OCH_3), 495 (M − 43), 478 (M − HOAc), 449 (M − 43 − 46), 418 (M − 2HOAc), 358 (M − 3HOAc), and 299 (M − 3HOAc − 59).

Methyl 3α,7α,12α-Triacetoxy-16-hydroxy-16,17-seco-5β-androstan-17-oate (6b). A solution of aldehyde **7a** (30 mg) and $NaBH_4$ (20 mg) in CH_3OH (5 mL) was stirred at room temperature for 0.5 h. The reaction mixture was poured into ice water and extracted with EtOAc. After washing the EtOAc layer with dilute HCl solution and then H_2O, the organic solvent was evaporated. Recrystallization of the residue from hexane–EtOAc afforded 20 mg of **6b:** mp 193–195 °C; ^1H NMR δ 5.19 (peak, 2H, 7β,12β-H's), 4.57 (hump, 1H, 3β-H), 3.62 (s, 3H, OCH_3), 3.61 (peak, 2H, C-16), 2.10, 2.07, and 2.03 (s, 3H each 3α,7α,12α-OAc's), 1.25 (s, 3H, C-18), and 0.93 (s, 3H, C-19); *m/e* 436 (M − HOAc), 394, 362, 334, 302, 274 (100), and 213 (100).

Anal. Calcd for $C_{26}H_{40}O_9$: C, 62.89; H, 8.12. Found: C, 62.78; H, 7.88.

Acetylation of **6b** with pyridine–Ac_2O yielded tetraacetate **6c:** ^1H NMR δ 4.97 (peak, 2H, 7β,12β-H's), 4.54 (hump, 1H, 3β-H), 3.93 (peak, 2H, C-16), 3.60 (s, 3H, OCH_3), 2.10, 2.05, 2.02, and 1.96 (s, 3H, each, OAc's), 1.17 (s, 3H, C-18), and 0.93 (s, 3H, C-19).

Acknowledgment. This investigation was supported by Grant 5-R01-CA15824, awarded by the National Cancer Institute, DHEW.

Registry No.—**1,** 51102-05-7; **2a,** 61543-86-0; **2b,** 52840-09-2; **3,** 61543-87-1; **4,** 61543-88-2; **5,** 61543-89-3; **6a,** 61543-90-6; **6b,** 61543-91-7; **6c,** 61543-92-8; **7b,** 61543-93-9; **7c,** 61543-94-0; **7d,** 61543-95-1; **7e,** 61543-96-2; **8,** 61543-97-3; methyl cholate, 1448-36-8; phenyl bromide, 108-86-1; 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene, 61543-98-4; NBS, 128-08-5; 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one, 61543-99-5; ozone, 10028-15-6; diazomethane, 334-88-3.

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Terpenes and Terpenoids. 5. The Four Isomeric Thujanols. Their Preparative Chemistry, Conformation, and Reactivity. A Comprehensive Study

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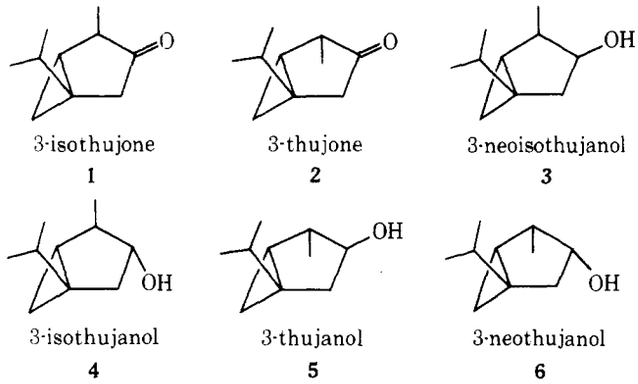
The preparative chemistry (50–100-g scale) of (−)-3-isothujone (**1**), (+)-3-thujone (**2**), (−)-3-neoisothujanol (**3**), (−)-3-isothujanol (**4**), (+)-3-thujanol (**5**), and (+)-3-neothujanol (**6**) was developed. As starting material was utilized western red cedar (*Thuja plicata Don*) leaf oil containing 80–90% of **1**. Conformation and reactivity of alcohols **3–6** were studied by three probes: lanthanide shift reagent (LSR) induced ^1H NMR chemical shifts and their conformational interpretation, rate of chromium trioxide oxidation, and rate of acetic anhydride–pyridine acetylation. Shifts induced by $Eu(thd)_3$ indicated a slightly developed boatlike conformation (**3a–6a**) with a dihedral angle of 14 ± 4° between C2–C3 and/or C3–C4. Positionally analogous protons in *trans-* and *cis*-2-methycyclopentanol (**9, 10**) showed shifts very similar to those in **3–6.** Rates of chromium trioxide oxidation of alcohols **3–6, 9,** and **10** in AcOH at 25.0 ± 0.1 °C follow (alcohol, $k_2 \times 10^2$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3,** 36.3, 6.91; **4,** 27.9, 5.31; **5,** 17.7, 3.37; **6,** 55.3, 10.5; **9,** 7.36, 1.40; **10,** 15.4, 2.93. Rates of acetic anhydride–pyridine acetylation follow (alcohol, $k_2 \times 10^5$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3,** 14.3, 1.36; **4,** 4.49, 0.42; **5,** 19.4, 1.84; **6,** 0.912, 0.086; **9,** 16.2, 1.54; **10,** 5.22, 0.49. Oxidation and acetylation rates were adequately rationalized by comparison with rates of 2- and 3-substituted cyclopentanols. They supported results observed in the LSR–NMR study. LSR-induced shifts in thujones **1** and **2** indicated a flat, five-membered ring, i.e., an overall L-shaped conformation of these two ketones.

The two isomeric thujones (**1, 2**) and the four isomeric thujanols **3–6** (Scheme I) form a unique group of monoterpenes derived from bicyclo[3.1.0]hexane.[2,3] The ketones are fairly common in nature, whereas the alcohols are relatively rare. The recent review by Whittaker and Banthorpe[4] covering the past 25 years has shown that despite considerable work carried out on various aspects of the chemistry of **1–6** the overall picture remains rather fragmented. In particular, with regard to alcohols **3–6** a systematic study correlating quantitatively their reactivity and exploring their conformation was notably absent. One reason for this may have been the tedious preparation of pure alcohols **3–6** in larger quantities.[5,6,7a]

The present paper deals with two subjects. The first is an extension and conclusion of our work[8,9] concerning the preparation of alcohols **3–6.** Simple procedures have now been developed, which make them easily accessible starting with a single abundant source, viz., western red cedar (*Thuja plicata Don*) leaf oil.[10]

The second subject is the study of conformation and reactivity of these alcohols. As probes we applied the ^1H NMR–LSR technique using $Eu(thd)_3$, rate of chromium trioxide oxidation, and rate of acetylation. The overall conformation of the bicyclohexane skeleton of the thujanols may be boatlike (**3a–6a**), L-shaped with a flat five-membered ring (**3–6**), or chairlike (**3b–6b**). Bergqvist and Norin[6] and Tori[11] proposed on the basis of NMR coupling constants a well-developed boatlike conformation (**1a–6a**) in thujanols as well as in thujones.[12] However, limitations to the conformational interpretation of *J* constants in bicyclo[*n*.1.0] compounds were voiced.[4,13] Later Norin et al.[7b] utilized the $Eu(thd)_3$ LSR reagent to study 3-neoisothujanol (**3**) and 3-thujanol (**5**) and confirmed the suggested boatlike conformation. We found[9] by IR that under conditions of extreme dilution in nonpolar solvents **3** and **5** may exist in a chairlike conformation (**3b, 5b**) due to the intramolecular hydrogen bond between OH and the edge of the cyclopropane ring. As suggested by one referee of

Scheme I. Nomenclature[a] of Thujones (1, 2) and Thujanols (3–6)

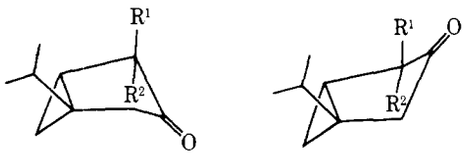


3-isothujone 1 | 3-thujone 2 | 3-neoisothujanol 3

3-isothujanol 4 | 3-thujanol 5 | 3-neothujanol 6

[a] Systematic nomenclature proposed by H. C. Brown et al. [S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, 34, 3015 (1969)], based on the utilization of neo and iso prefixes in concert with their utilization in other terpene groups. For details of historic background and rationale of proposal see Brown's paper. In the present paper, as in our previous work, we adopted this systematic nomenclature.

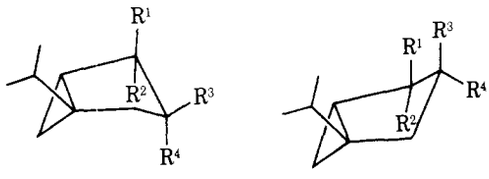
the present paper, the concentrations in NMR measurements were much higher and a preferred intermolecular H bonding with concomitant conformational change to the boat form was possible. With regard to conditions prevailing in preparative work Banthorpe and his group[14] had to consider the possibility of any of the three conformations, depending on specific circumstances, in order to accommodate results of various chemical transformations. Later they concluded[4] that the 2, 3, and 4 positions of the thujane skeleton may be flexible enough to adopt any of the three conformations depending on specific reaction conditions, solvent, dilution, and reagent. We approached this problem by choosing as models *trans*- and *cis*-2-methylcyclopentanol (**9, 10**) and viewing the thujane skeleton as a methylene bridged cyclopentane. If indeed the assumption of conformational flexibility was warranted (regarding positions 2, 3, and 4) then it could be modeled on the known conformational flexibility (and also uncertainty) of cyclopentane and its derivatives.[15–18] In fact, our present results point clearly in this direction. The two methylcyclopentanols appear to be, in the absence of more suitably substituted compounds, acceptable models providing adequate background for a reasonable, though limited, interpretation of the behavior of thujanols **3–6.**



1a, 2a **1b, 2b**

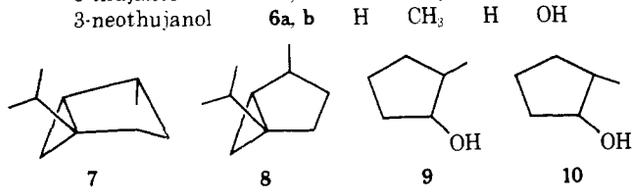
3-isothujone **1a, b** $R^1 = CH_3$; $R^2 = H$

3-thujone **2a, b** $R^1 = H$; $R^2 = CH_3$

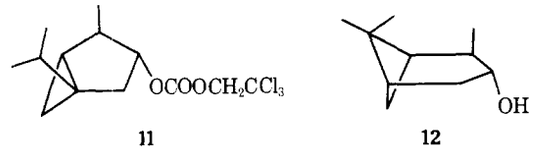


3a–6a **3b–6b**

		R^1	R^2	R^3	R^4
3-neoisothujanol	**3a, b**	CH_3	H	OH	H
3-isothujanol	**4a, b**	CH_3	H	H	OH
3-thujanol	**5a, b**	H	CH_3	OH	H
3-neothujanol	**6a, b**	H	CH_3	H	OH

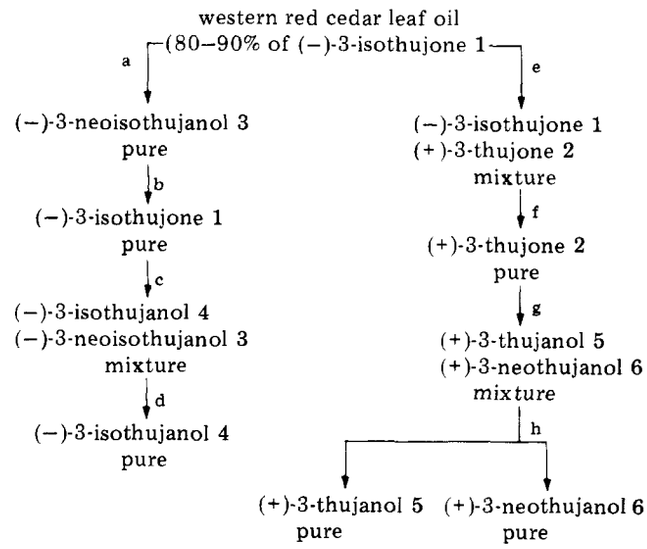


7 **8** **9** **10**



11 **12**

Scheme II. Approach to Pure Thujones (1, 2) and Thujanols (3–6) Starting from Western Red Cedar (*Thuja Plicata Don*) Leaf Oil



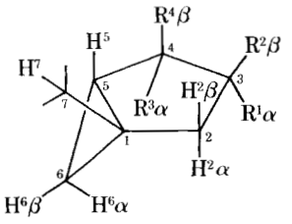
a, Meerwein–Ponndorf–Verley reduction;[19,20] b, oxidation with chromium trioxide;[21] c, reduction with lithium aluminum hydride;[14,23] d, separation with trichloroethyl chloroformate;[22] e, epimerization with sodium hydroxide;[8] f, separation with sodium bisulfite;[8] g, reduction with sodium borohydride;[9,24] h, column chromatography separation on alumina.[9,24]

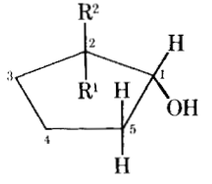
Results and Discussion

Preparative Chemistry of Thujanols 3–6. As single source for the preparation of thujanols **3–6** we used western red cedar leaf oil which contains 80–90% of (−)-3-isothujone (**1**). The development of its transformation into pure alcohols **3–6** and ketones **1** and **2** is outlined in Scheme II. The individual steps outlined therein can be carried out on a 50–100-g scale. This includes steps g and h described by us previously[9,24] for gram quantities only.

Proton Magnetic Resonance Shifts Induced by Eu(thd)$_3$ in Thujanols 3–6 and Thujones 1, 2. The use of lanthanide shift reagents (LSR), most commonly those derived from Eu^{3+}, for the study of stereochemistry and conformation is now a generally accepted technique. From extensive reviews by and work of Cockerill et al., Saunders and Williams, and others[25–27] one may conclude that in relatively simple molecules it is possible to neglect the angular factor of the McConnel–Robertson equation and use a linear correlation between the distance (r and Å) of the donor atom or its lone electron pair from the respective proton and the magnitude of the induced shift G_{LSR} of the latter.[28–30] This assumption was made by Norin et al.[7b] in their study of neoisothujanol (**3**) and thujanol (**5**). In our study we included all

Table Ia. Induced Chemical Shifts $G_{Eu(thd)_3}$ of Protons on C2, C4, C5, C6, C7, and C4 Methyl Group (=C10) in the Four Isomeric Thujanols (3–6) and Protons on C2, C5, and C2 Methyl Group in *trans*- and *cis*-2-Methylcyclopentanol (9, 10)



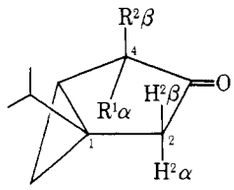


Proton or methyl group	Positional and configurational relationship to 3 OH group	3-Neoisothujanol $R^1, R^3 = H$; $R^2 = OH$; $R^4 = CH_3$	3-Isothujanol $R^2, R^3 = H$; $R^1 = OH$; $R^4 = CH_3$	3-Thujanol $R^1, R^4 = H$; $R^2 = OH$; $R^3 = CH_3$	3-Neothujanol $R^2, R^4 = H$; $R^1 = OH$; $R^3 = CH_3$
H2α	2 trans	8.69		8.02	
	2 cis		14.10		14.48
H2β	2 trans		7.60		7.35
	2 cis	13.10		13.01	
H4α	2 trans	9.01			
	2 cis		13.81		
H4β	2 trans				7.93
	2 cis			13.35	
$CH_3$4α	2 trans			6.10	
	2 cis		4.87		10.00
$CH_3$4β	2 trans				
	2 cis	9.20			
H5	3 trans		4.85		5.60
	3 cis	4.35		4.25	
H6α		3.13	13.50	4.58	14.47
H6β		2.55	4.95	2.62	5.30
H7		2.93	3.32	2.39	3.19

Proton or methyl group	Positional and configurational relationship to OH group	*trans*-2-Methylcyclopentanol $R^1 = H$; $R^2 = CH_3$	*cis*-2-Methylcyclopentanol $R^1 = CH_3$; $R^2 = H$	Cyclopentanol[a] $R^1, R^2 = H$
H2	2 trans		8.31	8.65
	2 cis	13.41		15.30
H5	2 trans	8.10	7.95	8.65
	2 cis	13.60	14.05	15.30
$CH_3$2	2 trans	5.60		
	2 cis		9.61	

[a] Reference 26.

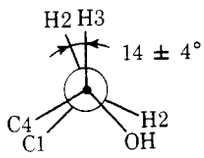
Table Ib. Induced Chemical Shifts $G_{Eu(thd)_3}$ of Protons on C2, C4, and C4 Methyl Group (=C10) in the Two Isomeric Thujones 1 and 2



Proton or methyl group	(3)-Isothujone 1 $R^1 = H$; $R^2 = CH_3$	(3)-Thujone 2 $R^1 = CH_3$; $R^2 = H$
H2α	3.50	3.41
H2β	3.50	3.35
H4α	4.28	
H4β		4.05
$CH_3$4α		2.73
$CH_3$4β	3.20	

four thujanols **3–6** and *trans*- and *cis*-2-methylcyclopentanol (**9, 10**) as models. Additionally, we investigated the two ketones **1** and **2.** Results are summarized in Tables Ia and Ib for the alcohols and ketones, respectively.

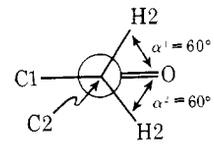
In the alcohols **3–6** the absence of a highly developed chair- or boatlike conformation with a dihedral angle in the 45–60° range between C2–C3 or C3–C4 is immediately apparent. Most fortuitously results obtained with alcohols **4** and **6** (not included in Norins[7b] study) produced rather unambiguous information regarding their conformation. Values of $G_{Eu(thd)_3}$ for protons 2α, 4α, and 6α in isothujanol (**4**) and for protons 2α and 6α in neothujanol (**6**) are practically identical. Therefore, they should be equidistant from oxygen at C3.[31] This will be compatible with only one conformation of C3 relative to C2 and C4 and will in turn depend on the bond angle C4–C5–C6 determining the angle between the planes of the three- and five-membered rings at their juncture. From crystallographic measurements on various bicyclo[3.1.0]-hexane systems[33,34] several values (115.0, 117.4, 118.3, and 123.3°) were assigned to this angle. With a conservative value of 120° and using Dreiding models we found that equidistance of the three protons (at C2, C4, and C6) from oxygen at C3 would be 2.65 ± 0.07 Å and would require only a slight bending of the C3 tip of the five-membered ring toward a boatlike conformation with a dihedral angle estimated at 14 ± 4° between C2 and C3 or C3 and C4[35] as shown:



Striking similarities between *G* values of analogous protons (relative to OH) of the four thujanols **3–6,** of the methylcyclopentanols **9** and **10** and cyclopentanol itself indicate, first, that also alcohols **3** and **5** will have a similar dihedral angle between C2 and C3 and, second, that the conformational behavior of thujanols in the C2–C3–C4 region strongly resembles that of model methylcyclopentanols and cyclopentanol itself.[16–18,36]

Our result is in reasonable agreement with observations made by Norin et al.[7b] on alcohols **3** and **5.** His recorded *G* values were in accord with a projected "flap angle" of 25° (plane delineated by C2, C3, and C4 vs. plane delineated by C1, C2, C4, and C5) for the cyclopentane ring portion of the bicyclohexane system. Since Norins' and our approaches were slightly different in some details (see ref 7b) it may well be that the two results simply represent limits of possible accuracy inherent to the LSR conformational probe when utilized in its primitive form, i.e., with disregard to the angular factors.

Results obtained with thujones **1** and **2** are summarized in Table Ib. Induced shifts of ketonic protons are generally lower than those of alcohols.[25a,b] Therefore only *G* values of protons neighboring the CO group are presented there. It was shown[25a,b] that in cyclic ketones the shift is proportional only to the distance between oxygen of the CO group and the respective proton, the angular vector being negligible. Since shifts of the C2, C4, and C4 Me (= C10) protons are in both ketones very similar, it is fair to conclude that a planar five-membered ring conformation predominates in these two ketones. There is further supporting evidence for this proposition. According to the Barfield–Grant equation[37,38] J_{gem} depends on the angle at which the C=O plane dissects the H–C–H angle of the neighboring CH_2 group. The extremely high $J_{2\alpha,2\beta}$ = 19 Hz in both ketones[6,11] is compatible with only one arrangement, that one in which C=O bisects the H–C–H angle of the neighboring CH_2 group symmetrically, viz.



Any other arrangement would necessitate a lower *J* since 19 Hz is the highest value implied in the Barfield–Grant equation. Extensive data supplied by Cookson et al.[39] leave little doubt in this direction. Cyclopentanone shows *J* = 19.0–19.5 Hz whereas in ketones like cyclohexanone in which α^1 does not equal α^2 *J* = 16.0 Hz or less.[40,41]

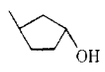
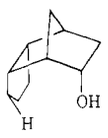
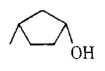
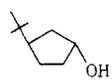
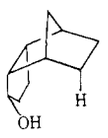
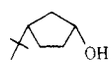
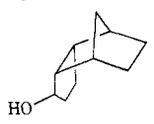
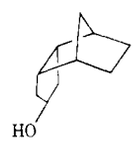
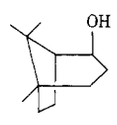
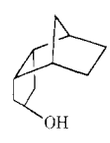
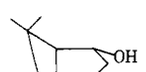
Rate of Chromium Trioxide Oxidation of Thujanols 3–6. It was postulated that the magnitude of ground state steric interactions involving the OH group of alcohols is directly related to their rate of oxidation with chromium trioxide.[18,42–44] However, Pasto and Rao[45] have shown that transition state energy differences, most probably caused by torsional angle effects, may be an important factor, depending on specific stereochemistry in the ground and transition states. Inspection of models of alcohols **3–6** indicated that in the critical C2–C3–C4 region torsional interactions may play an important role. Also, polar (inductive) effects have occasionally been invoked but without a firm quantitative background.[18,46–49] Despite these limitations we had hoped that the rate of chromium trioxide oxidation of alcohols **3–6** could provide reasonable information about their conformation and reactivity. As models we included the two methylcyclopentanols **9** and **10** and isopinocampheol (**12**). Results are summarized in Table II. Oxidation rates of alcohols available from the literature and pertinent to the subsequent discussion are given in Table III.

Thujanol (**5**) (CH_3 and OH trans) shows the lowest rate of oxidation. It is 2.5 times higher than that of *trans*-2-methylcyclopentanol (**9**). This enhancement can be attributed to the influence of the 1,3 relationship between OH and *i*-Pr groups. Richer et al.[50] showed that *cis*-3-*tert*-butylcyclopentanol (**16**) and *cis*-3-methylcyclopentanol (**14**) were oxidized respectively 1.7 and 3.4 times faster than cyclopentanol.[51] Admittedly, no model concerning a 2,4-disubstituted cyclopentanol is available. Comparing thujanol (**5**) (CH_3, OH trans) with neoisothujanol (**3**) (CH_3, OH cis), the oxidation rate is enhanced by a factor of 2.04 paralleling the enhancement (2.09) when going from *trans*- to *cis*-2-methylcyclopentanol (**9** → **10**). The two alcohols (**4** and **6**) with the OH group cis to the methylene bridge of cyclopropane were interesting with regard to the

Table II. Rate Constants of Chromic Acid Oxidation and Acetic Anhydride–Pyridine Acetylation of Thujanols (3–6), 2-Methylcyclopentanols (9, 10), and Isopinocampheol (12)

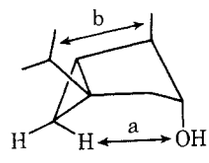
Alcohol		Chromic acid in 90% acetic acid t = 25.0 ± 0.1 °C		Acetic anhydride in pyridine t = 25.0 ± 0.1 °C	
		$k_2 \times 10^2$, L mol^{-} s^{-1}	Relative rate cyclopentanol = 1	$k_2 \times 10^5$, L mol^{-1} s^{-1}	Relative rate cyclopentanol = 1
3-Neoisothujanol	3	36.3 ± 2.17	6.91	14.3 ± 0.5	1.36
3-Isothujanol	4	27.9 ± 1.46	5.31	4.49 ± 0.27	0.42
3-Thujanol	5	17.7 ± 0.39	3.37	19.4 ± 1.0	1.84
3-Neothujanol	6	55.3 ± 2.48	10.5	0.912 ± 0.018	0.086
trans-2-Methylcyclopentanol	9	7.36 ± 0.42	1.40	16.2 ± 1.2	1.54
cis-2-Methylcyclopentanol	10	15.4 ± 0.51	2.93	5.22 ± 0.37	0.49
Isopinocampheol	12	85.7 ± 4.81	16.3	30.5 ± 2.6	2.90
Cyclohexanol		3.43 ± 0.19	0.65	8.85 ± 0.55	0.84
Cyclopentanol		5.25 ± 0.24	1.0	10.5 ± 0.48	1.0

Table III. Relative Rates of Chromic Acid Oxidation of Various Alcohols (Cyclopentanol = 1)

13		2.61[a]	19		311[b]
14		3.42[a]			
15		1.45[a]	20		30.8[b]
16		1.70[a]	21		1.22[b]
17		2.31[b]	22		81.7[c]
18		1.79[b]	23		4.25[c]

[a] Reference 50. [b] I. Rothberg and R. V. Russo, *J. Org. Chem.*, **32**, 2003 (1967). [c] H. Favre, M. Lefebvre, and J. C. Richer, *Can. J. Chem.*, **37**, 403, 411, 417 (1959).

possibility of assessing the extent of steric interaction along a in **4a**. A pronounced boatlike conformation would manifest



4a

itself by a marked oxidation rate enhancement in comparison with alcohols **3** and **5**. However, alcohol **4** was oxidized only 1.57 times faster than **5**. Thus, the rate-enhancing effect of the CH_2 bridge in **4** is only negligibly higher than the analogous effect of the *i*-Pr group in thujanol (**5**).[52] This is indicative of the absence of any strongly developed boatlike conformation in **4a**, which will be a balance of two nonopposing interactions, viz., a and b. These will depend on slight torsional adjustments along the C2–C3–C4 perimeter.[53] Neothujanol (**6**) (CH_3, OH cis) was oxidized 1.98 times faster than isothujanol (**4**), which is again comparable to the *trans*- to *cis*-2-methylcyclopentanol rate change of 2.09. Isopinocampheol (**12**) was oxidized three times faster than **4** and did not appear to be a good model for the type a interaction in **4a**.[55] In summary, rates of chromium trioxide oxidation observed for thujanols **3–6** indicated absence of a strongly developed and rigid boatlike conformation and were compatible with deductions made on the basis of the NMR–LSR study. These rates were close to those of the model 2-methylcyclopentanols and other cyclopentanols recorded in the literature and confirmed the mobility of the thujane skeleton in the C2–C3–C4 region. However, in the absence of detailed knowledge about ground and transition state energies, the small differences in the observed rates do not permit us to draw any detailed conclusions about conformational differences between the individual alcohols.

Rate of Acetic Anhydride–Pyridine Acetylation of Thujanols 3–6. Acetylation of alcohols with Ac_2O–pyridine is an established method of conformational analysis.[18] Valuable data were acquired by Eliel et al.[57,58] in the cyclohexane series and by Buck et al.[59] on selected cyclohexane derivatives, 1,3-dioxane alcohols, and methoxycyclopentanols. However, there is no background information available in regard to alkyl-substituted cyclopentanols and bicyclic alcohols that could serve as models of **3–6**. Furthermore, the detailed mechanism of the acetylation reaction remains unexplored.[59] This poses limitations to the interpretation of any sets of results. Most probably, the first step is a hydrogen bond association of pyridine with –OH of the alcohol and specific steric requirements are involved since 2-methyl- and 2,6-dimethylpyridine are inactive as catalysts.[60] Results of our measurements on alcohols **3–6, 9, 10,** and **12** are summarized in Table II. Acetylation rates of compounds relevant to the subsequent discussion are shown in Table IV.

Whereas the rates of chromium trioxide oxidation ranged from 3.37 to 10.5 (cyclopentanol = 1), the rates of acetylation, reflecting accessibility of the OH group, varied in a much wider range, viz., 0.086–1.84. The rate of acetylation (1.84) of thujanol (**5**) is close to that of *trans*-2-methylcyclopentanol (**9**), indicating little influence of the *i*-Pr group.[61] A fourfold decrease in the acetylation rate of isothujanol (**4**) when compared with **5** would indicate a more pronounced steric effect of the H6α on the rate of acetylation than on the rate of oxidation. Inspection of models showed that, most probably, the H-bond association of pyridine with the OH group would assume a conformation with the pyridine ring positioned outward and the subsequent approach of anhydride would have

Table IV. Rates of Acetic Anhydride–Pyridine Acetylation of Various Alcohols

Alcohol	Relative rate of oxidation, cyclopentanol = 1
trans-2-Methylcyclohexanol (**24**)	1.09[a]
cis-2-Methylcyclohexanol (**25**)	0.242[a]
trans-2-Methoxycyclopentanol (**26**)	1.44[b]
cis-2-Methoxycyclopentanol (**27**)	0.403[b]
trans-2-Isopropylcyclohexanol (**28**)	1.12[a]
trans-2-Isopropyl-*cis*-5-methylcyclohexanol (**29**)	1.22[a]
trans-4-*tert*-Butylcyclohexanol (**30**)	1.02[a]

[a] Reference 58. [b] Reference 59. In both cases rate values were obtained under conditions identical with those used by us in this work.

to be from the cyclopropane shielded "inside". The high rate of acetylation of isopinocampheol (**12**) shed little light on this subject in contrast to what we hoped for.[62] The relationship between acetylation rates of the two alcohols with OH groups cis to the $-CH_2-$ bridge, viz., isothujanol (**4**) (CH_3, OH trans) and neothujanol (**6**) (CH_3, OH cis), 0.42 and 0.086, respectively, ratio 4.86, approaches the ratio of acetylation rates of *trans*- and *cis*-2-methylcyclopentanol, viz., 3.14. The combined effect of cis-positioned Me group and methylene bridge is larger with respect to acetylation than to chromic acid oxidation. A similar relationship fails for the two alcohols with β-oriented OH groups, viz., thujanol (**5**) and neoisothujanol (**3**) (CH_3, OH cis). The latter is acetylated at a rate only 25% lower than that of alcohol **5**. Apparently, subtle conformational adjustments are compensating for the expected retarding effect of the *cis*-Me group in **3**; its effect is more pronounced in the relative rates of oxidation of **3** and **5**. In summary, as in the case of chromium trioxide oxidations, the four thujanols strongly resemble the behavior of model cyclopentanols. Owing to the size of the Ac_2O–pyridine complex accommodated around the OH group, the boat conformation of alcohols with an α-oriented OH group appears more perceptible through this conformational probe.

Experimental Section

General. Gas–liquid partition chromatography was carried out as described previously.[8,9,19,63,64] A Pye 54 Series instrument with flame ionization detection was used. Elemental analyses were made by Galbraith Laboratories, Knoxville, Tenn., and by Mr. P. Borda, Department of Chemistry, University of British Columbia. Melting points were carried out in capillaries on a Kofler-type microscope hot stage. Solvents, where necessary, were dried with molecular sieve 4a for 72 h. The water content was then less than 0.02% as determined by IR.

(−)-3-Neoisothujanol (3). Small pieces of aluminum foil (9 g) prewashed with carbon tetrachloride were dissolved in 2-propanol (1.5 L). The dissolution was initiated with 40 mg of mercuric chloride.[19] To the solution was added at its boiling point 60 g of cedar leaf oil containing 86% (−)-3-isothujone (**1**). During 1 h 260 mL of *i*-PrOH was distilled off. Then the reaction was stopped by the addition of 90 g of tartaric acid in 200 mL of water. About 700 mL of aqueous *i*-PrOH was distilled off in vacuo and the residue was extracted with 3 × 200 mL of diethyl ether. The extract was washed with 5% aqueous sodium bicarbonate and evaporated. At this stage, four analogous batches were combined to yield 231 g of crude semisolid neoisothujanol. After 4 days standing at 0 °C the crystalline portion was filtered off (160 g). Two recrystallizations (100 mL each) from petroleum ether (bp 30–50 °C) gave 97 g of pure (−)-3-neoisothujanol, mp 66–67 °C, $[\alpha]^{23}_D$ −22.5° (*c* 2, C_2H_5OH) [lit.[5] mp 66–67 °C, $[\alpha]^{18}_D$ −22.5° (*c* 2, C_2H_5OH)] (no detectable impurity by GLC). *p*-Nitrobenzoate, mp 111 °C (lit.[5] 110 °C).

(−)-3-Isothujone (1). The procedure of Brown et al.[21] was applied. (−)-3-Neoisothujanol (**3**, 77 g, 0.5 mol) in diethyl ether (250 mL) was oxidized (25 °C, 2 h) with 250 mL of Brown's mixture. After a standard workup the product was distilled on a spinning band column to yield 71 g (93%) of (−)-3-isothujone, bp 78 °C (12 mm), $[\alpha]^{23}_D$ −20.5° (*c* 2, $CHCl_3$ [lit.[5] bp 74.5 °C (19 mm), $[\alpha]^{18}_D$ −19.95° (neat)]. This material showed on GLC less than 0.5% each of starting (−)-3-neoisothujanol and (+)-3-thujone (**2**) (formed by epimerization of **1**).

Reduction of (−)-3-Isothujone. A slurry of 3.4 g (0.09 mol) of lithium aluminum hydride in 170 mL of diethyl ether was cooled to below −40 °C. A solution of (−)-3-isothujone (20.0 g, 0.13 mol) in 80 mL of ether was added during 1 h at below −40 °C with stirring under a nitrogen blanket. The dropping funnel used was equipped with a small dry ice bath. Stirring was continued for 4 h. The flask was then packed into a dry ice box and left overnight. The reaction mixture was decomposed at room temperature by the addition, successively, of 4 mL of water, 3.5 mL of 15% sodium hydroxide solution, and 10 mL of water. The amorphous precipitate was filtered off and washed with 150 mL of diethyl ether and the washings were combined with the filtered ether phase. This was then distilled to dryness. The crude reduction mixture (19.0 g, 94%) contained 76.0% (−)-3-isothujanol, 16.2% (−)-3-neoisothujanol, 4.4% (+)-3-thujanol, and 2.5% (+)-3-neothujanol as determined by GLC.

(−)-3-Isothujyl 2,2,2-Trichloroethyl Carbonate (11). The preceding mixture (15.4 g, 0.1 mol) in 180 mL of pyridine was treated with 28 g (0.133 mol) of 2,2,2-trichloroethyl chloroformate (30 min, 10–20 °C). A lumpy precipitate formed but later disintegrated. Stirring was continued overnight at 20 °C. The mixture was quenched on ice (400 g) and extracted with 3 × 100 mL of benzene. The extract was washed, successively, with 3% hydrochloric acid, 5% sodium bicarbonate, and water. The residue obtained (32 g) after evaporation of benzene solidified upon cooling. The crude product was dissolved in hot methanol (70 mL) and left overnight at 0 °C. Filtration and washing (5 mL) gave 13.2 g (60% on (−)-3-isothujanol contained in reduction mixture) of pure carbonate **11**, mp 56 °C, single peak on GLC. Anal. Calcd for $C_{13}H_{19}Cl_3O_3$: C, 47.37; H, 5.81; Cl, 32.27. Found: C, 47.22; H, 5.84; Cl, 32.36.

(−)-3-Isothujanol (4). Carbonate **11** (32.9 g, 0.1 mol) dissolved in 600 mL of methanol and 25 mL of acetic acid was treated at reflux during 2 h with 150 g of zinc powder added in small portions. Reflux was continued for another 3 h. After cooling and settling the clear supernatant was decanted and the zinc was washed with methanol (400 mL). The combined methanol was evaporated and the residue was dissolved in 150 mL of methylene chloride. The solution was washed with 100 mL of 5% sodium bicarbonate and water (100 mL) and evaporated to dryness. Distillation gave 14.2 g (92%) of (−)-3-isothujanol, bp 50–52 °C (0.2 mm), mp 22 °C, $[\alpha]^{23}_D$ −9.0° (*c* 2, C_2H_5OH) [lit.[5] mp 22–23 °C, $[\alpha]^{20}_D$ −8.8° (*c* 1.3, C_2H_5OH)]. The alcohol was 99.5%+ by GLC. *p*-Nitrobenzoate mp 92 °C (lit.[6] mp 91–92 °C). This alcohol can be obtained by utilizing western red cedar leaf oil directly in the lithium aluminum hydride reduction. The (−)-3-isothujone (**1**) content should be around 90%. This can be achieved by removing low-boiling fractions by distillation through a short column. The starting material has to be dried, preferably by molecular sieve 4a for several days.

(+)-3-Thujanol (5) and (+)-3-Neothujanol (6). (+)-3-Thujone (**2**, 50 g, 0.33 mol) was reduced with 9.5 g (0.25 mol) of sodium borohybride in 500 mL of 2-propanol and 50 mL of water.[24] The reaction mixture was acidified with acetic acid to pH 6.5 and 350 mL of *i*-PrOH was distilled off in vacuo. The residue was diluted with 800 mL of a saturated sodium sulfate solution and extracted with 3 × 200 mL of methylene chloride. The solvent was evaporated. By GLC the residue contained 60% (+)-3-thujanol (**5**) and 40% (+)-3-neothujanol (**6**). Separation of the two alcohols was carried out on a column of alumina (4 × 130 cm, Woelm activity II). Neothujanol (**6**) was eluted first with cyclohexane–benzene (4:6, respectively). Thujanol (**5**) was eluted with cyclohexane–benzene (2:8, respectively). About 4 L of each solvent mixture was used. The solvents were evaporated and residual alcohols were distilled. (+)-3-Thujanol, bp 98–99 °C (14 mm), $[\alpha]^{23}_D$ +108° (*c* 2, $CHCl_3$) [lit.[5] bp 103 °C (16 mm), $[\alpha]_D$ +106.7° (neat)]. *p*-Nitrobenzoate, mp 78 °C (lit.[5] mp 78 °C). (+)-3-Neothujanol, bp 53–54 °C (0.3 mm), $[\alpha]^{23}_D$ +41.5° (*c* 2, $CHCl_3$) [lit.[7a] $[\alpha]_D$ +42.0° (*c* 1.8, $CHCl_3$)]. *p*-Nitrobenzoate, mp 89 °C (lit.[7a] mp 88–89 °C). Both alcohols were 99.5+% by GLC.

Repurification of Alcohols 3–6. Prior to their utilization in the NMR and kinetic measurement study all four alcohols were repurified by conversion into their *p*-nitrobenzoates;[5–7a] these were recrystallized to a constant melting point and hydrolyzed back to the alcohols, and the alcohols were distilled[5–7a] in vacuo. No impurities could be detected by GLC.

Other Alcohols. Cyclopentanol and cyclohexanol were obtained from commercial sources (Aldrich). *trans*-2-Methylcyclopentanol

(9) and isopinocampheol (12) were prepared by us previously.[65] *cis*-2-Methylcyclopentanol (10) was obtained on separating by column chromatography, in essence using the solvent system described above, a mixture of the cis and trans alcohols 9 and 10 resulting from a sodium borohydride reduction of 2-methylcyclopentanone. This was obtained by oxidizing *cis*-2-methylcyclopentanol using Brown's procedure.[21] All alcohols were repurified as *p*-nitrobenzoates, distilled, and evaluated by GLC. All showed less than 0.1% impurities. Melting and boiling points observed were in accord with the literature.

^{1}H NMR Chemical Shifts Induced by Eu(thd)$_3$ in Thujanols 3–6 and Methylcyclopentanols 9 and 10. In principle, the procedure of Demarco et al.[27] and Cockerill et al.[26] was followed. The alcohols were exactly weighed, about 20 mg ($1.0–1.5 \times 10^{-4}$ mol), and dissolved in 0.4 mL of dry deuteriochloroform to yield a solution ca. 0.3 M. A ground glass stoppered microtube was used. The weighed amount of purified (sublimation) Eu(thd)$_3$ was added to obtain molar ratios Eu(thd)$_3$/substrate of about 0.2, 0.4, and 0.55. This represents a range of 20–50 mg of reagent added. For each ratio studied a separate alcohol solution was used and duplicate runs were made for each ratio. After dissolution of the Eu complex the generally clear solution was filtered through a glass sinter filter into a NMR tube using nitrogen pressure. Spectra were measured on a Varian HA-100 instrument. The observed induced shifts for all protons were identified and plotted against the molar ratio Eu(thd)$_3$/substrate. For all protons there was very good linear relationship between the molar ratio and induced shift in the measured range. The gradient $G_{Eu(thd)_3}$ was established in the usual manner.[25a,b] Agreement between duplicate runs was ±5% or better.

Chromium Trioxide Oxidation of Alcohols. Oxidation rates were measured as described by Roček et al.[47] The thermostated cell holder of a Cary 15 recording spectrophotometer was kept at 25 ± 0.1 °C. Cells, 1 cm path, were placed in the holder about 30 min before measurement. All solutions to be used were kept in a thermostated bath at the same temperature. The substrate alcohol solutions were transfered into the cells about 15 min before reaction start. Chromic acid solution was introduced into the cell using a syringe which had been kept at 25 °C. The mixture in the cell was then gently stirred with the syringe to assure rapid homogenization. Subsequently, the time vs. absorption (350 nm) recording system was started and the absorption was recorded automatically. Acetic acid (90%) was prepared by diluting acetic acid (analytical grade, 900 mL) with distilled water to 1000 mL at 25 °C. Chromic acid (analytical grade, British Drug Houses) solutions were prepared no later than 3 h before each measurement. During this time the loss of chromic acid as determined spectrophotometrically was negligible. Concentration of substrate alcohols was in the $2–5 \times 10^{-3}$ M range. Concentration of chromium trioxide stock solutions was in the same range. Since only 0.2 mL was used for 4 mL of the alcohol substrate solution the alcohol excess was in the 15–30 times range. Excellent straight line plots were obtained for the log A vs. time relationship over the first 60–70% of the reaction. These were used for calculating the first-order rate constant k_1. Second-order rate constants were obtained from k_1 and the initial alcohol concentration. Each measurement was duplicated using the same stock solutions. A total of three stock solutions was made up for each alcohol with corresponding fresh chromium trioxide solutions. Thus, values in Table II represent an average of six measurements on three independently prepared solutions.

Acetic Anhydride–Pyridine Acetylation of Alcohols. Acetylation rates of alcohols 3–6, 9, 10, and 12 were determined exactly as discribed by Eliel and Lukach.[57] Equimolar quantities of acetic anhydride and alcohol were used. Concentrations were about 1×10^{-1} mol/L. Second-order rate constants were evaluated from slopes of best fit lines obtained by plotting reciprocal of acetic anhydride concentration vs. time following the approach of Buck et al.[59] Generally good linearity was observed to 80–90% of reaction completion. All reactions proceeded to at least 95% completion. Examination of products by GLC and ^{1}H NMR indicated that alcohol acetates were the only reaction products. Values in Table II are averages of three runs. The value obtained for cyclohexanol is in excellent agreement with that obtained by Eliel et al.[57] and Buck et al.[59] for the same compound.

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Registry No.—1, 546-80-5; 2, 471-15-8; 3, 21653-20-3; 4, 21653-18-9; 5, 7712-79-0; 6, 21653-19-0; 9, 25144-04-1; 10, 25144-05-2; 11, 61558-19-8; 12, 27779-29-9; 2,2,2-trichloroethyl chloroformate, 17341-93-4; cyclohexanol, 108-93-0; cyclopentanol, 96-41-3.

References and Notes

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(30) The LS reagent did not alter the substrate conformation since J did not change throughout the applied range of concentrations of Eu(thd)$_3$.[25a,b]
(31) The main condition allowing this assumption requires that θ of the McConnel–Robertson equation is in or below the 30–40° range.[25a,b] Inspection of models indicated that this condition was satisfied. A value of 3.0 Å for the distance Eu–O was used. Since Demarco et al.[32] have shown that in systems similar to ours Eu^{3+} tends to adopt a cis configuration to the geminal proton in the >CH–OH grouping we would expect that these angles could be actually much smaller.
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(40) We may note the striking similarity between cyclopentanone and the thujones, analogous to that between the methylcyclopentanols and thujanols.
(41) Our conclusion is in contrast with that of Tori[11] who proposed a boat form in both ketones with a dihedral angle of 30–40° between C2–C3 and C3–C4. Norin et al.[6] indicated a similar conformation.
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(51) The possibility that the cyclopropane methylene bridge as an additional substituent in position 3 (relative to OH) could contribute to the rate enhancement cannot be excluded. Rates of oxidation of the trans–cis pairs of alcohols **13–14**, **15–16**, and **17–18** are very similar within each pair. However, the question of an additive effect is open.
(52) We may use the same approach that we applied in estimating the effect of the *i*-Pr group in thujanol (**5**) and view the $-CH_2-$ bridge as remotely comparable to $-CH_3$. Then, *cis*-3-methylcyclopentanol (**14**) is oxidized 3.42 times faster than cyclopentanol.[50] This comes very close to the observed rate (5.31) for isothujanol (**4**), in which an additional effect of the neighboring methyl group will be present.
(53) An –OH group located at a conformationally mobile section of a five-membered ring, which itself is a part of a bicyclic system, can escape severe steric interactions through slight torsional adjustments when compared to an –OH group located at a rigid position of such a bicyclic system. A good example is the pair of alcohols **19** and **20**. The size of the molecule itself appears unimportant as shown by the rate of oxidation of alcohol **21**. Displacement of an OH group by only 0.3 Å is sufficient to reduce ground state interactions to ⅓ of their original magnitude.[43,44,54] This corresponds to about 12° in angular rotation, a value close to the 14° indicated for the torsional angle between C2–C3 (and C3–C4) by our LSR study.
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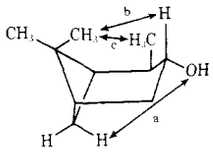
(55) Sen and Jones[56] proposed on the basis of a H^1 NMR study that in the analogous aminopinane the NH_2 group is pseudoequatorial. We assume an analogous conformation in isopinocampheol:



Dreiding models reveal strong steric interaction along b and c. Extent of the boatlike conformation is given by the balance of these two interactions. Oxidation will relieve b and (depending on the conformation of the resulting ketone) possibly c. Relief of the latter type is, to a degree, illustrated by comparing alcohols **22** and **23.**
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(61) Actually, a slight rate enhancement effect is present. Such effects, caused by remote alkyl groups, were observed in the cyclohexane series, e.g., **28** and **29** of Table IV. Effects of alkyl groups were discussed by Eliel.[57,58] Interpretation of results on the basis of axial and equatorial characteristics comparable to the cyclohexane series is not quite applicable. Rates of acetylation and their ratios in alcohols **9** and **10** in comparison to **24** and **25** are an example. Rates of acetylation of the two methylcyclopentanols **9** and **10** are very similar to the rates of the two methoxycyclopentanols **26** and **27**, Table IV.
(62) Actually, it would support the conformation of isopinocampheol as indicated in ref 55. There, the approach of Ac_2O along a would encounter little hindrance. However, the acetylation rate of **12** still remains obscure when it is compared with, e.g., *p*-*tert*-butylcyclohexanol (**30**).
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Synthetic Studies on Terpenoids. 5.[1] Syntheses of γ- and δ-Lactones from β-(2,7-Dimethyl-1,2-dihydroxycycloheptyl)propionic Acid[2]

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Starting from 2,7-dimethylcycloheptanone, the lactones VII, VIII, XIV, XVI, XX, and XXI have been synthesized and their conformation and stereochemistry studied. XVI represents the partial structure of IIa. VII and XXI represent the partial structures of III and IIc, respectively. Isomerization of δ-lactone to γ-lactone in the presence of acid has been discussed.

The γ-lactone moiety associated with sesquiterpene monolactones involves the isopropyl group. The other lactonic moiety in the recently discovered sesquiterpene dilactones,[3] which are again related to pseudoguaianolides (I), is formed through fission of the cyclopentane ring at a, viz., vermecrin[4] and greenein,[5] or at b, viz., psilostachyins[6] (IIa–c) and canambrin[7] (III). Experiments have been initiated in this laboratory and reported earlier[2] with a view to developing methods for building up stereospecifically different types of the lactonic functions associated with the cycloheptane ring. The compounds so formed may represent partial structures of IIa–c and III with defined stereochemical assignments at each of the three asymmetric centers present in some of these model compounds. Another aspect of interest is to study the relative rate of formation of different types of lactones, γ- and/or δ-, consistent with conformational stability of the highly mobile cycloheptane ring.

In a previous publication,[8] the lactone IV has been synthesized, its identity with one of the degradation products from xanthumin has been established, and its conformation has been discussed.

2,7-Dimethylcycloheptanone required for these studies was synthesized by two different methods. The condensation product from ethyl 6-bromohexanoate[9] and diethyl methylmalonate on hydrolysis and subsequent esterification afforded diethyl α-methylsuberate. This was also prepared through the fission of ethyl 2-methylcycloheptanone-2-carboxylate in the presence of a catalytic amount of sodium ethoxide.[10] The diester was subjected to cyclization according to modified high-dilution technique.[11] The cyclized product was methylated in situ to afford 2-ethoxycarbonyl-2-7-dimethylcycloheptanone and this on hydrolysis gave 2,7-dimethylcycloheptanone. The ketone was found by GC analysis to be a mixture (4:1) of two components. These were separated by