Synthesis of Some Tetrahydrosantonin Derivatives with Functionalised Angular Substituents Based on Remote Oxidation

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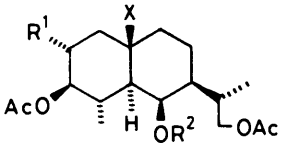
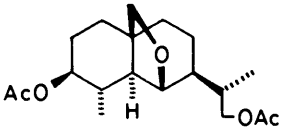
On treatment with lithium di-isopropylamide, the tosylhydrazone (**3b**) of tetrahydrosantonin (**3a**) provided the olefin (**4**) regioselectively, from which the bromohydrin (**5**) was obtained by the addition of hypobromous acid. Photochemical remote oxidation of (**5**) was executed in the presence of lead tetra-acetate and iodine to give the bromo dilactone (**8**) as the major product. Tetrahydrosantonin derivatives with functionalised angular substituents (**10**)—(**18**) were efficiently derived from (**8**).

Santonin and its hydro derivatives have been frequently employed as useful chiral starting materials for the synthesis of a variety of sesquiterpenoids.[1] Santonin derivatives carrying oxidised angular substituents are also important starting materials for the synthesis of natural products with such functional groups. In the synthesis of rishitin, for example, Masamune *et al.* have derived such an intermediate (**1a**) by the Barton reaction of the nitrite (**1b**),[2] and Takase *et al.* reported oxidation of the angular methyl group of the similar hydroxy derivative (**1c**) with lead tetra-acetate to afford (**2**).[3] As an alternative oxidation of the angular methyl groups of santonin derivatives, a substrate with its 2-axial hydroxy group was first employed by us.[4] In our approach the oxidation can be carried out without affecting the stereochemistry of the γ-lactone ring originally involved in santonin, an advantage over earlier procedures[2,3] where stereochemical inversion of the lactone moiety was necessary. Our strategy has also been employed by Tatsuno *et al.*, who obtained a tetrahydrofuran derivative by using mercuric oxide as the oxidant.[5]

Here we describe the detail of our own angular methyl oxidation of tetrahydrosantonin (**3a**) and some further transformations of functionality in the resulting lactone (**8**).



(**1**)



(**2**)

a; X = CH=NOH, R^1 = OAc, R^2 = H

b; X = Me, R^1 = OAc, R^2 = NO

c; X = Me, R^1 = R^2 = H

It is known that for remote oxidation of inactive carbons, the stereochemical disposition of groups participating in the oxidation is of crucial importance. In this context, we planned to introduce an axial hydroxy group into the hydrosantonin structure at an appropriate position without affecting the original stereochemistry of the γ-lactone ring by the addition reaction of hypobromous acid to a hydrosantonin derivative containing an olefinic bond at the Δ^2 position. The well-documented regio- and stereo-selective (di-axial) electrophilic addition of hypobromous acid to cholest-2-ene[6] allowed us to predict the predominant formation from the olefin (**4**) of the bromohydrin (**5**), which bears the axial hydroxy group at its C-2 position.

The tosylhydrazone (**3b**), obtained from tetrahydrosantonin (**3a**),[7] was therefore treated with lithium di-isopropylamide[8] in tetrahydrofuran to yield the olefin (**4**) regioselectively in good yield (Scheme 1). Treatment of (**4**) with *N*-bromosuccinimide in dimethyl sulphoxide containing a small amount of water[9] gave the bromohydrin (**5**) in excellent yield. To confirm the expected regioselectivity, compound (**5**) was oxidised with Jones reagent, and the resulting bromo ketone (**6**) was then dehydrobrominated with lithium carbonate in *N*,*N*-dimethylacetamide to give an enone the spectral data of which were consistent with the proposed structure (**7**).

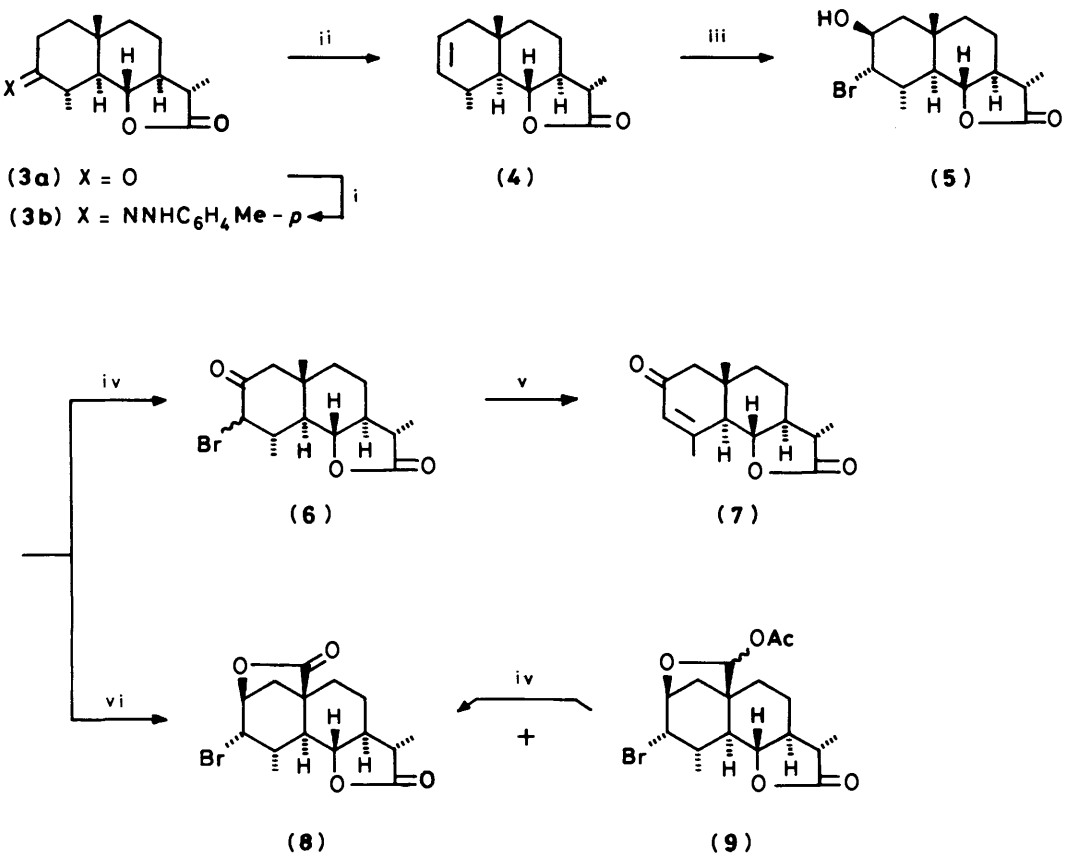
Irradiation of the bromohydrin (**5**) in refluxing cyclohexane in the presence of lead tetra-acetate and iodine with a tungsten lamp produced two products (88:12)† in good yield. The spectral and microanalytical data for the major product indicated that it was the bromo dilactone (**8**), while the ^{1}H n.m.r. spectrum of the minor product showed the presence of an acetoxy group in the molecule. Although additional chemical evidence for identification of the minor product as the hemiacetal acetate (**9**) was provided by its oxidation to the dilactone (**8**) we were unable to assign the configuration of the acetoxy group; the total yield of compound (**8**) was 71%. Since remote oxidation of alcohols generally gives cyclic ethers and/or hemiacetals as major products under similar conditions,[10] the predominant formation of the lactone ring is exceptional.

With the dilactone (**8**) in hand, we then studied some structural modifications of this product to derive chiral intermediate such as (**13**), (**16**), (**18**), which had potential for natural product synthesis.

Reductive cleavage of compound (**8**) to give the unsaturated acid (**10a**) was achieved either with zinc in acetic acid or with zinc–silver couple and ethanol; the latter gave the unsaturated ester (**10b**) with diazomethane. Oxidation of compound (**10a**) with peracid provided the hydroxy lactone (**11**), which was immediately oxidised with Jones reagent to afford the oxo lactone (**12**). The clean formation of (**11**) from (**10a**) implied the same stereoselectivity of the peracid oxidation as described for the addition of hypobromous acid to (**5**). Reductive lactone-ring cleavage of (**12**) was performed with chromium (II) chloride and the product was then esterified with diazomethane to afford the tetrahydrosantonin derivative (**13**) in 38—42% overall yield from (**8**). As described in the Experimental section, compound (**10b**) could be prepared in 40—50% overall yield from (**3a**) without purification of the intermediates.

Attempts at direct selective reduction of the angular substituents of (**10**), either by reduction of a mixed anhydride of (**10a**) and ethoxyformic acid with sodium borohydride[11] or of (**10b**) with sodium anilinoborohydride,[12] proved fruitless. In an indirect reduction method, compound (**10b**) was first reduced with an excess of di-isobutylaluminium hydride to give the

† When calcium carbonate was added as an acid scavenger, the ratio of (**8**) to (**9**) was changed to *ca.* 3:1.



Scheme 1. *Reagents:* i, *p*-$MeC_6H_4SO_2NHNH_2$, MeOH; ii. Pr^i_2NLi, THF; iii, *N*-bromosuccinimide, *aq.* Me_2SO; iv, Jones reagent; v, Li_2CO_3, DMA; vi, $Pb(OAc)_4$, I_2, *hv*, cyclohexane

lactol (**14a**) and this was then oxidised with Jones reagent to yield the formyl lactone (**15**). The latter was also obtained by reduction of the minor photo-oxidation product (**9**) with zinc–acetic acid in good yield. Reduction of compound (**15**) with sodium borohydride followed by acetylation of the product provided compound (**16**) in 50—55% overall yield from (**8**).

In a similar way to the epoxidation of (**10a**), compound (**14b**), which was obtained on methylation of (**14a**) with methyl orthoformate together with the formate (**14c**) in varied ratios depending on reaction conditions, yielded the tetrahydrofuran derivative (**17a**) with peracid. To derive the oxo lactone (**18**) from (**17a**) directly, the latter compound was submitted to Jones oxidation, but formation of the desired compound (**18**) resulted only in a low yield of product, probably because for complete hydrolysis of the acetal group long exposure to the acidic reagent was necessary. In contrast, brief treatment of compound (**17a**) with the same oxidant provided (**17b**) quantitatively. The product so obtained was then hydrolysed with aqueous sulphuric acid and this was followed by oxidation with Jones reagent in the same flask. By this procedure, the oxo lactone (**18**) was obtained from (**14b**) in 36—41% overall yield from compound (**8**). Compound (**18**) has also been synthesised from tetrahydrosantonin (**3a**) by an alternative procedure.[5]

The hydrosantonin derivatives described here have potential as starting materials for the chiral synthesis of natural products, and indeed compound (**16**) has been employed by us for the synthesis of optically active deoxyvernolepin.[13]

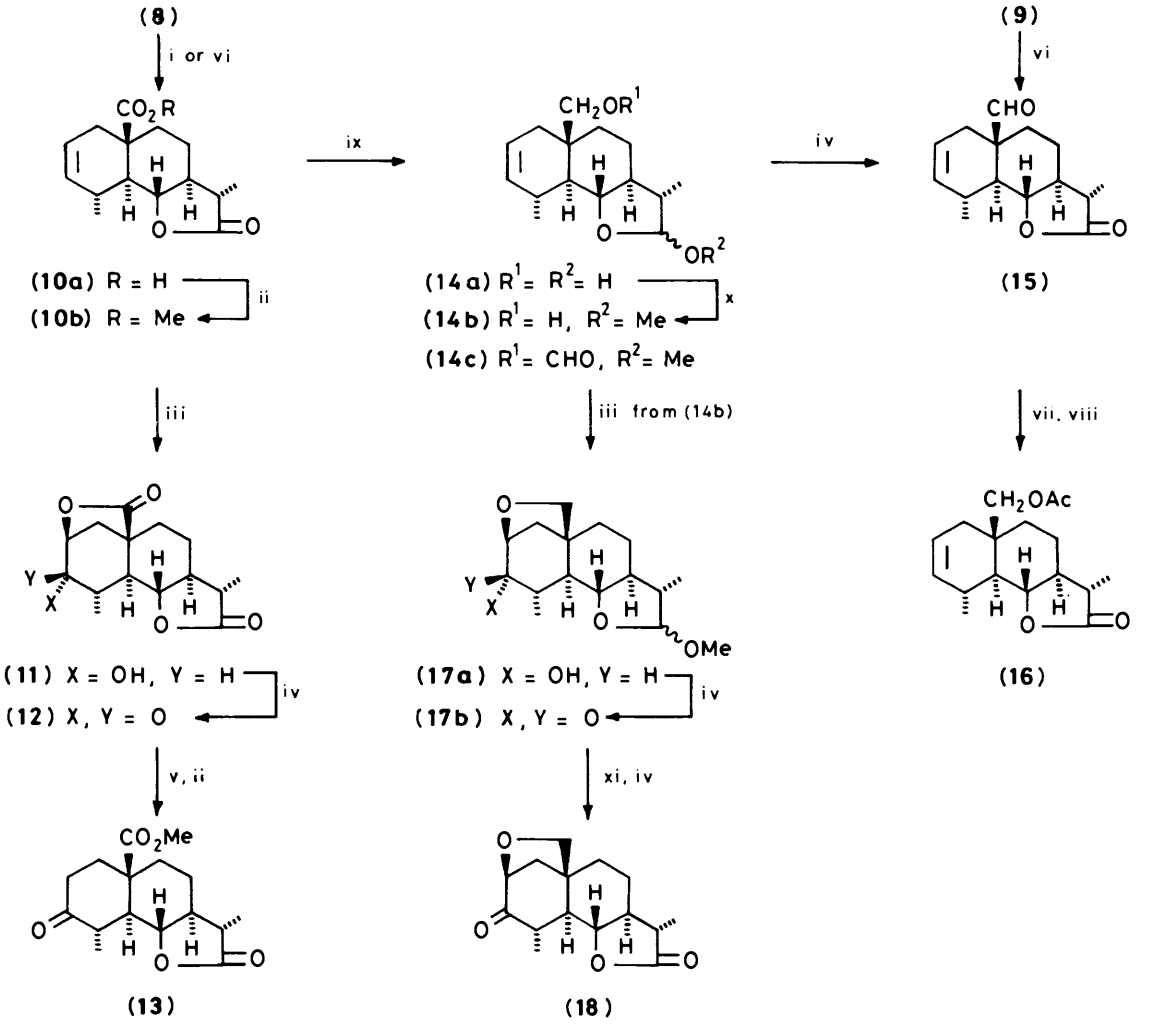
Experimental

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 C-60HL (60 MHz) or PS-100 (100 MHz)* spectrometer in deuteriochloroform with tetramethylsilane as internal standard. Chemical shift values and coupling constants (*J*) are given in δ and Hz, respectively. I.r. spectra were recorded on a Hitachi EPI-S2 or JASCO A-3 spectrophotometer and absorption maxima are shown in frequency (cm^{-1}). Specific rotation was measured with a JASCO DIP-181 polarimeter in acetone. Anhydrous magnesium sulphate was used for drying extracts. Silica gel (Kieselgel 60 Art 7734) was used for column chromatography and Kieselgel GF_{254} was employed for thin-layer chromatography (t.l.c.). Solvents for elution were shown in parentheses.

(3S,3aS,5aS,9R,9aS,9bS)-3,5a,9-*Trimethyl*-3a,4,5,5a,6,9,9a,9b-*octahydronaphtho*[1,2-b]*furan*-2(3H)-*one* (**4**).—A mixture of tetrahydrosantonin[7] (20 g, 80 mmol), tosylhydrazide (16 g, 86 mmol), and methanol (100 ml) was refluxed gently for 20 min and then kept at room temperature overnight. Precipitated crystals were filtered off, washed with a small amount of cold methanol, and dried *in vacuo* to give (**3b**) (33.11 g, 99%), m.p. 179—182 °C (decomp.), $\nu_{max.}$(KBr) 1 765; δ 0.99 (s, 3 H), 1.20 (d, 3 H, *J* 7), 1.23 (d, 3 H, *J* 7), 3.70 (t, 1 H, *J* 9), and 7.30 and 7.82 (ABq, 2 H, *J* 8 each) (Found: C, 63.2; H, 7.35; N, 6.9; S, 7.9. $C_{22}H_{30}N_2O_4S$ requires C, 63.15; H, 7.18; N, 6.70; S, 7.66%).

Finely powdered compound (**3b**) obtained above was added to a stirred solution of lithium di-isopropylamide, prepared from di-isopropylamine (55.5 ml, 396 mmol) and butyl-lithium (1.54M in hexane; 234 ml, 360 mmol) in tetrahydrofuran (THF).

* Data taken at 100 MHz are asterisked in the Experimental section.



Scheme 2. *Reagents:* i, Zn–Ag, EtOH; ii, CH_2N_2; iii, *m*-$ClC_6H_4CO_3H$, $CHCl_3$; iv, Jones reagent; v, $CrCl_2$, acetone; vi, Zn, HOAc; vii, $NaBH_4$, MeOH; viii, Ac_2O, Py; ix, Bu^i_2AlH, toluene; x, $CH(OMe)_3$, *p*-TsOH; xi, *aq.* H_2SO_4

After 2 h at −78 °C, the mixture was gradually warmed to *ca.* −15 °C, and further kept at the same temperature for 3 h. After being set aside at room temperature overnight, the mixture was carefully acidified with dilute hydrochloric acid, and then extracted with ether. The ethereal layer was washed with aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated. The crude product was purified by column chromatography (dichloromethane) to give the *title compound* (**4**) (14.46 g, 78%), m.p. 145.5—146.5 °C (from ether), $[\alpha]_D^{18}$ −5.5° (*c* 0.53), $\nu_{max.}$(KBr) 1 768 and 1 655; δ 1.20 (d, 3 H, *J* 6), 1.22 (d, 3 H, *J* 6), 3.80 (t, 1 H, *J* 10), and 5.48 (s, 2 H) (Found: C, 76.75; H, 9.25. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

(3S,3aS,5aS,7S,8S,9S,9aS,9bS)-8-*Bromo*-7-*hydroxy*-3,5a,9-*trimethyl*-3a,4,5,5a,6,7,8,9,9a,9b-*decahydronaphtho*[1,2-b]-*furan*-2(3H)-*one* (**5**).—To a stirred mixture of compound (**4**) (117 mg, 0.5 mmol), water (3 ml), and dimethyl sulphoxide (25 ml), *N*-bromosuccinimide (180 mg, 1.0 mmol) was added at once, and the mixture was stirred for 30 min, while the temperature was kept at *ca.* 18 °C with cooling. The mixture was poured onto water and extracted with ether, and the extract was washed with water and brine and dried. Removal of ether from the extract gave the title compound (**5**) (165 mg, 99%), m.p. 118—120 °C (from benzene–cyclohexane), $[\alpha]_D^{18}$ +7.5° (*c*, 0.65), $\nu_{max.}$(KBr) 3 450 and 1 750; δ 1.25 (s, 3 H), 1.17 (d, 6 H, *J* 3), 3.90 (m, 1 H), and 4.22 (m, 2 H) (Found: C, 54.3; H, 7.1; Br, 23.75. $C_{15}H_{23}BrO_3$ requires C, 54.40; H, 6.99; Br, 24.15%).

In experiments with larger amounts (*ca.* 15 g) of compound (**4**), the reaction mixture was poured onto ice–water, and then set aside in a cold room overnight. The precipitate was then filtered off, washed with cold water, and dried (90—95%). Extraction of the aqueous layer with a mixture of ether and dichloromethane gave an additional compound (**5**) (5—10%). The product was sufficiently pure for the next reaction.

(3S,3aS,5aR,7S,8S,9S,9aS,9bS)-8-*Bromo*-3,9-*dimethyl*-2-*oxo*-2,3,3a,4,5,5a,6,7,8,9,9a,9b-*dodecahydronaphtho*[1,2-b]*furan*-5a,7-*carbolactone* (**8**) *and* (1R,4S,5S,8S,9S,10S,11S,12S)-14ξ-*Acetoxy*-11-*bromo*-5,10-*dimethyl*-7,13-*dioxa*-1,4,8,9,12-*tetracyclo*[10.2.1.$0^{1,9}$.$0^{4,8}$]*pentadecan*-6-*one* (**9**) [*Photo-oxidation of the Bromohydrin* (**5**)].—Iodine (250 mg, 0.98 mmol) was added to a vigorously stirred and gently refluxing solution of compound (**5**) (130 mg, 0.39 mmol) and lead tetra-acetate (1 g, 2.25 mmol) in cyclohexane (10 ml). The solution was irradiated with a 200 W tungsten lamp for 1 h under gentle reflux. After dilution with water, the reaction mixture was extracted with ethyl acetate, and the extract was washed with aqueous sodium thiosulphate, water, and brine, and dried. Evaporation of the solvent gave a solid, which was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 100:3) to afford the carbo-

lactone (**8**) (87 mg, 65%), m.p. 193—194 °C (from benzene–cyclohexane), $[\alpha]_D^{18}$ −49.6° (*c* 0.53), $\nu_{max.}$ 1 780; δ* 1.22 (d, 3 H, *J* 4), 1.28 (d, 3 H, *J* 4), 3.82 (t, 1 H, *J* 10), 4.20 (t, 1 H, *J* 4), and 4.57 (t, 1 H, *J* 4) as the major product (Found: C, 52.4; H, 5.8; Br, 23.05. $C_{15}H_{19}O_4Br$ requires C, 52.49; H, 5.54; Br, 23.30%). From a less polar fraction the acetate (**9**) (14 mg, 9%), m.p. 159—162 °C (from benzene–cyclohexane), $[\alpha]_D^{18}$ +35.0° (*c* 0.40), $\nu_{max.}$ 1 780 and 1 730; δ 1.26 (d, 3 H, *J* 6), 1.32 (d, 3 H, *J* 9), 3.83 (t, 1 H, *J* 10), 4.38 (t, 1 H, *J* 4), 4.83 (t, 1 H, *J* 4), and 6.16 (s, 1 H), was isolated. (Found: C, 52.80; H, 6.12; Br, 21.13. $C_{17}H_{23}BrO_5$ requires C, 52.73; H, 5.94; Br, 20.65%).

Oxidation of the Acetate (**9**) *to the Carbolactone* (**8**).—An excess of Jones reagent (0.5 ml, 0.35 mmol) was added to a stirred solution of compound (**9**) (100 mg, 0.26 mmol) in acetone (7 ml) and the mixture was further stirred at room temperature for 40 min. After dilution with water, the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried, and evaporated and the residue was purified by column chromatography (dichloromethane–ethyl acetate, 100:3) to give compound (**8**) (56 mg, 63%).

(3S,3aS,5aR,9R,9aS,9bS)-5a-*Methoxycarbonyl*-3,9-*dimethyl*-3a,4,5,5a,6,9,9a,9b-*octahydronaphtho*[1,2-b]*furan*-2(3H)-*one* (**10b**).—For reductive cleavage of compound (**8**), two methods were examined.

Method (a). A suspension of zinc–silver couple (8.5 g) in a mixture of compound (**8**) (1.0 g, 2.9 mmol) and ethanol (20 ml) in ether (100 ml) was stirred at room temperature for several days. The mixture was filtered, and the filtrate was diluted with water and extracted with ether. The ethereal layer were extracted with aqueous potassium carbonate. The alkaline extract was acidified with 6M hydrochloric acid with ice–water cooling, and the acid liberated was extracted with ether. The organic layer was washed with water and brine, dried and evaporated to give compound (**10a**) (590 mg, 76%) as a semisolid; this upon treatment with diazomethane in ether afforded (**10b**) quantitatively, m.p. 124—126 °C (from benzene–cyclohexane), $[\alpha]_D^{18}$ −17.8° (*c* 1.52), $\nu_{max.}$ 1 770 and 1 720; δ 1.13 (d, 3 H, *J* 3), 1.26 (d, 3 H, *J* 3), 4.63 (t, 1 H, *J* 10), and 5.50 (m, 2 H) (Found: C, 69.25; H, 8.25. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97%).

This procedure was inadequate for the large-scale preparation of (**10a**) because of fluctuating yields, probably a result of the varying activity of the zinc–silver couple used.

Method (b). A mixture of compound (**8**) (1.2 g, 3.50 mmol), zinc powder (4 g), and acetic acid (50 ml) was stirred at 70 °C for 3 days and then filtered. After concentration of the filtrate under reduced pressure, the oil obtained was dissolved in ether and extracted with aqueous sodium hydrogen carbonate. The extract was acidified with 6M hydrochloric acid with ice–water cooling, and the solution was then extracted with ether. The organic layer was washed with water and brine, dried, and evaporated to leave slightly impure compound (**10a**) (655 mg) as an oil. The ethereal extract gave recovered compound (**3a**), which afforded additional (**10a**) (147 mg) by the same reduction procedure (combined yield, 83%).

In experiments for the preparation of compound (**10b**) starting with a 20 g scale of (**3a**), each step was monitored with t.l.c. for almost complete consumption of the substrate used; the crude reaction product obtained upon work-up was used for the next reaction without purification. In this successive procedure, a mixture of the photo-oxidation products (**8**) and (**9**) was oxidised with several portions of Jones reagent (*ca.* 15—20 ml) and a longer oxidation time (4—5 days) was preferable. For reductive cleavage of compound (**8**), method (b) was more convenient and the crude acid, after esterification with diazomethane, could readily be purified by rough column chromatography. The overall yield of compound (**10b**) was 40—50% from (**3a**).

(3S,3aS,5aR,7S,9S,9aS,9bS)-3,9-*Dimethyl*-2,8-*dioxo*-2,3,3a,4,5,5a,6,7,8,9,9a,9b-*dodecahydronaphtho*[1,2-b]*furan*-5a,7-*carbolactone* (**12**).—A solution of compound (**10a**) (2.26 g, 8.6 mmol), obtained by method (b) and *m*-chloroperoxybenzoic acid (80% in purity; 2.3 g, 10.7 mmol) in chloroform (100 ml) was stirred at room temperature overnight. After removal of most of the solvent, the mixture was dissolved in ethyl acetate and washed with aqueous potassium carbonate, water, and brine, and dried. The crude solid obtained by evaporation was treated with an excess of Jones reagent (*ca.* 20 ml) in acetone (70 ml) at room temperature for 2 h. After removal of most of the solvent and dilution with water, the mixture was extracted with ethyl acetate. The extract was washed with aqueous potassium carbonate, water, and brine, dried, and evaporated to give compound (**12**) (1.45 g, 61%) as crystals, m.p. 223—224 °C (from benzene–cyclohexane), $[\alpha]_D^{25}$ +103.3° (*c* 0.67), $\nu_{max.}$(KBr) 1 778 and 1 720; δ 1.20 (d, 3 H, *J* 7), 1.30 (d, 3 H, *J* 7), 4.02 (t, 1 H, *J* 10), and 4.65 (d, 1 H, *J* 6) (Found: C, 64.25; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.73; H, 6.52%).

(3S,3aS,5aR,9S,9aS,9bS)-5a-*Methoxycarbonyl*-3,9,-*dimethyl*-3a,4,5,5a,6,7,9a,9b-*octahydronaphtho*[1,2-b]*furan*-2(3H),8(9H)-*dione* (**13**).—A mixture of compound (**12**) (1.44 g, 5.2 mmol), acetone (100 ml), and a chromium(II) chloride solution [prepared from chromium(III) chloride (20 g), zinc (40 g), mercuric chloride (3.2 g), concentrated hydrochloric acid (2 ml), and water (40 ml)][14] was stirred overnight. After half the acetone had been evaporated, the solution was diluted with water and extracted with aqueous potassium carbonate. The aqueous layer was acidified with 6M hydrochloric acid with ice–water cooling. The acid liberated was extracted with ethyl acetate, and the extract was washed with water and brine, dried, and evaporated to leave a semisolid, which was treated with diazomethane in ether to give the *title compound* (**13**) (1.25 g, 82%) as crystals, m.p. 127—129 °C (from benzene–cyclohexane), $[\alpha]_D^{25}$ +17.6° (*c* 0.93), $\nu_{max.}$(KBr) 1 770, 1 725, and 1 715; δ 1.15 (d, 3 H, *J* 3), 1.27 (d, 3 H, *J* 3), 3.73 (s, 3 H), and 4.55 (t, 1 H, *J* 10) (Found: C, 65.05; H, 7.85. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53%).

(3S,3aS,5aR,9R,9aS,9bS)-5a-*Formyl*-3,9-*dimethyl*-3a,4,5,5a,-6,9,9a,9b-*octahydronaphtho*[1,2-b]*furan*-2(3H)-*one* (**15**) *from Compound* (**9**).—Five portions of zinc powder (100 mg) were added to a stirred mixture of *compound* (**9**) (61 mg, 0.16 mmol), acetic acid (5 ml), and water (0.1 ml) at 50 °C over 2 h. The reaction mixture was stirred for an additional 1 h, and then passed through a Celite column with ether as eluant. The eluate was washed with water and brine, dried, and evaporated to give an oil, which was purified by preparative t.l.c. (ether–light petroleum, 1:1) to afford the *title compound* (**15**) (28 mg, 72%) as crystals, m.p. 128—130 °C (from ether–light petroleum), $[\alpha]_D^{25}$ −23.5° (*c* 0.51), $\nu_{max.}$(KBr) 1 770 and 1 725; δ* 1.24 (d, 3 H, *J* 7), 4.40 (t, 1 H, *J* 11), 5.60 (br s, 2 H), and 9.45 (d, 1 H, *J* 2) (Found: C, 72.8; H, 8.25. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

(3S,3aS,5aR,9R,9aS,9bS)-5a-*Acetoxymethyl*-3,9-*dimethyl*-3a,4,5,5a,6,9,9a,9b-*octahydronaphtho*[1,2-b]*furan*-2(3H)-*one* (**16**).—Sodium borohydride (30 mg, 0.8 mmol) was added to a solution of compound (**15**) (156 mg, 0.62 mmol) in methanol (10 ml), and the mixture was stirred at room temperature for 2 h. After dilution with water, the product was extracted with ether. The crude oil (147 mg) obtained by evaporation was dissolved in a mixture of acetic acid (0.5 ml) and pyridine (18 ml) and left at room temperature for 3 days. The mixture was then poured onto ice–water and extracted with ether. The extract was

washed with water, aqueous cupric sulphate, and water, and then evaporated to leave an oil. The oil was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 100:3) to afford the *title compound* (**16**) (143 mg, 77%) as crystals, m.p. 97—98.5 °C (from ether–light petroleum), $[\alpha]_D^{25}$ −29.8° (*c* 0.86), $\nu_{max.}$(KBr) 1 770 and 1 720; δ* 1.20 (d, 3 H, *J* 7), 1.21 (d, 3 H, *J* 7), 2.04 (s, 3 H), 4.07 and 4.27 (ABq, *J* 11 each), and 5.48 (br s, 2 H) (Found: C, 69.95; H, 8.55. $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%).

(3S,3aS,5aR,9R,9aS,9bS)-5a-*Hydroxymethyl*-2-*methoxy*-3,9-*dimethyl*-3a,4,5,5a,6,9,9a,9b-*octahydronaphtho*[1,2-b]*furan* (**14b**) *and Its Formate* (**14c**).—Di-isobutylaluminium hydride (0.25 g, 1.7 mmol) was added to a stirred solution of compound (**10b**) (140 mg, 0.53 mmol) in toluene (5 ml) at −78 °C. After being stirred for 2 h, the reaction was quenched with 6M hydrochloric acid, and the product was extracted with ether. The extract was washed with 6M hydrochloric acid several times, water, and brine, dried, and evaporated. This afforded a crude oil which was passed through a short silica gel pad with dichloromethane as eluant to give an oil (147 mg). A mixture of (**14a**) (72 mg), trimethyl orthoformate (0.1 ml), a catalytic amount of toluene-*p*-sulphonic acid and dichloromethane (5 ml) was stirred at 0 °C for 2 h. After addition of aqueous sodium hydrogen carbonate, the product was extracted with ether. The extract was washed with water and brine, dried, and evaporated to give an oil, which was purified by preparative t.l.c. to afford oily (**14b**) (37 mg, 44%) and (**14c**) (30 mg, 40%): (**14b**) $\nu_{max.}$(liquid film) 3 440; δ 1.10 (d, 3 H, *J* 6), 1.20 (d, 3 H, *J* 6), 3.40 (s, 3 H), 3.60 (br s, 2 H), 4.63 (d, 1 H, *J* 4), and 5.52 (m, 2 H) (Found: C, 72.3; H, 10.05. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%); (**14c**) $\nu_{max.}$ (liquid film) 1 720; δ 1.12 (d, 3 H, *J* 7), 1.22 (d, 3 H, *J* 6), 3.38 (s, 3 H), 4.23 (br s, 2 H), 4.63 (d, 1 H, *J* 4), and 5.50 (br s, 2 H) (Found: C, 73.15; H, 8.95. $C_{17}H_{26}O_4$ requires C, 73.34; H, 9.39%).

The Acetate (**16**) *from the Ketone* (**10b**).—The lactol (**14a**) (1.49 g, 5.9 mmol), obtained from (**10b**) (1.36 g) by reduction in the same manner as described above, was dissolved in acetone (50 ml), and Jones reagent (10 ml) was added to it at 0 °C. After 5 min at the same temperature, methanol was added to reduce excess of the oxidant, and the mixture was diluted with water and extracted with ether. Sodium borohydride (0.15 g, 4 mmol) was added in portions to a solution of crude (**15**) (1.02 g), obtained by work-up of the above extract and identified by ^{1}H n.m.r. spectroscopy, in methanol (15 ml) at 0 °C over 15 min. After dilution with water, the product was extracted with ether, and the extract was washed with water and brine, dried, and evaporated. This gave an oil (1.04 g), which was warmed with acetic anhydride (5 ml) and pyridine (20 ml) at 70 °C for 20 h. The reaction mixture was diluted with water and extracted with ether and the extract was washed with water, aqueous cupric sulphate, and water, and dried. The crude product obtained by evaporation of the extract was purified by column chromatography (dichloromethane) to give pure (**16**) (680 mg) and a fraction (262 mg) contaminated with a small amount of impurity.

(1R,4S,5S,8S,9S,10S,11S,12S)-6-*Methoxy*-5,10-*dimethyl*-7,13-*dioxa*-1,4,8,9,12-*tetracyclo*[10.2.1.0^{1,9}.0^{4,8}]*pentadecan*-11-*ol* (**17a**).—A solution of compound (**14b**) (80 mg, 0.3 mmol) and *m*-chloroperoxybenzoic acid (80% purity; 80 mg, 0.37 mmol) in chloroform (5 ml) was stirred at room temperature overnight; it was then diluted with ether (30 ml) and washed with aqueous potassium carbonate, water and brine, dried, and evaporated. The crude oil so obtained was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 10:1) to give the *title compound* (**17a**) (57 mg, 67%) as powder, $\nu_{max.}$(KBr) 3 440; δ* 1.20 (d, 3 H, *J* 7), 1.21 (d, 3 H, *J* 6), 3.40 (s, 3 H), 3.34 and 4.00 (ABq, 1 H, *J* 8 each), 4.23 (t, 1 H, *J* 4), and 4.60 (d, 1 H, *J* 4) (Found: C, 68.15; H, 9.3. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28%).

(1R,4S,5S,8S,9S,10S,12S)-6-*Methoxy*-5,10-*dimethyl*-7,13-*dioxa*-1,4,8,9,12-*tetracyclo*[10.2.1.0^{1,9}.0^{4,8}]*pentadecan*-11-*one* (**17b**).—Jones reagent (0.5 ml) was added to a solution of compound (**17a**) (61 mg, 0.22 mmol) in acetone (10 ml), and the solution was stirred at room temperature for several min. After dilution with water, the mixture was extracted with ether, and the ethereal layer was washed with water and brine, dried, and evaporated. The oil so obtained was purified by preparative t.l.c. (ether–light petroleum, 1:1) to give the title compound (**17b**) (60 mg, 98%) as an oil, $\nu_{max.}$ (liquid film) 1 715; δ 1.10 (d, 3 H, *J* 6), 1.27 (d, 3 H, *J* 6), 3.40 (s, 3 H), and 4.63 (d, 1 H, *J* 4). (Found: C, 68.26; H, 8.26. $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%).

(1R,4S,5S,8S,9S,10S,12S)-5,10-*Dimethyl*-7,13-*dioxa*-1,4,8,9,12-*tetracyclo*[10.2.1.0^{1,9}.0^{4,8}]*pentadecane*-6,11-*dione* (**18**).—A mixture of compound (**17b**) (140 mg, 0.5 mmol), 3 drops of sulphuric acid, and aqueous acetone (20:1) (10.5 ml) was refluxed for 20 h. Jones reagent (1.5 ml) was added and the mixture was stirred at 0 °C for several h. After dilution with water, the mixture was extracted with ether, and the extract was washed with aqueous sodium hydrogen carbonate, water, and brine, dried, and evaporated to give the *title compound* (**18**) (94 mg, 71%) as crystals, m.p. 184—185.5 °C (from benzene–cyclohexane) (lit.,[5] 196—198 °C), $[\alpha]_D^{25}$ +130.9° (*c* 0.51), $\nu_{max.}$(KBr) 1 780 and 1 710; δ* 1.21 (d, 3 H, *J* 3), 1.28 (d, 3 H, *J* 3), 3.65 (d, 1 H, *J* 8), 3.97 (t, 1 H, *J* 11), and 4.28 (d, 1 H, *J* 8) (Found: C, 68.1; H, 7.8. $C_{15}H_{20}O_4$ requires C, 68.18; H, 7.57%).

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