Total Synthesis of Kanshone A, a Sesquiterpene Isolated from *Nardostachys chinensis* (Valerianaceae)

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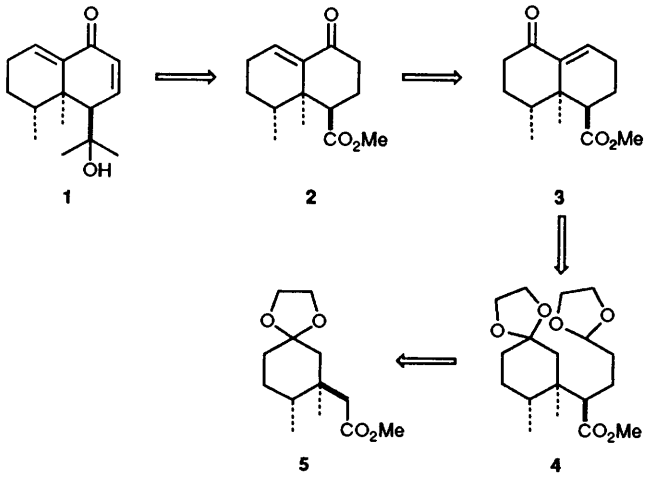
Kanshone A, isolated from *Nardostachys chinensis* (Valerianaceae), has been synthesized in 9 steps by stereoselective alkylation of the derivative methyl (5,5-ethylenedioxy-1,2-dimethylcyclohexyl)-acetate and an intramolecular aldol cyclization followed by methylation and introduction of a double bond.

Kanshone A **1** is a sesquiterpene isolated from a plant used in Chinese folk medicine *viz. Nardostachys chinensis* Batalin (Valerianaceae) ('Kanshoko' in Japanese), and its structure as well as those of the kanshones B, C, D and E were determined by Hikino and his group.[1] Their structures are highly related to those of aristolane sesquiterpenes and are of a type rather rare in Nature. They also exhibit antihepatotoxicity. Kanshone A **1** has a cross-conjugated system, a *cis*-dimethyl arrangement, and an α,α-dimethyl-substituted alcohol moiety. Since one of the *cis*-dimethyl groups and the dimethyl-substituted alcohol group of compound **1** are axially oriented, their construction would seem to be rather difficult. In the continuation of our synthetic study on the sesquiterpenoids, we have accomplished the first total synthesis of kanshone A **1**, which we now describe in detail.

Recently we reported the total synthesis of chiloscyphone during which we used the reaction of the enolate of the methyl ester **5** with allyl bromide.[2] This afforded the desired isomer preferentially and the ratio of these isomers was *ca.* 3:1 judging from the ^{13}C NMR spectrum. Therefore our synthetic plan is based on the alkylation of ester **5** with an appropriate C_3 carbon unit (**5** ⟶ **4**). A bicyclic enone **3** would be prepared by an intramolecular aldol cyclization and kanshone A **1** could then be constructed through an enone **2** prepared by Wharton reaction and oxidation (see the retrosynthetic Scheme 1).



Scheme 1

The methyl ester **5**, derived from 3,4-dimethylcyclohex-2-enone through a 5-step conversion,[2] was treated with lithium diisopropylamide (LDA) followed by 2-(2-bromoethyl)-1,3-dioxolane in the presence of hexamethylphosphoric triamide (HMPA) to afford the diacetal **4** in 54% yield. The crude product was inspected by ^{13}C NMR spectroscopy, which showed that only one isomer had been produced. The

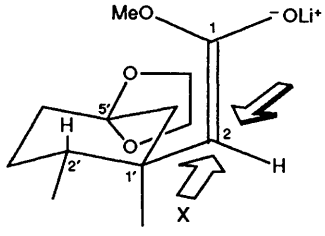


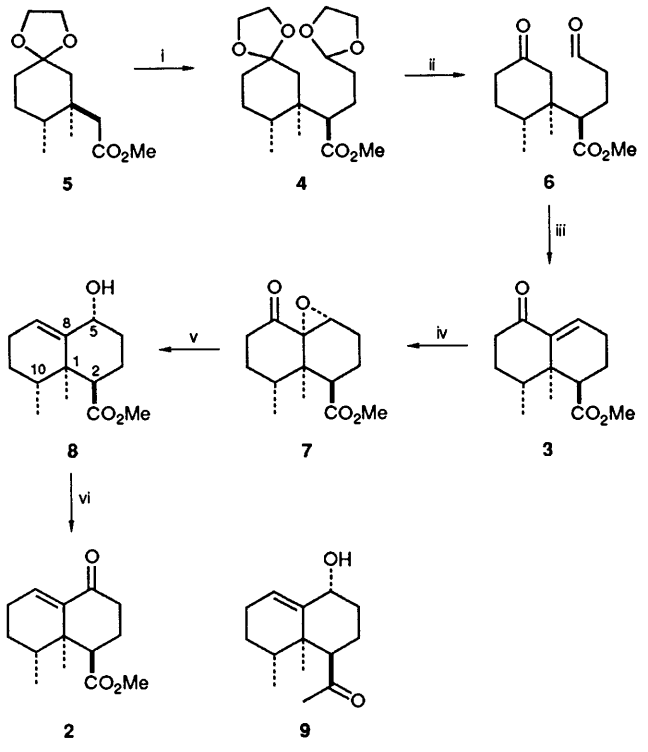
Fig. 1 The conformation of the enolate of ester **5**

stereochemistry at this position was inferred to be the same as that reported previously[2] and this was verified at a later stage by nuclear Overhauser effect (NOE) experiments. These facts suggest that the enolate derived from this ester was alkylated from the side of the acetal as shown in Fig. 1. The enolates in the eclipsed forms are apparently less stable. When the oxygen function is below the cyclohexane ring, in other words when the C-1 carbon is between C-2′ and the C-1′ methyl group or between C-6′ and the C-1′ methyl group, both the alkyl groups act as centres of steric hindrance. Therefore when the oxygen function is above the cyclohexane ring, namely when the C-1 carbon is between C-2′ and C-6′, the alkyl halide comes close to the enolate from the less hindered acetal side, since there is a methyl group (attached to C-2′) on the other side.

Deprotection of both the acetal groups in compound **4** with TsOH in acetone–water gave a keto aldehyde **6**, which was treated again with TsOH in dry benzene under reflux to afford an enone **3** by an intramolecular aldol condensation in 64% yield from compound **4**. Transposition of the carbonyl group and the double bond was carried out in three steps including a Wharton reaction.[3] The enone **3** was epoxidized by hydrogen peroxide in the presence of sodium hydroxide. The epoxide **7** was refluxed in aq. hydrazine to afford an allylic alcohol **8**, which was converted into the enone **2** by Swern oxidation[4] (Scheme 2).

The stereochemistry of the alcohol **8** was established by ^1H NMR spectroscopy. When the proton at δ 1.24 due to the methyl group at the C-1 position was irradiated, NOEs with the secondary methyl group (δ 0.86, d) and the methine proton at C-2 (δ 2.78, dd) were observed (Fig. 2). This experiment clearly shows that the two methyl groups are *cis* oriented and that the methoxycarbonyl group is *trans* to both methyl groups and is axially oriented. The configuration of the hydroxy group at C-5 was assigned, by measurement of the value of the coupling contants of the methine proton at δ 4.33 (t, *J* 2.9 Hz), to be α-axial.

Methylation of compound **8** with methyllithium in diethyl ether or tetrahydrofuran (THF) did not give the desired α,α-dimethyl alcohol but instead gave the intermediate methyl ketone **9**. Even if a large excess of MeLi was used to treat the methyl ketone **9**, starting material was completely recovered. Protection of the hydroxy group as a tetrahydropyran-2-yl



Scheme 2 *Reagents and conditions:* i, LDA–HMPA, 2-(2-bromoethyl)-1,3-dioxolane; ii, TsOH, aq. acetone; iii, TsOH, PhH, reflux; iv, H_2O_2, NaOH; v, aq. NH_2NH_2, reflux; vi, Swern oxidation

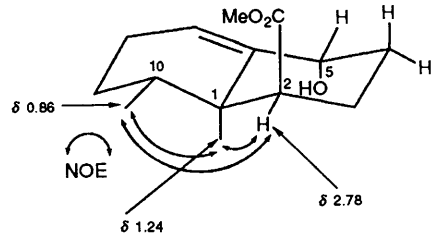


Fig. 2 The stereochemisty of compound **8**

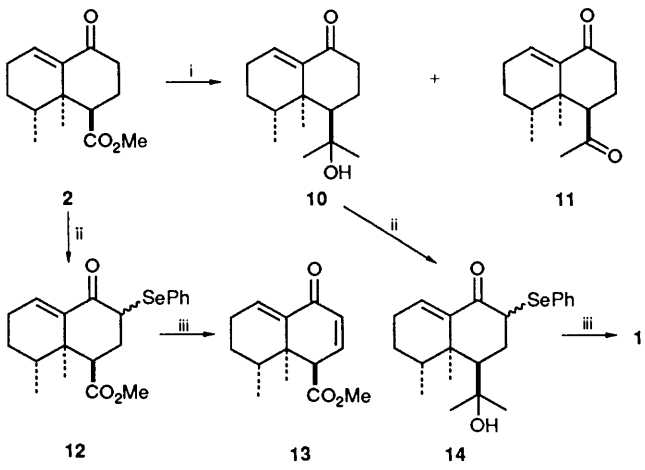
(THP) ether did not change the situation. However, treatment of the enone **2** with a large excess of methyllithium in dry THF at room temperature afforded the desired α,α-dimethyl alcohol **10** and the methyl ketone **11** in the ratio 1.8 : 1. These two products were separable by HPLC. Therefore we attemped methylation of the ester **13** prepared in two steps from compound **2** (LDA PhSeBr; H_2O_2). Treatment of ester **13** with a large excess of methyllithium in diethyl ether or THF at room temperature gave neither the α,α-dimethyl alcohol nor the methyl ketone, but instead the product was mostly the recovered starting material. It is not yet clear why only in the case of compound **2** did the reaction with MeLi occur to give the desired α,α-dimethyl alcohol (Scheme 3). The enone system in compound **2** is presumably enolizable very easily.

The α,α-dimethyl alcohol **10** was subjected to phenylselenenylation (LDA, PhSeBr) and deselenenylation (H_2O_2) to afford kanshone A **1**, whose spectral data (IR and ^1H NMR) were completely identical with those of an authentic sample sent by Professor Endo, Tohoku University, Japan.

Thus we have accomplished the first total synthesis of kanshone A **1** starting from the cyclohexyl acetate derivative **5** in 9 steps.

Experimental

General.—See ref. 2. NMR *J*-values are given in Hz.



Scheme 3 *Reagents and conditions:* i, MeLi, THF; ii, LDA, PhSeBr; iii, H_2O_2, THF, 0 °C ⟶ room temp.

Alkylation of Methyl (5,5-*Ethylenedioxy*-cis-1,2-*dimethylcyclohexyl*)*acetate* **5**.—A solution of compound **5** (5 g) in dry THF (20 cm^3) was added to a solution of LDA prepared from diisopropylamine (23 cm^3) and Bu^nLi (1.6 mol dm^{-3}, 28.4 cm^3) in dry THF (40 cm^3) at −78 °C and the mixture was stirred for 1 h. HMPA (60 cm^3) was added and a solution of 2-(2-bromoethyl)-1,3-dioxolane (3.46 cm^3) in dry THF (20 cm^3) was introduced slowly. The mixture was stirred at room temperature for 48 h before the addition of water. The products were extracted with diethyl ether and the extract was washed successively with 1 mol dm^{-3} HCl and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *bis*(*ethylene acetal*) **4** (4.6 g, 54%); ν_{max}(film)/cm^{-1} 1720; δ_H 0.90 (3 H, d, *J* 6), 0.98 (3 H, s), 3.66 (3 H, s), 3.88–3.92 (8 H, m) and 4.83 (1 H, t, *J* 4.3); δ_C 15.3 (Me), 18.4 (Me), 21.4 (CH_2), 28.7 (CH_2), 32.7 (CH_2), 34.7 (CH_2), 37.5 (CH), 39.6 (CH_2), 39.9 (C), 50.9 (OMe), 55.2 (CH), 63.4 (CH_2), 64.4 (CH_2), 64.7 (CH_2 × 2), 104.1 (CH), 109.4 (C) and 175.0 (CO); *m*/*z* 342 (M^+), 311, 285, 169 and 99 (base) (Found: M^+, 342.2044. $C_{18}H_{30}O_6$ requires M, 342.2043).

Deprotection of Methyl 5-(1,3-*Dioxolan*-2-*yl*)-2-[(1R*,2R*)-5,5-*ethylenedioxy*-1,2-*dimethylcyclohexyl*]*valerate* **4** *and Intramolecular Aldol Condensation.*—A solution of compound **4** (7 g) in acetone (140 cm^3)–water (70 cm^3) was treated with TsOH (700 mg) under reflux for 1 h. The mixture was extracted with diethyl ether and the extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the keto aldehyde **6** (4.7 g, 91%); ν_{max}(film)/cm^{-1} 1720 and 1700; δ_H 0.89 (3 H, s), 0.98 (3 H, d, *J* 6), 3.71 (3 H, s) and 9.74 (1 H, br s); *m*/*z* 236 (M − 18)$^+$, 208, 197, 153 and 125 (base).

A solution of the keto aldehyde **6** (4.7 g) in benzene (800 cm^3) was treated with TsOH (471 mg) under reflux with the aid of a Dean–Stark water separator for 1 h. The mixture was extracted with benzene, and the extract was washed successively with 5% aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *enone* **3** (3.1 g, 70%); ν_{max}(film)/cm^{-1} 1710, 1670 and 1600; δ_H (400 MHz) 0.97 (3 H, d, *J* 6.8), 1.00 (3 H, s), 2.78 (1 H, dd, *J* 4.8 and 2.8), 3.67 (3 H, s) and 6.64 (1 H, t, *J* 3.9); δ_C 15.1 (Me), 20.6 (CH_2), 20.9 (Me), 22.5 (CH_2), 27.5 (CH_2), 34.6 (CH), 39.6 (C), 39.7 (CH_2), 46.3 (CH), 51.1 (OMe), 134.3 (CH=), 141.9 (C=), 173.8 (CO_2) and 201.5 (CO); *m*/*z* 236 (M^+), 204, 176, 159 (base), 135 and 91 (Found: M^+, 236.1387. $C_{14}H_{20}O_3$ requires M, 236.1412).

Epoxidation of Methyl (1R*,2R*,10R*)-1,10-*Dimethyl*-7-*oxobicyclo*[4.4.0]*dec*-5-*ene*-2-*carboxylate* **3**.—To a stirred solution of **3** (1 g) in methanol (100 cm^3) at 0 °C were added 4 mol dm^{-3} aq. NaOH (1.5 cm^3) and 30% H_2O_2 (3 cm^3) successively. The mixture was stirred for 3 h before work-up. Water was added and the mixture was extracted with diethyl ether. The extract was washed successively with 10% aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the *epoxide* **7** (1.2 g, 95%); ν_{max}(film)/cm^{-1} 1720; δ_H (400 MHz) 0.95 (3 H, d, *J* 7), 1.13 (3 H, s), 3.28 (1 H, dd, *J* 2.4 and 1.5), and 3.68 (3 H, s); δ_C 15.5 (Me), 16.3 (Me), 18.4 (CH_2), 21.2 (CH_2), 27.5 (CH_2), 34.7 (CH), 39.8 (CH_2), 45.3 (CH), 50.9 (OMe), 61.5 (CH), 64.8 (C), 174.0 (CO_2) and 205.9 (CO); *m/z* 252 (M^+), 237 (base), 177 and 151 (Found: M^+, 252.1384. $C_{14}H_{20}O_4$ requires M, 252.1362).

Wharton Reaction of Methyl (1R*,2R*,5R*,6S*,10R*)-1,10-*Dimethyl*-7-*oxo*-5,6-*epoxybicyclo*[4.4.0]*decane*-2-*carboxylate* **7**.—A solution of compound **7** (826 mg) in aq. hydrazine (80%; 10 cm^3) was heated under reflux for 0.5 h. Water was added and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *alcohol* **8** (298 mg, 39%); ν_{max}(film)cm^{-1} 3400 and 1720; δ_H(400 MHz) 0.86 (3 H, d, *J* 6.6), 1.24 (3 H, s), 2.78 (1 H, dd, *J* 5.0 and 2.1), 3.62 (3 H, s), 4.33 (1 H, t, *J* 2.9) and 5.73 (1 H, t, *J* 3.5); δ_C 15.0 (Me), 19.5 (CH_2), 21.0 (Me), 25.5 (CH_2), 26.9 (CH_2), 27.7 (CH_2), 35.8 (CH), 38.5 (C), 48.8 (CH), 50.7 (OMe), 73.6 (CH), 127.9 (CH=), 142.0 (C=) and 174.5 (CO); *m/z* 238 (M^+), 223, 220, 183, 179, 163, 161 (base), 145, 123, 119 and 105 (Found: M^+, 238.1575. $C_{14}H_{22}O_3$ requires M, 238.1569).

Swern Oxidation of Methyl (1R*,2R*,5R*,10R*)-5-*Hydroxy*-1,10-*dimethylbicyclo*[4.4.0]*dec*-6-*ene*-2-*carboxylate* **8**.—A solution of dimethyl sulphoxide (0.17 cm^3) in CH_2Cl_2 (0.5 cm^3) was added to a solution of oxalyl dichloride (0.1 cm^3) in CH_2Cl_2 (2.5 cm^3) at −78 °C under argon and the mixture was stirred for 2 min. A solution of the alcohol **8** (240 mg) in CH_2Cl_2 (1 cm^3) was added dropwise at the same temperature and the mixture was then stirred for 15 min. Triethylamine (0.7 cm^3) was added and the temperature was raised to 0 °C. Water was added after 30 min and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *enone* **2** (117 mg, 49%); ν_{max}(film)/cm^{-1} 1715, 1680 and 1615; δ_H 0.97 (3 H, d, *J* 6.2), 1.00 (3 H, s), 3.67 (3 H, s) and 6.70 (1 H, t, *J* 4.0); δ_C 15.0 (Me), 20.5 (Me), 20.8 (CH_2), 25.0 (CH_2) 25.7 (CH_2), 34.3 (CH_2), 34.6 (CH), 40.0 (C), 45.9 (CH), 50.7 (OMe), 134.2 (CH=), 141.4 (C=), 173.6 (CO_2) and 199.5 (CO); *m/z* 236 (M^+), 221, 177, 161, 135 (base) and 91 (Found: M^+, 236.1423. $C_{14}H_{20}O_3$ requires M, 236.1413).

Methylation of Methyl (1R*,2R*,10R*)-1,10-*Dimethyl*-5-*oxobicyclo*[4.4.0]*dec*-6-*ene*-2-*carboxylate* **2**.—To a stirred solution of ester **2** (100 mg) in dry THF (10 cm^3) at 0 °C was added MeLi (1 mol dm^{-3}; 4.3 cm^3). The mixture was stirred at room temperature for 5 h. Water was added and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, filtered, and evapoated under reduced pressure to afford a residue, which was separated by HPLC [Chemcopak, CHEMCOSORB, 5-Si-U, 7.5 × 250 mm; hexane–EtOAc (4:1)] to give the *tertiary alcohol* **10** (20.3 mg, 20%) and the *ketone* (10 mg). For compound **10**: ν_{max}(film)/cm^{-1} 3450, 1670 and 1610; δ_H 0.97 (3 H, d, *J* 6.4), 1.02 (3 H, s), 1.32 (3 H, s), 1.37 (3 H, s) and 6.75 (1 H, t, *J* 4.1); δ_C 16.5 (Me), 21.1 (CH_2), 25.4 (Me), 25.8 (CH_2), 26.5 (CH_2), 28.8 (Me), 33.3 (CH), 33.4 (Me), 35.0 (CH_2), 41.9 (C), 48.6 (CH), 74.7 (C), 135.4 (CH=), 144.0 (C=) and 201.6 (CO); *m/z* 236 (M^+), 218, 203, 178, 163, 136, 109, 91, 79, 59, 43 and 41 (base) (Found: M^+, 236.1841. $C_{15}H_{22}O_2$ requires M, 236.1776). For compound **11**: ν_{max}(film)/cm^{-1} 1700, 1680 and 1610; δ_H 0.97 (3 H, d, *J* 6.4), 0.97 (3 H, s), 2.30 (3 H, s) and 6.70 (1 H, d, *J* 4.0); *m/z* 220 (M^+), 205, 177, 159, 135 (base), 121, 108, 91, 77 and 43 (Found: M^+, 220.1562. $C_{14}H_{20}O_2$ requires M, 220.1463).

Phenylselenenylation of Methyl (1R*,2R*,10R*)-1,10-*Dimethyl*-5-*oxobicyclo*[4.4.0]*dec*-6-*ene*-2-*carboxylate* **2**.—A solution of compound **2** (100 mg) in dry THF (1 cm^3) was added to LDA prepared from diisopropylamine (0.07 cm^3) and BuLi (1.6 mol dm^{-3}; 0.32 cm^3) in dry THF (1 cm^3) at −78 °C. The mixture was stirred for 1 h and a solution of PhSeBr (150 mg) in dry THF (1 cm^3) was added slowly. After addition was complete, the mixture was stirred at 0 °C for 2 h. Water was added and the mixture was extracted with diethyl ether. The extract was washed successively with 1 mol dm^{-3} HCl and brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *selenide* **12** (70.3 mg, 42%); ν_{max}(film)/cm^{-1} 1720, 1675 and 1610; δ_H 0.85 (3 H, s), 0.91 (3 H, d, *J* 6.2), 3.65 (3 H, s), 4.6 (1 H, dd, *J* 10.9 and 9.3), 6.74 (1 H, t, *J* 3.9) and 7.2–7.7 (5 H, m); *m/z* 392 (M^+), 235, 175, 147, 135, 107, 91 (base), 77, 55 and 41 (Found: M^+, 392.0859. $C_{20}H_{24}O_3Se$ requires M, 392.0891).

Preparation of Methyl (1R*,2R*,10R*)-1,10-*Dimethyl*-5-*oxobicyclo*[4.4.0]*deca*-3,6-*diene*-2-*carboxylate* **13**.—To a stirred solution of the selenide **12** (18 mg) in THF (0.25 cm^3) at 0 °C was added 30% aq. H_2O_2 (0.015 cm^3). The mixture was stirred at room temperature for 2 h. Water was added and the mixture was extracted with diethyl ether. The extract was washed successively with 10% aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and evaporated to afford the *dienone* **13** (6.3 mg, 54%); ν_{max}(film)/cm^{-1} 1730, 1665 and 1610; δ_H 1.01 (3 H, d, *J* 6), 1.10 (3 H, s), 3.49 (1 H, d, *J* 6.6), 3.67 (3 H, s), 6.26 (1 H, d, *J* 6), 6.78 (1 H, dd, *J* 9.9 and 6.6) and 6.98 (1 H, t, *J* 4.1); δ_C 15.4 (Me), 21.0 (Me), 25.7 (CH_2), 26.1 (CH_2), 35.1 (CH), 41.9 (C), 52.2 (Me), 52.5 (CH), 131.6 (CH=), 136.8 (CH=), 139.1 (C=), 142.2 (CH=), 170.7 (CO_2) and 186.9 (CO); *m/z* 234 (M^+), 219, 187, 175, 159, 133 (base), 105, 91, 77, 55 and 41 (Found: M^+, 234.1271. $C_{14}H_{18}O_3$ requires M, 234.1256).

Phenylselenenylation of [(5R*,6R*,7R*)-5-(1-*Hydroxy*-1-*methylethyl*)-6,7-*dimethylbicyclo*[4.4.0]*dec*-1(10)-*en*-2-*one* **10**.—A solution of compound **10** (28.1 mg) in dry THF (1 cm^3) was added to LDA prepared from diisopropylamine (0.036 cm^3) and BuLi (1.6 mol dm^{-3}; 0.17 cm^3) in dry THF (1 cm^3) at −78 °C. The mixture was stirred for 1 h and a solution of PhSeBr (42.5 mg) in dry THF (1 cm^3) was added slowly. After addition was complete, the mixture was stirred at 0 °C for 2 h. Water was added and the mixture was extracted with diethyl ether. The extract was washed successively with 1 mol dm^{-3} HCl and brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc gradient) to give the *selenide* **14** (13.9 mg, 30%); ν_{max}(film)/cm^{-1} 3450, 1695 and 1620; δ_H 0.92 (3 H, d, *J* 6.6), 1.02 (3 H, s), 1.41 (3 H, s), 1.46 (3 H, s), 4.26 (1 H, d, *J* 10.4), 6.89 (1 H, t, *J* 3.8) and 7.2–7.7 (5 H, m); *m/z* 392 (M^+), 374, 332, 290, 217, 175, 105, 91 and 59 (base) (Found: M^+, 392.1189. $C_{21}H_{28}O_2Se$ requires M, 392.1256).

Preparation of Kanshone A **1**.—To a stirred solution of compound **14** (13 mg) in THF (1 cm^3) at 0 °C was added 30% aq. H_2O_2 (0.057 cm^3). The mixture was stirred at room temperature for 2 h. Water was added and the mixture was

extracted with diethyl ether. The extract was washed successively with 10% aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and evaporated to afford a residue, which was purified by HPLC [Chemcopak, CHEMCOSORB, 5-Si-U, 7.5 × 250 mm; hexane–EtOAc (4:1)] to give kanshone A **1** (2 mg, 24%); ν_{max}(MeOH)/nm 245 (ε 5300 dm^3 mol^{-1} cm^{-1}); ν_{max}(film)/cm^{-1} 3430, 1665, 1625 and 1610; δ_H(400 MHz) 1.01 (3 H, d, *J* 6.6), 1.08 (3 H, s), 1.17 (3 H, s), 1.26 (3 H, s), 2.27 (1 H, m), 2.62 (1 H, d, *J* 6.8), 6.19 (1 H, dd, *J* 10.3 and 0.7), 6.94 (1 H, dd, *J* 10.3 and 6.8) and 7.01 (1 H, t, *J* 4.0); δ_C(100 MHz) 16.8 (Me), 23.9 (Me), 24.6 (Me), 26.1 (CH_2), 26.4 (CH_2), 32.5 (Me), 33.3 (CH), 42.1 (C), 54.4 (CH), 76.3 (C), 129.3 (CH=), 137.1 (CH=), 141.5 (C=), 150.5 (CH=) and 187.6 (CO); *m/z* 216 $(M - 18)^+$, 201, 176, 161, 134, 119, 105, 91 and 59 (base).

Acknowledgements

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