Chiral Cyclobutanones as Versatile Synthons: the First Enantioselective Total Synthesis of (+)-Laurene

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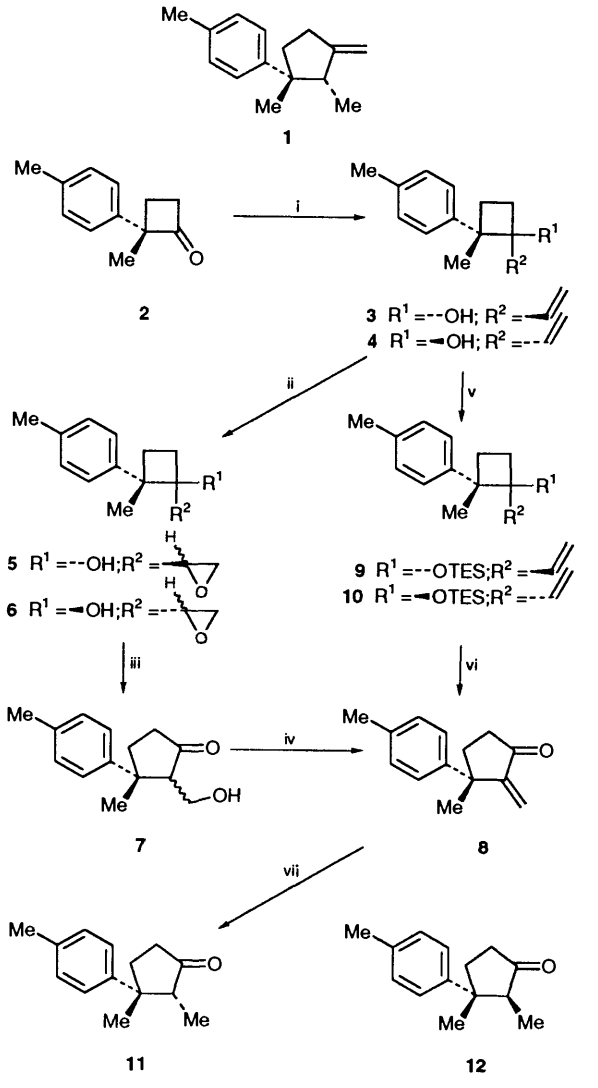
A novel and convenient route to the thermodynamically unstable ketone **11** *via* the cyclopentanone **8** which was synthesised by palladium-mediated ring expansion of the chiral siloxyvinylcyclobutanes **9** and **10** has been developed. This leads to an enantioselective total synthesis of (+)-laurene **1**.

(1)-Laurene **1**, a sesquiterpene hydrocarbon which has been isolated from Laurencia species and the marine red algae *Laurencia elate*,[1] has a flexible carbon framework suitable for the construction of similar biologically important compounds.[2] Despite the relatively simple substitution pattern on the cyclopentane ring of (+)-laurene **1**, the *cis*-1,2-relationship of the secondary methyl group with the *p*-tolyl group has made both the stereoselective and enantioselective synthesis of this sesquiterpene difficult.[3] During our work[4] directed towards the enantioselective construction of cyclobutanones and its application in the synthesis of biologically interesting compounds, we have developed a novel enantioselective approach to (+)-laurene **1** starting from the chiral cyclobutanone **2** and herein we describe the results.†

(*S*)-2-Methyl-2-(*p*-tolyl)cyclobutanone **2** [79% enantiomeric excess (e.e.)], easily prepared[4f] by tandem asymmetric epoxidation and enantiospecific ring expansion of 2-cyclopropylidene-2-(*p*-tolyl)ethanol as a key step, was subjected to Grignard reaction with vinylmagnesium bromide in the presence of cerium trichloride to give the easily separable allyl alcohols **3** and **4** in 59 and 24% yields, respectively. The diastereoisomeric mixture of the epoxides **5** (95%) and **6** (68%) was derived by the epoxidation [*m*-chloroperbenzoic acid (MCPBA)] of **3** and **4** respectively (the ratio of the isomers for **5** could not be determined, but the corresponding isomer ratio for **6** was determined as 2:3). The epoxide **5** was then treated with acid (BF_3·Et_2O) to effect ring expansion[5] of the cyclobutane ring to give the cyclopentanone **7** (although this product seems to be a single product on its NMR spectrum, its stereochemistry could not be determined). The dehydration of this was effectively achieved by mesylation in the presence of an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the enone **8** (76% overall yield from **5**). Alternatively, the conversion of **3** and **4** into **8** was achieved more effectively by palladium-catalysed ring expansion.[6] Thus, the triethylsilyl (TES) ethers **9** and **10**, prepared in 90 and 95% yields from **3** and **4** respectively, were subjected to ring expansion in the presence of a catalytic amount of bis(acetonitrile)palladium chloride and *p*-benzoquinone to give the enone **8** in 86 and 70% yields, respectively.

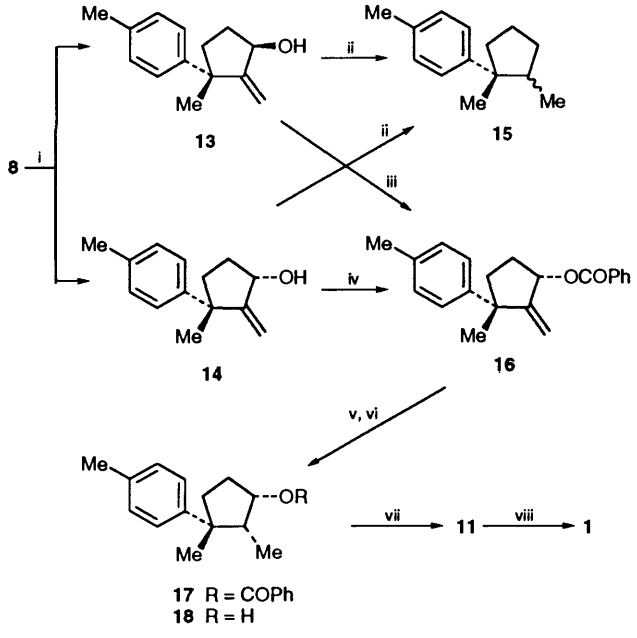
Since the direct hydrogenation of the enone **8** to afford the thermodynamically unstable ketone **11** and its diastereoisomer **12** showed poor selectivity (89% yield, in the ratio 3:2) the stereoselective conversion was achieved as follows. Reduction ($NaBH_4$, $CeCl_3$) of the enone **8** gave the allyl alcohols **13** (72%) and **14** (19%). The former was converted into the benzoate **16** (98%) with inversion of chirality at the hydroxy group under Mitsunobu conditions (diethyl azodicarboxylate, Ph_3P, $PhCO_2H$). The benzoate thus obtained was identical with the sample prepared (99%) by esterification (PhCOCl, pyridine) of the minor alcohol **14**. Although the direct catalytic hydrogenation of either the allyl alcohol **13** or **14** gave only the hydrogenolysis products **15** as a diastereoisomeric mixture, the catalytic hydrogenation (H_2, Rh-alumina) of the benzoate **16** afforded **17** (92%) stereoselectivity which on hydrolysis (LiOH) gave the alcohol **18** (100%). The conditions for the



Scheme 1 *Reagents and conditions:* i, vinylmagnesium bromide, $CeCl_3$, tetrahydrofuran (THF), −78 °C, 1 h; ii, MCPBA, CH_2Cl_2, 0 °C, 3 h; iii, BF_3·Et_2O, THF, −78 °C, 4 h; iv, $MeSO_2Cl$, DBU, CH_2Cl_2, room temp., 6 h; v, Et_3SiO Tf, 2,6-dimethylpyridine, CH_2Cl_2, room temp., 30 min; vi, $PdCl_2(MeCN)_2$, *p*-benzoquinone, THF, reflux, 2 h; vii, H_2, Rh-alumina, AcOEt, room temp., 3 h

† A part of this work has been published in *J. Chem. Soc., Commun.*, 1992, 1695.

oxidation of **18** were carefully examined* and tetrapropylammonium perruthenate. (Pr_4NRuO_4) catalysed oxidation[7] was found to be the best for this purpose. This afforded solely the desired ketone **11** (92%) no epimerised product being detected. Finally, the methylenation* of the ketone **11** was effected by the Nozaki Lombardo procedure[8] (Zn, $TiCl_4$, CH_2Br_2) to give (+)-laurene **1** (40%) {$[\alpha]_D^{25}$ +34.7 (*c* 0.15, EtOH); lit.,[1a] $[\alpha]_D^{23}$ +48.7 (*c* 1.2, EtOH)}. We have not been able to determine the enantiomeric excess of the final product but since it has a positive rotation its absolute stereochemistry must be identical with that of the natural compound.



Scheme 2 *Reagents and conditions:* i, $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 5 min; ii, H_2, Pd-C, AcOEt, room temp., 2 h; iii, $EtO_2CN{=}NCO_2Et$, Ph_3P, benzene, room temp., 3 h; iv, PhCOCl, pyridine, room temp., 1.5 h; v, H_2, Rh-alumina, EtOH, room temp., 6 h; vi, LiOH, MeOH–H_2O, reflux, 2.5 h; vii, Pr_4NRuO_4, *N*-methylmorpholine *N*-oxide, 4 Å molecular sieves, CH_2Cl_2, room temp., 12 h; viii, Zn, $TiCl_4$, CH_2Br_2, CH_2Cl_2–THF, room temp., 12 h

Thus, we have completed the first enantiomerically enriched total synthesis of (+)-laurene by a route applicable to the enantioselective synthesis of similar biologically important compounds.

Experimental

General Methods.—M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. NMR spectra were obtained on JEOL FX-90 and JNM GX-500 spectrometers. Chemical shifts were recorded relative to internal $SiMe_4$. Mass spectra were taken on Hitachi M-52 G and JEOL-TMS-OISG-2 spectrometers. Optical rotations were measured with a JASCO-DIP-340 polarimeter. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue obtained when the organic layer was separated, dried over anhydrous Na_2SO_4, and the solvent was evaporated off under reduced pressure. All new compounds described in this Experimental section were homogeneous on TLC.

(1R,2S)- *and* (1S,2S)-2-*Methyl*-2-p-*tolyl*-1-*vinylcyclobutanols* **3** *and* **4**.—To a stirred suspension of cerium chloride ($CeCl_3$) (2.29 g, 9.3 mmol) in tetrahedrofuran (THF) (20 cm^3) at −78 °C was added a 1.0 mol dm^{-3} solution of vinylmagnesium bromide in THF (9.3 cm^3, 9.3 mmol). After the mixture had been stirred for 1 h at −78 °C, a solution of the (*S*)-cyclobutanone **2** (531 mg, 3.05 mmol) in ether (5 cm^3) was added to the above solution at the same temperature and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with saturated aq. NH_4Cl and extracted with ether. The residue upon work-up was chromatographed with hexane–ethyl acetate (98:2, v/v) to give the (1S,2S)-*cyclobutanol* **4** (146 mg, 24%) as an oil from the first fraction and the (1R,2S)-*cyclobutanol* **3** (366 mg, 59%) as needles from the second fraction.

Compound **3** m.p. 84.0–84.3 °C (from hexane); $[\alpha]_D^{25}$ +3.2 (*c* 3.13, $CHCl_3$) (Found: M^+, 202.1315. $C_{14}H_{18}O$ requires *m/z*, 202.1357); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H(500 MHz, $CDCl_3$) 1.50 (3 H, s, Me), 1.80 (1 H, m, CH*H*Me), 2.04 (1 H, br s, OH), 2.04–2.18 (2 H, m, CH*H*CMe), 2.25–2.37 (1 H, m, C*H*HCOH), 2.30, s, Ph *Me*), 4.91 (1 H, d, *J* 10.4, CH=C*H*H), 5.24 (1 H, d, *J* 17.7, CH=CH*H*), 5.76 (1 H, dd, *J* 10.4 and 17.7, C*H*=CH_2) and 6.93 and 7.07 (each 1 H, each d, *J* 8.0); *m/z* 202 (M^+).

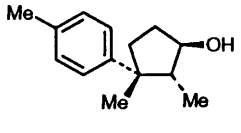
Compound **4** $[\alpha]_D^{20}$ +30.8 (*c* 3.41, $CHCl_3$) (Found: M^+, 202.1358. $C_{14}H_{18}O$ requires *m/z*, 202.1358); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H(90 MHz, $CDCl_3$) 1.40 (3 H, s, Me), 1.63–2.91 (5 H, m, OH and CH_2CH_2), 2.33 (3 H, s, Ph*Me*). 5.18 (1 H, dd, *J* 11.7 and 1.8, CH=CH*H*), 5.32 (1 H, dd, *J* 18.0 and 1.8, CH=CH*H*), 6.25 (1 H, dd, *J* 10.8 and 1.8 C*H*=CH_2) and 6.98–7.29 (4 H, m, C_6H_4); *m/z* 202 (M^+).

(1S,2S)-1-(1,2-*Epoxyethyl*)-2-*methyl*-2-p-*tolylcyclobutanol* **5**.—To a stirred solution of the (1*R*,2*S*)-cyclobutanol **3** (196 mg, 0.97 mmol) in CH_2Cl_2 (6 cm^3) was added *m*-chloroperbenzoic acid (MCPBA) (627 mg, 2.90 mmol) at 0 °C and the reaction mixture was stirred for 3 h at room temperature; it was then diluted with 10% aq. NaOH, and extracted with CH_2Cl_2. The residue upon work-up was chromatographed with hexane–ethyl acetate (96:4, v/v) to give the *epoxide* **5** (202 mg, 95%) as a powder (Found: M^+, 218.1312. $C_{14}H_{18}O_2$ requires *m/z*, 218.1306); ν_{max}($CHCl_3$)/cm^{-1} 3400 (OH); δ_H(500 MHz, $CDCl_3$), 1.49 (1 H, s, OH), 1.51 (3 H, s, Me), 1.75–2.38 (4 H, m, CH_2CH_2), 2.31 (3 H, s, Ph*Me*), 2.48 (1 H, t, *J* 4.6, C*H*OCH_2), 2.83 (2 H, m, CHO*C*H_2) and 6.98–7.16 (4 H, m, C_6H_4); *m/z* 218 (M^+).

(1R,2S)-1-(1,2-*Epoxyethyl*)-2-*methyl*-2-p-*tolylcyclobutanol* **6**.—By following the same procedure described above, the (1*S*,2*S*)-cyclobutanol **4** (45 mg, 0.22 mmol) afforded the *epoxide* **6** (32.8 mg, 68%) as an oil. In this case the pure diastereoisomers **6a** (12.4 mg, 26%) and **6b** (20.4 mg, 42%) were obtained by chromatography with hexane–ethyl acetate (95:5, v/v) for analysis.

Compound **6a** $[\alpha]_D^{25}$ +52.6 (*c* 1.03, $CHCl_3$) (Found: M^+, 218.1324. $C_{14}H_{18}O_2$ requires *m/z* 218.1306); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H(90 MHz, $CDCl_3$), 1.56 (3 H, s, Me), 1.50–3.00 (7 H, m, CH_2CH_2, OH, CHO*C*H_2), 2.32 (3 H, s, Ph*Me*), 3.24–3.40 (1 H, m, C*H*OCH_2) and 7.15 (4 H, br, s, C_6H_4); *m/z* 218 (M^+).

* It has been pointed out[3a] that the ketone **11** was easily epimerised into the thermodynamically more stable isomer **12** on the oxidation of the alcohol **I** and the methylenation of **11** under Wittig conditions.



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Compound **6b** $[\alpha]_D^{25}$ +30.3 (*c* 1.70, $CHCl_3$) (Found: M^+, 218.1297. $C_{14}H_{18}O_2$ requires *m/z*, 218.1306); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H(90 MHz, $CDCl_3$) 1.54 (3 H, s, Me), 1.50–2.90 (7 H, m, CH_2CH_2, OH, $CHOCH_2$), 2.34 (3 H, s, Ph*Me*), 3.12–3.30 (1 H, m, $CHOCH_2$) and 7.16 (4 H, br, s, C_6H_4); *m/z* 218 (M^+).

(3S)-3-*Methyl*-2-*methylene*-3-p-*tolylcyclopentanone* **8**.—To a solution of the epoxide **5** (64.8 mg, 0.30 mmol) in CH_2Cl_2 (1 cm^3) was added BF_3·Et_2O (0.3 cm^3) at −78 °C and the reaction mixture was stirred for 4 h at the same temperature; it was then treated with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v) to give the alcohol **7** (61.3 mg, 95%) as an oil. To a solution of the alcohol **7** (60.5 mg, 0.27 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.14 cm^3, 0.9 mmol) was added methanesulfonyl chloride (MsCl) 0.05 cm^3, 0.6 mmol) at 0 °C and stirring was continued for 6 h at room temperature. The reaction mixture was treated with 10% aq. HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated aq. $NaHCO_3$ and NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (95:5, v/v) to give the *enone* **8** (43.9 mg, 80%) as an oil, $[\alpha]_D^{25}$ −211.47 (*c* 1.63, $CHCl_3$) (Found: M^+, 200.1189. $C_{14}H_{16}O$ requires *m/z*, 200.1200); ν_{max}(neat)/cm^{-1} 1720 (C=O); δ_H (90 MHz, $CDCl_3$) 1.57 (3 H, s, Me), 1.79–2.71 (4 H, m, CH_2CH_2), 2.32 (3 H, s, Ph *Me*), 5.30 and 6.25 (each 1 H, each d, *J* 0.7, C=CH_2) and 7.01–7.28 (4 H, m, *Ph*Me): *m/z* 200 (M^+). By following the same procedure, the epoxide **6** (8.2 mg, 0.04 mmol) afforded the *enone* **8** (5.7 mg, 76%).

(1R,2S)- *and* (1S,2S)-2-*Methyl*-2-p-*tolyl*-1-*triethylsiloxy*-1-*vinycyclobutanes* **9** *and* **10**.—To a stirred solution of the (1*R*,2*S*)-cyclobutanol **3** (33.6 mg, 0.17 mmol) and 2,6-dimethylpyridine (0.04 cm^3, 0.33 mmol) in CH_2Cl_2 (1.5 cm^3) was added triethylsilyl trifluoromethanesulfonate (TESOTf) (0.06 cm^3, 0.25 mmol) at 0 °C and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ and brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (97:3, v/v) to give the (1R,2S)-*silyl ether* **9** (47.1 mg, 90%) as an oil. By following the same procedure, the (1*S*,2*S*)-cyclobutanol **4** (67.0 mg, 0.34 mmol) afforded the (1S,2S)-*silyl ether* **10** (99.4 mg, 95%) as an oil.

Compound **9** $[\alpha]_D^{25}$ −3.3 (*c* 0.20, $CHCl_3$) (Found: M^+, 316.2223. $C_{20}H_{32}OSi$ requires *m/z*, 316.2221); δ_H(90 MHz, $CDCl_3$) 0.41–0.80 [6 H, m, $Si(CH_2Me)_3$], 0.81–1.5 [9 H, m, $Si(CH_2Me)_3$], 1.45 (3 H, s, Me), 1.29–2.46 (4 H, m, CH_2CH_2), 2.29 (3 H, s, Ph*Me*), 4.82 (1 H, dd, *J* 10.8 and 2.7, CH=C*H*H), 5.10 (1 H, dd, *J* 18.0 and 2.7, CH=CH*H*), 5.63 (1 H, dd, *J* 18.0 and 10.8, C*H*=CH_2) and 6.81–7.16 (4 H, m, C_6H_4); *m/z* 316 (M^+).

Compound **10** $[\alpha]_D^{25}$ −33.9 (*c* 0.40, $CHCl_3$) (Found: M^+, 316.2200. $C_{20}H_{32}OSi$ requires *m/z*, 316.2221); δ_H (90 MHz, $CDCl_3$) 0.16–0.53 [6 H, m, $Si(CH_2Me)_3$], 0.56–0.86 [9 H, m, $Si(CH_2Me)_3$], 1.23 (3 H, s, Me), 1.45–2.71 (4 H, m, CH_2CH_2), 2.31 (3 H, s, Ph*Me*), 5.18 (1 H, dd, *J* 10.8 and 1.8, CH=C*H*H), 5.22 (1 H, dd, *J* 18.0 and 1.8, CH=CH*H*), 6.12 (1 H, dd, *J* 18.0 and 10.8, C*H*=CH_2) and 6.91–7.10 (4 H, m, C_6H_4); *m/z* 316 (M^+).

(3S)-3-*Methyl*-2-*methylene*-3-p-*tolylcyclopentane* **8** via *Palladium-catalysed Ring Expansion*.—A solution of the silyl ether **9** (23.7 mg, 0.08 mmol), bis(acetonitrile)palladium(II) chloride (2.0 mg, 0.075 mmol), and *p*-benzoquinone (16.2 mg, 0.15 mmol) in THF (1 cm^3) was refluxed for 2 h. The residue upon evaporation of the solvent was chromatographed with hexane to give the enone **8** (12.9 mg, 86%) as an oil. By following the same procedure, the silyl ether **10** (87.5 mg, 0.3 mmol) afforded the enone **8** (38.6 mg, 70%) as an oil. The enone **8** thus obtained was identical with the sample prepared from the epoxides **5** and **6**.

(2R,3R)- *and* (2S,3R)-2,3-*Dimethyl*-3-p-*tolylcyclopentanones* **11** *and* **12**.—A mixture of the enone **8** (5.0 mg, 0.025 mmol), a catalytic amount of Rh-alumina and ethyl acetate (1.5 cm^3) was stirred for 3 h under an atmosphere of hydrogen at room temperature before being filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (4:1 v/v) to give a mixture of the ketones **11** and **12** (4.5 mg, 89%) as an oil (Found: M^+, 202.1346. $C_{14}H_{18}O$ requires *m/z*, 202.1358); ν_{max}(neat)/cm^{-1} 1740 (C=O); δ_H(500 MHz, $CDCl_3$) 0.82 (1.8 H, d, *J* 6.8, *Me*CHCO), 1.03 (1.2 H, d, *J* 6.8, *Me*CHCO), 1.19 (1.2 H, s, ArC*Me*), 1.41 (1.8 H, s, ArC*Me*), 2.00–2.54 (5 H, m, CH_2CH_2, C*H*Me), 2.33 (1.8 H, s, Ar*Me*), 2.35 (1.2 H, s, Ar*Me*) and 7.05–7.34 (4 H, m, C_6H_4); *m/z* 202 (M^+).

(1R,3S)- *and* (1S,3S)-3-*Methyl*-2-*methylene*-3-p-*tolylcyclopentanols* **13** *and* **14**.—To a stirred solution of the enone **8** (44.5 mg, 0.22 mmol) and cerium chloride heptahydrate (82 mg, 0.22 mmol) in MeOH (1 cm^3) was added sodium borohydride ($NaBH_4$) (8.4 mg, 0.22 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. It was then diluted with ether and washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (97:3, v/v) to give the (1R,3S)-*alcohol* **13** (32.1 mg, 72%) as an oil from the first fraction and the (1S,3S)-*alcohol* **14** (8.3 mg, 19%) as an oil from the second fraction.

Compound **13** $[\alpha]_D^{25}$ −154.8 (*c* 2.08, $CHCl_3$) (Found: M^+, 202.1375. $C_{14}H_{18}O$ requires *m/z*, 202.1358); ν_{max}(neat)/cm^{-1} 3400 (OH); δ_H (500 MHz, $CDCl_3$) 1.49 (3 H, s, Me), 1.50–2.15 (5 H, m, CH_2CH_2, OH), 2.31 (S H, s, Ph*Me*), 4.58 (1 H, br, s, C*H*OH), 5.05 and 5.40 (each 1 H, each d, *J* 2.0, C=CH_2), 7.22 and 7.90 (each 2 H, each d, *J* 8.6, C_6H_4); *m/z* 202 (M^+).

Compound **14** $[\alpha]_D^{25}$ −65.8 (*c* 0.46, $CHCl_3$) (Found: M^+, 202.1373. $C_{14}H_{18}O$ requires *M*, 202.1358); ν_{max}(neat)/cm^{-1} 3400 (OH); δ_H (500 MHz, $CDCl_3$) 1.44 (3 H, s, Me), 1.56 (1 H, s, OH), 1.52–1.64 (1 H, m, CH*H*CMe), 1.66–1.76 (1 H, m, CH*H*COH), 1.96–2.10 (1 H, m, C*H*HCMe), 2.21–2.34 (1 H, m, CH*H*COH), 2.32 (3 H, s, Ph*Me*), 4.62 (1 H, d, *J* 5.5, C*H*OH), 4.97 and 5.39 (each 1 H, each d, *J* 1.8, C=CH_2) and 7.11 and 7.32 (each 2 H, each d, *J* 8.6, C_6H_4); *m/z* 202 (M^+).

(1R,2R)- *and* (1R,2S)-1,2-*Dimethyl*-1-p-*tolylcyclopentane* **15**.—A mixture of the alcohol **13** (2.8 mg, 0.014 mmol), a catalytic amount of 10% Pd–carbon, and ethyl acetate (1.5 cm^3) was stirred for 2 h under the atmosphere of hydrogen at room temperature and then filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (93:7, v/v) to give the *cyclopentane* **15** (2.0 mg, 77%) as an oil (Found: M^+, 188.1542. $C_{14}H_{20}$ requires *m/z*, 188.1565); δ_H(500 MHz, $CDCl_3$) 0.84 (1.5 H, d, *J* 6.8, CH*Me*), 1.05 (1.5 H, d, *J* 6.8, CH*Me*), 1.22 (1.5 H, s, ArC*Me*), 1.41 (1.5 H, s, ArCMe), 2.33 (1.5 H, s, Ar*Me*), 2.36 (1.5 H, s, Ar*Me*), 2.03–2.67 (7 H, m, $(CH_2)_3CH$Me) and 7.04–7.40 (4 H, m, Ar); *m/z* 188 (M^+). By following the same procedure the alcohol **14** (6.8 mg, 0.034 mmol) afforded the cyclopentane **15** (5.6 mg, 89%) as an oil.

(1S,3S)-3-*Methyl*-2-*methylene*-3-p-*tolylcyclopentyl Benzoate* **16**.—*Method A* To a solution of the (1*R*,3*S*)-alcohol **13** (16.0 mg, 0.08 mmol), triphenylphosphine (Ph_3P) (60.0 mg, 0.24 mmol) and benzoic acid (29.0 mg, 0.24 mmol) in benzene (1 cm^3) was added diethyl azodicarboxylate (0.04 cm^3, 0.24 mmol) at 0 °C and stirring was continued for 3 h at room temperature. The residue upon evaporation of the solvent was chromato-

graphed with hexane–ethyl acetate (97:3, v/v) to give the benzoate **16** (23.8 mg, 98%) as an oil, $[\alpha]_D^{25}$ −47.8 (*c* 0.78, $CHCl_3$) (Found: M^+, 306.1608. $C_{21}H_{22}O_2$ *m/z*, requires 306.1620); $\nu_{max}(CHCl_3)$ cm^{-1} 1715 (C=O); δ_H(500 MHz, $CDCl_3$) 1.47 (3 H, s, Me), 1.72–1.90 (2 H, m, C*H*HCO, CH*H*CMe), 2.16–2.28 (1 H, m, C*H*HCMe), 2.28–2.40 (1 H, m, C*H*HCO), 2.33 (3 H, s, Ph*Me*), 5.12 and 5.56 (each 1 H, each d, *J* 1.2, C=CH_2), 5.90 (1 H, t, *J* 4.9, C*H*OCOPh) and 7.06–8.04 (9 H, m, C_6H_5, C_6H_4Me); *m/z* 306 (M^+).

Method B. To a solution of the (1*S*,3*S*)-alcohol **14** (5.0 mg, 0.025 mmol) in pyridine (1 cm^3) was added benzoyl chloride (0.02 cm^3, 0.17 mmol) at 0 °C and the mixture was stirred for 1.5 h at room temperature. It was then diluted with CH_2Cl_2 and washed with 10% HCl, saturated aq. $NaHCO_3$ and saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (99:1, v/v) to give the benzoate **16** (7.5 mg, 99%) as an oil, which was identical with the sample obtained by Method A.

(1S,2R,3S)-2,3-*Dimethyl*-3-p-*tolylcyclopentyl Benzoate* **17**.—A solution of the benzoate **16** (13.0 mg, 0.042 mmol) and a catalytic amount of Rh–alumina in EtOH (4.5 cm^3) was stirred for 6 h under the atmosphere of hydrogen after which the mixture was filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (95:5, v/v) to give the benzoate **17** (12.1 mg, 92%) as an oil, $[\alpha]_D^{25}$ +18.2 (*c* 0.68, $CHCl_3$) (Found: M^+, 308.1785. $C_{21}H_{24}O_2$ requires *m/z*, 308.1776); ν_{max}(neat)/cm^{-1} 1720 (C=O); δ_H(500 MHz, $CDCl_3$) 0.57 (3 H, d, *J* 7.3, CH*Me*), 1.66–2.44 (5 H, m, CH_2CH_2, C*H*Me), 1.31 (3 H, s, PhC*Me*), 2.32 (3 H, s, C_6H_4Me), 5.38 (1 H, m, C*H*OCOPh) and 7.08–7.30 (9 H, m, COC_6H_5, C_6H_4Me); *m/z* 308 (M^+).

(1S,2R,3S)-2,3-*Dimethyl*-3-p-*tolylcyclopentanol* **18**.—A solution of the benzoate **17** (5.0 mg, 0.016 mmol) and saturated aq. LiOH (0.5 cm^3) in MeOH (1.5 cm^3) was refluxed for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v) to give the (1R,2R,3S)-*alcohol* **18** (3.3 mg, 100%) as an oil, $[\alpha]_D^{25}$ +28.7 (*c* 0.51, $CHCl_3$) (Found: M^+, 204.1520. $C_{14}H_{20}O$ requires *m/z*, 204.1514); ν_{max}(neat)/cm^{-1} 3350 (OH): δ_H(500 MHz, $CDCl_3$) 0.69 (3 H, d, *J* 7.3, CH*Me*), 1.30 (3 H, s, PhC*Me*), 1.64–2.48 (5 H, m, CH_2CH_2, C*H*Me), 2.32 (3 H, s, C_6H_4Me) and 7.06–7.24 (4 H, m, C_6H_4); *m/z* 204 (M^+).

(2R,3S)-2,3-*Dimethyl*-3-p-*tolylcyclopentanone* **11**.—A mixture of the alcohol **18** (4.5 mg, 0.022 mmol), 4 Å molecular sieves (11 mg), tetrapropylammonium perruthenate (0.8 mg, 0.002 mmol), and 4-methylmorpholine *N*-oxide (3.9 mg, 0.033 mmol) and CH_2Cl_2 (1 cm^3) was stirred for 12 h at room temperature. The reaction mixture was directly chromatographed with CH_2Cl_2 to give *ketone* **11** (4.1 mg, 92%) as an oil, $[\alpha]_D^{25}$ +16.8 (*c* 0.40 $CHCl_3$) (Found: M^+, 202.1370. $C_{14}H_{18}O$ requires *m/z*, 202.1358); ν_{max}(neat)/cm^{-1} 1740 (C=O); δ_H(500 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 7.4, CH*Me*), 1.41 (3 H, s, C_4H_6CMe), 2.00–2.54 (5 H, m, CH_2CH_2, C*H*Me), 2.33 (3 H, s, C_6H_4Me) and 7.06 and 7.13 (each 2 H, each d, *J* 8.4, C_6H_4); *m/z* 202 M^+).

(+)-*Laurene* **1**.—To a stirred suspension of Zn (280 mg, 4.28 mmol) in THF (0.8 cm^3) was added 1 mol dm^{-3} solution of titanium tetrachloride in CH_2Cl_2 (0.7 cm^3, 0.7 mmol) and dibromomethane (0.16 cm^3, 2.28 mmol) at 0 °C and stirring was continued for 15 min at room temperature. To this mixture was added a solution of the ketone **11** (4.0 mg, 0.02 mmol) in THF (3 cm^3) and the reaction mixture was stirred for 12 h at the same temperature. It was then diluted with ether and treated with 10% HCl. The mixture was extracted with ether and the extract was washed with saturated aq. $NaHCO_3$ and brine. The residue upon work-up was chromatographed with hexane to give (+)-laurene **1** (1.6 mg, 40%) as an oil, $[\alpha]_D^{25}$ +34.7 (*c* 0.15, EtOH) (Found: M^+, 200.1567. $C_{15}H_{20}O$ requires *m/z*, 200.1565); δ_H(500 MHz, $CDCl_3$) 0.71 (3 H, d, *J* 7.4 CH*Me*), 1.28 (3 H, s, C_6H_4CMe) 1.76–1.84 (1 H, m, C*H*HCMe), 2.16–2.37 (1 H, m, CH*H*CMe), 2.31 (3 H, s, C_6H_4Me), 2.48–2.60 (3 H, m, CH_2C=CH_2, C*H*Me), 4.87 (2 H, br, s, C=CH_2) and 7.10 (4 H, s, C_6H_4); *m/z* 200 (M^+).

References

1 (*a*) T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa and T. Masamune, *Tetrahedron* 1969, **25**, 459; (*b*) J. G. Hall and J. A. Reiss, *Aust. J. Chem.*, 1986, **39**, 1401.

2 T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds. Vol. II, Terpenes*, Academic Press, New York, 1972; A. F. Thomas and Y. Bassiere, in *Total Synthesis of Natural Products* 1980–1986, ed. J. W. ApSimon, Wiley, New York, 1988, vol. 5, p. 228.

3 For the synthesis of (±)-laurene see: (*a*) J. E. McMurry and L. A. Von Beroldingen, *Tetrahedron*, 1974, **30**, 2027; (*b*) P. F. Schuda, S. J. Potlock and H. Ziffer, *Tetrahedron*, 1987, **43**, 463; (*c*) A. Srikrishna and G. Sundarababu, *Tetrahedron Lett.*, 1989, **30**, 3561; (*d*) *Tetrahedron*, 1991, **47**, 481.

4 (*a*) H. Nemoto, H. Ishibashi, M. Mori, S. Fujita and K. Fukumoto, *Heterocycles*, 1990, **31**, 1237; (*b*) *J. Chem. Soc., Perkin Trans. I*, 1990, 2835; (*c*) H. Nemoto, T. Yamada, H. Ishibashi, J. Takazawa and K. Fukumoto, *Heterocycles*, 1991, **32**, 863; (*d*) *J. Chem. Soc., Perkin Trans. I*, 1991, 3149; (*e*) H. Nemoto, H. Ishibashi and K. Fukumoto, *Heterocycles*, 1992, **33**, 549; (*f*) H. Nemoto, H. Ishibashi, M. Nagamochi and K. Fukumoto, *J. Org. Chem.*, 1992, **57**, 1707; (*g*) H. Nemoto, T. Tanabe, M. Nagamochi and K. Fukumoto, *Heterocycles*, 1993, **35**, 707.

5 This type of ring expansion of epoxy cyclobutanols has been examined closely, C.-S. Hwang and W. Reusch, *Heterocycles*, 1987, **25**, 589; C.-S. Hwang, D. L. Ward and W. Reusch, *J. Org. Chem.*, 1989, **54**, 4318.

6 For palladium-catalysed ring expansion, see: P. Boontanonda and R. J. Grigg, *J. Chem. Soc., Chem. Commun.*, 1977, 583; G. R. Clark and S. Thiensathit, *Tetrahedron Lett.*, 1985, **26**, 2503; L. S. Liebeskind, D. Mitchell and B. S. Foster, *J. Am. Chem. Soc.*, 1987, **109**, 7908; M. Demuth, B. Pandey, B. Wietfeld, H. Said and J. Viader, *Helv. Chim. Acta*, 1988, **71**, 1392; J. Ollivier, J.-Y. Legros, J.-C. Fiaud, A. de Meijere and J. Salaün, *Tetrahedron Lett.*, 1990, **31**, 4139; S. Kim, K. H. Uh, S. Lee and J. H. Park, *Tetrahedron Lett.*, 1991, **32**, 3395. For mercurinium ion-mediated ring expansion reaction, see: S. Kim and K. H. Uh, *Tetrahedron Lett.*, 1992, **33**, 4325.

7 W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625.

8 K. Takai, Y. Hatta, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1978, 2417; J. Hibino, T. Okazoe, K. Takai and H. Nozaki, *Tetrahedron Lett.*, 1985, **26**, 5579, 5581; L. Lombardo, *Org. Synth.*, 1987, **65**, 81.

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