Tetrahedron Vol 44, No 15, pp. 4837 to 4846, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

BICYCLO [3.3.1] NONANE APPROACH TO PINGUISANE TERPENOIDS. TOTAL SYNTHESIS OF (+) PINGUISONE.

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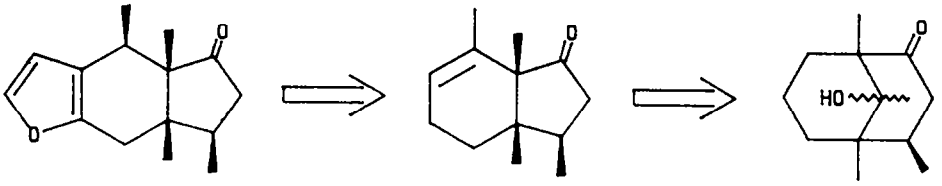
(*Received in UK* 17 *May* 1988)

Abstract - The total synthesis of (+) pinguisone 1, the sterically crowded unusual [5-6] fused-ring sesquiterpene, was accomplished by synthetic elaboration of the 3β,3aβ,7,7aβ-tetramethylbicyclo [4.3.0] non-6-en-1-one 2a prepared by acid catalyzed rearrangement of the easily accessible 1,4β,5,9-tetramethylbicyclo [3.3.1] nonan-9-hydroxy-2-one 3. This rearrangement constitutes an example of the scarcely observed 1,2 shift of a carbonyl group toward an electron deficient centre.

Since the isolation[1] and structure determination[2] of pinguisone 1, an increasing number of pinguisane terpenoids[3] have been found from various kinds of liverworts belonging to the genus *Hepaticae*. These compounds arouse interest from both the biological and the synthetic point of wiew. The biological function of pinguisane terpenoids is still obscure, but they may play a role as antifeedants.[4] As to the synthetic interest, it arises from their novel tricyclic skeleton, where a *cis*-junction in the hydrindane system and four *cis*-located methyl groups on adjacent carbons result in a very crowded system at the β face.[2]

This steric congestion is responsible for the difficulties encountered in the two previously reported total syntheses of pinguisone 1[5,6], where a step by step stereospecific introduction of the methyl groups into the bicyclo [4.3.0] nonane system was adopted.

From this point of view, we felt that a good route to pinguisane terpenoids could be the synthetic elaboration of the tetramethyl *cis*-hydrindenone 2a prepared through skeletal rearrangement of the more easily accessible tetramethylbicyclo [3.3.1] nonane derivative 3.[7,8]

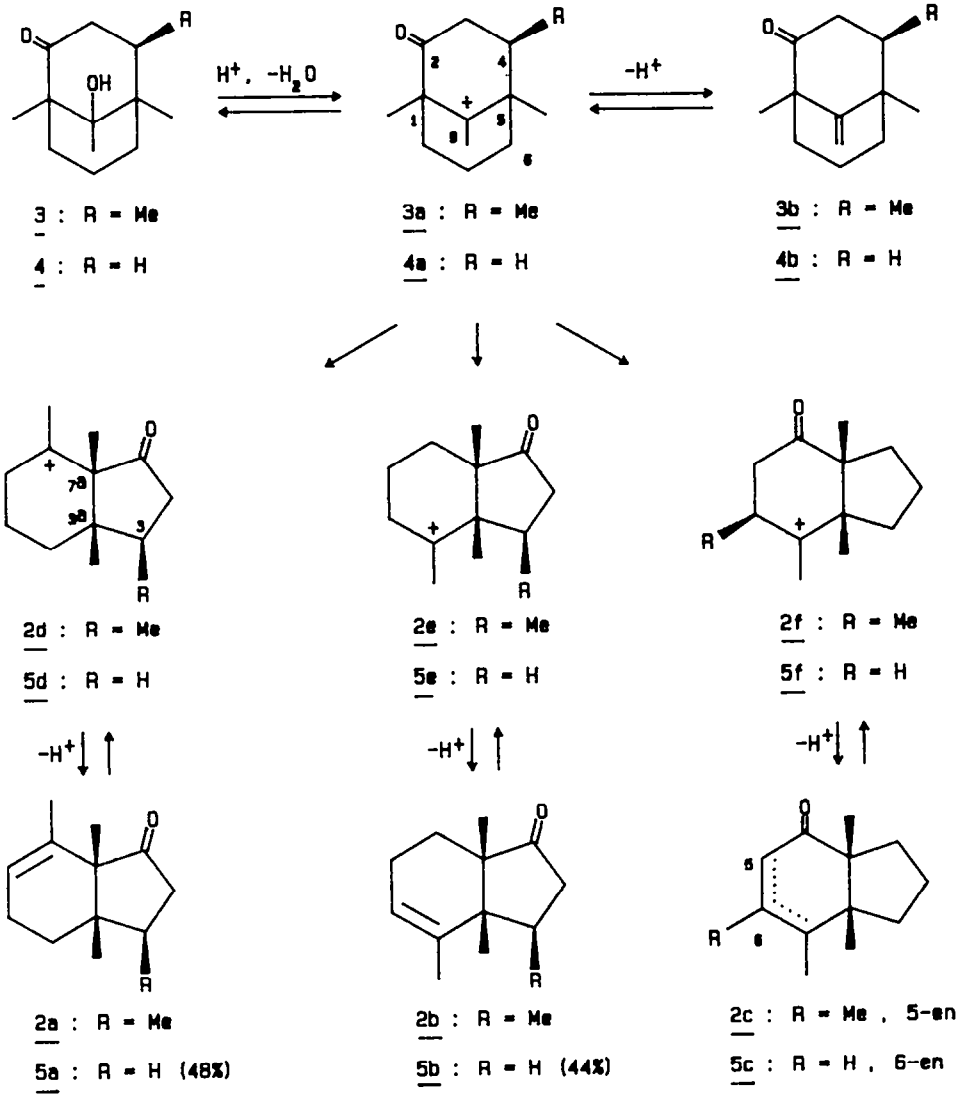


1 2a 3

In fact, one of us has reported that substituted *cis*-hexahydroindenones are obtained in high yield when substituted bicyclo [3.3.1] nonan-9-ols are dehydrated under acid catalysis.[7] The rearrangement takes place

through the shift to the C-9 of the bridgehead bonds and is strongly driven by the nature of substituents Namely, dehydration of ketols 4 (both epimers) leads to the kinetic methylene derivative 4b and to the rearrangement products 5a-b through the almost exclusive shift to the C-9 of the C-4 - C-5 and C-1 - C-2 bonds.[8] The shift of the C-5 - C-6 bond, with formation of 5c, represents only a 2% of the rearrangement. Migration of C-1 - C-2 bond in 4a offers a good example of the scarcely observed 1,2-shift of carbonyl groups toward electron deficient centres. For this process, Vogel and coworkers[9] have recently established a migratory aptitude higher than that of alkyl groups.

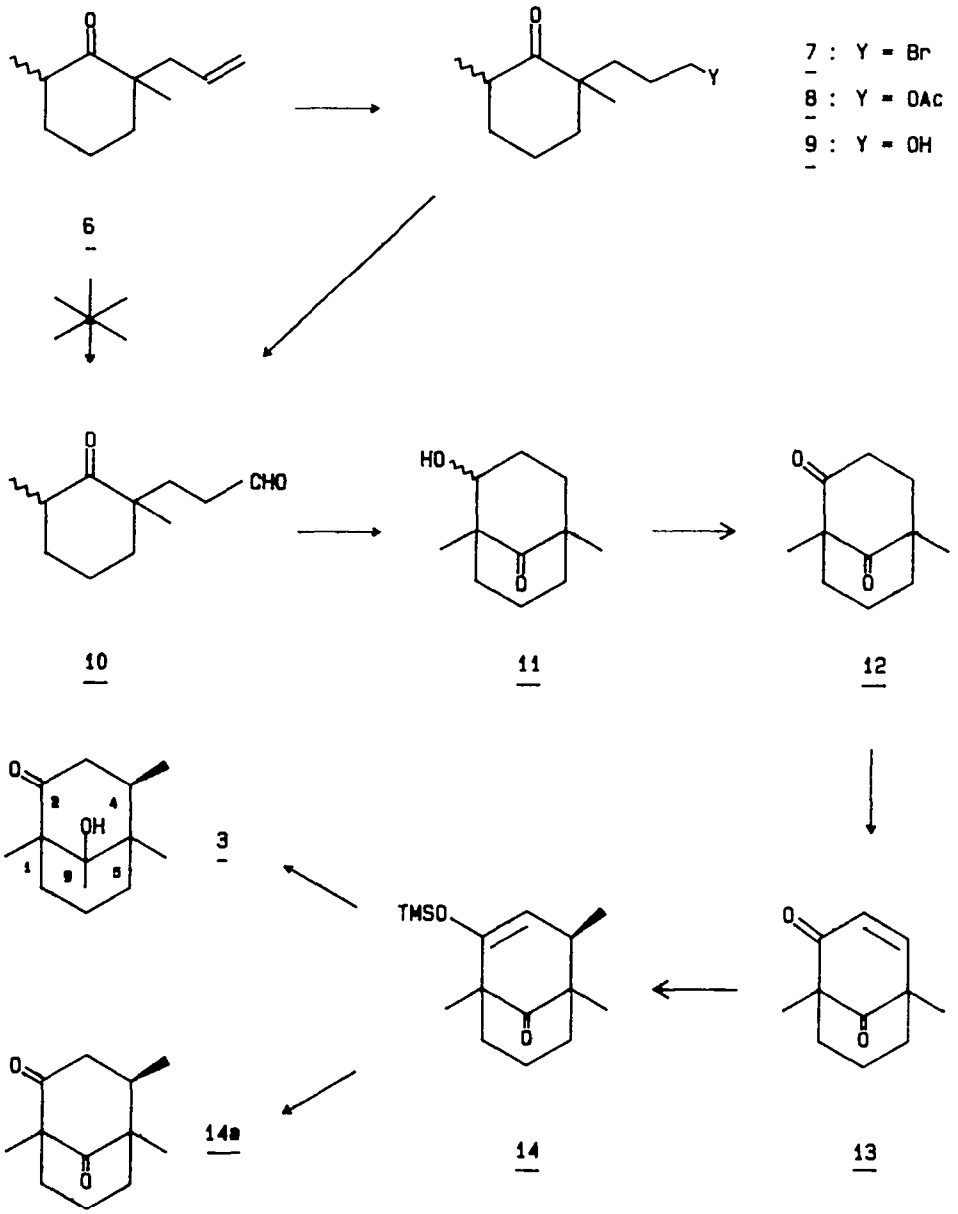
Scheme 2



Therefore, if this behaviour were general, dehydration of the ketol 3 should lead *inter alia* to the *cis*-hexahydroindenone 2a as a key intermediate for the synthesis of (±) pinguisone 1. We report here the results we have obtained.

The synthesis of ketol 3 was accomplished (SCHEME 3) starting from the allylcyclohexanone 6.[10] Since several attempts to oxidise 6 to aldehyde 10[11] were unsuccessful, the latter product was obtained by a longer route.

Scheme 3



Anti-Markovnikov hydrobromination of 6 gave the bromide 7, which was converted into the acetoxy derivative 8. Basic hydrolysis of the latter followed by PDC oxydation gave the ketoaldehyde 10 in good yield. Acid catalyzed intramolecular aldol condensation afforded the known ketols 11 as an *endo-exo* mixture of epimers[12] which were oxidized to dione 12; this latter was converted into the enedione 13 through the usual bromination-dehydrobromination procedure. Conjugate addition of $LiMe_2Cu$ on 13 took place at the *exo*-side (*vide*

infra), as expected,[13] and quenching of the reaction mixture with Me_3SiCl gave the silylenolether 14 as the only 4-*exo* epimer. As a consequence of the presence of the 4-*exo* methyl group, the subsequent methylation at C-9 of compound 14 by the action of two moles of methyllithium took place at the opposite side and afforded the 9-*syn*-hydroxy epimer 3 as the only product.

Configurations at C-4 and C-9 in the latter compound were confirmed by ^{1}H-NMR data. In fact, due to the 9-*syn* hydroxy group, the 4-*exo*-methyl group in the ketol 3 shows a downfield shift (1.11 δ) if compared with the same group in compound 14 (0.78 δ) and in the corresponding dione 14a (0.85 δ) where the 4-*exo*-methyl group falls in the shielding cone of the carbonyl group at C-9.

Dehydration-rearrangement of 3 (SCHEME 2), carried out as previously described for the model compound 4,[8] mainly proceeded through 1,2 shift to C-9 of C-1 - C-2 and C-4 - C-5 bonds, as expected, and gave the hexahyroindenones 2a and 2b in 55% and 27% yield respectively. Migration of C-5 - C-6 bond was not negligible here and afforded compound 2c in 18% yield, while for short reaction times or low amount of catalyst, the presence of the 9-methylene derivative 3b was detected as kinetic product. When silica-supported *p*-toluenesulfonic acid was used as a catalyst,[14] the required key product 2a was produced in higher percentage (65%), while 2b and 2c were formed in 17% and 14% yield respectively. Structures 2a-c followed from spectroscopic considerations similar to those already described for compounds 5a-c.[8] Moreover, the chemical shift of the three methyl groups at C-3, C-3a and C-7a in 2a are very similar to those reported for the same methyl groups in pinguisone 1.[2]

Differences in behaviour between ketol 3 and the model compound 4 can be attributed to the presence of the 4-*exo*-methyl group in 3, which introduces negative eclipsing effects in the transition states for ions 2d and 2e. As a consequence, the relative stability of ion 2f is enhanced and a higher amount of compound 2c is formed. The higher amount of 2a with respect to 2 (3.8 : 1 molar ratio) is an aspect that does not correspond to the results obtained in the rearrangement of the model compound 4 (SCHEME 2) where 5a and 5b were obtained in 1 : 1 molar ratio. This fact could be explained as a result of the poorer migratory aptitude of secondary alkyl groups with respect to the primary ones which are known to migrate slower than carbonyls.[9]

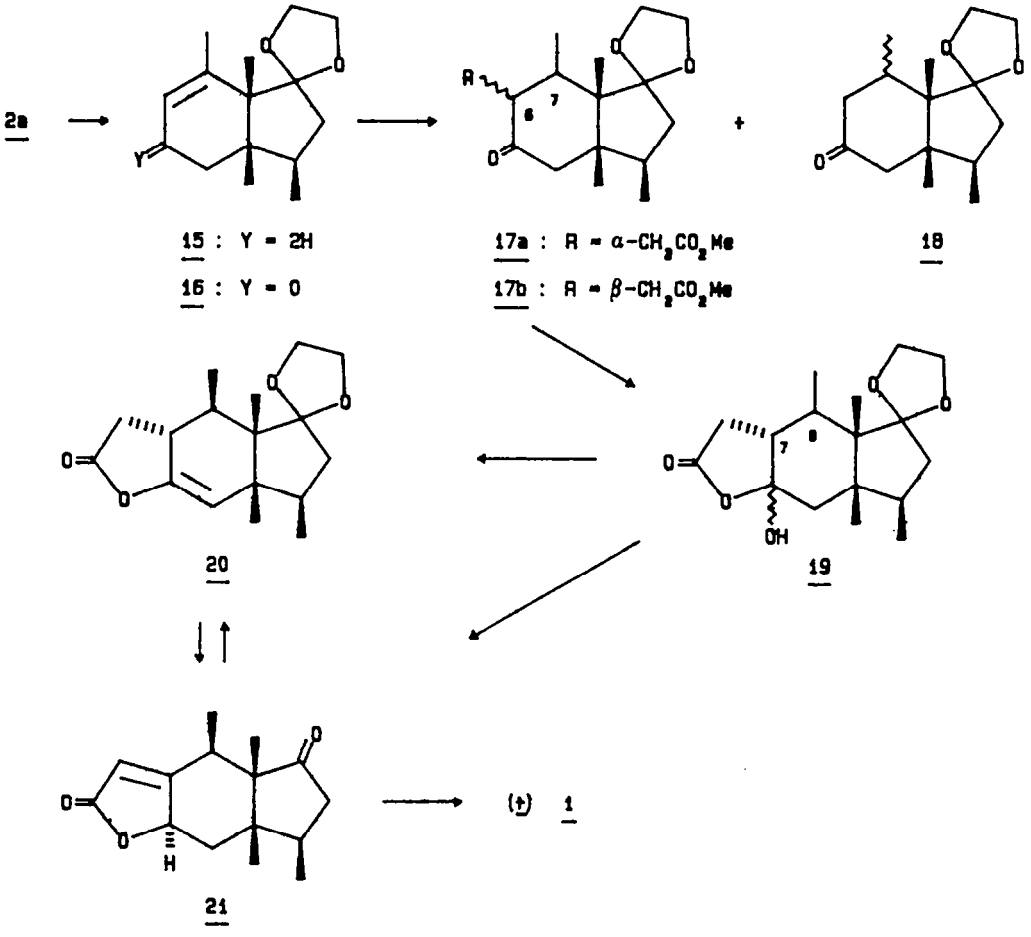
With the key synthetic intermediate 2a in the hand, the synthesis of (±) pinguisone 1 was carried out as follows (SCHEME 4).
After protection of 2a as 1,3-dioxolane 15, allylic oxidation gave the enone 16 which was converted to the γ-ketoesters 17a-b (9 : 1 *via* GC) by Birch reduction followed by quenching of the intermediate enolate with methylbromoacetate. Under these conditions the reduction product 18 was also formed (24%) together with a cyclopropane derivative known as a condensation product of methylbromoacetate.[15] Configurations at C-6 and C-7 in 17a were established by ^{1}H-NMR after basic hydrolysis to the corresponding γ-ketoacid which exists as the lactonic hemiacetal 19, while the epimeric situation at C-6 in 17b (not isolated) was tentatively assigned as a consequence of the conversion of the 9 : 1 mixture 17a-b to a 1 : 1 mixture under the action of sodium methoxide.

In the ^{1}H-NMR spectrum of 19, the protons at C-7 and C-8 (2.76 and 1.70 δ respectively) show, *inter alia*, a coupling constant (J = 12.0 Hz) characteristic of a *trans* diaxial situation, the same *trans* configuration being extendible to the protons at C-6 and C-7 in the precursor 17.

Dehydration of the lactonic hemiacetal 19 was first attempted by treating 19 with acetic anhydride and *p*-toluenesulfonic acid as a catalyst at room temperature. Under these conditions only the enol lactone 20 was obtained as the kinetic product. However, since the latter compound was not suitable for the next step,[16] a prolonged heating of 20 in Ac_2O/TsOH at 110°C was tried, which resulted in formation of the more stable butenolide 21, with contemporary loss of the acetalic protection. The same result was obtained by

direct heating of 19 at 110°C. A similar equilibrating situation between enol-lactones and butenolides has already been described for different systems.[17]

Scheme 4



Conversion of 21 to (±) pinguisone 1 was achieved taking advantage of the well known aptitude of DIBAH to reduce butenolides[16] and the described inertness of the carbonyl group of pinguisone 1 towards LAH. Thus DIBAH reduction of 21 at -20°C, followed by an acidic workup afforded (±) 1 in 60% yield.

EXPERIMENTAL

M.ps are uncorrected. ^{1}H-NMR spectra were recorded with either Varian EM 360 or XL 300 instruments using $CDCl_3$ as a solvent and TMS as an internal standard. ^{13}C-NMR spectra were carried out with a Varian XL 300 spectrometer, IR spectra with a Perkin Elmer 297 spectrometer and mass spectra by means of a Kratos MS-80 instrument. GC analyses were carried out on a HP-5880A Chromatograph by using a 25 m long capillary column (OV 101). Unless otherwise stated, column chromatographies were carried out on silica gel (50 : 1 weight ratio) by eluting with light petroleum (40-70°)-ethyl acetate mixtures. Dry sodium sulfate was always used in drying organic extracts. Where not reported boiling points were not determined because of thermal instability of the oily products.

2-(3-Bromopropyl)-2,6-dimethylcyclohexanone (7). A stirred solution of 2-allyl-2,6-dimethylcyclohexanone 6[10] (7.50 g, 45.1 mmoles) in 1.3 l of prepurified dry n-pentane was irradiated at room temperature with a high pressure Hg-Hanovia quartz lamp and streamed with N_2. Nitrogen stream was substituted with dry HBr and the reaction was carried out for 4.5 h. The resulting dark yellow solution was washed with $Na_2S_2O_3$ (satd. soln.) and brine. Drying and solvent removal gave 7 (11.0 g, 95%) as a *cis-trans* mixture not further purified. $IR_{\nu max}$ (CCl_4) 2970, 2940, 2870, 1710 cm^{-1}. ^1H-NMR: δ 3.50-3.22 (m, 2H; CH_2Br), 2.81-1.21 (m, 11H), 1.15 and 0.97 (ss, 3H; C_2-CH_3), 0.96 (d, J = 6.5 Hz, 3H; C_6-CH_3). MS, *m/z* (% rel. int.): 248/246 (M^+, isotopic pair, 1.4), 190/188 (37), 167 (100).

2-(3-Oxyacetylpropyl)-2,6-dimethylcyclohexanone (8). A benzenic solution (25 ml) of 7 : (10.6 g, 42.5 mmoles) and $(n\text{-}Bu)_4NCl$ (2.0 g, 6.7 mmoles) was added to an aqueous solution (75 ml) of potassium acetate (75 g) and the mixture was vigorously stirred at 75°C for 2 h. Extraction with Et_2O, drying and solvent removal gave 8 (9.0 g, 94%) as an oily *cis-trans* mixture not further purified. $IR_{\nu max}$ (CCl_4) 2970, 2940, 2870, 1740, 1705 cm^{-1}. ^1H-NMR: δ 4.13-3.80 (m, 2H; CH_2OAc), 2.83-0.80 (m, 11H), 1.96 (s, 3H; $-CO_2-CH_3$), 1.12 and 0.93 (ss, 3H; C_2-CH_3), 0.92 (d, J = 6.0 Hz, 3H; C_6-CH_3).

2-(3-Hydroxypropyl)-2,6-dimethylcyclohexanone (9). Acetate 8 (8.5 g, 37.6 mmoles) was hydrolized with 5% KOH in EtOH (200 ml) at room temperature for 1 h. The solution was concentrated *in vacuo*, brine (100 ml) was added and the suspension extracted with Et_2O. The organic phase was washed with H_2O, dried and evaporated to give 9 (5.5 g, 79%) as an oily *cis-trans* mixture not further purified. $IR_{\nu max}$ (CCl_4) 3640, 2930, 2870, 1705 cm^{-1}. ^1H-NMR: δ 3.53 (brt, J = 6.0 Hz, 2H; CH_2-OH), 3.00-0.77 (m, 11H), 2.85 (s, 1H; OH), 0.97 (brs, 3H; C_2-CH_3), 0.95 (d, J = 7.0 Hz, 3H; C_6-CH_3). MS, *m/z* (% rel. int.): 184 (M^+, 2), 166 (62), 151 (26), 136 (95), 108 (100).

3-(2-Oxo-1,3-dimethylcyclohexyl)-propanale (10). Ketol 9 (5.0 g, 27.1 mmoles) and PDC (20.4 g, 54.2 mmoles) were suspended in dry CH_2Cl_2 (200 ml) and refluxed under stirring for 3 h. Filtration through Florisil®, washing with Et_2O and solvent removal gave 10 (4.2 g, 84%) as a low melting *cis-trans* mixture. An analytical sample was obtained by evaporative distillation. Bp 77-79°C/1.5 mmHg. $IR_{\nu max}$ (CCl_4) 2970, 2930, 2870, 2720, 1730, 1710 cm^{-1}. ^1H-NMR: δ 9.73 (brt, J = 2 Hz, 1H; CHO), 3.00-0.80 (m, 11H), 1.00 and 0.97 (ss, 3H; C_1-CH_3), 0.97 (d, J = 6.0 Hz, 3H; C_3-CH_3). MS, *m/z* (% rel. int): 182 (M^+, 21), 167 (8), 166 (15), 140 (10), 126 (58), 125 (100).

exo- and *endo*-2-Hydroxy-1,5-dimethylbicyclo [3.3.1] nonan-9-one (11).[12a] A solution of compound 10 (4.0 g, 21.9 mmoles) in dioxane (50 ml) was slowly added at 0°C to a stirred solution of HCl 7 N (70 ml) in dioxane (50 ml). The resulting light solution was stirred at room temperature overnight, then cautiously neutralized with solid $NaHCO_3$. Water was added and the suspension extracted with Et_2O. The ethereal phase was washed with brine and the solvent was evaporated to give 11 as an *exo/endo* mixture (3.6 g, 96%). mp 37-51°C, lit. 35-50°C.[12a]

1,5-Dimethylbicyclo [3.3.1] nonan-2,9-dione (12).[12b] Ketol 11 (3.5 g, 19.2 mmoles) and PDC (14.5 g, 21.9 mmoles) were suspended in dry CH_2Cl_2 (100 ml) and refluxed under stirring for 2 h. Filtration through Florisil® and solvent removal afforded the already known 12 as a low melting solid (2.9 g, 85%). A sublimed analytical sample melted at 48°C (lit. 47-48°C).[12b]

1,5-Dimethylbicyclo [3.3.1] non-3-en-2,9-dione (13). Dione 12 (2.9 g, 16.1 mmoles) in 10 ml of dry THF was added at 0°C to a stirred solution of pyridinium bromide perbromide (5.2 g, 10.6 mmoles) in dry THF (200 ml) and stirring was mantained for 0.5 h. The resulting light yellow suspension was filtered into an 1 : 1 solution of NaCl (satd. soln.) and 0.1 N $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2. Washing of the organic phase with brine, drying and solvent removal afforded the 1,5-dimethyl-3-*endo*-bromobicyclo [3.3.1] nonan-2,9-dione (12a) (3.8 g, 90%) which was immediately dehydrohalogenated. $IR_{\nu max}$ (CCl_4) 1735, 1712 cm^{-1}. ^1H-NMR: δ 4.50 (dd, J_g = 5.0 and 2.5 Hz, 1H; C_3-H_β), 2.74 (dd, J_g = 16.5 and 5.0 Hz, 1H; C_4-H_β), 2.25 (dd, J_g = 16.5 and 2.5 Hz, 1H, C_4-H_α), 3.00-0.84 (m, 6H), 1.35 (s, 3H; C_1-CH_3), 1.24 (s, 3H; C_5-CH_3). MS, *m/z* (% rel. int.): 260/258 (M^+, isotopic pair, 5). Bromide 12a (3.8 g, 14.5 mmoles), lithium carbonate (3.6 g) and lithium bromide (5.9 g) were dissolved in DMF (50 ml) and warmed at 100°C under stirring for 2 h. The resulting mixture was poured into brine and extracted twice with Et_2O and CH_2Cl_2. The organic phases were washed with brine and water, dried and evaporated to give 13 (2.0 g, 78%) as a liquid not further purified. $IR_{\nu max}$ (CCl_4) 2940, 1730, 1675 cm^{-1}. ^1H-NMR: δ 6.71 (d, J = 10.0 Hz, 1H; C_4-H), 6.30 (d, J = 10.0 Hz, 1H; C_3-H), 2.33-0.60 (m, 6H), 1.23 (s, 3H; C_1-CH_3), 1.13 (s, 3H; C_5-CH_3). MS, *m/z* (% rel. int.): 178 (M^+, 97), 163 (100), 135 (65).

1,4β,5-Trimethylbicyclo [3.3.1] non-2-en-2-trimethylsilyloxy-9-one (14). A stirred suspension of dry CuI (4.1 g, 21.6 mmoles) in dry Et_2O (60 ml) was cooled at -25°C under N_2 and methyllithium (1.6 M in Et_2O, 27.0 ml) was added through a rubber septum with a syringe. After 15 min stirring the enone 13 (1.9 g, 10.7 mmoles) in 50 ml of dry Et_2O was added and the mixture was left under stirring at -20°C for 2 h. At the end a solution of distilled Me_3SiCl (5.8 g) in Et_2O (30 ml) was added and the resulting white suspension was stirred at -20°C for additional 2 h. Filtration and solvent removal afforded 14 (2.5 g, 88%) as an oil, pure (97%) *via* GC. $IR_{\nu max}$ (CCl_4) 2960, 2880, 1715, 1660 cm^{-1}. ^1H-NMR: δ 4.86 (d, J = 4.5 Hz, 1H; C_3-H), 2.91-0.89 (m, 7H), 0.97 (s, 3H; C_1-CH_3), 0.89 (s, 3H; C_5-CH_3), 0.78 (d, J = 7 Hz, 3H; C_4-CH_3). MS, *m/z* (% rel. int.): 266 (M^+, 85), 251 (100), 223 (47), 197 (60).

1,4β,5-Trimethylbicyclo [3.3.1] nonan-2,9-dione (14a). The silylenolether 14 (0.05 g) was dissolved in a THF/AcOH/H_2O mixture (0.5 ml) and stirred for 1 h. Neutralization with $NaHCO_3$, extraction with Et_2O, drying and solvent removal left 14a (0.03 g). $IR_{\nu max}$ (CCl_4) 2960, 2850, 1730, 1705 cm^{-1}. ^1H-NMR: δ 3.26-0.74 (m, 9H), 1.15 (s, 3H; C_1-CH_3), 1.14 (s, 3H; C_5-CH_3), 0.85 (d, J = 7.0 Hz, 3H; C_4-CH_3). MS, *m/z* (% rel. int.): 194 (M^+, 30), 125 (100), 81 (12).

9-syn-Hydroxy-1,4β,5,9-tetramethylbicyclo [3.3.1] nonan-2-one (3). Silylenolether 14 (2.3 g, 8.6 mmoles) in dry THF (60 ml) was placed in a flask equipped with rubber septum and N_2 stream and cooled at -78°C. A 1.6 M solution of MeLi in Et_2O (11.3 ml, 18.1 mmoles) was added by a syringe and the mixture was stirred at -78°C for 1 h. The resulting suspension was poured into aqueous NH_4Cl (60 ml satd. soln.) and thoroughly washed with brine, dried and evaporated to give 3 (1.7 g, 97%) as a solid. mp (from hexane) 75.5-76.5°C. $IR_{\nu max}$ (CCl_4) 3630, 2980, 2880, 1705 1100 cm^{-1}. ^1H-NMR: δ 2.640 (dd, J_g = 16.06 and 8.79 Hz, 1H; C_3-H_α), 2.480 (dd J_g = 16.06 and 7.33 Hz, 1H; C_3-H_β), 1.860 (ddq, J_g = 8.79, 7.33 and 7.40 Hz, 1H; C_4-H_α), 1.70-1.30 (m, 6H), 1.400 (brs, 1H; OH), 1.220 (s, 3H; C_9-CH_3), 1.105 (d, J = 7.40 Hz, 3H; C_4-CH_3), 1.078 (s, 3H; C_1-CH_3), 1.037 (s, 3H; C_5-CH_3). ^{13}C-NMR: δ 212.42 (C_2), 78.76 (C_9), 53.27 (C_1), 48.02 (C_3), 41.79, 39.38 (C_5), 37.09, 35.80 (C_4), 21.90, 21.54, 19.77, 19.71, 17.81. MS *m/z* (% rel. int.): 210 (M^+, 23), 192 (19), 177 (11), 149 (27), 123 (100). HRMS, found: 210.163. Calc. for $C_{13}H_{22}O_2$: 210.162.

Dehydration-rearrangement of 3. Isolation of 3 β,3aβ,7,7aβ-tetramethyl 2,3,3a,4,5,7a-hexahyroinden-1-one (2a), 3β,3aβ,4,7aβ-tetramethyl-2,3,5a,6,7,7a-hexahydroinden-1-one (2b) and 3aβ,6,7,7aβ-tetramethyl-1,2,3,3a,7,7a-hexahydro inden-4-one (2c). Compound 3 (1.5 g, 7.1 mmoles) in dry benzene (0.5 l) was added to *p*-toluenesulfonic acid adsorbed on silica gel (30 g)[14] and the mixture was heated at 60°C under stirring for 20 min. Light petroleum 30-50° (150 ml) was added, the suspension poured into a chromatographic column and eluted with Et_2O. Solvent removal with a Vigreux column left a crude oily residue (1.2 g) which was adsorbed on silica gel (120 g) and eluted with pentane-Et_2O (95 : 5). The first compound eluted (0.22 g, 16%) was identified as 2b. $IR_{\nu max}$ (CCl_4) 3020, 2850, 1735 cm^{-1}. ^1H-NMR: δ 5.49 (brm, 1H; C_5-H), 2.65-0.63 (m, 7H), 1.54 (m, 3H; C_4-CH_3), 0.98 (s, 3H; C_{7a}-CH_3), 0.94 (d, J = 6.5 Hz, 3H; C_3-CH_3), 0.70 (s, 3H; C_{3a}-CH_3). ^{13}C-NMR: δ 219.72 (C_1), 132.81 (C_6), 124.38 (C_5), 59.19 (C_{7a}), 43.44 (C_{3a}), 42.36, 30.14, 25.76, 22.35, 19.60, 18.20, 16.49, 13.92. MS,*m/z* (% rel. int.): 192 (M^+, 43), 177 (6), 149 (11), 122 (100). HRMS, fuond 192.1507. Calc. for $C_{13}H_{20}O$: 192.1513.
The second compound eluted was 2a (0.60 g, 59%). $IR^{\nu max}$ (CCl_4) 3030, 2980, 2880, 1740 cm^{-1}. ^1H-NMR: δ 5.35 (brm, 1H; C_6-H), 2.70-0.77 (m, 7H), 1.71 (m, 3H; C_7-CH_3), 1.09 (d, J = 6.5 Hz, 3H; C_3-CH_3), 0.86 (s, 3H; C_{7a}-CH_3), 0.81 (s, 3H; C_{3a}-CH_3). ^{13}C-NMR: δ 220.94 (C_1), 132.20 (C_7), 121.67 (C_6), 53.79 (C_{7a}), 46.45 (C_{3a}), 43.56, 36.29, 28.38, 21.89, 21.34, 16.94, 16.08, 14.86. MS, *m/z* (% rel. int.): 192 (M^+, 32), 177 (6), 122 (100). HRMS, found 192.153. Calc. for $C_{13}H_{20}O$: 192.1513.
Subsequent elution gave a mixture (0.16 g, 12%, 2 peaks via GC) identified as 2c. Repeated preparative chromatography allowed the isolation of a small pure sample of the more abundant one. $IR_{\nu max}$ (CCl_4) 3030, 2980, 2880, 1670, 1640 cm^{-1}. ^1H-NMR: δ 5.78 (m, 1H; C_5-H), 2.77-0.77 (m, 7H), 1.88 (m, 3H; C_6-CH_3), 1.12 (d, J = 7.0 Hz, 3H; C_7-CH_3), 1.00 (s, 3H; C_{4a}-CH_3), 0.97 (s, 3H; C_{7a}-CH_3). MS, *m/z* (% rel. int.): 192 (M^+, 15), 96 (100).
The reaction was repeated with an analytical sample of 3 using n-eicosane as an internal GC standard and afforded 2a, 2b and 2c in 65%, 17% and 14% yield respectively.

Dehydration-rearrangement of 3. Isolation of 1,4β,5-trimethyl-9-methylenebi cyclo [3.3.1] nonan-2-one (3b). Compound 3 (0.10 g) was dissolved in dry benzene (2 ml), p-toluenesulfonic acid (13 mg) was added and the mixture was refluxed for 2 h using a Dean-Stark trap. GC analysis showed 2a (21%), 2b (12%), 2c (6%) and a new product (60%). After neutralization and extraction with Et_2O, solvent removal left a crude residue (80 mg) which was adsorbed on a preparative plate and eluted to give 3b (45 mg, 50%). $IR_{\nu max}$ (CCl_4) 3100,

2980, 2850, 1705, 1635 cm^{-1}. ^{1}H-NMR: δ 4.98 (brs, 1H; C_9=CH), 4.69 (brs, 1H; C_9=CH), 2.96-0.77 (m, 9H), 1.20 (s, 3H; C_1-CH_3), 1.13 (s, 3H; C_5-CH_3), 0.93 (d, J = 6.5 Hz, 3H; C_4-CH_3). MS, *m/z* (% rel. int): 192 (M^+, 50), 177 (100). Compound 9b (10 mg) was refluxed in dry benzene with *p*-TsOH (molar ratio 1 : 0.5) as a catalyst and was completely consumed in 2 h to give 2a, 2b and 2c in 55%, 27% and 18% yield respectively (*via* GC).

1,1-Ethylenedioxy-3β,3aβ,7,7aβ-tetramethyl-2,3,3a,4,5,7a-hexahydroindene (15). Compound 2a (0.70 g, 3.6 mmoles), ethyleneglycol (7.5 mmoles) and p-toluenesulfonic acid (0.3 mmoles) were refluxed in dry benzene (35 ml) using a Dean-Stark trap and adding some molecular sieves. After two days the mixture was filtered, washed with $NaHCO_3$ and the aqueous phase extracted with Et_2O. The collected organic phases were dried and evaporated to dryness to afford a crude mixture (0.82 g). Column chromatography gave 2a (0.13 g, 20%) and 15 (0.66 g, 80%). $IR_{\nu max}$ (CCl_4) 3020, 2960, 2880, 1070 cm^{-1}. ^{1}H-NMR: δ 5.30 (m, 1H; C_6-H), 3.83 (m, 4H; O-$(CH_2)_2$-O), 2.50-0.67 (m, 7H), 1.71 (m, 3H; C_7-CH_3), 1.02 (d, J = 6.5 Hz, 3H; C_3-CH_3), 0.99 (s, 3H; C_{7a}-CH_3), 0.81 (s, 3H; C_{3a}-CH_3). ^{13}C-NMR: δ 140.25 (C_7), 120.27 (C_6), 116.58 (C_1), 64.52 (C_{1a}), 64.10 (C_{1b}), 49.91 (C_{7a}), 46.18 (C_{3a}), 44.67, 40.24, 26.11, 22.49, 21.35, 17.75, 14.45, 14.17. MS *m/z* (% rel. int.): 236 (M^+, 2); 113 (100); 107 (15); 99 (43).
The residual substrate 2a was recycled as above to give additional 15 (0.12 g).

1,1-Ethylenedioxy-3β,3aβ,7,7aβ-tetramethyl-2,3,3a,4,5,7a-hexahydroinden-5-one (16). A stirred suspension of dried CrO_3 (6.2 g) in dry CH_2Cl_2 (70 ml) was cooled at -20°C, 3,5-dimethylpyrazol (7.9 g) was quickly added and the deep red mixture was stirred for 15 min. Ketal 15 (0.75 g, 3.2 mmoles) was added dropwise and temperature was kept at -20°C for 2 h. At the end 10% aqueous NaOH (20 ml) was added and stirring was continued at 0°C for 1 h. The mixture was extracted with Et_2O, the extracts washed with brine, dried and evaporated to give a crude mixture (0.78 g). Column chromatography gave 1,1-ethylenedioxy-7-formyl-3β,3aβ,7aβ-trimethyl-2,3,3a,4,5,7a-hexahydroinden-5-one (16a) (0.07 g, 8%); $IR_{\nu max}$ (CCl_4) 2960, 2960, 2725, 1700, 1690 cm^{-1}. ^{1}H-NMR: δ 9.18 (s, 1H; CHO), 6.15 (s, 1H; C_6-H), 3.50-3.27 (m, 4H; O-$(CH_2)_2$-O), 2.36 (d, J = 16.6 Hz, 1H; C_4-H_α), 1.86 (d, J = 16.6 Hz, 1H; C_4-H_β), 2.20-1.00 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H; C_3-CH_3), 1.04 (s, 3H; C_{7a}-CH_3), 0.84 (s, 3H; C_{3a}-CH_3). MS, *m/z* (% rel. int.): 264 (M^+, 2), 113 (100), 99 (55).
Subsequent elution afforded 16 (0.66 g, 82%). $IR_{\nu max}$ (CCl_4) 3030, 2980, 2940, 1675, 1620, 1070 cm^{-1}. ^{1}H-NMR: δ 5.802 (q, J = 1.25 Hz, 1H; C_6-H), 3.95-3.75 (brm, 4H; O-$(CH_2)_2$-O), 2.587 (d, J =17.03 Hz, 1H; C_4-H_α), 2.391 (ddq, J_g = 9.82, 9.63 and 6.86 Hz, 1H; C_3-H), 2.198 (dd, J_g = 14.07 and 9.63 Hz, 1H; C_2-H), 2.166 (d, J = 17.03 Hz, 1H; C_4-H_β), 1.946 (d, J = 1.25 Hz, 3H; C_7-CH_3), 1.844 (dd, J_g = 14.07 and 9.82 Hz, 1H; C_2-H), 1.137 (s, 3H; C_{7a}-CH_3), 1.088 (d, J = 6.86 Hz, 3H; C_3-CH_3), 0.943 (s, 3H; C_{3a}-CH_3). ^{13}C-NMR: δ 198.36 (C_5), 166.03 (C_7), 125.35 (C_6), 117.13 (C_1), 65.01 (C_{1a}), 64.46 (C_{1b}), 53.97 (C_{7a}), 49.38 (C_{3a}), 44.23, 43.80, 38.56, 21.97, 17.84, 17.05, 14.66. MS *m/z* (% rel. int.): 250 (M^+, 3), 113 (100), 99 (72), 86 (71). HRMS, found: 250.1563. Calc. for $C_{15}H_{22}O_3$: 250.15688.

1,1-Ethylenedioxy-3β,3aβ,7β,7aβ-tetramethyl-6-carbomethoxymethyl-perhydroinden-5-one (17a), 1,1-ethylenedioxy-3β,3aβ,7,7aβ-tetramethyl-perhydroinden-5-one (18) and 3-hydroxy-1β,6β,9β,12β-tetramethyl-7βH-10,10-ethylenedioxy-5-oxo-4-oxatricyclo [7.3.0.0^{3,7}] dodecane (19). Lithium wires (37 mg, 5.3 mmoles) were dissolved in dry liquid ammonia (50 ml) under stirring and argon atmosphere at -78°C. After 30 min stirring, a solution of enone 16 (0.60 g, 2.4 mmoles) and t-butanol (0.14 g, 1.9 mmoles) in dry THF (10 ml) was added through a syringe and the mixture was stirred at -78°C for 30 min. Methylbromoacetate (0.9 g, 5.8 mmoles) in THF (3 ml) was added and the resulting suspension was left at room temperature until ammonia was evaporated. Water (50 ml) was added, the suspension extracted with Et_2O and the organic phase washed with brine and dried. Solvent removal left a residue which was adsorbed on silica gel and eluted (CH_2Cl_2-AcOEt 9 : 1) to afford 1,2,3-*trans*-tricarbomethoxycyclopropane[15] and a mixture of 17a-b [in 9 : 1 molar ratio (74% *via* GC). GC-MS coupling: *m/z* (% rel. int.): 324 (M^+, 5), 293 (23), 231 (7), 113 (100)] and 18 (24% *via* GC). The mixture 17a-b and 18 (0.72 g) was immediately suspended in a 2 M solution of K_2CO_3 in H_2O/MeOH (1 : 1, 100 ml) and stirred at room temperature overnight. Water was added and the alkaline suspension thoroughly extracted with Et_2O. The organic phase was washed with brine, dried and evaporated to give 18 (0.14 g, 24% referred to 16). $IR_{\nu max}$ (CCl_4) 2975, 1720, 1065 cm^{-1}. ^{1}H-NMR: δ 3.95-3.70 (m, 4H; O-$(CH_2)_2$-O), 2.476 (dd, J_g = 16.70 and 13.86 Hz, 1H; C_2-H_β), 2.302 (ddq, J_g = 13.86, 3.91 and 6.95 Hz, 1H; C_3-H), 2.290 (d, J = 15.54 Hz, 1H; C_4-H_α), 2.066 (d, J = 15.54 Hz, 1H; C_4-H_β), 2.049 (dd, J_g = 16.70 and 3.91 Hz, 1H; C_2-H_α), 1.970 (dd, J_g = 13.35 and 7.98 Hz, 1H; C_6-H_β), 1.837 (m, 1H; C_7-H), 1.551 (dd, J_g = 13.35 and 11.29 Hz, 1H; C_6-H_α), 1.013 (s, 3H; C_{3a}-CH_3), 1.002 (d, J = 6.89 Hz, 3H; C_7-CH_3), 0.987 (d, J= 6.95 Hz, 3H; C_3-CH_3), 0.916 (s, 3H, C_{7a}-CH_3). MS *m/z* (% rel. int.): 252 (M^+, 0.8); 113 (100); 99 (19).

The alkaline mother liquor was cooled at 0°C and cautiously acidified at pH 5 under stirring with NH_4Cl. Extraction with Et_2O, drying and solvent removal afforded 19 (0.54 g, 73% referred to 18). mp (from light petroleum-AcOEt) 158-159°C. $IR_{\nu max}$ (CCl_4) 3510, 2980, 1750 cm^{-1}. ^1H-NMR: δ 3.91-3.74 (m, 4H; O-$(CH_2)_2$-O), 2.666 (ddd, J_g = 12.00, 4.33 and 6.60 Hz, 1H; C_7-H_β), 2.665 (dd, J_g = 17.23 and 6.60 Hz, 1H; C_6-H_α), 2.561 (dd, J_g = 17.25 and 4.33 Hz, C_6-H_β), 2.545 (ddq, J_g = 9.59, 9.56 and 6.00 Hz, 1H; C_{12}-H_α), 2.527 (d, J = 14.40 Hz, 1H; C_2-H_α), 2.202 (d, J = 14.40 Hz, 1H; C_2-H_β), 2.193 (dd, J_g = 14.28 and 9.39 Hz, 1H; C_{11}-H_α), 1.708 (dq, J_g = 12.00 and 6.60 Hz, 1H; C_8-H_α), 1.564 (dd, J_g = 14.28 and 9.86 Hz, 1H; C_{11}-H_β), 1.426 (brs, 1H; C_3-OH), 1.04 (d, J = 6.54 Hz, 6H; C_8-CH_3 and C_{12}-CH_3), 1.057 (s, 3H; C_9-CH_3), 0.859 (s, 3H; C_1-CH_3). ^{13}C-NMR: δ 186.81 (C_5), 136.20 (C_3), 117.31 (C_{10}), 65.12 (C_{10a}), 64.21 (C_{10b}), 55.07 (C_9), 47.97 (C_1), 46.94, 46.85, 43.96, 43.77, 32.74, 29.67, 18.04, 17.52, 17.42, 15.25.
HRMS, found: 310.1770. Calc. for $C_{17}H_{26}O_5$: 310.1780.

Equilibration of 17a-b. A small sample of the mixture 17a-b (9 : 1 *via* GC) and 18 was dissolved in methanol containing a trace of sodium and left at room temperature overnight. GC analysis showed 17a-b in 1 : 1 ratio while 18 was unaffected.

1β,8β,9β,12β-Tetramethyl-7βH-10,10-ethylenedioxy-5-oxo-4-oxatricyclo [7.3.0.$0^{3,7}$] dodec-2-ene (20). Keto acid 19 (20 mg, 0.06 mmoles) was dissolved in 0.3 ml of acetic anhydride, one crystal of *p*-TsOH was added and the solution was left at room temperature. After 2 h, the mixture was poured into saturated solution of $NaHCO_3$ (10 ml) and stirred until CO_2 evolution ceased. The aqueous solution was extracted with $CHCl_3$ and the organic phase was dried. Solvent removal left a crude mixture which was purified by PLC to give 20 (15 mg, 85%). $IR_{\nu max}$ (CCl_4) 2960, 2880, 1815, 1715, 1115, 1085 cm^{-1}. ^1H-NMR: δ 5.247 (d, J = 1.84 Hz, 1H; C_2-H), 4.00-3.78 (m, 4H; O-$(CH_2)_2$-O), 2.784 (dddd, J_g = 11.02, 10.66, 8.86 and 1.84 Hz, 1H; C_7-H_β), 2.769 (dd, J_g = 19.05 and 8.86 Hz, 1H; C_6-H_β), 2.291 (ddq, J_g = 10.50, 5.90 and 7.10 Hz, 1H; C_{12}-H_α), 2.265 (dd J_g = 19.05 and 10.66 Hz, 1H; C_6-H_α), 2.074 (dd, J_g = 13.60 and 10.50 Hz, 1H; C_{11}-H_β), 1.481 (dq, J_g = 11.02 and 6.50 Hz, 1H; C_8-H_α), 1.404 (dd, J_g = 13.60 and 5.90 Hz, 1H; C_{11}-H_α), 0. 998 (d, J = 7.10 Hz, 3H; C_{12}-CH_3), 0.993 (s, 3H; C_9-CH_3), 0.982 (d J = 6.50 Hz, 3H; C_8-CH_3), 0.901 (s, 3H; C_1-CH_3). MS *m/z* (% rel. int.): 292 (M^+, 6), 220 (7), 205 (25), 179 (14), 113 (100).

1β,8β,9β,12β-Tetramethyl-3αH-5-oxo-4-oxatricyclo [7.3.0.$0^{3,7}$] dodec-6-en-10-one (21). Ketoacid 19 (0.30 g, 0.97 mmoles) was dissolved in distilled acetic anhydride (3 ml) containing 0.5% of *p*-TsOH and heated at 110°C for 20 h. The resulting mixture was poured into excess of aqueous $NaHCO_3$ (satd. soln.) and stirred until CO_2 evolution ceased. Extraction with $CHCl_3$, drying of the organic phase and solvent removal left a crude residue which was purified by column chromatography to afford pure 21 (0.2 g, 71%). mp (from hexane-AcOEt) 136-137°C. $IR_{\nu max}$ (CCl_4) 2980, 2920, 1760, 1740, 1645 cm^{-1}. ^1H-NMR: δ 5.850 (dd, J_g = 2.93 and 1.57 Hz, 1H; C_6-H), 4.845 (ddd, J_g = 11.70, 6.34 and 1.57 Hz, 1H; C_3-H_α), 2.714 (dd, J_g = 20.29 and 9.28 Hz, 1H; C_{11}-H_α), 2.617 (qd, J_g = 6.78 and 2.93 Hz, 1H; C_8-H_α), 2.262 (ddq, J_g = 9.39, 9.28 and 7.05 Hz, C_{12}-H_α), 2.025 (dd, J_g = 12.70 and 6.34 Hz, 1H; C_2-H_α), 1.804 (dd, J_g = 20.29 and 9.39 Hz, 1H; C_{11}-H_β), 1.544 (dd, J_g = 12.70 and 11.70 Hz, 1H; C_2-H_β), 1.365 (d, J = 6.78 Hz, 3H; C_8-CH_3), 1.167 (s, 3H; C_9-CH_3), 1.091 (d, J = 7.05 Hz, 3H; C_{12}-CH_3), 0.942 (s, 3H; C_1-CH_3). ^{13}C-NMR: δ 220.84 (C_{10}), 174.17 (C_5), 172.73 (C_7), 113.76 (C_6), 78.43 (C_3), 55.49 (c_9), 50.36 (C_1), 42.56, 39.65, 38.95, 30.44, 17.70, 16.64, 15.35, 13,07. MS *m/z* (% rel. int.): 248 (M^+, 9); 164 (15); 124 (100); 110 (33). HRMS, found: 248.14035. Calc for $C_{15}H_{20}O_3$: 248.14123.

(±) Pinguisone (1). A solution of butenolide 21 (50 mg, 0.20 mmoles) in dry THF (2.0 ml) was cooled at -25°C under stirring and N_2 stream, then a 17% solution of DIBAH (0.23 ml) was added by a syringe and the mixture was stirred at -25°C for 40 min. 2 N Sulfuric acid (0.5 ml) was added and stirring was continued at -5°C for 15 min. At the end the mixture was poured into ice/water and extracted with Et_2O. The extracts were washed with $NaHCO_3$, dried and evaporated to leave a solid (35 mg). Column chromatography gave pure 1 (28 mg, 60%, crystallized from n-heptane, mp 63°C, lit.[2] 63°C), whose spectroscopic properties were superimposable with those described in the literature[2].

Acknowledgement. We are indebted to the Italian Board of Education (MPI) for financial support.

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