Experiments on the Synthesis of Tetracycline. Part 16.[1] Improved Photocyclic Preparation of 12-Keto-Derivatives and their Deprotection using Benzeneseleninic Anhydride

By **Derek H. R. Barton,*** Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France
Maria T. Bielska, José M. Cardoso, Nigel J. Cussans, and **Steven V. Ley,** Department of Chemistry, Imperial College, London SW7 2AY

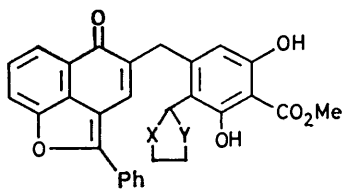
Improved methods for the photocyclisation of 4-[2-(1,3-dithiolan-2-yl)benzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (6; X = Y = S) and 4-[2-(1,3-dithiolan-2-yl)-3,5-dihydroxy-4-methoxycarbonylbenzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (1; X = Y = S) to their tetracyclic analogues are described. Deprotection of the C-12 thioacetal unit in the cyclised products was achieved using benzeneseleninic anhydride. Introduction of a 6α-methyl substituent and an amide grouping into C-2 of certain tetracyclic substrates provides compounds which have potential use for tetracycline synthesis.

As part of our continuing efforts [1] towards the preparation of suitably functionalised and protected tetracycline precursors, we have substantially improved the scale and yield of intermediate tetracyclic products employing a base-catalysed photocyclisation reaction, and developed new methods for their conversion into deprotected 12-keto-synthons.

Earlier [2] we showed that the acid-catalysed photocyclisation of suitably functionalised tricyclic 1,3-dioxolans (1; X = Y = O) and 1,3-oxathiolans (1; X = O, Y = S) afforded the required tetracyclic products in moderate yield, and only in the cases where the phenolic groups in ring A were protected as methyl ethers (2; $R^1 = R^2 = Me$, $R^3 = OMe$; X = Y = O and X = O, Y = S).

Whilst conversion into the corresponding amides (2; $R^1 = R^2 = Me$, $R^3 = NH_2$; X = Y = O and X = O, Y = S), reaction with ethereal methyl-lithium to give (3), and ozonolysis of the furan to give (4), was compatible with the 1,3-dioxolan protecting group, its subsequent cleavage to regenerate the 12-keto-group and demethylation of the phenolic ethers failed to afford the desired unmasked tetracyclic product, except under conditions when 6-methylpretetramid (5) was the only isolable product.

Therefore, in order to proceed with this approach, the following objectives had to be achieved: (*i*) improved yields of tetracyclic products by photocyclisation of tricyclic intermediates; (*ii*) the protection of the phenolic groups (if at all) by easily removable yet photolytically stable substituents; and (*iii*) deprotection of the masked 12-keto-functionality by a method compatible with the



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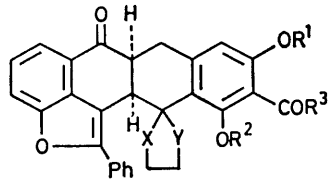

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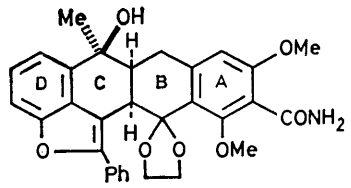

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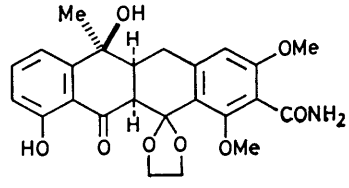

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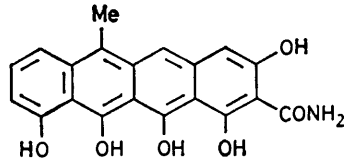

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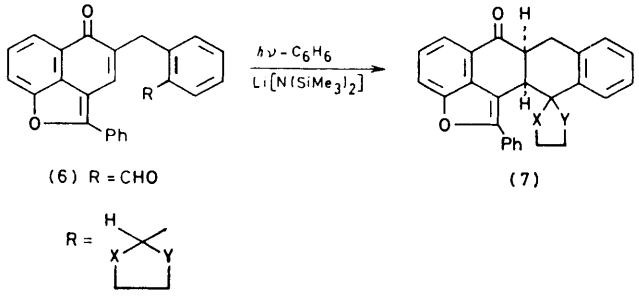
acid-sensitive 6β-hydroxy-substituent and which proceeds in good yield.

RESULTS AND DISCUSSION

In order to investigate the first condition, replacements for the 1,3-dioxolan and 1,3-oxathiolan groups were studied in the ring-A-unsubstituted model, employing the base-catalysed photocyclisation conditions developed later.[3]

The tricyclic 1,3-thiazolidine (6; X = S, Y = NH), 3-methyl-1,3-thiazolidine (6; X = S, Y = NMe), and 1,3-dithiolan [4] (6; X = Y = S) were each prepared from the tricyclic aldehyde (6; R = CHO) and the appropriate aminothiol or dithiol under standard conditions,[5] and converted into the corresponding tetracyclic product (7) by irradiation in deoxygenated benzene at reflux temperature in the presence of a catalytic base. Photolysis was initially performed using three 250-W tungsten filament lamps [providing 73—80% yield of (7; X = Y = S)] at a rate of 85 min g^{-1}. We subsequently discovered that irradiation with a single Atlas A1-233, 650-W tungsten quartz–halogen lamp gave slightly better yields of (7; X = Y = S) (75—85%) at a superior rate of only 6 min g^{-1}. In all cases, the most efficient catalytic base was found to be lithium bis(trimethylsilyl)amide,[6] and optimum yields were obtained in the presence of approximately 0.25 mol equiv. of base.



The unsubstituted 1,3-thiazolidine (7; X = S, Y = NH) was formed as a single epimer and in low yield (19—20%), probably due to the lability of the N–H bond to attack by the catalytic base resulting in competitive radical-anion formation. In contrast, the substituted product (7; X = S, Y = NMe) was obtained in higher yield (58—65%) as a 1 : 1 mixture (by n.m.r.) of α-thia-β-aza- and α-aza-β-thia-epimers, analogous to those observed for the 1,3-oxathiolans,[4] presumably due to the closer equivalence in radius of the NMe and S moieties.

As with the 1,3-dioxolans, the 1,3-thiazolidines were chosen for their known hydrolytic lability; therefore their propensity to liberate the masked 12-keto-group to give the tetracyclic diketone (8) [7] was examined under a variety of conditions (Table 1).[8-11]

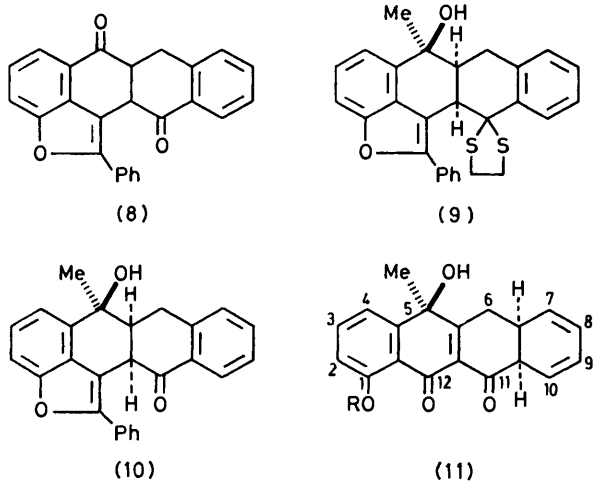
The various reagents gave only low yields of the diketone (8) or utilised acidic conditions, which would have been inapplicable to the acid-sensitive C-6 alcohol derivatives. We concluded that the thiazolidines were unsuitable substrates for our synthetic sequence.

The 1,3-dithiolan (7; X = Y = S) proved to be the most convenient derivative to prepare (the corresponding 1,3-dithian [12] and 1,3-diselenan [13] were abandoned due to their thermal and photolytic instabilities) and its reaction with ethereal methyl-lithium proceeded smoothly at −78 °C to yield the alcohol (9). A suitable method for the smooth dethioacetalisation of (9) was now sought.

TABLE 1

Thiazolidine	Reagents (at room temperature)	Ref.	Yield of (8) (%)
(7; X = S, Y = NH)	$AgNO_3$,HNO_3, 30 min	9	64
(7; X = S, Y = NMe)	$AgNO_3$,HNO_3, 1 day	9	15
(7; X = S, Y = NMe)	NBS, aqueous Me_2CO 72 h	9	17
(7; X = S, Y = NMe)	$HgCl_2$,$CaCO_3$,MeCN, 72 h	10	32
(7; X = S, Y = NMe)	$HgO,BF_3{\cdot}Et_2O$, 72 h	11	39
(7; X = S, Y = NMe)	$NaIO_4$, aqueous 1,4-dioxan, 12 h	12	0

Many methods have been reported for the cleavage of 1,3-dithiolans, involving alkylation–hydrolysis,[14-18] oxidative cleavage,[10,19-22] photolysis,[23] and electrolysis.[24] After many unsuccessful attempts to regenerate the 12-keto-group using several of the standard techniques, which often resulted in general decomposition of the substrates, we realised that a selective, mild, neutral (or slightly basic) procedure for the cleavage of 1,3-dithiolans was required. We have developed a mild oxidative method to achieve this using benzeneseleninic anhydride,[25] which was applicable to the tetracyclic compounds described here.

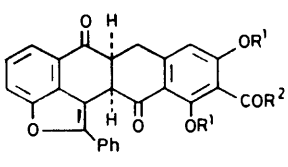


The reaction of (7; X = Y = S) with a partial suspension of benzeneseleninic anhydride in dry dichloromethane at room temperature over 3.5 h afforded the model diketone (8) in 63% yield. By a slight modification of the reaction conditions (dry tetrahydrofuran at 40 °C with three drops of pyridine to scavenge any traces of acid) the C-6 alcohol (9) reacted smoothly with benzeneseleninic anhydride to give (10) in 78% yield. Subse-

quent ozonolysis of (10) at −78 °C, and decomposition of the ozonide with dimethyl sulphide, gave the diketo-benzoate (11; R = PhCO) in 76% yield. Solvolysis with sodium methoxide in methanol, followed by careful re-acidification with solid carbon dioxide, afforded the fully deprotected ring-A-unsubstituted tetracycline (11; R = H) in 92% yield. Attempts were then made to apply this methodology to the ring-A-substituted 1,3-dithiolan analogue.

Although we discovered that protection of the diphenolic groups only as methyl ethers was essential during the acid-catalysed photocyclisation of the 1,3-dioxolan (1; X = Y = O), an unexpected bonus of the base-catalysed reaction was that the 1,3-dithiolan (1; X = Y = S) could be photocyclised to (2; X = Y = S, $R^1 = R^2 = H$, R^3 = OMe) as the free diphenol. By optimisation of the photolysis conditions (Table 2) a *ca.* 60% yield of tetracyclic product was routinely obtained on a 2-g scale.

In order to test the new 1,3-dithiolan deprotection on the ring-A-substituted product, the 6-keto-ester (2; X = Y = S, $R^1 = R^2 = H$, R^3 = OMe) was successfully reacted with benzeneseleninic anhydride in dichloromethane at room temperature to afford the highly fluorescent 6,12-diketo-ester (12; $R^1 = H$, R^2 = OMe) in 64% yield. However, this favourable reaction on the free diphenolic ester proved to be an exceptional case. Transformation of the ester (2; X = Y = X, $R^1 = R^2 = H$, R^3 = OMe) to the amide (2; X = Y = S, $R^1 = R^2 = H$, $R^3 = NH_2$) proceeded well in tetrahydrofuran–0.880 ammonia, but the analogous 1,3-dithiolan deprotection was unsuccessful under the same conditions.



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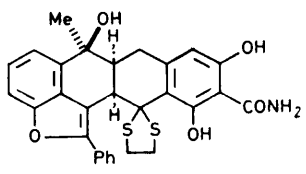

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Since the ester group appeared to provide a significant protective role during the benzeneseleninic anhydride reaction, before proceeding to studies of the C-6 alcohol compound (13), interconversion of the diketo-ester (12; $R^1 = H$, R^2 = OMe) to the diketo-amide (12; $R^1 = H$, $R^2 = NH_2$) was attempted. Any such method of hydrolysis and subsequent amidation had also to be compatible with the acid-sensitive C-6 alcohol (13); therefore basic conditions were chosen. Direct reaction of the ester with aqueous ammonia in tetrahydrofuran at room temperature or below only resulted in degradation of the 1,4-diketone moiety, as did alcoholic alkali (KOH–MeOH) and many other bases (*e.g.* imidazole and tetramethylguanidine). Trimethylsilyl iodide [26] proved too vigorous for the substrate, even in the presence of pyridine and with or without quenching with ammonia; therefore this approach was not investigated further.

It was suspected that the presence of the free diphenolic groups contributed towards the undesired behaviour of the amide. Derivatisation of the diphenol keto-ester (2; X = Y = S, $R^1 = R^2 = H$, R^3 = OMe) gave sequentially the mono-3-*O*-ethylcarbonate (2; X = Y = S, $R^1 = CO_2Et$, $R^2 = H$, R^3 = OMe), and with difficulty, the 1,3-*O*-bis(ethylcarbonate) (2; X = Y = S, $R^1 = R^2 = CO_2Et$, R^3 = OMe) under phase-transfer conditions and more forcing conditions, using potassium hydride, respectively, with ethyl chloroformate. We did not, however, have the means to study the dethioacetalisation of the latter compound. We also report the preparation of (13) although this compound too could not be processed further.

TABLE 2

Ring-A-substituted photocyclisations

Starting material (1; X = Y = S) (mg)	Solvent (benzene) (l)	Mol. equiv. of base	Reaction time (min)	Yield of (2; X = Y = S, $R^1 = R^2 = H$, R^3 = OMe) (mg)	(%)
510	2	0.22	15	252	49
503	2	0.26	10	270.5	55
1 002	4	0.26	15	501	50
1 000	4	0.28	15	525	52.5
999	4.5	0.26	15	680	68
2 000	4.5	0.22	60	1 170	58.5

This synthetic approach to the tetracycline structure has been discontinued.

EXPERIMENTAL

Melting points were determined using a Kofler hotstage apparatus and are uncorrected. Infrared spectra were recorded (in Nujol unless otherwise stated) on Perkin-Elmer 157 and 298 spectrometers; n.m.r. spectra were recorded using a Varian EM 360A machine for solutions in $CDCl_3$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a V.G. Micromass 7070 spectrometer at 70 eV. Solvents were purified and dried by standard techniques.

Preparation of (6; X = S, Y = NH).—4-(2-Formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one [7] (300 mg, 0.82 mmol) and 2-aminoethanethiol (72 mg, 1.1 equiv.) were heated in boiling benzene (40 ml) for 12 h under nitrogen in the dark, water being continuously removed by a Dean–Stark head. Removal of the solvent and preparative layer chromatography afforded 4-[2-(1,3-thiazolidin-2-yl)benzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (6; X = S, Y = NH) as a glass (343 mg, 98%); $\nu_{max.}$ 3 500, 1 645, 1 590, 1 575, and 695 cm^{-1}; $\lambda_{max.}$ 249, 266, and 402 nm (ε 14 800, 17 000, and 25 200); δ 8.0—7.3 (12 H, m), 5.8 (1 H, s), 4.2 (2 H, s), 3.1 (4 H, s), and 2.2 (NH, br); *m/e* 423 (M^+) and 362.

Preparation of (6; X = S, Y = NMe).—As above 4-(2-formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one (300 mg) with *N*-methyl-2-aminoethanethiol (101 mg) in benzene gave 4-[2-(3-methyl-1,3-thiazolidin-2-yl)benzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (6; X = S, Y = NMe) (262 mg, 73%); $\nu_{max.}$ 1 650, 1 600, and 1 580 cm^{-1}; $\lambda_{max.}$ 250, 267, and 402 nm (ε 12 500, 17 600, and 26 300); δ 8.0—7.1 (12 H, m), 5.06 (1 H, s), 4.06 (2 H, br), 3.3—2.6 (4 H, m), and 2.18 (3 H, s); *m/e* 437 (M^+), 377, and 362.

Preparation of (6; X = S, Y = S).—4-(2-Formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one (1 g, 2.7 mmol) was added to benzene (40 ml, dry), acetic acid (50 ml), ethane-1,2-dithiol (2 ml) and $BF_3{\cdot}Et_2O$ (1 ml). After 75 min the reaction mixture was poured into saturated sodium hydrogencarbonate (300 ml) and the product extracted with dichloromethane.

Removal of the solvent gave a pale yellow solid which after chromatography gave 4-[2-(1,3-dithiolan-2-yl)benzyl]-2-phenylnaphtho[1,8-*bc*]furan-5-one (6; X = S, Y = S) (1.12 g, 93%), m.p. 184—187 °C (lit.,[3b,4] 185 °C); $\nu_{max.}$ 1 636, 1 560, 1 260, 1 060, 765, and 690 cm^{-1}; $\lambda_{max.}$ 267 and 395 nm (ε 16 000 and 28 400); δ 8.0—7.1 (12 H, m), 5.93 (1 H, s), 4.13 (2 H, d, *J* 2 Hz), and 3.4 (4 H, m).

Photocyclisation (*General Method*).—The thioacetal (*ca.* 1 g) was added to rigorously dried and de-gassed benzene (600 ml) together with a catalytic amount of freshly prepared lithium hexamethyldisilazide (100 mg). The mixture was photolysed using an Atlas A1-233, 650-W quartz–halogen lamp in an internal-well system at reflux temperature until u.v. indicated complete reaction. The cooled benzene solution was washed with KH_2PO_4 (100 ml, saturated) and water (100 ml). After drying ($MgSO_4$) the solvent was removed under reduced pressure to afford the crude cyclised product (7) which was purified by crystallisation.

Photocyclisation of (6; X = S, Y = NH).—Compound (6; X = S, X = NH) (254 mg, 0.6 mmol) after 6 min afforded 6aα,12aα-*dihydro*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(7H),2′-[1,3]*thiazolidine*]-6-*one* (7; X = S, Y = NH) (53.2 mg, 20%), m.p. 175—176 °C (decomp.) (from $CHCl_3$–EtOH); $\nu_{max.}$ 1 700 cm^{-1}; $\lambda_{max.}$ 275, 295 (sh), 307 (sh), and 350 nm (ε 20 350, 13 500, 9 900, and 13 500); δ 8.0—7.2 (12 H, m), 4.38 (1 H, d, *J* 5 Hz), and 4.2—2.6 (7 H, m) (Found: C, 76.65; H, 4.95; N, 3.2; S, 8.0. $C_{27}H_{21}NO_2S$ requires C, 76.6; H, 4.9; N, 3.3; S, 7.55%).

Photocyclisation of (6; X = S, Y = NMe).—Compound (6; X = S, Y = NMe) (130 mg, 0.29 mmol) after 5 min afforded 6aα,12aα-*dihydro*-3′-*methyl*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(7H),2′-[1,3]*thiazolidine*]-6-*one* (7; X = S, Y = NMe) (84 mg, 65%), m.p. 192—194 °C (decomp.) (from $CHCl_3$–EtOH); $\nu_{max.}$ 1 700 cm^{-1}; $\lambda_{max.}$ 278 and 354 nm (ε 23 500 and 11 600); δ 8.0—7.2 (Ar, m), 4.46 (1 H, *J* 6 Hz), 4.0—2.4 (m), 2.08 (s), and 1.63 (s) (Found: C, 76.7; H, 5.15; N, 3.1. $C_{28}H_{23}NO_2S$ requires C, 76.9; H, 5.25; N, 3.2%).

Photocyclisation of (6; X = S, Y = S).—Compound (6; X = S, Y = S) (1 g, 2.3 mmol) after 15 min afforded 6aα,-12aα-dihydro-1-phenylspiro[naphthaceno[1,12-*bc*]furan-12(7*H*),2′-[1,3]dithiolan]-6-one (7; X = S, Y = S) (752 mg, 75%), m.p. 226—229 °C (lit.,[3b,4] 221—228 °C); $\nu_{max.}$ 1 690, 1 255, 1 070, 760, and 700 cm^{-1}; $\lambda_{max.}$ 276 and 354 nm (ε 21 000 and 10 500); δ 8.0—7.17 (12 H, m), 4.75 (1 H, d, *J* 3 Hz), and 4.0—2.7 (7 H, m).

Preparation of the Alcohol (9).—The ketone (7; X = Y = S) (150 mg, 0.34 mmol) was added to dry THF (15 ml) under nitrogen and cooled to −78 °C. Methyl-lithium (1 ml, 1.8M in ether) was added dropwise. After 30 min a further portion of methyl-lithium was added. The reaction was quenched by the addition of solid NH_4Cl (2 g) at −78 °C followed by water (2 ml). After warming to room temperature the mixture was extracted with dichloromethane. Removal of the solvent gave a mixture of starting ketone and desired alcohol (9) (150 mg). The above cycle was repeated twice to afford a crude product which after preparative layer chromatography gave 6aα,12aα-dihydro-6α-methyl-1-phenylspiro[naphthaceno[1,12-*bc*]furan-12(7*H*),-2′-[1,3]-dithiolan]-6β-ol (9) (54 mg, 35%), m.p. 218—220 °C; $\nu_{max.}$ 3 400 cm^{-1}; $\lambda_{max.}$ 310 nm (ε 15 800); δ 7.85—7.02 (12 H, m), 4.27 (1 H, br), 3.32—2.72 (7 H, m), 1.76 (1 H, s), and 1.52 (3 H, s).

Reaction of (7; X = S, Y = S) *with Benzeneseleninic Anhydride*.—Compound (7; X = S, Y = S) (63.3 mg, 0.144 mmol) and benzeneseleninic anhydride (60 mg, 0.167 mmol) were stirred together in *dry* methylene chloride (2 ml) at room temperature under a nitrogen atmosphere for 3.5 h. Saturated sodium hydrogencarbonate (1 ml) was added and the products were extracted with more methylene chloride. Addition of methanol caused the product to crystallise to afford *cis*-6aα,12aα-dihydro-1-phenylnaphthaceno[1,12-*bc*]-furan-6(7*H*),12-dione (8) (32 mg, 63%), m.p. 225 °C (decomp.) (lit.,[7] 234—235 °C); $\nu_{max.}$ 1 700 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 260, 275 (sh), 280 (sh), 295, 305 (sh), and 360 nm (ε 42 300, 29 600, 26 100, 24 200, 20 500, and 17 800); δ 8.0—7.2 (12 H, m), 4.78 (1 H, d, *J* 7 Hz), and 4.1—3.1 (3 H, m).

Reaction of the Alcohol (9) *with Benzeneseleninic Anhydride*.—To the alcohol (9) (60.6 mg) in dry tetrahydrofuran (10 ml) was added benzeneseleninic anhydride (107.6 mg) and dry pyridine (3 drops). After 50 h at 40 °C the reaction was worked up as above to afford *cis*-6aα,12aα-dihydro-6β-hydroxy-6α-methyl-1-phenylnaphthaceno[1,12-*bc*]furan-12(6*H*,7*H*)-one (10) (39.7 mg, 78%), m.p. 180—183 °C (from benzene–light petroleum–methanol) (lit.,[3b,4] 177—190 °C); $\nu_{max.}$ 3 400 and 1 680 cm^{-1}; $\lambda_{max.}$ 245, 298 (sh), 311, and 325 (sh) nm (ε 23 300, 25 900, 28 200, and 16 300); δ 8.0—7.2 (12 H, m), 4.2 (1 H, d *J* 5 Hz), 3.4—3.2 (2 H, m), 2.8 (1 H, m), and 1.75 (3 H, s).

Ozonolysis of (10).—Compound (10) (30.8 mg) was dissolved in dry chloroform–methanol (1 : 1) (10 ml), and pyridine (0.5 ml), cooled to −78 °C, and treated with O_3 for 3 h. Excess of O_3 was removed by flushing with dry nitrogen. Dimethyl sulphide (1 ml) was added and the reaction mixture allowed to warm to room temperature. After stirring overnight evaporation of solvents and excess of reagents under reduced pressure gave the crude product, which after chromatography gave 5,5aα,6,11,11aα,12-*hexahydro*-5β-*hydroxy*-5α-*methyl*-11,12-*dioxonaphthacen*-1-*yl benzoate* (11; R = COPh) (25.6 mg, 76%), m.p. 187—190 °C (from benzene–light petroleum); $\nu_{max.}$ 3 500, 1 730, 1 680, 1 603, 1 270, and 1 230 cm^{-1}; $\lambda_{max.}$ 228, 257 (sh), 309, 381, and 400 (sh) nm (ε 22 400, 17 500, 14 500, 19 600, and 15 400); δ 8.4—7.2 (Ar-H), 3.5 (1 H), 3.1 (1 H), and 1.7 (3 H, s) (Found: C, 75.6; H, 4.8. $C_{26}H_{20}O_5$ requires C, 75.75; H, 4.85%).

Hydrolysis of (11; R = PhCO).—Compound (11; R = PhCO) (6.7 mg) was dissolved in dry methanol (2 ml) and treated with methanol–sodium methoxide (1 ml containing 60 μmol base) for 100 min at room temperature. Water (2 ml) was added followed by $CHCl_3$ (10 ml) and sufficient solid carbon dioxide to restore the colour of the original yellow solution. Evaporation of the solvent gave a residue which after chromatography afforded 5aα,11aα-*dihydro*-

1,5β-*dihydroxy*-5α-*methylnaphthacene*-11(5H),12(6H)-*dione* (11; R = H) (4.6 mg, 92%), m.p. 150—155 °C (decomp.); $\nu_{max.}$ 1 680 and 1 610 cm^{-1}; $\lambda_{max.}$ 220, 239, 285, 305, 388, and 406 nm (ε 12 200, 8 750, 4 200, 3 900, 14 500, and 12 800); δ 12.3 (1 H, s), 7.48—7.0 (7 H, m), 3.23 (1 H, s), 3.15 (1 H, t, *J* 3.5 Hz), 1.78 (2 H, d, *J* 3.5 Hz), 1.54 (3 H, s), and 1.26 (1 H, s) (Found: C, 73.85; H, 5.2. $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%).

Preparation of (1; X = Y = S).—4-(2-Formyl-3,5-dihydroxy-4-methoxycarbonylbenzyl)-2-phenylnaphtho-[1,8-*bc*]furan-5-one [3] (200 mg, 0.45 mmol) was dissolved in benzene (6 ml) and acetic acid (9 ml). Ethane-1,2-dithiol (1.2 ml) and boron trifluoride–ether (0.5 ml) were added and the mixture stirred at room temperature for 30 min. The reaction was quenched by the addition of water and the organic layer washed with saturated sodium hydrogencarbonate solution. After drying, solvent and excess of ethanedithiol were removed *in vacuo* at 80 °C to leave a residue which after crystallisation from ethyl acetate–ethanol gave 4-(2-[1,3-*dithiolan*-2-*yl*]-3,5-*dihydroxy*-4-*methoxycarbonylbenzyl*)-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (1; X = Y = S) (209 mg, 90%), m.p. 145—147 °C; $\nu_{max.}$ 3 350, 1 660, and 1 630 cm^{-1}; $\lambda_{max.}$ (CH_2Cl_2) 238, 252, 264, and 401 nm (ε 30 180, 26 230, 27 780, and 28 100); δ 3.4—3.65 (4 H, m), 4.1 (3 H, s), 4.35 (2 H, s), 6.4 (1 H, s), and 7.30 (1 H, s) (Found: C, 65.05; H, 4.1; S, 12.1. $C_{29}H_{22}O_6S_2$ requires C, 65.64; H, 4.18; S, 12.08%).

Photocyclisation of (1; X = Y = S).—Compound (1; X = Y = S) (510 mg, 0.96 mmol) in benzene (2 l) with a catalytic amount of lithium hexamethyldisilazide (35.9 mg, 0.22 mmol), after 15 min irradiation afforded *methyl* 6aα,-12aα-*dihydro*-9,11-*dihydroxy*-6-*oxo*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(6H,7H)-2′-[1,3]*dithiolan*]-10-*carboxylate* (2; X = Y = S, R^1 = R^2 = H, R^3 = OMe) (252 mg, 49%, m.p. 241 °C (decomp.); $\nu_{max.}$ 1 670 and 1 630 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 243, 266, and 349 nm (ε 26 000, 23 500, and 17 000); δ 11.1 (1 H, s), 9.33 (1 H, s), 7.99—7.26 (8 H, m), 6.44 (1 H, s), 4.73 (1 H, d *J* 5 Hz), 4.03 (3 H, s), 3.9—2.8 (6 H, m), and 2.0—1.7 (1 H, m) (Found: C, 65.45; H, 4.25; S, 12.45. $C_{29}H_{22}O_6S_2$ requires C, 65.6; H, 4.18; S, 12.08%).

Reaction of (2; X = Y = S, R^1 = R^2 = H, R^3 = OMe) *with Benzeneseleninic Anhydride*.—To a solution of (2; X = Y = S, R^1 = R^2 = H, R^3 = OMe) (120 mg, 0.23 mmol) in CH_2Cl_2 (3 ml) at room temperature was added benzeneseleninic anhydride (81.5 mg, 0.23 mmol) in one portion. After 16 h the crude precipitated product was filtered, washed with ether to remove $(PhSe)_2$, and crystallised from methanol to afford *methyl* cis-6aα,7,12,12aα-*tetrahydro*-9,11-*dihydroxy*-6,12-*dioxo*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-10-*carboxylate* (12; R^1 = H, R^2 = OMe) (65.4 mg, 64%), m.p. 252 °C (decomp.); $\nu_{max.}$ (KBr) 3 550—3 300, 3 050, 2 800, 1 685, 1 665, 1 620, 1 580, 1 440, 1 240, and 760 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 260, 275 (sh), 294, 337, and 358 nm (ε 23 800, 22 500, 21 000, 17 200, and 13 600), δ 8.06—7.28 (8 H, m), 6.58 (1 H, s), 5.87 (1 H, s), 4.85 (1 H, d *J* 5 Hz), 4.01—3.09 (3 H, m), 3.95 (3 H, s), and 1.53 (2 MeOH) (Found: C, 67.1; H, 4.9. $C_{27}H_{18}O_7 \cdot 2MeOH$ requires C, 67.2; H, 5.0%).

Preparation of (2; X = Y = S, R^1 = R^2 = H, R^3 = NH_2).—To a suspension of the ester (2; X = Y = S, R^1 = R^2 = H, R^3 = OMe) (500 mg, 0.94 mmol) in tetrahydrofuran (7 ml) was added 0.880 ammonia solution (5 ml) and the mixture stirred at room temperature for 22 h. Work-up using saturated potassium dihydrogenphosphate solution afforded 6aα,12aα,*dihydro*-9,11-*dihydroxy*-6-*oxo*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(6H,7H)-2′-[1,3]-*dithiolan*]-10-*carboxamide* (2; X = Y = S, R^1 = R^2 = H, R^3 = NH_2) (363 mg, 75%), m.p. 211 °C (decomp.); $\nu_{max.}$ 3 400, 3 300—3 100, 1 680, 1 655, and 1 620 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 243, 266, and 349 nm (ε 26 000, 23 500, and 17 000); δ 10.1 (1 H, s), 8.7 (1 H, s), 8.01—7.29 (8 H, m), 6.54 (1 H, s), 4.91 (1 H, d, *J* 5 Hz), 4.15—2.89 (9 H, m), and 1.98—1.8 (1 H, m) (Found: C, 65.3; H, 4.2; N, 2.7. $C_{28}H_{21}NO_5S_2$ requires C, 65.22; H, 4.11; N, 2.72%).

Preparation of the Monocathylate (2; X = Y = S, R^1 = CO_2Et, R^2 = H, R^3 = OMe).—To a stirred solution of (2; X = Y = S, R^1 = R^2 = H, R^3 = OMe) (200 mg, 0.38 mmol) and tetrabutylammonium hydrogensulphate (300 mg, 0.89 mmol) in ethanol-free chloroform (5 ml) was added aqueous sodium hydroxide (0.1M, 14 ml) at room temperature under nitrogen. After 1 h the dark organic phase was separated, dried ($MgSO_4$), and ethyl chloroformate (0.1 ml) added. Solvent was removed under reduced pressure to give a residue which after chromatography afforded *methyl* 9-*ethylcarbonato*-6aα,12aα,*dihydro*-11-*hydroxy*-6-*oxo*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(6H,7H)-2′-[1,3]-*dithiolan*]-10-*carboxylate* (2; X = Y = S, R^1 = CO_2Et, R^2 = H, R^3 = OMe) (120 mg, 53%), m.p. 199—200 °C; $\nu_{max.}$ 1 767, 1 698, 1 670, and 1 622 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 246, 280, and 355 nm (ε 27 630, 24 660, and 17 980); δ 8.1—7.21 (m), 6.7 (1 H, s), 4.7 (2 H, d), 4.32 (2 H, q), 3.8 (3 H, s), 3.6—2.27 (m), and 1.4 (3 H, t) (Found: C, 63.95; H, 4.25; S, 11.15. $C_{32}H_{26}O_8S_2$ requires C, 63.77; H, 4.35; S,10.64%).

Preparation of the Dicathylate (2; X = Y = S, R^1 = R^2 = CO_2Et, R^3 = OMe).—The monocathylate (prepared above) (36 mg, 0.06 mmol) was dissolved in tetrahydrofuran and an excess of potassium hydride was added. After 30 min ethyl chloroformate (0.1 ml) was added and the mixture was boiled for 30 min. Solvent was removed from the cooled reaction mixture and the residue chromatographed to afford *methyl* 9,11-*bis*(*ethylcarbonato*)-6aα,12aα-*dihydro*-6-*oxo*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(6H,7H)-2′-[1,3]-*dithiolan*]-10-*carboxylate* (2; X = Y = S, R^1 = R^2 = CO_2Et, R^3 = OMe) (22 mg, 55%); $\nu_{max.}$ 1 768, 1 731, 1 698 (sh), 1 672 (sh), 1 660, and 1 615 cm^{-1}; $\lambda_{max.}$ (CH_2Cl_2) 242, 278, and 355 nm (ε 29 160, 25 430, and 17 860); δ 8.0—7.26 (m), 7.06 (1 H, s), 4.7 (d, *J* 5 Hz), 4.52 (2 H, q), 4.14 (2 H, q), 3.78 (3 H, s), 3.74—2.74 (m), 1.74 (3 H, d), 1.38 (3 H, t), and 1.2 (3 H, t) (Found: C, 62.0; H, 4.4. $C_{35}H_{30}O_{10}S_2$ requires C, 62.3; H, 4.48%).

Preparation of (13).—To a solution of the keto-amide (2; X = Y = S, R^1 = R^2 = H, R^3 = NH_2) (279.6 mg, 0.54 mmol) in *dry* tetrahydrofuran (20 ml) at −78 °C under nitrogen was added methyl-lithium (9 ml, 1.5M in ether, 25 equiv.). After stirring for 40 min saturated NH_4Cl solution was added and the mixture allowed to warm to 0 °C. Water and ether were added and the organic phase separated and dried. Partial removal of the solvent and trituration with methanol gave 6aα,12aα-*dihydro*-6β,9,11-*trihydroxy*-6α-*methyl*-1-*phenylspiro*[*naphthaceno*[1,12-bc]*furan*-12(6H,7H)-2′-[1,3]-*dithiolan*]-10-*carboxamide* (13; R = H) (224 mg, 78%), m.p. 198 °C (decomp.); $\nu_{max.}$ (KBr) 3 450, 3 350—2 900, 1 695, 1 655, 1 605, 1 415, 1 280, 1 260, 1 085, 1 045, 775, and 760 cm^{-1}; $\lambda_{max.}$ (CH_2Cl_2), 250, 296, 312, and 324 nm (ε 14 500, 14 500, 14 000, and 14 000); δ 13.3 (1 H, s), 10.0 (1 H, s), 8.0—7.38 (8 H, m), 6.52 (1 H, s), 4.87 (1 H, d, *J* 5 Hz), 4.06—2.7 (7 H, m), and 1.58 (3 H, s) (Found: C, 65.25; H, 4.65; N, 2.45. $C_{29}H_{25}NO_5S_2$ requires C, 65.52; H, 4.74; N, 2.63%).

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