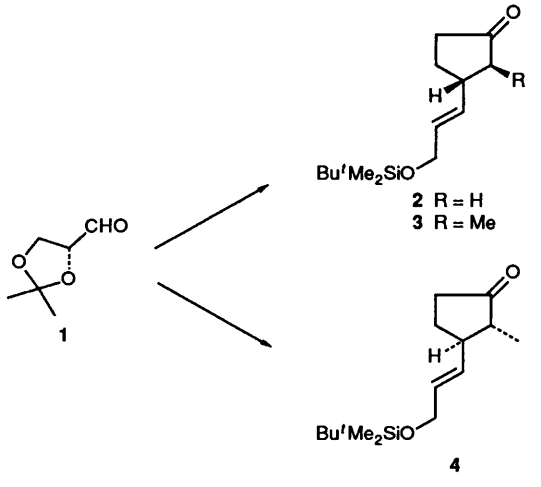
Highly Enantioselective Synthesis of (−)-Chokol A

Toshio Suzuki,* Hitoshi Tada and Katsuo Unno
Department of Pharmaceutical Science, Akita University Hospital, Hondo 1-1-1, Akita 010, Japan

Stereoselective introduction of a methyl group into the (3*S*)-2-methylcyclopentanone **3**, followed by Claisen rearrangement of the vinyl ether **10** derived from the allyl alcohol **7** provided separable methyl esters **6a** and **6b**. Reduction of **6a** and subsequent homologation of the side-chain afforded the pivaloyl ester **16** after protection of the primary alcohol **15** with pivaloyl chloride. Cleavage of the double bond of compound **16**, followed by sodium borohydride reduction of the resultant aldehyde **17**, produced a mixture of the diols **18** and **19** leading to (−)-chokol A **5**. Its enantiomeric excess was determined based on examination of the ^{1}H NMR spectrum of its MTPA ester **25**.

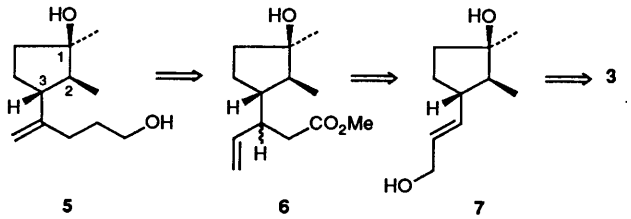
Chokol A, a fungitoxic, modified sesquiterpene isolated from the timothy grass *Phleum pratense* infected by the fungus *Epichloe typhina*,[1] has been shown initially by spectral evidence, and confirmed by syntheses of both racemic and optically active forms,[2,3] to possess the structure **5** including the absolute stereochemistry shown.

As part of our programme aimed at the synthesis of biologically active natural products using simple chiral templates, we have reported total syntheses of the indole alkaloids (−)-dihydrocorynantheol[4] and antirhine[5] *via* the cyclopentanone **2**[6] derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde **1**. Recently, we also disclosed that '*trans*-hydrindanonepropionic acid'[7] and des-AB-cholestanone,[8] efficiently derived *via* the (3*S*)-and (3*R*)-2-methylcyclopentanone **3** and **4** from **1** (Scheme 1), could be potential intermediates for steroids and vitamin D_3.



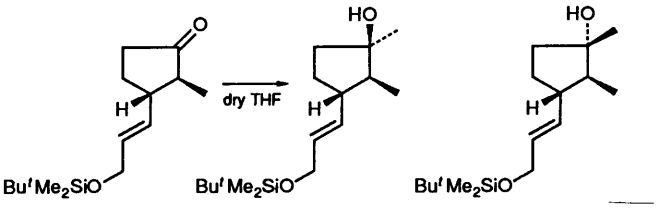
Scheme 1

In this context, we report here an enantioselective total synthesis of (−)-chokol A from the (3*R*)-2-methylcyclopentanone **3**. The retrosynthetic plan is outlined in Scheme 2. Stereoselective introduction of a methyl group from the less



Scheme 2

Table 1 Reaction of the methylcyclopentanone **3** with MeLi and $MeCeCl_2$



Entry	Reagent	Reaction conditions: Temp. (°C)	Products: 8:9:SM[a]	Yield (%)
1	3.5 mol equiv. MeLi	−78 to r.t.[b]	37:21:42	26.4
2	1.2 mol equiv. $MeCeCl_2$	−78	41:9:50	47.8
3	1.8 mol equiv. $MeCeCl_2$	−78	77:23:0	99.8

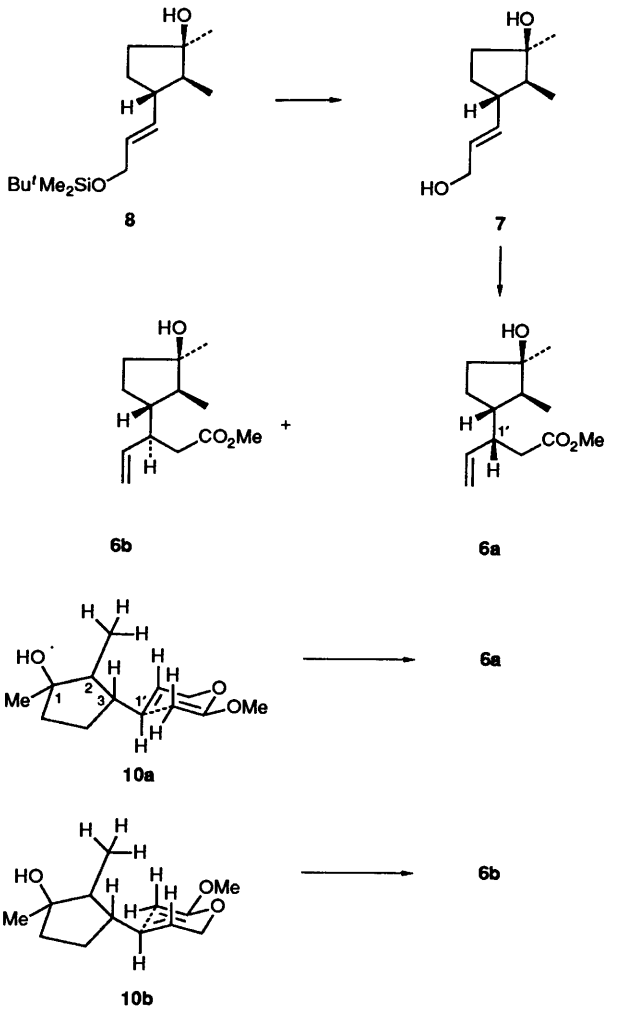
[a] SM = starting material. [b] Room temperature.

hindered α-side to compound **3**, followed by Claisen rearrangement of the vinyl ether **10** derived from the allyl alcohol **7**, may provide the methyl ester **6** possessing the requisite functional group for further elaboration of the side-chain at C-3 in chokol A **5**.

First, stereoselective introduction of a methyl group into the (3*S*)-methylcyclopentanone **3** was examined and the results are summarised in Table 1. As shown in Table 1, reaction of **3** with methyllithium gave disappointing results. However, satisfactory results were obtained by using 1.8 mole equivalents of methylcerium dichloride.[9]

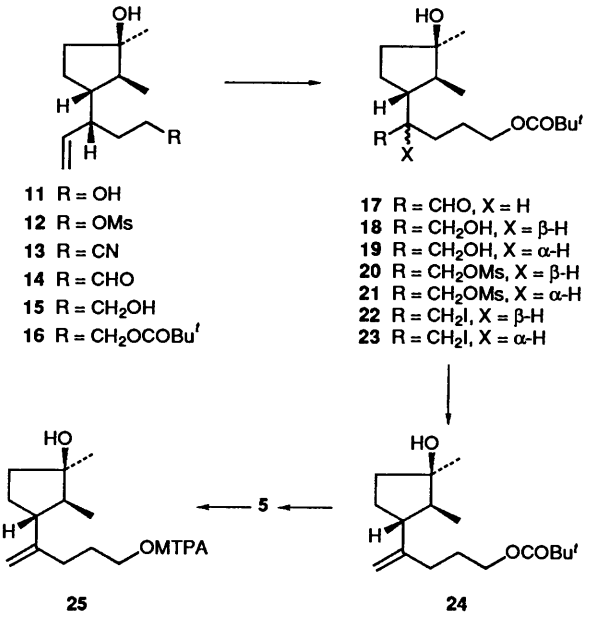
Removal of the silyl group from compound **8** followed by Claisen rearrangement of the vinyl ether **10** of the resultant allyl alcohol **7** provided the separable methyl esters **6a** and **6b** along with the starting material in 51.1, 18.9 and 5.0% yield, respectively. Although no spectroscopic evidence for the configuration of C-1′ in each of the products **6a** and **6b** could be obtained, their configurations were tentatively assigned based on the conformational analysis of the corresponding preferred chair-like transition states **10a** and **10b** in which the bulky cyclopentanone group is located in an equatorial arrangement and the relative stereochemistry between C-3–H and C-1′–H is *trans*. Hence rearrangement would occur preferentially far from the methyl group at C-2 to provide diastereoisomer **6a** as the main product (Scheme 3).

Reduction of the methyl ester **6a** with lithium aluminium hydride, followed by selective mesylation of the primary alcohol **11**, provided, in 90.1% overall yield, the monomesate **12**, which on treatment with potassium cyanide gave the cyanide **13**.



Scheme 3

Partial reduction of nitrile **13** with an excess of diisobutylaluminium hydride (DIBAH), followed by brief treatment of the resulting aldehyde **14** with an excess of sodium borohydride afforded the diol **15** in 77.9% overall yield. Selective protection of the primary hydroxy group in diol **15** with pivaloyl chloride, followed by sequential treatment of the resulting ester **16** with osmium tetraoxide, sodium periodate, and sodium borohydride provided, *via* the aldehyde **17**, the separable alcohol **18** and its C-1′ isomer **19** in 73.5 and 19.8% overall yield, respectively. Selective mesylation of the primary hydroxy group in diol **18**, followed by treatment of the resulting mesate **20** with an excess of sodium iodide, gave the iodide **22** which, on treatment, without purification, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the protected chokol A **24** in 55.0% overall yield from diol **18**. Similar treatment of diol **19** proceeded smoothly *via* intermediates **21** and **23** to provide compound **24**, in 33.6% overall yield from diol **19**. Finally, mild hydrolysis of the pivaloyl ester **24** with potassium carbonate furnished, in almost quantitative yield, (−)-chokol A **5**, identified by comparison of the IR and ^{1}H NMR spectra and TLC behaviour of the synthetic material with those of the natural material. Chokol A **5** was also synthesised from the methyl ester **6b** by using the same sequence described above in 24.2% overall yield. Enantiometric excess of the synthetic material thus obtained was determined to be 93.3% based on examination of the ^{1}H NMR spectrum of the corresponding ester **25** derived from reaction of chokol A **5** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA). Mash postulated that the actual optical rotation for natural (−)-chokol A is approximately −58° and concluded that the enantiomeric excess of his synthetic material was 80%.[3] Thus, chokol A **5** was synthesised from readily available compound **3** in 16.1% overall yield (see Scheme 4).



Scheme 4

Experimental

IR spectra were recorded on a JASCO IR-810 spectrophotometer. Mass spectra were obtained on a JEOL-JMS-OISG-2 spectrometer. NMR spectra were taken for solutions in deuteriochloroform (tetramethylsilane as internal standard) on JEOL JNM-PMX-60, JEOL JNM-EX-270 and JEOL JNM-GX-400 instruments. *J*-Values are in Hz. Optical rotations were measured on a JASCO-DIP-4 automatic polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. All products described in the Experimental section were homogeneous by TLC.

(1R,2S,3S)-3-[3′-(tert-*Butyldimethylsiloxy*)*prop*-1′(E)-*enyl*]-1,2-*dimethylcyclopentanol* **8** *and* (1S,2S,3S)-3-[3′-(tert-*Butyldimethylsiloxy*)*prop*-1′(E)-*enyl*]-1,2-*dimethylcyclopentanol* **9**.—Cerium dichloride (276 mg, 0.74 mmol) was heated at 140 °C *in vacuo* for 2 h and dry tetrahydrofuran (THF) (2 cm^3) was added under nitrogen to the stirred product at room temperature. After being stirred, the suspension was cooled to −78 °C and then methyllithium (1.4 mol dm^{-3} in diethyl ether; 476 mm^3, 0.67 mmol) was added. After the mixture had been kept for 30 min at the same temperature, a solution of the cyclopentanone **3**[7] (100 mg, 0.37 mmol) in dry THF (1.5 cm^3) was added during 10 min and the mixture was stirred for 2 h at −78 °C under nitrogen. The reaction was quenched with saturated aq. ammonium chloride and the mixture was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (10 g). First elution with hexane–ethyl acetate (95:5) gave *compound* **8** (81 mg, 76.6%), $[\alpha]_D$ −41.5 (*c* 0.14, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 3600 and 3300–3550 (OH); δ_H (60 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.92 (3 H, d, *J* 6, Me), 0.93 (9 H, s, Bu^t), 1.27 (3 H, s, Me), 4.26–4.36 (2 H, m, CH_2OSi) and 5.57–5.73 (2 H, m, CH=CH) (Found: M$^+$, 284.2173. $C_{16}H_{32}O_2Si$ requires M, 284.2173); further elution with the same solvent provided the isomer **9** (24.7 mg, 23.2%), $[\alpha]_D$ −20.4 (*c* 0.08, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 3600 and 3300–3550 (OH); δ_H(60 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.92 (3 H, d, *J* 6, Me), 0.93 (9 H, s, Bu^t), 1.15 (3 H, s, Me), 4.03–4.20

(2 H, m, CH_2OSi) and 5.40–5.57 (2 H, m, CH=CH) [Found: *m/z* 227.1469 ($M^+ - 57$). $C_{12}H_{23}O_2Si$ requires *m/z* 227.1468 (M − 57)].

(1R,2S,3S)-3-[3′-*Hydroxyprop*-1(E)-*enyl*]-1,2-*dimethylcyclopentanol* **7**.—A solution of the protected allyl alcohol **8** (237 mg, 0.83 mmol) and toluene-*p*-sulfonic acid (PTSA) (20 mg) in methanol (2 cm^3) was stirred for 2 h at room temperature and the solvent was evaporated off to leave a residue, which was extracted with chloroform. The extract was washed successively with saturated aq. sodium hydrogen carbonate and brine, and then dried ($MgSO_4$). Removal of the solvent, and chromatography of the residue on silica gel (5 g) with hexane–ethyl acetate (7:3) as eluent, afforded the allyl alcohol **7** (143 mg, 99.4%) as a syrup, $[\alpha]_D$ −30.3 (*c* 1.40, $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 3600 and 3300–3550 (OH); δ_H(60 MHz; $CDCl_3$) 0.87 (3 H, s, *J* 6, Me), 1.20 (3 H, s, Me), 3.93–4.10 (2 H, m, CH_2OH) and 5.42–5.67 (2 H, m, CH=CH) [Found: *m/z* 152.1198 ($M^+ - 18$). $C_{10}H_{16}O$ requires *m/z* 152.1200 (M − 18)].

(3R,1′S,2′S,3′R)-*Methyl* 3-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)*pent*-4-*enoate* **6a** *and* (3S,1′S,2′S,3′R)-*Methyl* 3-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)*pent*-4-*enoate* **6b**.—A mixture of the allyl alcohol **7** (140 mg, 0.823 mmol), trimethyl orthoacetate (495 mg, 4.12 mmol), and propionic acid (6 mg, 0.082 mmol) in xylene (5 cm^3) was stirred and heated at 150 °C for 1.5 h with removal of methanol by distillation. Excess of trimethyl orthoacetate and xylene were removed under reduced pressure to leave a residue, which was extracted with diethyl ether. The extract was washed successively with saturated aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with hexane–ethyl acetate (9:1) as eluent to give the *methyl ester* **6a** (93.8 mg, 51.1%) as a syrup, $[\alpha]_D$ −23.6 (*c* 0.17, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3300–3550 (OH) and 1731 (C=O); δ_H(60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, Me), 1.20 (3 H, s, Me), 2.37 (1 H, br s, OH, exchanged with D_2O), 3.58 (3 H, s, CO_2Me), 4.95 (1 H, dd, *J* 10 and 2, CH=C*H*H), 4.97 (1 H, dd, *J* 18 and 2, CH=CH*H*) and 5.68 (1 H, ddd, *J* 18, 10 and 8, C*H*=CH_2) (Found: M^+, 226.1561. $C_{13}H_{22}O_3$ requires M, 226. 1567); and the *methyl ester* **6b** (35.1 mg, 18.9%) as a syrup, $[\alpha]_D$ −37.0 (*c* 0.28, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3300–3550 (OH) and 1732 (C= O); δ_H(60 MHz; $CDCl_3$) 0.90 (1 H, d, *J* 6, Me), 1.18 (3 H, s, Me), 2.37 (1 H, br s, OH, exchanged with D_2O), 3.60 (3 H, s, CO_2Me), 4.97 (1 H, dd, *J* 18 and 2, CH=C*H*H), 5.00 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.67 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2) (Found: M^+, 226.1563).

(1R,2S,3S,1′R)-3-(3′-*Hydroxy*-1′-*vinylpropyl*)-1,2-*dimethylcyclopentanol* **11**.—A solution of the methyl ester **6a** (61 mg, 0.27 mmol) in dry THF (2 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (31 mg, 0.81 mmol) in dry THF (5 cm^3) at 0 °C and the mixture was stirred for 2 h at room temperature. The reaction was quenched with diethyl ether and brine. After being stirred for 15 min at room temperature, the mixture was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was purified by preparative TLC (PLC) on silica gel developed with chloroform–methanol (9:1) to provide the *alcohol* **11** (53 mg, quantitative yield) as a syrup, $[\alpha]_D$ −49.8 (*c* 0.53, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3300–3550 (OH); δ_H(60 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 6, Me), 1.26 (3 H, s, Me), 3.57 (2 H, t, *J* 7, CH_2OH), 4.93 (1 H, dd, *J* 18 and 2, CH=C*H*H), 4.95 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.67 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2) (Found: M^+, 198.1616. $C_{12}H_{22}O_2$ requires M, 198.1618).

(1R,2S,3S,1′R)-1,2-*Dimethyl*-3-(3′-*methylsulfonyloxy*-1′-*vinylpropyl*)*cyclopentanol* **12**.—To a stirred, ice-cooled alcohol **11** (53 mg, 0.268 mmol) and 4-(dimethylamino)pyridine (DMAP) (49 mg, 0.402 mmol) in dry dichloromethane (2 cm^3) was added dropwise methanesulfonyl chloride (36.9 mg, 0.322 mmol) and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with water and the mixture was then diluted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with chloroform as eluent, to provide the *monomesyl ester* **12** (66.6 mg, 90.1%) as a syrup, $[\alpha]_D$ −37.3 (*c* 0.57, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 (OH); δ_H(60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, Me), 1.20 (3 H, s, Me), 2.97 (3 H, s, SO_2Me), 4.13 (2 H, t, *J* 7, CH_2OSOMe), 4.93 (1 H, dd, *J* 18 and 2, CH=C*H*H), 5.0 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.57 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2) (Found: M^+, 276.1393. $C_{13}H_{24}O_4S$ requires M, 276.1393).

(4R,1′S,2′S,3′R)-4-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)-*hex*-5-*enonitrile* **13**.—A mixture of the monomesate **12** (55.4 mg, 0.2 mmol) and potassium cyanide (55.2 mg, 0.8 mmol) in dimethyl sulfoxide (DMSO) (1.5 cm^3) was stirred and heated at 62 °C for 2 h and then diluted with water (3 cm^3). The mixture was extracted with diethyl ether and the extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with hexane–ethyl acetate (7:3) as eluent to provide the cyanide **15** (40.3 mg, 97.0%) as a syrup, $[\alpha]_D$ −75.0 (*c* 0.4, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3300–3550 (OH) and 2250 (CN); δ_H(60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, Me), 1.23 (3 H, s, Me), 2.27 (2 H, t, *J* 7, CH_2CN), 5.0 (1 H, dd, *J* 18 and 2, CH=C*H*H), 5.05 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.53 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2); *m/z* 207 (M^+).

(4R,1′S,2′S,3′R)-4-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)-*hex*-5-*en*-1-*ol* **15**.—To a stirred solution of the cyanide **13** (40 mg, 0.193 mmol) in dry toluene (3 cm^3) was added dropwise DIBAH (1.0 mol dm^{-3} in hexane; 1.16 cm^3) during 5 min at −78 °C under nitrogen. The mixture was stirred for 4 h at −78 °C, and then quenched with saturated aq. ammonium chloride; it was then stirred for an additional 10 min. The precipitate was filtered off through a Celite pad and washed with diethyl ether. The combined filtrate and washings were washed with brine, dried ($MgSO_4$), and then evaporated to leave the practically pure aldehyde **14** (45 mg) as a syrup; $\nu_{max}(CHCl_3)/cm^{-1}$ 2720 (CH) and 1722 (C=O); δ_H(60 MHz; $CDCl_3$) 9.67 (1 H, t, 1.5). This compound was used in the next reaction without further purification.

To a stirred solution of the aldehyde **14** (45 mg) in methanol (2 cm^3) was added portionwise sodium borohydride (20 mg, 0.53 mmol) and the mixture was stirred for 1.5 h at 0 °C. After addition of water, the solvent was evaporated off and the resultant residue was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with chloroform as eluent to give the *alcohol* **15** (31.9 mg, 77.9%, two-step overall yield) as a syrup, $[\alpha]_D$ −38.7 (*c* 0.31, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3300–3550 (OH); δ_H(60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, Me), 1.20 (3 H, s, Me), 3.48 (2 H, t, *J* 7, CH_2OH), 4.83 (1 H, dd, *J* 18 and 2, CH=C*H*H), 4.90 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.57 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2) (Found: M^+, 212.1778. $C_{13}H_{24}O_2$ requires M, 212.1777).

(4R,1′S,2′S,3′R)-4-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)-*hex*-5-*enyl Pivalate* **16**.—To a stirred solution of the alcohol **15** (22.9 mg, 0.108 mmol) and DMAP (15.8 mg, 0.123 mmol) in dry dichloromethane (1 cm^3) at 0 °C was added dropwise pivaloyl chloride (13 mg, 0.108 mmol) and the mixture was stirred for

5.5 h at 0 °C. The reaction was quenched by addition of water and the mixture was then diluted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with chloroform as eluent to provide the pivaloyl ester **16** (27 mg, 84.1%) as a syrup, $[\alpha]_D$ −17.1 (*c* 0.27, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3300–3550 (OH) and 1718 (C=O); δ_H(60 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 6, Me), 1.12 (3 H, s, Me), 1.17 (9 H, s, Bu^t), 4.0 (2 H, t, *J* 7, $CH_2O_2CBu^t$), 4.90 (1 H, dd, *J* 18 and 2, CH=C*H*H), 4.93 (1 H, dd, *J* 8 and 2, CH=CH*H*) and 5.57 (1 H, ddd, *J* 18, 8 and 8, C*H*=CH_2); *m/z* 296 (M^+).

(4S/4R,1′S,2′S,3′R)-5-*Hydroxy*-4-(3′-*hydroxy*-2′,3′-*dimethylcyclopentyl*)*pentyl Pivalate* **18** *and* **19**.—To a stirred solution of the pivaloyl ester **16** (100 mg, 0.388 mmol) in 1,4-dioxane (2 cm^3) was added dropwise a solution of osmium tetraoxide (0.393 mol dm^{-3} in 1,4-dioxane; 86 mm^3, 0.034 mmol) and the mixture was stirred for 15 min in the dark at room temperature in order to allow the osmate ester to form. After dilution with water (0.4 cm^3), a solution of sodium periodate (181 mg, 0.845 mmol) in water (0.8 cm^3) was added during 5 min and the mixture was stirred for an additional 2.5 h at room tempeature. Solid residue was filtered off and the filtrate was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to give the practically pure aldehyde **17** (115 mg) as a mixture of diastereoisomers at C-1′ (C-4 in systematic numbering); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3300–3550 (OH) and 1724 (C=O); δ_H(60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, Me), 1.17 (9 H, s, Bu^t), 1.27 (3 H, s, Me) and 8.03 (1 H, t, *J* 1.5, CHO). This compound was used in the next reaction without further purification.

To a stirred solution of the aldehyde **17** (115 mg) in methanol (3 cm^3) was added portionwise sodium borohydride (50 mg, 1.32 mmol) and the mixture was stirred for 5 min at 0 °C. After addition of water, the solvent was evaporated off and the residue was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel (5 g) with chloroform as eluent to provide the alcohol **18** (74.5 mg, 73.5%, two-step overall yield) as a syrup, $[\alpha]_D$ −33.9 (*c* 0.20, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3300–3550 (OH) and 1722 (C=O); δ_H(60 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 6, Me), 1.17 (9 H, s, Bu^t), 1.22 (3 H, s, Me), 3.53 (2 H, d, *J* 6, CH_2OH) and 4.0 (2 H, t, *J* 7, $CH_2O_2CBu^t$) [Found: *m/z* 282.2188 (M^+ − 18). $C_{17}H_{30}O_3$ requires *m/z* 282.2193 (M − 18); and the alcohol **19** (20.1 mg, 19.8%, two-step overall yield) as a syrup, $[\alpha]_D$ −34.0 (*c* 0.20, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3300–3550 (OH) and 1724 (C=O); δ_H(60 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 6, Me), 1.18 (9 H, s, Bu^t), 1.23 (3 H, s, Me), 3.62 (2 H, br s, CH_2OH), and 4.0 (2 H, t, *J* 7, CH_2OCOBu^t) [Found: *m/z* 282.2189 (M^+ − 18)].

(4S,1′S,2′S,3′R)-4-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)-5-(*methylsulfonyloxy*)*pentyl Pivalate* **20**.—To a stirred solution of the alcohol **18** (50.3 mg, 0.168 mmol) and DMAP (26.6 mg, 0.218 mmol) in dry dichloromethane (2 cm^3) was added methanesulfonyl chloride (23.1 mg, 0.202 mmol) and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with water and the mixture was diluted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was purified by PLC on silica gel developed with chloroform–methanol (95:5) to afford the monomesate **20** (49.6 mg, 78.3%) as a syrup, $[\alpha]_D$ −34.2 (*c* 0.16, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 (OH) and 1725 (C=O); δ_H(60 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 6, Me), 1.22 (9 H, s, Bu^t), 1.23 (3 H, s, Me), 2.97 (3 H, s, SO_2Me), 4.0 (2 H, t, *J* 6, $CH_2O_2CBu^t$) and 4.10 (2 H, d, *J* 6, CH_2OMs) [Found: *m/z* 282.2201 (M^+ − 96). $C_{17}H_{30}O_3$ requires *m/z* 282.2195 (M − 96)].

(4R,1′S,2′S,3′R)-4-(3′-*Hydroxy*-2′,3′-*dimethylcyclopentyl*)-5-(*methylsulfonyloxy*)*pentyl Pivalate* **21**.—To a stirred solution of the alcohol **19** (20 mg, 0.067 mmol) and DMAP (16.3 mg, 0.133 mmol) in dry dichloromethane (1 cm^3) was added dropwise methanesulfonyl chloride (27.5 mg, 0.24 mmol) and the mixture was stirred for 24 h at 0 °C. After usual work-up, the residue was purified by PLC on silica gel developed with chloroform–methanol (95:5) to provide the monomesate **21** (11.6 mg, 46.0%) as a syrup, $[\alpha]_D$ −35.0 (*c* 0.11, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 (OH) and 1722 (C=O); δ_H(60 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 6, Me), 1.22 (9 H, s, Bu^t), 1.30 (3 H, s, Me), 3.12 (3 H, s, SO_2Me) and 3.93–4.53 (4 H, m, $CH_2O_2CBu^t$ and CH_2OMs) [Found: *m/z* 282. 2197 (M^+ − 96)].

Chokol A Pivaloyl Ester **24** *from Mesate* **20** *or* **21**.—A mixture of the monomesate **20** (41.8 mg, 0.111 mmol) and sodium iodide (66.3 mg, 0.442 mmol) in dry acetone (5 cm^3) was stirred and heated for 4 h at 70 °C and the solvent was evaporated off to leave a residue, which was extracted with diethyl ether. The extract was washed successively with 5% aq. sodium thiosulfate and brine, and then dried ($MgSO_4$). Evaporation of the solvent left the iodide **22** (43.6 mg) and this compound was used in the next reaction without further purification.

A solution of the iodide **22** (43.6 mg, 0.106 mmol) and DBU (64.5 mg, 0.424 mmol) in dry benzene (5 cm^3) was stirred and heated for 8 h at 75 °C under nitrogen and then the solvent was evaporated off to leave a residue, which was extracted with diethyl ether. The extract was washed successively with 1 mol dm^{-3} aq. hydrochloric acid and brine, and then dried ($MgSO_4$). Evaporation of the solvent left a residue, which was purified by PLC on silica gel developed with hexane–ethyl acetate (65:35) to provide *chokol A pivaoloyl ester* **24** (21.9 mg, 70.2%, two-step overall yield) as a syrup, $[\alpha]_D$ −32.5 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 (OH) and 1722 (C=O); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 6.8, Me), 1.20 (9 H, s, Bu^t), 1.28 (3 H, s, Me), 2.05 (2 H, t, *J* 7.6, $CH_2{=}\overset{|}{C}CH_2$), 2.38 (1 H, ddd, *J* 9.0, 9.0 and 9.0), 4.08 (2 H, t, *J* 6.5, $CH_2O_2CBu^t$), 4.77 (1 H, d, *J* 1.5, $CH\overset{|}{H}{=}\overset{|}{C}$–) and 4.81 (1 H, d, *J* 1.5, $CH\overset{|}{H}{=}\overset{|}{C}$–) (Found: M^+, 282.2196. $C_{17}H_{30}O_3$ requires M, 282.2204).

A mixture of the monomesate **21** (25.2 mg, 0.067 mmol) and sodium iodide (40 mg, 0.266 mmol) in dry acetone (3 cm^3) was stirred and heated for 6 h at 70 °C. After work-up, the resultant iodide **23** was treated with DBU (40.6 mg, 0.266 mmol) in dry benzene (2 cm^3) at 70 °C and the residue was purified by PLC on silica gel developed with chloroform–methanol (96:4) to provide chokol A pivaloyl ester **24** (13.7 mg, 73.0%, two-step overall yield), identified by comparison of the IR and ^1H NMR spectra and TLC behaviour of the product with those of the authentic compound.

Chokol A **5**.—A mixture of the pivaloyl ester **24** (20 mg, 0.071 mmol) and potassium carbonate (10 mg) in methanol (1 cm^3) was stirred for 4 h at room temperature. Evaporation of the solvent left a residue, which was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was purified by PLC on silica gel developed with hexane–ethyl acetate (3:7) to provide chokol A **5** (13.9 mg, quantitative yield) as a syrup {$[\alpha]_D$ −54.8 (*c* 0.13, EtOH); lit.,[3] $[\alpha]_D$ −46.3 (*c* 1.07, EtOH), 80% ee}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3300–3550 (OH); δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, d, *J* 6.8, Me), 1.26 (3 H, s, Me), 2.03 (2 H, t, *J* 7.8, $CH_2{=}\overset{|}{C}CH_2$), 2.40 (1 H, ddd, *J* 9.0, 9.0 and 9.0, $CH_2{=}\overset{|}{\underset{|}{C}}{-}\overset{|}{C}H$), 4.78 (1 H, d, *J* 1.2, $C\overset{|}{H}H{=}\overset{|}{C}$–) and 4.80

(1 H, d, J 1.2, CHH=C–) [Found: m/z 180.1504 ($M^+ - 18$). $C_{12}H_{20}O$ requires m/z 180.1512 (M − 18)], identified by comparison of the IR and ^{1}H NMR spectra and TLC behaviour of the synthetic material with those of the natural material.

MTPA Ester **25** *of Chokol A.*—A solution of dicyclohexylcarbodiimide (13.5 mg, 0.066 mmol) in dry dichloromethane (1 cm^3) was added to a mixture of chokol A **5** (6.5 mg, 0.0328 mmol), (*R*)-(+)-MTPA (15.4 mg, 0.066 mmol) and DMAP (4 mg, 0.0328 mmol) in dry dichloromethane (2 cm^3). After being stirred for 24 h at room temperature the reaction mixture was diluted with diethyl ether and washed successively with 10% aq. hydrochloric acid, saturated aq. sodium hydrogen carbonate, and brine. Evaporation of the solvent left a residue, which was purified by PLC on silica gel developed with hexane–ethyl acetate (1:1) to provide the MTPA ester **25** of chokol A (13 mg, 96%) as a syrup, $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 1746 (C=O); δ_H(270 MHz; $CDCl_3$) 0.85 (3 H, d, J 6.9, Me), 1.27 (3 H, s, Me), 2.35 (1 H, ddd, J 9.0, 9.0 and 9.0), 3.52 (0.1 H, s, Me), 3.55 (2.9 H, s, Me), 4.26–4.43 (2 H, m, CH_2O), 4.73 (1 H, s, CHH=C–) 4.81 (1 H, s, CHH=C), 7.34–7.45 (3 H, m, Ph) and 7.47–7.57 (2 H, m, Ph); m/z 414 (M^+).

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References

1 T. Yoshihara, S. Togiya, H. Koshino, S. Sakamura, T. Shimanuki, T. Sato and A. Tajimi, *Tetrahedron Lett.*, 1985, **26**, 5551.
2 W. Oppolzer and A. F. Cunningham, *Tetrahedron Lett.*, 1986, **27**, 5467.
3 E. A. Mash, *J. Org. Chem.*, 1987, **52**, 4142.
4 T. Suzuki, E. Sato, K. Unno and T. Kametani, *Chem. Pharm. Bull.*, 1986, **34**, 1584.
5 T. Kametani, T. Suzuki, E. Sato, M. Nishimura and K. Unno, *J. Chem. Soc., Chem. Commun.*, 1982, 1201; T. Suzuki, E. Sato, K. Unno and T. Kametani, *Chem. Pharm. Bull.*, 1986, **34**, 3135.
6 T. Kametani, T. Suzuki, E. Sato, M. Nishimura and K. Unno, *J. Chem. Soc., Chem. Commun.*, 1982, 123.
7 T. Suzuki, E. Sato, K. Unno and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2263.
8 T. Suzuki, E. Sato, K. Unno and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1988, 724.
9 T. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, 1984, **25**, 4233.

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