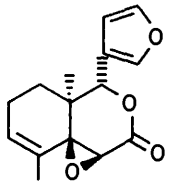
Synthetic Studies on Terpenoid Compounds. Part 27.[1] Total Synthesis of Calodendrolide

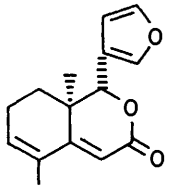
Taskashi Tokoroyama,* Yasuhito Kotsuji, Haruhiko Matsuyama, Takashi Shimura, Kenji Yokotani, and Yoshiyasu Fukuyama
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

A synthesis of calodendrolide (**1**) was explored starting from 4,7a-dimethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one (**4**). The synthesis of key aldehyde ester (**5**) by a route involving derivation of α,β;γ,δ-diepoxy compound (**8**) and selective removal of the γ,δ-epoxy group failed. The second approach was based on the regio- and stereo-selective epoxidation of derived dienol (**9**), making use of the orientation effect of the hydroxy group, which successfully gave α,β-epoxidised derivative (**10**) with correct stereochemistry. Treatment of the key intermediate (**5**), obtained from compound (**10**), with 3-lithiofuran afforded (±)-calodendrolide (**1**) together with its epimer (**6**).

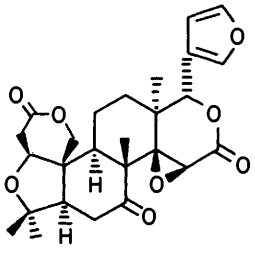
Calodendrolide is a naturally occurring C_{15} degraded limonoid,[2] which has been isolated from *Calodendrorum Capense* Thunb. (fam. Rutaceae).[3] The assigned structure (**1**) is remarkable in that it retains the C/D ring structure of limonin (**2**), the representative of a unique and abundant class of terpenoids (limonoid or tetranortriterpenoid).[4] The identity of the absolute configuration with that of limonoids, deduced on the basis of an ORD study,[3] has substantiated the biogenetic origin of calodendrolide. In continuation of the synthetic studies on degraded limonoids,[5–7] we describe here the total synthesis of calodendrolide (**1**).



(**1**)

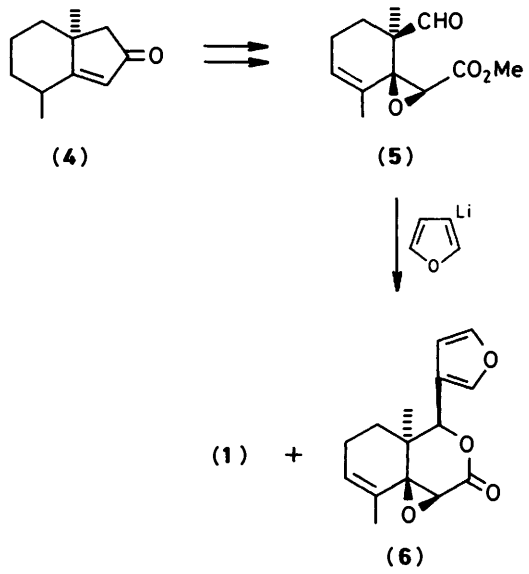


(**3**)



(**2**)

Our strategy for the synthesis is based on the derivation of a key aldehyde-ester (**5**) from 4,7a-dimethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one (**4**), the starting material for our previous synthesis of pyroangolensolide (**3**),[6] and the chemoselective reaction of the former with 3-furyl-lithium, which will afford the target compound (**1**) together with its epimer (**6**) (Scheme 1). The necessary steps for the conversion of (**4**) into (**5**) are: (1) the introduction of a hydroxy group at C-1 and subsequent ring cleavage, (2) the formation of a double bond between C-4 and C-5, and (3) the stereoselective epoxidation of the double bond between C-3 and C-3a. Steps (1) and (2) are the processes already described in the synthesis of

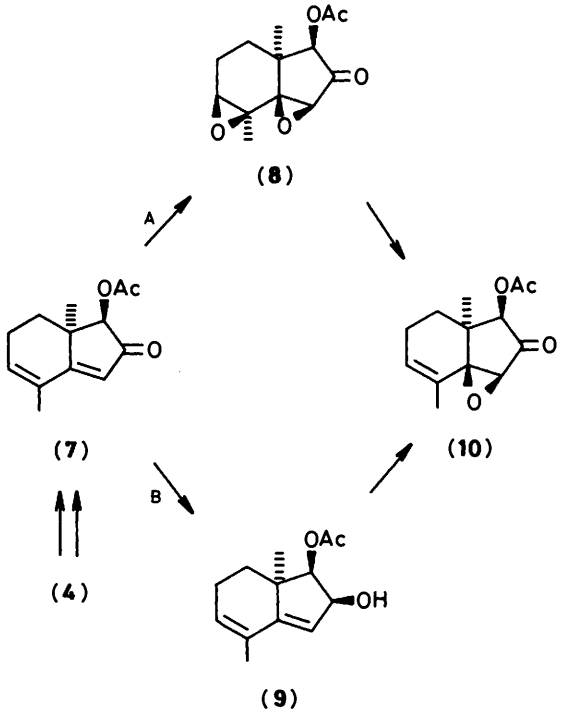


(**4**) (**5**) (**1**) + (**6**)

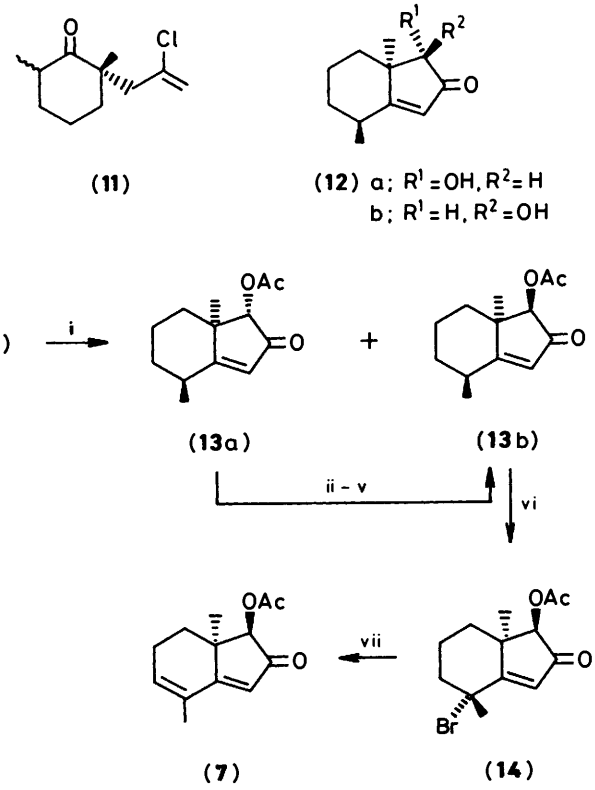
Scheme 1.

pyroangolesolide (**3**)[6] and which can be routinely performed. The problem is step (3), in which the epoxidation is to be done regioselectively in the presence of the double bond between C-4 and C-5. For the solution of this task we envisaged two measures as shown in Scheme 2. One (route A) is the derivation of the α,β;γ,δ-diepoxide (**8**) followed by selective removal of the γ,δ-epoxide group at an appropriate stage. The other (route B) relied on the expectation that the epoxidation of β-dienol (**9**) might proceed both regio- and stereo-selectively by the directing effect of the hydroxy group. Stereocontrol in the epoxidation of an allyl alcohol has now been authenticated,[8,9] but the regiocontrolled epoxidation of an α,β;γ,δ-dienol is of little precedent to our best knowledge, though it would mechanistically be quite feasible. We studied the former method first.

The starting indenone derivative (**4**) was prepared by Wichterle annelation of 2,6-dimethylcyclohexanone as described previously.[6,10] An additional alkylation procedure using lithium di-isopropylamide (LDA) as base afforded monoalkylation product (**11**) in 45% yield, comparable to those by previous methods but with less dialkylation (*ca.* 10%). Upon treatment with lead tetra-acetate (LTA) the indenone derivative (**4**) afforded a diastereoisomeric mixture of α-acetoxylated



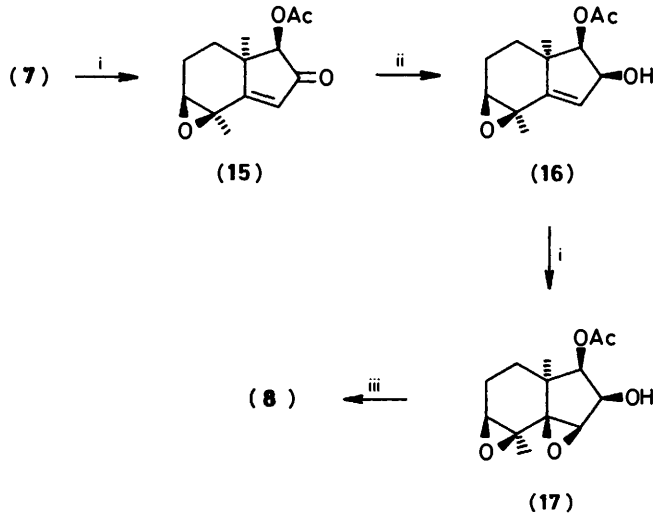
Scheme 2.



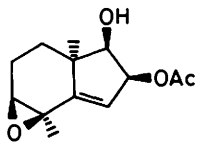
Scheme 3. *Reagents and conditions:* i, PTA, C_6H_6, heat; ii, DBU, C_6H_6, heat; iii, K_2CO_3, aq. MeOH; iv, recrystallisation (diethyl ether–light petroleum or ethyl acetate); v, Ac_2O, C_5H_5N; vi, NBS, CCl_4, heat; vii, Li_2CO_3, DMF.

products (**13a**) and (**13b**). The isomerisation of the configuration at C-1 during the base hydrolysis was not always as easy as stated previously.[6] On such occasions the isomerisation was secured by treatment of the acetoxylation mixture with 1,8-diazabicyclo[5.4.0]-7-undecane (DBU) in refluxing benzene which gave an equilibrium mixture of epimers (**13a**) and (**13b**) in a 1:3 ratio. Hydrolysis of this mixture followed by crystallisation furnished β-hydroxy ketone (**12b**), of which acetylation gave pure acetate (**13b**). Treatment of acetate (**13b**) with *N*-bromosuccinimide (NBS) afforded a bromide (**14**), which exhibited a ^{1}H NMR signal due to the angular methyl group at a deshielded position (δ 1.48), and in which the bromine atom had the α-configuration. Reaction of compound (**14**) with base led to the formation of dienone (**7**) (Scheme 3).

The next stage is the protection of the γ,δ-double bond in compound (**7**) as an epoxide group prior to the requisite stereoselective introduction of an epoxide ring at the α,β-position. The oxidation of the dienone (**7**) with peracid produced γ,δ-monoepoxide (**15**) in high yield. The configuration of the epoxy ring in compound (**15**) was tentatively assigned to be β from mechanistic considerations: attack of the reagent from the α-side would be hindered by the angular methyl group. For the introduction of the second epoxy group to the epoxy derivative (**15**), the path by way of β-allyl alcohol (**16**) was employed. Careful reduction of enone (**15**) with sodium borohydride in a mixture of methanol and tetrahydrofuran (THF) at 0 °C afforded the desired β-alcohol (**16**) as the major product (51% yield). The reaction at room temperature resulted in a lower yield of compound (**16**), since a considerable amount of isomeric product (**18**) tended to form by migration of the acetyl group. The β-configuration the hydroxy group in the product (**16**) was supported by the ^{1}H NMR spectrum which exhibited a signal due to the proton attached to the hydroxy-bearing carbon atom at δ 4.74 as a doublet of doublets with $J_{1,2}$ 6 Hz. Inspection of a molecular model indicated that the dihedral angles between the C-1 and C-2 protons were approximately 15° in β(*cis*)-alcohol and 120° in α(*trans*)-alcohol, and by application of the Karplus rule the observed coupling-constant value was in favour of the assignment as the former. The $J_{1,2}$-values in closely related 1-bromo-2-deuterio-indenes are 6 Hz and 2 Hz in *cis*- and *trans*-isomers respectively.[11] Epoxidation of the allyl alcohol (**16**) smoothly afforded the α,β;γ,δ-diepoxy alcohol (**17**). The configuration of the newly introduced epoxy ring is thought to β from Henbest's rule.[8] Consistent with this assignment was the observed coupling constant ($J_{2,3}$) value of 1.3 Hz in the ^{1}H NMR spectrum. The dihedral angle between the C-2 and C-3 protons as estimated from the model examination was approximately



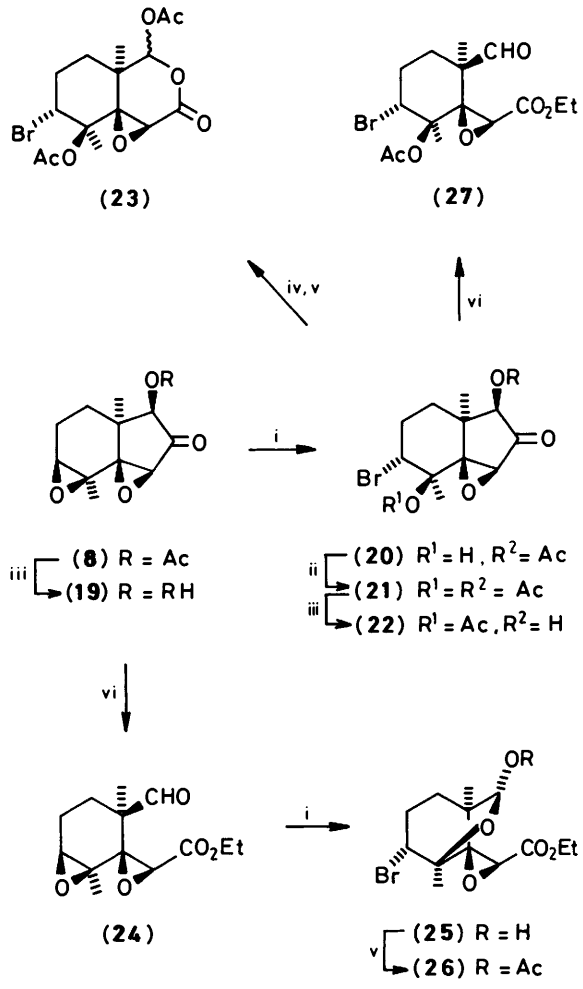
Scheme 4. *Reagents:* i, MCPBA, CH_2Cl_2; ii, $NaBH_4$, THF–MeOH; iii, DMSO, DCC, H_3PO_4.



(18)

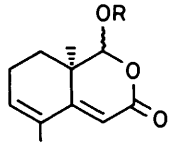
60° and 30° respectively for α- and β-epoxy compounds. In view of the fact that vicinal coupling constants of epoxide groups on a cyclopentane ring are generally much smaller than the estimated values from the Karplus equation,[12] the magnitude of the $J_{2,3}$ coupling constant can be regarded as evidence in favour of the above assignment. The transformation of compound (**17**) to the corresponding ketone (**8**) needed some procedural investigation, since oxidation with Collins' reagent gave the diepoxy ketone (**8**) only in low yield. Among the several methods tested the Moffatt oxidation[13] using phosphoric acid as the acidic reagent resulted in the best yield (82%) (Scheme 4).

Having the requisite diepoxide (**8**) in hand, attention was then directed to the selective conversion of the γ,δ-epoxy ring into a double bond. Attempted deoxygenation of compound (**8**) directly to the monoepoxy derivative (**10**) using a variety of reagents (Zn, NaI, NaOAc, water;[14] PPh_3–CBr_4,[15] then Zn–Ag couple;[16] Ph_3PSe, CF_3CO_2H;[17] WCl_6, BuLi[18]) met with uniform failure,[19] resulting in the formation of complex mixtures. The reason might be ascribed to the instability of the product (**10**) under the reaction conditions used, since compound (**10**) is a vinyl epoxide and moreover the epoxide ring is particularly strained due to its location on the fused cyclopentanone ring. Upon treatment with 5% hydrobromic acid–acetic acid, the γ,δ-epoxide ring in compound (**8**) was selectively cleaved to give a halogenohydrine derivative (**20**) in 89% yield. Since the product (**20**) was acetylated only under forcing conditions (isopropenyl acetate–toluene-*p*-sulphonic acid (PTSA) in place of acetic anhydride in pyridine), the hydroxy group must be tertiary, a fact implicating diequatorial cleavage of the γ,δ-epoxide ring in compound (**8**) (*vide infra*). The reason for this irregularity would be partially explained by steric hindrance to the approach of the nucleophile from the α-side of the molecule attributable to the axial angular methyl group located in a 1,3-relationship. On hydrolysis of the secondary acetoxy group and subsequent cleavage of the so-formed α-ketol group with LTA the diacetate (**21**) furnished a lactol, which was acetylated to give lactol acetate (**23**), the ^1H NMR spectrum of which exhibited a signal due to the proton on the carbon bearing the bromine atom at δ 5.56 as a doublet of doublets with coupling constants of 6 and 12 Hz. This evidence corroborated the equatorial nature of the bromine atom as assumed above. Attempted elimination reaction of the bromohydrines (**20**), (**21**), and (**23**) with zinc dust in ethanol or acetic acid and Zn–Ag couple in ether[16] all failed to give the desired olefinic products, presumably because of the diequatorial disposition of the relevant functional groups. For securing of the diaxial relationship of the bromohydrine grouping the diepoxy ketone (**8**) was converted into a monocyclic aldehyde ester (**24**) and then the γ,δ-epoxy ring was cleaved to give a hemiacetal (**25**) which was converted into an acetate (**26**). Compounds (**25**) and (**26**) were again found to be quite stable to treatment with Zn–Ag couple in ether or Zn–acetic acid. Next the bromohydrine (**21**) was converted by hydrolysis and subsequent treatment with LTA in the presence of ethanol into a monocyclic aldehyde ester (**27**) (Scheme 5), which would be more flexible in conformation. In fact compound (**27**) exhibited a ^1H NMR signal due to the C-5 proton at δ 5.40 with a half-height width ($w_{\frac{1}{2}}$) of 6 Hz, which indicated the axial disposition of the bromine atom. Exposure of the bromohydrin acetate (**27**) to activated zinc dust in refluxing ethanol resulted in the



Scheme 5. *Reagents:* i, 5%HBr–AcOH; ii, CH_2=CMeOAc, PTSA; iii, $NaHCO_3$, aq. AcOH; iv, PTA, aq. AcOH; v, Ac_2O, C_5H_5N; vi, PTA, EtOH–C_6H_6.

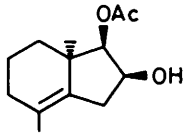
formation of a complex mixture of products, from which a dienic pseudoester (**28**) was separated and characterised. Compound (**28**) showed absorption bands at 1 705, 1 630, and 1 600 cm^{-1} in its IR spectrum and in the ^1H NMR spectrum two signals, at δ 5.74 (1 H, s) and 6.08 (1 H, m), were observed in the vinylic proton region. These spectral data are in good accord with those of the diene lactol (**29**) obtained previously.[6] The desired elimination did occur but the product vinyl epoxide ethyl ester corresponding to compound (**5**) could not survive in the reaction conditions. Thus, our first approach having failed to reveal anything of promise we turned our attention to the second approach, more straightforward and yet more challenging.



(28) R = Et
(29) R = OH

The first task in this route was the reduction of the dienone (**7**) stereoselectively to the β-alcohol (**9**), in which the choice of the procedure was found to be important. Treatment of compound (**7**) with sodium borohydride in methanol, di-isobutylaluminium

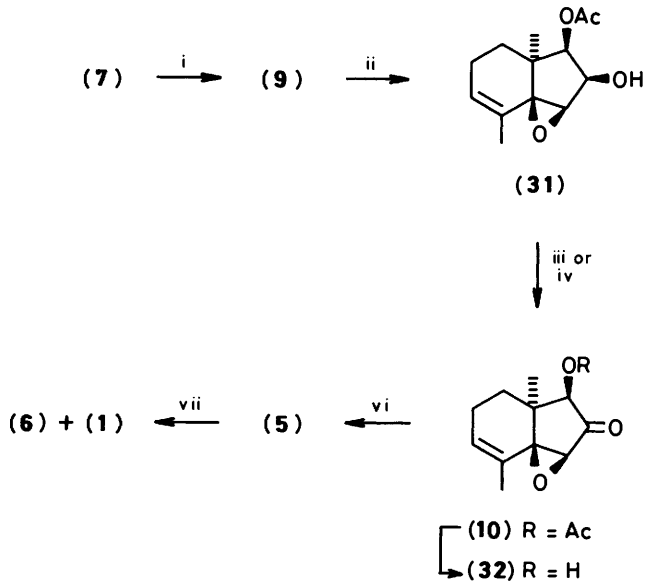
hydride (DIBAH) in toluene, 9-borabicyclo[3.3.1]nonane (9-BBN) in THF, or lithium tri-t-butoxylaluminium hydride gave only low yields of the desired product (**9**). In the case of the last named reagent a considerable amount (*ca.* 3:1 ratio) of 1,6-reduction product (**30**) was obtained. This situation was



(**30**)

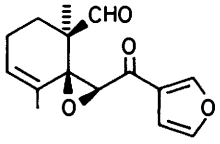
relieved by the application of Luche's procedure (sodium borohydride reduction at the presence of cerium trichloride),[20] of which application to compound (**7**) afforded the dienol (**9**) as a single stereoisomer in excellent yield. The stereochemistry of the hydroxy group in compound (**9**) was assigned to be β from the coupling constant ($J_{1,2}$) of 5.9 Hz observed in the ^{1}H NMR spectrum with similar considerations as in the case of the alcohol (**16**). The epoxidation of the dienol (**9**) was first examined according to the Sharpless method,[9,21] but only a complex mixture of products was obtained. The result of the oxidation with *m*-chloroperbenzoic acid (MCPBA) in the presence of sodium hydrogen carbonate proved promising. Analysis of ^{1}H NMR spectrum of the crude product revealed that two kinds of epoxide were formed in a 4:1 ratio. The minor signals were assignable to the γ,δ-epoxy compound (**16**) by comparison with the authentic spectrum which was already in hand (*vide ante*). The major product was sensitive to acidic conditions, and was isolable only in low yield by preparative TLC on silica gel in the presence of triethylamine. In the ^{1}H NMR spectrum the product exhibited a doublet (J 1.5 Hz) at δ 1.58 for the vinyl methyl protons, a doublet (J ~1.2 Hz) at δ 3.87 for the epoxy proton, and a multiplet at δ 5.77 for the vinyl protons, which substantiated the formulation as the α,β-epoxidised product (**31**). The β-configuration of the epoxy ring predicted from Henbest's rule is also in conformity with the value of the coupling constant between C-2 and C-3 protons ($J_{2,3}$), provided that the discussion for the case of compound (**17**) is taken into account. In the case of 14α,15α-steroidal epoxides the observed coupling constants ($J_{15,16}$) for *trans* and *cis* protons are ~0 and ~0.7 Hz respectively.[12]

Subsequently the oxidation of the epoxy alcohol (**31**) to the corresponding ketone (**10**) was investigated on the epoxidation mixture above, which turned out to be difficult and necessitated much experimentation before the best conditions were found. Compound (**31**) was much more sensitive than the diepoxy alcohol (**17**). An extensive survey of conventional mild methods for the oxidation of a secondary alcohol, *i.e.* $CrO_3{\cdot}2C_5H_5N$ (Collins); $CrO_3Cl^-{\cdot}C_5H_5NH^+$ (PCC), CH_3CO_2Na; $Cr_2O_7^{2+}{\cdot}C_5H_5NH^+$ (PDC), molecular sieves 3Å; $SO_3{\cdot}C_5H_5N$, Et_3N, DMSO;[22] DMSO, $(COCl)_2$, Et_3N (Swern); DMSO, $(CF_3CO)_2O$;[23] DMSO, P_2O_5, Et_3N,[24] *etc.*, failed to reveal anything of promise. Ultimately, Moffatt oxidation in the presence of phosphoric acid and pyridine was found to afford the desired ketone (**10**). After scrutiny of the reagent equivalents compound (**10**) was obtained in 47% yield from the dienol (**9**) in the most favourable case. However, the yield in this reaction was not always reproducible, being sensitive to the unknown factors. A somewhat more convenient alternative is the Griffith method [*N*-methylmorpholine *N*-oxide (NMO), tetrapropylammonium per-ruthenate (TPAP)],[25] which effected a consistent yield of 30–40%. The epoxy ketone (**10**) thus obtained was subjected to mild alkaline hydrolysis with utmost care and the unstable α-ketol (**32**) thus obtained was, without purification, treated with LTA in methanol. Eventually the aldehyde ester (**5**) was obtained in 69% yield from compound (**10**) (Scheme 6).



Scheme 6. *Reagents:* i, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; ii, MCPBA, CH_2Cl_2, $NaHCO_3$; iii, DMSO, DCC, H_3PO_4, C_5H_5N; iv, NMO, TPAP, molecular sieves 4 Å, CH_2Cl_2; v, K_2CO_2. aq. MeOH; vi, PTA, MeOH–C_6H_6; vii, 3-furyl-lithium, THF.

With the key intermediate (**5**) in hand, we proceeded to the final stage of the synthesis. In the reaction of compound (**5**) with 3-lithiofuran three sites for nucleophilic attack are possible: (i) the aldehyde group, (ii) the ester group, and (iii) the vinyl epoxide system. The higher reactivity of an aldehyde group could be thwarted in the present case by the steric congestion of its surroundings. In fact treatment of compound (**5**) with 3-lithiofuram at −78 °C afforded only minute amounts of the furanoid lactone fraction together with the aldehyde ketone (**33**)



(**33**)

which exhibited a signal for the epoxy proton at δ 3.94 and that for the aldehyde proton at δ 9.64 in addition to the resonances assigned to a 3-furyl group in the ^{1}H NMR spectrum. The reaction in the presence of additives like 12-crown ether-4, lithium chloride, and hexamethylphosphoramide (HMPA) or the use of the transmetallated 3-furyl-lithium reagents (with cerium[26] or zinc[27]) did not improve the situation. The best result was secured by the inverse addition procedure in which a solution of 3-furyl-lithium was introduced to a solution of compound (**5**) by way of a cannula. In this way a diastereoisomeric mixture of compound (**1**) and (**6**) (~1:1) was obtained in 16% yield. The final separation was achieved with the aid of high-performance liquid chromatography (HPLC). The earlier effluent was identified as (±)-calolendrolide (**1**) by comparison of the spectral data (IR, ^{1}H and ^{13}C NMR) with those of an authentic sample.[3] The later one was (±)-epicaloendrolide (**6**), as corroborated by spectral evidence. In particular the proton signal due to the angular methyl group appeared at δ 1.21, whereas the corresponding signal in compound (**1**) appeared at δ 0.99, this fact reflecting the different relative disposition of the furan rings and the methyl groups in each compound.

In summary we have accomplished the total synthesis of (±)-calolendrolide, which has a structure common with the C/D

rings of limonin. The crucial step was the regio- and stereoselective epoxidation of a feasible α,β;γ,δ-dienol intermediate. Some of the conversion steps were strenuous and entailed the use of sophisticated procedures. The chemoselectivity problem in the reaction of the aldehyde ester (**5**) has not yet been solved sufficiently and awaits exploitation of either a suitable organometallic procedure or other devices. Furthermore the present work may provide a lesson in connection with synthetic design such that a more direct route, even if it appears more difficult, could ultimately lead to greater success.

Experimental

M.p.s were determined with a Yanagimoto micro hot-stage apparatus and are uncorrected. IR spectra were recorded on a JASCO A-100 spectrometer. ^{1}H NMR spectra were taken with a Hitachi R-90H, JEOL PS-100, or JEOL GX-400 spectrometer and ^{13}C NMR spectra with a JEOL FX-100 (25 MHz) or GX-400 MHz (100 MHz) spectrometer for $CDCl_3$ solutions with tetramethylsilane as internal standard. High-resolution mass spectra were measured on a JEOL D-300 instrument. Microanalyses were performed at the microanalytical laboratory, Faculty of Science, Osaka City University by Mr. J. Goda. Column chromatography was on Merck Kieselgel or Fuji-Davison silica gel BW-820-MH. Preparative TLC (PLC) was performed on Merck Art 5744 or 7747 plates (Kieselgel $60F_{254}$). Diethyl ether, THF, 1,2-dimethoxyethane (DME), and benzene were distilled from sodium–benzophenone before use. Dimethylformamide (DMF) and dimethyl sulphoxide (DMSO) were distilled from calcium hydride. Tetra- and di-chloromethane were distilled over phosphorus pentaoxide. Reactions requiring anhydrous conditions was carried out under an atmosphere of nitrogen or argon in a flame-dried flask. Extract solutions were dried with anhydrous magnesium sulphate before evaporation of solvent. Light petroleum refers to the fraction boiling in the range 40–60 °C.

(4S*,7aS*)-4,7a-*Dimethyl*-1,4,5,6,7,7a-*hexahydro*-2H-*inden*-2-*one* (**4**).—The title compound was prepared from 2,6-dimethylcyclohexanone as described previously.[6] Only additional matters are described.

(a) *Preparation of* 2-(2-*chloroallyl*)-2,6-*dimethylcyclohexanone* (**11**).—To a solution of LDA prepared from di-isopropylamine (24 ml) in DME (50 ml) and 1.5M-butyl-lithium in hexane (100 ml, 150 mmol) was added at −78 °C, during 10 min, a solution of 2,6-dimethylcyclohexanone (17.0 g, 135 mmol) in DME (20 ml) and the mixture was stirred for 30 min. 2,3-Dichloroprop-1-ene (46.7 ml, 281 mmol) was added dropwise during 30 min, followed by the addition of HMPA (50 ml, 251 mmol). After being stirred at −78 °C for a further 30 min, the resulting mixture was allowed to warm to room temperature by removal of the solid CO_2–acetone bath and was then neutralised by 2M-hydrochloric acid. The product was isolated by extraction with ethyl acetate followed by distillation. Compound (**11**) was obtained as a pale yellow oil (20.7 g, 45%), b.p. 78.9 °C at 0.1 mmHg.

(b) The title compound (**4**) was obtained as crystals, m.p. 33–34 °C; δ_C(100 MHz) 18.20 (q), 21.92 (t), 24.58 (q), 32.58 (d), 36.66 (t), 40.76 (t), 43.59 (s), 52.49 (t), 124.1 (d), 192.8 (s), and 203.8 (s).

(1R*,4S*,7aR*)-1-*Acetoxy*-4,7a-*dimethyl*-1,4,5,6,7,7a-*hexahydro*-2H-*inden*-2-*one* (**13b**).—Treatment of the crude acetoxylated mixture [3.47 g, (**13b**):(**13a**) 1:1][6] with DBU (4.1 ml, 27.4 mmol) in dry benzene (30 ml) under reflux afforded a mixture (2.6 g) with an isomer ratio of 3:1, of which hydrolysis gave, after recrystallisation, (1*R**,4*S**,7a*R**)-1-hydroxy-4,7a-dimethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one (**12b**) as needles, δ_C(25 MHz) 18.3 (q), 20.8 (q), 21.9 (t), 33.4 (d), 35.7 (t), 39.0 (t), 47.6 (s), 83.8 (d), 120.5 (d), 189.2 (s), and 206.7 (s).

Acetylation of compound (**12b**) furnished the title compound as needles, m.p. 78–79 °C (from diethyl ether); δ_C 17.92 (q), 20.05 (q), 20.62 (q), 21.48 (t), 33.11 (d), 35.81 (t), 39.27 (t), 46.98 (s), 82.59 (d), 122.2 (d), 170.6 (s), 189.7 (s), and 201.5 (s).

(1R*,7aR*)-1-*Acetoxy*-4,7a-*dimethyl*-1,6,7,7a-*tetrahydro*-2H-*inden*-2-*one* (**7**).—A mixture of the acetoxy ketone (**13b**) (4.83 g, 217 mmol), NBS (4.77 g, 26.8 mmol), dibenzoyl peroxide (36 mg, 0.15 mmol), and tetrachloromethane (70 ml) was heated under reflux for 3.5 h. After removal of solid material by filtration, the solvent was evaporated off to leave a reddish brown oil (7.75 g) which crystallised on storage in a refrigerator. Recrystallisation from diethyl ether–light petroleum gave (1R*,4R*,7aR*)-1-*acetoxy*-4-*bromo*-4,7a-*dimethyl*-1,4,5,7,7a-*hexahydro*-2H-*inden*-2-*one* (**14**) as needles, m.p. 89.0–89.5 °C (Found: C, 52.0; H, 5.7. $C_{13}H_{17}BrO_3$ requires C, 51.84; H, 5.69%); ν_{max}(CCl_4) 1 760, 1 730, and 1 600 cm^{-1}; δ_H 1.42 (3 H, s, Me), 2.04 (3 H, s, CBrMe), 2.20 (3 H, s, OAc), 4.92 (1 H, s, C*H*OAc), and 6.04 (1 H, s, COCH=).

The crude bromination product obtained above was dissolved in DMF (70 ml) and heated with lithium carbonate (10.0 g, 135 mmol) at 100–120 °C for 30 min. The precipitate was filtered off and 2M-hydrochloric acid was added to the filtrate. The product was extracted with ethyl acetate and the combined organic layers were washed successively with water, saturated aqueous sodium hydrogen carbonate, and brine. Evaporation of the solvent afforded the title dienone (**7**) as a reddish oil (4.69 g) which was sufficiently pure for further reaction; ν_{max}($CHCl_3$) 1 745, 1 710, and 1 380 cm^{-1}; δ_H(400 MHz) 1.06 (3 H, s, Me), 1.93 (3 H, dd, *J* 1.5 and 1.8 Hz, MeC=), 2.21 (3 H, s, Ac), 2.36 (2 H, m, CH_2CH=), 5.15 (1 H, s, C*H*OAc), 5.90 (1 H, s, COCH=), and 6.09 (1 H, m, CH_2CH=); δ_C 18.65 (q), 20.25 (q), 20.71 (q), 23.79 (t), 32.65 (t), 43.81 (s), 82.68 (d), 119.6 (d), 128.9 (s), 136.3 (d), 170.7 (s), 175.4 (s), and 201.3 (s).

1(R*,4R*,5S*,7aR*)-1-*Acetoxy*-4,5-*epoxy*-4,7a-*dimethyl*-1,4,5,6,7,7a-*hexahydro*-2H-*inden*-2-*one* (**15**).—To a solution of the dienone (**7**) (2.0 g, 9 mmol) in dichloromethane (30 ml) was added MCPBA (84% purity; 2.18 g, 10 mmol) and the mixture was stirred for 20 h at room temperature. Diethyl ether (50 ml) was added and the solution was washed successively with 10% aqueous sodium carbonate and brine. The residue (2.1 g) left after evaporation of the solvent crystallised on storage in refrigerator. Recrystallisation from methanol or diethyl ether–light petroleum afforded pure *epoxy enone* (**15**) as needles, m.p. 134–135 °C (Found: C, 66.1; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%); ν_{max}($CHCl_3$) 1 750, 1 730, 1 620, and 1 230 cm^{-1}; δ_H 1.04 (3 H, s, Me), 1.58 (3 H, s, MeC–O), 2.16 (3 H, s, Ac), 3.32 (1 H, m, CH_2CH–O), 5.04 (1 H, s, C*H*OAc), and 6.28 (1 H, s, COCH=).

(1R*,2S*,4R*,5S*,7aR*)-1-*Acetoxy*-4,5-*epoxy*-4,7a-*dimethyl*-2,4,5,6,7,7a-*hexahydro*-1H-*inden*-2-*ol* (**16**).—A solution of the epoxy compound (**15**) (290 mg, 1.23 mmol) in a mixture of THF (2.0 ml) and absolute methanol (1.0 ml) was cooled to 0 °C and to this stirred solution was added sodium borohydride (93 mg, 2.45 mmol). After having been stirred for 1 h the mixture was acidified by acetic acid and the product was extracted with diethyl ether. The combined organic layers were washed successively with saturated aqueous sodium hydrogen carbonate and brine. Evaporation of the solvent furnished the *alcohol* (**16**) as crystals (171 mg, 59%), m.p. 141–142 °C (from diethyl ether) (Found: C, 65.5; H, 7.6. $C_{13}H_{18}O_4$ requires C, 65.6; H, 7.61%); ν_{max}(CCl_4) 3 460, 1 735, 1 640, 1 240, 1 040, and 920 cm^{-1}; δ_H 0.94 (3 H, s, Me), 1.48 (3 H, s, MeC–O), 2.12 (3 H, s, Ac), 3.14 (1 H, dd, *J* 2.5 and 4 Hz, CH_2CH–O), 3.60 (1 H, br s, OH), 4.50 (1 H, d, *J* 6 Hz, C*H*OAc), 4.74 (1 H, dd, *J* 2 and 6 Hz, =CHC*H*OH), and 5.90 (1 H, d, *J* 2 Hz, =C*H*CHOH).

When the reduction was conducted in methanol at room temperature, a considerable amount of (1*R**,2*S**,4*R**,5*S**,7a*R**)-2-acetoxy-4,5-epoxy-4,7a-dimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-2-ol (**18**), ν_{max} 3 400, 1 738, 1 655, 1 255, and 1 030 cm^{-1}; δ_H 1.00 (3 H, s, Me), 1.50 (3 H, s, MeC–O), 2.06 (3 H, s, Ac), 2.50 (1 H, br d, *J* 6 Hz, OH), 3.12 (1 H, br s, CH–O), 3.74 (1 H, t, *J* 6 Hz, C*H*OH), 5.28 (1 H, dd, *J* 3 and 6 Hz, C*H*OAc), and 5.96 (1 H, d, *J* 3 Hz), formed as a by-product in addition to the alcohol (**16**) (17% *vs.* 38% yield).

(1R*,2R*,3R*,3aS*,4S*,5S*,7aS*)-1-*Acetoxy*-3,3a;4,5-*diepoxy*-4,7a-*dimethyl*-2,3,3a,4,5,6,7,7a-*octahydro*-1H-*indene* (**17**).—A mixture of the crude alcohol (**16**) (480 mg, 2, mmol) in dichloromethane (10 ml) and MCPBA (70% purity; 500 mg, 2 mmol) was kept at room temperature overnight. The reaction mixture was washed successively with 10% aqueous sodium carbonate, water, and brine. Evaporation of the solvent gave a crystalline residue (421 mg), which was recrystallised from chloroform–diethyl ether to afford the epoxy alcohol (**17**) as needles, m.p. 189–190 °C (Found: C, 60.7; H, 7.05. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%); $\nu_{max}(CHCl_3)$ 3.440, 1 740, and 1 230 cm^{-1}; $\delta_H(CDCl_3–C_5D_5N)$ 0.94 (3 H, s, Me), 1.28 (3 H, s, MeC–O), 2.06 (3 H, s, Ac), 3.12 (1 H, br s, CH–O), 3.26 (1 H, br s, OH), 3.84 (1 H, d, *J* 1.3 Hz, OCHC*H*OH), 4.12 (1 H, dd, *J* 1.3 and 6 Hz, C*H*OH), and 4.38 (1 H, d, *J* 6 Hz, C*H*OAc).

(1R*,3S*,3aS*,4S*,7aS*)-1-*Acetoxy*-3,3a;4,5-*diepoxy*-4,7a-*dimethyl*-1,3,3a,4,5,6,7,7a-*octahydro*-2H-*inden*-2-*one* (**8**).—To a solution of the diepoxy alcohol (**17**) (250 mg, 1.0 mmol) in a mixture of DMSO (3 ml) and benzene (3 ml) were added successively dicyclohexylcarbodi-imide (DCC) (620 mg, 3.0 mmol) and 4M-anhydrous phosphoric acid in DMSO (0.25 ml, 1 mmol), and the mixture was stirred at room temperature for 4.5 h. After addition of ethyl acetate (10 ml) and a solution of oxalic acid (270 mg) in methanol, the mixture was stirred for 20 min. The white precipitate formed was removed by filtration and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate and brine. Evaporation of the solvent left an oily residue mixed with crystals of the urea, which was triturated with diethyl ether. Evaporation of the ether from the extract solution afforded crystals, which were recrystallised from diethyl ether–light petroleum to yield the *diepoxy ketone* (**8**) as prisms, m.p. 108–109 °C. Chromatography (silica gel) of the mother liquor gave a further crop of compound (**8**) (28 mg, 84% in total) (Found: C, 62.1; H, 6.4. $C_{13}H_{16}O_5$ requires C, 61.89; H, 6.39%); $\nu_{max}(CHCl_3)$ 1 780, 1 760, and 1 220 cm^{-1}; δ_H 0.97 (3 H, s, Me), 1.30 (3 H, s, MeC–O), 2.12 (3 H, s, Ac), 3.24 (1 H, m, CH–O), 3.80 (1 H, s, CH–O), and 5.32 (1 H, s, C*H*OAc). Oxidation of compound (**17**) with Collins' reagent resulted in a lower yield (38%) of compound (**8**).

(1R*,3S*,3aS*,4R*,5R*,7aS*)-1-*Acetoxy*-5-*bromo*-3,3a-*epoxy*-4-*hydroxy*-4,7a-*dimethyl*-1,3,3a,4,5,6,7,7a-*octahydro*-2H-*inden*-2-*one* (**20**).—A 5% solution of hydrogen bromide in acetic acid (5 ml) was added dropwise to the diepoxy ketone (**8**) (400 mg, 1.58 mmol) in a flask cooled at 0 °C and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with chloroform and washed successively with saturated aqueous sodium hydrogen carbonate and brine. Evaporation of the solvent left a reddish oil, which crystallised upon trituration with diethyl ether when cooled. Recrystallisation from chloroform–diethyl ether afforded the *bromohydrin* (**20**) as prisms (471 mg, 89%), m.p. 137–138 °C (Found: C, 46.9; H, 5.1. $C_{13}H_{17}BrO_5$ requires C, 46.45; H, 5.04%); $\nu_{max}(CHCl_3)$ 3 560, 1 780, 1 760, and 1 220 cm^{-1}; δ_H 1.12 (3 H, s, Me), 1.52 (3 H, s, *Me*COH), 2.16 (3 H, s, Ac), 3.75 (1 H, s, COCH–O), 4.16 (1 H, m, CH_2CHBr), and 5.38 (1 H, s, C*H*OAc).

(1R*,3R*,3aS*,4R*,5R*,7aS*)-1,4-*Diacetoxy*-5-*bromo*-3,3a-*epoxy*-4,7a-*dimethyl*-1,3,3a,4,5,6,7,7a-*octahydro*-2H-*inden*-2-*one* (**21**).—A mixture of the bromohydrin (**20**) (100 mg, 0.03 mmol), isopropenyl acetate (8 ml), and PTSA (40 mg) was stirred at room temperature for two days. After the mixture had been stirred with potassium carbonate powder for a few min, the mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in diethyl ether and washed successively with saturated aqueous sodium hydrogen carbonate, water, and brine. Evaporation of the solvent gave the diacetate (**21**) as crystals (120 mg, 100%), which were recrystallised from diethyl ether to afford pure *diacetate* (**21**) as needles, m.p. 116.5–118 °C (Found: C, 48.1; H, 5.25. $C_{15}H_{19}BrO_6$ requires C, 48.01; H, 5.10%); ν_{max} 1 780, 1 750, and 1 230 cm^{-1}; δ_H 1.12 (3 H, s, Me), 1.90 (3 H, s, *Me*C–OAc), 2.03 (3 H, s, Ac), 2.16 (3 H, s, Ac), 3.87 (1 H, s, COCH–O), 4.52 (1 H, m, CH_2CHBr), and 5.32 (1 H, s, C*H*OAc).

(4S*,4aS*,5S*,6R*,8aR*)-1,5-*Diacetoxy*-6-*bromo*-4,4a-*epoxy*-5,8a-*dimethylperhydro*-2-*oxanaphthalen*-2-(1H)-*one* (**23**).—A mixture of the bromohydrin acetate (**21**) (70 mg, 0.18 mmol), sodium hydrogen carbonate (100 mg), methanol (3 ml), and water (1 ml) was stirred at room temperature overnight. Work-up afforded the corresponding hydroxy acetate (**22**) as an oil (57 mg, 0.17 mmol), ν_{max} 3 520, 1 770, and 1 740 cm^{-1}.

To a solution of this product in a mixture of acetic acid (3 ml) and water (1 ml, 0.05 mmol) was added LTA (100 mg, 0.23 mmol). The mixture was stirred at room temperature overnight and then quenched by the addition of water. The product was extracted with diethyl ether and the combined organic layers were washed successively with water and brine. Evaporation of the solvent left a yellow oil (70 mg), which was acetylated with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature for 2 h. Work-up furnished the *lactol acetate* (**23**) as crystals, which were recrystallised from diethyl ether to give pure compound (**23**) (55 mg, 76%), m.p. 165 °C (Found: C, 46.3; H, 4.95. $C_{15}H_{19}BrO_7$ requires C, 46.05; H, 4.90%); $\nu_{max}(CHCl_3)$ 1 770, 1 750, 1 210, and 920 cm^{-1}; δ_H 1.28 (3 H, s, Me), 1.76 (3 H, s, *Me*C–OAc), 2.02 (3 H, s, OAc), 2.12 (3 H, s, OAc), 3.80 (1 H, s, O–$CHCO_2$), 5.56 (1 H, dd, *J* 6 and 12 Hz, Br$CH$$CH_2$), and 6.44 (1 H, s, O–C*H*OAc).

(1S*,2S*,3S*,3'S*,6R*)-*Ethyl* 2,3-*Epoxy*-6-*formyl*-2,6-*dimethylcyclohexanespiro*-2'-*oxirane*-3'-*carboxylate* (**24**).—The epoxy ketone (**8**) (147 mg, 0.58 mmol) was treated with sodium hydrogen carbonate (60 mg) in a mixture of methanol (3 ml) and water (0.9 ml) at room temperature overnight. Extraction of the product with chloroform, washing of the organic layers with brine, and evaporation of the solvent gave the corresponding ketol (**19**) as crystals (109 mg, 94%), m.p. 150–151 °C (from diethyl ether); $\nu_{max}(CHCl_3)$ 3 550, 3 440, 1 767, 1 225, 1 110, and 895 cm^{-1}; δ_H 0.86 (3 H, s, MeC–O), 3.40 (1 H, br s, CH–O), 3.78 (1 H, s, CH–O), and 4.16 (1 H, s, CHOH).

LTA (305 mg, 0.69 mmol) was added to a solution of the ketol (**19**) (97 mg, 0.46 mmol) in a mixture of ethanol (6 ml) and benzene (2 ml), and the mixture was stirred at room temperature for 1 h, when a white precipitate formed. Benzene was added, the precipitate was filtered off, and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate, water, and brine. The crystalline residue (110 mg, 94%) left after evaporation of the solvent was recrystallised from diethyl ether to give pure *aldehyde ester* (**24**), m.p. 123.5–124.5 °C (Found: C, 61.3; H, 7.0. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%); $\nu_{max}(CHCl_3)$ 2 980, 2 750, 1 750, 1 730, and 1 220 cm^{-1}; δ_H 0.95 (3 H, s, Me), 1.28 (3 H, s, MeC–O), 1.30 (3 H, t, *J* 7 Hz, CH_2*Me*), 3.20 (1 H, m, OC*H*CH_2), 3.70 (1 H, s, CH–O), 4.20 (2 H, m, C*H*$_2$Me), and 9.62 (1 H, s, CHO).

(1R*,3'S*,4R*,5R*,8S*)-*Ethyl* 7-*Acetoxy*-4-*bromo*-1,5-

dimethyl-6-oxabicyclo[3.2.1]*hexane-8-spiro-2'-oxirane-3'-carboxylate* (**26**).—A solution of the aldehyde ester (**24**) (15 mg, 0.059 mmol) in acetic acid (0.5 ml) was cooled to 5 °C, when a 2.5% solution (0.5 ml) of hydrobromic acid in acetic acid was added dropwise. After having been stirred for 5 min, the reaction mixture was diluted with chloroform and washed successively with saturated aqueous sodium hydrogen carbonate and brine. The residual oil (20 mg) left after evaporation of the solvent was purified by silica gel chromatography gave (1*R**,3'*S**,4*R**,8*S**)-4-bromo-7-hydroxy-1,5-dimethyl-6-oxabicyclo[3.2.1]hexane-8-spiro-2'-oxirane-3'-carboxylate (**25**) as an oil, ν_{max}($CHCl_3$) 3 380, 1 650, 1 260, 1 090, 1 025, 990, and 960 cm^{-1}; δ_H 0.86 (3 H, s, Me), 1.28 (3 H, s, Me), 1.35 (3 H, t, *J* 6 Hz, CH_2*Me*), 2.66 (1 H, d, *J* 11 Hz, OH), 3.82 (1 H, s, CH–O), 4.20 (1 H, m, CHBr), 4.30 (2 H, m, CH_2Me), and 4.95 (1 H, d, *J* 11 Hz, OC*H*OH).

Treatment of the hemiacetal (**25**) with acetic anhydride and pyridine in the usual way gave the title *acetate* (**26**) as an oil, ν_{max} ($CHCl_3$) 1 750, 1 220, and 1 108 cm^{-1}; δ_H 0.76 (3 H, s, Me), 1.24 (3 H, s, Me) 1.35 (3 H, t, *J* 6 Hz, CH_2*Me*), 2.12 (3 H, s, OAc), 3.72 and 3.76 (1 H in total, s, CH–O), 4.24 (2 H, m, CH_2Me), 4.26 (1 H, m, CHBr), and 6.00 and 6.07 (1 H in total, s, OC*H*OAc).

(1S*,2R*,3R*,3'S*,6R*)-*Ethyl 2-Acetoxy-3-bromo-6-formyl-2,6-dimethylcyclohexanespiro-2'-oxirane-3'-carboxylate* (**27**).—The ketol (**22**), obtained by the hydrolysis of diacetate (**21**) (35 mg, 0.093 mmol), was dissolved in a mixture of ethanol (1.5 ml) and benzene (0.8 ml), and the solution was cooled to 0 °C. After addition of LTA (53 mg, 0.12 mmol), the mixture was stirred at room temperature for 1.5 h. Work-up as before gave the aldehyde ester (**27**) as an oil, ν_{max}($CHCl_3$) 2 730, 1 750, 1 730, and 1 220 cm^{-1}; δ_H 0.92 (3 H, s, Me), 1.38 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.64 (3 H, s, *Me*C–OAc), 2.02 (3 H, s, OAc), 3.60 (1 H, CH–O), 4.30 (2 H, q, *J* 6 Hz, CH_2Me), 5.40 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, CHBr), and 9.60 (1 H, s, CHO).

Treatment of the Aldehyde Ester (**27**) *with Zinc in Ethanol.*—A mixture of the aldehyde ester (**27**) (21 mg) and zinc dust (35 mg) in ethanol (2 ml) was refluxed for 3.5 h. After being cooled, the insoluble material was removed by filtration and the filtrate was evaporated to leave an oil (17 mg). PLC on a silica gel plate gave a fraction (7 mg) which was fluorescent under UV light, δ_H 1.1 (3 H, s, Me), 1.26 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.87 (3 H, br s, CH=C*Me*), 3.66 and 4.12 (2 H in total, m, OCH_2Me), 4.96 (1 H, s, O–C*H*OEt), 5.74 (1 H, s, =$CHCO_2$), and 6.08 (1 H, s, CH_2C*H*=).

On the basis of a good correspondence of the ^{1}H NMR signals to those of the dienol lactol (**29**), the structure (**28**) was assigned to the product.

(1R*,2S*,7aR*)-1-*Acetoxy-4,7a-dimethyl-2,6,7,7a-tetrahydro-1H-inden-2-ol* (**9**).—A solution of the crude dienone (**7**) (4.69 g, 21.3 mmol) in methanol (100 ml) was mixed with cerium trichloride heptahydrate (16.0 g, 42.9 mmol) and the mixture was stirred until the dissolution was complete. To this solution cooled at 0 °C was added portionwise sodium borohydride (2.68 g, 708 mmol) and the mixture was stirred for 15 min. After addition of pieces of ice, the reaction mixture was carefully neutralised with 2M-hydrochloric acid. Most of the methanol was evaporated off under diminished pressure and the product was extracted with ethyl acetate. The combined extracts were washed successively with 2M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. The orange-coloured oil (4.73 g) left after evaporation of the solvent was purified by chromatography on a column of silica gel (6.70 g). Elution with hexane–diethyl ether (5:1–3:1) afforded the *dienol* (**9**) as a pale yellow oil [3.55 g, 73% from (**13b**)], ν_{max} 3 500, 1 720, 1 470, and 1 250 cm^{-1}; δ_H(400 MHz) 0.99 (3 H, s, Me), 1.78 (3 H, d, *J* 2 Hz, CH=C*Me*), 2.15 (3 H, s, OAc), 3.61 (1 H, br s, OH), 4.53 (1 H, d, *J* 5.9 Hz, =C*H*CHOH), and 5.61 (1 H, m, C*H*=CMe); δ_C 18.36 (q), 18.50 (q), 21.03 (q), 23.04 (t), 33.83 (t), 45.46 (s), 79.25 (d), 92.25 (d), 119.3 (d), 127.6 (d), 128.4 (s), 147.2 (s), and 173.1 (s).

(1R*,2S*,3R*,3aS*,7aS*)-3-*Acetoxy-1,7a-epoxy-3a,7-dimethyl-2,3,3a,4,5,7a-hexahydro-1H-inden-2-ol* (**31**).—A solution of the dienol (**9**) (197 mg, 0.89 mmol) in dichloromethane (8 ml) containing solid sodium hydrogen carbonate (448 mg, 5.33 mmol) was cooled to −20 °C and MCPBA (70%; 289 mg, 117 mmol) was added portionwise. After the mixture had been stirred at −20 ~ −10 °C for 1 h, diethyl ether was added and the solution was washed successively with 10% aqueous sodium sulphite, aqueous sodium hydrogen carbonate, and brine. Evaporation of the solvent afforded an oil (197 mg) which was a mixture of epoxides (**31**) and (**16**) in the ratio ~4:1 as revealed from the integral of the vinyl and epoxy proton signals in the ^{1}H NMR spectrum. The isomer mixture was separated twice by PLC on silica gel plates with a solvent mixture (hexane–diethyl ether 1:4) containing triethylamine to give pure epoxide alcohol (**31**) as an oil, ν_{max}($CHCl_3$) 3 500, 1 745, 1 725, and 1 240 cm^{-1}; δ_H(400 MHz), 0.96 (3 H, s, Me), 1.58 (3 H, d, *J* 1.5 Hz, *Me*CH=), 2.22 (2 H, m, CH_2CH=), 3.20 (1 H, d, *J* 5.9 Hz, OH), 3.87 (1 H, br s, CH–O), 4.22 (1 H, dd, *J* 5.9 and 6.1 Hz, C*H*OH), 4.50 (1 H, d, *J* 6.1 Hz, C*H*OAc), and 5.77 (1 H, br s, CH_2C*H*=); δ_C 15.69 (q), 16.99 (q), 20.98 (q), 23.07 (t), 28.19 (t), 40.97 (s), 61.97 (s), 68.21 (d), 76.62 (d), 84.20 (d), 127.0 (s), 130.7 (d), and 172.3 (s).

(1S*,3R*,3aS*,7aS*)-3-*Acetoxy-1,7a-epoxy-3a,7-dimethyl-1,3,3a,4,5,7a-hexahydro-2H-inden-2-one* (**10**).—(a) *By Moffatt oxidation.* A solution of the crude epoxidation mixture (197 mg), obtained as above, in benzene (0.4 ml) was mixed with DCC (556 mg, 2.70 mmol), pyridine (0.17 ml, 0.87 mmol), and DMSO (1.6 ml, 22.5 mmol). To this mixture was added 2M-anhydrous phosphoric acid in DMSO (0.2 ml, 0.40 mmol) and the resulting solution was stirred at room temperature for 3.5 h. The precipitated urea was removed by filtration, and ethyl acetate and water were added to the filtrate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer and extracts were washed thoroughly with aqueous sodium carbonate and then with brine. The oily product (419 mg) obtained by evaporation of the solvent was chromatographed on a column of silica gel (25 g). Elution with hexane–diethyl mixture (3:2) afforded the *epoxy ketone* (**10**) as crystals [97 mg, 46.6% from (**9**)], m.p. 61–62 °C (from diethyl ether) (Found: C, 65.9; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%); ν_{max}($CHCl_3$) 1 770, 1 740, and 1 475 cm^{-1}; δ_H(400 MHz) 0.97 (3 H, s, Me), 1.59 (3 H, d, *J* 1.8 Hz, CH=C*Me*), 2.17 (3 H, s, OAc), 3.76 (1 H, s, COCH–O), 5.45 (1 H, s, C*H*OAc), and 5.92 (1 H, m, CH=); δ_C 15.86 (q), 16.83 (q), 20.66 (q), 22.78 (t), 27.82 (t), 39.27 (s), 58.68 (d), 70.86 (s), 79.04 (d), 125.3 (s), 132.3 (d), 170.0 (s), and 204.0 (s).

(b) *By Griffith oxidation.* The epoxidised mixture (191 mg, 0.86 mmol) was dissolved in dichloromethane (7 ml) and mixed with NMO (160 mg, 1.32 mmol), TPAP (1.5 mg, 1.0 mol%), and molecular sieves 4 Å. The mixture was stirred at room temperature for 44 h, and then filtered. The filtrate was washed successively with 10% aqueous sodium hydrogen sulphite, brine, and saturated aqueous copper sulphate. Evaporation of the solvent left an oily product (18.5 mg), which was purified by silica gel chromatography to give the epoxy ketone (**10**) (87 mg, 40.2%).

(1S*,3'S*,6R*)-*Methyl-6-Formyl-2,6-dimethylcyclohex-2-ene-1-spiro-2'-oxirane-3'-carboxylate* (**5**).—A solution of the epoxy ketone (**10**) (106 mg, 0.45 mmol) in a mixture of methanol (5 ml) and water (1.2 ml) was stirred with potassium carbonate (65 mg, 0.47 mmol) at 0 °C for 45 min. Most of the methanol was evaporated off carefully under diminished pressure and water

was added. The product was extracted with ethyl acetate and the combined extracts were washed with brine. Removal of the solvent gave (1*S**,3*R**,3a*S**,7a*S**)-β-1,7a-epoxy-3-hydroxy-3a,7-dimethyl-1,3a,4,5-hexahydro-2*H*-inden-2-one (**32**) as an unstable oil (104 mg), ν_{max}($CHCl_3$) 3 460, 1 760, 1 225, and 1 095 cm^{-1}; δ_H 0.85 (3 H, s, Me), 1.56 (3 H, d, *J* 2.4 Hz, *Me*C=CH), 2.34 (2 H, m, C*H*$_2$CH=), 3.13 (1 H, br s, OH), 3.74 (1 H, s, COCH–O), 4.29 (1 H, s, C*H*OH), and 5.87 (1 H, m, CH_2C*H*=).

A solution of the ketol (**32**) (104 mg, 0.53 mmol) in a mixture of methanol (2 ml) and benzene (2 ml) was cooled to 0 °C and LTA (90%; 269 mg, 0.61 mmol) was added. After the mixture had been stirred at room temperature for 1 h, the reaction was quenched by the addition of 2M-hydrochloric acid. The white precipitate formed was removed by filtration and the filtrate was extracted with ethyl acetate. The extract was washed successively with 2M-hydrochloric acid and brine, and the solvent was evaporated off. The semicrystalline residue thus obtained (104 mg) was purified by chromatography on a column of silica gel (5 g). Elution with hexane–diethyl ether mixture (4:1) afforded the *aldehyde ester* (**5**) as needles (from diethyl ether) [69 mg, 69.1% from (**10**)], m.p. 69–70 °C; ν_{max}($CHCl_3$) 3 025, 1 750, and 1 725 cm^{-1}; δ_H(400 MHz) 1.02 (3 H, s, Me), 1.63 (3 H, d, *J* 1.1 Hz, CH=C*Me*), 2.22 (2 H, m, C*H*$_2$CH=), 3.72 (3 H, s, CO_2Me), 3.79 (1 H, s, CH–O), 6.03 (1 H, m, CH_2C*H*=), and 9.70 (1 H, s, CHO); δ_C 14.58 (q), 17.19 (q), 21.17 (t), 29.45 (t), 47.15 (s), 51.90 (q), 55.55 (s), 64.60 (d), 129.6 (s), 132.7 (d), 168.2 (s), and 201.3 (s).

(±)-*Calodendrolide* (**1**) *and Epicalodendrolide* (**6**).—A solution of 3-furyl-lithium [prepared [28] from 3-bromofuran (0.05 ml, 0.35 mmol) in THF (0.5 ml) and butyl-lithium solution (1.5M in hexane; 0.25 ml, 0.38 mmol)] was added dropwise to a solution of the aldehyde ester (**5**) (79 mg, 0.37 mmol) in THF (1.5 ml) at −78 °C during 10 min. At this temperature the mixture was stirred for 1.5 h and then the cooling bath was removed. To the reaction mixture (having warmed to ambient temperature) were added successively water and 2M-hydrochloric acid. The products were extracted with ethyl acetate and the extract was washed successively with water, 2M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. Evaporation of the solvent left a yellow oil (103 mg), which was chromatographed on a column of silica gel (15 g). Elution with hexane–diethyl ether mixture (9:1–4:1) afforded a mixture of products (**1**) and (**6**) in approximately equal amounts (16.2 mg, 16%). Separation of both compounds was carried out by HPLC on a 'Resolve silica gel' column (10 cm cartridge) and hexane–ethyl acetate (95:5) mixture as solvent to give (±)-*Calodendrolide* (**1**), m.p. 146–149 °C; ν_{max}($CHCl_3$) 3 150, 1 740, 1 600, 1 505, 1 280, 1 025, 875, and 835 cm^{-1}; δ_H(400 MHz) 0.99 (3 H, s, Me), 1.66 (3 H, dd, *J* 1.5 and 2.4 Hz, CH_2CH=C*Me*), 2.21 (2 H, m, C*H*$_2$CH=), 3.97 (1 H, s, COCH–O), 5.53 (1 H, s, CHOCO), 6.00 (1 H, m, CH_2C*H*=), 6.39 (1 H, m, fr), and 7.42 (2 H, m, fr); δ_C 13.32 (q), 16.96 (q), 22.02 (t), 27.68 (t), 37.33 (s), 55.03 (d), 65.44 (s), 77.40 (d), 110.0 (d), 120.1 (d), 126.2 (d), 132.9 (s), 141.1 (d), 143.1 (d), 167.8 (s); *m*/*z* 260 (M^+) (Found: M^+, 260.1077. $C_{15}H_{16}O_4$ requires *M*, 260.1049). The IR and ^1H and ^{13}C NMR spectra were superimposable with those of the natural specimen measured under the same conditions and with the same instruments. *Epicalodendrolide* was then eluted, and showed m.p. 76–79 °C; ν_{max}($CHCl_3$) 3 150, 1 745, 1 205, 1 020, 960, 948, 885, and 838 cm^{-1}; δ_H(400 MHz) 1.21 (3 H, s, Me), 1.61 (3 H, br s, CH=C*Me*), 2.23 (1 H, m, C*H*$_2$CH=), 3.99 (1 H, COCH–O), 5.72 (1 H, s, CHOCO), 6.00 (1 H, m, CH_2C*H*=), 6.45 (1 H, m, fr), and 7.44 (2 H, m, fr); δ_C 14.39 (q), 16.88 (q), 21.98 (t), 27.45 (t), 38.70 (s), 54.98 (d), 65.27 (s), 74.67 (d), 102.5 (d), 113.9 (s), 125.8 (d), 132.9 (s), 144.0 (d), 145.2 (d), and 167.2 (s); *m*/*z* 260 (M^+) (Found: M^+, 260.1020).

Acknowledgements

We thank Professor J. M. Cassady of Purdue University for the gift of an authentic sample of calodendrolide. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

1 Part 22, T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Moden, and H. Iio, *Tetrahedron*, 1988, **44**, 6607; Part 23, T. Tokoroyama, M. Tsukamoto, T. Asada, and H. Iio, *Tetrahedron Lett.*, 1987, **28**, 6645; Part 24, T. Tokoroyama and R.-L. Pan, *ibid.*, 1989, **30**, 197; Part 25, H. Iio, K. Fujimori, Y. Yamagiwa, M. Monden, and T. Tokoroyama, *J. Chem. Soc., Perkin Commun.*, 1989, 1359; Part 26, H. Iio, Y. Matsumoto, K. Shimokata, K. Shibata, and T. Tokoroyama, *ibid.*, p. 1360.
2 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, *Prog. Phytochem.*, 1970, **2**, 385.
3 J. M. Cassady and C.-S. Liu, *J. Chem. Soc., Chem. Commun.*, 1972, 86.
4 For reviews on limonoids see: ref. 2; D. A. H. Taylor in 'Progress in the Chemistry of Organic Natural Products,' eds. W. Herz, H. Griesebach, and G. W. Kirby, Springer, Wien, 1984, vol. 45, p. 1; J. D. Connolly and R. A. Hill, *Nat. Prod. Rep.*, 1986, **3**, 427.
5 Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.*, 1972, 3401; T. Tokoroyama, Y. Fukuyama, T. Kubota, and K. Yokotani, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1557.
6 Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.*, 1973, 4869; T. Tokoroyama, Y. Fukuyama, and Y. Kotsuji, *J. Chem. Soc., Perkin Trans. 1*, 1988, 445.
7 See S. E. Drews, P. A. Grieco, and J. C. Huffman, *J. Org. Chem.*, 1985, **50**, 1309.
8 H. B. Henbest, *Proc. Chem. Soc.*, 1962, 74; G. Berti, in 'Topics in Stereochemistry,' eds. N. L. Allinger and E. L. Eliel, Wiley-Interscience, New York, 1973, vol. 7, p. 93.
9 K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1989, **12**, 63.
10 A novel preparation of this compound has been reported: E. J. Corey and A. K. Ghosh, *Tetrahedron Lett.*, 1987, **28**, 175.
11 N. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, 1963, **85**, 2248.
12 K. Tori, T. Kameno, and T. Nakagawa, *J. Org. Chem.*, 1964, **29**, 1136.
13 K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1965, **87**, 5670.
14 J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.
15 N. S. Isaacs and D. Kirkpatrick, *Tetrahedron Lett.*, 1972, 3869.
16 M. Denis, C. Girard, and J. M. Conia, *Synthesis*, 1972, 549.
17 D. L. J. Clive and C. V. Denyer, *J. Chem. Soc., Chem. Commun.*, 1973, 253.
18 K. B. Sharpless, M. A. Umbreit, M. J. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, 1972, **94**, 6538.
19 For a recent review on this transformation see: H. N. C. Wong, C. C. M. Fok, and T. Wong, *Heterocycles*, 1987, **26**, 1345.
20 J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; J.-L. Luche, L. Rodriguez-Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, 1978, 601.
21 K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136; S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. Michaelson, and J. D. Cutting, *ibid.*, 1974, **96**, 5254.
22 J. R. Parikh and W. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.
23 S. L. Huang and K. Omura, *J. Org. Chem.*, 1976, **41**, 3329.
24 D. F. Taber, J. C. Amedio, Jr., and K.-V. Jung, *J. Org. Chem.*, 1987, **52**, 5621.
25 W. P. Griffith, S. V. Ley, G. P. Whitcombe, and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625.
26 T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904.
27 E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298.
28 Y. Fukuyama, K. Kawashima, T. Miwa, and T. Tokoroyama, *Synthesis*, 1974, 443.

Paper 9/04930D
Received 17*th November* 1989
Accepted 21*st December* 1989