** The signals were split further by 0.7 — 1.1 Hz because of the 5-bond coupling with 9-proton.

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