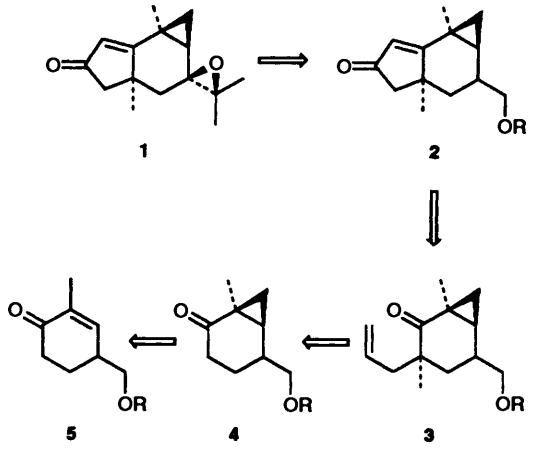
Studies on the Structure of the Sesquiterpene Caespitenone Isolated from *Porella* Species of Liverwort

Motoo Tori, Yoshihiro Kohama, Katsuyuki Nakashima and Yoshinori Asakawa*
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770, Japan

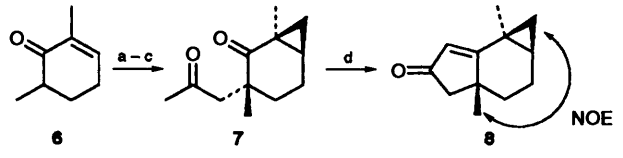
Models of caespitenone, previously isolated from the liverwort *Porella caespitans* var. *setigera*, have been synthesized and their spectral data compared with those of this natural product. The discrepancy between these data prompted us to investigate the Colombian liverwort *Porella swartziana*, from which this compound was isolated and its structure has been revised by extensive 2D NMR techniques and chemical transformations to establish an africanane-type skeleton. The absolute configuration has also been determined.

Caespitenone is a sesquiterpene isolated from the liverwort *Porella caespitans* var. *setigera* and its structure has been reported to have a pseudoguaiane skeleton as depicted in structure **1**.[1] Since the absolute configuration has not been determined and the relative configuration of the epoxide was only tentatively shown,[2] we planned a synthesis of this compound. The hydrindenone system[3] can be synthesized by an intramolecular aldol reaction of a suitably substituted cyclohexanone fused to a cyclopropane ring, which can be prepared by alkylation of the cyclohexenone derivative as shown in Scheme 1. Prior to the actual synthesis, we prepared



Scheme 1 Synthetic plan

two model compounds, **8** and **11**, in order to compare the similarity of their spectral data with those of the natural compound **1**. The synthetic effort toward the natural caespitenone **1** has been carried out, but the final two steps to obtain a tetrasubstituted double bond and epoxidation failed. We had to stop at this stage of the synthesis. Comparison of the data of the final synthetic product **19** with those of the natural product did not allow any useful conclusions to be drawn at this stage. We felt that collection of the same liverwort must be the shortest way to knowledge not only of the relative but also of the absolute configuration of the epoxide. However, we encountered a related liverwort, *P. swartziana*, which was collected in Colombia.[4] On studying the chemical constituents of this liverwort we found caespitenone as a major constituent. Modern techniques of 2D NMR spectroscopy as well as chemical transformations made it possible to solve the true structure of this natural product, and the structure of caespitenone **1** should be revised to **20**. Thus our former synthetic effort did not help to elucidate the real structure. This

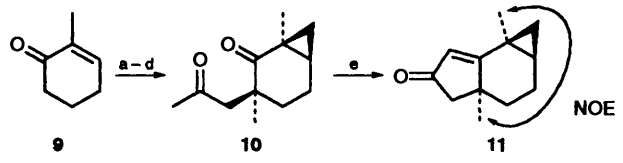


Scheme 2 *Reagents:* (a) $Me_3SO^+ I^-$, NaH, DMSO; (b) Bu^{t}OK, CH_2=C(Me)CH_2Cl; (c) O_3, Me_2S; (d) Bu^{t}OK, Bu^{t}OH–Et_2O

is why the spectral data of our synthetic models, **8** and **11**, as well as our final product **19** were qualitatively different from those of natural product. Here we report our former efforts to synthesize a compound of structure **1**, and our structural revision to **20**, including the absolute configuration.

Results and Discussion

Syntheses of Models.—2,6-Dimethylcyclohex-2-enone **6**[5] was treated with trimethyloxosulfonium iodide in the presence of sodium hydride in dimethylsulfoxide DMSO[6] to afford a cyclopropane derivative, which was alkylated with 3-chloro-2-methylpropene/Bu^{t}OK to give a product in high yield, which is *trans* alkylated with respect to the preexisting cyclopropane ring. Alkylation always occurred from the other face of the cyclohexane to that of the cyclopropane ring. Ozonolysis of this compound gave a diketone **7**. Intramolecular aldol cyclization of **7** produced a *trans* model **8**. The relative structure of compound **8** was revealed by the nuclear Overhauser effect (NOE) experiment as shown in Scheme 2. The *cis* model **11** was



Scheme 3 *Reagents:* (a) $Me_3SO^+ I^-$, NaH, DMSO; (b) LDA, CH_2=$CHCH_2$Br; (c) Bu^{t}OK, MeI; (d) O_2, $PdCl_2$, CuCl, aq. DMF; (e) Bu^{t}OK, Bu^{t}OH–Et_2O

also prepared, starting from 2-methylcyclohex-2-enone **9** by a similar route through a diketone **10** as shown in Scheme 3. A comparison of the data for models **8** and **11** with the natural product is shown in Fig. 1. The data for the models do not compare well with those of the natural product, specially the IR data which are completely different (see Experimental section).

Synthetic Work toward Compound **1** (*Scheme* 4).—The isobutyl enol ether **12**[7] was treated with lithium diisopropylamide

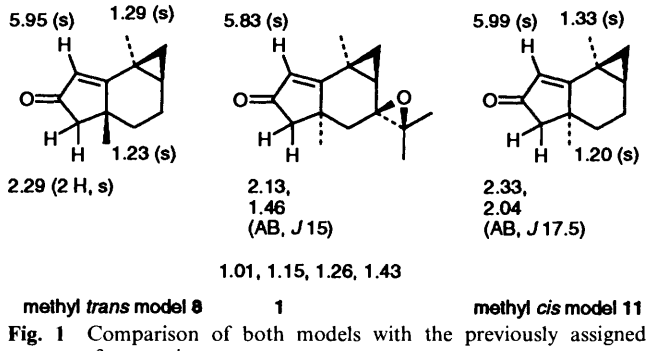
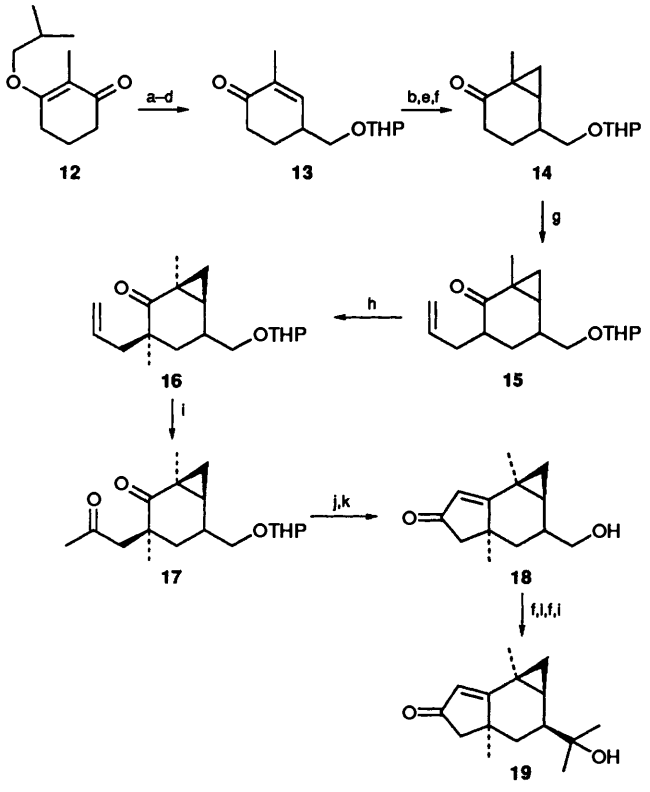


Fig. 1 Comparison of both models with the previously assigned structure for caespitenone



Scheme 4 *Reagents:* (a) LDA, $NCCO_2Me$; (b) $LiAlH_4$; (c) H_2SO_4; (d) dihydropyran, PPTS; (e) Et_2Zn, CH_2I_2, CH_2Cl_2; (f) PDC, CH_2Cl_2; (g) LDA, $CH_2{=}CHCH_2Br$; (h) Bu^{t}OK, MeI; (i) O_2, $PdCl_2$, CuCl, aq. DMF; (j) Bu^{t}OK, Bu^{t}OH–Et_2O; (k) PPTS, MeOH; (l) MeMgI

(LDA)–$NCCO_2Me$ followed by reduction ($LiAlH_4$), acid treatment and tetrahydropyranylation to afford an enone **13**. Since attempted cyclopropanation of enone **13** using trimethyloxosulfonium iodide failed, the enone **13** was reduced and the alcohol product was treated with diethyl zinc–diiodomethane followed by oxidation [pyridinium dichromate (PDC)] to give a cyclopropane ketone **14**. The ketone **14** was alkylated with LDA–allyl bromide followed by methylation (Bu^{t}OK–MeI) to yield a *cis* dimethyl cyclopropane ketone **16**. The stereochemistry was deduced from the results with the model ketone (Scheme 3). Wacker oxidation of the ketone **16** gave the diketone **17**.[8] Intramolecular aldol condensation (Bu^{t}OK–Bu^{t}OH) and deprotection [pyridinium toluene-*p*-sulfonate (PPTS)–MeOH] afforded a tricyclic alcohol **18**. Oxidation (PDC) of alcohol **18** to the aldehyde followed by Grignard reaction (MeMgI) gave an alcohol, which was further oxidized by PDC to the ketone and this was then methylated to afford compound **19**. The stereochemistry of the alcohol **19** was fully studied by 2D NMR techniques, but attempted dehydration of the alcohol **19** to a tetrasubstituted olefin using

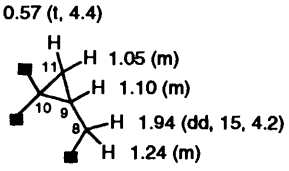


Fig. 2 The partial structure of caespitenone **20**, with ^1H NMR data for C-8–11 protons

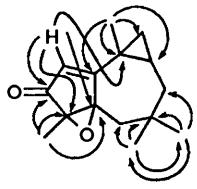


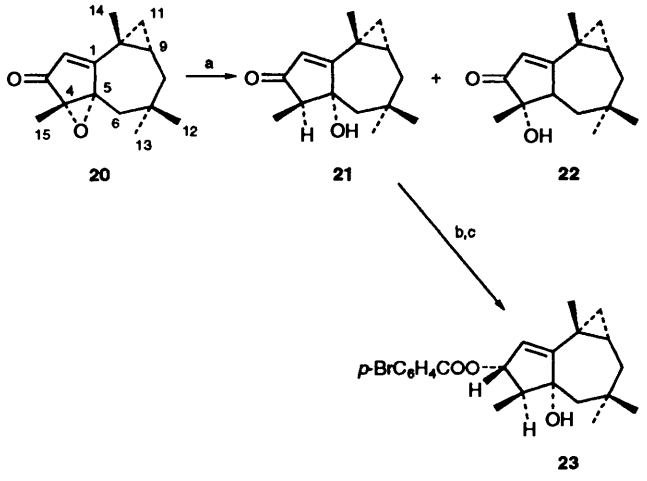
Fig. 3 Long-range correlations detected by the HMBC spectrum of caespitenone **20**

SiO_2–$FeCl_3$ conditions[9] and other methods failed due to complete decomposition of the starting material.

Isolation of Caespitenone from the Liverwort Porella swartziana.—We have been looking for species of liverwort which biosynthesize caespitenone so that more information can be gained to establish the compound's stereochemistry. *P. swartziana* was collected, and this liverwort is very close to the species *P. caespitans* var. *setigera*.[4] We found that caespitenone was the main constituent of this species. The molecular formula was determined to be $C_{15}H_{20}O_2$ by high-resolution mass spectrometry (HRMS). The ^{13}C NMR spectrum and distortionless enhancement by polarization transfer (DEPT) experiment indicated the presence of four methyl, three methylene, two methine and six quaternary carbons. Thus the degree of unsaturation was six. Since there was one olefin (δ_C 128.5 and 180.0) and one carbonyl group (δ_C 200.1) the compound must be tetracyclic. The second oxygen atom was thus deduced to be an ether, which turned out to be an epoxide (δ_C 60.8 and 66.5). These spectral features are of course the same as those found fourteen years ago.[1] However, a ^1H–^1H homonuclear chemical-shift correlation spectroscopy (COSY) experiment suggested the presence of the partial structure shown in Fig. 2, and the 2D heteronuclear multiple bond coherence (HMBC) spectrum showed the long-range correlations shown in Fig. 3. The methyl group at C-4 (δ_H 1.45; δ_C 8.4) had three correlation peaks (C-3, -4 and -5). This means that the methyl group at C-4 must be next to the carbonyl group and attached to the epoxide ring. The methyl group at C-10 (δ_H 1.24; δ_C 26.5) correlated to C-1, -9, -10 and -11, suggesting that it is attached to the cyclopropane ring and that the cyclopropane ring should be next to the olefin. Furthermore, the geminal dimethyl group (C-12 and -13) did not correlate to the epoxide ring but to two methylene carbons (C-6 and -8) and the quaternary carbon (C-7). These observations cannot be explained by the old structure **1**, but fit the africanane[10] skeleton well. Thus the skeleton of caespitenone was not a pseudoguaiane, but an africanane and its planar structure was established as **20**. As this compound had many quaternary carbons, the HMBC spectrum helped very much in solving the structure.

The stereochemistry was not so easy to establish, because no significant NOE was detected in this molecule. Attempted reduction of compound **20** with either $NaBH_4$ or $LiAlH_4$ resulted in complete decomposition. The only successful reaction was Miyashita's reaction to open the epoxide ring.[11] Compound **20** was treated with PhSeSePh–$NaBH_4$ in the presence of AcOH in MeOH. Compounds having an α-substituent always gave a mixture of diastereoisomers as

reported in the literature.[12] However, in our case the normal reduction product (the major one) **21** was pure in its stereochemistry, namely the methyl group α to the carbonyl group had a more stable configuration (Scheme 5). The minor



Scheme 5 *Reagents:* (a) $NaBH_4$, PhSeSePh, EtOH–AcOH; (b) $NaBH_4$, $CeCl_3$; (c) *p*-BrC_6H_4COCl

product **22** was presumably produced by an attack from the other side of the epoxide. Fortunately, NOEs between the hydroxy-group proton and 4-H, and also the hydroxy-group proton and 11-H$^{\alpha}$ were observed in the NOESY spectrum of compound **21** in $(CD_3)_2SO_6$ solution. Furthermore, in [$^2H_5$]-pyridine solution, the chemical shifts for 4-H, 11-H$^{\alpha}$, 6-H$^{\alpha}$ and 8-H$^{\alpha}$ were shifted significantly downfield, indicating that these protons are on the same side of the hydroxy group. The relative stereochemistry was thus established as shown in the formula.

The absolute configuration was determined by the CD spectrum of the *p*-bromobenzoate **23** derived from the ketone **21**. Ketone **21** was reduced by $NaBH_4$–$CeCl_3$ to yield a sole product. The alcohol (diol) was treated with *p*-bromobenzoyl chloride to afford the monobenzoate **23**, whose relative stereochemistry was determined by the NOE between 3-H and the methyl group at C-4 and also by that between 4-H and the hydroxy-group proton in $(CD_3)_2SO$. The bromobenzoate **23** showed the (−)-Cotton effect, indicating the absolute configuration shown in Fig. 4.[13] Africanol[14] was the first compound in this class of sesquiterpenoids to be reported when it was isolated from *Lemnalia africana*. The sesquiterpene belonging to this skeleton was also isolated from the higher plant *Senecio oxyriifolius* (Compositae).[15] Similar sesquiterpenes have been found in the liverwort *Porella caespitans* var. *setigera* recently.[16,17]

Although an attempted synthesis of the compound having the structure **1** previously proposed for caespitenone failed, we have found that the natural product is present in the Colombian liverwort *P. swartziana* as a main constituent. Extensive 2D NMR analysis as well as chemical transformations resulted in the structure being revised to formula **20** which has an africanane skeleton. The absolute configuration was also established by application of the allyl benzoate chirality rule to the allylic benzoate **23** derived from caespitenone **20**.

Experimental

IR spectra were measured with a JASCO FT/IR-5300 or a Shimadzu IR-408 spectrophotometer. ^1H and the ^{13}C NMR spectra were taken with a JEOL JNM FX90Q (90 MHz), a JEOL JNM GX400 (400 MHz) or a Varian Unity 600 (600 MHz) spectrometer. *J*-Values are given in Hz. Mass spectra including high-resolution mass spectra were taken with a JEOL

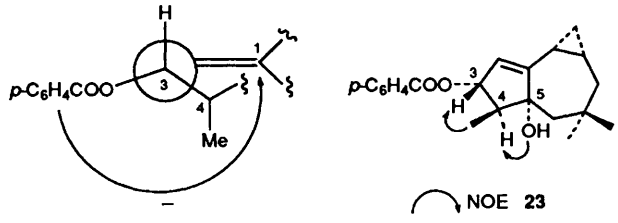


Fig. 4 The relative and absolute stereochemistry of the *p*-bromobenzoate **23**

JMS AX-500 or a JEOL JMS HX-100 spectrometer. CD spectra were measured with a JASCO J-500 spectrometer. Specific rotations were measured by a JASCO DIP-140 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC.

Preparation of Model Compounds.—Preparation of the cyclopropane diketone **7**. 2,6-Dimethylcyclohex-2-enone **6** (1.39 g) was treated with trimethyloxosulfonium iodide (2.64 g) and sodium hydride (430 mg) in dimethyl sulfoxide (DMSO) (18 cm^3) at room temp. for 2 h. The usual work-up and column chromatographic purification (SiO_2; hexane–EtOAc, gradient) afforded 1,3-dimethylbicyclo[4.1.0]heptan-2-one (1 g, 64%); ν_{max}(film)/cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.68–0.80 (1 H, m), 0.98–1.15 (3 H, d × 2, Me) and 1.21 (3 H, s, Me); *m/z* 138 (M^+), 123, 95, 82, 68 (100%) and 53.

A solution of this ketone (1 g) in dry benzene (15 cm^3) was treated with Bu^{t}OK (983 mg) at 0 °C and then methallyl chloride (3-chloro-2-methylpropene) (1.43 cm^3) was added into this solution. The mixture was stirred at room temp. for 1 h. The usual work-up and column chromatographic purification (SiO_2; hexane–EtOAc, gradient) afforded (1*S**,3*R**,6*R**)-1,3-dimethyl-3-(2-methylprop-2-enyl)bicyclo[4.1.0]heptan-2-one (533 mg, 40%); ν_{max}(film)/cm^{-1} 1675 and 1640; δ_H(90 MHz; $CDCl_3$) 0.73–0.82 (1 H, m), 1.04 (3 H, s), 1.23 (3 H, s), 1.69 (3 H, s), 1.97 (1 H, d, *J* 13.2), 2.36 (1 H, d, *J* 13.2) and 4.6–4.8 (2 H, m); δ_C(22.5 MHz; $CDCl_3$) 16.1, 18.6, 20.6, 24.2, 24.6, 25.8, 27.6, 29.1, 44.1, 46.8, 114.8, 142.2 and 214.6; *m/z* 177, 107, 93, 67 and 55 (100%).

Ozone was bubbled through a solution of this ketone (500 mg) in dichloromethane (25 cm^3) at −78 °C until a blue colour persisted. Dimethyl sulfide (5 cm^3) was added and the mixture was kept at room temp. for 3 h. Column chromatographic purification (SiO_2; hexane–EtOAc, gradient) afforded the *dione* **7** (230 mg, 45%); ν_{max}(film)/cm^{-1} 1670; δ_H(90 MHz; $CDCl_3$) 0.69–0.88 (1 H, m), 1.13 (3 H, s), 1.26 (3 H, s), 2.10 (3 H, s), 2.42 (1 H, d, *J* 16.0) and 2.82 (1 H, d, *J* 16.0); δ_C(22.5 MHz; $CDCl_3$) 16.6, 19.0, 20.6, 25.8, 26.1, 28.3, 30.7, 31.1, 43.0, 53.1, 206.6 and 213.5; *m/z* 194 (M^+), 179, 151, 136, 118, 96, 81 and 68 (Found: HRMS, M^+, 194.1282. $C_{12}H_{18}O_2$ requires M, 194.1307).

Preparation of the trans*-ketone* **8**. A solution of the ketone **7** (22 mg) in dry diethyl ether (0.46 cm^3)–Bu^{t}OH (1 cm^3) was treated with Bu^{t}OK (92 mg) at room temp. for 1.2 h. The usual work-up afforded the (2S*,4R*,7R*)-2,7-*dimethyltricyclo*-[5.3.0.0^{2,4}]*dec*-1(10)-*en*-9-*one* **8** (14.5 mg, 75%); ν_{max}(film)/cm^{-1} 1685; δ_H(90 MHz; $CDCl_3$) 1.09 (1 H, dd, *J* 7.8 and 4.4), 1.23 (3 H, s), 1.29 (3 H, s), 1.40–1.46 (2 H, m), 1.99–2.07 (1 H, m), 2.29 (2 H, s) and 5.95 (1 H, s); δ_C(22.5 MHz; $CDCl_3$) 20.9 (t), 21.9 (s), 24.4 (t), 24.4 (q), 27.1 (q), 28.3 (d), 36.2 (t), 43.3 (s), 54.9 (t), 126.4 (d), 191.1 (s) and 206.4 (s); *m/z* 176 (M^+), 161, 148, 134, 133, 119, 105, 91, 79 and 77 (Found: HRMS, M^+, 176.1189. $C_{12}H_{16}O$ requires M, 176.1201).

Preparation of the ketone **10**. Trimethyloxosulfonium iodide (10.4 g) was treated with sodium hydride (1.89 g) in DMSO (59 cm^3) at 0 °C and a solution of 2-methylcyclohex-2-enone **9**[5]

(5 g) in DMSO (11 cm^3) was added. The reaction mixture was stirred for 2 h at room temp. before work-up. Purification by silica gel column chromatography (hexane–EtOAc, gradient) afforded 1-methylbicyclo[4.1.0]heptan-2-one (3.73 g, 66%); ν_{max}(film)/cm^{-1} 1680; δ_H(90 MHz; $CDCl_3$) 0.86 (1 H, dd, *J* 15.6 and 4.9) and 1.21 (3 H, s); δ_C(22.5 MHz; $CDCl_3$) 17.5, 18.9, 19.3, 21.4, 25.8, 29.2, 36.0 and 209.6; *m/z* 124 (M^+), 109, 95, 82, 67 and 54.

A solution of this ketone (1.31 g) in dry tetrahydrofuran (THF) (6.5 cm^3) was added into a solution of LDA prepared from BuLi (1.6 mol dm^{-3}; 6.9 cm^3) and diisopropylamine (1.6 cm^3) in dry THF (25 cm^3) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and allyl bromide (1.3 cm^3) was added. The reaction mixture was stirred at room temp. for 3 h before work-up. Purification by silica gel column chromatography (hexane–EtOAc, gradient) afforded 3-allyl-1-methylbicyclo[4.1.0]heptan-2-one (800 mg, 46%); ν_{max}(film)/cm^{-1} 1680 and 1640; δ_H(90 MHz; $CDCl_3$) 0.67–1.03 (1 H, m), 1.21 (3 H, s), 4.93–5.12 (2 H, m) and 5.48–5.99 (1 H, m); δ_C(22.5 MHz; $CDCl_3$) 14.8, 19.8, 19.9, 21.1, 21.4, 22.4, 23.3, 24.8, 27.9, 28.5, 29.3, 34.3, 35.4, 43.3, 45.8, 116.1, 116.5, 135.7, 136.4, 21.3 and 211.2; *m/z* 164 (M^+), 149, 135, 123, 109, 94, 68 (100%), 67 and 53.

A solution of 3-allyl-1-methylbicyclo[4.1.0]heptan-2-one (800 mg) in dry benzene (33 cm^3) was treated with Bu^{t}OK (1.46 g) at 0 °C and MeI (3 cm^3) was added. The reaction mixture was heated under reflux for 12 h. The usual work-up and chromatographic purification (SiO_2; hexane–EtOAc, gradient) afforded (1*S**,3*S**,6*R**)-3-allyl-1,3-dimethylbicyclo-[4.1.0]heptan-2-one (640 mg, 73%); ν_{max}(film)/cm^{-1} 1680 and 1640; δ_H(90 MHz; $CDCl_3$) 0.67 (1 H, dd, *J* 15.2 and 4.9), 1.02 (3 H, s), 1.21 (3 H, s), 4.9–5.1 (2 H, m) and 5.4–5.9 (1 H, m); δ_C(22.5 MHz; $CDCl_3$) 14.8, 18.0, 20.6, 24.0, 25.2, 27.8, 28.1, 43.6, 44.5, 117.7, 134.5 and 213.5; *m/z* 178 (M^+), 163, 135, 123, 108, 96, 68, 67, 53 and 40 (100%).

A mixture of CuCl (280 mg), $PdCl_2$ (160 mg), dimethylformamide (DMF) (2.8 cm^3) and water (0.34 cm^3) was treated with oxygen for 15 min and to this mixture was added a solution of the above ketone (500 mg) in DMF (1 cm^3). The mixture was stirred for 20 h at room temp. The pH was adjusted to 1 with hydrochloric acid (3 mol dm^{-3}) and the mixture was extracted with diethyl ether. The ethereal solution was washed with saturated aq. NaCl and was then dried over $MgSO_4$. After evaporation of the solvent the residue was purified by silica gel column chromatography (hexane–EtOAc, gradient) to give (1S*,3S*,6R*)-1,3-*dimethyl*-3-(2-*oxopropyl*)*bicyclo*[4.2.1]*heptan*-2-*one* **10** (280 mg, 51%); ν_{max}(film)/cm^{-1} 1670; δ_H(90 MHz; $CDCl_3$) 0.77 (1 H, dd, *J* 15.6 and 4.8), 1.0 (3 H, s), 1.22 (3 H, s), 2.07 (3 H, s), 2.27 (1 H, d, *J* 18) and 3.19 (1 H, d, *J* 18); δ_C(22.5 MHz; $CDCl_3$) 15.9, 17.9, 20.5, 23.4, 24.7, 26.9, 27.6, 30.0, 42.6, 51.9, 206.2 and 213.1; *m/z* 194 (M^+), 179, 151, 136, 108, 96, 81, 68 and 43 (100%) (Found: HRMS, M^+, 194.1310. $C_{12}H_{18}O_2$ requires M, 194.1307).

Preparation of the cis-*ketone* **11**.—A solution of the dione **10** (25 mg) in Bu^{t}OH (1.2 cm^3) and dry diethyl ether (0.5 cm^3) was treated with Bu^{t}OK (105 mg) at room temp. for 1.2 h. The usual work-up and chromatographic separation (SiO_2; hexane–EtOAc, gradient) afforded (2S*,4R*,7S*)-2,7-*dimethyltricyclo*-[5.3.0.$0^{2,4}$]*dec*-1(10)-*en*-9-*one* **11** (17.7 mg, 78%); ν_{max}-(film)/cm^{-1} 1695, 1670 and 1610; δ_H(90 MHz; $CDCl_3$) 0.51 (1 H, t, *J* 5.3), 0.81 (1 H, dd, *J* 17.3 and 4.8), 1.20 (3 H, s), 1.33 (3 H, s), 1.58 (1 H, dd, *J* 13.7 and 7.1), 1.83 (1 H, dd, *J* 13.7 and 5.1), 2.11 (1 H, d, *J* 17.3), 2.26 (1 H, d, *J* 17.6) and 5.99 (1 H, s); δ_C(22.5 MHz; $CDCl_3$) 17.7 (s), 18.1 (t), 19.0 (d), 19.0 (t), 24.0 (q), 25.7 (q), 28.7 (t), 41.3 (s), 50.6 (t), 126.7 (d), 191.4 (s) and 207.9 (s); *m/z* 176 (M^+), 161, 148, 134, 133, 129, 105 (100%) and 91 (Found: HRMS, M^+, 176.1198. $C_{12}H_{16}O$ requires M, 176.1202).

Synthetic Work toward Compound **1**.—*Preparation of the enone* **13**. A solution of compound **12**,[7] the isobutyl enol ether of 2-methylcyclohexane-1,3-dione (10 g) in dry THF (10 cm^3) was added to a solution of LDA prepared from BuLi (1.6 mol dm^{-3}; 75 cm^3) and diisopropylamine (17 cm^3) in dry THF (80 cm^3) at −78 °C. After 1 h, methyl cyanomethoate (4.6 cm^3) was added dropwise. The reaction mixture was stirred at room temp. for 12 h. The usual work-up afforded a residue, which was used directly in the next step.

The residue was reduced by $LiAlH_4$ (2 g) in dry diethyl ether (250 cm^3) at room temp. for 1 h. After addition of EtOAc to decompose the excess of reagent, 10% H_2SO_4 was added until the pH became 1 and then the mixture was stirred for 1 h. The usual work-up gave a residue, which was treated with a solution of dihydropyran (10 cm^3) in dry dichloromethane (30 cm^3) in the presence of PPTS (1 g) at room temp. for 5 h. The usual work-up and chromatographic purification (SiO_2; hexane–EtOAc, gradient) afforded 2-*methyl*-4-(*tetrahydropyran*-2-*yloxymethyl*)*cyclohex*-2-*enone* **13** (5.7 g, 46%); ν_{max}(film)/cm^{-1} 1670; δ_H(90 MHz; $CDCl_3$) 1.80 (3 H, br s), 4.61 (1 H, m) and 6.70 (1 H, m); *m/z* 224 (M^+), 206, 194, 110 and 85 (100%) (Found: HRMS, M^+, 224.1434. $C_{13}H_{20}O_3$ requires M, 224.1412).

Preparation of the ketone **14**. The ketone **13** (10 g) was reduced by $LiAlH_4$ (1.69 g) in dry diethyl ether (80 cm^3) at room temp. for 1 h. Then wet diethyl ether was added and the mixture was neutralized by addition of saturated aq. NH_4Cl. Work-up afforded the corresponding enol (10.1 g), which was used without purification.

To a stirred solution of the alcohol (10.1 g) in dry dichloromethane (80 cm^3) was added an ethereal solution of $ZnEt_2$ (49 cm^3) slowly at 0 °C. Then diiodomethane (3.9 cm^3) was added and the mixture was stirred at room temp. for 5 h. Water was added and the mixture was extracted with chloroform. The organic phase was washed successively with 10% H_2SO_4 and saturated aq. NaCl, dried over $MgSO_4$ and evaporated to give a residue (8.31 g), which was treated with PDC (19.5 g) in dry dichloromethane (60 cm^3) at room temp. for 12 h. The mixture was filtered through Celite and the filter was washed with diethyl ether. The organic phase was washed successively with 1 mol dm^{-3} HCl and saturated aq. NaCl, dried over $MgSO_4$, and evaporated to afford a residue, which was purified by HPLC [Develosil 60–10; 20 × 250 mm; hexane–EtOAc (3:2) 5 cm^3 min^{-1}] to give 1-*methyl*-5-(*tetrahydropyran*-2-*yloxymethyl*)*bicyclo*[4.1.0]*heptan*-2-*one* **14** (7.75 g, 73%); ν_{max}(film)/cm^{-1} 1680; δ_H(90 MHz; $CDCl_3$) 0.97 (1 H, dd, *J* 7.7 and 4.8), 1.22 (3 H, s) and 4.60 (1 H, br s); *m/z* 238 (M^+), 210, 165, 136, 124, 109, 95, 85 (100%), 67 and 57 (Found: HRMS, M^+, 238.1557. $C_{14}H_{22}O_3$ requires M, 238.1569).

Preparation of the ketone **15**. A solution of the ketone **14** (1 g) in dry THF (5 cm^3) was added into LDA prepared from BuLi (1.6 mol dm^{-3}; 3.15 cm^3) and diisopropylamine (0.7 cm^3) in dry THF (20 cm^3) at −78 °C. The mixture was stirred at −78 °C for 1 h and then the temperature was raised to 0 °C. The mixture was added to allyl bromide (3.63 cm^3) and was stirred for 0.5 h. The usual work-up and purification by silica gel column chromatography (hexane–EtOAc, gradient) afforded 3-*allyl*-1-*methyl*-5-(*tetrahydropyran*-2-*yloxymethyl*)*bicyclo*[4.1.0]*heptan*-2-*one* **15** (678 mg, 58%); ν_{max}(film)/cm^{-1} 1670 and 1630; δ_H(90 MHz; $CDCl_3$) 0.78–0.91 (1 H, m), 1.23 (3 H, s), 4.60 (1 H, br s), 4.91–5.15 (2 H, m) and 5.4–5.9 (1 H, m); *m/z* 278 (M^+), 205, 193, 176, 163, 135, 121, 109, 93, 85 (100%), 67 and 57 (Found: HRMS, M^+, 278.1845. $C_{17}H_{26}O_3$ requires M, 278.1882).

Preparation of the ketone **16**. To a stirred solution of the ketone **15** (1 g) in dry benzene (20 cm^3) were added Bu^{t}OK (605 mg) and MeI (0.27 cm^3). The solution was stirred at room temp. for 1 h and then was heated at reflux for 0.5 h. The

usual work-up and column chromatography (hexane–EtOAc, gradient) afforded (1S*,3R*,5ζ,6S*)-3-*allyl*-1,3-*dimethyl*-5-(*tetrahydropyran*-2-*yloxymethyl*)*bicyclo*[4.1.0]*heptan*-2-*one* **16** (940 mg, 89%); ν_{max}(film)/cm^{-1} 1670; δ_H(90 MHz; $CDCl_3$) 1.05 (3 H, s), 1.22 (3 H, s), 4.60 (1 H, br s), 4.90–5.15 (2 H, m) and 5.4–5.9 (1 H, m); *m/z* 292 (M^+), 219, 208, 192, 178, 120, 107, 85 (100%), 67 and 57 (Found: HRMS, M^+, 292.2064. $C_{18}H_{28}O_3$ requires M, 292.2039).

Wacker oxidation of the ketone **16**. A mixture of CuCl (677 mg), $PdCl_2$ (330 mg), DMF (6 cm^3) and water (0.7 cm^3) was treated under oxygen for 15 min. A solution of the ketone **16** (1.8 g) in DMF (2.1 cm^3) was added and this mixture was stirred under oxygen for 20 h. The usual work-up and column chromatography (SiO_2; hexane–EtOAc, gradient) afforded (1S*,3S*,5ζ,6S*)-1,3-*dimethyl*-3-(2-*oxopropyl*)-5-(*tetrahydropyran*-2-*yloxymethyl*)*bicyclo*[4.1.0]*heptan*-2-*one* **17** (1.11 g, 56%); ν_{max}(film)/cm^{-1} 1710 and 1670; δ_H(90 MHz; $CDCl_3$) 1.00–1.15 (3 H, 2 × s), 1.2–1.3 (3 H, 2 × s), 2.08 (3 H, s) and 4.60 (1 H, br s); *m/z* 308 (M^+), 251, 224, 206, 194, 181, 167, 149, 136, 126 and 85 (100%) [Found: HRMS, 224.1459 ($M - C_5H_8O)^+$, $C_{13}H_{20}O_3$ requires *m/z*, 224.1412].

Preparation of the keto alcohol **18**. To a stirred suspension of Bu^{t}OK (2.9 g) in Bu^{t}OH (33.6 cm^3) and dry diethyl ether (7.3 cm^3) was added a solution of the dione **17** (1.11 g) in dry diethyl ether (7.3 cm^3). The mixture was stirred at room temp. for 1.2 h. The usual work-up and column chromatography (SiO_2; hexane–EtOAc) gave a ketone (880 mg), which was dissolved in MeOH (30 cm^3) and treated with PPTS (0.5 g) at room temp. for 10 h. The usual work-up, and purification by silica gel column chromatography (hexane–EtOAc, gradient) afforded (2S*,4S*,5ζ,7S*)-5-*hydroxymethyl*-2,7-*dimethyltricyclo*-[5.3.0.0^{2,4}]*dec*-1(10)-*en*-9-*one* **18** (129 mg, 17%); ν_{max}(film)/cm^{-1} 3400, 1670 and 1600; δ_H(400 MHz; $CDCl_3$) 0.45 (1 H, dd, *J* 5.4 and 4.9), 1.01 (1 H, dd, *J* 8.8 and 4.9), 1.24 (3 H, s), 1.36 (3 H, s), 2.11 (1 H, d, *J* 17), 2.26 (1 H, d, *J* 17), 3.75 (1 H, dd, *J* 10 and 6), 3.88 (1 H, dd, *J* 10 and 9) and 6.03 (1 H, s); δ_C(100 MHz; $CDCl_3$) 18.0 (s), 20.4 (t), 20.7 (d), 24.3 (q), 28.2 (q), 32.2 (t), 36.0 (d), 41.7 (s), 51.4 (t), 67.3 (t), 126.9 (d), 192.2 (s) and 208.5 (s); *m/z* 206 (M)$^+$, 188, 175 (100%), 161, 145, 133, 119, 105, 91, 77, 65 and 55 (Found: HRMS, M^+, 206.1296. $C_{13}H_{18}O_2$ requires M, 206.1307).

Preparation of the alcohol **19**. A solution of the primary alcohol **18** (129 mg) in dry dichloromethane (10 cm^3) was treated with PDC (356 mg) and powdered molecular sieves (3 Å, 250 mg) at room temp. for 2 h. The usual work-up afforded the corresponding aldehyde (64 mg), which was methylated with excess of MeMgI in diethyl ether at room temp. for 2 h. The usual work-up and column chromatography (SiO_2; hexane–EtOAc, gradient) gave a residue (36 mg). The residue was treated with PDC (90 mg) and powdered molecular sieves (3 Å, 250 mg) in dry dichloromethane (10 cm^3) at room temp. for 2 h. The usual work-up afforded a residue (14.8 mg), which was then treated with excess of MeMgI in diethyl ether at room temp. for 2 h. The usual work-up and silica gel column chromatography (hexane–EtOAc, gradient) and finally HPLC [Nucleosil 50–5; 7.6 × 250 mm; hexane–EtOAc (1:1), 3 cm^3 min^{-1}] afforded (2S*,4S*,5S*,7S*)-5-(2-*hydroxypropan*-2-*yl*)-2,7-*dimethyltricyclo*[5.3.0.0^{2,4}]*dec*-1(10)-*en*-9-*one* **19** (9.1 mg 6.2%); ν_{max}(film)/cm^{-1} 3400, 1700, 1670 and 1600; δ_H(400 MHz; $CDCl_3$) 0.64 (1 H, t, *J* 5, 3-H$^\beta$), 0.91 (1 H, dd, *J* 6.1 and 4.8, 3-H$^\alpha$), 1.09 (1 H, t, *J* 13, 6-H$^\beta$), 1.22 (3 H, s, 7-Me), 1.25 (1 H, m, 4-H), 1.27 (6 H, s, CH_2OH), 1.37 (3 H, s, 2-Me), 1.72 (1 H, dd, *J* 13 and 4.5, 6-H$^\alpha$), 2.15 (1 H, d, *J* 16.5, 8-H$^\beta$), 2.23 (1 H, m, 5-H), 2.28 (1 H, d, *J* 16.5, 8-H$^\alpha$) and 6.00 (1 H, s, 10-H); δ_C(100 MHz; $CDCl_3$) 16.5 (s), 17.3 (t), 20.7 (d), 24.1 (q), 26.8 (q), 27.7 (q), 27.8 (q), 30.1 (t), 39.8 (d), 42.6 (s), 51.2 (t), 73.4 (s), 126.8 (d), 190.6 (s) and 208.1 (s); EI *m/z* 204, 203, 182, 149, 126 (100%), 59 and 43; CI (CH_4) *m/z* 235 $(M + 1)^+$ (100%) [Found: HRMS (CI–CH_4), $(M + 1)^+$, 235.1680. $C_{15}H_{23}O_2$ requires *m/z*, 235.1698].

Isolation of Caespitenone **20** *from* Porella swartziana.—Dried liverwort (301 g) was pulverized, and extracted with diethyl ether for 2 weeks to yield a crude extract (15.6 g). Part of this extract (5.2 g) was subjected to Sephadex LH-20 [dichloromethane–MeOH (1:1)] and silica gel column chromatography (hexane–EtOAc, gradient) to afford six fractions. The second fraction was pure caespitenone (1.15 g); $[\alpha]_D^{20}$ −267 (*c* 1.36, $CHCl_3$); λ_{max}(EtOH)/nm 223 (ε 5260) and 282 (3700); CD (EtOH); λ_{max}/nm 286 (Δε −7.50), 354 (Δε −3.35); ν_{max}(film)/cm^{-1} 1715 and 1600; δ_H(400 MHz; $CDCl_3$) 0.57 (1 H, t, *J* 4.4, 11-H$^\beta$), 1.01, (3 H, s, 13-H_3), 1.05 (1 H, m, 11-H$^\beta$), 1.10 (1 H, m, 9-H), 1.13 (3 H, s, 12-H_3), 1.24 (1 H, m, 8-H$^\alpha$), 1.24 (3 H, s, 14-H_3), 1.45 (3 H, s, 15-H_3), 1.50 (1 H, d, *J* 14, 6-H$^\alpha$), 1.94 (1 H, dd, *J* 15 and 4.2, 8-H$^\beta$), 2.14 (1 H, d, *J* 14, 6-H$^\beta$) and 5.92 (1 H, s, 2-H); δ_C(100 MHz; $CDCl_3$) 8.4 (C-15), 19.5 (C-10), 21.3 (C-9), 23.3 (C-11), 26.5 (C-14), 28.9 (C-12), 30.8 (C-13), 34.2 (C-6), 34.5 (C-7), 42.7 (C-8), 60.8 (C-4), 66.5 (C-5), 128.5 (C-2), 180.0 (C-1) and 200.1 (C-3); *m/z* 232 (M^+, 100%), 217, 204, 189, 175, 161, 147, 133, 119, 105, 91, 83, 77, 69, 55 and 43 (Found: HRMS, M^+, 232.1447. $C_{15}H_{20}O_2$ requires M, 232.1464).

Reduction of Caespitenone **20** *with Miyashita's Reagent*.—A solution of diphenyl diselenide (946 mg) in EtOH (8 cm^3) was treated with $NaBH_4$ (230 mg) at room temp. for 10 min. To this solution was added a solution of caespitenone (469 mg) in EtOH (2 cm^3)–AcOH (0.08 cm^3). The mixture was stirred at room temp. for 1 h. Water was added and the mixture was extracted with EtOAc. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated to afford a residue (1.27 g), which was separated by silica gel column chromatography (hexane–EtOAc, gradient) to yield the alcohol **21** (337 mg) and its regioisomer **22** (61 mg). *Compound* **21**; m.p. 141–143 °C (from hexane); $[\alpha]_D^{22}$ −171.4 (*c* 1.44, $CHCl_3$); ν_{max}(film)/cm^{-1} 3380, 1680 and 1570; δ_H(400 MHz; $CDCl_3$) 0.84 (3 H, s), 0.98 (3 H, s), 1.08 (1 H, d, *J* 7.3), 1.29 (3 H, s), 1.87 (1 H, dd, *J* 14 and 9.2), 1.98 (1 H, dd, *J* 6.4 and 3.9), 2.13 (1 H, dd, *J* 15 and 7.1), 2.50 (1 H, q, *J* 7.3) and 6.06 (1 H, s); δ_C(100 MHz; $CDCl_3$) 7.57 (q), 24.4 (s), 26.6 (q), 26.7 (t), 28.4 (d), 28.5 (q), 32.5 (s), 34.6 (1), 36.9 (t), 50.6 (t), 59.0 (d), 81.1 (s), 128.1 (d), 183.8 (s) and 204.3 (s); *m/z* 234 (M^+), 219, 216, 201, 178, 173 (100%), 149, 135, 121, 107, 91, 77, 67, 55 and 41 (Found: HRMS, M^+, 234.1619. $C_{15}H_{22}O_2$ requires *M*, 234.1620).

Compound **22**; λ_{max}(EtOH)/nm 210.5 (ε 1970); CD (EtOH) Δε −3.2 (237 nm), +1.6 (310. nm); ν_{max}(film)/cm^{-1} 3450 and 1750; δ_H(400 MHz; C_6D_6) −0.05 (1 H, m), 0.32 (1 H, m), 0.86 (3 H, s), 0.99 (3 H, s), 1.04 (3 H, s), 1.18 (3 H, s), 1.72 (1 H, m), 1.96 (1 H, d, *J* 14), 2.23 (1 H, dt, *J* 14 and 3.1), 2.55 (1 H, ddd, *J* 22, 3.1 and 0.7), 2.75 (1 H, ddd, *J* 22, 3.1 and 0.7) and 2.92 (1 H, s, OH); δ_C(100 MHz; C_6D_6) 19.0 (q), 19.4 (s), 21.0 (d) 22.6 (q), 23.2 (q), 29.1 (q), 31.3 (s), 31.5 (q), 36.9 (t), 39.9 (t), 43.8 (t), 79.4 (s), 136.9 (s), 139.3 (s) and 217.2 (s); *m/z* 234 (M)$^+$, 219, 216, 178, 173, 163, 149, 135, 121, 107, 91 and 77 (Found: HRMS, M^+, 234.1612).

Preparation of the Bromobenzoate **23**.—The ketone **21** (19 mg) was reduced by $NaBH_4$ (10 mg) in the presence of $CeCl_3$ (98 mg) in MeOH (1 cm^3) at room temp. for 1 h. The usual work-up afforded a diol (19 mg), which was treated with *p*-bromobenzoyl chloride (36 mg) and 4-(dimethylamino)pyridine (10 mg) in pyridine (0.5 cm^3)–dry dichloromethane (3 cm^3) at room temp. for 5 h. The usual work-up and preparative TLC gave the bromobenzoate **23** (7.5 mg); CD (EtOH) Δε −11.2 (236 nm); ν_{max}(film)/cm^{-1} 3300, 1720 and 1600: δ_H(400 MHz; [$^2H_6$]DMSO) 0.88 (3 H, s), 0.90 (3 H, s), 1.02 (3 H, d, *J*

7.1), 1.14 (3 H, s), 2.20 (1 H, dd, *J* 14 and 7), 2.29 (1 H, m), 4.75 (1 H, s, OH), 5.27 (1 H, dd, *J* 7.8 and 1.5), 5.59 (1 H, d, *J* 1.8), 7.75 (2 H, d, *J* 8.8) and 7.90 (2 H, d, *J* 8.5).

Acknowledgements

We thank Dr. R. Gradstein, University of Utrecht, The Netherlands, for collection of the liverwort and also its identification. The 600 MHz NMR spectra by Miss Y. Kan and the MS spectra by Miss Y. Okamoto (both at this university) are gratefully acknowledged. We also thank Dr. Masao Toyota (at this university) for valuable discussions. Correction of the manuscript by Dr. Malcolm S. Buchanan is greatly acknowledged. This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan.

References

1 Y. Asakawa, Y. Yamamura, T. Waki and T. Takemoto, *Phytochemistry*, 1980, **19**, 603.
2 Y. Asakawa, in *Progress in the Chemistry of Organic Natural Products*, eds. W. Herz, H. Grisebach and G. W. Kirby, Springer-Verlag, Wien, 1982, vol. 42, p. 1.
3 M. Tori, *Rev. Latinoam. Quím.*, 1991, **22**, 73 (*Chem. Abstr.*, **119**, 160586z).
4 M. Tori, K. Nakashima, M. Toyota and Y. Asakawa, *Tetrahedron Lett.*, 1993, **23**, 3751.
5 E. W. Warnhoff, D. G. Martin and W. S. Johnson, *Org. Synth.*, 1963, Coll. Vol. 4, 162.
6 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1986, **87**, 1353.
7 J. Panouse and C. Sanié, *Bull. Soc. Chim. Fr.*, 1956, 1272.
8 R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, London, 1985.
9 E. Keinan and Y. Mazur, *J. Org. Chem.*, 1978, **43**, 1020.
10 J. D. Connolly and R. A. Hill, *Dictionary of Terpenoids*, Chapman and Hall, London, 1991.
11 M. Miyashita, T. Suzuki and A. Yoshikoshi, *Tetrahedron Lett.*, 1987, **28**, 4293.
12 M. Miyashita, T. Suzuki and A. Yoshikoshi, *Tetrahedron Lett.*, 1988, **29**, 347; 1989, **30**, 1819; M. Miyashita, M. Hoshino, T. Suzuki and A. Yoshikoshi, *Chem. Lett.*, 1988, 507.
13 N. Harada and K. Nakanishi, *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, CA, 1983.
14 B. Tursch, J. C. Braekman, D. Daloze, P. Fritz, A. Kelecom, R. Karlsson and D. Losman, *Tetrahedron Lett.*, 1974, 747.
15 F. Bohlmann and C. Zdero, *Phytochemistry*, 1978, **17**, 1669.
16 M. Toyota, F. Nagashima, K. Shima and Y. Asakawa, *Phytochemistry*, 1992, **31**, 183.
17 Y. Asakawa, *J. Hattori Bot. Lab.*, 1982, **53**, 283 (*Chem. Abstr.*, **97**, 212730r).

Paper 4/02302A
Received 19*th April* 1994
Accepted 27*th June* 1994