Acta Chemica Scandinavica B 28 (1974) 492—500

Syntheses in the Camphor Series. Alkylation of Quinones with Cycloalkyl Radicals. Attempted Syntheses of Lagopodin A and Desoxyhelicobasidin

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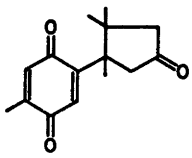
In an attempt to synthesize lagopodin A and desoxyhelicobasidin, a new synthesis of (3*R*)-3-carboxy-3,4,4-trimethylcyclopentanone and (1*R*)-1,2,2-trimethylcyclopentanecarboxylic acid was worked out together with several other reactions in the camphor series. For the same purpose alkylation of quinones with cycloalkyl radicals derived from cycloalkane carboxylic acids by decarboxylation with silver ion sand peroxydisulphate was investigated and several cycloalkyl derivatives were prepared. It was not possible to add the sterically hindered trimethyl cyclopentyl radicals to quinones. The structure *22* is suggested for a camphorlactone claimed to be *21*.[8]

In previous papers [1,2] we have described the alkylation of quinones with radicals from the decarboxylation of carboxylic acids with silver ions and peroxydisulphate (Eqns. 1 and 2)

$$Ag^+ + S_2O_8^{2-} \rightarrow Ag^{2+} + SO_4^{\cdot -} + SO_4^{2-} \quad (1)$$

$$Ag^{2+} + RCOOH \rightarrow R^{\cdot} + CO_2 + H^+ + Ag^+ \quad (2)$$

In the present work the alkylation of quinones with cycloalkylradicals was investigated in order to examine the possibility of synthesizing the naturally occurring terpenoid quinones lagopodin A [3] *1* and desoxyhelicobasidin [4] *2* by this method.



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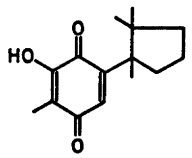

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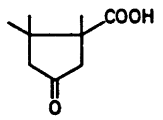
During the search for a convenient synthesis of the carboxylic acids *3* and *4*, required for this purpose, some other useful reactions in the



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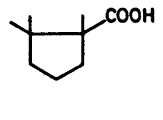

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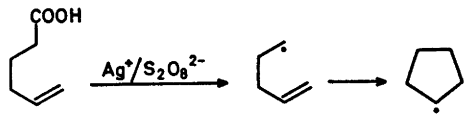
camphor series were discovered. These are discussed in the section containing the syntheses of *3* and *4*.

RESULTS

Alkylation of 1,4-naphthoquinones 5. The alkylation of 1,4-naphthoquinone *5* and 2-methyl-1,4-naphthoquinone *6* with cycloalkylradicals (C_3-C_6) gave the corresponding cycloalkylquinones in fair yields (Table 1).

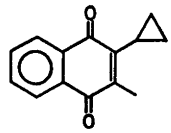
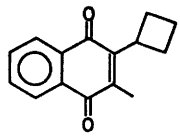
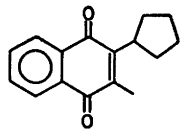
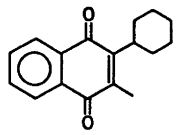
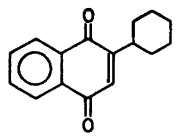
The possibility of generating cyclopentylradicals indirectly by the cyclisation of an open chain unsaturated radical (Eqn. 3) was also examined.



(3)

When 5-hexenoic acid was decarboxylated in the presence of 2-methyl-1,4-naphthoquinone, 2-methyl-3-(4-pentenyl)-1,4-naphthoquinone *12* was isolated. Only traces of the cyclopentylquinone *9* could be detected.

Table 1. Alkylation of quinones with cycloalkyl radicals.

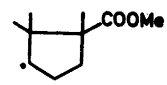
Quinone	Carboxylic acid	Product	Yield %	m.p.
6	Cyclopropane-	7 	37	82-83°
6	Cyclobutane-	8 	56	59-60°
6	Cyclopentane-	9 	42	96-97°
6	Cyclohexane-	10 	46	78-79°
5	Cyclohexane-	11 	55	87-88° (lit.[5] 87-88)

Synthesis of 3 and 4. Since the published syntheses of the optically active [3] or the racemic[6] *3* are rather complicated, a new route to *3* and *4* in their optically active forms was investigated.

Oxidative decarboxylation of (1*R*)-*cis*-camphoric acid-1-methylester *13* with lead tetraacetate in the presence of cupric ions by the method of Kochi [7] gave (1*R*)-1,2,2-trimethylcyclopent-3-ene-carboxylic acid methylester *14*.

Alkaline hydrolysis of *14* gave the corresponding carboxylic acid *15* which was hydrogenated catalytically to *4* (1*R*-configuration).

The oxidative decarboxylation of *13* was also performed by the use of silver ion-peroxydisulphate-cupric ions in water-acetonitrile in the same yield but with higher conversion of *13*. In this reaction the presence of pyridine proved essential for the oxidation of the intermediate radical *16* to *14* by the cupric ions. When the reaction was carried out in the absence of pyridine, a mixture of *14* and the saturated ester *17* (Scheme 1) was formed.



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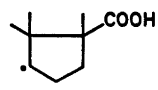
To investigate the selectivity of the oxidative decarboxylation between secondary and tertiary carboxyl groups with both lead tetraacetate and silver ion-peroxydisulphate, camphoric acid was decarboxylated by both oxidants under conditions similar to those in the syntheses of *14*.

Two radicals, *18* and *19*, result from the decarboxylation of the secondary and the tertiary carboxylic group, respectively.



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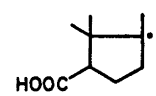

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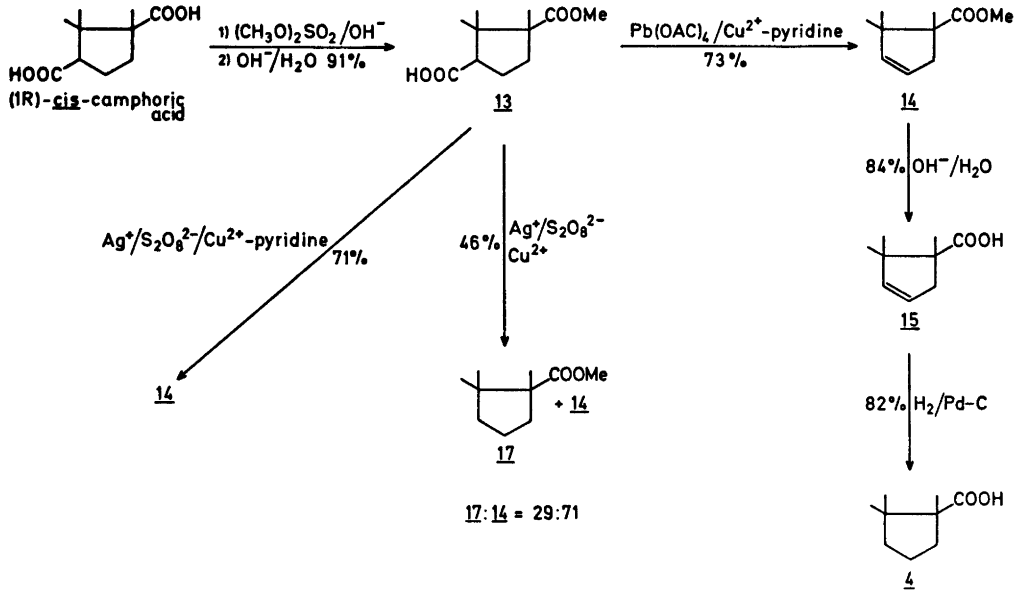
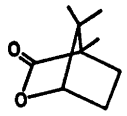


Scheme 1.

The main products in both reactions were the lactones *20* and *21* formed from *18* and *19*, respectively, probably by internal ligand-transfer,



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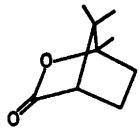

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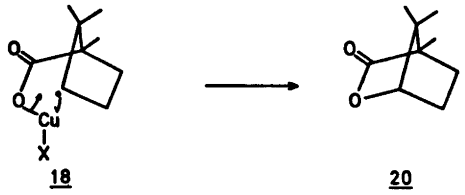
and analogously *19*→*21*.



18 20

The expected products, cyclopentenoic acids (formed analogously to *14*) were only present in small amounts.

These results show that the tertiary carboxylic group is decarboxylated much faster than the secondary by both reagents.

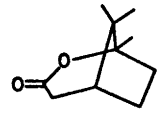
The spectra and physical data of *21* were very different from those published by Hayashi *et al.*[8] for a compound claimed to be *21*. Their data

Table 2. Ratio[a] of products from decarboxylation of camphoric acid.

Oxidant	*20* (%)	*21* (%)	total yield (%)
$Pb(OAc)_4$	17	83	64
$Ag^+/S_2O_8^{2-}$	5	95	57

[a] Determined by GLC.

are in better agreement with the structure *22*, also considered by these authors. A comparison of the two sets of data is given in Table 3.



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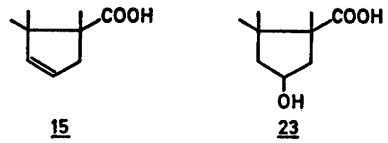
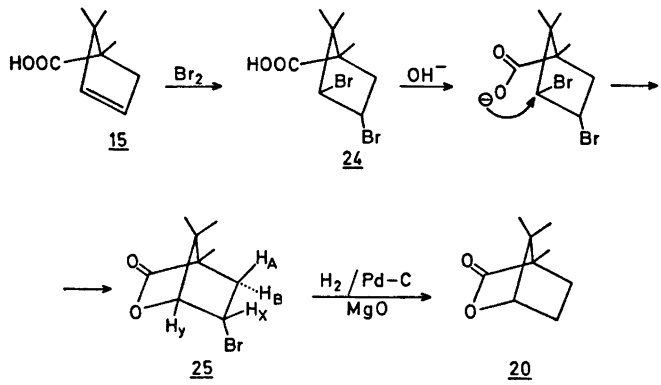
Attempts to bring about the conversion *15*→*23* by hydroboration of *15* or its tetrabutyl-



15 23 (5)

Table 3. Comparison of the physical data of *21* and *22*.

	Compound *21*	Compound of Hayashi *et al.*[8] *22*
IR	1775 cm^{-1} (5-membered lactone), supports *21*	1730 cm^{-1} (6-membered lactone), supports *22*
NMR	see Experimental, supports *21*	integral of methyl signals: other protons = 9:7, supports *22*
MS	no peaks beyond 154 (M^+ for *21*). Fragmentation pattern very similar to *20*, supports *21*	peak at 168 (M^+ for *22*). Fragmentation pattern very different from that of *20*, supports *22*
Analysis	see Experimental, supports *21*	supports both *21* and *22*
M.p.	113 – 115 °C	156 – 157 °C



15 24 25 20

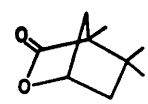
Scheme 2.

ammonium salt with disiamylborane, followed by oxidation with hydrogen peroxide by the method of Brown,[9] were unsuccessful.

Bromination of *15* gave a dibromoderivative *24* which, when treated *in situ* with aqueous sodium carbonate, gave a bromolactone *25*. Catalytical hydrogenation of *25* gave *20* which on hydrolysis and oxidation would lead to an isomer of the desired keto acid *3*.

The *endo*-configuration of *25* was deduced as follows: The carboxylate ion in the dibromacid *24* substitutes the bromine atom in *trans* position, and since the addition of bromine to the double bond proceeds in a *trans* fashion, the bromine of *25* is located *cis* to the lactone bridge (Scheme 2).

Treatment of *15* with *p*-toluenesulphonic acid in refluxing toluene gave the desired lactone *26*, together with a minor amount (13 %) of *20*. It proved impossible to separate *20* from *26*



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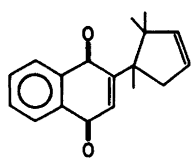
by other means than preparative GLC so the mixture was hydrolyzed and the (1*R*)-*cis*-4-hydroxy-1,2,3-trimethylcyclopentanecarboxylic acid *23* was purified by crystallization from water.

Oxidation of *23* by chromic acid in a 2-phase system gave *3* in good yield.

Attempted syntheses of lagopodin A and desoxyhelicobasidin 2. As a model of the synthesis of desoxyhelicobasidin we used naphthoquinone with *4* but without success, partly because of the low solubility of *4* in water and aqueous acetonitrile which caused formation of a 2-phase system on addition of peroxydisulphate



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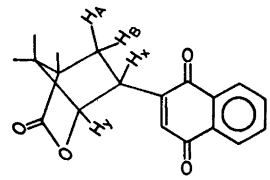

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and thereby ineffective decarboxylation of *4*. The same reaction using *4* as its silver- or tetrabutylammonium salt or *4* together with a weak base like 2,6-lutidine, gave no alkylated naphthoquinone, although *4* was consumed in these reactions.

To overcome the solubility problem, we tried to carry out the alkylation with *15* instead of *4* but in this reaction the simple alkylated naphthoquinone *27* was not obtained.

Instead *28* was formed as the only isolable quinone product in a yield of 41 % (apparently only the *endo*-isomer).

The *endo* structure was preferred for the following reason: The NMR coupling constants, of the H_A, H_B, and H_x protons, of *28* are in reasonably good agreement (Table 4) with those of the bromolactone *25* which for reasons already mentioned should be the *endo*-isomer.

We are not, however, able to find sufficient NMR data of related structures in the literature to justify a definite assignment.

Table 4. ^1H Coupling constants (Hz) of *25* and *28*.

Compounds	J_{AB}	J_{AX}	J_{BX}	J_{XY}
25	−15.2	10.1	4.0	2.0
28	−13.9	10.7	5.1	1.7

Two mechanisms, 5A and 5B, for the formation of *28* can be formulated, see below.

In view of the small gain in energy by cyclization of *29* compared with the greater amount of energy liberated by a decarboxylation, *30* is preferred to *29* as intermediate.

The mechanism B has also been proposed by Moriarty [10] for the oxidation of various alkenecarboxylic acids by lead tetraacetate.

Attempts to alkylate toluquinone with *3* to give lagopodin A and isomers also failed, indicating that the steric hindrance of the tertiary cycloalkyl radicals in the alkylation step is of such a magnitude that the fast oxidation of these radicals by Ag^{2+} or $SO_4^{\cdot-}$ prevails.

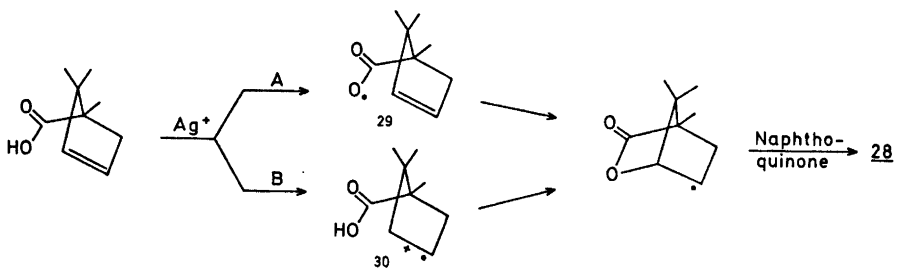
In agreement with this alkylation with 1-methylcyclohexanecarboxylic acid also gave very poor yields.

EXPERIMENTAL

Melting points are uncorrected. *NMR* spectra were recorded on a Varian A-60, *IR* spectra on a Perkin-Elmer Infracord, and *UV* spectra on a Perkin-Elmer 402 spectrometer. Analytical GLC was performed with a Perkin-Elmer F11 chromatograph. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Calculation of *NMR* shifts and coupling constants was made by means of the LAOCN-3 programme.

Alkylation of quinones. Details of the reaction have been described earlier.[1]

General procedure. To a vigorously stirred water-acetonitrile solution of the quinone, the



carboxylic acid, and silver nitrate at 60 – 65 °C an aqueous solution of ammonium peroxydisulphate was added during 45 min. After a further 10 min stirring at 60 – 65 °C, the mixture was cooled to room temperature and extracted with ether. The ether phase was washed with aqueous $NaHCO_3$ until neutral, dried, and evaporated. The crude products were chromatographed, either on TLC plates (silica gel Merck); procedure A: eluent 20 % ether in petrol ether; procedure B: eluent CH_2Cl_2 or on a column of neutral aluminia; procedure C: eluent CH_2Cl_2.

2-Cyclopropyl-3-methyl-1,4-naphthoquinone, 7. To 2-methyl-1,4-naphthoquinone (1.72 g, 0.01 mol), cyclopropanecarboxylic acid (1.29 g, 0.015 mol), and silver nitrate, 0.5 g, in acetonitrile (25 ml) and water (60 ml) was added ammonium peroxydisulphate (3.42 g, 0.015 mol) in water (15 ml). Chromatography (procedure B) of the crude product gave *7*, 780 mg (37 % based on the quinone), m.p. 82 – 83 °C (from CH_3OH). (Found: C 78.6; H 5.82. Calc. for $C_{14}H_{12}O_2$: C 79.2; H 5.70). UV (EtOH) λ_{max} nm (log ε): 246 (4.21), 251 (4.21), 274 (4.10), 333 (3.5). IR (CCl_4): cm^{-1} 1660(s), 1595 (m). NMR (CCl_4): δ 0.8 – 1.3 (4 H, m), 1.3 – 2.0 (1 H, m), 2.20 (3 H, s), 7.4 – 8.1 (4 H, m).

2-Cyclobutyl-3-methyl-1,4-naphthoquinone, 8. To 2-methyl-1,4-naphthoquinone (0.86 g, 0.005 mol), cyclobutanecarboxylic acid (0.75 g, 0.0075 mol), and silver nitrate (0.5 g) in acetonitrile (20 ml) and water (20 ml) was added ammonium peroxydisulphate (1.71 g, 0.0075 mol) in water (10 ml). Chromatography (procedure B) of the crude product gave *8*, 630 mg (56 % calculated on the quinone), m.p. 59 – 60 °C (from methanol). (Found: C 79.7; H 6.46. Calc. for $C_{15}H_{14}O_2$: C 79.6; H 6.24). UV (EtOH): λ_{max} nm (log ε) 245 (4.23), 251 (4.22), 274 (4.17), 332 (3.4). IR (CCl_4): cm^{-1} 1660(s), 1595(m). NMR (CCl_4): δ 1.7 – 2.8 (6 H, m), 2.07 (3 H, d, $J = 1$), 3.2 – 4.0 (1 H, m), 7.5 – 8.1 (4 H, m). On irradiation of the multiplet at 3.2 – 4.0 ppm, the doublet at 2.07 ppm collapsed into a singlet.

2-Cyclopentyl-3-methyl-1,4-naphthoquinone, 9. To 2-methyl-1,4-naphthoquinone (0.86 g, 0.005 mol), cyclopentanecarboxylic acid (0.86 g, 0.0075 mol), and silver nitrate (0.5 g) in acetonitrile (70 ml) and water (20 ml) was added ammonium peroxydisulphate (1.71 g, 0.0075 mol) in water (10 ml). Chromatography (procedure B) of the crude product gave *9*, 510 mg (43 % based on the quinone), m.p. 96 – 97 °C (from CH_3OH). (Found: C 79.6; H 6.77. Calc. for $C_{16}H_{16}O_2$: C (79.6; H 6.71). UV (EtOH): λ_{max} nm (log ε) 246 (4.24), 250 (4.24), 269 (4.16), 276 (4.18), 332 (3.5). IR (CCl_4): cm^{-1} 1660(s), 1595(m). NMR (CCl_4): δ 1.3 – 2.2 (8 H, m), 2.17 (3 H, s), 2.9 – 3.5 (1 H, m), 7.5 – 8.1 (4 H, m).

2-Cyclohexyl-3-methyl-1,4-naphthoquinone, 10. The general procedure was followed. To 2-methyl-1,4-naphthoquinone (1.72 g, 0.01 mol), cyclohexanecarboxylic acid (1.92 g, 0.015 mol) and silver nitrate (0.5 g) in acetonitrile (40 ml) and water (40 ml) was added ammonium peroxydisulphate (3.42 g, 0.015 mol) in water (20 ml). Chromatography (procedure A) gave *10*, 1.16 g (46 % calculated on the quinone), m.p. 78 – 79 °C. (Found: C 80.0; H 7.24. Calc. for $C_{17}H_{18}O_2$: C 80.3; H 7.15). UV (EtOH): λ_{max} nm (log ε) 246 (4.28), 250, sh, 269, sh, 275 (4.11), 331 (3.5). IR (CCl_4): 1660(s), 1595(m). NMR (CCl_4): δ 1.0 – 2.2 (10 H, m), 2.17 (3 H, s), 2.4 – 3.1 (1 H, m), 7.5 – 8.1 (4 H, m).

2-Cyclohexyl-1,4-naphthoquinone, 11. To 1,4-naphthoquinone (1.58 g, 0.01 mol), cyclohexanecarboxylic acid (1.92 g, 0.015 mol), and silver nitrate (0.5 g) in acetonitrile (22 ml) and water (20 ml) was added ammonium peroxydisulphate (3.42 g, 0.015 mol) in water (15 ml). Chromatography (procedure A) of the crude product gave *11*, 1.32 g (55 % based on the quinone), m.p. 87 – 88 °C (lit.[5] 87 – 88 °C). UV (EtOH): λ_{max} nm (log ε) 248 (4.25), 253 (4.24), 267 (4.17), 334 (3.5). IR (CCl_4): cm^{-1} 1665(s), 1615(m), 1595(m). NMR (CCl_4): δ 0.9 – 2.4 (10 H, m), 2.4 – 3.2 (1 H, m), 6.61 (1 H, d, $J = 1$), 7.5 – 8.2 (4 H, m).

3-Methyl-2-(4-pentenyl)-1,4-naphthoquinone, 12. To 1-methyl-1,4-naphthoquinone (1.72 g, 0.01 mol), 5-hexenoic acid (1.71 g, 0.015 mol), and silver nitrate (0.5 g) in acetonitrile (25 ml) and water (25 ml) was added ammonium peroxydisulphate (3.42 g, 0.015 mol) in water (15 ml). Chromatography (procedure B) of the crude product gave *12*, 920 mg (38 % based on the quinone), m.p. 46 – 47 °C. (Found: C 79.6; H 6.75. Calc. for $C_{16}H_{16}O_2$: C 80.0; H 6.71). UV (EtOH): λ_{max} nm (log ε) 249 (4.19), 267 (4.15), 273 (4.15), 333 (3.4). IR (CCl_4): cm^{-1} 1660(s), 1620(m), 1595(m). NMR (CCl_4): δ ~1.5 (2 H, distorted quintet, $J = 7$), 2.1 (2 H, b, t, $J = 7$), 2.10 (3 H, s), 2.5 (2 H, d, t, $J_1 = 8$, $J_2 = 7$), 4.8 – 5.3 (2 H, m), 5.5 – 6.2 (1 H, m), 7.5 – 8.1 (4 H, m). Only traces of *9* could be detected by TLC.

2-(endo-5-(1,7,7-Trimethyl-2-oxo-3-oxa)-bicyclo[2.2.1]heptyl)-1,4-naphthoquinone, 28. To 1,4-naphthoquinone (0.79 g, 0.005 mol), *15* (0.93 g, 0.006 mol), and silver nitrate (0.5 g) in acetonitrile (15 ml) and water (20 ml) was added ammonium peroxydisulphate (1.30 g, 0.0057 mol) in water (8 ml). Chromatography (procedure C) gave *28*, 640 mg (41 % calculated on the quinone), m.p. 132 – 133 °C (after recrystallization from methanol and from cyclohexane). $[\alpha]_D^{25} = -158°$ (ethanol, $c = 0.5$) (Found: C 72.9; H 5.79. Calc. for $C_{19}H_{18}O_4$: C 73.5; H 5.84). UV (EtOH): λ_{max} nm (log ε) 248 (4.21), 254 (4.21), 264 (4.09), 339 (3.4). IR (CCl_4): cm^{-1} 1795(s), 1665(s), 1625(m), 1600(m). NMR ($CDCl_3$): δ 1.09 (3 H, s), 1.15 (3 H, s), 1.17 (3 H, s), 1.71* (1 H, A part of ABXYZ system), 2.32* (1 H, B part), 3.84* (1 H, X part), 4.50 (1 H, d, Y part, $J_{XY} = 1.7$), 6.82 (1 H, d, Z part, $J_{XZ} = 1.5$), 7.6 – 8.2 (4 H, m) $J_{AB}^* = -13.9$, $J_{AX}^* = 10.7$, $J_{BX}^* = 5.1$. The signal at δ 3.84, which appeared as four triplets, was changed

* Calculated values.

into four doublets, $J = 1.7$, by irradiation of the doublet at 6.82.

Dimethyl-(1R)-cis-camphorate was prepared by the method of Riedel [11] in a yield of 97 %. NMR (CCl_4): δ 0.72 (3 H, s), 1.18 (3 H, s), 1.21 (3 H, s), 1.3 – 2.9 (5 H, m), 3.65 (6 H, s).

(1R)-cis-Camphoric acid-1-methylester, 13. 123 g (0.54 mol) of dimethyl-(1*R*)-*cis*-camphorate and potassium hydroxide (0.54 mol) were dissolved in methanol (800 ml) and water (400 ml) and left at room temperature for 3 days. The solution was refluxed for 30 min and the methanol was distilled off. The aqueous phase was washed with ether, acidified with conc. HCl and extracted with CH_2Cl_2. Drying and evaporation of the CH_2Cl_2 phase gave 108 g (94 %) of almost pure *13*, m.p. 85 – 86 °C (from petrol ether) (lit.[12] 86 – 87 °C) $[\alpha]_D^{25} = +43°$ (ethanol $c = 2$). IR (CCl_4): cm^{-1} 2500 – 3200(s), 1735(s), 1705(s). NMR (CCl_4): δ 0.83 (3 H, s), 1.20 (3 H, s), 1.28 (3 H, s), 1.3 – 3.0 (5 H, s), 3.67 (3 H, s), 11.7 (1 H, s).

Decarboxylation of (1R)-cis camphoric acid-1-methylester, 13 *with lead tetraacetate. Preparation of 15.* A mixture of 47 g (0.22 mol) of *13*, lead tetraacetate (111 g, 90 % pure, 0.22 mol), neutral cupric acetate (7.2 g), and pyridine (11 g) in benzene (450 ml) was refluxed with stirring for 2 h. The reaction mixture was filtered, washed with dilute nitric acid to remove pyridine and copper salts and extracted with aqueous potassium carbonate until neutral. On acidification of the alkaline washings, 13 g of *13* were recovered. The benzene phase was dried and distilled. The fraction boiling at 180 – 186 °C was (1*R*)-1,2,2-trimethylcyclopent-3-ene-1-carboxylic acid methylester, *14*, 19.5 g (73 % based on converted *13*). (For use in the hydrolysis it is only necessary to distil off the benzene). $n_D^{22} = 1.4501$, $[\alpha]_D^{25} = +113°$ (ethanol, $c = 1$). IR (CCl_4): cm^{-1} 1735(s), 1620(w). NMR (CCl_4): δ 0.88 (3 H, s), 1.13 (3 H, s), 1.18 (3 H, s), 2.0 (1 H, distorted d, $J \sim 17$), 3.2 (1 H, distorted d, $J \sim 17$), 3.66 (3 H, s), 5.3 (1 H, m), 5.5 (1 H, m).

Decarboxylation of 13 *with* $Ag^+/S_2O_8^{2-}$. To a stirred mixture of *13* (21.4 g, 0.1 mol) cupric sulphate (6 g), silver sulphate (4 g), and pyridine (6 ml) in water (150 ml) and acetonitrile (100 ml) at 60 – 70 °C was added ammonium peroxydisulphate (30.6 g, 0.13 mol) in water (50 ml) during 1 h while the pH was kept at 6 – 7 by addition of 4 M sodium hydroxide. After a further 10 min stirring, 4 M sulphuric acid (100 ml) was added and the mixture was cooled and extracted three times with petrol ether. The organic phase was dried and the petrol ether was distilled off together with some acetonitrile leaving almost pure *14* (11.8 g, 70 %) containing less than 1 % of *17* (GLC, 5 % SE-30, using authentic samples as references). In the absence of pyridine it was necessary to use more acetonitrile (140 ml) and less water (90 ml) to bring *13* in solution, and the crude product was very impure and had to be distilled before GLC analysis. The fraction, boiling at 106 – 130 °C/45 mm, (7.8 g, 46 %) was collected and found to contain *14* (71 %) and *17* (29 %) by GLC.

1,2,2-Trimethylcyclopent-3-ene-1-carboxylic acid, 15. A solution of *14* (7.7 g, 0.046 mol) and potassium hydroxide (35 g, 0.63 mol) in methanol (170 ml) and water (15 ml) was refluxed for 20 h. The methanol was distilled off, the residue was dissolved in water and washed with ether. The aqueous phase was cooled to 0 °C, acidified with conc. HCl, and the precipitated (1*R*)-1,2,2-trimethylcyclopent-3-ene-1-carboxylic acid *15* filtered, washed with cold water, and dried. Yield: 5.9 g (84 %), m.p. 157 – 158 °C (from formic acid or aqueous formamide or after sublimation at 120 °C/10 mm, lit.[13] 157 – 159.5 °C). $[\alpha]_D^{25} = +122°$ (ethanol, $c = 1$). IR ($CHCl_3$): cm^{-1} 2500 – 3500(s), 1705(s), 1625(w). NMR (CCl_4): δ 1.02 (3 H, s), 1.17 (3 H, s), 1.27 (3 H, s), 2.0 (1 H, distorted d, $J = 17$), 3.2 (1 H, distorted d, $J = 17$), 5.3 (1 H, m), 5.5 (1 H, m), 11.9 (1 H, s).

Decarboxylation of (1R)-cis-camphoric acid by lead tetraacetate. Preparation of 20 and 21. Camphoric acid (10 g, 0.05 mol), lead tetraacetate (27.8 g, 90 % pure, 0.055 mol), neutral cupric acetate (2 g), and pyridine (3 ml) were refluxed in benzene (200 ml) for 3 h. The mixture was washed with 30 % nitric acid, water, and aqueous sodium carbonate, successively, dried, and evaporated *in vacuo* at room temperature leaving 4.9 g (64 %) of a mixture of *20*, 17 % and *21*, 83 % (GLC). On acidification of the sodium carbonate phase, *ca.* 1.5 g of acidic material – mainly camphoric acid – was obtained.

Decarboxylation of (1R)-cis-camphoric acid with Ag^+*/persulphate.* Camphoric acid (10, g, 0.05 mol), cupric sulphate (2 g), silver sulphate (2 g), pyridine (3 ml), water (200 ml), and acetonitrile (20 ml) were stirred at 60 – 65 °C while 13.68 g (0.06 mol) of ammonium peroxydisulphate in water (50 ml) were added during 70 min. During the addition, the pH was kept at 5 – 7 by addition of diluted NaOH. After a further 10 min stirring at 60°C, 2 M H_2SO_4 (50 ml) was added and the mixture was extracted with ether. The ether extract was washed with aqueous sodium carbonate, dried, and evaporated to give 4.4 g (57 %) of a mixture of *20* and *21* (5:95, GLC). Small amounts of acidic material could be obtained on acidification of the carbonate phase. Preparative GLC 10 % PEG) of the mixture gave *21*, m.p. 113 – 115 °C $[\alpha]_D^{25} = +12.6°$ (ethanol, $c = 0.5$). (Found: C 70.0; H 9.10. Calc. for $C_9H_{14}O_2$: C 70.1; H 9.15). IR (KBr): cm^{-1} 1775(s). NMR (CCl_4): δ 0.95 (3 H, s), 1.06 (3 H, s), 1.29 (3 H, s), 1.5 – 2.1 (4 H, m), 2.28 (1 H, distorted dd). MS Mass % of base peak): 154 (5) M^+, 139 (5), 126 (31), 111 (27), 108 (26), 95 (100).

Lactonisation of 1,2,2-trimethylcyclopent-3-ene-carboxylic acid, 15. Preparation of 26 and 20. 15 (8.55 g, 0.056 mol) and *p*-toluenesulfonic acid (4.3 g, 0,0027 mol) were refluxed for 20 h in

toluene (70 ml). The mixture was extracted with aqueous sodium carbonate. On acidification of the carbonate washing, *15* (1.35 g) was recovered by extraction with CH_2Cl_2. The toluene phase was dried and evaporated *in vacuo* at room temperature. The residue was sublimated at 115 °C/10 mm to give 4.08 g (57 %) of a mixture of (1*R*)-*cis*-4-hydroxy-1,2,2-trimethylcyclopentane carboxylic acid lactone, *26*, and the isomeric 3-hydroxy carboxylic acid lactone, *20*, ratio 87:13 (GLC, 10 % PEG). This mixture could not be separated by crystallization. The *IR* spectrum of the mixture was almost identical with the spectrum of *26*, published by Faigle and Karrer.[14] NMR (CCl_4) of *26*: (after substraction of the signals from 20) δ 0.97 (3 H, s), 1.07 (3 H, s), 1.10 (3 H, s), 1.7 (2 H, m), 1.9 (2 H, m), 4.6 (1 H, m).

(1R)-cis-4-Hydroxy-1,2,2-trimethylcyclopentanecarboxylic acid, 23. The lactone mixture of *20* and *26* (4 g) was refluxed for 20 h with 40 g KOH in 160 ml of methanol and 80 ml of water. The methanol was evaporated and the aqueous phase washed with ether, acidified with conc. HCl and extracted with several portions of CH_2Cl_2. The CH_2Cl_2 phase was dried and evaporated and the residue recrystallized from water giving pure *23* (2.95 g, 66 %), m.p. 199 – 200 °C (lit.[15] 200 °C). $[\alpha]_D^{25} = +14°$ (ethanol, $c = 4$). IR (KBr): cm^{-1} 3400(s), 2500 – 3100(s), 1700(s). NMR (D_2O, K_2CO_3): δ 0.93 (3 H, s), 0.98 (3H, s), 1.01 (3 H, s), 1.38 – 2.37 (4 H, m), 4.07 – 4.50 (1 H, m).

(3R)-3-Carboxy-3,4,4-trimethylcyclopentanone, 3. To *23* (1.5 g, 0.087 mol) dissolved in a 2-phase system consisting of ether (20 ml), water (10 ml), and dimethoxyethane (3.5 ml) was added at 25 °C a mixture of $Na_2Cr_2O_7.2H_2O$ (1.6 g, 0.054 mol), and conc. H_2SO_4 (1 g) in water (15 ml) with vigorous stirring during 15 min. After further 4 h of stirring, the organic layer was separated and the aqueous phase extracted several times with ether. The combined organic phases were dried and evaporated to give *3* (1.20 g, 81 %), m.p. 220 – 221 °C (from H_2O (lit.[3] 221 °C). $[\alpha]_D^{25} = +23°$ (ethanol, $c = 2$). IR ($CHCl_3$): cm^{-1} 2500 – 3500(s), 1745(s), 1700(s). NMR ($CDCl_3$): δ 1.14 (3 H, s), 1.21 (3 H, s), 1.35 (3 H, s), 2.20 and 3.01 (2 H, AB system, $J_{AB} = 19$), 2.36 (1H, b , s), ~11 (1 H, b, s).

(1R)-1,2,2-Trimethylcyclopentanecarboxylic acid, 4. 15 (10.0 g, 0.065 mol) in 100 ml alcohol was hydrogenated over 5 % Pd/C (0.6 g) for 20 h at room temperature and 1 atm. The solution was filtered and evaporated and the residue recrystallized from acetonitrile to give *4* (8.3 g, 82 %), m.p. 191 – 192 °C (lit.[16] 192 – 193 °C). $[\alpha]_D^{25} = +20°$ (ethanol, $c = 1$). IR (CCl_4): cm^{-1} 2500 – 3300(s), 1700(s). NMR (CCl_4): δ 0.98 (3 H, s), 1.07 (3 H, s), 1.18 (3 H, s), ~1.6 (5 H, m), 2.0 – 2.7 (1 H, m), 11.77 (1 H, s).

Methyl-(1R)-1,2,2-trimethylcyclopentanecarboxylate, 17. To *4* (4.68 g, 0.03 mol) and sodium hydroxide (1.6 g, 0.039 mol) in 20 ml of water at 40 °C was added dimethyl sulphate (3.4 ml, ~0.036 mol). The temperature was kept at 60 °C for 1 h and excess of NaOH was added. The product *17* was extracted with ether and distilled (3.6 g, 71 %), b.p.$_{760}$ 176 – 180 °C. $n_D^{24} = 1.4448$. $[\alpha]_D^{25} = +8.4°$ (ethanol, $c = 3$). IR (film): cm^{-1} 1740(s). NMR (CCl_4): δ 0.81 (3 H, s), 1.01 (3 H, s), 1.10 (3 H, s), 1.6 (5 H, m), 2.0 – 2.7 (1 H, m), 3.59 (3 H, s).

(1R,3S)-3-Bromo-cis-4-hydroxy-1,2,2-trimethylcyclopentanecarboxylic acid lactone, 25. To *15* (10.0 g, 0.065 mol) in chloroform (30 ml) kept below 5 °C was added bromine (11.5 ml, 0.072 mol) during 1 h. After the addition, the mixture was stirred at 5 °C for 30 min. The $CHCl_3$ was evaporated and the residue was stirred vigorously with 10 % Na_2CO_3 (120 ml) for 1 h. Extraction of the mixture with methylene chloride, drying, and evaporation gave 13.8 g of a crystalline product which was recrystallized from petrol ether (b.p. 60 °C) to give pure bromolactone *25* (11.9 g, 72 %), m.p. 90.5 – 91.5 °C. (Found: C 46.5; H 5.75; Br 34.2. Calc. for $C_9H_{13}O_2Br$: C 46.4; H 5.62; Br 34.3). $[\alpha]_D^{25} = -71°$ (ethanol, $c = 1$). IR (CCl_4): cm^{-1} 1795(s). NMR (CCl_4): δ 1.01 (3 H, s), 1.04 (3 H, s), 1.09 (3 H, s), 1.82* (1 H, A part of ABXY system), 2.60* (1 H, B part), 4.26* (1 H, X part), 4.53* (4 H, Y part). $J_{AB}^* = -15.2$. $J_{AX}^* = 4.0$. $J_{BX}^* = 10.1$. $J_{XY}^* = 2.0$.

Catalytic hydrogenation of bromolactone, 25. 25 (2.34 g, 0.01 mol) in methanol (20 ml) was hydrogenated over 1 g of 5 % Pd/C and 4 g of MgO (1 atm. 25 °C) until slightly more than 0.01 mol of hydrogen was consumed (28 h). The solution was filtered, diluted with water (100 ml) and extracted 5 times with methylene chloride. The organic phase was washed with aqueous K_2CO_3, dried, and evaporated and the residue sublimated at 100 °C/10 mm to give *20*, 910 mg (59 %), m.p. (from ether) 162 – 164 °C (lit.[17] 165 – 167 °C). The IR spectrum was identical with that published by Faigle and Karrer,[14] $[\alpha]_D^{25} = -19°$ (ethanol, $c = 2$). NMR (CCl_4): δ 0.92 (3 H, s), 0.98 (3 H, s), 1.01 (3 H, s), 1.4 – 2.1 (4 H, m), 4.23 (1 H, m). MS: Mass (intensity – % of base peak): 154 (2) M^+, 140 (2), 126 (10), 111 (10), 108 (15), 97 (18), 95 (100).

* Calculated values.

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Received December 22, 1973.