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MARINE TOXINS. SYNTHESIS OF THE SPIRO-BENZOQUINONEFURAN UNIT IN STYPOLDIONE

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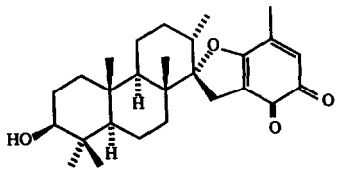
Summary: A synthesis of the unusual spiro-benzoquinonefuran unit (13) present in the marine toxin stypoldione (1), using the strategy (9)→(10)→(12)→(13), is described.

Stypoldione (1) and stypotriol (2) belong to a rare class of marine toxins produced by the brown alga Stypodium zonale.[1] The two molecules, together with some of their co-metabolites, show pronounced narcotic and hyperactive effects upon reef-dwelling fish. Stypoldione (1) is particularly active, and has also been found to show antitumoral properties and inhibit cell division in the fertilised sea urchin egg assay.[2] Two closely related diterpene-hydroquinone metabolites, mediterraneol A (3) and cystoseirol A (4), have been isolated from the marine alga Cystoseira mediterranea,[3] and it seems likely that the four compounds (1)→(4) have a similar biosynthetic origin, e.g.(1) from (5) via (6). The novel structures shown by these new marine metabolites, together with their unusual mode of biological action, combine to make them desirable targets for synthetic investigations.[4] In this Letter, we outline a synthesis of the spiro-benzoquinonefuran unit, i.e. (13), present in stypoldione (1), using a strategy, viz (9) →(10) →(12) →(13), which has close similarities to the probable biogenesis of this portion of the natural product.

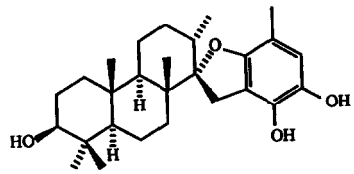
Thus, conversion of 2-bromo-6-methylbenzoquinol[5] to the corresponding bis(methoxymethyl)(MOM) derivative (7a) (BuLi, THF, 0°C; then MOMCl, 0°C→25°C), followed by treatment of (7a) with n-butyllithium (1.2 equivs., -40°C, 0.5h) led to the lithio derivative (7b) which was then reacted with cyclogeranyl bromide(8)[6] in the presence of cuprous iodide (0.5 equivs)(-40°C→25°C over 2h)

to give the coupled product (9) in 64% yield.[7] Epoxidation of (9), using m-chloroperbenzoic acid (1.3 equivs., CH_2Cl_2,25°C,16h), next produced the epoxide (10, colourless oil, 91%), which on treatment with lithium aluminium hydride- aluminium chloride (0°C, Et_2O, 18 days) followed by chromatography, resulted in regiospecific reduction and cleavage of the MOM protecting groups leading to the crystalline t-carbinol (11; 79%), m.p. 164.5 - 166°C, δ_H 0.76 (Me), 0.98 (d, J 7 Hz, CHMe), 1.13 (Me), 1.6-1.8 (m, 6H), 2.2 (ArMe), 2.3 (br, OH), 2.7 (d, J 15 Hz, CHHAr), 3.06 (d, J 15Hz, CHHAr), 3.49 (q, J 7Hz, (CHMe), 4.35 (br, OH), 6.45 (d, J 3Hz, Ar), 6.5 (d, J 3Hz, ArH), 8.78 (br, OH). Exposure of the quinol t-carbinol (11) to catalytic p-toluenesulphonic acid ($CHCl_3$, reflux, 7 days) then resulted in smooth cyclisation to the spiro-dihydrofuran derivative (12; 90%) which was obtained as an amorphous semi-solid, δ_H 0.7 (d,J 6.4Hz, CHMe), 0.8 (Me), 0.95 (Me), 1.1-1.9 (m,6H), 2.11 (ArMe), 2.77 (d, J 16.5Hz, CHHAr), 3.13 (d, J 16.5Hz, CHHAr), 5.76 (br, OH), 6.4 (br, ArH), 6.44 (br, ArH) p.p.m. The relative stereochemistry of the adjacent chiral centres in (12) was confirmed through an X-ray crystal structure determination on the corresponding 4-nitrobenzoate derivative, m.p. 123-5°C (EtOAc).[8]

The synthesis of the spiro-benzoquinonefuran unit (13) in stypoldione (1) was finally completed by treatment of (12) with Fremy's salt (potassium nitrosodisulphonate) (2.6 equivs., KH_2PO_4, Me_2CO-H_2O,2h), which gave (13; 77%) as a deep red solid, m.p. 111-3°C, λ_{max} (EtOH) 272(5000), 471(1150) nm., ν_{max} ($CHCl_3$) 1685, 1650, 1630, 1585 $cm.^{-1}$, δ_c15.4(q), 16.7 (q), 21.1(t), 22.0(q), 24.5(q), 30.5(t), 30.9(t), 36.0(t), 36.9(d), 38.2, 102.5, 114.6, 128.6(d), 143.2, 170.3, 174.4, 182.8 p.p.m. Reduction of the o-benzoquinone (13), using sodium dithionite in aqueous ethanol (1 min., 25°C), led to the corresponding catechol (14; 97%), a cream solid, m.p. 143-5°C, λ_{max} (EtOH)295,(3600)nm which became oxidised back to the quinone (13) in quantitative yield, immediately on exposure to air. Both the spiro-benzoquinonefuran (13) and the catechol (14) showed n.m.r. spectroscopic data which were superimposable on all of the signals associated with the CDE ring portions of the corresponding natural products stypoldione (1) and stypotriol (2) respectively[1]. In addition, both stypoldione and the analogue (13) showed a similar growth



(1)



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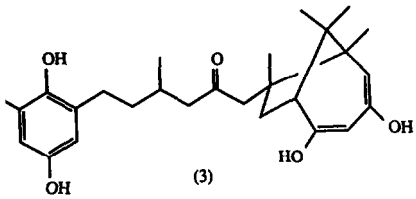

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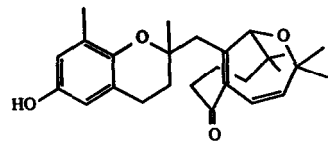

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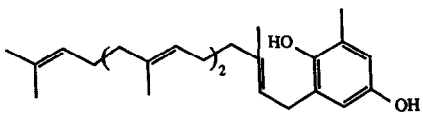

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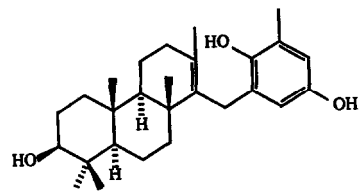

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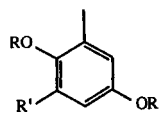
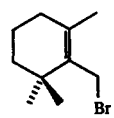


(7)
a, R' = Br; b, R' = Li



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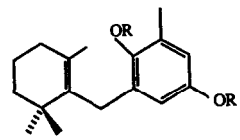

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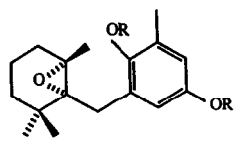

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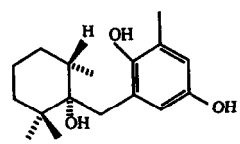
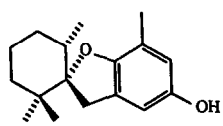


(11)

R = $MeOCH_2$-



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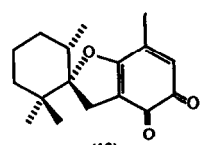

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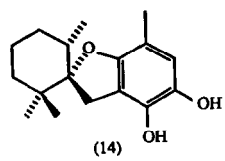

(14)

inhibition of mouse P388 leukaemia cells *in vitro* with a 96% inhibition at 1 x 10^{-4}M and 17% inhibition at 1 x 10^{-6}M.[9]

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7. Satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data were obtained for all new compounds.
8. We thank Dr M J Begley of this department for this determination; full details will be described in a separate publication.
9. We thank Dr E B Rapson (Wellcome Research Laboratories, Beckenham) for this information.]

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