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RADICAL CYCLISATIONS ONTO 2(5H)-FURANONE AND MALEATE ELECTROPHORES LEADING TO SPIRO- AND LINEAR-FUSED γ-LACTONE RING SYSTEMS

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Summary: Radical cyclisations involving α-acetal methyl centres and 2(5H)-furanone and maleate electrophores allow the facile syntheses of spiro- and linear-fused γ-lactone ring systems e.g. (6), (10), (14) and (19), found in the ginkgolides.

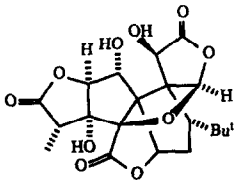
An extraordinarily wide range of linear, angular and spiro-fused γ-butyrolactone ring systems are found amongst natural product structures. Perhaps nowhere is this feature better illustrated than in the tetra- and hexa-cyclic lactones ginkgolide B (1) and bilobalide (2), found in the ginko tree Ginkgo biloba[1], which are amongst the most structurally complex molecules yet found in Nature. The 'ginkgolides' have aroused considerable interest recently with the finding that ginkgolide B (BN 52021) is a potent and specific antagonist of platelet activating factor (PAF), which is believed to be a key mediator of asthma[2]. The structural complexity of molecules like the ginkgolides, suggests that any approach to their synthesis must be based on sound methodology for elaborating the wide array of ring-fused γ-lactone sub-units found within their molecular frameworks.[3] In recent years, several research groups and our own, have demonstrated the considerable scope that free-radical C→C bond forming reactions have over traditional methodology in the synthesis of unusual structures and ring systems.[4] We have now investigated the possibilities for intramolecular radical cyclisations onto 2(5H)-furanone and maleate electrophores, as a synthetic entry to some of the spiro- and linear-fused γ-lactone ring systems found in the ginkgolides. In this Letter, we show how this strategy allows the facile syntheses of the ring-fused lactones (6), (10) (14) and (19) from the easily available precursors (4), (8), (12) and (18c) respectively.

Thus, controlled reduction of dimethylmaleic anhydride, using lithium tri-t-butoxyaluminium hydride in glyme at -20°C, first led to the 4-hydroxy-2-butenolide (3, 67%), which was obtained as colourless crystals, m.p. 81°C, ν_{max} 1750, 1690 cm.$^{-1}$, δ_H 6.0 (br, CHOH), 5.7 (br,OH), 2.05 (Me), 1.85 (Me).[5] Treatment of (3) with 1,2-dibromoethyl ethyl ether in the presence of triethylamine (-78°C→0°C), next led to a mixture of diastereoisomers of the

sensitive bromo-acetal (4), which was not purified rigorously, but instead treated with tri-n-butylstannane in the presence of AIBN (C_6H_6, reflux, 1 h) to afford a diastereoisomeric mixture of the linear-fused lactone-acetals (5).[6] Oxidation of a solution of (5) in methylene dichloride, using m-chloroperbenzoic acid-boron-trifluoride etherate[7], followed by crystallisation then gave the cyclic acetal-bis-lactone structure (6) as colourless needles, m.p. 116.5-117°C, ν_{max} 1800, 1000cm.$^{-1}$, δ_H 5.87 (OCHO), 2.7 (q, J 7 Hz, CH_3CH), 2.61 (d, J 18 Hz, OCOCHH), 2.32 (d, J 18 Hz, OCOCHH), 1.43 (Me), 1.27 (d, J 7 Hz, CHMe); δ_C10.0(q), 21.8(q), 34.9(t), 44.4(d), 47.2(s), 106.0(s), 173.5(s), 174.4(s) p.p.m. The anti-relationship between the two methyl groups in the bicyclic molecule(6) was established from n.O.e difference spectra; thus irradiation at δ1.43 (angular Me) in the p.m.r. spectrum enhanced the C-H signal at δ2.7 by 2.4%, and irradiation at δ1.27 enhanced the signal at δ5.87 (OCHO) by 1.6%.

The synthesis of the unusual spiro-fused bis-lactone (10) was achieved via the bromo-acetal intermediate produced from the known natural product hydroxymethyl 2-butenolide (7)[8]. Thus, treatment of (7) with a mixture of bromine in ethyl vinyl ether in methylene dichloride in the presence of triethylamine at -78°C first afforded the bromo-acetal (8; 78%). Reaction between (8) and Bu_3SuH-AIBN then led to the spiro-system (9; 88%) which upon oxidation using Jones' reagent at 0°C gave the spiro-bis lactone (10)[9] as colourless needles, m.p. 211-3°C, ν_{max} 1785 cm.$^{-1}$, δ_H4.4 (2 x CH_2CO), 2.82 (d, J 17.8 Hz, CHHCO), 2.79 (d, J 17.8Hz, CHHCO); δ_C38.7(CH_2CO), 45.0, 76.0(CH_2OCO), 206 p.p.m.

To explore the use of other 'acrylate' electrophores, in radical cyclisations leading to the spiro-fused oxyanhydride (14) we also synthesised the substituted methoxymaleic anhydride (13) together with the substituted maleate (12b). Thus, a Claisen condensation between ethyl hex-5-enoate and diethyl oxalate followed by methylation (Me_2SO_4, K_2CO_3, Me_2CO, reflux) of the resulting keto-ester first gave the methyl ether (11). Hydroboration-oxidation of (11) ($BH_3.Me_2S$ then 30% aq. H_2O_2-3M NaOH) next led to the carbinol (12a; 75%) which was then converted into the bromide (12b; $Cl_2Br.C.CBrCl_2$,PPh_3; 60%). Saponification of the substituted maleate (11) in the presence of aqueous methanolic potassium hydroxide, followed by treatment with thionyl chloride (reflux, 0.5 h) provided the corresponding maleic anhydride, which upon treatment with thiophenol (AIBN, 80°C, 1 h), led to the phenylsulphide (13) obtained as colourless crystals, m.p. 44-5°C (Et_2O-petrol).[10] All attempts to cyclise (13) to the spiro-anhydride (14) (or to 15), under a range of radical initiation conditions, led to failure; either (13) was recovered unchanged, or complex mixtures of products were produced. By contrast, radical cyclisation of the bromide (12b) in the presence of Bu_3SnH-AIBN (C_6H_6 reflux, 1 h), proved to be particularly facile, and gave rise to the spiro bis-ester (16) in 95% yield. Saponification of (16) (aq. methanolic KOH, reflux 9 h) followed by cyclodehydration of the resulting succinic acid ($SOCl_2$ reflux, 4 h), then



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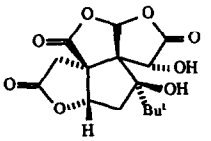

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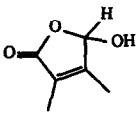

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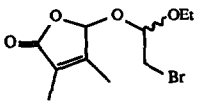

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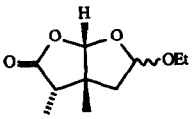

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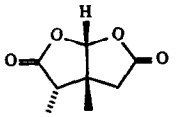

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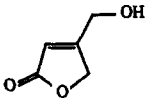

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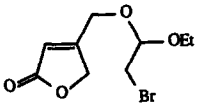

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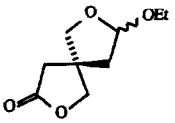

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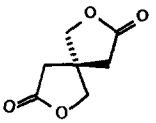

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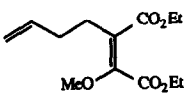

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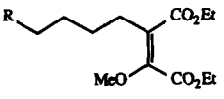
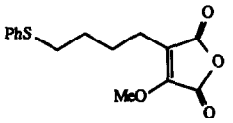


(12)
a, R = OH, *b*, R = Br



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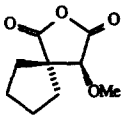

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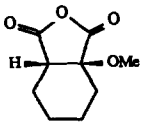

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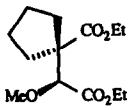

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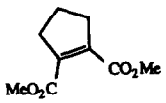

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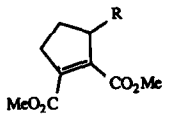
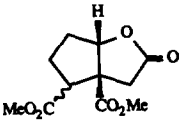


(18)

a R = Br, *b* R = OH,
c R = OCH(OEt)CH_2Br



(19)

provided the oxyanhydride (14), as an oil, ν_{max} 1786(s), 1855(w) cm.$^{-1}$, δ_H 4.0 (CHOMe), 3.66(OMe), 1.5-1.95 (br, 8H).

As a corollary to the above studies, we also prepared the linear-fused lactone bis-ester (19) starting from the cyclopentene diester (17),[11] following: bromination (NBS, $CHCl_3$, hν) to (18a), hydrolysis (NaOCHO, dioxan, 50°C, then KOH, MeOH, H_2O) to (18b), conversion to the bromo-acetal (18c), and finally radical cyclisation (Bu_3SnH-AIBN) and oxidation (Jones, 0°C). This sequence resulted in the formation of a 1:1 mixture of α- and β- sec-ester epimers of the bicycle (19) in good overall yield from (17). Further work is in progress to evaluate alternative furanone, maleate and maleic anhydride electrophores in radical cyclisation reactions for applications in natural products synthesis.

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