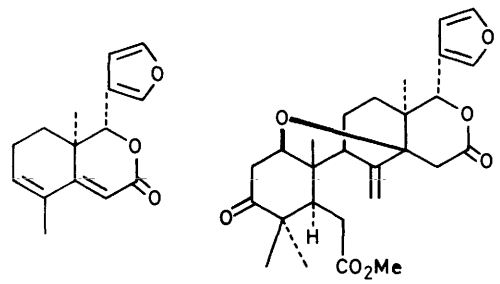
Synthetic Studies on Terpenoid Compounds. Part 14.[1] Total Synthesis of Pyroangolensolide[2]

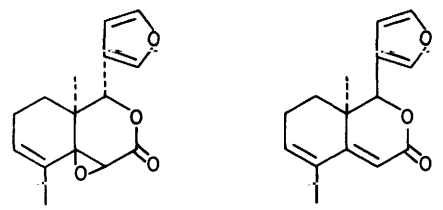
Takashi Tokoroyama,* Yoshiyasu Fukuyama, and (in part) Yasuhito Kotsuji
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

4,8-Dimethyl-1,4,5,6,7,7a-hexahydroinden-2-one (**7**), obtained by Wichterle annelation of 2,6-dimethylcyclohexanone, was converted into 1-hydroxy-5,8-dimethyl-1,7,8,9-tetrahydro-3*H*-2-benzopyran-3-one (**26**). Treatment of compound (**26**) with 3-lithiofuran afforded pyroangolensolide (**1**) together with its diastereoisomer (**4**).

Pyroangolensolide (**1**), a pyrolysis product of methyl angolensate (**2**)[3] is a representative of B-ring cleaved limonoids and contains a C/D ring structure characteristic of such compounds.[4] Notably, compound (**1**) has been correlated with calodendrolide (**3**),[5] a naturally occurring degraded limonoid, and this fact has provided the basis for the assignment of structure to the latter. In the course of our synthetic studies on limonoid and related compounds,[1] pyroangolensolide (**1**) seemed to be a target of some importance and here we report both its synthesis and that of its diastereoisomer (**4**). Recently, Grieco and co-workers[6] published an alternative synthesis of both compounds and confirmed their structures by a single-crystal *X*-ray analysis of (**4**).



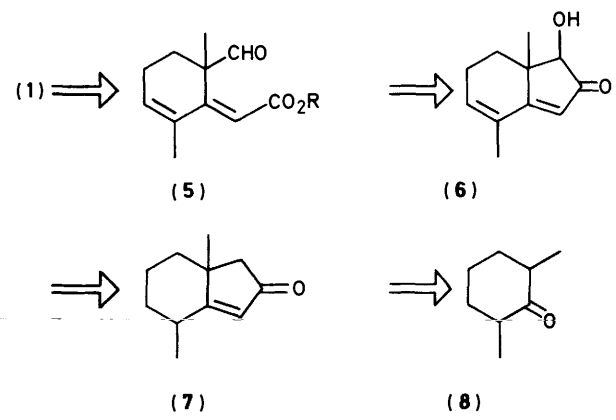
(**1**) (**2**)



(**3**) (**4**)

Our synthetic plan is illustrated in Scheme 1. When we disconnect the β-furyl anion synthon first, the aldehyde ester (**5**) emerges as an obvious key intermediate. The necessary functionalities and *Z*-geometry of the acrylate side-chain could be conveniently secured by ring cleavage of the bicyclic ketol (**6**), which, in turn, would be derivable from hexahydroindenone (**7**). Thus the starting point of our synthesis was the preparation of 4,8-dimethyl-1,4,5,6,7,7a-hexahydroinden-2-one (**7**).

The alkylation of 2-butylthiomethylene-6-methylcyclohexanone (**9**)[7] with 2,3-dichloropropene followed by hydrolysis of the resulting product with 90% sulphuric acid afforded the diketone (**11**). Although the aldol cyclization of (**11**) and



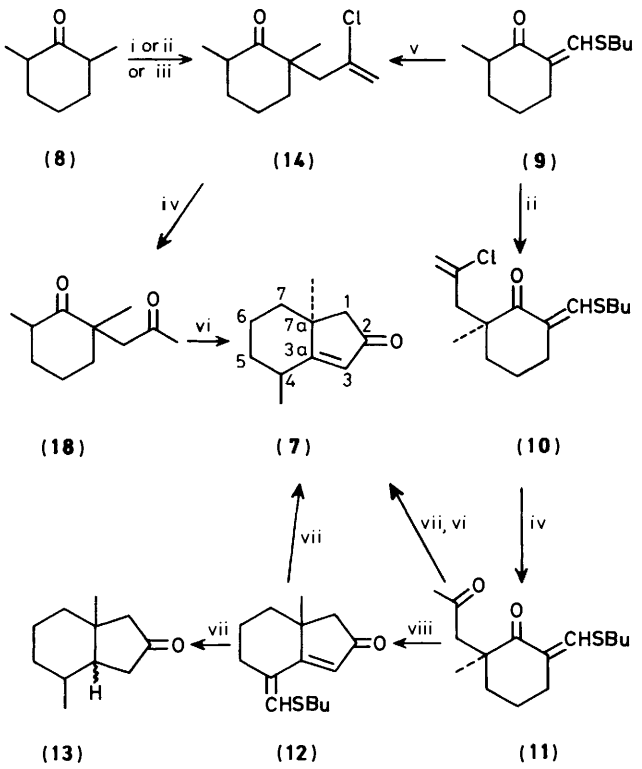
(**5**) (**6**)

(**7**) (**8**)

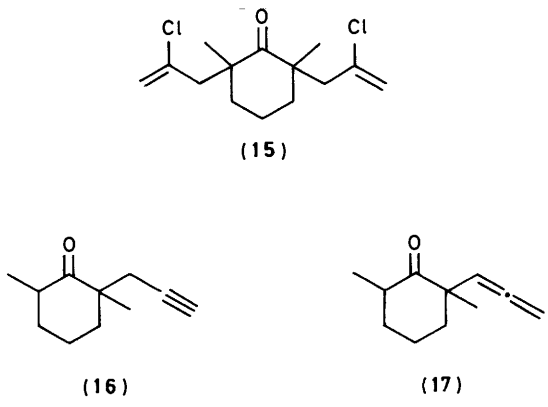
Scheme 1.

subsequent reduction of the resulting product with Raney Ni gave the desired enone (**7**)[8] contaminated with the corresponding dihydro compound (**13**), reversal of the reaction sequence gave compound (**7**) as the sole product in 34% overall yield from (**9**). The n.m.r. spectrum of (**7**) indicated that this product was stereochemically almost homogeneous and the *trans*-dimethyl structure is reasonably assigned on the grounds of thermodynamic stability. The application of Coat's reduction–alkylation procedure[9] to (**9**), using 2,3-dichloropropene as the alkylating agent, led to the formation of the product (**14**) in 74% yield.

Compound (**14**) was prepared more conveniently by the direct alkylation of 2,6-dimethylcyclohexanone (**8**) under the conditions specified in Scheme 2 in yields of 34—46% with recovery of starting material (< 30%). The reaction with sodium hydride in dimethoxyethane (DME) resulted in the best conversion, although considerable amounts of the dialkylated product (**15**) were formed. In the transformation with potassium t-butoxide in benzene, prolonged heating brought about the formation of the elimination products (**16**) and (**17**) from (**14**) in increasing amounts. It was noted that product (**14**) obtained by the alkylation of (**8**) was a mixture of the diastereoisomers (**14a**) and (**14b**) in approximately equal amounts (t.l.c. and ^{1}H n.m.r.), while the product from (**9**) represented the single isomer (**14b**). The acid hydrolysis of (**14**) from (**8**) afforded the corresponding diketones (**18**) as a mixture of diastereoisomers which were separable by silica gel chromatography. The stereochemical relationship in (**14**) and (**18**) could be assigned on the basis of ^{1}H n.m.r. chemical shifts (see Experimental section for the detailed data). The 2-methyl signal for (**14a**) and (**18a**) was deshielded compared with that for (**14b**) and (**18b**) respectively, while the reversed relationship was observed for the methylene resonance of the propenyl or acetonyl chains. This fact indicates that the

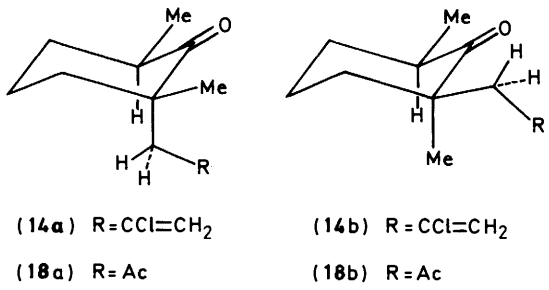


Scheme 2. *Reagents:* i, NaH, DME, $ClCH_2CCl{=}CH_2$; ii, NaH, THF–DMF, $ClCH_2CCl{=}CH_2$: iii, Bu^{t}OK, benzene, $ClCH_2CCl{=}CH_2$; iv, 90% H_2SO_4; v, Li, liq. NH_3, H_2O, THF, then $ClCH_2CCl{=}CH_2$; vi, KOH, MeOH; vii, Raney Ni, EtOH; viii, Bu^{t}OK, Bu^{t}OH, benzene

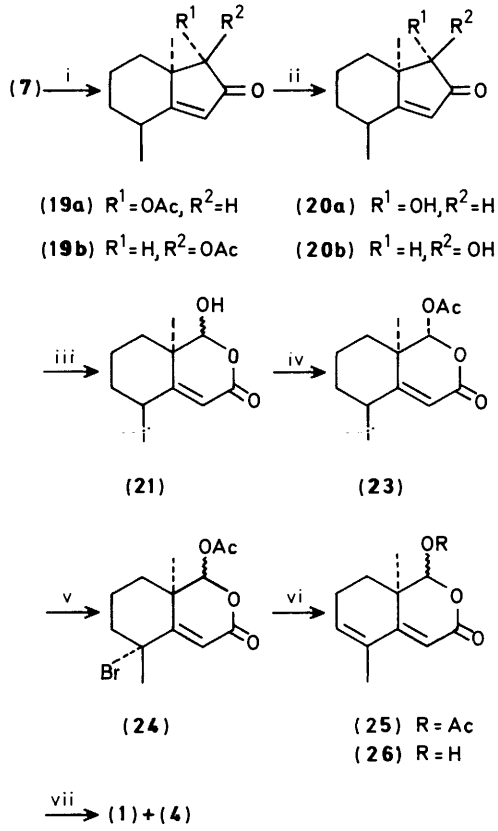


methyl and the methylene groups respectively are equatorially disposed to lie within the deshielding zone of the carbonyl group on one side in (**14a**) and (**18a**) and on the other in (**14b**) and (**18b**). Treatment of compound (**18**) with potassium hydroxide in methanol smoothly effected the conversion into (**7**). The yield of (**7**) from (**14**) was 74%. The Wichterle procedure for the annelation starting from (**8**) would be the method of choice in view of convenience and expediency for the preparation of our first sub-goal (**7**), although the yields in the alkylation reaction were modest (*ca.* 55% of the converted material).

The synthetic operations in the next stage were the introduction of an olefinic bond between C-4 and C-5, and bond cleavage between C-1 and C-2. Treatment of the hydroindenone intermediate (**7**) with lead tetra-acetate in refluxing benzene



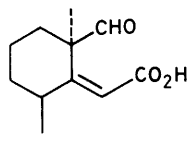
afforded the acetoxy ketone as a mixture of epimers (**19a**) and (**19b**) in a ratio of *ca.* 1:2. Hydrolysis with potassium carbonate in aqueous methanol gave a crystalline ketol (**20b**) in 74.4% yield as the major product accompanied by a small amount of the epimer (**20a**), which was isolable from the mother liquor



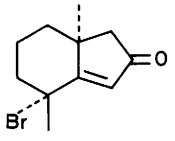
Scheme 3. *Reagents:* i, $Pb(OAc)_4$, benzene; ii, K_2CO_3, H_2O, MeOH; iii, $Pb(OAc)_4$, H_2O, AcOH; iv, Ac_2O, pyridine; v, NBS, CCl_4; vi, Li_2CO_3, DMF; vii, 3-furyl-lithium, THF

after the crystallization of (**20b**). The configuration of the hydroxy groups in (**20a**) and (**20b**) was assigned as shown by the comparison of the ^1H n.m.r. chemical shifts. The angular methyl signal of (**20a**) was more deshielded than that of (**20b**) as a result of the anisotropy effect of the neighbouring hydroxy group (δ 1.33 *vs.* 1.12). The configurational correlation between (**19**) and (**20**) was effected by the preparation of pure (**19b**) by the acetylation of (**20b**). Thus subsidiary signals observed in the ^1H n.m.r. spectrum of the acetoxylation product above could be ascribed to (**19a**). The chemical shifts of the angular methyl groups in (**19a**) and (**19b**) were δ 1.38 and 1.08 respectively.

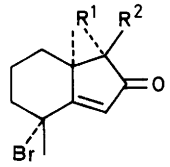
Equilibration with respect to the C-1 configuration had, therefore, occurred during the base hydrolysis. This conclusion is in conformity with the relative conformational stability of (**19a**) and (**19b**) both as revealed by inspection of models and also by the ease of the reagent attack in the formation of (**19**). When the reaction with lead tetra-acetate was applied to the bromo ketone (**27**) obtained by treatment of (**7**) with *N*-bromosuccinimide (NBS), a mixture of the epimeric acetates (**28a**) and (**28b**) was obtained in a ratio of 1:4 with elimination products (**29a**) and (**29b**). The configuration of the bromine atom in (**27**) was deduced to be α from the ^{1}H n.m.r. spectrum where the proton signal due to the angular methyl group was observed at a deshielded position (δ 1.58), the large paramagnetic anisotropy effect of the bromine atom being responsible. The angular methyl signals in (**28a**) and (**28b**) appeared at δ 1.72 and 1.42 respectively.



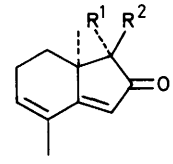
(**22**)



(**27**)



(**28a**) R^1=OAc, R^2=H
(**28b**) R^1=H, R^2=OAc



(**29a**) R^1=OAc, R^2=H
(**29b**) R^1=H, R^2=OAc

Although cleavage of the ketol (**20b**) failed with periodic acid it was smoothly effected with lead tetra-acetate to give an epimeric mixture (*ca.* 1:1) of the lactols (**21**) in 93.5% yield. The lactol structures were substantiated by i.r. absorption at 3 320 (OH), 1 700 (CO), and 1 620 cm^{-1} (double bond), and n.m.r. signals for the quaternary methyls (δ 1.2 and 1.5), the secondary methyl (δ 1.16), the hemiacetal proton (δ 5.30), and the vinyl protons [δ 5.76 and 5.80 (*J* 1.20 and 1.23)]. There was no evidence of an aldehyde signal in the n.m.r. spectra which suggests that the formyl carboxylic acid (**22**)/lactol equilibrium strongly favours the latter. As a result of steric requirements in the acetate, acetylation of the lactol mixture (**21**) furnished the single acetate (**23**) to which the α-orientation has been assigned on the basis of its conformational stability. On treatment with NBS the lactol acetate (**23**) was converted almost quantitatively into the bromo compound (**24**). The bromo substituent was introduced on the same side of the molecule as the angular methyl group as evidenced by the deshielded signal (δ 1.62) for the latter. Upon treatment with lithium carbonate and *N*,*N*-dimethylformamide (DMF) under reflux (**24**) afforded the dehydrobrominated product (**25**), which was hydrolysed to give the diene lactol (**26**), an equivalent of the key intermediate (**5**) conceived at the outset, in an overall yield of 79% from (**21**). Reaction of the lactol (**21**) with NBS gave directly the diene (**24**) albeit in lower yield (64%).

Finally, the crucial intermediate (**26**) was allowed to react with 3-lithiofuran. The reaction, proceeding slowly even at room temperature, took 2 days for completion. Chromatographic separation of the products afforded the diastereoisomeric β-furanoid lactones, m.p. 146—148 and 140—141 °C, in a ratio of 7:3 in 50% yield. The angular methyl signal for the major product was exhibited at δ 1.04 and for the minor at δ 1.38. When the diamagnetic shielding effect of the furan ring is taken in account, it is concluded that the major product is pyroangolensolide (**1**) with a *cis* configuration for the angular methyl group and the furan ring, and the minor product *epi*-angolensolide (**4**). The identity of the synthetic product with authentic pyroangolensolide was confirmed by a comparison of the i.r. and ^{1}H n.m.r. spectra*

Experimental

6-Butylthiomethylene-2-(2-chloroallyl)-2-methylcyclohexanone (**10**).—2-Butylthiomethylenecyclohexanone (**9**) (10.6 g, 0.05 mol) was added dropwise to a stirred suspension of potassium t-butoxide (11.2 g, 0.1 mol) in benzene under nitrogen atmosphere during 20 min and the stirring was continued for 1 h. 2,3-Dichloropropene (16.7 g, 0.15 mol) was added dropwise and the mixture was stirred at room temperature for 4 h and then heated under reflux for a further 4 h. After cooling, the mixture was diluted with water and the product extracted with ether. The ether layer was washed successively with 2M-HCl, saturated aqueous sodium hydrogen carbonate and brine, and dried ($MgSO_4$). Distillation afforded the *alkylated product* (**10**) (7 g, 49%) as colourless oil, b.p. 100 °C at 0.08 mmHg; $\nu_{max.}$(film) 1 660, 1 630, 1 540, 890, and 850 cm^{-1}; δ_H (100 MHz, $CDCl_3$) 1.02 (3 H, t, *J* 7 Hz, CH_2Me), 1.16 (3 H, s, Me), 2.40 (1 H, d, *J* 14 Hz, $CH_2CCl{=}CH_2$), 2.86 (2 H, t, *J* 7 Hz, SCH_2CH_2), 2.94 (1 H, d, *J* 14 Hz, $CH_2CCl{=}CH_2$), 5.10 (1 H, s, $=CH_2$), 5.22 (1 H, s, $=CH_2$), and 7.40 (3 H, t, *J* 2 Hz, =CHSBu).

6-Butylthiomethylene-2-methyl-2-(2-oxopropyl)cyclohexanone (**11**).—The chloroallyl ketone (**10**) (7.0 g, 24 mmol) was added in one portion to 90% sulphuric acid solution (80 ml) cooled to 0 °C. The mixture was vigorously stirred for 40 min during which time there was copious evolution of hydrogen chloride. The mixture was then poured onto ice and the product extracted with ether. The organic extract was washed with water, 10% aqueous sodium carbonate, and brine, and then dried. Evaporation of the solvent left the diketone (**11**) as a yellow oil, which was sufficiently pure for the next reaction; $\nu_{max.}$ 1 720, 1 660, and 1 550 cm^{-1}; δ_H 0.94 (3 H, t, *J* 7 Hz, CH_2Me), 1.02 (3 H, s, Me), 1.96 (3 H, s, COMe), 2.24 (1 H, d, *J* 16 Hz, CH_2CO), 2.80 (2 H, t, *J* 7 Hz, SCH_2CH_2), 3.04 (1 H, d, *J* 16 Hz, CH_2CO), and 7.20 (1 H, t, *J* 2 Hz, =CHBu).

4-Butylthiomethylene-8-methyl-1,4,5,6,7,7a-hexahydroinden-2-one (**12**).—A solution of the diketone (**11**) (6.4 g, 24 mmol) in anhydrous benzene (30 ml) was added dropwise to a solution of potassium t-butoxide (7.0 g, 0.07 mol) in anhydrous t-butyl alcohol and the mixture was stirred at room temperature for 18 h. It was then acidified with 2M-HCl, concentrated under reduced pressure to remove most of t-butyl alcohol, and extracted with ether. The organic extract was washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to provide an oil which was chromatographed on a column of silica gel (50 g). Elution with benzene–ethyl acetate (9:1) afforded the *indenone* (**12**) (5.4 g, 90%); $\nu_{max.}$(film) 3 060, 1 700, and 1 680 cm^{-1}; δ_H 0.96 (3 H, t, *J* 7.5 Hz, $MeCH_2$), 1.16 (3 H, s, Me), 2.16 (2 H, s, CH_2CO), 2.72 (2 H, t, *J* 7 Hz, SCH_2CH_2), 5.68 (1 H, C=CHCO), and 6.36 (1 H, d, *J* 2 Hz, =CHSBu).

* These data were kindly sent by Dr. K. Jewers of Tropical Products Institute, Ministry of Overseas Development, England, to whom we are grateful.

2-(2-*Chloroallyl*)-2,6-*dimethylcyclohexanone* (**14**).—(a) *From* 2,6-*dimethylcyclohexanone*. (i) By sodium hydride in dimethoxyethane (DME). A mixture of 2,6-dimethylcyclohexanone (40.59 g, 0.32 mol) and 2,3-dichloropropene (44 g, 0.39 mol) in DME (100 ml) was added to a suspension of sodium hydride (50% oil dispersion; 18 g, 0.35 mol) during 1 h under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and at 80—90 °C for 40 h. It was then poured onto ice–water and extracted with ether. The ether extract was washed successively with water, 2M hydrochloric acid, saturated aqueous hydrogen carbonate and brine, dried, and evaporated to leave an oil which was distilled. The fraction boiling in a range of 70—90 °C at 0.4 mmHg was collected (29.753 g, 46%); $\nu_{max.}$(film) 1 705, 1 625, 880, and 850 cm^{-1}. Mainly it consisted of a diastereoisomeric mixture of the monoalkylated products (**14a**) and (**14b**) in *ca.* equal amounts (^1H n.m.r.). These were separable by silica gel chromatography: (1*S**,6*R**)-2-(2-*chloroallyl*)-2-,6-*dimethylcyclohexanone* (**14a**); δ_H 1.01 (3 H, d, *J* 6 Hz, CH*Me*), 1.26 (3 H, s, Me), 2.63 (2 H, br s, a contiguous ABq, *J* 15 Hz, $CH_2CCl{=}CH_2$), and 5.09 and 5.22 (each 1 H, br s, $=CH_2$), and the (1*R**,6*R**) *compound* (**14b**); δ_H 0.99 (3 H, d, *J* 6 Hz, CH*Me*), 1.07 (3 H, s, Me), 2.42 and 3.02 (2 H, ABq, *J* 15 Hz, $CH_2CCl{=}CH_2$), 2.89 (1 H, m, COC*H*MeCH), and 5.09 and 5.22 (each 1 H br s, $=CH_2$). The higher boiling fraction contained mainly the dialkylated product (**15**) as a diastereoisomeric mixture; $\nu_{max.}(CHCl_3)$ 1 690, 1 630, and 890 cm^{-1}; δ_H 1.14 (3 H, s, Me), 1.19 (3 H, s, Me), 2.35, 2.88; 2.49, 2.83 (pairs of ABq, 2 H in total, $CH_2CCl{=}CH_2$), and 5.06 and 5.23 (each 1 H, br s, $=CH_2$).

(ii) By sodium hydride in tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF).[11] 2,6-Dimethylcyclohexanone (**8**) (18.9 g, 0.15 mol) was heated under reflux for 3 h with sodium hydride (60% oil dispersion; 7.3 g, 0.18 mol) in THF (180 ml) and DMF (230 ml). The mixture was then cooled in an ice-bath whilst 2,3-dichloropropene (2 g, 0.225 mol) was added dropwise; it was then stirred at ambient temperature for 96 h. Work-up as above afforded an oily product (30.4 g) which was distilled to give a diastereoisomeric mixture of (**14a**) and (**14b**) (10.16 g, 33.8%) with recovery of some (**8**) (4.16 g, 22%).

(iii) By potassium t-butoxide in benzene. To a stirred suspension of potassium t-butoxide (93 g, 0.833 mol) in dry benzene (850 ml) was added dropwise a solution of 2,6-dimethylcyclohexanone (70 g, 0.555 mol) in benzene (130 ml) during 25 min. After the mixture had been stirred for 1 h, a solution of 2,3-dichloropropene (123 g, 1.11 mol) in benzene (130 ml) was added during 45 min with ice-bath cooling. The reaction was continued at ambient temperature for 1 h and then under reflux for 8 h. The reaction mixture was diluted with water and extracted with ether, and the extract washed with 2M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, and dried. It was then evaporated to leave an oily residue which was fractionally distilled. After the recovery of 2,6-dimethylcyclohexanone (13.6 g, 19%), two fractions were obtained: (I) (13.8 g), b.p. 32—72 °C; (II) (39.5 g, 35%), b.p. 74—94 °C. The i.r. spectrum of the fraction I indicated that it was a mixture of the acetylenic compound (**16**) ($\nu_{max.}$ 3 300 and 2 120 cm^{-1}) and the allenic compound (**17**) ($\nu_{max.}$ 1 950 and 860 cm^{-1}) produced by dehydrohalogenation of the alkylated products (**14**). Fraction II represented the desired compounds (**14**).

(b) *From* 6-*butylthiomethylene*-2-*methylcyclohexanone* (**9**): *Coat's Reduction-alkylation Procedure*.—A solution of compound (**9**) (2.1 g, 10 mmol) in THF (30 ml) containing water (360 mg, 20 mmol) was added dropwise to a solution of metallic lithium (416 mg, 0.06 mol) in liquid ammonia (200 ml) during 30 min. Subsequently, 2,3-dichloropropene (6.66 g, 60 mmol) dissolved in THF (50 ml) was added during 10 min and the mixture stirred for 30 min whilst ammonia was allowed to evaporate. The residue was worked up and the oil obtained (3.6 g) was chromatographed on a column of silica gel (90 g). Elution with light petroleum–benzene (9:1) afforded compound (**14b**) (1.48 g, 74%).

4,8-*Dimethyl*-1,4,5,6,7,7a-*hexahydroinden*-2-*one* (**7**).—(a) *From* 2-(2-*chloroallyl*)-2,6-*dimethylcyclohexanone* (**14**). The diastereoisomeric mixture (**14**) (13.6 g, 60 mmol) was added in one portion to the vigorously stirred 90% sulphuric acid solution cooled to 0 °C and the stirring was continued for 10 min. The reaction mixture was poured into ice and work-up gave a diastereoisomeric mixture of the diketones (**18a**) and (**18b**) as an oil (15 g). The isomers were separated by silica gel chromatography to furnish (2*S**,6*R**)-2,6-dimethyl-2-(2-oxopropyl)cyclohexanone (**18a**); δ_H 1.02 (3 H, d, *J* 7 Hz, CH*Me*), 1.23 (3 H, s, Me), 2.12 (3 H, s, COMe), 2.33 and 2.78 (2 H, ABq, *J* 17 Hz, CH_2CO), 2.48 (1 H, m, C*H*MeCO) and (2*R**,6*R**)-2,6-*dimethyl*-2-(2-*oxopropyl*)*cyclohexanone* (**18b**); δ_H 0.98 (3 H, s, Me), 1.01 (3 H, d, *J* 7 Hz, CH*Me*), 2.06 (3 H, s, COMe), 2.62 (1 H, m, C*H*MeCO), and 2.63 and 2.91 (2 H, ABq, *J* 17 Hz, CH_2CO). For preparative purposes the diketone mixture was used in the subsequent reaction without separation of the isomers. A solution of the diketone mixture obtained above in MeOH (120 ml) was mixed with 1M aqueous potassium hydroxide (40 ml) and the mixture was stirred at room temperature for a few hours; it was then heated under reflux for 1 h. Most of MeOH was removed by evaporation under reduced pressure and water was added to the residue. Ether extraction gave an oily product which was distilled to give the *title compound* (**7**) as a colourless oil [9.87 g, 89% from (**14**)]; b.p. 78—80 °C at 0.7 mmHg (crystallized upon refrigerated storage) (Found: C, 80.25; H, 9.75. $C_{11}H_{16}O$ requires C, 80.44; H, 9.83%); *m*/*z* 164 (M^+); $\lambda_{max.}$ 233 nm (ε, 13 600); $\nu_{max.}$ 3 080, 1 718, and 1 616 cm^{-1}; δ 1.16 (3 H, d, *J* 6 Hz, CH*Me*), 1.26 (3 H, s, Me), 2.14 (2 H, d, a contiguous ABq, *J* 18 Hz, $COCH_2$), and 5.64 (1 H, d, *J* 2 Hz, COCH=CCH).

(b) *From* 6-*butylthiomethylene*-2-*methyl*-2-(2-*oxopropyl*)-*cyclohexanone* (**11**). A mixture of the diketone (**11**) (3.18 g, 12 mmol) and W-2 Raney Ni (15 g) in anhydrous EtOH (50 ml) was heated under reflux for 2 h. The metal was filtered off with the aid of Celite and the filtrate was evaporated under reduced pressure. The crude product (2.5 g) thus obtained was dissolved in MeOH (30 ml) and mixed with aqueous 1M potassium hydroxide (10 ml). The mixture was stirred at room temperature for 18 h and then heated under reflux for 1 h. Work-up afforded compound (**7**) (1.42 g, 72%).

(1*R**,7a*R**)-1-*Hydroxy*-4,8-*dimethyl*-1,4,5,6,7,7a-*hexahydroinden*-2-*one* (**20b**).—Lead tetra-acetate (37 g, 0.084 mol) was added to a solution of compound (**7**) (9.8 g, 59.7 mmol) in dry benzene (300 ml) and the mixture was refluxed for 20 h. The precipitated lead acetate was filtered off and the filtrate was washed successively with water, saturated aqueous sodium hydrogen carbonate and brine, and then dried. Evaporation of the solvent afforded a mixture of the acetates (**19a**) and (**19b**); $\nu_{max.}$ 1 750, 1 720, 1 660, and 1 230 cm^{-1}; δ 1.08 and 1.38† (3 H in total, s, Me), 1.17 (3 H, d, *J* 7 Hz, CH*Me*), 2.14 (3 H, s, OAc), 4.76† and 4.86 [1 H in total, s, COC*H*(OAc)]and 5.62† and 5.76 (1 H in total, d, *J* 2 Hz, COCH=CCH). The acetate mixture, without further purification, was dissolved in a mixture of MeOH (250 ml) and water (100 ml). After addition of potassium carbonate (11 g, 0.08 ml), the mixture was stirred at room temperature for 16 h. It was then concentrated under reduced pressure, diluted with water, and extracted with ether. Evaporation of the extract left a crystalline residue, which was recrystallised from ether–

† Smaller signals due to (1*S**,7a*R**)-acetate (**19a**): see text.

light petroleum to give the *title ketol* (**20b**) (8.0 g, 74.4%), m.p. 121—123 °C (Found: C, 73.5; H, 9.0. $C_{11}H_{26}O_2$ requires C, 73.3; H, 8.95%); $\nu_{max.}$($CHCl_3$) 3 390, 1 702, 1 690, 1 600, 1 255, 1 087, 968, and 815 cm^{-1}; δ_H 1.12 (3 H, s, Me), 1.20 (3 H, d, *J* 6 Hz, CH*Me*), 2.91 (1 H, d, *J* 2 Hz, CHO*H*), 3.69 (1 H, d, *J* 2 Hz, COC*H*OH), and 5.71 (1 H, d, *J* 2 Hz, COC*H*=CCH). Fractional crystallization of the material from the mother liquor afforded (1*S**,7a*R**)-1-*hydroxy*-4,8-*dimethyl*-1,4,5,6,7,7a-*hexahydroinden*-2-*one* (**20a**), m.p. 108—112 °C (Found: C, 73.3; H, 9.05. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%); $\nu_{max.}$($CHCl_3$) 3 535, 3 400, 1 718, 1 603, 1 247, 1 192, 1 082, and 850 cm^{-1}; δ_H 1.18 (3 H, d, *J* 6 Hz, CH*Me*), 1.33 (3 H, s, Me), 2.73 (1 H, d, *J* 3 Hz, CHO*H*), 3.83 (1 H, d, *J* 3 Hz, COC*H*OH), and 5.79 (1 H, d, *J* 1.5 Hz, COC*H*=CCH). The acetylation of compound (**20b**) with acetic anhydride and pyridine provided the pure *acetate* (**19b**) as crystals, m.p. 80.5—82 °C (from ether–light petroleum) (Found: C, 70.7; H, 8.25. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%); $\nu_{max.}$($CHCl_3$) 1 730, 1 610, 1 230, 1 070, and 865 cm^{-1}; δ_H 1.08 (3 H, s, Me), 1.17 (3 H, d, *J* 7 Hz, CH*Me*), 2.14 (3 H, s, OAc), 4.86 (1 H, s, COC*H*OAc), and 5.76 (1 H, d, *J* 2 Hz, COC*H*=CCH).

Lactol (**21**).—Lead tetra-acetate (7.54 g, 17 mmol) was added to a solution of the ketol (**20b**) (2.1 g, 17 mmol) in acetic acid (40 ml) containing water (7 ml). The mixture was stirred at 50 °C for 3 h. The precipitate was filtered off and the filtrate shaken with ether and water. The ether layer was washed thoroughly with brine and the solvent was evaporated to give the *lactol* (**21**) as a crystalline mass (2.13 g, 93.3%); recrystallization from ether afforded needles, m.p. 150—151 °C (Found: C, 67.09; H, 8.07. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.22%); $\nu_{max.}$($CHCl_3$) 3 320, 1 700, 1 620, 1 230, and 990 cm^{-1}; δ_H 1.16 (3 H, d, *J* 6 Hz, C*HMe*), 1.20 and 1.26 (3 H in total, s, Me), 5.30 (1 H, s, CO_2CHOH), and 5.76 and 5.80 (1 H in total, d, *J* 1.2 and 1.5 Hz, OCOC*H*=CCH).

Lactol Acetate (**23**).—The lactol (**21**) (2.13 g, 11 mmol) was treated with acetic anhydride (6 ml) and pyridine (8 ml) at room temperature overnight. Work-up furnished the *acetate* (**23**) (2.089 g, 81.3%) as needles, m.p. 121—122 °C (from EtOH) (Found: C, 65.25; H, 7.55. $C_{23}H_{18}O_4$ requires C, 65.53; H, 7.61%); $\nu_{max.}$($CHCl_3$) 1 770, 1 730, 1 610, and 1 030 cm^{-1}; δ_H 1.16 (3 H, d, *J* 7 Hz, CH*Me*), 1.26 (3 H, s, Me), 2.18 (3 H, s, OAc), 5.82 (1 H, d, *J* 2 Hz, OCOC*H*=CCH), and 6.16 (1 H, s, CO_2CHOAc).

Bromo-lactol Acetate (**24**).—A mixture of compound (**23**) (1.92 g, 8 mmol), NBS (1.46 g, 8.2 mmol), dibenzoyl peroxide (10 mg), and carbon tetrachloride (40 ml) was refluxed for 15 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The crystalline residue was recrystallized from EtOH to afford the *bromo-lactol acetate* (**24**) as needles (2.48 g, 97.8%), m.p. 127—130 °C (Found: C, 49.1; H, 5.45. $C_{13}H_{17}BrO_4$ requires C, 49.22; H, 5.40%); $\nu_{max.}$($CHCl_3$) 1 765, 1 730, and 1 610 cm^{-1}; δ_H 1.62 (3 H, s, Me), 2.08 (3 H, s, CBrMe), 2.18 (3 H, s, OAc), 6.08 (1 H, s, OCOCH=C), and 6.24 (1 H, s, CO_2CHOAc).

Lactol Diene (**26**).—(a) *From the bromo-lactol acetate* (**24**). The crude acetate (**24**) (319 mg, 1.01 mmol) dissolved in anhydrous DMF (10 ml) was mixed with lithium carbonate (638 mg, 9.36 mmol) and the mixture was refluxed for 30 min. The mixture was allowed to cool when saturated brine was added to it and the product extracted with ethyl acetate. The organic layer was washed successively with 2M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, and then dried and evaporated to afford the lactol diene acetate (**25**) as an oil (196 mg). This was treated with potassium carbonate (180 mg, 1.3 mmol) in a mixture of MeOH (10 ml) and water (5 ml) with stirring at ambient temperature for 1 h. The mixture was evaporated under reduced pressure to remove most of the methanol after which it was diluted with water and extracted with ethyl acetate. The extract solution washed, dried, and evaporated and the crystalline residue recrystallized from MeOH to give compound (**26**) as needles, m.p. 160—161 °C [110 mg, 79% from (**24**)] (Found: C, 67.65; H, 7.25. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.26%); M^+, 194; $\nu_{max.}$($CHCl_3$) 3 320, 1 690, 1 630, 1 600, 995, and 820 cm^{-1}; δ_H 1.14 and 1.16 (3 H in total, s, Me), 1.88 (3 H, br s, CH=C*Me*), 2.30 (2 H, m, CH_2CH=C), 4.80 (1 H, s, CO_2CHOH), 5.36 and 5.40 (1 H in total, s, CO_2CHOH), 5.78 and 5.82 (1 H in total, s, C=C*H*CO_2), and 6.16 (1 H, m, C=C*H*CH_2).

(b) *Treatment of the lactol* (**21**) *with* NBS. A solution of compound (**21**) (175 mg, 0.90 mmol) in a mixture of chloroform (4 ml) and carbon tetrachloride (9 ml) was heated under reflux with NBS (164 mg, 0.92 mmol) and dibenzoyl peroxide (2 mg) for 2 h. The reaction mixture was evaporated and the residue triturated with carbon tetrachloride. Removal of the solvent from the extract furnished an oily product (336 mg) which was chromatographed on a column of silica gel (10 g) with benzene–ethyl acetate (8:2) as eluant to afford the diene lactol (**26**) (114 mg, 64%) as crystals (from ether), m.p. 155—157 °C.

Pyroangolensolide (**1**) *and* epi-*Pyroangolensolide* (**4**).—A solution of β-furyl-lithium, prepared [10] by the addition of butyl-lithium (15% hexane solution; 2 ml) to a solution of 3-bromofuran (441 mg, 3 mmol) in THF (5 ml), was added during 10 min to a solution of the diene lactol (**26**) (300 mg, 1.5 mmol) at −78 °C under a nitrogen atmosphere. The solid CO_2–acetone bath was removed and the mixture was stirred at ambient temperature for 24 h. After addition of ice, the products were extracted with ether and the combined ether layers were washed with 2M hydrochloric acid, water, and brine, dried, and evaporated to give an oily product (450 mg). This was chromatographed on a column of silica gel (30 g) with benzene–ethyl acetate (95:5) as eluant to afford (±)-*pyroangolensolide* (**1**) (121 mg), m.p. 146.2—146.8 °C [from MeOH, (−)-form [3] 149 °C] (Found: C, 73.35; H, 6.6. Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%); *m/z* 244 (M^+), 148, 133, 105, and 95; $\lambda_{max.}$(EtOH) 277 nm (ε 19 300); $\nu_{max.}$($CHCl_3$) 1 710, 1 630, 1 600, 1 500, and 880 cm^{-1}; δ_H 1.04 (3 H, s, Me), 1.91 (3 H, d, *J* 2 Hz, CH=C*Me*), 2.28 (2 H, m, CH_2CH=C), 5.14 (1 H, s, CO_2CHFr), 5.88 (1 H, s, C=C*H*CO_2), 6.18 (1 H, t, *J* 4 Hz, C=C*H*CH_2), 6.51 (1 H, d, *J* 2 Hz, β-FrH), 7.48 (1 H, d, *J* 2 Hz, α-FrH), and 7.54 (1 H, s, α-FrH). The product was identified by comparison of its i.r. and ^{1}H n.m.r. spectra with those of an authentic sample.[3] Continued elution with the same solvent mixture as above gave (±)-epi-*pyroangolensolide* (**4**) as needles, m.p. 140—141.3 °C (from MeOH) (Found: C, 73.35; H, 6.59. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%); *m/z* 244 (M^+) 148, 133, 105, 95, and 91; $\lambda_{max.}$ 278 nm (ε 17 300); $\nu_{max.}$($CHCl_3$) 1 710, 1 630, 1 500, and 870 cm^{-1}; δ_H 1.37 (3 H, s, Me), 1.87 (3 H, d, *J* 2 Hz, CH=C*Me*), 2.28 (2 H, m, Hz, CH_2CH=C), 5.12 (1 H, s, CO_2CHFr), 5.91 (1 H, s, C=C*H*CO_2), 6.17 (1 H, t, *J* 4 Hz, C=C*H*CH_2), 6.32 (1 H, d, *J* 2 Hz, β-FrH), 7.36 (1 H, d, *J* 2 Hz, α-FrH), and 7.44 (1 H, s, α-FrH).

References

1 Part 13, T. Tokoroyama, Y. Fukuyama, and K. Yokotani, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1557.

2 Preliminary communication, Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.*, 1973, 4869.

3 J. B. Davis, V. M. Godfrey, K. Jewers, A. H. Manchanda, F. V. Robinson, and D. A. H. Taylor, *Chem. Ind. (London)*, 1970, 201; see also K. Jewers, A. H. Manchanda, and D. A. H. Taylor, *ibid.*, 1972, 976.

4 D. L. Dreyer in 'Progress in the Chemistry of Organic Natural Products,' ed. L. Zechmeister, Springer, Wien, 1968, vol. 26, p. 190;

J. D. Connolly, K. H. Overton, and J. Polonsky, in *Progr. Phytochem.*, 1970, **2**, 385.
5 J. M. Cassady and C.-S. Liu, *J. Chem. Soc., Chem. Commun.*, 1974, 443.
6 S. E. Drews, P. A. Grieco, and J. C. Huffman, *J. Org. Chem.*, 1985, **50**, 1309.
7 R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615, 1620.
8 A. B. Smith, III, and R. K. Dieter, *Tetrahedron*, 1981, **37**, 2407.
9 R. M. Coat and R. L. Soerby, *J. Am. Chem. Soc., 1971,* **93**, 1027.
10 Y. Fukuyama, K. Kawashima, T. Miya, and T. Tokoroyama, *Synthesis*, 1974, 443.
11 P. J. Kocienski and J. M. Ansell, *J. Org. Chem.*, 1977, **42**, 1102.

Received 19*th January* 1987; *Paper* 7/087