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NEO-CLERODANE DITERPENES FROM *SALVIA THYMOIDES**

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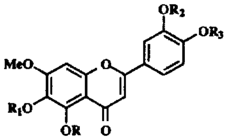
Key Word Index—*Salvia thymoides*; Labiatae; neo-clerodane diterpenes; thymonin; 7β-hydroxythymonin; flavonoids.

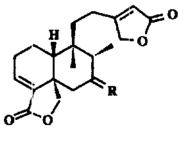
Abstract—The investigation of *Salvia thymoides* afforded, in addition to known triterpenes and flavones, four neo-clerodane diterpenoids, 7α-hydroxy-neo-cleroda-3,13-dien-18,19:15,16-diolide, 7-oxo-neo-cleroda-3,13-dien-18,19:15,16-diolide, 6α,18,19-trihydroxy-neo-cleroda-3,13-dien-15,16-olide (thymonin) and 6α,7β,18,19-tetrahydroxy-neo-cleroda-3,13,-dien-15,16-olide (7β-hydroxythymonin). The last two compounds have not been previously described. The structures of these compounds were established by chemical and spectroscopic methods. The absolute stereochemistry of thymonin was determined by X-ray analysis of a bromo derivative. © 1997 Elsevier Science Ltd

INTRODUCTION

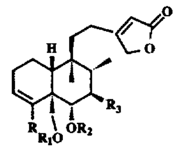
In continuation with our studies on *Salvia* species [1, 2] we have analysed *S. thymoides* Benth., a perennial shrub classified in the section *Flocculosae* (subgenus *Calosphace*, fam. Labiatae). In previous work on this species [3] the authors described the isolation of betulinic and oleanolic acids, 5-hydroxy-6,7,3′,4′-tetramethoxyflavone (**1**), eupatorin (**2**) and a 5,10-seco-clerodanic acid. This last compound was previously isolated from a *Pulicaria* species [4]. As a result of our investigation of *S. thymoides* we isolated, in addition to the above mentioned compounds (except the last two), sitosterol, betulin, 5,6-dihydroxy-7,3′,4′-trimethoxyflavone (**3**), 5,6,4′-trihydroxy-7,3′-dimethoxyflavone (**4**) and the diterpenoids **7** and **8** [5, 6], all of them previously described. Also the new neo-clerodane derivatives, thymonin (**9**) and 7β-hydroxythymonin (**12**), were isolated from this plant.

1 R = H, $R_1 = R_2 = R_3$ = Me
2 R = R_2 = H, $R_1 = R_3$ = Me
3 R = R_1 = H, $R_2 = R_3$ = Me
4 R = $R_1 = R_3$ = H, R_2 = Me
5 R = Ac, $R_1 = R_2 = R_3$ = Me
6 R = $R_1 = R_3$ = Ac, R_2 = Me

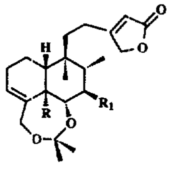




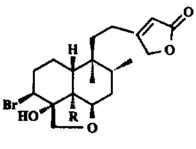
7 R = α-OH, β-H
8 R = O



9 R = CH_2OH, $R_1 = R_2 = R_3$ =H
10 R = CH_2OAc, $R_1 = R_2$ = Ac, R_3 =H
11 R = CHO, $R_1 = R_2 = R_3$ =H
12 R = CH_2OH, $R_1 = R_2$ = H, R_3 = OH
13 R = CH_2OAc, R_1 = Ac, R_2 = H, R_3= OAc
14 R = CH_2OAc, $R_1 = R_2$ = Ac, R_3 =OAc



15 R = CH_2OH, R_1 = H
16 R = CH_2OAc, R_1 = H
17 R = CHO, R_1 = H
18 R = CH_2OH, R_1 = OH



19 R = CH_2OAc

RESULTS AND DISCUSSION

The structures of flavones **1**, **3** and **4** were established by spectroscopic means (UV, EM and ^{1}H NMR). The physical and spectral data of these compounds and their acetyl derivatives **5** and **6** agree well with those published [7–10], except for the mp of compound **4** and that of its triacetyl derivative **6** [9]. In spite of this difference, the ^{13}C NMR (Table 1) and long-range HETCOR NMR spectra of compounds **1** and **3**–**6** were congruent with the proposed structures.

Thymonin (**9**, $C_{20}H_{30}O_5$) was the major component in the extract. It showed an IR spectrum with hydroxyl (3386 cm^{-1}), β-substituted butenolide (1783, 1748 cm^{-1}) and double bond (1638 cm^{-1}) absorptions. Its ^{1}H NMR spectrum confirmed the presence of the β-substituted butenolide which is characterized by the

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Table 1. ^{13}C NMR spectral data of compounds **1**, **3**–**6** (75 MHz, $CDCl_3$)

C (Mult.)	**1**	**3**^{a}	**4**^{a}	**5**^{b}	**6**^{a,c}
2 (*s*)	163.9	162.8	163.4	161.9	161.5
3 (*d*)	104.4	102.9	102.4	107.2	108.3
4 (*s*)	182.6	181.4	181.6	176.6	176.0
5 (*s*)	153.2	145.5	145.6	139.6	141.7
6 (*s*)	132.6	129.3	129.3	142.2	130.7
7 (*s*)	158.7	153.1	153.1	157.7	156.3
8 (*d*)	90.6	89.7	89.8	98.2	98.3
9 (*s*)	153.1	149.2	149.3	154.1	155.6
10 (*s*)	106.1	104.7	104.8	111.2	111.2
1′ (*s*)	123.7	122.8	121.6	124.0	130.0
2′ (*d*)	108.7	108.2	108.7	108.7	110.2
3′ (*s*)	149.3	148.3	147.2	149.3	151.7
4′ (*s*)	152.3	151.2	149.7	152.0	142.6
5′ (*d*)	111.1	110.5	115.1	111.2	123.5
6′ (*d*)	120.1	119.0	119.5	119.8	119.1
OMe (*q*)	60.8	55.3	55.4	61.6	56.7
	56.3	55.1	55.3	56.4	56.2
	56.1	55.0		56.1	
				56.0	

^{a} Determined in $CDCl_3$-DMSO-d_6; ^{b} AcO signals: 169.6 *s*, 21.0 *q*; ^{c} AcO signals: 168.4 *s* (2 ×), 167.7 *s*, 20.8 *q*, 20.7 *q*, 20.1 *q*.

broad signal at δ 5.77 assigned to H-14 and a doublet at δ 4.68 (2H, $J = 2$ Hz) attributed to the C-16 protons. This functionality was present in compounds **7** and **8**. The ^{1}H NMR spectrum of **9** also showed a singlet at δ 0.74 (3H) and a doublet at δ 0.82 (3H, $J = 6.3$ Hz) ascribed to C-20 and C-17 methyl groups, respectively. The chemical shift exhibited by these methyl groups in the ^{13}C NMR spectrum indicated an A/B-*trans* ring fusion [5]. The AB-systems at δ 4.32 and 4.13 ($J = 12$ Hz) and δ 4.18 and 3.66 ($J = 11.2$ Hz) were assigned, respectively, to the C-18 and C-19 hydroxymethylene groups. The broad signal at δ 5.77 was attributed to the vinylic H-3 and the double doublet at δ 3.72 ($J = 10.2$, 5 Hz) was assigned to a proton geminal to an hydroxy group. This group was located at C-6 with an α-equatorial orientation as indicated by the H-6 *J* values which are similar to those observed in ajugarins [11]. From the above mentioned, thymonin must be 6α,18,19-trihydroxy-neo-cleroda-3,13-dien-15,16-olide. This formulation was supported by ^{13}C, COSY and HETCOR NMR experiments as well as by the preparation of some derivatives.

Acetylation of **9** produced the triacetyl derivative **10** whose ^{1}H NMR spectrum showed the signals for the C-6, C-18 and C-19 protons, shifted to down field. Allylic oxidation of **9** gave the α,β-unsaturated aldehyde **11**. In the ^{1}H NMR spectrum of this derivative the signal for H-3 appeared as a triplet at δ 6.99 and H-18 as a singlet at δ 9.32.

Thymonin (**9**) easily forms an acetonide. In fact, this derivative was obtained by the catalytic action of an acidic bentonite [12] on an acetone solution of **9**. In the ^{1}H NMR spectrum of the acetonide, the signals for the C-18 protons appeared at different chemical shift (δ 4.65 and 3.81, $J = 13.5$ Hz) with respect to those of **9**, indicating that the C-18 hydroxy group was involved in the ketal formation. Since the signals for the C-6 and C-19 protons remained practically unaffected, two alternative structures were formulated for this derivative: structure **15** or that with a 18,19 ketal function. In order to distinguish these possible structures, the ketal derivative was acetylated. The ^{1}H NMR spectrum of the acetyl derivative showed a down field shift of the C-19 proton signals (δ 4.73 and 4.33, $J = 12$ Hz), establishing its structure as **16** and consequently, the structure **15** for the ketal. Further support to these assumptions was provided by the production of the derivative **17** through oxidation of compound **15**. The ^{1}H NMR and ^{13}C NMR spectra of **17** revealed the presence of a non-conjugated aldehydic function in the molecule, which must be located at C-19 (H-19: δ 10.18 *s*; C-19: δ 204.6 *d*).

In order to establish the absolute configuration of thymonin (**9**) we prepared a bromo-derivative by bromination (Br_2/CCl_4) of the acetyl ketal **16**. The EI-mass spectrum of the resulting product (**19**) exhibited the $[M+2]^+$ and $[M]^+$ ions at *m/z* 472 and 470 in accordance with a molecular formula $C_{22}H_{31}BrO_6$. In its ^{1}H NMR and ^{13}C NMR spectra, the signals for the vinylic C-3, C-4 and H-3 did not appear, instead of those, a one proton signal at δ 4.37 (1H, *dd*, $J = 12.6$, 6 Hz) was observed. A HETCOR experiment showed correlation between this signal and a carbon signal (δ 58.6 *d*) whose chemical shift was in agreement with a methine bearing bromine. The ^{13}C NMR spectrum of **19** showed a singlet signal at δ 84.9, which was not present in the corresponding spectrum of **16**. It was attributed to a tertiary carbon bearing a hydroxy group (IR: 3578 cm^{-1}). These facts support the addition of HOBr to the C-3 double bond of **16** and the previously mentioned signals were assigned to H-3, C-3 and C-4, respectively. A β-orientation of the C-3 bromine was proposed on the basis of the H-3 (*vide supra*) *J* values.

The ^{13}C NMR spectrum of **19** exhibited the signals for C-6 and C-18 shifted to low field (δ C_{C-6} 79.9; δ_{C-18} 76.9) as compared with those observed for compound **16** (δ C_{C-6} 73.8; δ_{C-18} 66.8). This, and the absence of the acetonide signals in the NMR spectra of **19**, led us to propose the presence of a C-6, C-18 epoxy group. This functionality has been found in some neo-clerodanes isolated from *Teucrium* species [13]. Comparison of the H-6 *J* values of **19** (*t*, $J = 2.7$ Hz) and **16** (*dd*, $J = 11.4$, 4.8 Hz) strongly suggested that the formation of the 6,18-epoxy ring involves inversion of the configuration at C-6. A possible mechanism for the formation of compound **19** is shown in Scheme 1.

The above conclusions on the structure of **19** were supported by a single-crystal X-ray analysis (Fig. 1). This analysis also established its absolute stereochemistry, including that of C-4, which could not be determined before, as 19-acetyloxy-3(*S*)-bromo-6(*R*),18-epoxy-neo-clerod-13-en-15,16-olide. From

Table 2. ^{1}H NMR spectral data of compounds **9–19** (300 MHz, TMS as internal standard)†

H	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
3	5.77 br*	5.89 *t*	6.99 *t*	5.81*	5.82 *t*	5.93 *t*	5.68 *t*	5.65 *t*	5.82 *dd*	5.75 *t*	4.37 *dd*
		3.6	3.8		3.6	3.6	3.5	3.3	4.2, 3.2	3.3	12.6, 6
6	3.72 *dd*	4.76 *dd*	3.79 *dd*	3.45 *d*	3.60 *dd*	5.04 *d*	3.76 *dd**	3.67 *dd**	3.83 *dd*	3.55 *d*	4.25 *t*
	10.2, 5	11.5, 4.6	11, 5	10	10, 6	10	12, 4.5	11.4, 4.8	12.5, 5	10	2.7
7	a	a	a	3.54 *t*	5.13 *dd*	5.24 *br t*	a	a	a	3.64 *br t*	a
				10	11, 10	10				10	
14	5.77 *br**	5.80 *t*	5.81 *t*	5.83 *t**	5.85 *t*	5.87 *t*	5.81 *t*	5.84 *t*	5.85 *t*	5.85 *t*	5.84 *t*
		1.6	1.5	1.8	1.8	1.8	1.5	1.5	1.6	1.5	1.5
16	4.68 *d*	4.70 *d*	4.69 *d*	4.74 *d*	4.72 *d*	4.74 *d*	4.70 *d*	4.73 *d**	4.73 *d*	4.72 *d*	4.74 *d*
	1.7	1.6	1.5	1.8	1.8	1.8	1.5	1.5	1.6	1.5	1.5
17	0.82 *d*	0.82 *d*	0.86 *d*	1.0 *d*	0.87 *d*	0.86 *d*	0.87*d*	0.88 *d*	0.93 *d*	1.05 *d*	0.80 *d*
	6.3	6.6	6.6	6.6	6.6	6.6	6.3	6.5	6.6	6.9	6.9
18	4.32 *br d*	4.59 *br d*		4.32 *br d*	4.86 *br d*		4.65 *br d*	4.54 *br d*	4.08 *br d*	4.63 *br d*	4.33 *d*
	12	12	9.32 *s*	12	13.2	4.54 *br s*	13.5	13.5	13.5	13.5	10.5
18′	4.13 *d*	4.47 *d*		4.20 *br d*	4.76 *br d*		3.81 *d*	3.71 *d**	3.71 *d*	3.83 *d*	3.76 *d*
	12	12		12	13.2		13.5	13.5	13.5	13.5	10.5
19	4.18 *d*	4.66 *d*	4.24 *d*	4.12 *d*	4.46 *d*	4.56 *d*	4.23 *d*	4.73 *d**		4.13 *dd*	4.45 *d*
	11.2	12	11.7	11.5	12.3	12	12	12	10.18 *s*	12, 3.5	12.6
19′	3.66 *d*	4.27 *d*	3.44 *dd*	3.73 *d*	4.37 *d*	4.46 *d*	3.76 *d**	4.33 *d*		3.81 *br d*	4.41 *d*
	11.2	12	11.7, 2	11.5	12.3	12	12	12		12	12.6
20	0.74 *s*	0.80 *s*	0.82 *s*	0.87 *s*	0.92 *s*	0.98 *s*	0.82 *s*	0.87 *s*	0.67 *s*	0.94 *s*	0.84 *s*
Me_2C							1.35 *s*	1.37 *s*	1.35 *s*	1.43 *s*	
							1.32 *s*	1.32 *s*	1.31 *s*	1.39 *s*	
AcO		2.00 *s*			2.13 *s*	2.10 *s*		1.99 *s*			2.1 *s*
		1.97 *s*			2.08 *s*	2.04 *s*					
		1.96 *s*			2.06 *s*	2.04 *s*					
						2.01 *s*					
HO			2.90 *br*		2.56 *d*						
					6						

* Superimposed signals.

† Signals for protons at C-1, C-7, C-8 and C-11 appeared in a complex multiplet centred at ≈δ 1.6. Signals for protons at C-2 and C-12 appeared in a complex multiplet centred at ~δ 2.1.

this finding we can infer that the structure of the natural product thymonin is as depicted in **9**.

The second new diterpenoid isolated from *S. thymoides* was formulated as **12**. This was established by 1D and 2D homo and heteronuclear NMR studies. The ^{1}H NMR spectra of compounds **9** and **12** showed a close similarity. The only difference was an additional hydroxy group in **12** whose presence was evident from the signals at δ 3.54 (t, $J = 10$ Hz) and δ 72.2 (d) in its ^{1}H NMR and ^{13}C NMR spectra. The signal at δ 3.54 was coupled with a doublet at δ 3.45 ($J = 10$ Hz) attributed to H-6, therefore the additional hydroxy group was located at C-7. The J values of H-7 indicated a *trans*-diaxial relationship with H-6β and H-8β and consequently, a β-equatorial orientation of the C-7 hydroxy group. This was further supported by the chemical shift of the C-17 methyl group (δ 10.5 q) in the ^{13}C NMR spectrum [14]. Preparation of triacetyl (**13**), tetraacetyl (**14**) and acetonide (**18**) derivatives of **12** proved the presence of the four hydroxy groups in the molecule and confirmed the proposed structure **12** for 7β-hydroxythymonin.

EXPERIMENTAL

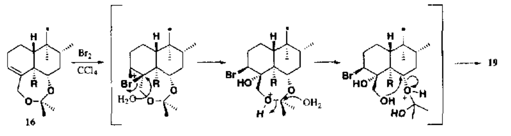
Plant material. *Salvia thymoides* Benth was collected in September 1994 in the State of Oaxaca, México. A voucher specimen was deposited at the Herbarium of the Instituto de Biología, UNAM MEXU-598867).

Isolation of the constituents of S. thymoides. Dried and ground aerial parts of the plant (1.34 kg) were extracted with Me_2CO to obtain, after solvent evapn, 114.1 g of extract. Partition of this extract between petrol–C_6H_6 (7:3) and MeOH–H_2O (4:1) afforded 35.86 g of a less polar and 66.8 g of a polar extract, respectively.

The polar extract was chromatographed over a silica gel column eluted with mixts. of petrol–EtOAc of increasing polarity. Frs eluted with petrol–EtOAc (19:1, 9:1 and 17:3) (22.8 g) were combined with the less polar extract. Frs eluted with petrol–EtOAc (3:2, 3:1 and 3:7) gave, after extensive CC in several solvent systems 5-hydroxy-6,7,3′,4′-tetramethoxyflavone (**1**, 408.5 mg); 5,6-dihydroxy-7,3′,4′-trimethoxyflavone

Table 3. ^{13}C NMR spectral data of compounds **9**, **10**, **12**, **13** and **15**–**19** (75 MHz, $CDCl_3$)

C (mult)	**9**	**10**	**12**	**13**	**15**	**16**	**17**	**18**	**19**
1 *t*	17.5	17.5	17.1	17.7	17.7	17.8	17.4	18.0	21.8
2 *t*	25.9	25.9	25.4	25.8	26.1	26.1	26.2	26.1	36.7
3 *d*	130.6	133.8	127.7	130.0	127.9	128.5	129.4	128.8	58.6
4 *s*	142.6	136.1	142.4	137.2	140.9	139.4	137.6	139.8	84.9
5 *s*	48.1	44.5	47.0	46.8	46.1	45.4	57.0	46.4	51.5
6 *d*	75.9	76.9	79.6	77.5	75.1	73.8	72.3	80.4	79.9
7 *t*	36.6	32.4	72.2 *d*	76.6 *d*	34.5	34.7	34.2	70.6 *d*	31.9
8 *d*	34.6	34.2	40.4	39.9	35.7	35.7	35.6	41.8	30.2
9 *s*	38.3	38.2	38.3	39.1	37.9	38.0	38.0	38.9	38.3
10 *d*	45.6	45.7	44.5	44.9	45.4	45.6	47.6	44.9	42.0
11 *t*	35.2	35.0	35.0	35.6	35.3	35.4	35.2	35.7	35.7
12 *t*	22.1	21.9	21.4	22.1	22.2	22.1	22.1	22.2	21.9
13 *s*	170.5	170.5	170.5	172.0	170.3	170.5	169.7	169.9	169.8
14 *d*	115.1	115.3	114.0	115.6	115.2	115.3	115.5	115.4	115.5
15 *s*	173.9	173.6	173.1	173.5	173.7	173.8	173.6	173.7	170.3
16 *t*	73.0	72.9	72.4	72.9	72.9	73.0	72.9	73.0	73.0
17 *q*	15.5	15.3	10.5	11.1	15.5	15.6	15.5	11.2	15.2
18 *t*	67.7	68.2	65.7	67.1	68.4	66.8	66.4	67.4	76.9
19 *t*	64.0	64.2	63.1	63.6	64.6	64.0	204.6 *d*	64.4	62.6
20 *q*	17.9	17.5	18.4	18.2	18.2	18.1	18.8	19.5	17.5
$\underline{\mathrm{Me}_2}\mathrm{C}$ *q*					24.4	24.6	24.5	25.4	
					24.2	24.4	24.3	24.4	
$\mathrm{Me}_2\underline{\mathrm{C}}$ *s*					101.5	101.3	101.5	102.4	
$\mathrm{Me}\underline{\mathrm{C}}\mathrm{O}$ *s*		170.3		170.4		170.3			169.8
		171.0		169.4					
		169.8		169.4					
$\underline{\mathrm{Me}}\mathrm{CO}$ *q*		21.4		21.2		21.2			21.1
		21.1		21.1					
		20.9		21.0					



Scheme 1.

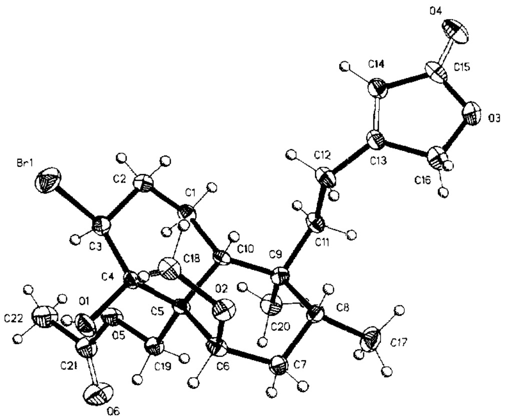


Fig. 1. Computer generated perspective drawing of **19**.

(**3**, 52.1 mg); 5,6,4′-trihydroxy-7,3′-dimethoxyflavone (**4**, 1.03 g) and the diterpenes **7** (1.554 g); **8** (382 mg) and thymonin (**9**, 15.8 g). Frs eluted with petrol–EtOAc (3:7) and EtOAc afforded, after repeated CC, 7*β*-hydroxythymonin (**12**, 1.31 g).

The less polar extract was decoloured with activated charcoal and submitted to CC (silica gel, petrol–EtOAc gradient elution). Frs eluted with petrol–EtOAc (19:1) gave sitosterol (383.4 mg). Elution with petrol–EtOAc (17:3) gave the mixt. of betulinic acid and betuline (3.61 g; mp 277–283°) in a *ca* 2:1 ratio. Frs eluted with petrol–EtOAc (4:1 and 7:3) afforded the mixt. of ursolic and oleanolic acids (15.2 g). The mixt. of betulinic acid and betuline (106 mg) was acetylated (pyridine–Ac_2O). The resulting mixt. was chromatographed on a silica gel column eluted with petrol–EtOAc (97:3). Acetyl betulinic acid (62.4 mg; mp 292–294°) and diacetyl betuline (33.2 mg; mp 220–224°) were obtained and identified by comparison of their physical and spectroscopic properties with those reported in the lit. [15–17]. Sitosterol, ursolic and oleanolic acids were identified by comparison with authentic samples (TLC, mp, IR, ^{1}H NMR).

5-Hydroxy-6,7,3′,4′-tetramethoxyflavone (**1**). Mp 198–200°; acetyl derivative, mp 182–184°. Identified by comparison of their mp, UV, EM and ^{1}H NMR data with those described in the lit. [7, 8]. ^{13}C NMR see Table 1.

5,6-*Dihydroxy-7,3',4'-trimethoxyflavone* (**3**). Mp 244–247°. Identified by comparison of their mp, UV, EM and ^{1}H NMR data with those reported in the lit. [9, 10]. ^{13}C NMR see Table 1.

5,6,4'-*Trihydroxy-7,3'-dimethoxyflavone* (**4**). Mp 270–272°. (lit. [9] 248–250°); triacetyl derivative, mp 245–246° (lit. [9] 224°). Identified by comparison of their UV, EM and ^{1}H NMR data with those described in the lit. [9, 10]. ^{13}C NMR see Table 1.

Compounds **7** *and* **8**. These compounds were identified by comparison of their spectroscopic features with those reported in the lit. [5, 6].

Thymonin (**9**). Colourless gum; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3386, 1783, 1748, 1638, 1450, 1383, 1216, 1170, 1062, 1028, 998, 892, 853. EI-MS *m/z* (rel. int.): 350 [M]$^+$ ($C_{20}H_{30}O_5$; < 1); 332 (35), 314 (14), 301 (73), 284 (100), 269 (9), 259 (12), 201 (28), 191 (23), 171 (56), 167 (37), 136 (53), 118 (91), 105 (57), 91 (52), 79 (34), 55 (27), 41 (33).

7β-Hydroxythymonin (**12**). Colourless gum; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3389, 1780, 1746, 1636, 1446, 1384, 1175, 1135, 1031, 985, 893, 846. EI-MS *m/z* (rel. int.): 366 [M]$^+$ ($C_{20}H_{30}O_6$; not observed), 348 (54) 330 (21), 317 (9), 300 (25), 285 (8), 259 (33), 217 (23), 201 (26), 187 (48), 167 (39), 161 (45), 134 (56), 121 (67), 105 (88), 91 (99), 79 (72), 55 (83), 41 (100).

Preparation of compound **10**. A soln of **9** (88.3 mg) in pyridine (1 ml) and Ac_2O (1 ml) was left to stand for 3 hr. After the usual work up 94.3 mg of **10** were obtained as a gum. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1779, 1746, 1638, 1448, 1374, 1252, 1036, 965, 918, 888, 851. FAB-MS (*m*-nitrobenzyl alcohol) *m/z* (rel. int.): 477 [MH]$^+$ ($C_{26}H_{36}O_8$; 2), 475 [MH-H$_2$]$^+$ (6), 449 (3), 417 (14), 415 (3), 357 (8), 329 (7), 315 (12), 313 (19), 297 (97), 283 (10), 185 (20), 145 (19), 131 (24), 119 (20), 105 (26), 91 (31), 43 (100).

Preparation of compound **11**. MnO_2 (1 g) was added to a soln of **9** (106 mg) in $CHCl_3$ (10 ml). The reaction mixt. was stirred by 21 hr, filtered and evapd. Crude **11** was purified by CC (silica gel, $CHCl_3$–MeOH, 19:1). 43.9 mg of **11** were obtained as a unstable gum. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3337, 1782, 1748, 1671, 1638, 1614, 1473, 1449, 1416, 1172, 1087, 1052, 930, 892, 853.

Preparation of compounds **13** *and* **14**. A fr. containing crude **12** (52 mg) was acetylated (Ac_2O–pyridine). The reaction mixt. obtained after the usual work up was purified by CC (silica gel, petrol–EtOAc 7:3). 26.8 mg of **13** and 17.3 mg of **14** were obtained. Compound **13**. Colourless gum; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3479, 1782, 1740, 1638, 1432, 1368, 1243, 1174, 1098, 1032, 980, 893, 854. EI-MS *m/z* (rel. int.): 492 [M]$^+$ ($C_{26}H_{36}O_9$; not observed); 474 (3), 450 (3), 432 (5) 414 (27), 390 (6), 372 (9), 330 (39), 312 (62), 299 (68), 281 (14). 253 (8), 215 (9), 201 (36), 187 (31), 171 (23), 159 (23), 145 (21), 133 (18), 119 (24), 105 (31), 91 (29), 79 (18), 69 (15), 55 (17), 43 (100). Compound **14**. Colourless gum; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1782, 1747, 1638, 1431, 1369, 1248, 1176, 1144, 1039, 974, 893, 855.

Preparation of compound **15**. Bentonite (5 g) was added to a soln of **9** (3.32 g, *ca* 95% purity) in Me_2CO (30 ml). The suspension was stirred by 1.5 hr, filtered and evapd. The residue was purified by CC (silica gel, petrol–EtOAc, 3:1). Compound **15** (3.42 g) was obtained as crystals from EtOAc–petrol; mp 174–176°; $[\alpha]_D$ −93.26° (MeOH, *c* 0.193); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3506, 1783, 1751, 1640, 1382, 1236, 1070, 1037, 998, 892, 854. EI-MS *m/z* (rel. int.): 390 [M]$^+$ ($C_{23}H_{34}O_5$; 7), 372 (3), 359 (6), 342 (21), 314 (12), 302 (100), 284 (66), 273 (40), 209 (53), 189 (38), 174 (48), 165 (39), 145 (33), 118 (52), 105 (48), 98 (63), 91 (63), 81 (43), 69 (25), 55 (32), 41 (35).

Preparation of compound **16**. A soln of **15** (767.2 mg) in pyridine (3 ml) and Ac_2O (3 ml) was left to stand for 1 hr. After the usual work up, 826.8 mg of **16** were obtained as a gum. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1783, 1748, 1714, 1673, 1640, 1523, 1425, 1058, 1034, 928, 893, 854. EI-MS *m/z* (rel. int.): 432 [M]$^+$ ($C_{25}H_{36}O_6$; 8), 414 (2), 374 (13), 359 (10), 332 (3), 314 (16), 301 (3), 283 (8), 209 (76), 191 (13), 173 (12), 165 (43), 145 (20), 119 (27), 106 (70), 91 (50), 79 (24), 55 (21), 43 (100), 41 (23).

Preparation of compound **18**. Bentonite (1 g) was added to a soln of **12** (117 mg) in Me_2CO (10 ml). The suspension was stirred by 25 min, filtered and the solvent evapd. The residue was crystallized from Me_2CO–petrol to give 127.6 mg of **18**. Mp 247–248°; $[\alpha]_D$ −66.92 ($CHCl_3$, *c* 0.130); IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3452, 1781, 1743, 1639, 1462, 1378, 1215, 1161, 1144, 1050, 1021, 1005, 935, 890, 854. EI-MS *m/z* (rel. int.): 406 [M]$^+$ ($C_{26}H_{34}O_6$; 19), 388 (3), 375 (8), 358 (9), 318 (23), 300 (67), 272 (100), 257 (22), 187 (50), 159 (58), 145 (26), 133 (32), 119 (34), 105 (61), 91 (63), 79 (41), 69 (31), 67 (32), 55 (40), 41 (52).

Preparation of compound **19**. A 10% soln of Br_2 in CCl_4 (2 ml) was added dropwise to a soln of **16** (73.6 mg) in CCl_4 (10 ml). The reaction mixt. was left to stand for 30 min. The unreacted Br_2 was eliminated as usual. The residue obtained after solvent evapn was purified by CC (silica gel, petrol–EtOAc, 3:2) to give 22.5 mg of **19**. Mp 192–195° (≈170° dec); IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3578, 1784, 1750, 1639, 1440, 1369, 1172, 1039, 925, 893, 858. EIMS *m/z* (rel. int.): 472 [M+2]$^+$ ($C_{22}H_{31}{}^{81}BrO_6$; < 1), 470 [M]$^+$ ($C_{22}H_{31}{}^{79}BrO_6$; < 1), 4.54 (2), 452 (2), 429 (6), 427 (6), 412 (5), 373 (26), 331 (23), 313 (17), 301 (29), 299 (24), 287 (9), 203 (13), 189 (16), 173 (15), 159 (16), 133 (20), 105 (27). 91 (33), 79 (24), 55 (27), 43 (100).

X-ray data of compound **19**. Compound **19** crystallized in the orthorhombic space group $P2_12_12_1$ with $a = 8.8773$ (3), $b = 9.7736(2)$ Å, $c = 24.7051(6)$ Å, $V = 21.4349(9)$ Å^3, $Z = 4$, $D_{\mathrm{calc}} = 1.461$ g cm^{-3}. Unit cell and intensity data were measured on a Siemens P4/PC diffractometer using CuKα radiation ($\lambda = 1.54178$ Å). Of 3156 unique reflections, 2826 were considered observed ($F > 4\sigma(F)$). Lorentz polarization and absorption (face-indexed method) effects, were applied. The function $S[w(|F_o|^2 - |F_c|^2)^2]$ was minimized, in which $w = 1.0/[s|F_o|^2 + 0.0008|F_c|^2]$ and the number of variables was 265. The structure was solved by direct methods (SIR 92) [18] and refined by full-matrix least squares using Siemens SHELXTL PLUS (PC version) [19]. Final $R = 0.038$, $R_w = 0.044$, $S = 1.04$. The maximum negative and positive peaks in the final difference map were -0.55 and 0.40 eÅ^{-3}, respectively. Absolute configuration was established by the method of Rogers [20] ($\eta = 0.99$ (6)).

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