Transformation of Santonin into (+)-Deoxyvernolepin and Related Dilactones

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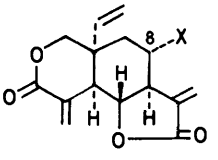
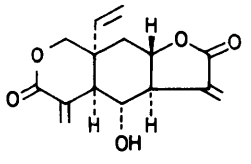
Ozonolysis followed by acetylation of the (3*S*,3a*S*,5a*R*,9*R*,9a*S*,9b*S*)-5a-hydroxymethyl-2-methoxy-3,9-dimethyl-2,3-decahydronaphtho[1,2-*b*]furan (**7**) derived from (−)-α-santonin gave an unexpected product, (3*S*,3a*S*,6*R*,7*S*,7a*S*)-7-[(*S*)-2-formylethyl]-2-methoxy-3-methyloctahydrobenzofuran-6-spiro-3′-furan-5′-one (**13**), which served as the key intermediate for the synthesis of (+)-deoxyvernolepin (**2**) and related unsaturated lactones (**4**)—(**6**). Some unsaturated lactones obtained were submitted to a preliminary test for antitumour activity.

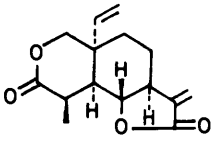
From the view point of biological activities, *inter alia*, antitumour activity, vernolepin (**1**) and vernomenin (**3**), sesquiterpene lactones isolated from *Vernonia hymenolepis*, have aroused much attention in the past decade.[1] Natural products bearing α-methylene lactone entities are frequently biologically active, and it is intriguing to know how the α-methylene-γ- and -δ-lactone structures in compounds (**1**) and (**3**) contribute to the activity.[2] Some total and formal syntheses of these natural bislactones and related compounds have been achieved in racemic forms,[3] while racemic deoxyvernolepin (±)-(**2**) is noteworthy in its strong antitumour activity against human lymphoblastic leukemia cells.[2b] This finding has also prompted synthetic studies towards optically active deoxyvernolepin (+)-(**2**) which has the same absolute configuration as natural (**1**) except for its C-8 position. Here we describe details of the synthesis of (+)-deoxyvernolepin starting with tetrahydrosantonin,[4] which also allowed us to prepare the related unsaturated lactones (**4**)—(**6**) for a study of structure-activity relationships.



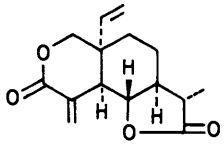
(**1**) X = OH
(**2**) X = H



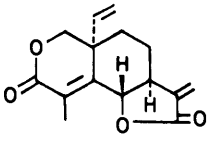
(**3**)



(**4**)



(**5**)

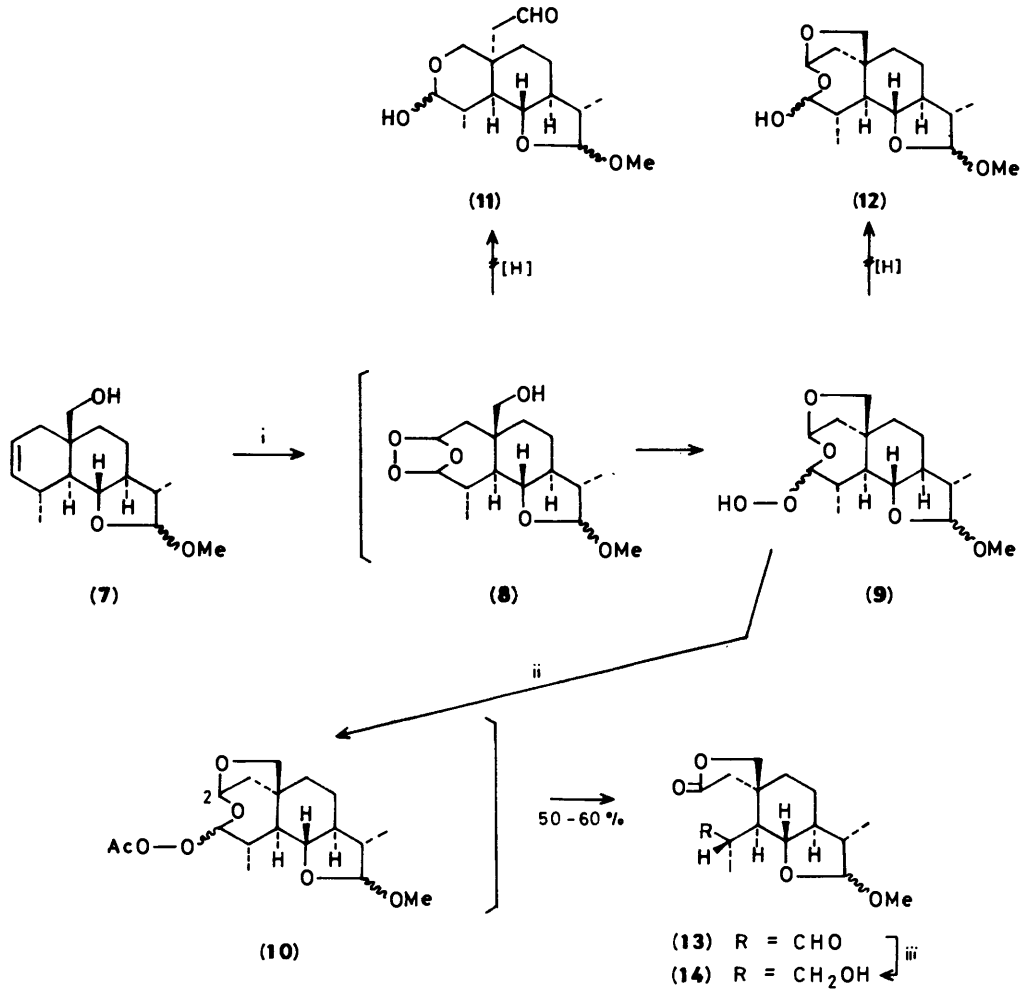


(**6**)

In the expectation that proximate group participation of the angular hydroxymethyl would give a product such as (**11**) or (**12**), the acetal[5] (**7**) derived from tetrahydrosantonin was submitted to ozonisation (Scheme 1). While oxidation of (**7**) with a slight excess of ozone in dichloromethane followed by reduction with dimethyl sulphide gave a complex mixture, treatment of the ozonisation solution with acetic anhydride and pyridine at room temperature unexpectedly provided the formyl-lactone (**13**) in moderate yield. The structure of (**13**) was supported by i.r. (2 700, 1 770, and 1 715 cm^{-1}) and ^1H n.m.r. (slightly broadened singlet at δ 9.65) spectral evidence. Since this product was unstable, it was immediately reduced with sodium borohydride to give the corresponding alcohol (**14**).

The formation of this unexpected product (**13**) could be rationalized as shown in Scheme 1. The molozonide ring in (**8**) is opened by attack of the angular hydroxymethyl group to give the tricyclic hydroperoxide (**9**) as expected, which was then acetylated to afford acetyl peroxide (**10**). The abstraction of its acidic hydrogen at C-2 with pyridine caused fragmentation to yield compound (**13**). Recently Schreiber *et al.* have also observed a similar *intermolecular* reaction of molozonides with alcohols and subsequent fragmentation of the resulting alkoxy hydroperoxide with acetic anhydride–triethylamine.[6]

Since the constitution of compound (**14**) seemed to be suitable for elaboration to the target molecules, the following reaction sequence was performed: after tetrahydropyranylation of compound (**14**), the product was reduced with lithium aluminium hydride and acetylated with acetic anhydride and pyridine. The tetrahydropyranyloxy group in the product was then hydrolysed with pyridinium toluene-*p*-sulphonate[7] in methanol to give (**15**). The primary hydroxy group in (**15**) was oxidised with Jones reagent to give a carboxylic acid, which was then treated with alkali to hydrolyse the acetyl protective groups. The acidic product obtained provided the lactone (**16**) on acidic work-up. To convert the hydroxyethyl group in (**16**) to



Scheme 1. *Reagents:* i, O_3; ii, Ac_2O, Py; iii, $NaBH_4$

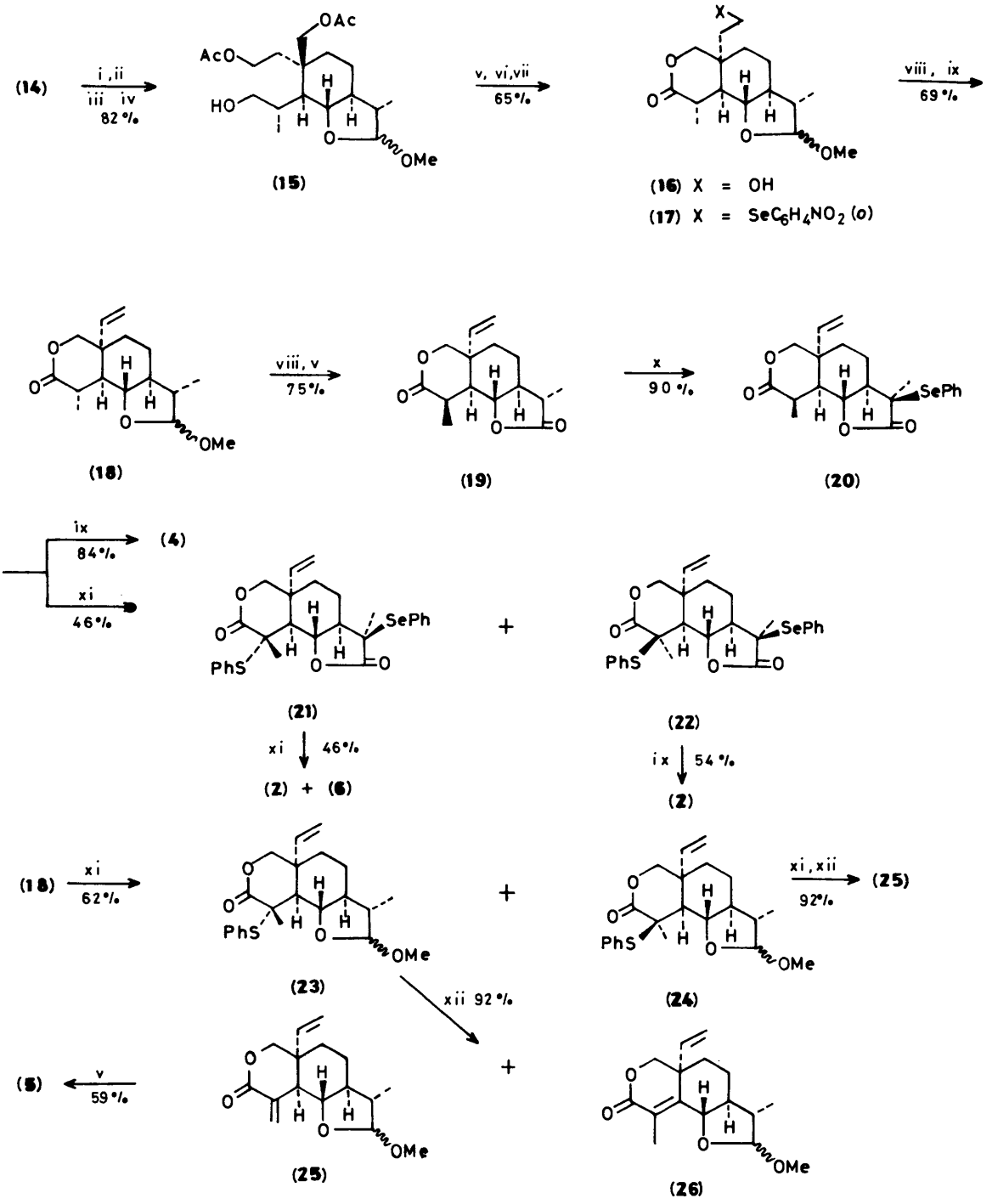
a vinyl group, Grieco's procedure[8] was applied to it. Thus it was treated with *o*-nitrophenylselenenyl cyanide and tributylphosphine to give (**17**), which was then oxidised with hydrogen peroxide to yield the vinyl compound (**18**).

Assuming the stereochemical integrity of the α-orientated secondary methyl on ring A of (**7**) throughout the sequence described above, this methyl group should have an axial configuration in (**18**). To confirm this assumption, (**18**) was treated with potassium t-butoxide in t-butyl alcohol at 35 °C for several hours. A new compound was observed on t.l.c., although inseparable on a preparative scale. ^{1}H N.m.r. spectroscopy indicated the product to be a mixture of a new compound and the substrate (**18**) (ratio *ca.* 1:1); the major difference in spectral characteristics of these two compounds was the coupling patterns of the grouping CH_2O, *i.e.* an AB quartet and a singlet for the substrate and the new compound respectively. This result showed partial epimerisation of the secondary methyl group in (**18**) on base treatment and hence demonstrated the stereochemical integrity of the axial methyl group throughout the transformation.

Since, contrary to our expectation, the direct oxidation of compound (**18**) with Jones reagent resulted in a low yield of the desired lactone (**19**), the former compound was submitted to acid hydrolysis with hydrochloric acid in refluxing tetrahydrofuran, the hydrolysis proceeding slowly at room temperature. The resulting hemiacetal was oxidised by Jones reagent to yield (**19**) in an acceptable yield. We checked here again the stereochemistry of the secondary methyl group on the δ-lactone ring in (**19**) by lithium di-isopropylamide enolisation-protonation, and unchanged (**19**) was recovered. Taking into account of kinetic protonation from the convex face, this result seemed to indicate that the methyl inverted to β-equatorial during the above acid hydrolysis/Jones oxidation step of compound (**18**).

Fortunately, the selenenylation of compound (**19**) with diphenyl diselenide selectively provided the monoselenylated product (**20**), and successive oxidative elimination of the phenylselenenyl group in the product with hydrogen peroxide gave (**4**) as the sole product, and this result also allowed us to depict the stereochemistry of the phenylselenenyl group in (**20**). Sulphenylation of (**20**) with diphenyl disulphide gave a diastereoisomeric mixture of (**21**) and (**22**). The major compound (**21**) was oxidised with hydrogen peroxide at room temperature to give (+)-deoxyvernolepin (**2**),[8] as identified by spectral comparison with authentic material, and its regioisomer (**6**) in a ratio of 1:3. On the other hand, the minor compound (**22**) yielded only (**2**) on hydrogen peroxide oxidation. It is noteworthy that the oxidative elimination of the phenylsulphenyl groups in (**21**) and (**22**) proceeded at an unusually low temperature. These results of the elimination reaction allowed us to assign the stereochemistry of the sulphenylation products (**21**) and (**22**) as depicted.

The acetal (**18**) was phenylsulphenylated with diphenyl disulphide to provide a mixture of compounds (**23**) and (**24**) in a ratio of 73:26. Both compounds were submitted to peracid



Scheme 2. *Reagents:* i, dihydropyran; ii, $LiAlH_4$; iii, Ac_2O, Py; iv, pyridinium toluene-*p*-sulphonate; v, Jones reagent; vi, 0.5M aq. NaOH; vii, 6M aq. HCl; viii, *o*-$O_2NC_6H_4SeCN$, Bu_3P; ix, 30% H_2O_2; x, Pr^i_2NLi, Ph_2Se_2; xi, Pr^i_2NLi, Ph_2S_2; xii, *m*-$ClC_6H_4CO_3H$

oxidation to give a mixture of (**25**) and (**26**), and only (**25**) respectively. The isomer (**25**) was then transformed to the lactone (**5**) by Jones oxidation. We thus secured, in optically active forms, a set of unsaturated lactones (**2**), (**4**), (**5**), and (**6**) possessing the deoxyvernolepin framework.

With these compounds in hand, the lactones (**2**), (**4**), and (**5**) were submitted to the preliminary *in vivo* bioassay against mouse leukemia cells (P-388) using mice (CDF_1). As seen in the Table, (+)-deoxyvernolepin (**2**) was proven to be somewhat more potent against this leukemia than the other two lactones, and the result seemed to indicate that both unsaturated γ- and δ-lactone units in (**2**) contribute to the observed antitumour activity.

Experimental

General.—M.p.s were determined with a Yamato melting point apparatus and are uncorrected. ^1H N.m.r. spectra were recorded on a JEOL Model-60 (60 MHz) or PS-100 (100 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard; † indicates that δ values are at 100 MHz. Coupling constants (*J*) are given in Hz. I.r. spectra were

Table. Preliminary *in vivo* test of the antitumour activity of some unsaturated lactones against mouse leukemia cells (P-388)

Compound[a]	Survival ratio (%)[b]
(**2**)	121
(**4**)	114
(**5**)	114

[a] The test compound (30 mg/kg) was given to a mouse (CDF_1) by injecting its aqueous suspension with 0.1% Tween-80. [b] A ratio of median survival days of mice treated with a test compound to those of untreated mice.

recorded on a JASCO A-3 spectrometer and absorption maxima are shown in frequency (cm^{-1}). Exact masses were obtained on a JMS-OISC-G2 mass spectrometer. Optical rotations were measured on a JASCO DIP-181 polarimeter in acetone at 18 °C. Anhydrous magnesium sulphate was used for drying extracts. Kieselgel 60 Art. 7734 and Art. 7730 were used for column chromatography and preparative thin-layer chromatography (t.l.c.), respectively. Solvents for elution were shown in parentheses. Microanalyses were performed in the Microanalytical Laboratory of this institute.

(3S,3aS,6R,7S,7aS)-7-[(S)-2-*Hydroxymethylethyl*]-2-*methoxy*-3-*methyloctahydrobenzofuran*-6-*spiro*-3′-*furan*-5′-*one* (**14**).—The unsaturated lactone[5] (**7**) (5.00 g, 18.8 mmol) was divided into four equal portions, and each portion was dissolved in dichloromethane (80 ml). Ozone was bubbled through each solution at −78 °C until it turned slightly blue, when it was then quickly warmed to room temperature. After being passed through a short pad of anhydrous magnesium sulphate, acetic anhydride (2.5 ml) and pyridine (5 ml) were added. Four runs were combined and stirred at room temperature overnight. The mixture was concentrated under reduced pressure, and ether (125 ml) was added to the residue. The ethereal solution was washed with water, aqueous cupric sulphate and water, and dried. Evaporation gave oily compound (**13**), a pure sample of which was obtained by preparative t.l.c. (dichloromethane–ethyl acetate, 10:1); $\nu_{max.}$(liquid film) 1 770 and 1 715; δ 9.65 (slightly br s, 1 H) and 3.20 (s, 3 H). Crude compound (**13**) obtained above was dissolved in methanol (25 ml), and sodium borohydride was added portionwise until (**13**) was no longer detected on t.l.c. After dilution with water, the mixture was extracted with ether, and the extract was washed with water and brine, and dried. An oil obtained by evaporation was purified by column chromatography (dichloromethane–ethyl acetate, 10:1) to afford the *lactone* (**14**) (3.06—3.56 g, 55—64%); $\nu_{max.}$(film) 3 450 and 1 780; δ 2.26 and 2.60 (ABq, 1 H, *J* 18 each), 3.40 (s, 3 H), 3.97 and 4.33 (ABq, 1 H, *J* 9 each), and 4.61 (d, 1 H, *J* 9) (Found: C, 64.25; H, 8.95. $C_{16}H_{26}O_5$ requires C, 64.40; H, 8.78%).

(3S,3aS,6R,7S,7aR)-6-(2-*Acetoxyethyl*)-6-*acetoxymethyl*-7-[(S)-2-*hydroxymethylethyl*]-2-*methoxy*-3-*methyloctahydrobenzofuran* (**15**).—After a solution of (**14**) (515 mg, 1.72 mmol), dihydropyran (200 mg, 2.37 mmol), pyridinium toluene-*p*-sulphonate[7] (100 mg, 0.39 mmol) in dichloromethane (20 ml) had been stirred at room temperature overnight, brine was added, and the mixture was further stirred for an additional 30 min. The organic layer was dried and evaporated to give an oil (700 mg). Lithium aluminium hydride (150 mg) suspended in ether (50 ml) was added to a solution of the oil in ether (50 ml), and the mixture was refluxed for 1 h. Wet ether was then added to the solution in an ice–water bath to decompose the excess of reagent. Drying followed by evaporation of the ethereal layer afforded an oil, to which pyridine (10 ml) and acetic anhydride (2 ml) were added. The mixture was stirred at 50 °C overnight. The resulting solution was poured into ice–water and stirred for 1 h. The product was extracted with ether, and the ethereal layer was washed with water, aqueous cupric sulphate, water, and brine, and then dried. Removal of the ether gave an oil (786 mg).

A solution of the oil and pyridinium toluene-*p*-sulphonate[7] (100 mg, 0.39 mmol) in methanol (20 ml) was refluxed for 2 h and diluted with water. The ethereal extract of the solution was washed with water and brine. After drying, the solvent was removed to give an oil, which was purified by t.l.c. (dichloromethane–ethyl acetate, 5:1) to give oily (**15**) [551 mg, 82% yield from (**14**)]; $\nu_{max.}$(film) 3 450 and 1 740; δ 2.07 (s, 3 H), 2.11 (s, 3 H), 3.40 (s, 3 H), 3.5—4.4 (m, 7 H), and 4.63 (d, 1 H, *J* 4) (Found: C, 61.8; H, 9.25. $C_{20}H_{34}O_7$ requires C, 62.15; H, 8.87%).

(3S,3aS,5aR,9S,9aS,9bS)-5a-(2-*Hydroxyethyl*)-2-*methoxy*-3,9-*dimethyldecahydrofuro*[2,3-f][2]*benzopyran*-8-*one* (**16**).—Jones reagent (7 ml) was added to a solution of compound (**15**) (650 mg, 1.68 mmol) in acetone (10 ml), and the mixture was stirred at room temperature for 40 min. After dilution with water, the mixture was extracted with ether; the latter was then extracted with 5% aqueous potassium carbonate. The aqueous layer was acidified with dilute hydrochloric acid whilst being cooled with ice–water and the acidic product was extracted with ether. The ethereal layer was washed with water and brine, dried, and evaporated to give an oil (590 mg). This was dissolved in a mixture of 0.5M aqueous sodium hydroxide (5 ml) and methanol (10 ml) and the mixture stirred at room temperature overnight. After dilution with water, the reaction mixture was acidified with dilute hydrochloric acid whilst being cooled with ice–water and extracted with ether. The ethereal layer was washed with water and brine, dried, and evaporated to give the title compound (**16**) as an *oil* (327 mg, 65%); $\nu_{max.}$($CHCl_3$) 3 450 and 1 715; δ 1.15 (d, 3 H, *J* 6), 1.39 (d, 3 H, *J* 6), 3.36 (s, 3 H), 3.5—4.5 (m, 5 H), and 4.63 (d, 1 H, *J* 4) (Found: C, 64.1; H, 9.2. $C_{16}H_{26}O_5$ requires C, 64.40; H, 8.78%).

(3S,3aS,5aR,9S,9aS,9bS)-2-*Methoxy*-3,9-*dimethyl*-5a-[2-(o-*nitrophenylseleno*)*ethyl*]*decahydrofuro*[2,3-f][2]*benzopyran*-8-*one* (**17**).—Tributylphosphine (505 mg, 2.5 mmol) in tetrahydrofuran (5 ml) was added to a solution of compound (**16**) (380 mg, 1.27 mmol) and *o*-nitrobenzeneselenenyl cyanide (350 mg, 1.54 mmol) in tetrahydrofuran (15 ml), and the solution was stirred at room temperature for 3 h. Evaporation of the resulting solution under reduced pressure gave a brownish yellow solid. The solid was passed through a short silica gel column with the aid of dichloromethane to give a yellow solid, which was purified by preparative t.l.c. (dichloromethane) to give the title compound as a *powder* (**17**) (450 mg, 73%), m.p. 168—169 °C (from cyclohexane–ethyl acetate); $\nu_{max.}$(KBr) 1 725; δ 1.10 (d, 3 H, *J* 7), 1.25 (d, 3 H, *J* 7) 3.39 (s, 3 H), 3.5—4.5 (m, 3 H), 4.63 (d, 1 H, *J* 4), and 7—8 (m, 4 H) (Found: C, 55.05; H, 6.05, N, 2.9. $C_{22}H_{29}NO_6Se$ requires C, 54.77; 6.02; N, 2.90%).

(3S,3aS,5aR,9S,9aS,9bS)-2-*Methoxy*-3,9-*dimethyl*-5a-*vinyldecahydrofuro*[2,3-f][2]*benzopyran*-8-*one* (**18**).—Hydrogen peroxide (30%; 1 ml) was added to a solution of compound (**17**) (217 mg, 0.45 mmol) in tetrahydrofuran (8 ml) at 0 °C, and the mixture was stirred at room temperature overnight. After dilution with water, the mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried, and evaporated to give an oil. This was purified by column chromatography (dichloromethane) to afford the title compound (**18**) as an *oil* (85 mg, 94%); $\nu_{max.}$($CHCl_3$) 1 718; δ† 1.14 (d, 3 H, *J* 7), 1.40 (d, 3 H, *J* 7), 2.72 (m, 1 H), 3.40 (s, 3 H), 3.72 (t, 1 H, *J* 10), 4.14 and 4.44 (ABq, 1 H, *J* 12 each), 4.68 (d, 1

H, *J* 4), and 5.0—6.0 (ABXm, 3 H) (Found: C, 68.4; H, 8.6. $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%).

Base Treatment of Compound (**18**).—A mixture of compound (**18**) (150 mg, 0.53 mmol) and potassium t-butoxide (95 mg, 0.84 mmol) in t-butyl alcohol (5 ml) was stirred at 35 °C for 4 h. After dilution with water followed by acidification with dilute hydrochloric acid, the product was extracted with ether, and the ethereal layer was washed with water and brine, dried, and evaporated to give an oil (150 mg). This was shown by ^{1}H n.m.r. spectroscopy to be a mixture consisting of approximately equal amounts of unchanged compound (**18**) and the epimerisation product; δ 1.14, (d, 3 H, *J* 7), 1.40 (d, 3 H, *J* 7), 2.90 (m, 1 H), 3.38 (s, 3 H), 3.68 (t, 1 H, *J* 10), 4.28 (s, 2 H), 4.62 (d, 1 H, *J* 4), and 5.0—6.0 (ABXm, 3 H).

(3S,3aS,5aR,9R,9aS,9bS)-3,9-*Dimethyl*-5a-*vinyldecahydrofuro*[2,3-f][2]*benzopyran*-2,8-*dione* (**19**).—A solution of compound (**18**) (560 mg, 2.0 mmol) and 6M hydrochloric acid in acetone (15 ml) was refluxed for 3 h after which it was diluted with water and extracted with ether. The ethereal layer was washed with water and brine, dried, and evaporated to give an oil, which was separated by column chromatography (dichloromethane–ethyl acetate, 10:1) to afford the hydrolysis product (444 mg) and unchanged compound (**18**). Recovered compound (**18**) was recycled to give additional product (66 mg). Jones reagent (5 ml) was added to a solution of the product (510 mg, 1.9 mmol) in acetone (30 ml) at 0 °C and the mixture was stirred for 30 min at room temperature. It was then diluted with water and the oxidation product extracted with ether–dichloromethane (4:1). The organic layer was washed with water and brine, dried, and evaporated to provide an oil which was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 10:1) to give crystalline compound (**19**) (396 mg, 75%), m.p. 127—129 °C (from ether–dichloromethane); $\nu_{max.}$(KBr) 1 770 and 1 740; δ 1.24 (d, 3 H, *J* 7), 1.40 (d, 3 H, *J* 7), 2.32 (m, 1 H), 2.72 (m, 1 H), 4.02 (t, 1 H, *J* 10), 4.13 and 4.40 (ABq, 1 H, *J* 12 each), and 5.2 —5.9 (m, 3 H); $[\alpha]_D$ +47.7° (*c* 0.52) (Found: C, 67.95; H, 7.65. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%).

Base Treatment of Compound (**19**).—A solution of compound (**19**) (5 mg) and lithium di-isopropylamide (2.5 equiv.) in tetrahydrofuran (2 ml) was kept at −40 to −50 °C for 40 min after which it was acidified with dilute hydrochloric acid with ice–water cooling. The mixture was extracted with ether and the extract was washed with water and brine, dried, and evaporated to give recovery of compound (**19**).

(3R,3aS,5aR,9R,9aS,9bS)-3,9-*Dimethyl*-3-*phenylseleno*-5a-*vinyldecahydrofuro*[2,3-f][2]*benzopyran*-2,8-*dione* (**20**).—A solution of compound (**19**) (50 mg, 0.19 mmol) in a mixture of tetrahydrofuran (2 ml) and hexamethylphosphoric triamide (0.1 ml) was added, at −50 °C, to a solution of lithium di-isopropylamide which was prepared from a hexane solution of butyl-lithium (1.54M; 0.32 ml, 0.5 mmol) and di-isopropylamine (0.075 ml) in tetrahydrofuran (2.5 ml); the mixture was stirred at the same temperature for 40 min. A solution of diphenyl diselenide (80 mg, 0.25 mmol) in tetrahydrofuran (1.5 ml) was then added to the above enolate solution, and the mixture was further stirred at *ca.* −43 °C for 1 h. The mixture was then acidified with dilute hydrochloric acid and the product extracted with dichloromethane–ether (1:4). The extract was washed with water and brine, dried, and evaporated to give a solid, which was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 20:1) to give crystalline *compound* (**20**) (72 mg, 90%), m.p. 114—115 °C (from aqueous methanol); $\nu_{max.}$(KBr) 1 770 and 1 740; δ 1.35 (d, 3 H *J* 6), 1.52 (s, 3 H), 2.7 (m, 1 H), 3.9—4.5 (m, 3 H), 5.0—6.0 (m, 3 H), and 7.2—7.5 (m, 5 H) (Found: C, 60.3; H, 5.95. $C_{21}H_{24}O_4Se$ requires C, 60.14; H, 5.73%).

(3aS,5aR,9R,9aS,9bS)-9-*Methyl*-3-*methylene*-5a-*vinyldecahydrofuro*[2,3-f][2]*benzopyran*-2,8-*dione* (**4**).—Hydrogen peroxide (30%; 1.5 ml) was added to a solution of compound (**20**) (148 mg, 0.35 mmol) in tetrahydrofuran (7 ml) at 0 °C, and the mixture was stirred at room temperature overnight. After dilution with water, the reaction mixture was extracted with ether–dichloromethane (4:1). The extract was washed with water and brine, dried, and evaporated to give a solid, which was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 10:1) to afford crystalline compound (**4**) (78 mg, 84%), m.p. 173–174 °C (from aqueous methanol); ν_{max}(KBr) 1 770 and 1 730; δ 1.41 (d, 3 H, *J* 8), 2.1 (m, 1 H), 2.7 (m, 1 H), 3.98 (t, 1 H, *J* 11), 4.10 and 4.32 (ABq, 1 H, *J* 12 each), 5.46 (d, 1 H, *J* 3), 5.2–6.0 (m, 3 H), and 6.14 (d, 1 H, *J* 3); $[\alpha]_D$ + 50.5° (*c* 0.37) (Found: C, 68.5; H, 6.95. $C_{15}H_{18}O_4$ requires C, 68.68, H, 6.92%).

(+)-*Deoxyvernolepin* (**2**).—A solution of compound (**20**) (80 mg, 0.19 mmol) in a mixture of tetrahydrofuran (2 ml) and hexamethylphosphoric triamide (0.2 ml) was added, at −78 °C, to a solution of lithium di-isopropylamide prepared from 1.54M butyl-lithium (0.32 ml, 0.49 mmol) and di-isopropylamine (0.075 ml) in tetrahydrofuran (2.5 ml), and the mixture was stirred at −50 °C for 40 min. A solution of diphenyl disulphide (130 mg, 0.59 mmol) in tetrahydrofuran (2 ml) was then added to the above enolate solution. Stirring was further continued, while the reaction temperature was allowed to rise up to 0 °C over 2 h. After acidification with dilute hydrochloric acid, the reaction mixture was extracted with dichloromethane–ether (1:4). The extract was washed with water and brine, dried, and evaporated to provide an oil which was purified by preparative t.l.c. (benzene–acetone, 20:1) to give compounds (**21**) (34 mg, 34%) and (**22**) (12 mg, 12%), and unchanged (**20**) (26 mg). Compound (**21**) δ 1.37 (s, 3 H), 1.50 (s, 3 H), 4.30 (t, 1 H, *J* 11), 5.6—6.2 (m, 3 H), and 7.2—7.7 (m, 10 H); compound (**22**) 1.42 (s, 3 H), 1.48 (s, 3 H), 5.2—6.2 (m, 3 H), and 7.2—7.7 (m, 10 H).

Hydrogen peroxide (30%; 0.3 ml) was added to a stirred solution of compound (**21**) (45 mg, 0.085 mmol) in tetrahydrofuran (2.5 ml) at 0 °C over 3 h, and the solution was stirred at room temperature for 2 h. After dilution with water, the product was extracted with ether–dichloromethane (4:1), and the extract was washed with water and brine, dried, and evaporated to give an oil. This was purified by preparative t.l.c. (benzene–acetone, 20:1) to afford compounds (**2**) (6 mg, 27%) and (**6**) (2 mg, 9%). The former was identified by comparison with the spectra of the authentic specimen: compound (**2**) m.p. 113—116 °C (from aqueous methanol); $\nu_{max.}$($CHCl_3$) 1 780 and 1 730; δ 3.94 (t, 1 H, *J* 12), 4.20 and 4.56 (ABq, 1 H, *J* 12 each), 5.16—5.80 (ABXm, 3 H), 5.48 (d, 1 H, *J* 3), 5.90 (d, 1 H, *J* 1), 6.14 (t, 1 H, *J* 3), and 6.70 (t, 1 H, *J* 1); $[\alpha]_D$ + 19.0° (*c* 0.32) (lit.,[9] $[\alpha]_D$ +37.5°) (*c* 0.33, $CHCl_3$) (Found: M^+, 260.1027. $C_{15}H_{16}O_4$ requires *M*, 260.1047). Compound (**6**) m.p. 200—201 °C (washed with cold aqueous methanol); $\nu_{max.}$(KBr) 1 780 and 1 710; δ 2.10 (d, 3 H, *J* 2), 4.00 (d, 2 H, *J* 4), 4.90 (dd, 1 H, *J* 12 and 2), 5.16—6.04 (m, 3 H), 5.46 (d, 1 H, *J* 4), and 6.18 (d, 1 H, *J* 4) (Found: *M*, 260.1037. $C_{15}H_{16}O_4$ requires *M*, 260.1047).

Oxidation of compound (**22**) (15 mg, 0.028 mmol) with 30% hydrogen peroxide under the similar conditions gave compound (**2**) (4 mg, 54%).

(3S,3aS,5aR,9aS,9bS)-3-*Methyl*-9-*methylene*-5a-*vinyldecahydrofuro*[2,3-f][2]*benzopyran*-2,8-*dione* (**5**).—A solution of compound (**18**) (70 mg, 0.25 mmol) in a mixture of tetrahydrofuran (2.5 ml) and hexamethylphosphoric triamide

(0.3 ml) was added, at −50 °C, to a solution of lithium di-isopropylamide prepared from 1.54M butyl-lithium (0.17 ml, 0.26 mmol), and di-isopropylamine (0.06 ml) in tetrahydrofuran (2 ml). The solution was stirred for 40 min after which diphenyl disulphide (96 mg, 0.44 mmol) in tetrahydrofuran (2 ml) was added. The solution was stirred while the reaction temperature was allowed to rise gradually to 0 °C over 1 h. After acidification with hydrochloric acid, the mixture was extracted with ether, and the extract was washed with water and brine, dried, and evaporated to afford a viscous oil. This was separated by preparative t.l.c. (methylene dichloride) to give compound (**23**) (44 mg, 45%); $\nu_{max.}(CHCl_3)$ 1 730; δ 1.57 (s, 3 H), 3.39 (s, 3 H), and 7.2—7.7 (m, 5 H) and (**24**) (17 mg, 17%); $\nu_{max.}(CHCl_3)$ 1 730; δ 1.10 (d, 3 H, *J* 6), 1.57 (s, 3 H), 3.47 (s, 3 H), and 7.2—7.6 (m, 5 H).

m-Chloroperbenzoic acid (80% assay; 23 mg, 0.1 mmol) in dichloromethane (2 ml) was added to a solution of compound (**23**) (44 mg, 0.1 mmol) in the same solvent (3 ml) at room temperature. After compound (**23**) had almost completely reacted (t.l.c. monitoring), the reaction mixture was directly separated by preparative t.l.c. (dichloromethane) to give compound (**25**) (14 mg, 44%); $\nu_{max.}(CHCl_3)$ 1 715; δ 3.32 (3 H, s), 5.88 (br s, 1 H), and 6.58 (br s, 1 H), and (**26**) (15 mg, 48%); $\nu_{max.}(CHCl_3)$ 1 705; δ 2.13 (d, 3 H, *J* 2) and 3.40 (s, 3 H).

A similar oxidation of compound (**24**) (17 mg, 0.04 mmol) with the peracid (9 mg, 0.04 mmol), followed by chromatographic separation gave compound (**25**) (11 mg, 92%) as the sole product.

An excess of Jones reagent was added to a solution of compound (**25**) (20 mg) in acetone (2 ml), and the mixture was stirred at room temperature for 20 h. After dilution with water, the mixture was extracted with ether, and the extract was washed with water and brine, dried, and evaporated to give an oil. This was purified by t.l.c. (dichloromethane–ethyl acetate, 10:1) to give compound (**5**) as an *oil* (11 mg, 59%); $\nu_{max.}(CHCl_3)$ 1 790 and 1 725; δ 1.27 (d, 3 H, *J* 7), 3.90 (t, 1 H, *J* 10), 4.21 and 4.56 (ABq, 1 H, *J* 12 each), 4.9—5.9 (m, 3 H), 5.83 (br s, 1 H), and 6.17 (br s, 1 H); $[\alpha]_D$ +57.2° (*c* 0.54) (Found: C, 69.85; H, 7.2. $C_{15}H_{18}O_4$ requires C, 68.63; H, 6.92%).

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