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Analogues of the Histamine Liberating Dihydroxysesquiterpene Lactone Thapsigargin. Synthesis, X-Ray Analysis and Chemistry

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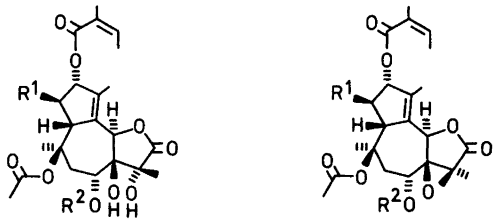
Racemic modifications of three isomeric 3-methyl-3,3a-dihydroxyhexahydrobenzofuran-2-ones and three isomeric 3-methyl-3,3a-dihydroxyoctahydrocyclohepta[*b*]furan-2-ones were prepared *via* stereospecific oxidation of the corresponding *α,β*-unsaturated lactones by potassium permanganate or hydrogen peroxide. The relative configurations of the respective compounds were determined by X-Ray analysis or ^{1}H NMR spectroscopy. Treatment with thionyl chloride in pyridine converted the synthetic diols into cyclic sulfites or products formed by elimination.

Extracts of roots from species of the umbelliferous genus *Thapsia* have for centuries been remedies for the release of rheumatic pain.[1] Two potent skin irritants, thapsigargin (*1a*) and thapsigargicin (*1b*), have been isolated from the root of *T. garganica* L.[2,3] Phytochemical



1a,b,c 10a,b,c

a R^1 = -O(C=O)(CH$_2$)$_6$CH$_3$, R^2 = (C=O)CH$_2$CH$_3$

b R^1 = -O(C=O)(CH$_2$)$_6$CH$_3$, R^2 = (C=O)CH$_2$CH$_3$

c R^1 = H, R^2 = (C=O)CH(CH$_3$)CH$_2$CH$_3$

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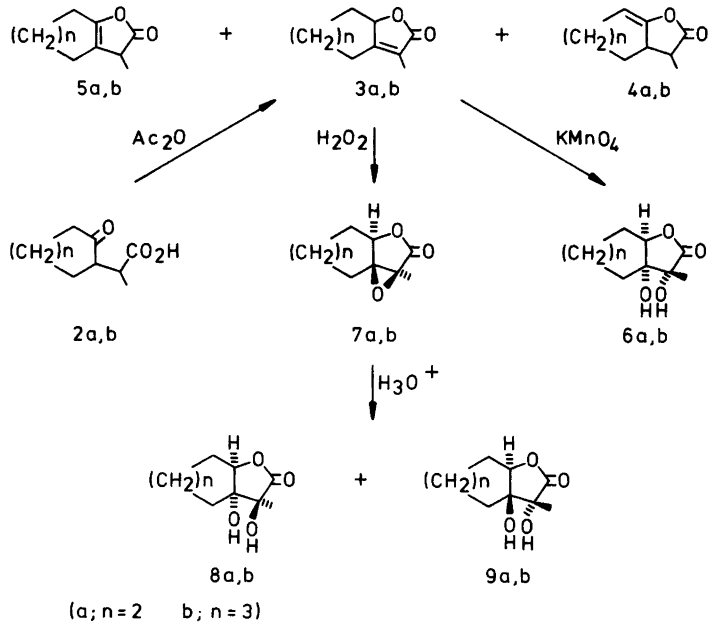
investigations have demonstrated the presence of closely related 7,11-dihydroxyguaianolides in a number of individuals belonging to the species *T. transtagana, T. maxima,* and *T. villosa.*[4,5] The pronounced ability of *1a* to release histamine from rat mast cells[6–8] has encouraged us to synthesize a number of model compounds in order to study the molecular requirements for this activity. The present paper reports the synthesis of three of the four possible diastereomeric racemic pairs of 3-methyl-3,3a-dihydroxyhexahydrobenzofuran-2-ones and three of the diastereomeric racemic pairs of 3-methyl-3,3a-dihydroxyoctahydrocyclohepta[*b*]furan-2-ones, and the crystal structure determination of 3-methyl-*r*-3,*t*-3a-dihydroxy-*trans*-octahydrocyclohepta[*b*]furan-2-one *9b* at room temperature (rt) and 110 K.

In contrast to *1a* and *1b* none of the synthetic diols was converted into an epoxide by treatment with thionyl chloride.

RESULTS AND DISCUSSION

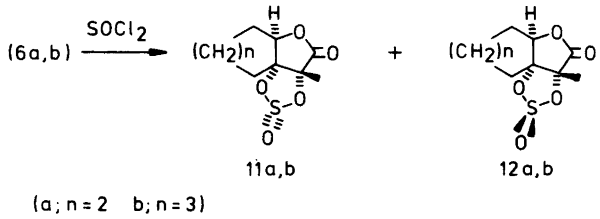
The synthesis of the 2,3-dihydroxybutanolides were performed as shown in Scheme 1. As shown for analogous cyclization reactions[9] heating of the γ-keto acids *2a* and *2b* with acetic anhydride afforded a mixture of the isomeric butenolides *3a*, *4a*, and *5a* and *3b*, *4b*, and *5b*, respectively. In accordance with the stereochemical outcome in analogous homocyclic systems,[10] oxidation of the butenolides *3a* and *3b* with permanganate gave the *cis* annelated *cis* diols *6a* and *6b*. The *cisoid vicinal* dihydroxy moieties were verified by rapid periodic promoted cleavages of *6a* and *6b*. In *6a cis* annelation was evident from the absence of a large coupling between the methine and the *vicinal* methylene protons. Consequently, the methine proton must be equitorial and the methine-oxygen bond axial, which excludes the possibility of a *trans* annelation. The *cis* annelation in *6b* was established by a nuclear Overhauser experiment (NOE). Irridiation of the signal originating in the hydroxy group attached to C3a afforded a 2 % increment of the signal due to the methine proton.



Scheme 1.

Table 1. ^{13}C NMR data of the diols *6a*, *6b*, *8a*, *8b*, *9a*, and *9b*, the epoxides *7a* and *7b*, the sulfites *11a*, *11b*, *12a*, and *12b*, and the hydroxybutenolides *15a* and *15b*. Chemical shifts (δ-values).

Comp.	Solv.	C=O	C			CH	CH_2					CH_3
6a	CD_3OD	179.12	78.08		76.34	80.89	31.32	26.22	22.11	21.35		16.31
6b	$CDCl_3$	179.25	79.18		75.98	90.02	32.05	31.07	30.55	26.11	22.32	21.74
7a	CD_3OD	175.3	71.03		62.0	79.70	33.75	25.68	25.25	23.19		9.2
7b	$CDCl_3$	173.04	72.12		60.77	83.16	31.20	30.22	28.13	24.94	23.83	10.05
8a	CD_3OD	180.64	79.86		76.99	79.10	30.29	25.95	21.08	20.81		18.80
8b	CD_3OD	180.35	81.92		77.81	92.36	32.31	31.86	31.33	27.16	22.91	17.89
9a	CD_3OD	180.25	78.35		77.91	83.66	27.47	24.60	24.33	20.81		16.20
9b	CD_3OD	179.97	81.53		79.25	85.38	29.90	26.89	26.05	25.52	25.26	16.12
11a	$CDCl_3$	172.13	94.38		85.93	80.35	30.34	29.75	21.46	20.26		17.23
11b	$CDCl_3$	172.35	97.25		86.63	88.86	32.89	32.35	29.96	26.06	23.03	18.10
12a	$CDCl_3$	171.91	92.11		87.66	79.70	31.26	29.96	21.83	20.53		18.10
12b	$CDCl_3$	171.70	96.71		88.86	87.77	33.92	31.48	30.12	26.06	22.65	19.51
15a	$CDCl_3$	173.05	161.24	120.93	103.81	–	38.20	26.71	25.09	22.27		8.02
15b	$CDCl_3$	173.21	163.35	124.13	108.36	–	37.87	29.15	26.39	25.36	24.06	8.13



Scheme 2.

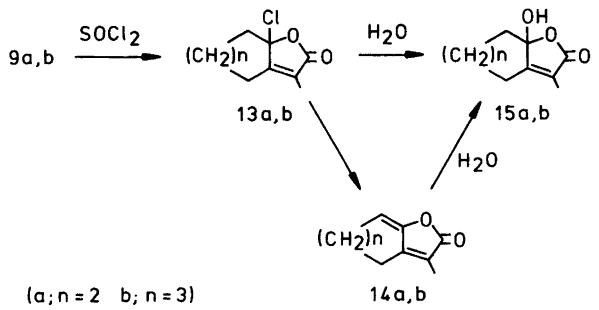
In contrast to permanganate, reaction between the small hydrogen peroxide molecule and a hydrindenic or hydrazulenic system will favour formation of *trans* annelated products.[10] By analogy, the only epoxides isolatable after oxidation of *3a* and *3b* with hydrogen peroxide were assigned the structures of *7a* and *7b*, respectively.

Acidic hydrolysis of *7a* and *7b* afforded in both cases a mixture of the two *vicinal trans* diols *8a* and *9a*, *8b* and *9b*, respectively. None of the glycols was cleaved by periodic acid, proving the presence of *trans* dihydroxy moieties. The absence of a large coupling between the methine proton of *8a* and the *vicinal* methylene protons, established a *cis* annelation of the rings. As the resonance signals of the hydroxy protons coincided with the methylene protons, NOE experiments could not be performed on *8b* and *9b*. The relative configuration of *9b* was established by an X-ray structure analysis (see X-RAY ANALYSES).

It is well documented that acyclic- and cyclic *cis* diols and some cyclic *trans* diols form cyclic sulfites by treatment with thionyl chloride.[11] In accordance, thionyl chloride reacted with *6a* and *6b* to yield a mixture of the two isomers *11a* and *12a* and *11b* and *12b*, respectively (Scheme 2). The isomers were separated and identified taking advantage of the anisotropic effect of the sulfoxide group.[12] Comparison of analogous resonance signals in the ^{1}H NMR spectra of *11a* and *12a* or *11b* and *12b* revealed a location at lower field of the signals from the methine protons in *11a* and *11b*, whereas the opposite is the case for the signals from the methyl protons (Table 2).

Table 2. ^{1}H NMR data of the diols *6a, 6b, 8a, 8b, 9a,* and *9b,* the epoxides *7a* and *7b,* the sulfites *11a, 11b, 12a,* and *12b,* and the hydroxybutenolides *15a* and *15b.* Chemical shifts (δ-values) of $CDCl_3$-solutions. Multiplicities and *J*-values (Hz) are shown in parentheses.

Comp.	MHz	CH_2	CH_3	CH
6a	270	1.11–2.23 (m)	1.31 (s)	4.52 (dd; 2.5, 2.5)
6b	–	1.22–2.11 (m)	1.45 (s)	4.44 (dd; 1.7, 12.0)
7a	–	1.33–2.46 (m)	1.55 (s)	4.41 (dd; 6.6, 10.7)
7b	–	1.33–2.04 (m)	1.54 (s)	4.56 (dd; 3.9, 7.3)
8a	–	1.33–2.20 (m)	1.44 (s)	4.24 (dd; 2.5, 2.5)
8b	–	1.4 –2.12 (m)	1.42 (s)	4.36 (dd; 6.3, 6.3)
9a	–	1.34–2.09 (m)	1.45 (s)	4.49 (dd; 4.8, 12.4)
9b	–	1.57–2.16 (m)	1.40 (s)	4.68 (dd; 4.4, 11.7)
11a	90	1.36–2.46 (m)	1.71 (s)	4.88 (dd; 7.0, 10.5)
11b	60	1.35–2.35 (m)	1.62 (s)	4.92 (dd; 3.0, 12.0)
12a	90	1.36–2.71 (m)	1.84 (s)	4.58 (dd; 7.3, 10.8)
12b	–	1.35–2.73 (m)	1.77 (s)	4.60 (dd; 2.5, 10.8)
15a	–	1.43–2.66 (m)	1.78 (d; 1.5)	
15b	60	1.45–2.65 (m)	1.78 (s)	



Scheme 3.

Stereochemistry makes cyclic sulfite formation very unlikely for a number of cyclic *trans* diols, including thapsigargin *1a*, thapsigargicin *1b*, and trilobolide *1c*. The latter three are converted into the corresponding epoxides *10a*, *10b*, or *10c*, respectively, by treatment with thionyl chloride.[2,13] Beside these sesquiterpene diols, only one further thionyl chloride promoted epoxide formation (a steroid diol) has been described.[14] Since attempts to develop reagents for transformation of free diols into epoxides have only led to the discovery of two reagents, dimethylformamide dimethylacetal and diaryldialkoxysulfurane,[15]an investigation of the reaction between thionyl chloride and the synthesized *trans* diols was undertaken.

None of the *trans* diols *8a*, *8b*, *9a*, or *9b* was transformed into an epoxide by thionyl chloride. The main product from the *trans* annelated *trans* diol *9b* after aqueous work-up was *15b* (Scheme 3). Investigation (TLC) of the reaction mixture before addition of water showed the presence of intermediates which were easily hydrolyzed to give *15b*. Possible structures for these intermediates are *13b* and *14b*, as 4-chloro- and 4-alkylidene-2-butenolides easily react with water to give 4-hydroxy-2-butenolides,[16] and thionyl chloride treatment of *15b* afforded products showing the same TLC behaviour as the observed intermediates.

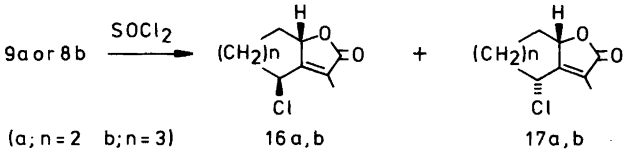
Besides *15a* the reaction mixture from *9a* contained a fraction which (^{1}H NMR) consisted of a mixture of *16a* and *17a*. Thionyl chloride converted *8b* into a mixture of *16b* and *17b* (^{1}H NMR; Scheme 4), whereas *8a* was inert.

Compounds containing a 4-hydroxy-2-butenolide moiety have interesting biological activity including anti-tumour effects.[17,18] Compound *15b* showed activity (T/C 120 at 50 mg/kg) against P388 lymphocytic leukemia in mice, whereas *15a* was inactive.

None of the synthesized diols *6a*, *6b*, *8a*, *8b*, *9a*, or *9b* provoked a histamine release from rat peritoneal mast cells.[19]

X-RAY ANALYSES

The crystallographically obtained molecular structure of *9b* at 110 K is shown in Fig. 1 together with the numbering scheme used. The structure determination proves that the two



Scheme 4.

Table 3. Molecular dimensions for compound *9b*. Estimated standard deviations are given in parentheses.

Bond lengths (Å)	rt	110 K	Valency angles (°)	rt	110 K
O1–C8a	1.475(3)	1.478(3)	C8a–O1–C2	110.2(2)	110.2(2)
O1–C2	1.335(3)	1.342(3)	O1–C2–C3	109.6(2)	109.4(2)
C2–O2	1.205(3)	1.206(4)	O1–C2–O2	121.7(2)	121.7(2)
C2–C3	1.528(3)	1.525(4)	C3–C2–O2	128.7(2)	128.9(3)
C3–C3a	1.538(3)	1.544(4)	C2–C3–C3a	100.8(2)	101.2(2)
C3–CMe	1.502(4)	1.506(4)	C2–C3–CMe	113.5(2)	113.6(2)
C3–O3	1.433(3)	1.431(3)	C3a–C3–CMe	117.6(2)	117.0(2)
C3a–O3a	1.433(3)	1.432(3)	O3–C3–CMe	113.2(2)	113.6(2)
C3a–C8a	1.522(3)	1.528(4)	C2–C3–O3	102.7(2)	102.9(2)
C3a–C4	1.520(4)	1.524(4)	C3a–C3–O3	107.2(2)	106.8(2)
C4–C5A	1.60(2)	1.625(9)	C3–C3a–C8a	100.9(2)	100.4(2)
C4–C5B	1.42(2)	1.32(1)	C3–C3a–O3a	108.4(2)	108.3(2)
C5A–C6A	1.41(3)	1.53(1)	C8a–C3a–O3a	105.9(2)	106.3(2)
C5B–C6B	1.59(2)	1.51(2)	C4–C3a–O3a	111.6(2)	111.9(2)
C6A–C7A	1.43(2)	1.52(1)	C4–C3a–C3	114.3(2)	114.3(2)
C6B–C7B	1.66(2)	1.52(2)	C4–C3a–C8a	114.9(2)	114.7(2)
C7A–C8	1.51(2)	1.503(8)	C3a–C4–C5A	116.1(7)	114.5(4)
C7B–C8	1.54(2)	1.61(2)	C3a–C4–C5B	117.7(6)	125.0(6)
C8–C8a	1.506(4)	1.512(4)	C4–C5A–C6A	125(1)	119.8(6)
			C4–C5B–C6B	112(1)	114(1)
			C5A–C6A–C7A	125(1)	113.4(7)
			C5B–C6B–C7B	104(1)	113(1)
			C6A–C7A–C8	114(1)	112.7(5)
			C6B–C7B–C8	115(1)	119.5(9)
			C7A–C8–C8a	113.4(7)	116.0(4)
			C7B–C8–C8a	114.9(6)	108.6(5)
			C8–C8a–C3a	118.5(2)	117.5(2)
			C3a–C8a–O1	103.9(2)	103.9(2)
			C8–C8a–O1	107.7(2)	106.9(2)

rings are *trans*-fused and that the hydroxy groups at C3 and C3a are *trans* to each other. Consequently, the relative configuration at the asymmetric centres in 3*RS*, 3a*SR* and 8a*RS*.

Bond distances and valency angles involving the nonhydrogen atoms are given in Table 3. Torsional angles are given in Table 4. The molecular disorder has severely reduced the accuracy of the molecular dimensions involving the atoms C5A, C5B, C6A, C6B, C7A, and C7B, but the average values of the $C_{sp^3}-C_{sp^3}$ bonds [1.519 (rt) and 1.518 Å (110 K)] and the $C_{sp^3}-C_{sp^3}-C_{sp^3}$ angles [115.9 (rt) and 115.7° (110 K)] in the cycloheptane rings compare reasonably well with those expected. The corresponding values of bond distances and valency angles in the remainder parts of the respective rt and 110 K molecules are not significantly different and are quite normal.

The molecular conformations found at rt and 110 K are similar and are described by the torsion angles (Table 4). The conformations of the γ-lactone rings are distorted envelopes with C3a on the flap of the envelope. The cycloheptane rings assume twist-chair conformations.[20]

As molecular flexibility is a factor of importance in the study of biologically active molecules, the conformational mobility of the cycloheptane rings of *9b* has further been studied using Allinger's Molecular Mechanics 2 (MM2) programme.[21–23] All parameters

Table 4. Torsion angles (°) for compound *9b*. Estimated standard deviations are given in parentheses.

	XRAY A(RT)	XRAY B(RT)	XRAY A(110K)	XRAY B(110K)	MM2 C	MM2 C′	MM2 D	MM2 D′	MM2 E
Cycloheptane ring									
C8a–C3a–C4–C5	−38.2(8)	−64.7(7)	−32.6(5)	−60.5(8)	−68.1	−59.8	−82.0	−31.2	7.9
C3a–C4–C5–C6	−20(2)	66(1)	−38.9(8)	49(1)	56.8	69.5	36.2	−43.9	−66.9
C4–C5–C6–C7	66(2)	−87(1)	84.4(8)	−72(1)	−76.6	−87.3	36.4	88.4	17.4
C5–C6–C7–C8	−67(2)	85(1)	−71.1(9)	85(1)	83.2	51.9	−83.2	−71.2	64.2
C6–C7–C8–C8a	58(1)	−25(1)	59.2(8)	−27(1)	−29.1	20.0	74.4	54.5	−44.8
C7–C8–C8a–C3a	−78.4(7)	−51.0(7)	−78.8(5)	−50.0(6)	−46.6	−78.0	−62.4	−72.8	−46.7
C8–C8a–C3a–C4	82.1(3)		83.8(3)		86.3	80.0	76.3	83.2	73.1
Lactone ring									
C3–C3a–C8a–O1	−35.1(2)		−35.3(3)		−28.9	−34.0	−36.1	−31.6	−37.2
C3a–C8a–O1–C2	20.7(2)		20.6(3)		15.8	20.4	22.8	17.1	23.7
C8a–O1–C2–C3	3.5(3)		3.9(3)		5.1	2.7	1.3	5.8	0.9
O1–C2–C3–C3a	−25.6(2)		−26.3(3)		−23.3	−24.3	−24.3	−25.7	−24.6
C2–C3–C3a–C8a	35.9(2)		36.5(2)		30.4	34.0	35.0	33.4	35.7
Substituents									
O2–C2–O1–C8a	−179.0(2)		−178.9(2)		−176.9	−178.4	−179.5	−176.6	−179.7
O1–C2–C3–O3	84.9(2)		84.1(2)		92.5	91.3	91.3	90.3	90.9
O1–C2–C3–CMe	−152.4(2)		−152.6(2)		−147.8	−148.5	−148.2	−150.0	−148.4
O3a–C3a–C3–O3	153.1(2)		153.3(2)		161.0	164.9	165.3	166.4	168.4
O3a–C3a–C3–CMe	84.0(1)		84.0(2)		38.0	41.7	42.2	42.9	45.2

needed were included in the programme except one, the torsional parameter O3–C3–C2–O1 for which the values V_1=0.40, V_2=−0.30, and V_3=−0.07 were chosen. Full energy minimization was performed with repect to all internal coordinates. Some results of these calculations are shown in Table 4 and Fig. 2.

The calculations show a global minimum corresponding to the twist-chair conformation *C* (Table 4); by rotation about the C7–C8 bond *C* may easily pass into *C'*, which is 6 kJ mol^{-1} less stable, and no significant barrier has to be surmounted. By pseudorotation, *C* may further flip over a barrier of about 17 kJ mol^{-1} into the twist-chair conformation *D*, which is 5 kJ mol^{-1} above the global minimum, or it may flip over a barrier of about 39 kJ mol^{-1} into the twist-boat *E*, which is 19 kJ mol^{-1} above the global minimum. By rotation about the C4–C5 bond *D* may easily flip over a barrier of about 5 kJ mol^{-1} into the twist-chair conformation *D'*, which is 4 kJ mol^{-1} above the global minimum.

The pseudorotation of the cycloheptane ring is accompanied by some flexing of the lactone ring, which adopts C3a envelope conformations in *C'*, *D* and *E* and is midway between C3a envelope and half-chair conformations in *C* and *D'*.

Among the two twist-chair conformations of the cyclohexane ring found in the crystalline state conformation *B* at 110 K with a site occupation factor (s.o.f.) of 0.35 is similar to conformation *C* at the global minimum, while conformation *A* (s.o.f.=0.65) is similar to conformation *D'*.

The molecular packing is illustrated in Fig. 3. The hydrogen bonding potential of the molecule is fully utilized. Hydrogen bond distances and angles are given in Table 5. All other *inter*-molecular contacts correspond to van der Waal's interactions, the shortest contact between non-hydrogen atoms being between C2 and O3 ($\frac{1}{2}$−x, $\frac{1}{2}$+y, z), 3.354(3) (rt) and 3.339(4) Å (110 K).

EXPERIMENTAL

M.p.s were determined in open capillary tubes and are corrected. All evaporations were carried out in a rotary evaporator under a water-pump vacuum with a flask temperature less

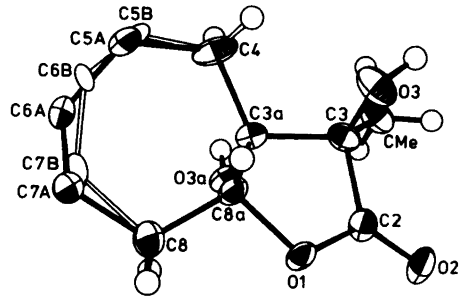


Fig. 1. Perspective drawing[34] of molecule *9b* (110 K), showing the numbering of the atoms and the thermal ellipsoids for the non-hydrogen atoms with a probability of 50 %. Hydrogen atoms are represented as spheres of arbitrary radius. The hydrogen atoms bonded to C5A, C5B, C6A, C6B, C7A, and C7B are not shown.

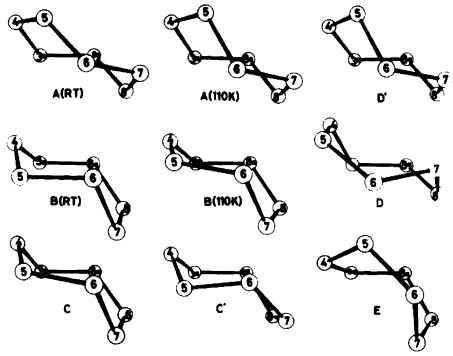


Fig. 2. Conformations of the cycloheptane ring[34] of compound *9b* as determined by X-ray analyses and force field calculations (MM2).

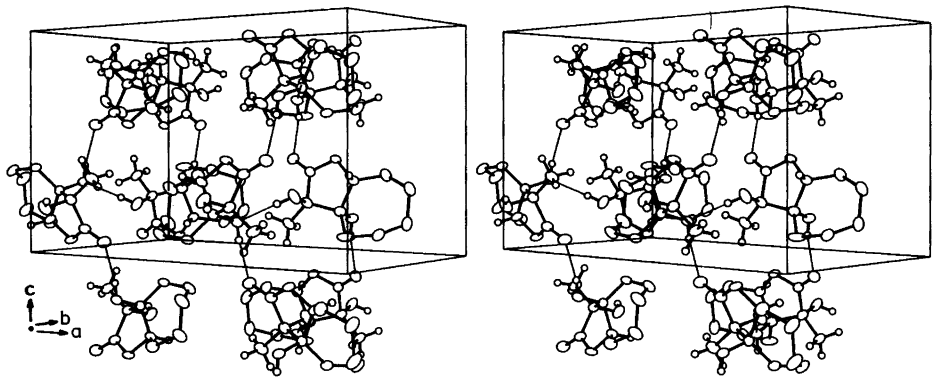


Fig. 3. Stereoscopic drawing[34] of the molecular packing of compound *9b* (110 K). Hydrogen bonds are drawn with solid lines. The methylene hydrogen atoms are not shown.

than 40 °C. IR spectra were measured with a Perkin-Elmer 457 spectrophotometer. ^{1}H NMR spectra were obtained on either a Varian EM 360 L (60 MHz), a JEOL FX 90 Q (90 MHz), or a Brucker HX-270 S (270 MHz). ^{13}C NMR spectra were obtained on the JEOL FX 90 Q (22.5 MHz).

*(RS) 3-Methyl-4,5,6,7-tetrahydro-7a*H*-benzofuran-2-one* (3a), *(RS) 3-methyl-3a,4,5,6-tetrahydro-3*H*-benzofuran-2-one* (4a), *and (RS) 3-methyl-4,5,6,7-tetrahydro-3*H*-benzofuran-2-one* (5a). Compound (*2a*)[24] (22.8 g) was refluxed with acetic anhydride (70 ml) for 2 h with continuous distillation of the acetic acid formed. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in ether, washed with aqueous saturated sodium hydrogen carbonate solution, and dried with calcium chloride. After evaporation fractional distillation at 1.6 kPa gave a mixture of *4a* and *5a* (b.p. 130–140 °C; 1.8 g) and *3a*[24] (b.p. 150–156 °C; 7.0 g). Chromatography of the mixture (0.5 g) on silica gel with toluene-ethyl acetate (6:1) as eluant gave *4a* (70 mg) and *3a* (70 mg). Ball-tube distillation at 26 Pa yielded crystalline *4a*, m.p. *ca.* 30 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 5.25 (1 H, q, *J* 2 Hz), 1.29 (3 H, d, *J* 6.1 Hz), and 1.3–2.5 (8 H, m). ^{13}C NMR ($CDCl_3$): δ 176.90, 150.41, 100.40, 43.34, 41.61, 27.42, 22.81, 21.51, and 13.27. IR (KBr): 1802, 1710, 1130, 1060, and 1038 cm^{-1}. (Found: C 70.44; H 8.16. Calc. for $C_9H_{12}O_2$: C 71.03; H 7.95 %).

Data for *5a:* ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.29 (3 H, d, J 6.1 Hz) and 1.3–2.5 (9 H, m). ^{13}C NMR ($CDCl_3$): δ 180.09, 148.63, 115.80, 40.93, 22.46, 22.32, 22.13, 21.02, and 14.17. IR (KBr): 1798, 1197, 1018, and 990 cm^{-1}. Previously a lactone boiling at 141–142 °C at 0.6 kPa has been assigned the structure of *4a*[25] and a lactone distilling 134–140 °C at 0.5 kPa has been assigned the structure of *5a*.[26]

(RS) 3-Methyl-4,5,6,7,8,8a-hexahydrocyclohepta[b]*furan-2-one* (3b), *(RS) 3-methyl-3,3a,4,5,6,7-hexahydrocyclohepta*[b]*furan-2-one* (4b), *and (RS) 3-methyl-3,4,5,6,7,8-hexa-*

Table 5. Hydrogen bond distances (Å) and angles (°) for compound *9b* at room temperature (upper entries) and at 110 K (lower entries). Estimated standard deviations are given in parentheses.

A–H···B	A–H	H···B	A···B	∠AHB
O3–H3···O3a^{i}	0.77(3)	2.01(3)	2.776(3)	170(3)
	0.82(3)	1.92(3)	2.740(3)	172(3)
O3a–H3a···O2^{ii}	0.80(2)	2.01(2)	2.783(3)	163(2)
	0.78(3)	2.01(3)	2.761(3)	162(3)

Symmetry code: (i) $\frac{1}{2}-x,y-\frac{1}{2},z$; (ii) $\frac{1}{2}-x,\bar{y},\frac{1}{2}+z$.

hydrocyclohepta[b]*furan-2-one* (5b). A mixture of the three isomers *3b*, *4b*, and *5b* (15.6 g) was isolated from *2b*[27] (21.0 g) following the procedure described above for the preparation of *3a* and a mixture of *4a* and *5a*.

Column chromatography on silica gel with toluene-ethyl acetate (5:1) as eluant yielded *3b* (8.0 g), and *4b* (2.5 g). *3b*: b.p. 108 °C/66 Pa. ^{1}H NMR (60 MHz; $CDCl_3$): δ 4.86 (1 H, ddq), 1.80 (3 H, dd, J 1.5 and 1.5 Hz) and 1.1–2.7 (10 H, m). ^{13}C NMR ($CDCl_3$): δ 174.48, 165.67, 122.20, 83.42, 33.81, 29.90, 27.61, 26.18, 25.59, and 8.29. IR (film): 1750, 1670, 1098, and 1019 cm^{-1}; (Found: C 71.70; H 8.90. Calc. for $C_{10}H_{14}O_2$: C 72.26; H 8.49 %). *4b*: b.p. 84–88 °C/26 Pa. ^{1}H NMR (60 MHz; $CDCl_3$): δ 5.32 (1 H, ddd, J 2.2, 6.3, and 6.3 Hz), 1.18 (3 H, d, J 6.8 Hz), and 0.8–2.6 (10 H, m). ^{13}C NMR ($CDCl_3$): δ 177.09, 154.38, 105.23, 46.74, 42.10, 31.79, 29.37, 27.74, 25.13, and 14.30. IR (film): 1800, 1697, 1180, and 1038 cm^{-1}; (Found: C 70.75; H 8.77 %). *5b*[29] was seen as a contaminant by inspection of the ^{13}C NMR spectrum of *4b*.

(RS) *3-Methyl*-r-*3*,c-*3a-dihydroxy*-cis-*hexahydrobenzofuran-2-one* (6a). *A mixture of 3a* (3.10 g), potassium permanganate (3.22 g), magnesium sulfate heptahydrate (2.46 g), tetrabutylammonium hydrogen sulfate (20 mg), water (100 µl), and ethyl acetate (30 ml) was stirred for 18 h at room temperature. After addition of 500 µl of water and stirring for another hour the mixture was filtered and the precipitate extracted with water (15 ml). The aqueous extract was concentrated and the residue extracted with ethyl acetate. The extract was evaporated *in vacuo* and the residue chromatographed on silica gel with toluene–ethyl acetate (4:1) as eluant to give *3a* (1.7 g) and *6a* (0.82 g, 46 % based on consumed *3a*) m.p. 92.5–93 °C (from toluene–ethyl acetate). IR (KBr): 3440, 3325, 1750, and 1108 cm^{-1}. Anal. $C_9H_{14}O_4$: C, H.

(RS) *3-Methyl*-r-*3*,c-*3a-dihydroxy*-cis-*octahydrocyclohepta*[b]*furan-2-one* (6b). Compound *6b* was prepared from *3b* (5.5 g) using the procedure described above for preparation of *6a* to give the starting material *3b* (2.2 g) and *6b* (780 mg, 19 % based on consumed *3b*) m.p. 92–92.5 °C (from tetrachloromethane). IR (KBr): 3465, 3420, 3340, 1758, 1742, and 998 cm^{-1}. Anal. $C_{10}H_{16}O_4$: C, H.

(RS) *3-Methyl*-r-*3*,c-*3a-epoxy*-trans-*hexahydrobenzofuran-2-one* (7a). *A mixture of 3a* (2.5 g), 30 % hydrogen peroxide (10 ml), concentrated sulfuric acid (20 µl), and formic acid (20 ml) was heated to 55 °C. After 20 h the temperature was raised to 70 °C and the heating continued for further 4 h. The reaction mixture was evaporated *in vacuo* and the residue chromatographed on silica gel with toluene–ethyl acetate (4:1) as eluant to give *3a* (1.5 g), *15a* (80 mg), and *7a* (280 mg, 25 % based on consumed *3a*), m.p. 112–112.5 °C (from methanol); IR (KBr): 1770, 1102, and 1016 cm^{-1}. Anal. $C_9H_{12}O_3$: C, H.

(RS) *3-Methyl*-r-*3*,c-*3a-epoxy*-trans-*octahydrocyclohepta*[b]*furan-2-one* (7b). Compound *7b* was prepared from *3b* (12.1 g) using the same procedure as described for the preparation of *7a* but without addition of sulfuric acid. The compounds *3b* (6.5 g), *15b* (0.2 g), and *7b* (0.8 g, 13 % based on consumed *3b*) were isolated. An analytical sample of *7b* was purified by ball-tube distillation at 26 Pa. IR (film): 1775, 1115, and 1010 cm^{-1}. Anal. $C_{10}H_{14}O_3$: C, H.

(RS) *3-Methyl*-r-*3*,t-*3a-dihydroxy*-cis-*hexahydrobenzofuran-2-one* (8a) *and* (RS) *3-methyl*-r-*3*,t-*3a-dihydroxy*-trans-*hexahydrobenzofuran-2-one* (9a). A mixture of *7a* (0.43 g) water (3 ml), and 70 % perchloric acid (0.5 ml) was refluxed for 3 h. After cooling the mixture was neutralized with potassium hydrogen carbonate and filtered. The filtrate was evaporated *in vacuo* and the residue chromatographed on silica gel with toluene–ethyl acetate (3:1) as eluant to give *15a* (40 mg), *8a* (60 mg), and *9a* (190 mg). *8a:* m.p. 172–172.5 °C (from toluene–ethyl acetate). IR (KBr): 3400, 3340, 1765, and 1155 cm^{-1}. Anal. $C_9H_{14}O_4$: C, H. *9a:* m.p. 174–175 °C (from toluene–ethyl acetate). IR (KBr): 3520, 3360, 1750, and 1120 cm^{-1}. Anal. $C_9H_{14}O_4$: C, H.

(RS) *3-Methyl*-r-*3*,t-*3a-dihydroxy*-cis-*octahydrocyclohepta*[b]*furan-2-one* (8b) *and* (RS) *3-methyl*-r-*3*,t-*3a-dihydroxy*-trans-*octahydrocyclohepta*[b]*furan-2-one* (9b). A mixture of *7b* (3.7 g), water (37 ml), tetrahydrofurane (25 ml) and 70 % perchloric acid (6 ml) was refluxed for 3 h and worked up as described above for the hydrolysis of *7a* giving *7b* (2.0 g), *15b* (100 mg), a mixture of *8b* and *9b* (570 mg), and *9b* (430 mg): m.p. 153–153.5 °C (from toluene–ethyl acetate). The isomers were separated by HPLC on a Si-60 Knauer column (250×16 mm; 7 µm) with toluene–ethyl acetate (2:1) as eluant and RI detection to give *8b* (270 mg) and *9b* (185 mg). *8b:* m.p. 136–136.5 °C (from ethyl acetate). IR (KBr): 3520,

3400, 1750, and 990 cm^{-1}. Anal. for $C_{10}H_{16}O_4$: C, H. *9b:* m.p. 155–155.5 °C (from ethyl acetate). IR (KBr): 3350, 1760, and 985 xm^{-1}. Anal. $C_{10}H_{16}O_4$: C, H.

Treatment of the dihydroxy-lactones with thionyl chloride. Each of the dihydroxy-lactones *6a, 6b, 8a, 8b, 9a,* and *9b* was treated with thionyl chloride (20 equivalents) in pyridine (60 μl per mg of lactone) for 1 h at 0 °C. The respective reaction mixtures were poured into ice cold 4M hydrochloric acid (200 μl *per* mg of lactone) and extracted with ether. The pooled extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude products, except the product obtained from *6b,* were chromatographed on silica gel with toluene–ethyl acetate (9:1) as eluant.

Cyclic syn *sulfite of* 6a 11a: m.p. 95–96 °C (from toluene). IR (KBr): 1785, 1221, 1101, 1002, and 936 cm^{-1}. Anal. $C_9H_{12}O_5S$: C, H, S.

Cyclic anti *sulfite of* 6a 12a: m.p. 110–111 °C (from toluene). IR (KBr): 1786, 1225, 1095, 1000, and 930 cm^{-1}. Anal. $C_9H_{12}O_5S$: C, H, S.

Cyclic syn *sulfite of* 6b 11b. After addition of a few drops of toluene to the etheral extract *11b* precipitated as crystals m.p. 152–153 °C (from toluene). IR (KBr): 1776, 1227, 1108, 1002, and 925 cm^{-1}. Anal. $C_{10}H_{14}O_5S$: C, H, S.

Cyclic anti *sulfite of* 6b 12b. After several months *12b* precipitated from the mother liquor of *11b* m.p. 84–88 °C (from toluene–petroleum ether). IR (KBr): 1790, 1230, 1112, 1007, and 942 cm^{-1}. Anal. $C_{10}H_{14}O_5S$: C, H, S.

Table 6. Crystal data and experimental details for compound *9b.*

Molecular formula		$C_{10}H_{16}O_4$	
Molecular weight		200.24	
Crystal system		orthorhombic	
Space group		*Pbca* (No. 61)	
Temperature		rt	110 K
Diffractometer		Picker FACS-1	Enraf-Nonius CAD-4
Unit cell dimensions (Å)	a	18.431(3)	18.182(6)
	b	10.422(2)	10.305(8)
	c	10.872(2)	10.745(2)
Volume ($Å^3$)	U	2088	2013
Molecules per unit-cell	Z	8	8
Calculate density ($Mg\ m^{-3}$)	D_c	1.274	1.321
Observed density ($Mg\ m^{-3}$) (flotation)	D_m	1.28	–
Number of electrons per unit-cell	$F(000)$	864	864
Linear absorption coefficient (cm^{-1})	μ	0.91	0.95
Radiation (Å) (graphite monochromated)	$\lambda(MoK_\alpha)$	0.7107	0.7107
Scan-mode		θ–2θ	θ–2θ
Scan width	$\Delta 2\theta_h$	$1.50+0.346\tan\theta$	$\Delta\theta=1.00+0.350\tan\theta$
	$\Delta 2\theta_l$	$1.10+0.346\tan\theta$	
Maximum scan time (s)		–	120
Scan speed θ (° min^{-1})		0.5	0.91–4.0
Maximum requested $\sigma(I)/I$		–	0.02
Collection range (°)		$2.2<\theta\leq 24.0$	$2.2<\theta\leq 25.0$
Number of unique reflections measured		1636	1779
Number of reflections with $I>A\sigma(I)$		1052(A=2)	1084(A=3)
Number of parameters refined		184	185
$R=\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$		0.039	0.043
$R_W=\{\Sigma w\|\|F_o\|-\|F_c\|\|^2/\Sigma w\|F_o\|^2\}^{\frac{1}{2}}$		0.041	0.047

Table 7. Atomic positions and vibrational parameters ($\times 10^2$ Å^2) obtained from the X-ray analyses of compound *9b* at room temperature (upper entries) and at 110 K (lower entries). Estimated standard deviations are given in parentheses. The temperature factors are defined by: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$.

Atom	s.o.f	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	1.0	0.19079(9)	−0.0691(2)	0.0783(1)	5.9(1)	6.1(1)	3.07(9)	0.2(1)	−0.11(9)	0.52(8)
	1.0	0.18926(9)	−0.0715(2)	0.0751(2)	1.9(1)	4.4(1)	1.3(1)	0.25(9)	0.07(8)	0.64(8)
C2	1.0	0.2543(2)	−0.1015(2)	0.1285(2)	5.4(2)	4.4(2)	3.6(1)	0.1(1)	0.1(2)	−0.7(1)
	1.0	0.2536(2)	−0.1037(3)	0.1279(2)	2.1(1)	3.4(2)	1.9(1)	0.3(1)	−0.3(1)	−0.2(1)
C3	1.0	0.2413(1)	−0.1648(2)	0.2534(2)	4.9(2)	3.0(1)	3.8(1)	−0.2(1)	−0.6(1)	−0.1(1)
	1.0	0.2393(2)	−0.1652(3)	0.2547(3)	2.8(2)	2.4(1)	2.2(1)	0.0(1)	−0.6(1)	0.2(1)
C3a	1.0	0.1678(1)	−0.1057(2)	0.2889(2)	4.6(1)	2.7(1)	3.7(1)	−0.4(1)	0.0(1)	0.2(1)
	1.0	0.1647(1)	−0.1033(3)	0.2893(2)	2.5(2)	2.3(2)	1.9(1)	−0.5(1)	0.0(1)	0.1(1)
C8a	1.0	0.1309(1)	−0.0983(3)	0.1638(2)	4.7(2)	4.1(2)	4.4(2)	−0.1(1)	−0.6(1)	0.0(1)
	1.0	0.1279(1)	−0.0986(3)	0.1616(2)	1.8(1)	3.6(2)	1.8(1)	0.0(1)	0.2(1)	0.7(1)
C4	1.0	0.1262(2)	−0.1809(3)	0.3858(3)	6.5(2)	5.8(2)	4.9(2)	−1.2(2)	0.5(2)	1.4(2)
	1.0	0.1217(2)	−0.1772(3)	0.3883(3)	4.7(2)	4.5(2)	1.4(1)	−1.8(2)	0.1(1)	0.4(2)
C5A	0.5	0.040(1)	−0.164(2)	0.385(2)	6(1)	9(1)	11(1)	−2.5(7)	2.4(9)	0.5(8)
	0.65(1)	0.0329(5)	−0.1683(8)	0.3739(8)	2.9(5)	3.2(4)	2.8(5)	0.0(3)	1.3(4)	0.6(4)
C5B	0.5	0.0582(8)	−0.132(1)	0.424(1)	3.8(6)	7.4(8)	6.8(7)	−1.2(5)	1.0(5)	2.7(6)
	0.35(1)	0.0552(7)	−0.147(1)	0.427(1)	1.6(6)	1.8(5)	2.5(7)	−0.5(4)	0.7(5)	0.4(5)
C6A	0.5	0.0025(6)	−0.061(2)	0.329(1)	4.9(5)	14(1)	9.3(8)	−0.4(9)	1.1(5)	0(1)
	0.65(1)	−0.0028(3)	−0.040(1)	0.3340(6)	2.3(3)	4.6(6)	4.1(4)	1.0(3)	1.2(3)	1.5(4)
C6B	0.5	0.0001(7)	−0.136(1)	0.316(1)	4.3(5)	5.8(6)	10.5(9)	−0.9(5)	0.5(5)	0.6(6)
	0.35(1)	0.0002(5)	−0.124(2)	0.324(1)	1.0(4)	1.8(8)	3.7(6)	0.6(5)	0.0(4)	1.0(5)
C7A	0.5	0.0003(8)	−0.036(2)	0.199(1)	4.8(6)	10(1)	10(1)	1.3(6)	0.0(6)	−2.2(6)
	0.65(1)	−0.0043(4)	−0.0211(8)	0.1937(9)	2.3(3)	4.9(4)	3.8(5)	0.5(3)	0.3(3)	2.1(4)

C7B	0.5	0.0125(9)	0.002(1)	0.243(2)	6.3(7)	6.2(7)	10(1)	1.6(5)	−1.2(7)	0.6(7)
	0.35(1)	0.0124(6)	0.001(1)	0.254(2)	1.6(6)	3.1(6)	2.5(8)	0.6(4)	−0.3(5)	−0.6(6)
C8	1.0	0.0726(2)	0.0009(3)	0.1445(3)	6.1(2)	7.1(2)	6.4(2)	0.9(2)	−1.7(2)	0.3(2)
	1.0	0.0706(2)	0.0053(3)	0.1402(3)	2.1(2)	4.6(2)	3.1(2)	0.3(1)	−0.3(1)	0.8(2)
O2	1.0	0.3109(1)	−0.0844(2)	0.0754(2)	6.1(1)	8.2(1)	4.5(1)	−0.1(1)	1.5(1)	−0.1(1)
	1.0	0.3113(1)	−0.0881(2)	0.0747(2)	2.0(1)	5.1(1)	2.5(1)	0.30(9)	0.43(9)	−0.2(1)
CMe	1.0	0.3033(2)	−0.1484(3)	0.3417(3)	5.6(2)	5.3(2)	5.0(2)	0.1(1)	−0.9(2)	−0.0(2)
	1.0	0.3016(2)	−0.1477(3)	0.3455(3)	3.5(2)	3.1(2)	2.5(2)	0.0(1)	−1.2(1)	0.5(1)
O3	1.0	0.2282(1)	−0.2961(2)	0.2210(2)	7.4(1)	3.4(1)	7.5(1)	0.61(9)	−2.2(1)	−0.5(1)
	1.0	0.2249(1)	−0.2979(2)	0.2241(2)	3.4(1)	2.8(1)	4.0(1)	0.31(9)	−1.8(1)	−0.1(1)
O3a	1.0	0.1796(1)	0.0244(2)	0.3264(1)	6.4(1)	3.7(1)	3.35(9)	−0.38(8)	−0.2(1)	−0.27(8)
	1.0	0.1776(1)	0.0288(2)	0.3249(2)	2.9(1)	3.2(1)	1.8(1)	−0.28(9)	0.4(1)	0.1(1)

Atom	s.o.f	x	y	z	U_{iso}	Atom	s.o.f	x	y	z	U_{iso}
H3a	1.0	0.186(1)	0.027(2)	0.399(2)	4.5	H8a	1.0	0.114(1)	−0.184(2)	0.144(2)	4.4
	1.0	0.183(2)	0.029(3)	0.396(3)	2.6		1.0	0.110(1)	−0.184(3)	0.139(2)	2.4
H3	1.0	0.257(1)	−0.339(3)	0.252(3)	6.1	H41	1.0	0.132(1)	−0.266(3)	0.363(2)	5.7
	1.0	0.257(2)	−0.345(3)	0.253(3)	3.4		1.0	0.135(2)	−0.263(3)	0.376(3)	3.5
H1Me	1.0	0.347(1)	−0.190(2)	0.311(2)	5.3	H42	1.0	0.152(1)	−0.175(2)	0.456(2)	5.7
	1.0	0.345(2)	−0.190(3)	0.313(2)	3.0		1.0	0.139(2)	−0.149(3)	0.463(3)	3.5
H2Me	1.0	0.312(1)	−0.061(3)	0.358(2)	5.3	H81	1.0	0.60(1)	−0.004(2)	0.059(2)	6.6
	1.0	0.312(1)	−0.056(3)	0.363(3)	3.0		1.0	0.059(2)	0.004(3)	0.054(3)	3.3
H3Me	1.0	0.290(1)	−0.185(2)	0.419(2)	5.3	H82	1.0	0.094(1)	0.077(3)	0.160(2)	6.6
	1.0	0.291(1)	−0.188(3)	0.423(3)	3.0		1.0	0.093(1)	0.090(3)	0.155(2)	3.3

*(RS) 3-Methyl-7a-hydroxy-4,5,6,7-tetrahydro-7a*H*-benzofuran-2-one* (15a): m.p. 128–131 °C (decomp.) (from toluene). IR (KBr): 3300, 1720, 1685, 1260, and 960 cm^{-1}. Anal. $C_9H_{12}O_3$: C, H.

(RS) 3-Methyl-8a-hydroxy-4,5,6,7,8,8a-hexahydrocyclohepta[b]*furan-2-one* (15b): m.p. 114.5–115 °C (decomp.) (from toluene); IR (KBr): 3270, 1728, 1710, 1670, 1148, and 938 cm^{-1}. Anal. $C_{10}H_{14}O_3$: C, H.

*3-Methyl-4-chloro-4,5,6,7-tetrahydro-7a*H*-benzofuran-2-ones* 16a *and* 17a. One of the isomers was isolated as an oil. ^{1}H NMR (90 MHz; $CDCl_3$): δ 5.15 (1 H, dd, J 2.2 and 2,6 Hz) 5.00 (1 H, ddq, J 1.9, 6.1 and 11.2 Hz) 1.89 (3 , d, J 1.9 Hz) and 2.6–1.1 (6 H, m). ^{13}C NMR ($CDCl_3$): δ 173.38, 158.31, 121.58, 78.45, 51.69, 34.78, 33.92, 17.50, and 8.51. IR (KBr): 1755, 1685, 1036, and 752 cm^{-1}. The other isomer was detected in the ^{13}C NMR spectrum of the crude product (173.8, 156.9, 122.3, 79.9, 55.4, 38.5, 33.2, 21.5, and 9.7).

3-Methyl-4-chloro-4,5,6,7,8,8a-hexahydrocyclohepta[b]*furan-2-ones* 16b *and* 17b. One of the isomers was isolated as an oil. ^{1}H NMR (60 MHz; $CDCl_3$): δ 5.2 (1 H), 4.8 (1 H), 1.92 (3 H, dd, J 1.0 and 2.1 Hz), and 2.5–1.35 (8 H, m). ^{13}C NMR ($CDCl_3$): δ 173.48, 161.51, 128.63, 83.17, 53.64, 34.30, 33.10, 26.44, 23.30, an 9.70. IR (film): 1740, 1665, 1020, and 724 cm^{-1}. The other isomer was detected in the ^{13}C NMR of the crude product: δ 173.43, 161.51, 128.63, 81.16, 53.48, 36.68, 33.75, 25.36, 24.76, and 9.16.

*X-Ray-crystallographic analysis of 3-methyl-*r*-3,*t*-3a-dihydroxy-*trans*-octahydrocyclohepta*[b]*furan-2-one* (9b).

A single crystal of the size 0.30×0.30×0.13 mm was used for the determination of the unit cell parameters and for the collection of two sets of intensity data. The unit cell parameters and other information pertinent to data collection and refinement are given in Table 6. Intensities of three standard reflections measured periodically during the data collections showed no significant variations. The symmetry related reflections were averaged, and the estimated standard deviations for the measured intensities were based on counting statistics. No absorption corrections were made.

The structure was easily solved by direct methods with the MULTAN program[28] using the rt data set. The structure was refined by the full-matrix least-squares methods, the quantity minimized was $\Sigma w(|F_o|-k|F_c|)^2$, where the weights were initially taken as unity. The non-hydrogen atoms after initial isotropic refinement were refined anisotropically. The positions of the hydrogen atoms were obtained from intermediate difference maps. Because of the high thermal parameters for the C5, C6, and C7 atoms, the hydrogen atoms bonded to these atoms were placed in calculated positions (C–H=1.0 Å).

In subsequent full-matrix least-squares calculations an overall scale factor, atomic coordinates for all atoms, except those of the hydrogen atoms bonded to C5, C6, and C7, and anisotropic thermal parameters for the non-hydrogen atoms were refined. The thermal parameters for the hydrogen atoms were fixed at isotropic values corresponding to those of the atoms to which they are bonded. The weights used in the final cycles of refinement were given by $w^{-1}=[3\sigma^2(F_o)+0.0005F_o^2]$. The refinement converged at R=0.054 and R_w=0.062, with the greatest electron fluctuations (±0.26 e $Å^{-3}$) in the difference Fourier synthesis being in the vicinity of C6 and C7.

At this point the structure at 110 K was refined starting with the rt model coordinate set. The refinement was carried out in the same way as for the rt structure. The refinement converged at R=0.072 and R_w=0.084, $w^{-1}=[\sigma^2(F_o)+0.005F_o^2]$. An examination of a difference map and of the anisotropic vibration parameters indicated that the structure was partially disordered around C5, C6, and C7. In order to improve the model these three atoms were split into six partial atoms each with an s.o.f. of 0.5. Full-matrix least-squares refinement of this model converged at R=0.045 and R_w=0.051. In order to further improve the model, one variable was used to define the atomic occupation factors of the atoms C5A, C5B, C6A, C6B, C7A, and C7B in such a way that the sum of the atomic occupation factors over the alternative conformations was unity. The model refined to a final R=0.043 and R_w=0.047, which represents a significant improvement at the 99.5 % confidence level.[29] On the last cycle of least-squares refinement the values of maximum and average shift/error were 0.04 and 0.01, respectively. The greatest electron fluctuations in the final difference Fourier synthesis were ±0.24 e $Å^{-3}$.

Refinement of the rt structure splitting each of the atoms C5, C6, and C7 into two half-atoms resulted in a significant improvement of the rt model; final R=0.039 and

R_w=0.041, and the values of maximum and average shift/error were 0.05 and 0.01, respectively. The greatest fluctuations in the final difference Fourier synthesis were ±0.15 e $Å^{-3}$. Attempts were made to refine the site occupation factors of the six partial atoms, but this did not lead to an improvement of the model.

The least-squares refinements using the 110 K data were carried out using the SHELX 76 programme system.[30] All other calculations were carried out with the X-ray 76 programme system.[31]

The X-ray atomic scattering factors used were those of Cromer and Mann[32] for O, and C, and of Stewart, Davidson and Simpson[33] for H.

Table 7 lists the final positional and thermal parameters of the refined atoms. Lists of the final structure factors are available on request from the author LB.

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