# Absolute stereochemistry of chinesin I and II

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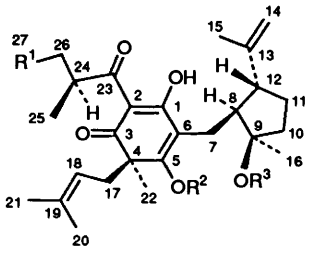
The absolute stereochemistry of chinesin I and II has been elucidated by synthetic and spectroscopic experiments. Tetrahydrochinesin I was degraded with ozonolysis and converted into the cyclopentane derivative **5** whose absolute stereochemistry was elucidated by synthesis from (−)-linalool. Degradation of chinesin I with $H_2SO_4$ gave (*S*)-2-methylbutyric acid. Finally, the absolute configuration of chinesin I was established as 4*R*, 8*S*, 9*R*, 12*R*, 24*S*.

Natural phloroglucinols have been reported to be strong antimicrobial plant constituents, *e.g.* humulon,[1] lupulon,[2] uliginosin A[3] and aspidin.[4] Recently, many antiviral natural phloroglucinols have been reported, *e.g.* sessiliflorols from *Melicope sessiliflora*,[5] isomallotochroman and related compounds from *Mallotus japonicus*,[6] euglobals from *Eucalyptus grandis*[7] and syzygiol from *Syzygium polycephaloides*.[8] Mallotojaponin and mallotochromene were isolated from *Mallotus japonicus* and reported to strongly inhibit HIV-reverse transcriptase activity.[9] Calanolides are HIV inhibitory coumarin derivatives from *Calophyllum lanigerum*.[10] Plants of the Guttiferae family are well known in Japanese folk medicine for their use with external wounds. Chinesin I **1** and II **2**, which were isolated from *Hypericum chinense* L. (Guttiferae) (Japanese name: byouyanagi)[11] have antimicrobial activity,[11] antiviral activity[12] and competitive inhibition activity against Leukotriene $D_4$ and Thromboxane $A_2$.[13] Earlier, we reported the structure–activity relationship for a series of synthetic phloroglucinol derivatives with antiviral activity against vesicular stomatitis virus (VSV) and herpes simplex virus type I and II (HSV-I and -II).[14] Most natural phloroglucinols have isoprene, monoterpene, or sesquiterpene components on the phloroglucinol ring. The structures of chinesin I and chinesin II differ only in their acyl chain, the former being a 2-methylbutyryl group and the latter a 2-methylpropionyl. Apart from that both contain a gem-substituted phloroglucinol ring, a monoterpene residue and other carbon chains with, in total, five asymmetric carbon atoms. The structurally related compounds, hypercalin A and hypercalin B were isolated together with chinesin II **2** from *Hypericum calycinum*, which showed molluscicidal activity against the schistosomiasis-transmitting snail *Biomphalaria glabreta*.[15] In spite of the interesting biological activities of chinesin I and II, their absolute configurations have not been determined. We report herein the unambiguous determination of the absolute stereochemistry of chinesin I and II.

## Results and discussion

In our preliminary report,[11] the relative conformation for all the chiral positions in chinesin I, **1** and chinesin II, **2** were reported except for those at C-4 and C-24. From accurate NOE and NOESY experiments of **1** using a 500 MHz instrument, an NOE was observed between 16-H and 22-H, which, taken in conjunction with the NOE data for **19** (Tables 1 and 3), signifies that these methyl groups are close to each other as a result of intramolecular hydrogen bonding between 5-OH and 9-OH (see Fig. 1).[11] These results are consistent with the relative configuration of chinesin II determined by X-ray crystallographic experiments.[15] The molecular model study showed



Chinesin I **1** $R^1$ = Me, $R^2$, $R^3$ = H
Chinesin II **2** $R^1$, $R^2$, $R^3$ = H
Chinesin I methyl ether **19** $R^1$ = Me, $R^2$ = H, $R^3$ = Me
Chinesin I methyl ether **20** $R^1$, $R^2$, $R^3$ = Me

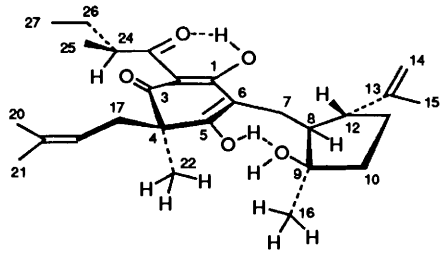


**Fig. 1**

that the atomic distance between the 16- and 22-hydrogens is *ca.* 3.2 Å in the conformation shown in Fig. 1.

Here we shall first describe our synthetic work to establish the absolute configuration on the five-membered ring of chinesin I, then our degradative work on chinesin I to determine the absolute configuration on the acyl chain and finally the establishment of the absolute stereochemistry of chinesin I and II.

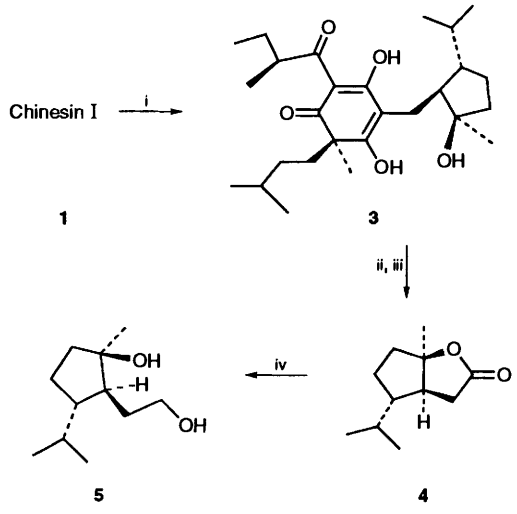
The specific rotation of the five-membered ring component **5** which was obtained by oxidative cleavage of tetrahydrochinesin II **3**, was compared with that of synthetic material prepared as follows from enantiomerically pure (−)-linalool **6**.

The isopropenyl and isopentenyl groups of chinesin I **1** were hydrogenated with $H_2$ and 5% Pd/C in AcOEt at 25 °C for 20 h to give tetrahydrochinesin I **3** (Scheme 1). Ozonolysis of **3**, followed by reduction with $LiAlH_4$ gave a diol **5** ($[\alpha]_D$ −38.4) (yield: 13.6% from **1**).

The diol **5** ($[\alpha]_D$ −35.4) was synthesized from (−)-linalool **6** to confirm the absolute configuration at C-8, C-9 and C-12 of chinesin I (Scheme 2). Epoxidation of linalyl acetate **7** obtained by acetylation of (−)-linalool with AcCl and *N*,*N*-diethylaniline in $CHCl_3$ (99%), with an equimolar amount of *m*-chloroperbenzoic acid (mCPBA) in $CH_2Cl_2$ at 0 °C gave the epoxide **8**

**Table 1** NMR data of chinesin I

| C | $^{13}C$ (INEPT) | $^{1}H$ (*J*/Hz) | COSY | $^{13}C$–$^{1}H$ COSY (long range) | NOESY |
|---|---|---|---|---|---|
| 1 | 189.9 | | | 1-OH, 7H(a) | |
| 2 | 106.4 | | | 1-OH | |
| 3 | 197.1 | | | 17H(a), 22H | |
| 4 | 53.2 | | | 17H(a), 22H | |
| 5 | 174.9 | | | 7H(b), 22H | |
| 6 | 108.4 | | | 1-OH, 7H(b) | |
| 7 | 21.2 ($CH_2$) | (a) 2.16dd (15, 3) | 8H | | |
| | | (b) 2.70dd (15, 11) | 8H | | |
| 8 | 50.2 (CH) | 1.80ddd (11, 11, 3) | 7H, 12H | 16H | 16H |
| 9 | 81.1 | | | 7H(b), 16H | |
| 10 | 43.3 ($CH_2$) | (a) 1.87m | 11H | 16H | |
| | | (b) 1.98m | 11H | | 15H, 16H |
| 11 | 28.6 ($CH_2$) | (a) 1.54m | 10H, 12H | | |
| | | (b) 1.86m | 10H, 12H | | 16H |
| 12 | 54.1 (CH) | 2.49ddd (11, 10, 7) | 8H, 11H | 14H, 15H | |
| 13 | 146.2 | | | 15H | |
| 14 | 111.6 ($CH_2$) | (a) 4.83qd (2, 1) | 15H | 15H | 15H |
| | | (b) 4.88qd (1,1) | 15H | | |
| 15 | 18.5 ($CH_3$) | 1.78dd (2, 1) | 14H | 14H | 10H, 14H, 16H, |
| 16 | 29.2 ($CH_3$) | 1.27s | | | 8H, 10H, 11H, |
| | | | | | 15H, 22H |
| 17 | 37.5 ($CH_2$) | (a) 2.54dd (15, 7) | 18H | 22H | 21H, 22H |
| | | (b) 2.67dd (15, 7) | 18H | | 21H |
| 18 | 118.8 (CH) | 4.77t (7) | 17H | 20H, 21H | 20H |
| 19 | 134.5 | | | 20H, 21H | |
| 20 | 17.9 ($CH_3$) | 1.56s | | | |
| 21 | 25.8 ($CH_3$) | 1.54s | | | |
| 22 | 24.6 ($CH_3$) | 1.37s | | | 16H, 17H |
| 23 | 207.6 | | | 1-OH, 24H, | |
| | | | | 25H, 26H(a) | |
| 24 | 42.1 (CH) | 3.89qt (7, 7) | 25H, 26H | 25H, 27H | |
| 25 | 16.9 ($CH_3$) | 1.11d (7) | 24H | | |
| 26 | 26.3 ($CH_2$) | (a) 1.40qdd (7, 14, 7) | 24H, 27H | 25H, 27H | |
| | | (b) 1.75qdd (7, 14, 7) | 24H, 27H | | |
| 27 | 11.9 ($CH_3$) | 0.91t (7) | 26H | | |
| 1-OH | | 19.23s | | | |
| 5-OH | | 19.52br | | | |
| 9-OH | | 3.51br | | | |



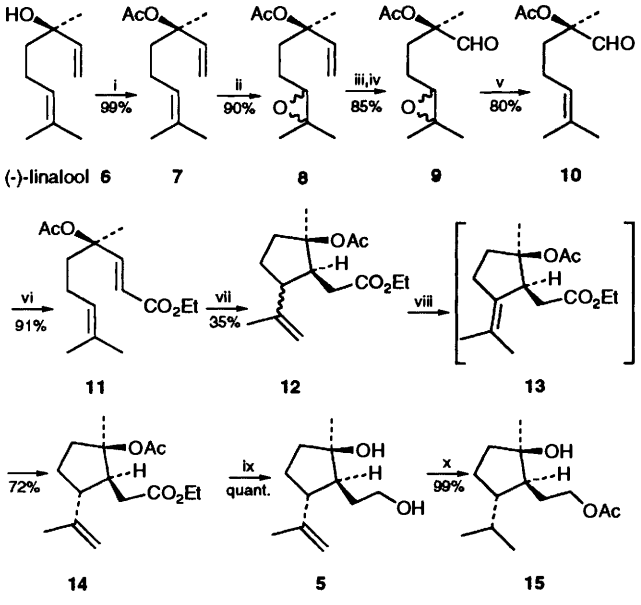

**Scheme 1** *Reagents:* i, Pd/C, $H_2$; ii, $O_3$; iii, $H_2O_2$; iv, $LiAlH_4$

regioselectively (90%). The epoxide **8** was treated with $O_3$ and the product reduced with $Me_2S$ in MeOH at −78 °C (85%) to give **9**; deprotection (Zn, NaI, $MeCO_2H$) of this gave the aldehyde **10** (80%). The aldehyde **10** was treated with a Wittig reagent ($Ph_3P{=}CHCO_2Et$) to give a *trans*-α,β-unsaturated ester **11** (91%), the cyclization of which to the cyclopentane **12** *via* an ene reaction could be realized in a highly stereocontrolled manner by heating it at 200 °C in a sealed tube (35%). The configuration of the isopropenyl-substituted carbon in the five-membered ring of **12** had, at this stage, still to be determined. The cyclopentane **12** was hydrogenated in the presence of 5% Pd/C in AcOEt to afford the desired compound **14** selectively (72%). It was established that this hydrogenation proceeded *via* the alkene intermediate **13**, stereoselective hydrogenation of this occurring from the β face, since a mixture of compounds **13** and **14** was obtained with a short hydrogenation time. Finally, the target diol **5** was obtained by reduction of **14** with $LiAlH_4$ in quantitative yield. The $^{1}H$ NMR and $^{13}C$ NMR spectra showed that the relative configuration of the synthetic material **5** ($[\alpha]_D$ −35.0) corresponded with that ($[\alpha]_D$ −38.4) obtained from chinesin I. Evidence for the stereochemistry of the synthetic sample of **5** was confirmed by the measurement of NOESY of the monoacetate **15** of synthetic sample the diol **5** in which NOE was observed between the isopropyl methyl groups and the other methyl group. The agreement of the specific rotation of the two specimens establishes that the absolute configuration of C-9 of chinesin I is consistent with the chiral carbon of (−)-linalool. These results indicated that the diol **5** possessed a 8*S*, 9*R*, 12*R* configuration. Absolute configuration at C-4 could be deduced to be 4*R* from the NOE experiments and the absolute configuration at C-9 as described above.

In addition, the C-24 configuration of chinesin I was determined by degradation with 67% $H_2SO_4$ (Scheme 3). Chinesin I, **1** was treated with 67% $H_2SO_4$ for 40 min at 100 °C to give 2-methylbutyric acid **16**, which was treated with PhOH in the presence of ethyl polyphosphate (PPE) [16] to give phenyl

**Table 2** NMR data of chinesin II

| C | $^{13}C$ (INEPT) | $^{1}H$ (*J*/Hz) |
|---|---|---|
| 1 | 189.9 | |
| 2 | 105.7 | |
| 3 | 197.0 | |
| 4 | 53.1 | |
| 5 | 175.0 | |
| 6 | 108.2 | |
| 7 | 21.1 ($CH_2$) | (a) 2.13dd (15, 12)<br>(b) 2.67dd (15, 3) |
| 8 | 50.1 (CH) | 1.76ddd (12, 12, 3) |
| 9 | 81.0 | |
| 10 | 43.2 ($CH_2$) | (a) 1.85m<br>(b) 1.95m |
| 11 | 29.4 ($CH_2$) | (a) 1.50m<br>(b) 1.81m |
| 12 | 54.1 (CH) | 2.46ddd (12, 11, 7) |
| 13 | 146.2 | |
| 14 | 111.6 ($CH_2$) | (a) 4.80qd (2, 1)<br>(b) 4.83qd (1, 1) |
| 15 | 18.4 ($CH_3$) | 1.74dd (2, 1) |
| 16 | 29.1 ($CH_3$) | 1.23s |
| 17 | 37.7 ($CH_2$) | (a) 2.50dd (15, 8)<br>(b) 2.64dd (15, 8) |
| 18 | 118.7 (CH) | 4.74t (8) |
| 19 | 134.6 | |
| 20 | 17.9 ($CH_3$) | 1.53s |
| 21 | 25.8 ($CH_3$) | 1.53s |
| 22 | 24.6 ($CH_3$) | 1.33s |
| 23 | 208.0 | |
| 24 | 35.7 (CH) | 4.00qq (7, 7) |
| 25 | 18.7 ($CH_3$) | 1.11d (7) |
| 26 | 19.1 ($CH_3$) | 1.10d (7) |
| 1-OH | | 19.14s |
| 5-OH | | 10.50br s |
| 9-OH | | 3.50br s |



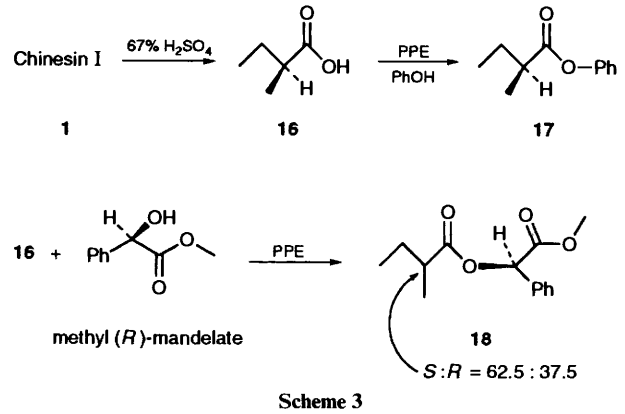

**Scheme 2** *Reagents and conditions:* i, AcCl, *N*,*N*-diethylaniline; ii, mCPBA, $CH_2Cl_2$; iii, $O_3$; iv, $Me_2S$; v, Zn, NaI, AcOH; vi, $Ph_3P{=}CHCO_2Et$; vii, sealed tube, 200 °C; viii, Pd/C; ix, $LiAlH_4$; x, $Ac_2O$, Pyr

2-methylbutyrate **17** ($[\alpha]_D$ +5.14). An authentic specimen of the phenyl ester ($[\alpha]_D$ +26.2) was prepared from (+)-2-methylbutyric acid (Aldrich Co.) by the same procedure (98% yield). The difference in optical rotations between the two samples may be caused by epimerization at C-24 of chinesin I during the treatment with 67% $H_2SO_4$ or during its separation from

**Table 3** NMR data of methyl ether **19**

| C | $^{13}C$ | $^{1}H$ (*J*/Hz) | NOESY |
|---|---|---|---|
| 1 | 189.8 | | |
| 2 | 106.3 | | |
| 3 | 196.5 | | |
| 4 | 53.0 | | |
| 5 | 174.7 | | |
| 6 | 108.3 | | |
| 7 | 20.5 | (a) 2.13dd (15, 12)<br>(b) 2.65dd (15, 3) | 5-OH<br>12H |
| 8 | 51.6 | 1.85ddd (12, 11, 3) | 15H, 16H |
| 9 | 85.7 | | |
| 10 | 36.0 | (a) 1.60ddd (13, 8, 4)<br>(b) 2.05td (6, 13) | 9-$OCH_3$<br>9-$OCH_3$ |
| 11 | 28.5 | (a) 1.50m<br>(b) 1.77m | |
| 12 | 53.7 | 2.43td (8, 11) | 7H(b) |
| 13 | 146.3 | | |
| 14 | 111.6 | (a) 4.81qd (1, 1)<br>(b) 4.85qd (2, 1) | |
| 15 | 18.4 | 1.76dd (2, 1) | 8H |
| 16 | 23.4 | 1.17 | 5-OH, 8H, 9-$OCH_3$ |
| 17 | 37.4 | (a) 2.50dd (14, 7)<br>(b) 2.69dd (14, 7) | 20H, 22H<br>20H, 22H |
| 18 | 118.9 | 4.76t (7) | |
| 19 | 134.4 | | |
| 20 | 17.9 | 1.57s | 17H, 22H |
| 21 | 25.8 | 1.55s | |
| 22 | 24.6 | 1.35s | 17H, 20H, 5-OH |
| 23 | 207.3 | | |
| 24 | 41.9 | 3.88qt (7, 7) | 27H |
| 25 | 16.8 | 1.10d (7) | 27H |
| 26 | 26.4 | (a) 1.38qdd (7, 12, 7)<br>(b) 1.73qdd (7, 12, 7) | |
| 27 | 11.9 | 0.91t (7) | 24H, 25H |
| 1-OH | | 19.23s | |
| 5-OH | | 10.15s | 7H(a), 9-$OCH_3$, 16H, 22H |
| 9-$OCH_3$ | 49.3 | 3.32s | 5-OH, 10H, 16H |

chinesin I. The value of the specific rotation of the ester **17** showed that the ratio, *S*:*R* was *ca.* 60:40. In fact, the $^{1}H$ NMR spectrum of the ester **18** which was synthesized from **16** and methyl (*R*)-mandelate, showed the ratio of the two diastereoisomers to be 62.5 (*S*) to 37.5 (*R*) in confirmation of the above estimate. This experiment proved that C-24 of chinesin I had an *S* configuration.




**Scheme 3**

In conclusion, it has been confirmed that the absolute stereochemistry of chinesin I is as shown in Fig. 1, 4*R*, 8*S*, 9*R*, 12*R*, 24*S*. Chinesin II **2** should have the same absolute configuration as chinesin I **1** except at C-24 which is achiral in chinesin II.

## Experimental

The NMR spectra were measured on a JEOL GX-270 and EX-270 spectrometers at 270 ($^1$H) and 67.89 MHz ($^{13}$C) for samples in $CDCl_3$ containing tetramethylsilane as internal standard; $J$ values are given in Hz. IR and UV spectra were measured on a JASCO IR-810 IR spectrometer and a JASCO UVDEC-460 spectrophotometer, respectively. Mass spectra were recorded on a JEOL JMS-SX-102A spectrometer. TLC was carried out on Kieselgel GF254 (0.25 mm thickness). Wakogel C-200 was used for column chromatography with hexane–ethyl acetate (EtOAc). HPLC was performed on a JASCO BIP-1 instrument (RI detector) with a column (10 × 250 mm) of LiChroprep Si-60 (Merck) (hexane–EtOAc) or Inertsil PREP-ODS (GL-Sciences Inc.) (MeOH–$H_2O$). $[\alpha]_D$ Values are recorded in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.

### Isolation of chinesin I 1 and II 2

The flowers (2.9 kg) of *Hypericum chinense* were collected in the campus of Tokyo University of Agriculture and Technology in June and extracted with methanol. The methanol extract was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The antimicrobial activity was tested by the paper-disk method against *Bacillus subtilis* (IFO 3734) for each fraction. The activity was found in the EtOAc phase. The EtOAc phase was chromatographed on silica gel with hexane–ethyl acetate and on ODS with methanol–water to afford two antimicrobial compounds which were named chinesin I **1** (4 g) and chinesin II **2** (1.7 g). The total content of each of the two compounds was calculated from the partial isolation yield by HPLC (ODS). Compound **1**, a liquid (Found: $M^+$, 444.2847. $C_{27}H_{40}O_5$ requires $M$, 444.2820); $[\alpha]_D$ +69 ($c$ 0.12, MeOH); $m/z$ 444 ($M^+$), 426, 375, 358, 357, 301, 237, 235, 179 and 122; $\lambda_{max}$(EtOH)/nm 224 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1.5 × 10$^4$) and 354 ($\varepsilon$ 1.2 × 10$^4$); $\nu_{max}$(neat)/cm$^{-1}$ 3362br, 3070, 2964, 2930, 2874, 1638, 1570, 1506, 1456, 1373, 1198 and 889. Compound **2**, a liquid; $m/z$ 430 ($M^+$), 428, 412, 392, 359, 343, 323, 301, 261, 223, 221, 195, 179, 167, 134 and 121; $[\alpha]_D$ +44.6 ($c$ 0.11, MeOH); $\lambda_{max}$(neat)/nm 224 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1 × 10$^4$), 283 (7 × 10$^3$) and 353 (8 × 10$^3$); $\nu_{max}$(neat)/cm$^{-1}$ 3400, 3070, 2966, 2932, 2872, 1640, 1571, 1517, 1459, 1437, 1374, 1237, 1103 and 891.

### Tetrahydrochinesin I 3

A mixture of chinesin I (455 mg), EtOAc (20 cm$^3$) and 5% Pd/C (50 mg) was stirred under $H_2$ at ambient pressure and room temperature for 20 h after which it was filtered through Celite and concentrated to afford **3** as a colourless oil (458 mg, 99%) (Found: $M^+ - H_2O$, 430.3092. $C_{27}H_{42}O_4$ requires $m/z$, 430.3083); $m/z$ 430 ($M^+ - H_2O$), 387, 360, 359, 307, 295, 237 and 123; $[\alpha]_D$ +114.0 ($c$ 0.12, MeOH); $\lambda_{max}$(EtOH)/nm 222 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1.8 × 10$^4$) and 356 (1.6 × 10$^4$); $\nu_{max}$(neat)/cm$^{-1}$ 3370, 2952, 2930, 2874, 1638, 1570, 1510, 1460, 1373, 1230 and 800; $\delta_H$ 19.28 (1 H, s), 19.21 (1 H, s), 3.91 (1 H, sextet, $J$ 7.4), 2.75 (1 H, br d, $J$ 14.0), 2.24 (1 H, m), 1.99 (1 H, m), 1.9–1.3 (14 H, m), 1.34 (3 H, s), 1.24 (3 H, s), 1.14 (3 H, d, $J$ 6.8), 1.00 (3 H, d, $J$ 6.8), 0.90 (6 H, m) and 0.82 (6 H, d, $J$ 6.8); $\delta_C$ 207.6, 197.1, 189.8, 174.8, 108.6, 106.4, 82.5, 53.1, 51.8, 49.6, 43.4, 42.1, 36.1, 34.1, 29.9, 28.3, 28.2, 26.4, 25.8, 23.9, 22.9, 22.6, 22.3, 21.4, 17.9, 16.8 and 11.9.

### Ozonolysis of tetrahydrochinesin 3

Ozone was bubbled through a solution of tetrahydrochinesin **3** (455 mg) in a mixture of MeOH (80 cm$^3$) and pyridine (4 cm$^3$) at −78 °C until the solution had turned blue. It was then flushed with Ar, warmed to 0 °C, and treated with 30% $H_2O_2$ (10 cm$^3$) at 0 °C. After the mixture had been stored at 0 °C for 5 h, it was stirred with $Me_2S$ (10 cm$^3$) at 0 °C for 5 h and then evaporated. The residue was dissolved in EtOAc and the solution washed with 1 mol dm$^{-3}$ HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to give a crude lactone **4** which was reduced without further purification. To a solution of crude **4** (109 mg) in THF (20 cm$^3$), $LiAlH_4$ (20 mg) was added at 0 °C and the mixture was stirred for 1 h at 0 °C. EtOAc was added to the mixture which was then washed with brine, dried and evaporated. The product was separated by chromatography on a silica gel column to afford 2β-(2-hydroxyethyl)-3α-isopropyl-1α-methylcyclopentan-1β-ol **5** (26 mg; 13.6% from **1**) (Found: $M^+ - H_2O$, 168.1518. $C_{11}H_{20}O$ requires $m/z$ 168.1514); $m/z$ 168 ($M^+ - H_2O$), 153, 125 and 107; $[\alpha]_D$ −38.4 ($c$ 0.43, EtOH); $\nu_{max}$(neat)/cm$^{-1}$ 3330 and 2950; $\delta_H$ 3.76 (1 H, ddd, $J$ 10.9, 7.0, 4.8), 3.64 (1 H, ddd, $J$ 10.9, 7.0, 4.8), 1.56–1.89 (7 H, m), 1.44 (1 H, ddd, $J$ 9.8, 7.6, 4.0), 1.31 (3 H, s), 1.22–1.33 (1 H, m), 0.92 (3 H, d, $J$ 6.8) and 0.79 (3 H, d, $J$ 6.8); $\delta_C$ 79.8, 60.5, 50.5, 48.9, 41.1, 31.0, 29.4, 28.2, 23.3, 22.1 and 17.0.

### Linalyl acetate 6

A mixture of (−)-linalool **7** (6.00 g), *N*,*N*-diethylaniline (3 g), acetyl chloride (1.5 g) and chloroform (100 cm$^3$) was stirred for 48 h at ambient temperature. The mixture was acidified with 2 mol dm$^{-3}$ HCl and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was chromatographed on a silica gel column to give (3*R*)-3,7-dimethylocta-1,6-dien-3-yl acetate **7** (7.56 g, 99%), a liquid; $\delta_C$ 169.9, 141.8, 131.7, 123.8, 113.0, 82.9, 39.7, 25.6, 23.6, 22.3, 22.1 and 17.5.

### Epoxidation of the acetate 7

mCPBA (70%; 3.6 g) was added to a $CH_2Cl_2$ solution of **7** and the mixture was stirred for 1 h at ambient temperature. It was then washed with saturated aqueous $NaHCO_3$, dried and evaporated. The residue was chromatographed on silica gel to afford a diastereoisomeric mixture of (3*R*)-3,7-dimethyl-6,7-epoxyoct-1-en-3-yl acetate **8** (3.50 g, 90%) as a liquid (Found: $M^+$, 152.1190. $C_{10}H_{16}O$ requires $M$, 152.1201); $m/z$ ($M^+$ − AcOH) 152, 141, 139, 125, 113, 111 and 109; $[\alpha]_D$ −7.4 ($c$ 0.28, EtOH); $\nu_{max}$(neat)/cm$^{-1}$ 2980, 1730 and 1710; $\delta_H$ 5.88–6.05 (1 H, m) × 2, 5.16 (2 H, m) × 2, 2.73 (1 H, t, $J$ 6.4) × 2, 2.15 (3 H, s) × 2, 1.82–2.08 (2 H, m) × 2, 1.40–1.70 (2 H, m) × 2, 1.57 (3 H, d, $J$ 2.0) and 1.55 (3 H, d, $J$ 2.0) and 1.32 (3 H, s) and 1.26 (3 H, s); $\delta_C$ 169.9 × 2, [141.5, 141.3], [113.6, 113.5], 64.0 × 2, 58.5 × 2, 36.3 × 2, 24.8 × 2, [23.7, 23.6], 23.4 × 2, 22.1 × 2, 18.6 × 4.

### Ozonolysis of the acetate 8

Ozone was bubbled through a solution of **8** (70 mg) in MeOH (20 cm$^3$) at −78 °C until the solution had turned blue. The solution was stirred with dimethyl sulfide (0.2 cm$^3$) for 30 min at ambient temperature and then evaporated. The residue was chromatographed on silica gel to give a mixture of (2*R*)-2-acetoxy-2,6-dimethyl-5,6-epoxyheptanal **9** (60.1 mg, 85%) as a liquid (Found: $M^+$, 214.1212. $C_{11}H_{18}O_4$ requires $M$, 214.1205); $m/z$ 214 ($M^+$), 199, 181, 171, 155, 143, 125, 114, 96, 85 and 71; $[\alpha]_D$ +12.0 ($c$ 0.25, MeOH); $\nu_{max}$(neat)/cm$^{-1}$ 3400, 2950, 1730, 1450, 1370 and 1250; $\delta_H$ [9.50 (1 H, s), 9.49 (1 H, s)], 2.73 (1 H, m) × 2, [2.13 (3 H, s), 2.14 (3 H, s)], 1.55–2.07 (4 H, m) × 2, 1.46 (3 H, s) × 2, 1.33 (3 H, s) × 2 and 1.29 (3 H, s) and 1.28 (3 H, s); $\delta_C$ 198.3 × 2, 170.5 × 2, [84.1, 84.0], 63.5 × 2, [58.5, 58.4], 31.6 × 2, 24.7 × 2, 22.6 × 2, 20.8 × 2, 18.5 × 2 and 18.4 × 2.

### Reduction of the epoxy aldehyde 9

A solution of **9** (4.00 g) in acetic acid (20 cm$^3$) was stirred with

NaI (5.6 g) and zinc powder (5 g) at ambient temperature for 2 h. After which the mixture was extracted with EtOAc and water. The organic layer was washed with saturated aqueous $NaHCO_3$, dried and evaporated. The residue was chromatographed on silica gel to give (2*R*)-2-acetoxy-2,6-dimethylhept-5-enal **10** (2.96 g, 80%) as a liquid (Found: $M^+$, 198.1250. $C_{11}H_{18}O_3$ requires *M*, 198.1256); *m/z* 198 ($M^+$), 138, 123, 109, 95, 82, 69 and 67; $[\alpha]_D$ + 47.8 (*c* 1.14, MeOH); $\nu_{max}$(neat)/$cm^{-1}$ 2970, 2920, 1730, 1440, 1360 and 1250; $\delta_H$ 9.47 (1 H, d, *J* 0.8), 5.05 (1 H, m), 2.12 (3 H, d, *J* 1.0), 1.95–2.12 (2 H, m), 1.68 (3 H, s), 1.62–1.89 (2 H, m), 1.60 (3 H, s) and 1.45 (3 H, d, *J* 0.7); $\delta_C$ 198.8, 170.5, 132.6, 123.0, 84.5, 35.3, 25.5, 21.4, 20.8, 18.5 and 17.5.

**Ethyl (4*R*)-4-acetoxy-4,8-dimethylnona-2,7-dienoate 11**

The stable Wittig reagent $Ph_3P{=}CHCO_2Et$ (2.5 g) was added to a solution of **10** (1.39 g) in benzene (20 $cm^3$) and the mixture was refluxed under an Ar atmosphere for 8 h after which it was diluted with diethyl ether. The organic layer was separated and concentrated under reduced pressure and the residue was chromatographed on a silica gel column to give the ester **11** (1.71 g, 91%) as a liquid (Found: $M^+$ − AcOH, 208.1544. $C_{13}H_{20}O_2$ requires *m/z* 208.1463); *m/z* 208 (M − AcOH), 193, 181, 165, 152, 135, 119, 98 and 93; $[\alpha]_D$ +6.7 (*c* 1.56, EtOH); $\lambda_{max}$(EtOH)/nm 209 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 1.7 × $10^4$); $\nu_{max}$(neat)/$cm^{-1}$ 2975, 1730, 1720 and 1240; $\delta_H$ 6.95 (1 H, d, *J* 15.7), 5.88 (1 H, d, *J* 15.7), 5.05 (1 H, br m), 4.20 (2 H, q, *J* 7.2), 2.04 (3 H, s), 1.72–1.98 (4 H, m), 1.67 (3 H, s), 1.58 (6 H, s) and 1.30 (3 H, t, *J* 7.2); $\delta_C$ 169.4, 166.3, 151.0, 132.2, 123.3, 119.3, 81.7, 60.5, 39.3, 25.6, 23.8, 22.3, 21.9, 17.6 and 14.2.

**Cyclization of the ester 11 to ethyl (2β-acetoxy-5ξ-isopropenyl-2α-methyl-1β-cyclopentyl)acetate 12**

A solution of **11** (45 mg) in toluene (30 $cm^3$) sealed in a tube was stirred at 200 °C for 30 h. After evaporation of the solvent, the products was separated by HPLC (ODS) to give **12** (15.8 mg, 35%) as a liquid (Found: $M^+$ − AcOH, 208.1508. $C_{13}H_{20}O_2$ requires *m/z* 208.1463); *m/z* 208 (M − AcOH), 193, 181, 163, 135, 121, 120, 105 and 91; $[\alpha]_D$ −28.9 (*c* 0.35, EtOH); $\nu_{max}$(neat)/$cm^{-1}$ 2975, 1735 and 1240; $\delta_H$ 4.87 (1 H, s), 4.96 (1 H, s), 4.14 (1 H, dq, *J* 10.8, 7.0), 4.06 (1 H, dq, *J* 10.8, 7.0), 2.59–2.73 (2 H, m), 1.95–2.30 (4 H, m), 1.92 (3 H, s), 1.73 (3 H, s), 1.68 (2 H, m), 1.58 (3 H, s) and 1.24 (3 H, t, *J* 7.0); $\delta_C$ 173.7, 170.0, 144.8, 112.3, 89.0, 60.2, 48.5, 46.5, 35.6, 30.8, 25.7, 25.3, 22.8, 21.9 and 14.2.

**Hydrogenation of 12**

A mixture of **12** (26 mg), 5% Pd/C (27 mg) in ethyl acetate (10 mg) was stirred under a $H_2$ atmosphere at ambient temperature for 50 h after which it was filtered through a Celite column and evaporated. The products were separated by HPLC (ODS, MeOH–$H_2O$) to give ethyl (2β-acetoxy-5α-isopropyl-2α-methyl-1β-cyclopentyl)acetate **14** (18.9 mg, 72%) as a liquid (Found: $M^+$, 210.1637. $C_{13}H_{22}O_2$ requires *m/z* 210.1620); *m/z* 210 (M − AcOH), 183, 167, 158, 139, 123, 107 and 93; $[\alpha]_D$ −43.1 (*c* 0.06, EtOH); $\nu_{max}$(neat)/$cm^{-1}$ 2950, 1730 and 1270; $\delta_H$ 4.19 (1 H, dq, *J* 13.0, 7.3), 4.14 (1 H, dq, *J* 13.0, 7.3), 4.13 (1 H, dq, *J* 13.0, 7.3), 4.10 (1 H, dq, *J* 13.0, 7.3), 2.54 (1 H, dd, *J* 15.6, 8.0), 2.28 (1 H, dd, *J* 15.6, 5.9), 2.27 (1 H, m), 1.96 (3 H, s), 1.55–2.04 (9 H, m), 1.52 (3 H, s), 1.27 (3 H, t, *J* 7.3), 0.93 (3 H, d, *J* 6.8) and 0.83 (3 H, d, *J* 6.8); $\delta_C$ 173.5, 170.2, 89.9, 60.3, 49.6, 49.5, 36.2, 34.9, 26.6 × 2, 23.6, 23.3, 22.1, 17.2 and 14.2.

**Reduction of the ester 14 with $LiAlH_4$ to the diol 5**

A mixture of the diol **14** (20 mg), $LiAlH_4$ (5 mg) and diethyl ether (10 $cm^3$) was stirred at 0 °C under Ar for 1 h after which the reaction was stopped by addition of an excess of EtOAc. The reaction mixture was extracted with 1 mol $dm^{-3}$ HCl and ether and the latter extract was washed with brine, dried and evaporated to give 3α-isopropyl-2β-(2-hydroxyethyl)-1α-methylcyclopentan-1β-ol **5** (12.4 mg, 99%) as a liquid; $[\alpha]_D$ −35.0 (*c* 0.17, EtOH) (IR, $^1H$ NMR and $^{13}C$ NMR are superimposable with those of **5** isolated from a natural source).

**Acetylation of the diol 5**

A solution of the diol **5** (10 mg) in pyridine (1 $cm^3$) and acetic anhydride (1 $cm^3$) was stirred at ambient temperature for 15 h after which the reaction was stopped by the addition of methanol. The mixture was extracted with EtOAc and 2 mol $dm^{-3}$ HCl and the former extract was washed with saturated aqueous $NaHCO_3$, dried and evaporated. Chromatography of the residue on a short column of silica gel gave 2β-(2-acetoxyethyl)-3α-isopropyl-1α-methylcyclopentan-1β-ol **15** (12.2 mg, 99%), as a liquid (Found: $M^+$ − AcOH − $H_2O$, 150.1397. $C_{11}H_{18}$ requires *m/z* 150.1409); *m/z* 150, 125, 110, 107 and 95; $[\alpha]_D$ −38.7 (*c* 0.06, EtOH); $\nu_{max}$(neat)/$cm^{-1}$ 3475, 2950, 1740 and 1240; $\delta_H$ 4.16 (2 H, t, *J* 6.8), 2.06 (3 H, s), 1.90 (1 H, septet, *J* 6.8), 1.53–1.77 (6 H, m), 1.25–1.43 (2 H, m), 1.30 (3 H, s), 0.92 (3 H, d, *J* 6.8) and 0.81 (3 H, d, *J* 6.8); $\delta_C$ 173.5, 82.9, 66.6, 52.7, 51.0, 43.6, 32.1, 32.0, 30.6, 30.2, 25.3, 24.6 and 19.1.

**Acid degradation of chinesin I 1 with sulfuric acid**

A mixture of chinesin I (500 mg) and 67% sulfuric acid (20 $cm^3$) was stirred at 100 °C for 40 min after which it was poured onto ice and was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$, dried and evaporated. Polyphosphate ester (PPE) (5 $cm^3$) and phenol (1 g) were added to the residue and the mixture was stirred at ambient temperature for 24 h. After this, the reaction mixture was extracted with water and EtOAc and the latter extract was washed with brine, dried and evaporated. The product was purified by chromatography on a silica gel column and HPLC (ODS) to give phenyl (2*S*)-2-methyl butyrate **17** (110 mg, 55%) as a liquid, $[\alpha]_D$ +5.14 (*c* 1.11, EtOH); $\delta_C$ 175.1, 150.8, 129.3, 125.6, 121.5, 41.1, 26.7, 16.5 and 11.5.

**Phenyl (2*S*)-2-methylbutanoate 17**

(+)-Methylbutyric acid (100 mg) was treated with PEE (5 $cm^3$) and phenol (1 g) and the mixture worked up as described in the preceding experiment to give the ester **17** (171 mg, 98%), $[\alpha]_D$ + 26.2 (*c* 1.23, EtOH).

**Methyl 2-(2-methylbutyryloxy)phenylacetate 18**

The acid **16** obtained by acid degradation of chinesin **I** (450 mg) was treated with PPE (5 $cm^3$) and methyl mandelate (200 mg) as in the synthesis of **17** to give a diastereoisomeric mixture (*R*:*S*, 62.5:37.5) of **18** (109 mg, 43%) (Found: $M^+$, 250.1181. $C_{14}H_{18}O_4$ requires *M*, 250.1205); *m/z* 250 ($M^+$), 236, 218, 204, 191, 177, 166, 149, 121, 105, 90, 85 and 71; $[\alpha]_D$ −101.3 (*c* 0.86, EtOH); $\lambda_{max}$(EtOH)/nm 203 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 8.5 × $10^3$); $\nu_{max}$(neat)/$cm^{-1}$ 2980, 2890, 1760, 1740, 1500, 1460, 1440, 1340, 1260, 1220, 1180, 1140 and 1040; $\delta_H$ 7.44–7.50 (2 H, m), 7.36–7.42 (3 H, m), 2 H [5.93(s) + 5.92(s)], 3.68 (3 H, s), 2.55 (1 H, septet, *J* 7.0), 1.75 (1 H, m), 1.53 (1 H, m), 3 H [1.25 (d, *J* 7.0) + 1.20 (d, *J* 7.0)], 3 H [0.99 (t, *J* 7.0) + 0.92 (t, *J* 7.0)]; $\delta_C$[175.9, 175.8], 169.2, 133.9, 129.1, 128.8 × 2, 127.5 × 2, [74.2, 74.1], 52.5, [40.8, 40.7], [26.7, 26.6], [16.6, 16.3], [11.5, 11.4].

**Methyl ethers 19 and 20 of chinesin I**

An ethereal solution of diazomethane was added at 0 °C to a solution of chinesin I (311.3 mg) in diethyl ether (10 $cm^3$). After 15 h at ambient temperature, the mixture was evaporated and the residue separated by chromatography on a silica gel column and by HPLC (Lichrosorb Si60 hexane–EtOAc) to give **19** (31.3

mg, 10%) and **20** (14.4 mg, 4%): **19**, a liquid $\lambda_{max}$(EtOH)/nm 320 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ $6 \times 10^3$) and 238 ($1.2 \times 10^4$); $\nu_{max}$(neat)/cm$^{-1}$ 3070, 2964, 2930, 2874, 2728, 1655, 1624, 1517, 1457, 1375, 1237, 1195, 1050 and 891; **20**, a liquid (Found: M$^+$, 472.3177. $C_{29}H_{44}O_5$ requires *M*, 472.3187); *m*/*z* 472, 440, 404, 403, 372, 371, 315, 289, 251, 249, 235, 233 and 193; $\nu_{max}$(neat)/cm$^{-1}$ 3068, 2964, 2934, 2872, 1654, 1559, 1527, 1458, 1436, 1369, 1202, 1130, 1101, 1079 and 887; $\delta_H$ 19.3 (1 H, s), 3.96 (3 H, s) and 3.18 (3 H, s).

## References


1 D. DeKeukeleire and M. Verzele, *Tetrahedron*, 1970, **26**, 385.
2 P. R. Ashurst, *Fortschr. Chem. Org. Naturstoff*, 1967, **25**, 63.
3 W. L. Parker and F. Johnson, *J. Am. Chem. Soc.*, 1968, **90**, 4716 and 4724.
4 W. Riedl and R. Mitteldorf, *Chem. Ber.*, 1956, **89**, 2595.
5 J. A. Chan, E. A. Shultis, S. A. Carr, C. W. DeBrosse, D. S. Eggleton, T. A. Francis, L. J. Hyland, W. P. Johnson, L. B. Killmer, D. B. Staiger and J. W. Westley, *J. Org. Chem.*, 1989, **54**, 2098.
6 M. Arisawa, A. Fujita, T. Hayashi, K. Hayashi, H. Ochiai and N. Morita, *Chem. Pharm. Bull.*, 1990, **38**, 1624.
7 M. Takasaki, T. Konoshima, T. Shingu, H. Tokuda, H. Nishino, A. Iwashima and M. Kozuka, *Chem. Pharm. Bull.*, 1990, **38**, 1444.
8 M. Nishizawa, H. Yamada, J. Sano, S. Ito, Y. Hayashi, H. Ikeda, Chairul, M. Shiro and H. Tokuda, *Tetrahedron Lett.*, 1991, **32**, 211.
9 H. Nakane, M. Arisawa, A. Fujita, S. Koshimura and K. Ono, *FEBS Lett.*, 1991, 93.
10 Y. Kashman, K. R. Gustafson, R. W. Fuller, J. H. Cardellina, J. B. McMahon, M. J. Currens, R. W. Buckhiet, Jr., S. H. Hughes, G. M. Cragg and M. R. Boyd, *J. Med. Chem.*, 1992, **35**, 2735.
11 M. Nagai and M. Tada, *Chem. Lett.*, 1987, 1337.
12 M. Tada, T. Takakuwa, M. Nagai and T. Yoshii, *Agric. Biol. Chem.*, 1990, **54**, 3061.
13 M. Tada, K. Chiba, T. Takakuwa and E. Kojima, *J. Med. Chem.*, 1992, **35**, 1209.
14 K. Chiba, T. Takakuwa, M. Tada and T. Yoshii, *Biosci. Biotech. Biochem.*, 1992, **56**, 1769; M. Tada, K. Chiba and T. Yoshii, in *Natural Products as Antiviral Agents*, C. K. Chu and H. G. Cutler ed., Plenum, New York, 1992, pp. 239–255.
15 L. A. Decosterd, H. Stoeckli-Evans, J. Chapuis, B. Sordat and K. Hostettmann, *Helv. Chim. Acta*, 1989, **72**, 1833.
16 Y. Kanaoka, O. Yonemitsu, K. Tanizawa and Y. Ban, *Chem. Pharm. Bull.*, 1964, **12**, 773.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