Synthetic Study of Pinguisane Terpenoids

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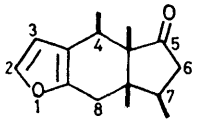
The synthesis of 7-*epi*-pinguisone (2) from (*S*)-(+)-2,3,7,7a-tetrahydro-7a-methylindene-1,5(6*H*)-dione (4) is described. The acylation of a carbanion derived from the conjugated addition of lithium dimethylcuprate to an αβ-unsaturated ketone is re-investigated. A new synthesis of condensed β-furanones is illustrated.

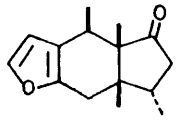
THE structurally novel compound pinguisone (1) is a component of the essential oil of *Aneura pinguis* L. Dum., a liverwort belonging to the genus *Hepaticae*. The isolation of this natural product was first reported in 1969 by Šorm *et al.*;[1] the structure and stereochemistry was determined by the same group of workers[2] and by our group.[3]

In 1973 the second natural substance belonging to the pinguisane group,[4] deoxypinguisone,[5] was isolated from the liverwort *Ptidilium ciliare* and its structure was determined by Herout *et al.*;[5] more recently new substances of the same group were isolated from the essential oils of *Porella* liverworts such as *Porella vernicosa*,[6] *P. densifolia*,[7,8] and *P. platyphylla*.[9]

Since these compounds have an unusual skeleton, are difficult to isolate from natural sources, and are required for biological tests,[10] we carried out stereoselective syntheses of pinguisone-like compounds. We report herein some of our experimental results and the total synthesis of 7-*epi*-pinguisone (2).



(1)



(2)

A careful analysis of the structure of pinguisone (1) reveals *a priori* a number of possible key reactions which might be used to construct the required bicyclic carbon skeleton. A Diels–Alder cycloaddition of a thiopyran[11] and 2,3,4-trimethylcyclopent-2-enone[12] gave poor results, reflecting the known, low reactivity or non-reactivity of αβ-dialkyl or αββ-trialkyl substituted αβ-unsaturated ketones.[13] For the same reason we rejected, too, approaches based both on a Diels–Alder reaction of *trans*-1-methoxy-3-trimethylsilyloxybuta-1,3-diene[14] and 2,3,4-trimethylcyclopent-2-enone and the photochemical cycloaddition of the latter to formylacetone.[15]

The approach which was finally adopted for the synthesis of compound (1) involved the diketone intermediate (4) which appeared to be easily accessible by stereo-controlled Robinson's annulation. This route had the advantage of utilizing readily available and inexpensive starting materials, but raised the problem of the stereospecific, stepwise introduction of the other three methyl groups on the same side of the indane skeleton.

RESULTS AND METHODS

The starting material chosen for the synthesis of the diketone (9) was the well known enedione (4), the (*S*)-(+)-enantiomer having been prepared, as reported by Hajos and Parrish,[16] from the triketone (3)[17] by an asymmetric aldol cyclization in the presence of a catalytic amount of (*S*)-(−)-proline. Since the bicyclic diketone (4) is synthesized from inexpensive compounds it is an obvious choice as the chiral synthon for the development of synthetic routes to some terpenoids. The absolute stereochemistry of pinguisane-like substances, ascertained by us,[3] requires the (*S*)-(+)-diketone (4) to be the enantiomer used for their synthesis.[18]

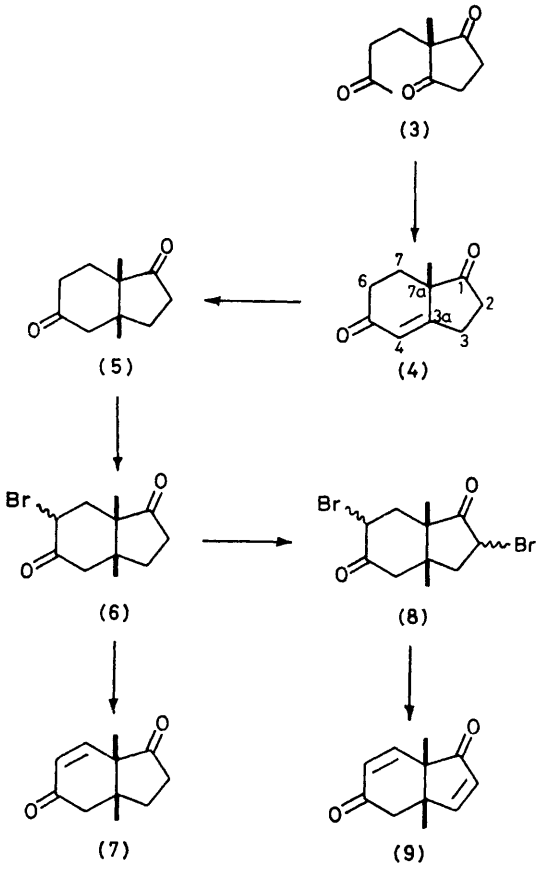
The introduction of the second angular methyl group into the 7a-methylindenedione (4) was accomplished by reaction with lithium dimethylcuprate.[19]

It is known that this reagent, as well as Grignard reagents in the presence of cuprous salts,[20] adds regio- and stereo-selectively to 4a-methyl-$\Delta^{1(8a)}$-2-octalones to give only the *cis*-4a,8a-dimethyl-2-decalones. Also, in the case of the diketone (4), the reaction with lithium dimethylcuprate at −25 °C is regio- and stereo-selective since only the *cis*-perhydroindenedione (5) was obtained in very high yields, organocuprates being relatively unreactive towards saturated ketones.[21]

Quenching of the enolate anion obtained by the conjugated addition of the reagent to compound (4) with acetyl chloride and the subsequent hydrolysis of the enol acetate[22] was not, in this case, more convenient and efficient than the direct conversion into the product using ammonium chloride quenching.[23] The structure (5) and the *cis*-junction between the six- and the five-membered rings are postulated on the basis of spectroscopic data and were demonstrated by *X*-ray analysis of the derivative (17). The i.r. spectrum of compound (5) shows absorptions at $\nu_{max.}$ 1 720 and 1 750 cm^{-1} typical of two carbonyl groups in the six- and five-membered rings and the ^1H n.m.r. spectrum shows two singlets at δ 1.05 and 1.04 assigned to two methyl groups on fully substituted carbons; moreover the c.d. of compound (5) is similar to a superimposition of the perhydro-*cis*-inden-1-one and -*cis*-inden-5-one c.d. curves.†

† An analysis of c.d. curves of these compounds and of others in the same series will be reported elsewhere.

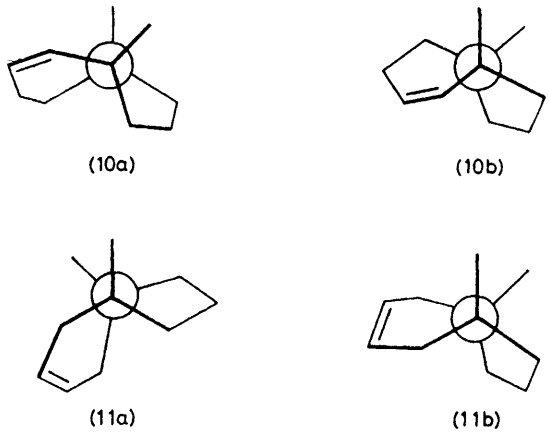
Reaction of the diketone (5) in acetic acid with an equimolecular amount of bromine gave, as the sole product, the bromo-derivative (6). Since the double bond in the six-membered ring is more stable than that in the five-membered ring and since the bromination



proceeds *via* the enol form,[24] it is obvious that the reaction takes place on the six- rather than on the five-membered ring; indeed, the reactivity at C-5 rather than at C-7 deserves further comment.*

Bromination of *cis*-4a,8a-dimethyl-2-decalone in an acidic medium [20a] affords the 3-, rather than the 1-bromo-derivative obtained from *cis*-4a-methyl-2-decalone and the 3-oxo-A/B-*cis*-steroids.[25] Application of the torsion angle concept [26] indicates that *trans*-2-decalone and *trans*-4a-methyl-2-decalone should be more stable as the Δ^2-enols rather than the Δ^1-enols; this prediction is in good agreement with experimental findings.[27] The reverse conclusion can be drawn for the *cis*-2-decalones for steric reasons and from theoretical calculations, even though the enthalpy differences between Δ^1- and Δ^2-enols are small and the interaction between the hydrogens are very difficult to estimate.[26] The differences between the pairs of enols in saturated *trans*- and *cis*-inden-2-ones seem to be more evident, the Δ^2-enol being the stable form for the *trans*-compound and the Δ^1-enol that for the *cis*-compound as shown by previous work.[28] Nevertheless, in the case of the diketone (5) the behaviour towards bromine is the reverse of that expected, but is similar to that of *cis*-4a,8a-dimethyl-2-decalone.

An analysis of stereo-models of *cis*-2,3,3a,6,7,7a-hexahydro- and *cis*-2,3,3a,4,7,7a-hexahydro-3a,7a-dimethyl-1*H*-indene [(10) and (11) respectively] reveals the existence of two stable conformations for each compound, in which the interaction between the two methyl groups is the lowest possible, the torsion angle being *ca.* 45°.



Whereas the indene (10) allows the six-membered ring to assume the half-chair conformation, the steric hindrance due to the five-membered ring and due to the C-9 methyl in (10a) and the C-8 methyl in (10b), from the α- and β-sides of the molecule respectively, are considerable obstacles to a reagent approaching C-1, from both the α- and β-sides. The indene (11) has the six-membered ring in a boat-like conformation, but the steric hindrance to attack by a reagent at C-3 is less severe.

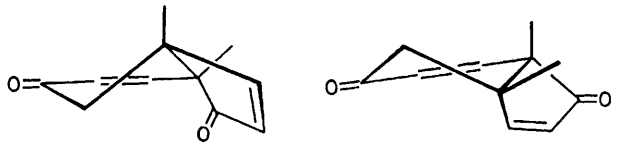
Dehydrobromination of the crude bromo-ketone (6) with calcium carbonate in dimethylacetamide [29] gave the indenedione (7). Attempts to obtain the same compound from the indene (5) with oxidants [30] or sulphur and selenium reagents,[31] gave either negative results or lower yields than the bromination–dehydrobromination procedure.

When the bromo-compound (6) was subjected to further bromination or the diketone (5) was brominated with an excess of reagent the dibromoindenedione (8) was obtained with complete regioselectivity as expected from the strong steric hindrance present in the six-membered ring. Dehydrobromination of the crude dibromo-compound (8) using the above mentioned procedure yielded the desired diene (9) contaminated by a small amount of the monoene (7). The i.r. and ^{1}H n.m.r spectra fully support the structure given, the i.r. spectrum showing absorption bands at $\nu_{max.}$ 1 725, 1 690, and 1 620 cm^{-1} due to αβ-unsaturated ketones in both the six- and five-membered rings. The signals due to the C-1 and C-2 protons appear as two clean doublets at δ

* In this paper C-*n* and C(*n*) refer to the numbering in the Figure (which is not the same as that of the IUPAC names).

7.48 and 6.05 with the typical coupling constant (J 6 Hz) of protons attached to a C=C bond in a five-membered ring, while the protons at C-4 and C-5 produced two clean doublets at δ 6.48 and 5.94 and have a coupling constant (J 10 Hz) as expected for protons attached to a C=C double bond in a six-membered ring; the two methyl groups at C-8 and C-9 gave singlets at δ 1.2 and 1.3 while the protons at C-7 gave a singlet at δ 2.57.

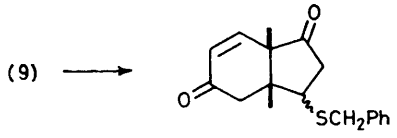
Dreiding models of the most stable conformations of the diene, (9a) and (9b), in which the torsion angle



(9a) (9b)

between the two methyl groups is *ca.* 45°, as in the structure of pinguisone,[3] and the influence of steric factors on conjugated addition to the two double bonds, do not easily explain the stereoselectivity of this reaction; the steric hindrance of the two rings on the α-side and that of the two methyl groups on the β-side of the molecule are approximately the same, though that of the C-9 methyl in (9a) and C-8 methyl in (9b) on an approaching reagent is considered more severe than the influence of the two rings.

In fact, preliminary experiments showed that conjugated addition of toluene-α-thiol to an equimolecular amount of the diene (9) afforded cleanly, and in high yield, a 45 : 55 mixture of the two diastereomers (12) as expected



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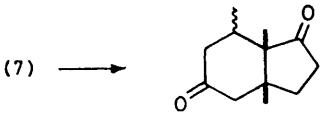


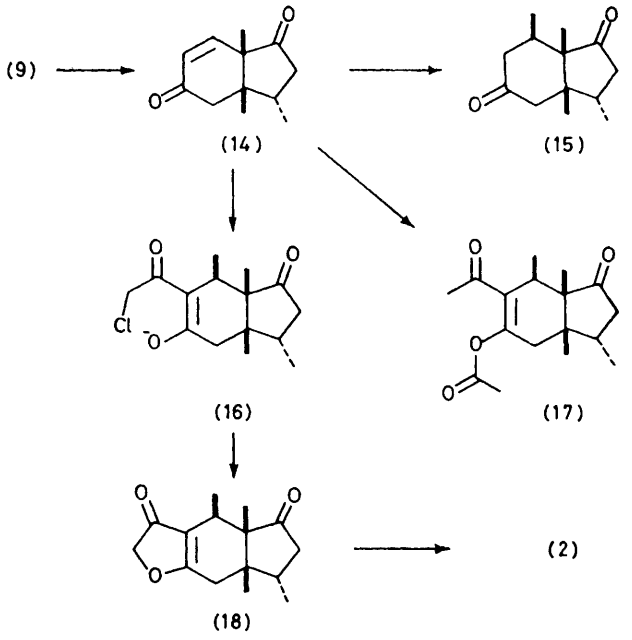
(13)

from the higher reactivity of the double bond in the five-membered ring. On the other hand, the reaction of the monoene (7) with lithium dimethylcuprate did not show a high degree of stereoselectivity, a 2 : 3 mixture of the diastereoisomers (13) being obtained.

However, conjugated methylation of the diene (9) with an equimolecular amount of lithium dimethylcuprate in ether gave only one diastereoisomer, the bulkiness of the reagent in this case evidently controlling the stereoselectivity of the reaction.

Having successfully introduced a third methyl group into the indene skeleton stereoselectively, compound (14) was treated with an excess of lithium dimethylcuprate. The reaction was sterically controlled and regiospecific and gave the indenedione (15), which has four methyl groups on four contiguous carbon atoms, in very high yield. On quenching the carbanion resulting from this methylation of (14) with acetyl chloride, compound (17) was obtained, presumably *via* a regioselective acylation at C-5 and a subsequent acylation of the intermediate β-diketone.

The structure and the stereochemistry of the product (17) were confirmed by i.r., u.v., ^{1}H n.m.r., ^{13}C n.m.r., and mass spectroscopy which were compatible with the data obtained from compound (14) and pinguisone.[3] The i.r. spectrum showed absorptions at $\nu_{max.}$ 1 760, 1 740, and 1 660 cm^{-1} indicating a carbonyl group attached to a



(14) (15) (16) (17) (18) (2)

five-membered ring and an acylated enolic form of a β-diketone;[32] the ^{1}H n.m.r. spectrum displayed two sharp singlets at δ 0.78 and 0.83 due to the angular methyl groups, two doublets (J 7 Hz) at δ 0.7 and 0.96 due to the methyl groups at C-1 and C-4, two sharp singlets at δ 2.03 and 1.68 due to the acetyl and the acetoxy-groups, respectively,[32] and a quadruplet at δ 3.4 (J 7 Hz) due to the proton at C-4. Absorption at $\lambda_{max.}$ 252 nm in the u.v. spectrum confirmed the presence of an acylated β-diketone system. The high field resonance (δ 0.7) of one secondary methyl group in comparison with the values obtained for pinguisone [2] (secondary methyl groups appear as doublets at δ 1.01 and 1.09) is presumably due to the α-configuration of the methyl at C-1 and the influence of the double bond on it.

The structure and the stereochemistry of (17) were confirmed by X-ray analysis; the Figure shows the molecular shape and numbering scheme used for the analysis, while bond distances and angles involving no hydrogens are given in Table 2. The C–H bond lengths

are in the range 0.89—1.06 Å (mean 0.99 Å) while bond angles involving hydrogens vary between 101(2) for H(7A)–C(7)–H(7B) and 118(2)° for H(12A)–C(12)–H(12C).

The Figure shows that the junction between the two rings is *cis*; on the other hand, comparison of the molecular structure of (17) with that of pinguisone (1) [3] indicates

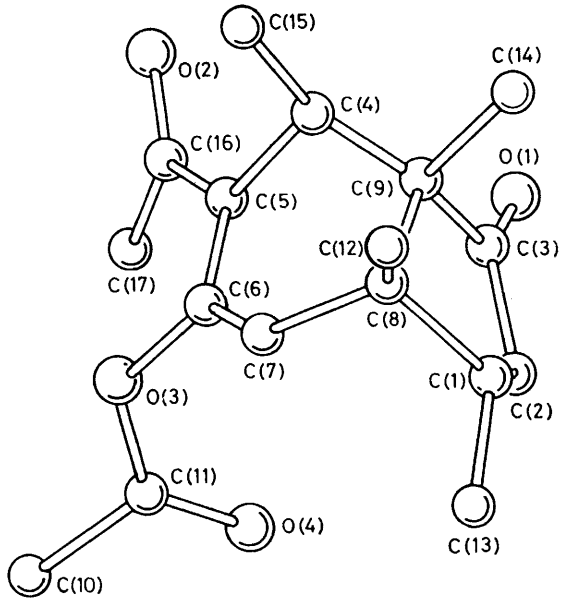


FIGURE The molecular structure of compound (17). For the sake of clarity, the hydrogen atoms are omitted

that the two common frameworks exhibit a different configuration at C-1. As inferred from the values of the torsion angles (Table 3), in the natural product the hydrogen at C-1 is *trans* with respect to the methyl group at C-8, while in (17) a *cis*-configuration is present; this implies that in pinguisone the carbon atoms C-12 and C-13, 2.973(6) Å apart, lie on the same side with respect to the plane defined by the atoms C-1, C-8, and C-9 while in compound (17) the two methyl groups lie on opposite sides and their distance is increased to 3.228(3) Å. The corresponding strain release reflects in the variation of the C(1)–C(8) bond length, 1.559(2) Å in (17) *vs.* 1.583(4) Å in (1).

It is evident that the overall configuration of the two frameworks is primarily dictated by interactions between the methyl groups bound to adjacent carbons. Therefore, it is to be expected that different steric relationships across the C(1)–C(8) single bond will induce different arrangements of the three methyl groups, which are mutually *cis*, and hence different conformations of the two rings. In fact, the torsion angles between the methyl groups across the bonds C(8)–C(9) and C(9)–C(4) have not only different absolute values in the two compounds, but also different signs (see Table 3). Consequently, the conformation of the six-membered ring, which is of the half-chair type in pinguisone, is boat-like in compound (17) (see the Figure). Furthermore, the distance between C-14 and C-15 is larger in (17)

TABLE 1

Atomic co-ordinates for compound (17)

Atom	*X*	*Y*	*Z*
C(1)	52 483(28)	23 401(20)	21 164(7)
C(2)	39 457(30)	36 494(22)	21 401(7)
C(3)	27 753(24)	35 204(19)	16 435(7)
C(4)	35 964(26)	30 373(18)	6 803(7)
C(5)	47 582(25)	44 357(18)	6 774(6)
C(6)	63 300(24)	44 222(18)	9 567(6)
C(7)	70 226(25)	31 048(21)	12 558(7)
C(8)	55 538(23)	20 541(17)	15 004(6)
C(9)	35 991(23)	23 680(17)	12 557(6)
C(10)	96 578(35)	73 655(27)	12 266(12)
C(11)	80 742(27)	63 678(21)	13 415(8)
C(12)	62 585(33)	4 725(21)	14 219(8)
C(13)	69 542(36)	25 239(29)	24 713(9)
C(14)	22 981(31)	10 315(22)	12 820(9)
C(15)	42 059(36)	19 834(25)	2 301(8)
C(16)	41 034(29)	56 791(21)	3 315(7)
C(17)	45 450(41)	72 467(26)	4 714(13)
O(1)	13 633(21)	41 927(18)	15 521(7)
O(2)	31 237(30)	54 138(20)	−563(7)
O(3)	76 211(17)	55 639(14)	8 972(5)
O(4)	72 489(27)	62 772(20)	17 555(7)
H(1)	4 540(33)	1 438(27)	2 246(8)
H(2A)	4 634(34)	4 625(27)	2 124(8)
H(2B)	3 230(37)	3 647(28)	2 454(10)
H(4)	2 305(28)	3 294(21)	618(7)
H(7A)	7 766(39)	2 543(28)	1 003(10)
H(7B)	7 919(34)	3 381(24)	1 516(9)
H(10A)	9 379(53)	8 043(42)	905(13)
H(10B)	9 813(61)	7 949(44)	1 556(16)
H(10C)	10 756(66)	6 821(51)	1 159(16)
H(12A)	6 372(34)	305(26)	1 015(9)
H(12B)	7 473(36)	371(25)	1 600(9)
H(12C)	5 452(35)	−234(28)	1 639(10)
H(13A)	6 608(34)	2 582(25)	2 863(10)
H(13B)	7 862(39)	1 635(33)	2 400(10)
H(13C)	7 573(31)	3 440(27)	2 393(8)
H(14A)	2 819(35)	185(29)	1 049(10)
H(14B)	2 180(35)	664(28)	1 667(10)
H(14C)	1 034(38)	1 292(28)	1 168(10)
H(15A)	5 459(50)	1 585(36)	299(12)
H(15B)	3 292(40)	1 120(33)	221(11)
H(15C)	4 188(34)	2 500(29)	−116(11)
H(17A)	4 441(41)	7 358(32)	854(13)
H(17B)	5 767(53)	7 477(42)	348(13)
H(17C)	3 783(52)	7 838(43)	291(15)

than in pinguisone [3.006(3) *vs.* 2.954(6) Å, respectively], while that between C-12 and C-14 is slightly shorter in the former than in the latter compound [2.934(3) in (17) *vs.* 2.956(6) Å in pinguisone].

As expected, and already outlined in the case of the interaction between C-12 and C-13, in both structures too short a contact between the vicinal methyl groups is prevented by a lengthening of the C–C bond between the carbon atoms to which these groups are bonded. Thus, the C(4)–C(9) bond distance, 1.545(2) Å in (17) is as long as 1.589(4) Å in pinguisone, while the values of the C(8)–C(9) bond length are 1.566(2) and 1.539(4) Å, respectively. The above-mentioned geometrical parameters indicate that structure (17), even if less strained than pinguisone, still possesses significant steric hindrance. This is also shown by the considerable distortions occurring at the angles C(6)–C(7)–C(8), 117.0(2), C(8)–C(9)–C(4), 115.3(1)°, and C(3)–C(9)–C(14), 105.7(1)°.

In contrast with previous reports [33] on the acylation of αβ-unsaturated ketones using lithium dimethylcuprate, it has recently been demonstrated [34] that this reaction, in solvents of low polarity, gives *C*-acylation rather than

TABLE 2

Molecular geometry (with standard deviations in parentheses) of compound (17)

(*a*) Bond lengths (Å)

C(1)–C(2)	1.517(3)	C(1)–C(13)	1.524(3)
C(2)–C(3)	1.496(3)	C(3)–O(1)	1.212(2)
C(3)–C(9)	1.537(2)	C(9)–C(14)	1.536(3)
C(9)–C(4)	1.545(2)	C(4)–C(15)	1.530(3)
C(4)–C(5)	1.521(2)	C(5)–C(16)	1.491(3)
C(5)–C(6)	1.331(2)	C(16)–C(17)	1.496(3)
C(6)–C(7)	1.490(3)	C(16)–O(2)	1.216(3)
C(7)–C(8)	1.550(2)	C(6)–O(3)	1.402(2)
C(8)–C(9)	1.566(2)	O(3)–C(11)	1.357(2)
C(8)–C(1)	1.559(2)	C(11)–C(10)	1.488(3)
C(8)–C(12)	1.533(3)	C(11)–O(4)	1.187(3)

(*b*) Bond angles (°)

C(8)–C(1)–C(2)	104.8(1)	C(9)–C(3)–O(1)	123.6(2)
C(1)–C(2)–C(3)	105.1(2)	C(3)–C(9)–C(4)	107.8(1)
C(2)–C(3)–C(9)	110.1(2)	C(3)–C(9)–C(14)	105.7(1)
C(3)–C(9)–C(8)	103.5(1)	C(4)–C(9)–C(14)	110.3(1)
C(8)–C(9)–C(4)	115.3(1)	C(8)–C(9)–C(14)	113.3(1)
C(9)–C(4)–C(5)	109.3(1)	C(9)–C(4)–C(15)	115.0(1)
C(4)–C(5)–C(6)	117.6(2)	C(5)–C(4)–C(15)	110.9(2)
C(5)–C(6)–C(7)	123.5(2)	C(4)–C(5)–C(16)	117.1(2)
C(6)–C(7)–C(8)	117.0(2)	C(6)–C(5)–C(16)	125.2(2)
C(7)–C(8)–C(9)	111.0(1)	C(5)–C(16)–O(2)	119.2(2)
C(9)–C(8)–C(1)	102.6(1)	C(5)–C(16)–C(17)	121.1(2)
C(7)–C(8)–C(12)	107.2(2)	C(17)–C(16)–O(2)	119.6(2)
C(1)–C(8)–C(12)	109.0(1)	C(5)–C(6)–O(3)	120.6(1)
C(7)–C(8)–C(1)	112.1(1)	C(6)–O(3)–C(11)	118.2(1)
C(9)–C(8)–C(12)	115.0(1)	O(3)–C(11)–C(10)	111.0(2)
C(8)–C(1)–C(13)	117.7(2)	C(10)–C(11)–O(4)	126.5(2)
C(2)–C(1)–C(13)	113.4(2)	O(4)–C(11)–O(3)	122.5(2)
C(2)–C(3)–O(1)	126.3(2)	O(3)–C(6)–C(7)	114.7(1)

TABLE 3

Selected torsion angles (°) of (17) and of pinguisone (ref. 3)

	(17)	Pinguisone
C(8)–C(1)–C(2)–C(3)	31.1(2)	11.4
C(1)–C(2)–C(3)–C(9)	−12.3(2)	−17.2
C(2)–C(3)–C(9)–C(8)	−11.2(2)	38.9
C(3)–C(9)–C(8)–C(1)	29.4(2)	−43.8
C(9)–C(8)–C(1)–C(2)	−37.8(2)	34.6
C(8)–C(9)–C(4)–C(5)	−55.1(2)	47.3
C(9)–C(4)–C(5)–C(6)	40.7(2)	−22.7
C(4)–C(5)–C(6)–C(7)	1.7(3)	0.3
C(5)–C(6)–C(7)–C(8)	−32.0(3)	−3.2
C(6)–C(7)–C(8)–C(9)	14.9(2)	30.6
C(7)–C(8)–C(9)–C(4)	27.0(2)	−54.1
C(12)–C(8)–C(1)–C(13)	72.9(2)	42.3
C(12)–C(8)–C(1)–H(1)	−47.2(14)	162.6
C(12)–C(8)–C(9)–C(14)	33.6(2)	−48.9
C(14)–C(9)–C(4)–C(15)	−59.5(2)	43.9

O-acylation in high yields, and the successful synthesis of (17) is a good example of this.

As a consequence, we tried to trap the enolate anion of the last methylation step with chloroacetyl chloride; as expected, *C*-acylation occurred, but the intermediate anion (16) did not react with the excess acid chloride and, in the presence of an excess of cuprate, afforded a β-furanone system *via* an intramolecular cyclization. In fact, the absorption bands due to the carbonyl group in the five-membered ring and due to the β-furanone system [35] which occur at $\nu_{max.}$ 1 740, 1 700, and 1 640 cm^{-1} are present in the i.r. spectrum of compound (18), the product of the reaction, while its u.v. spectrum shows a maximum at λ 260 nm and its ^1H n.m.r. spectrum, besides other signals, shows a broad singlet at δ 4.42 (2 H) attributable to protons bonded to C-11; all the data are in accord with the assigned structure.[35]

While the reduction of compound (18) with sodium borohydride affected not only the β-furanone system but, partially, also the carbonyl group in the five-membered ring, the reduction with a more bulky hydride, such as borabicyclononane (9-BBN) [36] was fully regioselective. Thus, treatment of compounds (18) with 9-BBN directly afforded 7-*epi*-pinguisone (2); evidently the reagent attacks the less hindered carbonyl at C-10 and the intermediate complex spontaneously eliminates borinic acid, presumably because of its bulkiness.

Introduction of the third methyl group at C-1 and of the fourth methyl group at C-4, and the formation of the β-furanone ring in one step, allows the synthesis of optically active 7-*epi*-pinguisone (2) to be achieved in few steps with very high stereoselectivity. The technique involving the quenching of an enolate with chloroacetyl chloride is a new method for the synthesis of furan derivatives and we are now investigating its application to the synthesis of natural products.

The described synthesis of 7-*epi*-pinguisone is applicable, with suitable variations, to pinguisone-like substances and to pinguisone itself, as will be described in a later paper.

EXPERIMENTAL

M.p.s were determined with a Kofler block apparatus and are uncorrected. I.r. spectra were obtained for solutions in chloroform (unless otherwise indicated) with a Perkin-Elmer 257 spectrophotometer. U.v. spectra were obtained for iso-octane solutions on a Cary 118 spectrophotometer. ^1H and ^{13}C N.m.r. spectra were recorded for deuteriochloroform solutions with a Varian XL 100 instrument ($SiMe_4$ as internal standard). The atom numbers used in the spectroscopic assignments refer to those shown in the crystallographic Figure and *not* to those given in the systematic name. Mass spectra were obtained on a Varian-Mat 112 spectrometer. Optical rotations were measured for benzene solutions with a Perkin-Elmer 141 polarimeter. Microanalysis were carried out in the microanalytical laboratory of our Department using a Perkin-Elmer 240 instrument. *X*-Ray analysis was performed using a four-circle Syntex diffractometer. Light petroleum refers to the fraction of b.p. 40—60 °C. Solutions were dried over sodium sulphate and solvents dried by standard procedures. All evaporations were carried out with a rotary evaporator under reduced pressure.

(+)-(3a*R*,7a*S*)-*Perhydro*-3a,7a-*dimethylindene*-1,5-*dione* (5).—A solution of methyl-lithium in diethyl ether (66.5 ml; 2M) was added in drops to a magnetically stirred mixture of cuprous iodide (12.7 g, 66.5 mmol) and anhydrous ether at −25 °C (solid CO_2–carbon tetrachloride). On completion of the reaction a small amount of cuprous iodide was added until a yellow precipitate appeared and then a solution of the enone (4)[16] (4.15 g, 25.3 mmol) in anhydrous diethyl ether (225 ml) was added in drops during 20 min. After 1 h at −25 °C, the reaction mixture was brought to room temperature and then poured into a saturated solution of ammonium chloride (300 ml). The ethereal layer was separated and the water phase was extracted three times

with diethyl ether. The combined extracts were washed with diluted ammonium chloride and then with water. Evaporation of the solvent afforded a crude product (4.25 g) which, after purification by silica gel chromatography (ether as eluant) and crystallization from di-isopropyl ether–iso-octane, gave pure (+)-(3a,R,7aS)-3a,7a-*dimethylindan*-1,5-*dione* (5) (3.7 g, 81.3%), m.p. 175 °C (exothermic process before melting); $[\alpha]_D^{25}$ 49.9 (*c* 1); $\nu_{max.}$ 1 750 and 1 720 cm^{-1}; δ_H 2.44 (2 H, t, *J* 7.5 Hz, 5-H), 2.22 (2 H, s, 7-H), 1.82 (2 H, t, *J* 7.5 Hz, 4-H), 1.05 (3 H, s, Me), and 1.04 (3 H, s, Me); δ_C 219.394 (s, C-3), 209.911 (s, C-6), 22.493 (q, C-14), and 17.420 (q, C-12); *m/e* 180 (M^+, 43%), 165 (12), 123 (77), 110 (100), 96 (65), and 82 (93) (Found: C, 73.3; H, 8.8. $C_{11}H_{16}O_2$ requires C, 73.33; H, 8.88%).

(+)-(3aR,7aS)-2,3,3a,7a-*Tetrahydro*-3a,7a-*dimethylindene*-1,5(4H)-*dione* (7).—A solution of bromine in acetic acid (5.53 ml, 1M) was added dropwise during 20 min to a magnetically stirred solution of the dione (5) (1 g, 5.53 mmol) in acetic acid (12 ml) at 5 °C. The cooled reaction mixture was neutralized by adding drops of aqueous sodium hydroxide (10%) and was then extracted with diethyl ether. The organic phase, washed with sodium hydrogencarbonate solution and water, and then dried gave, after evaporation, the crude monobromo-diketone (6) (1.46 g) which was immediately dehydrobrominated.

Calcium carbonate (0.583 g) was added in portions to a magnetically stirred solution of the crude brominated product (1.46 g) in anhydrous dimethylacetamide. The mixture was refluxed during 30 min, then cooled and filtered. The solid was thoroughly washed with ether and the combined organic solutions were diluted with water and extracted several times with ether. The extract was washed with water and brine, dried, and gave, after evaporation, the crude dione (7) (0.8 g) which was purified by silica-gel chromatography. Elution with light petroleum–ether (6 : 4) afforded the pure *compound* (7) (0.65 g, 66.0%) which was crystallized from iso-octane and sublimed (45 °C/0.8 mmHg), m.p. 75.3 °C, $[\alpha]_D^{25}$ 555.6 (*c* 1); $\nu_{max.}$ 1 750, 1 690, and 1 625 cm^{-1}; $\lambda_{max.}$ 214 nm (log ε 3.90); δ_H 6.40 (1 H, d, *J* 10 Hz, 4-H), 6.04 (1 H, d, *J* 10 Hz, 5-H), 2.44 (2 H, s, 7-H), 2.40 (2 H, m, 2-H), 1.86 (2 H, m, 1-H), 1.17 (3 H, s, Me), and 1.07 (3 H, s, Me); δ_C 217.118 (s, C-3), 197.727 (s, C-6), 149.118 (d, C-4), 128.646 (d, C-5), 23.479 (q, C-14), and 17.075 (q, C-12); *m/e* 178 (M^+, 60%), 163 (14), 136 (60), 108 (100), 91 (82), and 79 (37) (Found: C, 74.05; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.86%).

(+)-(3aR,7aS)-3a,7a-*Dihydro*-3a,7a-*dimethylindene*-1,5(4H)-*dione* (9).—As for compound (7), a solution of the diketone (5) (3.0 g, 16.6 mmol) in acetic acid (35 ml) and a solution of bromine in acetic acid (33.2 ml; 1M) gave a crude mixture of the 5-bromo-diketone (6) and the 2,5-dibromo-diketone (8) (6.0 g). The crude mixture (6.0 g) was immediately dehydrobrominated with calcium carbonate (3.5 g) and dimethylacetamide (100 ml). After refluxing during 2 h and work-up as described for (7), a mixture of the monoene (7) and the diene (9) was obtained and this was separated by silica-gel chromatography. Elution with light petroleum–ether (6 : 4) gave the pure diones (7) (0.32 g, 10.8%) and (9) (1.5 g, 51.4%) with an overall conversion of 62.3%. The *diene* (9) crystallized from di-isopropyl ether–iso-octane, m.p. 92.5 °C, $[\alpha]_D^{25}$ 47.2 (*c* 1); $\nu_{max.}$ 1 725, 1 690, and 1 620 cm^{-1}; δ_H 7.48 (1 H, d, *J* 6 Hz, 1-H), 6.48 (1 H, d, *J* 10 Hz, 4-H), 6.02 (1 H, d, *J* 6 Hz, 2-H), 5.94 (1 H, d, *J* 10 Hz, 5-H), 2.57 (2 H, s, 7-H), 1.30 (3 H, s, Me), and 1.20 (3 H, s, Me); δ_C 209.523 (s, C-3), 196.185 (s, C-6), 169.074 (d, C-1), 151.601 (d, C-4), 128.372 (d, C-2), 127.589 (d, C-5), 26.761 (q, C-14), and 16.745 (q, C-12); *m/e* 176 (M^+, 56%), 134 (56), 133 (20), 106 (100), 91 (74), and 79 (40) (Found: C, 74.95; H, 6.8. $C_{11}H_{12}O_2$ requires C, 75.00; H, 6.82%).

Reactions of the Monoene (7) *and the Diene* (9).—The reaction of the monoene (7) with lithium dimethylcuprate, under the same conditions as described for the preparation of compound (5), gave a mixture of the two methylated epimers (13) which was not separated, but directly examined by ^1H n.m.r. spectroscopy. The ratio between the two isomers was calculated on the basis of the ratio of couples of corresponding methyl groups.

Toluene-α-thiol (0.1 mmol) was added to a solution of the diene (9) (0.1 mmol) in tetrahydrofuran (THF) buffered at pH 9 with sodium tetraborate (0.1M). After being stirred for 2 h at room temperature the mixture was treated to the usual work-up to give a crude mixture of the two epimeric 3-benzylthio-compounds (12); this was not separated, but was directly examined by ^1H n.m.r. spectroscopy. The ratio between the two isomers was calculated on the basis of the ratio of two singlets at δ 3.80 and 3.88 (benzylic hydrogens).

(+)-(3S,3aS,7aS)-2,3,3a,7a-*Tetrahydro*-3,3a,7a-*trimethylindene*-1,5(4H)-*dione* (14).—A solution of methyllithium in ether (10.6 ml; 2M) was added in drops to a magnetically stirred mixture of cuprous iodide (2.02 g, 10.6 mmol) and anhydrous ether (60 ml) at −35 °C. On completion of the reaction, a solution of the diene (9) (1.25 g, 7.1 mmol) in anhydrous ether (60 ml) was added during 15 min; after 1 h at −35 °C, the reaction mixture was brought to room temperature and then poured into saturated ammonium chloride (50 ml). The ethereal layer was separated and the water phase extracted three times with ether. The combined extracts, washed successively with dilute ammonium chloride and water, were then dried and evaporated to give the crude product (2.2 g) which was purified by silica-gel chromatography. Elution with light petroleum–ether (8 : 2) gave the pure *dione* (14) (1.3 g, 95.6%) (after crystallization from di-isopropyl ether–iso-octane), m.p. 120—121 °C (73—75 °C at first melting), $[\alpha]_D^{25}$ 315.2 (*c* 1); $\nu_{max.}$ 1 740, 1 690, and 1 630 cm^{-1}; $\lambda_{max.}$ 242 nm (log ε 3.60); δ_H 6.57 (1 H, d, *J* 10 Hz, 4-H), 6.00 (1 H, d, *J* 10 Hz, 5-H), 2.21 (2 H, s, 7-H), 1.20 (3 H, s, Me), 1.06 (3 H, s, Me), and 1.02 (3 H, d, *J* 6.2 Hz, 13-H); δ_C 216.404 (s, C-3), 198.143 (s, C-6), 149.664 (d, C-4), 127.974 (d, C-5), 19.673 (q, C-14), 19.156 (q, C-12), and 12.759 (q, C-13); *m/e* 192 (M^+, 11%), 135 (8), 123 (100), 107 (52), 94 (40), 79 (36), 77 (21), and 69 (35) (Found: C, 74.95; H, 8.3. $C_{12}H_{16}O_2$ requires C, 75.00; H, 8.33%).

(+)-(3S,3aS,7S,7aS)-5-*Acetoxy*-6-*acetyl*-2,3,3a,4,7,7a-*hexahydro*-3,3a,7,7a-*tetramethylinden*-1-*one* (17).—To a solution of lithium dimethylcuprate prepared, as described before, from methyl-lithium in ether (4.91 ml; 2M) and cuprous iodide (0.936 g, 4.91 mmol), a solution of the diene (9) (0.35 g, 1.82 mmol), in anhydrous ether was added at −25 °C during 5 min. After 1 h at −25 °C, the reaction mixture was brought to room temperature; after a further hour, acetyl chloride (1.79 g, 22.8 mmol) in anhydrous ether (12 ml) was added during 30 min. The reaction mixture was left at room temperature for 30 min during which time the yellow colour gradually disappeared. The mixture was then poured into concentrated ammonia–crushed ice (v/w 1 : 2) and extracted three times with cold ether. The combined extracts were washed with cold diluted ammonia and water, and then dried and evaporated to give a crude

product (0.391 g) which was purified by chromatography on 60—100 mesh Florisil. Elution with light petroleum–ether (6 : 4) and crystallization from di-isopropyl ether gave the pure *ketone* (17) (0.35 g, 65.8%), m.p. 125—126 °C, $[\alpha]_D^{25}$ 84.6 (*c* 1); $\nu_{max.}$ 1 760, 1 740, and 1 660 cm^{-1}; $\lambda_{max.}$ 252 nm (log ε 3.88); δ_H 3.40 (1 H, q, *J* 7 Hz, 4-H), 2.03 (3 H, s, 11-H), 1.68 (3 H, s, Me–CO_2), 0.96 (3 H, d, *J* 7 Hz, 15-H), 0.7 (3 H, d, *J* 7 Hz, 13-H), 0.78 (3 H, s, 14-H), and 0.83 (3 H, s, 12-H); δ_C 220.057 (s, C-3), 196.238 (s, C-10), 168.714 (s, O–CO–), 152.142 (s, C-6), 130.628 (s, C-5), 55.394 (s, C-9), 44.075 (s, C-8), 42.883 (t, C-2), 37.817 (d, C-1), 36.030 (d, C-4), and 33.408 (t, C-7); *m/e* 292 (M^+, 2%), 250 (11), 232(10), 207 (6), 180 (14), 175 (9), 167 (9), and 125 (100) (Found: C, 69.8; H, 8.2. $C_{17}H_{24}O_4$ requires C, 69.86; H, 8.22%).

X-*Ray Crystal Structure Determination of* (+)-(3S,3aS,7S,7aS)-5-*Acetoxy*-6-*acetyl*-2,3,3a,4,7,7a-*hexahydro*-3,3a,7,7a-*tetramethylinden*-1-*one* (17).—$C_{17}H_{24}O_4$, M = 292.4. Orthorhombic, a = 7.245 (2), b = 9.058 (2), c = 24.693 (7) Å, U = 1 690.4 Å^3, Z = 4, D_m = 1.195, D_c = 1.197 g cm^{-3}, $F(000)$ = 632, space group $P2_12_12_1$, Cu-K_α radiation, λ = 1.5418 Å; μ(Cu-K_α) = 6.9 cm^{-1}.

Intensity data were obtained for a crystal of dimension *ca.* 0.40 × 0.45 × 0.13 mm, mounted on a computer-controlled four-circle diffractometer, equipped with a graphite monochromator, and using a variable rate θ–2θ scan technique. Background measurements were taken at both ends of the scan range, each for a time equal to one-half of the scan time. Three standard reflections were checked after every 50 intensity measurements; they showed no appreciable trend. In the range of measurements ($2\theta_{max.}$ 135°) 1 704 independent reflections were collected, of which 1 689, having scan count greater than background, were treated as observed. Each reflection was assigned a variance of $\sigma^2(I) = \sigma^2(I)_{c.s.} + (0.03S)^2$, where S is the scan count. The intensities and their standard deviations were corrected for Lorentz and polarization effects, but not for absorption.

The structure was solved by MULTAN.[37] All but one of the non-hydrogen atoms were derived from the *E*-map corresponding to the solution with the highest combined figure of merit; the remaining carbon atom was located from a subsequent difference map. The positions of all 24 hydrogen atoms were obtained from difference syntheses during the course of the refinement, which was by full-matrix least-squares minimization of the quantity $\Sigma\, w(|F_o| - |F_c|)^2$, with weights $w = 4F_o^2/\sigma^2(F_o^2)$ (w = 0 for the 15 unobserved reflections).

Final least-squares cycles included 287 parameters in a single matrix, co-ordinates and anisotropic temperature coefficients b_{ij} for the carbon and oxygen atoms, co-ordinates and isotropic B values for the hydrogen atoms, a scale factor, and a secondary extinction coefficient.[38] The final R was 0.0317 for the 1 689 observed reflections (0.0321 including unobserved); the final value of the extinction parameter was 13(3) × 10^{-6}. Atomic-form factors for carbon and oxygen were from ref. 39 and for hydrogen from ref. 40. Positional parameters are listed in Table 1; hydrogen atoms are numbered according to the carbon atoms to which they are attached. Final observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 23018 (13 pp.).*

(+)-3(2H)-*Oxo*-7-epi-*pinguisone* (18).—To a cold (−25 °C) solution of lithium dimethylcuprate (2.34 mmol) in anhydrous ether (15 ml), prepared as previously described from cuprous iodide (0.446 g) and methyl-lithium in ether (2.34 ml, 2M), a solution of the enedione (14) (0.157 g, 0.87 mmol) in anhydrous ether (10 ml) was added in drops during 5 min. After being stirred at −25 °C for 1 h, the reaction mixture was brought to room temperature. A solution of chloroacetyl chloride (10.8 mmol) in anhydrous ether (8 ml) was then added to it during 5 min. After 30 min at room temperature the yellow colour gradually disappeared. The mixture was poured into concentrated ammonia–crushed ice (v/w 1 : 2) and extracted three times with ether. The combined extracts were washed with cold diluted ammonia and water, and then dried. Evaporation gave a crude product (0.190 g), which was purified by silica-gel chromatography. Elution with light petroleum–ether (6 : 4) and crystallization from di-isopropyl ether gave pure (+)-3(2H)-oxo-7-*epi*-pinguisone (18) (0.158 g, 73.4%), m.p. 152—153 °C, $[\alpha]_D^{25}$ +83.1 (*c* 1); $\nu_{max.}$ 1 740, 1 700, and 1 640 cm^{-1}; $\lambda_{max.}$ 260 nm (log ε 3.97); δ_H 4.42 (2 H, br s, 11-H), 3.40 (1 H, q, *J* 7 Hz, 4-H), 1.21 (3 H, s, Me), 1.08 (3 H, s, Me), 1.17 (3 H, d, *J* 7 Hz, 15-H), and 1.07 (3 H, d, *J* 6 Hz, 13-H); δ_C 216.767 (s, C-3), 199.981 (s, C-10), 185.418 (s, C-6), 115.820 (s, C-5), and 74.410 (t, C-11); *m/e* 248 (M^+, 13%), 233 (11), 177 (36), 175 (16), 163 (22), 125 (39), 109 (100), 105 (25), and 81 (16) (Found: C, 72.5; H, 8.05. $C_{15}H_{20}O_3$ requires C, 72.58; H, 8.06%).

(+)-7-epi-*Pinguisone* (2).—Borabicyclononane (9-BBN) (0.384 g, 0.315 mmol, 5% excess) was added, under nitrogen, to a magnetically stirred solution (0 °C) of the furanone (18) (0.075 g, 0.3 mmol) in anhydrous THF (2 ml). The mixture was left for 2 h at 0 °C and then for 1 h at room temperature. Methanol (0.25 ml) was then added, the solution was evaporated, and the residue was treated with 2-aminoethanol (0.189 g, 0.315 mmol) in pentane (5 ml). The mixture was filtered and the precipitate washed three times with pentane (5 ml each). On evaporation of the combined extracts, a crude product (0.065 g) was obtained which was purified by silica-gel chromatography. Elution with light petroleum–ether (8 : 2) afforded the pure (+)-*epi*-pinguisone (2) (0.050 g, oil). The product, after further purification by preparative t.l.c., gave $[\alpha]_D^{25}$ 1.9 (*c* 2); $\nu_{max.}$ 1 744 and 1 515 cm^{-1}; $\lambda_{max.}$ 216 nm (log ε 3.81); δ_H 7.22 (1 H, m, 10-H), 6.24 (1 H, d, *J* 2 Hz, 11-H), 2.70 (1 H, dd, *J'* 17.5 Hz, *J''* 8.5 Hz, 2-H), 2.60 (1 H, dd, *J'* 17.5 Hz, *J''* 8.0 Hz 2-H), 2.41 (2 H, br s, 7-H), 1.18 (3 H, d, *J* 7.5 Hz, 15-H), 1.08 (3 H, d, *J* 6.5 Hz, 13-H), 1.20 (3 H, s, Me), and 1.10 (3 H, s, Me); δ_C 215.541 (s, C-3), 147.377 (s, C-6), 141.222 (d, C-11), 120.770 (s, C-5), 109.967 (d, C-10), 56.057 (s, C-9), 44.371 (s, C-8), 40.733 (t, C-2), 35.692 (d, C-1), 30.750 (d, C-4), 28.627 (t, C-7), 20.408 (q, Me), 18.241 (q, Me), 16.941 (q, Me), and 12.524 (q, Me); *m/e* 232 (M^+, 9%), 217 (6), 161 (6), 159 (14), 147 (7), 125 (4), 108 (100), 107 (11), 89 (26), 87 (23), 79 (21), and 73 (78) (Found: C, 77.45; H, 8.55. $C_{15}H_{20}O_2$ requires C, 77.58; H, 8.62%).

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