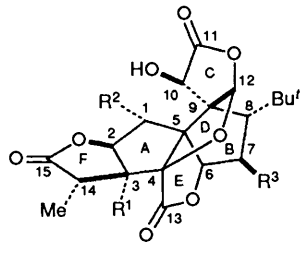
Studies on the Synthesis of Ginkgolides. Rapid Construction of the Spiro[4.4]nonane A and B Rings†

Mark R. DeLuca and Philip Magnus*
Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

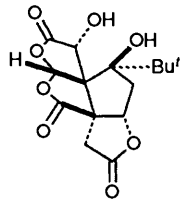
The functionalised spiro[4.4]nonane **30** is available from *tert*-butylcyclopentadiene **16** *via* spiroalkylation with **12b** to give **17/18**, followed by singlet oxygenation/aldolisation to the mixture of **21**, **22**, **25** and **26**. Oxidation of the mixture gave two enediones **28/29**, which were reduced with K-Selectride and the diastereoisomer **26** was separated and hydrogenated to give **30**.

The ginkgo tree, *Ginkgo biloba*, is the last surviving member of a family of trees (Ginkgoales) which first appeared on earth more than 200 million years ago. The Ginkgoales have since become extinct, except for the *Ginkgo biloba*, which has been identified in fossil remains that are 150 million years old. It is the oldest species of tree remaining on the earth.[1] The longevity of the ginkgo tree can be attributed to its remarkable ability to adjust to a wide variety of environments.[1] The ginkgo tree has been shown to be extremely resistant to insects and fungal diseases. A ginkgo tree has even survived the nuclear explosion at Hiroshima.[2] For over 5000 years, the tree has been part of the traditional Chinese pharmacopeia. An aqueous extract, obtained by boiling the leaves, is used to alleviate asthma and bronchitis.[2]

The chemical composition of the ginkgo tree has shown that the therapeutic effects can be accounted for by five distinct compounds, called ginkgolides. They were obtained by extraction of the leaves and roots of the tree.[3] The ginkgolides were first isolated in 1932 from the leaves of the *Ginkgo biloba*,[4] and structural studies in the early 1960s by Nakanishi, led to the separation of four distinct ginkgolides **1**–**4** (Scheme 1). The



Ginkgolide



Bilobalide 6

	R_1	R_2	R_3
Ginkgolide A **1**	OH	H	H
Ginkgolide B **2**	OH	OH	H
Ginkgolide C **3**	OH	OH	OH
Ginkgolide J **4**	OH	H	OH
Ginkgolide M **5**	H	OH	H

Scheme 1

correct structural determination of the ginkgolides by single crystal X-ray crystallography was reported by Sakabe *et al.*[5] In 1987, a fifth ginkgolide, ginkgolide **J4**, was discovered by Weinges *et al.*[6] The five ginkgolides all share the same 20 carbon cage structure, consisting of a *tert*-butyl side group, a spiro[4.4]nonane (A and B rings), a tetrahydrofuran ring (D ring), and three lactone rings (C, E and F rings). To date, the ginkgolides and bilobalide **6**,[7] another natural product isolated from *Ginkgo biloba*, are the only known natural products which contain a *tert*-butyl group.

Recently the ginkgolides have attracted a great deal of interest as antagonists of platelet-activating factor (PAF).[3] The ginkgolides are strong competitive inhibitors of PAF, and as a result have gained widespread use in research and in the treatment of various disorders associated with PAF. Corey *et al.*[8] were able to determine some of the structural features of the ginkgolide molecules that are important for PAF antagonist activity. The C(4)–C(12) ether bridge (ring D) is essential for activity. Protection of the alcohol groups, forming non-polar derivatives, significantly increases the inhibitory ability. It was also found that excellent activity could be retained even if the C(2)–C(3) lactone ring was missing, although some polar functionalization at C(1) and C(2) was shown to be necessary.

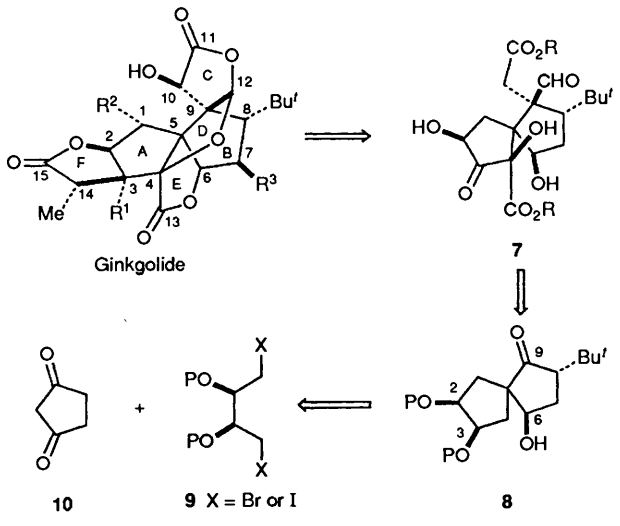
The widespread interest in PAF anatagonists has led to a number of synthetic studies of the ginkgolide molecules. In 1988, the first and only total synthesis of the ginkgolides was reported by Corey *et al.*[8] The first group to report synthetic studies on the ginkgolides was Weinges *et al.*[9] In 1987, Villhauer and Anderson[10] reported the first synthesis of the C, D and E rings of the ginkgolide skeleton. The use of a furan [2 + 2] photocyclization to build the ginkgolide skeleton has also been used by Crimmins.[11]

The most comprehensive synthetic study of the ginkgolides has been carried out by Corey's group. This work includes: the total synthesis of ginkgolide A,[12] the total synthesis of ginkgolide B,[8] an enantioselective modification of these synthetic routes,[13] and a new route for the synthesis of the B, C, D and E rings of the ginkgolides.[14] Corey has also reported the synthesis of simple ginkgolide derivatives, based on his earlier total syntheses,[8,12] which have helped determine some of the important structural features for the ginkgolides PAF inhibition activity.[15]

Results and Discussion

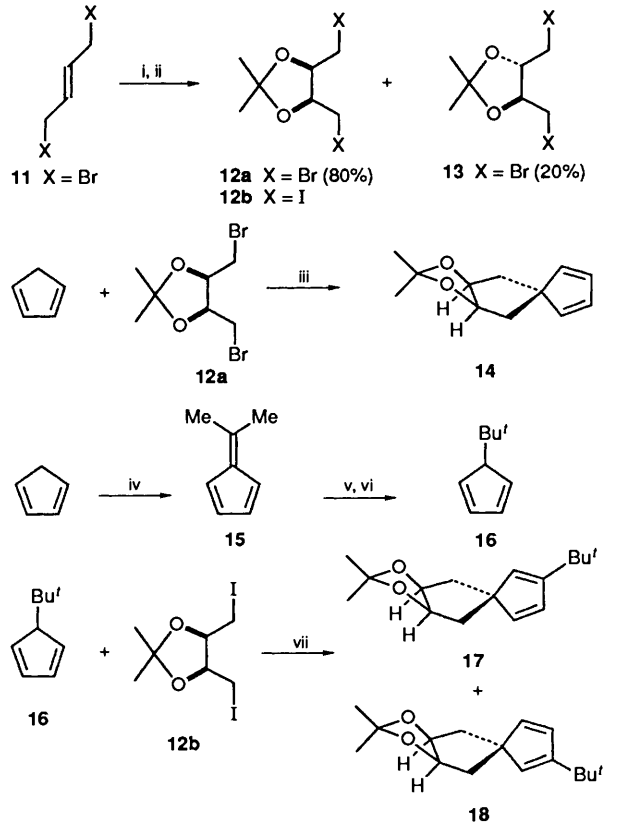
The ginkgolides all share the same complex hexacyclic structure consisting of a spiro carbocyclic system, three lactone rings, a tetrahydrofuran ring, and a *tert*-butyl group. The most important of these features, from a synthetic point of view, is the core spiro carbocyclic ring system (rings A and B).[16] The importance of this ring system is clearly shown in the structure **7**, proposed as a possible precursor to the ginkgolides (Scheme 2).[16] A plausible intermediate for the synthesis of the ginkgolide precursor **7** is the spiro[4.4]nonane **8**. The enolate anion of **10** on treatment with the dihalide **9** should give a spiro intermediate which could then be converted into the compound **8**. Investigation of this strategy began with the synthesis of the

† Submitted to mark the 150th anniversary of the Chemical Society/Royal Society of Chemistry.



Scheme 2

dihalide **12a** from *trans*-1,4-dibromobut-2-ene **11**, by the procedure of Semmelhack *et al.*[17] Oxidation of the dibromide **11** with MCPBA, followed by Lewis acid catalysed acetonide formation ($SnCl_4$, acetone) gave the desired dibromide as a mixture of *cis*-**12a** and *trans*-**13** isomers (4:1), Scheme 3.



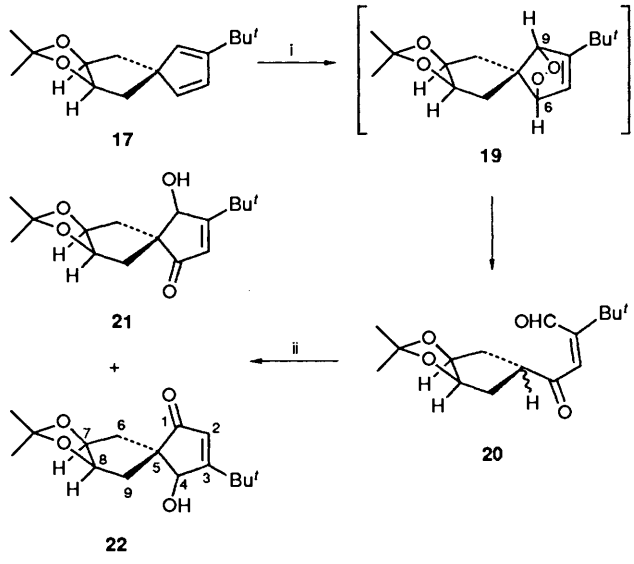
Scheme 3 *Reagents*: i, MCPBA; ii, $SnCl_4$, acetone; iii, NaH, THF; iv, acetone, KOH/EtOH; v, MeLi; vi, H_2O; vii, $NaNH_2$, THF

Spiroannulation of the diketone **10** with the dibromide **12a** using sodium hydride as the base failed. In all cases, only starting materials were obtained. It is known that the alkylation of the diketone **10** can be accomplished in aqueous basic solutions,[18] however, when a basic solution of the ketone **10** was treated with **12a** and heated at reflux only starting material was obtained. Further attempts using sodium amide in liquid ammonia also failed to produce any of the desired products. Finally, attempted spiroalkylation using the diiodide **12b** also failed.

During an investigation of spiro conjugation, Semmelhack *et al.*[17] alkylated **12a** with cyclopentadienyl anion to give **14**. For our purposes, this procedure was modified by using *tert*-butylcyclopentadiene **16**, which was readily made from cyclopentadiene. Condensation of cyclopentadiene with acetone in KOH/EtOH yielded dimethylfulvene **15** which on treatment with MeLi in Et_2O followed by aqueous work-up gave *tert*-butylcyclopentadiene **16** in 72% yield as a mixture of diene fluxional isomers.

Initial attempts at synthesizing the spirocycles **17** and **18** (using NaH, dibromide **12a**) gave only poor yields of the desired product. However, using sodium amide as the base, and the diiodide **12b** as the alkylating agent, a 1:1 mixture of the spiro[4.4]nonanes **17** and **18** could be obtained in 58% combined yield. Separation of these products could be achieved by repeated silica gel chromatography. The relative stereochemistry of **18** was determined by single crystal X-ray crystallography (unpublished result).

Attention was now focused on the introduction of oxygen functionality into the diene portion of the spiro[4.4]nonanes **17** and **18**. It is well known that the reaction of singlet oxygen (Δ^1O_2) with 1,3-dienes yields 1,4-endoperoxides, Scheme 4.[19]

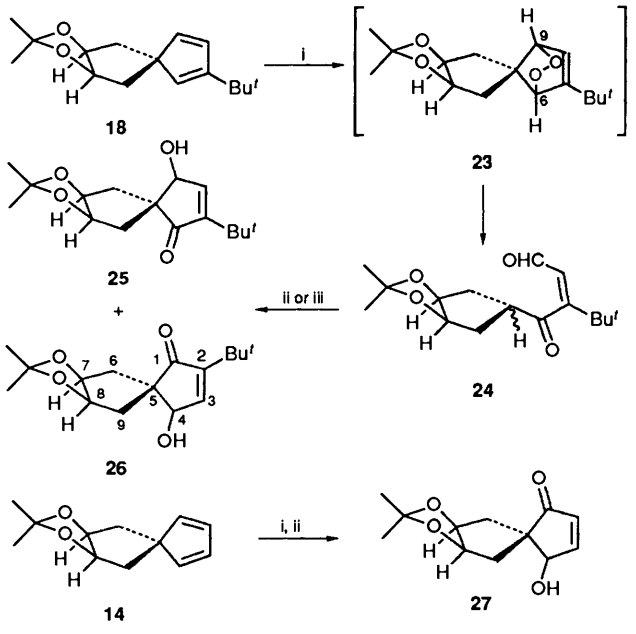


Scheme 4 *Reagents*: i, O_2, Rose Bengal, hv, MeOH; ii, silica gel/Et_2O or THF/aq. NaOH

These endoperoxides are readily decomposed to yield products which are functionalized with oxygen at the 1 and 4 position of the diene. When the spirononane **17** was treated with $^1O_2$ (generated *in situ* by the photosensitizer Rose Bengal), the aldehyde **20** was isolated as a mixture of epimers. Under no conditions could the endoperoxide intermediate **19** be isolated. Purification of the aldehydes **20** was difficult because of rapid irreversible aldol cyclisation to the hydroxyenones **21** and **22**, under both basic and acidic conditions. When **20** was stirred with silica gel at room temperature, aldol cyclization occurred to give the β-hydroxy enone **22** as the major product (10:1). When the aldehydes **20** were stirred in aqueous NaOH/THF, the β-hydroxy enone **22** was still the major product formed, but the selectivity was much lower (2:1). The stereoselectivity of the aldol reaction can be explained by approach of the aldehyde to the ketone enolate from the less hindered face of the molecule (convex), that is, the face opposite the acetonide group.

Separation of the diastereoisomers **21** and **22** was readily accomplished by silica gel chromatography. The less polar

β-hydroxy enone **21** shows (IR) significant intramolecular hydrogen bonding between the acetonide oxygen atoms and the alcohol substituent. The position of the *tert*-butyl group was readily determined by proton NMR spectroscopy, which shows the olefin proton at δ 6.04 and 5.96 for **21** and **22**, respectively. This was compared to the 2-H of 4-hydroxycyclopenten-1-one which appears at δ 6.18.[20] The relative stereochemistry of **25** was confirmed by single crystal X-ray crystallography (unpublished result). The mechanism for this fragmentation was extensively studied by Solomon *et al.* during their research of the decomposition of prostaglandin endoperoxides.[21] In our case, when the diene **17** was treated with singlet oxygen in a polar protic solvent, the products obtained consist of mainly the keto aldehydes **20**. Thus, after cycloaddition with singlet oxygen occurs, the resulting endoperoxide must undergo an immediate rearrangement similar to that seen by Solomon.[21]

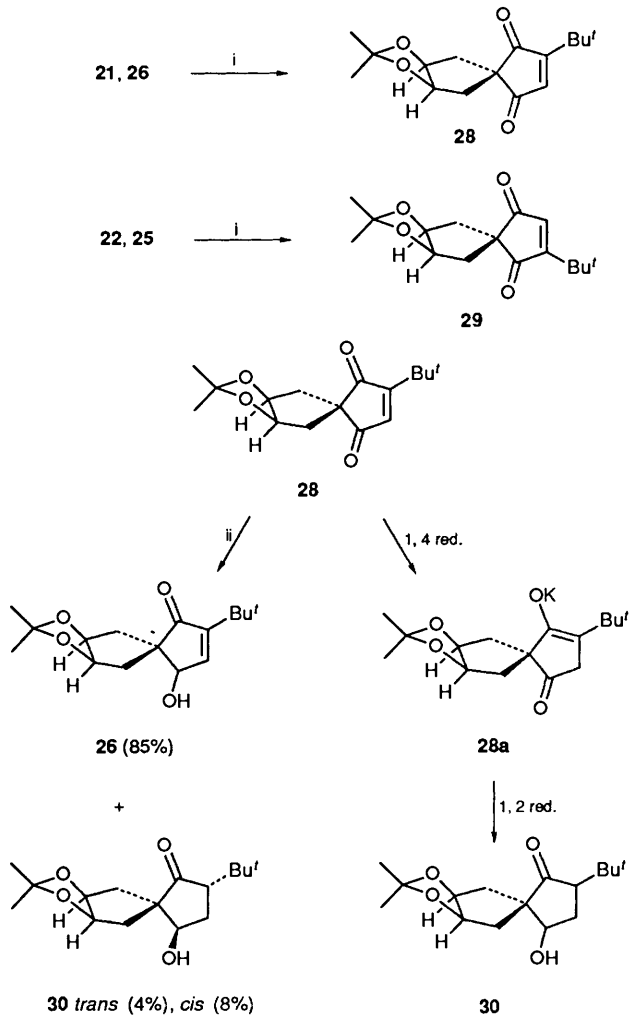


Scheme 5 *Reagents:* i, O_2, Rose Bengal, hv, MeOH; ii, silica gel/Et_2O; iii, THF/aq. NaOH

Similar results were obtained when the diene **18** was treated with singlet oxygen to give the epimeric aldehydes **24**, Scheme 5. The aldehyde intermediates **24** are unstable and undergo aldol condensation to form **25** and **26**. When treated with silica in ether, the yield of the β-hydroxy enones **25**/**26** was 38%, and the product ratio was 5:1 in favour of **25**. Base-catalysed aldol condensation gave the diastereoisomers **25**/**26** in 75% yield, the isomer **25** being the major product formed (6.5:1). The regiospecificity of the products **25** and **26** was determined by proton NMR analysis, which showed the olefin protons at δ 7.17 and 6.97, respectively. This was compared to the C(3) proton of 4-hydroxy-2-methyl-cyclopenten-1-one, which appears at δ 7.22.[20]

When the diene **14**[17] was treated with singlet oxygen, followed by silica gel/ether, only one regioisomer, the hydroxy enone **27**, was obtained. The stereochemistry of **27** was determined by observing the effect of concentration on the hydrogen bonding stretch in the infrared spectrum. As the concentration was decreased, the intensity of the peak due to the hydrogen bonding stretch was reduced, and the free hydroxy stretch intensity is increased (see Experimental section for further details).

Treatment of the β-hydroxy enones **21**,**26** and **25**,**22** with MnO_2 in benzene heated at reflux gave the corresponding enones **28** and **29** respectively in 70–80% yield, Scheme 6. We could, therefore, convert the four diastereoisomers into the two isomeric enediones **28** and **29**.



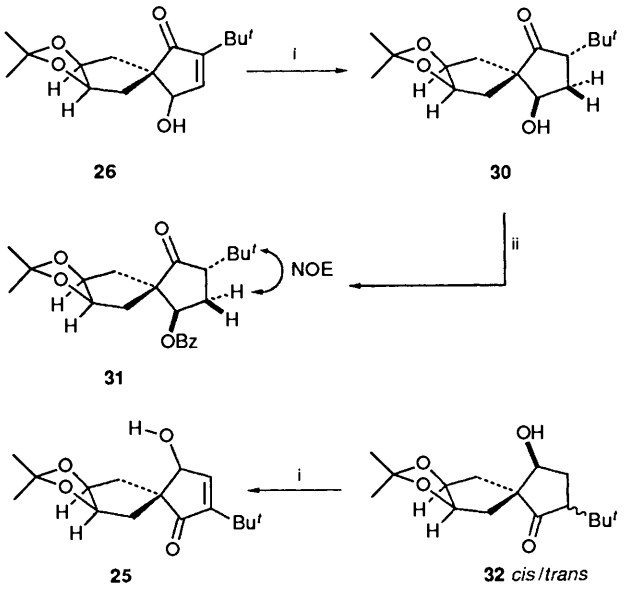
Scheme 6 *Reagents and conditions:* i, MnO_2, benzene, heat; ii, K-Selectride, THF, −78 °C

This oxidation was particularly useful for further confirmation of the stereochemistry and regiochemistry of the hydroxy enones **21** and **22**. Oxidation of **21** and **26** should give the same product. This proved to be the case as shown by GC and mixed NMR analysis. Similarly, the oxidation products of **22** and **25** were identical. From this information, the stereochemistry of **21** and **22** could be assigned as shown, since the stereochemistry of **25** was known by X-ray crystallography.

Attempted 1,4-reduction followed by 1,2-reduction of **28** using K-Selectride, with the intention of making **30**, gave largely the 1,2-adduct **26** with small amounts of the desired reduction product **30**.

Catalytic hydrogenation of an allylic alcohol is known to be a stereospecific process where the hydrogen is delivered from the same face as the hydroxy group, resulting in *trans* stereochemistry.[22] Catalytic hydrogenation of the allylic alcohol **26** using PtO_2 as the catalyst gave a single product **30**, Scheme 7. The stereochemistry was determined by conversion of **30** to the benzoate derivative **31** and NOE analysis of this product (see Experimental section for details).

In contrast, catalytic hydrogenation of the allylic alcohol **25** proceeded very slowly to give **32** (days instead of hours, *cf.* **26**), and no stereoselectivity was observed. Probably the strong hydrogen bond between the acetonide and the alcohol in **25** prevents coordination of the catalyst.



Scheme 7 *Reagents:* i, PtO_2, H_2; ii, benzoyl chloride, pyridine

Conclusions

The synthetic pathway begins with the synthesis of the spiro dienes **17** and **18**. These dienes are very difficult to separate by preparative chromatography, although, as it turns out, this separation is not necessary. Singlet oxygenation, followed by aldol condensation, gives a mixture of four products: **21**, **22**, **25** and **26**. Again, purification is not necessary for this step and the mixture of enones can be treated with MnO_2 to yield a mixture of two products, the enediones **28** and **29**. Separation of the isomers at this stage is difficult to achieve by preparative column chromatography. However, if the mixture of diones is reduced with K-Selectride (1 equiv., −78 °C), the resulting hydroxy enones **25** and **26** can be easily separated. This separation can be accomplished due to the intramolecular hydrogen bonding seen in diastereoisomer **25**. This interaction has a significant effect on the relative polarity of the hydroxyenones **25** (R_f 0.45) and **26** (R_f 0.14), as seen by their retention values on silica (eluting with 50% Et_2O/hexanes). Finally the hydroxy enone **26** can be stereoselectively reduced with PtO_2 to yield the desired saturated hydroxy enone **30**. Thus in five steps the protected version of **8**, namely **30** is available with the correct relative stereochemistry needed for the ginkolides.

Experimental

Melting points were taken on a Thomas–Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer or a 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B UV/VIS spectrophotometer in the indicated solvents. Proton NMR spectra were recorded on a General Electric QE-300 300 MHz spectrometer in the indicated solvent, and are reported in ppm downfield from TMS. Carbon-13 NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated, and are also reported in ppm downfield from TMS. All *J*-values are given in Hz. Elemental analyses were performed by Midwest Microlab in Indianapolis, Indiana. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminium-backed TLC plates. Preparative layer chromatography was performed using Merck 60 F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel. Gas–liquid chromatography was performed on a Hewlett Packard 5890 system, using an HP-1 capillary column.

Air and moisture sensitive reactions were performed under usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2, and benzene were distilled from calcium hydride under argon.

tert-*Butylcyclopentadiene* **16**.—A solution of MeLi (1.4 mol dm^{-3} in Et_2O; 800 cm^3, 1.12 mol) was added to a 2 dm^3 round bottom flask and cooled to −78 °C. A solution of dimethylfulvene **15**[23] (75.2 g, 0.709 mol) in Et_2O (500 cm^3) was slowly added and the reaction was allowed to warm to 25 °C during 16 h. The solution was cooled to 0 °C and water (250 cm^3) was slowly added. After addition was complete, the mixture was warmed to 25 °C, the layers were separated, and the Et_2O layer was dried ($MgSO_4$) and filtered. Fractional distillation gave a mixture of *tert*-butylcyclopentadiene regioisomers **16** as a yellow oil (62.5 g, 72%); b.p. 35–40 °C (13 mmHg); δ_H(90 MHz; $CDCl_3$) 6.62–5.83 (3 H, m), 2.95–2.94 (2 H, m) and 1.18 (9 H, s); *m/z* (EI) 122 (M^+) and 107 (base), 91.

cis-4,5-*Di*(*bromomethyl*)-2,2-*dimethyl*-1,3-*dioxolane* **12a**.—*trans*-1,4-Dibromobut-2-ene (50.6 g, 0.237 mmol) and 3-chloroperoxybenzoic acid (MCPBA, 54.4 g, 0.315 mmol) were dissolved in $CHCl_3$ (400 cm^3), and heated at reflux for 20 h. After this time, the solution was cooled to 25 °C and the chlorobenzoic acid filtered off. The filtrate was washed with $NaHSO_3$ (1 mol dm^{-3}; 2 × 200 cm^3), then with saturated aqueous $NaHCO_3$ (2 × 200 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. Fractional distillation gave *trans*-2,3-di(bromomethyl)oxirane (51.8 g, 95%) as a colourless oil. This epoxide (51.8 g, 0.255 mmol) was then dissolved in acetone (60 cm^3) and added to a solution of $SnCl_4$ (3.6 cm^3, 8.0 g, 0.031 mmol) and acetone (30 cm^3) in CCl_4 (40 cm^3). The mixture was heated for 4 h at 50 °C. After this time, the solution was cooled to 25 °C, and added to aqueous NaOH (1 mol dm^{-3}; 750 cm^3) to dissolve the tin residues. The layers were separated, and the organic layer was washed with aqueous NaOH (1 mol dm^{-3}; 150 cm^3), water (150 cm^3) and brine (50 cm^3). The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and distilled to yield the *cis*-dibromide **12a** (50.6 g, 78%) as a colourless oil, b.p. 75–85 °C (1 mmHg); δ_H(300 MHz; $CDCl_3$) 4.52–4.41 (2 H, m), 3.58–3.39 (4 H, m), 1.52 (3 H, s) and 1.37 (3 H, s) [lit.,[17] δ_H(90 MHz; $CDCl_3$) 4.8–4.3 (2 H, m), 3.7–3.5 (4 H, m), 1.47 (3 H, s) and 1.35 (3 H, s)].

cis-4,5-*Di*(*iodomethyl*)-2,2-*dimethyl*-1,3-*dioxolane* **12b**.—To a solution of the dibromide **12a** (50.6 g, 0.176 mmol) in acetone (1.0 dm^3), was added NaI (124 g, 0.827 mmol) and the mixture was refluxed for 24 h. After this time, the reaction was cooled, the NaBr filtered off, and the acetone removed *in vacuo*. The residue was dissolved in $CHCl_3$ (500 cm^3) and water (500 cm^3). The layers were separated and the aqueous layer was washed with $CHCl_3$ (250 cm^3). The combined organics were washed with aqueous $Na_2S_2O_3$ (1 mol dm^{-3}; 500 cm^3) and brine (500 cm^3). The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and distilled to give the desired diiodide **12b** (45.6 g, 68%) as a colourless oil, b.p. 100–110 °C; δ_H(300 MHz; $CDCl_3$) 4.56–4.42 (2 H, m), 3.57–3.22 (4 H, m), 1.58 (3 H, s) and 1.42 (3 H, s).

(±)-(7S,8R)-3-tert-*Butyl*-2,3-*isopropylidenedioxyspiro*[4.4]-*nona*-1,3-*diene* **17** *and* (±)-(7S,8R)-2-tert-*Butyl*-2,3-*isopropylidenedioxyspiro*[4.4]*nona*-1,3-*diene* **18**.—To a suspension of

$NaNH_2$ (13 g, 0.33 mol) in THF (210 cm^3) was added a solution of *tert*-butylcyclopentadiene **16** (20.4 g, 0.167 mol) and the diiodide **12b** (22.27 g, 0.0583 mol) in THF (90 cm^3) over a period of 2 h. After addition was complete, the mixture was stirred for an additional 1 h at 25 °C. The reaction mixture was quenched by addition of water (50 cm^3). The solution was diluted with Et_2O (50 cm^3) and the layers were separated. The aqueous layer was washed with additional Et_2O (50 cm^3) and the combined organics were dried ($MgSO_4$). Removal of solvent *in vacuo* and repeated silica gel chromatography (50% CH_2Cl_2/hexanes) gave two products **17** and **18** (9.72 g, 58%) in a 1:1 ratio.

Compound **17** crystallized from EtOH/H_2O as colourless plates, m.p. 93–93.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965s, 1643w, 1611w, 1384s, 1375s, 1364m and 1136s; λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1} 2890); δ_H(300 MHz; $CDCl_3$) 6.77 (1 H, dd, *J* 5.4, 2.1), 6.23 (1 H, dd, *J* 5.4, 1.8), 5.54 (1 H, t, *J* 1.8), 4.83 (2 H, m), 2.03 (2 H, ddd, *J* 14.4, 4.0, 1.4), 1.76 (2 H, d, *J* 14.4), 1.60 (3 H, s), 1.34 (3 H, s) and 1.12 (9 H, s); δ_C(75 MHz; $CDCl_3$) 153.98 (s), 143.64 (d), 131.40 (d), 128.09 (d), 109.76 (s), 81.58 (d), 61.48 (s), 39.12 (t), 31.85 (s), 29.41 (q), 26.08 (q) and 23.47 (q); *m/z* (EI) 248 (M^+), 233, 190, 175 and 119 (base); (Found: C, 76.89; H, 9.56. Calc. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74%).

Compound **18** crystallized from EtOH/H_2O as colourless needles, m.p. 102–102.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964s, 1653w, 1611w, 1384s, 1375s, 1365m and 1151s; λ_{max}(EtOH)/nm 253 (ε/dm^3 mol dm^{-1} 2870); δ_H(300 MHz; $CDCl_3$) 6.35 (2 H, m), 6.02 (1 H, dd, *J* 4.1, 2.8), 4.83 (2 H, m), 2.04 (2 H, ddd, *J* 14.1, 3.6, 1.2), 1.76 (2 H, d, *J* 14.4), 1.62 (3 H, s), 1.35 (3 H, s) and 1.13 (9 H, s); δ_H(300 MHz; C_6D_6) 6.74 (1 H, dd, *J* 2.0, 1.6), 6.38 (1 H, dd, *J* 5.3, 1.6), 5.92 (1 H, dd, *J* 5.3, 2.0), 4.45 (2 H, m, H), 1.87 (2 H, d, *J* 14.1), 1.70 (2 H, dd, *J* 14.1, 1.2), 1.67 (3 H, s), 1.21 (3 H, s) and 1.17 (9 H, s); δ_C(75 MHz; $CDCl_3$) 151.7 (s), 142.5 (d), 133.0 (d). 130.1 (d), 110.0 (s), 81.8 (d), 61.6 (s), 39.2 (t), 31.8 (s), 29.4 (q), 26.2 (q) and 23.7 (q); *m/z* (EI) 248 (M^+), 233, 190, 175 (base) and 119; (Found: C, 77.38; H, 9.56. Calc. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74%).

(±)-(7S,8R)-2-tert-*Butyl*-4-*hydroxy*-7,8-*isopropylidenedioxyspiro*[4.4]*non*-2-*enone* **26** *and* (±)-(7S,8R)-3-tert-*Butyl*-1-*hydroxy*-7,8-*isopropylidenedioxyspiro*[4.4]*non*-2-*one* **25**.—(*a*) *Acidic workup.* A solution of spirodiene **17** (168 mg, 0.677 mmol) and Rose Bengal (20 mg) in MeOH (40 cm^3) was irradiated with a 450 W arc lamp (Ace Glass-Hanoria) while oxygen was bubbled continuously through the solution. After 1 h, the solution was diluted with Et_2O (40 cm^3), filtered through alumina (5 g, neutral, Brockmann I) and the alumina washed with 50% Et_2O/MeOH (50 cm^3). After removal of the solvent *in vacuo*, the residue was dissolved in Et_2O (20 cm^3), treated with silica gel (10 g), and stirred for 24 h at 25 °C. The silica gel was filtered and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography to give, on elution with Et_2O/hexanes (1:1), two isomeric products in a 10:1 ratio –**26** (131.7 mg, 70%) and **25** (12.6 mg, 7%), total (153 mg, 77%).

(*b*) *Basic work-up.* A solution of spirodene **17** (168 mg, 0.677 mmol) and Rose Bengal (20 mg) in MeOH (40 cm^3) was irradiated with a 450 W arc lamp (Ace Glass-Hanoria) while oxygen was bubbled continuously through the solution. After 1 h, the solution was diluted with Et_2O (40 cm^3), filtered through alumina (5 g, neutral, Brockmann I) and the alumina washed with 50% Et_2O/MeOH (50 cm^3). After removal of the solvent *in vacuo*, the residue was dissolved in THF (10 cm^3), treated with aqueous NaOH (1 mol dm^{-3}; 1.0 cm^3) and stirred for 30 min at 25 °C. The solution was diluted with Et_2O (10 cm^3), washed with water (2 × 5 cm^3), brine (5 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by silica gel chromatography to give, on elution with Et_2O/hexanes (1:1), two isomeric products in a 2:1 ratio—**26** (110 mg, 58%) and **25** (55 mg, 29%), total (165 mg, 87%).

Compound **26** crystallized from Et_2O/pentane as colourless needles, m.p. 176–177 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2965, 1711, 1600 and 1072; λ_{max}(EtOH)/nm 221 (ε/dm^3 mol^{-1} cm^{-1} 6510); δ_H(300 MHz; $CDCl_3$) 6.97 (1 H, d, *J* 2.3), 4.74–4.79 (2 H, m), 4.40 (1 H, dd, *J* 6.1, 2.3), 2.39 (1 H, d, *J* 6.1, OH), 2.14–2.23 (2 H, m), 1.80–1.89 (2 H, m), 1.56 (3 H, s), 1.33 (3 H, s) and 1.18 (9 H, s); δ_C(75 MHz; $CDCl_3$) 205.84 (s), 154.47 (s), 151.53 (d), 113.47 (s), 80.77 (d), 76.64 (d), 61.97 (s), 40.97 (t), 37.56 (t), 31.78 (s), 28.08 (q), 27.68 (q) and 25.34 (q); *m/z* (CI) 281 (M + 1), 265, 263, 223 and 205 (base); (Found: C, 68.59; H, 6.68. Calc. for $C_{16}H_{24}O_4$: C, 68.49; H, 8.51%).

Compound **25** crystallized from Et_2O/pentane as colourless needles, m.p. 120–121 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2966, 1708, 1386 and 1045; λ_{max}(EtOH)/nm 220 (ε/dm^3 mol^{-1} cm^{-1} 5510); δ_H(300 MHz; $CDCl_3$) 7.17 (1 H, d, *J* 2.7), 4.84 (1 H, t, *J* 5.3), 4.78 (1 H, t, *J* 5.7), 4.73 (1 H, dd, *J* 2.6, 1.4), 3.97 (1 H, d, *J* 1.5, OH), 2.27 (1 H, dd, *J* 14.9, 2.6), 1.95 (1 H, dd, *J* 14.3, 6.0), 1.86 (1 H, dd, *J* 14.9, 5.0), 1.76 (1 H, dd, *J* 14.3, 2.9), 1.57 (3 H, s), 1.34 (3 H, s) and 1.19 (9 H, s); δ_C(300 MHz; $CDCl_3$) 208.55 (s), 154.34 (s), 152.92 (d), 109.48 (s), 81.80 (d), 80.84 (d), 75.20 (d), 58.98 (s), 44.41 (t), 36.15 (t), 31.75 (s), 28.13 (q), 25.55 (q) and 22.93 (q); *m/z* (CI) 281 (M + 1), 265, 263, 233 and 205 (base); (Found: C, 68.49; H, 8.51. Calc. for $C_{16}H_{24}O_4$: C, 68.49; H, 8.51%).

(±)-(7S,8R)-3-tert-*Butyl*-4-*hydroxy*-7,8-*isopropylidenedioxyspiro*[4.4]*non*-7-*enone* **22** *and* (±)-(7S,8R)-2-tert-*Butyl*-1-*hydroxy*-7,8-*isopropylidenedioxyspiro*[4.4]*non*-2-*en*-3-*one* **21**.—(*a*) *Acidic work-up.* A solution of spirodiene **18** (113 mg, 0.406 mmol) and Rose Bengal (20 mg) in MeOH (40 cm^3) was irradiated with a 450 W arc lamp (Ace Glass-Hanoria) while oxygen was bubbled continuously through the solution. After 1 h, the solution was diluted with Et_2O (40 cm^3), filtered through alumina (5 g, neutral, Brockmann I) and the alumina was washed with 50% Et_2O/MeOH (50 cm^3). After removal of the solvent *in vacuo*, the residue was dissolved in Et_2O (20 cm^3), treated with silica gel (10 g), and stirred for 24 h at 25 °C. The silica gel was filtered and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography to give, on elution with Et_2O/hexanes (1:1), two isomeric products in a 5:1 ratio—**22** (50 mg, 31%) and **21** (8.1 mg, 7%), total (48.1 mg, 38%).

(*b*) *Basic work-up.* A solution of spirodiene **18** (168 mg, 0.677 mmol) and Rose Bengal (20 mg) in MeOH (40 cm^3) was irradiated with a 450 W arc lamp (Ace Glass-Hanoria) while oxygen was bubbled continuously through the solution. After 1 h, the solution was diluted with Et_2O (40 cm^3), filtered through alumina (5 g, neutral, Brockmann I) and the alumina was washed with 50% Et_2O/MeOH (50 cm^3). After removal of the solvent *in vacuo*, the residue was dissolved in THF (10 cm^3), treated with aqueous NaOH (1 mol dm^{-3}; 1.0 cm^3) and stirred for 30 min at 25 °C. The solution was diluted with Et_2O (10 cm^3), washed with water (2 × 5 ml), brine (5 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by silica gel chromatography to give, on elution with Et_2O/hexanes (1:1), two isomeric products in a 2:1 ratio—**22** (49.4 mg, 49%) and **21** (27.3 mg, 26%), total (77 mg, 75%).

Compound **22** crystallized from Et_2O/pentane, m.p. 179–180 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3437, 3020, 2969, 1704, 1603, 1383, 1374 and 1074; λ_{max}(EtOH)/nm 223 (ε/dm^3 mol^{-1} cm^{-1} 10 600); δ_H(300 MHz; $CDCl_3$) 5.97 (1 H, s), 4.74 (2 H, m), 4.52 (1 H, d, *J* 8.1), 2.71 (1 H, d, *J* 8.7), 2.25 (1 H, dd, *J* 13.4, 5.5), 2.09 (1 H, dd, *J* 13.4, 6.0), 1.92 (1 H, dd, *J* 13.4, 5.4), 1.81 (1 H, dd, *J* 13.4, 5.5), 1.55 (3 H, s), 1.32 (3 H, s) and 1.28 (9 H, s); δ_C(75 MHz; $CDCl_3$) 207.38 (s), 185.52 (s), 127.49 (d), 113.43 (s),

80.85 (d), 80.50 (d), 79.20 (d), 61.51 (s), 41.98 (t), 36.17 (t), 35.02 (s), 29.18 (q), 27.58 (q) and 25.25 (q); *m/z* (CI) 281 (M + 1), 265 (base), 263, 223 and 205; (Found: C, 68.08; H, 8.61. Calc. for $C_{16}H_{24}O_4$: C, 68.53; H, 8.63%).

Compound **21** crystallized from Et_2O/pentane, m.p. 135–136 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3455, 2968, 1697, 1606, 1386, 1378 and 1045; λ_{max}(EtOH)/nm 223 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 10 600); δ_H(300 MHz; $CDCl_3$) 6.04 (1 H, s), 4.90 (1 H, d, *J* 1.7), 4.82 (1 H, t, *J* 5.3), 4.76 (1 H, t, *J* 5.8), 3.82 (1 H, d, *J* 1.9), 2.29 (1 H, dd, *J* 14.9, 2.6), 1.93 (1 H, dd, *J* 14.4, 5.8), 1.91 (1 H, dd, *J* 15.1, 4.7), 1.75 (1 H, dd, *J* 14.3, 2.6), 1.55 (3 H, s), 1.32 (3 H, s) and 1.28 (9 H, s); δ_C(75 MHz; $CDCl_3$) 209.57 (s), 186.85 (s), 128.39 (d), 109.47 (s), 81.74 (d), 80.80 (d), 78.01 (d), 59.03 (s), 44.62 (t), 35.52 (t), 35.13 (s), 29.29 (q), 25.59 (q) and 22.98 (q); *m/z* (CI) 280 (M + 1, base), 280 (M^+), 265, 263, 223 and 205; (Found: C, 68.57; H, 8.63. Calc. for $C_{16}H_{24}O_4$: C, 68.53; H, 8.63%).

(±)-(7S,8R)-7,8-*Isopropylidenedioxyspiro*[4.4]*nona*-1,3-*diene* **14**.—Following the procedure of Semmelhack,[17] freshly distilled cyclopentadiene was added to a suspension of NaH (13 g, 0.33 mol) in THF (210 cm^3). Dibromide **12a** (22.27 g, 0.0583 mol) in THF (90 cm^3) was then added over a period of 2 h. After addition was complete the mixture was stirred for an additional 1 h at 25 °C. The reaction was quenched by addition of water (50 cm^3). The solution was diluted with Et_2O (50 cm^3) and the layers were separated. The aqueous layer was washed with additional Et_2O (50 cm^3) and the combined organics were dried ($MgSO_4$). Removal of solvent and silica gel chromatography (50% CH_2Cl_2/hexanes) gave **14** (9.72 g, 58%); δ_H(300 MHz; $CDCl_3$) 6.81 (1 H, dt, *J* 5.2, 1.5), 6.27 (1 H, dt, *J* 5.2, 1.5), 6.17 (1 H, dt, *J* 5.3, 1.3), 6.03 (1 H, dt, *J* 5.2, 1.6), 4.83 (2 H, d, *J* 5.6), 2.07 (2 H, dd, *J* 13.2, 4.0), 1.73 (2 H, d, *J* 14.3), 1.59 (3 H, s) and 1.32 (3 H, s) [lit.,[17] (90 MHz; CCl_4) 6.86–6.68 (1 H, m), 6.4–5.8 (3 H, m), 4.84–4.65 (2 H, m), 1.90 (2 H, dd, *J* 4.0, 1.5), 1.80 (2 H, br s), 1.54 (3 H, s) and 1.28 (3 H, s)]; δ_C(75 MHz; $CDCl_3$) 143.55 (d). 142.22 (d), 129.48 (d), 127.39 (d), 109.74 (s), 81.50 (d), 62.13 (s), 38.46 (t), 25.98 (q) and 23.38 (q).

(±)-(7S,8R)-4-*Hydroxy*-7,8-*isopropylidenedioxyspiro*[4.4]-*non*-2-*en*-1-*one* **27**.—A solution of spirodiene **14** (100 mg, 0.521 mmol) and Rose Bengal (20 mg) in MeOH (40 cm^3) was irradiated with a 450 W arc lamp (Ace Glass-Hanoria) while oxygen was bubbled continuously through the solution. After 1 h, the solution was diluted with Et_2O (40 cm^3), filtered through alumina (5 g, neutral, Brockmann I) and the alumina washed with 50% Et_2O/MeOH (50 cm^3). After removal of the solvent *in vacuo*, the residue was dissolved in Et_2O (20 cm^3), treated with silica gel (10 g), and stirred for 24 h at 25 °C. The silica gel was filtered off and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography to give **27** on elution with Et_2O/hexanes (1:1), as a colourless oil (43.1 mg, 40%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3412, 3023, 1715, 1593, 1383, 1375 and 1071; δ_H(300 MHz; $CDCl_3$) 7.44 (1 H, dd, *J* 5.8, 2.1), 6.22 (1 H, dd, *J* 5.8, 1.0), 4.75 (2 H, m), 4.53 (1 H, br s), 2.76 (1 H, br s), 2.27–2.13 (2 H, m), 1.90–1.81 (2 H, m), 1.54 (3 H, s) and 1.31 (3 H, s); δ_C(75 MHz; $CDCl_3$) 207.55 (s), 161.03 (d), 133.70 (d), 113.59 (s), 80.72 (d), 80.68 (d), 78.86 (d), 60.40 (s), 40.95 (t), 37.31 (t), 27.60 (q) and 25.26 (q); *m/z* (CI) 225 (M + 1, base), 209, 207, 195, 167 and 149 (Found: C, 64.36; H, 7.33. Calc. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%).

The stereochemistry of the hydroxy enone **27** was shown by the following IR experiment. Nearly all alcohols will show a broad band around 3550–3200 cm^{-1} due to intermolecular or intramolecular hydrogen bonding. Only in very dilute solutions or the gase phase can the sharp 'free' hydroxy stretching (3650–3584 cm^{-1}) be seen. For alcohols which form intermolecular hydrogen bonds, if the concentration is reduced the 'free' hydroxy band will become stronger in intensity. However if the compound forms intramolecular hydrogen bonds, the intensity of the hydrogen bonded hydroxy band will not change significantly if the concentration is reduced. For the enone **27** the alcohol and the acetonide face away from each other making intramolecular hydrogen bonding impossible. Thus, if this is the correct stereochemistry for **27** the IR should change significantly as concentration is reduced. This is indeed the case. Based on this result we have assigned the stereochemistry for **27** as shown.

(±)-(7S,8R)-2-tert-*Butyl*-7,8-*isopropylidenedioxyspiro*[4.4]-*non*-2-*ene*-1,4-*dione* **28**.—(*a*) *From* **21**. Hydroxy enone **21** (103 mg, 0.368 mmol) was dissolved in anhydrous benzene (10 cm^3) and was treated with MnO_2 (400 mg, 4.6 mmol). The mixture was heated at reflux for 16 h. After this time, the solution was cooled to 25 °C and filtered through Celite with Et_2O. Removal of the solvent *in vacuo* gave the dione **28** as a yellow solid (80.4 mg, 79%).

(*b*) *From* **26**. Hydroxy enone **26** (15 mg, 0.054 mmol) was dissolved in anhydrous benzene (10 cm^3) and was treated with MnO_2 (400 mg, 4.6 mmol). The mixture was heated at reflux for 16 h. After this time, the solution was cooled to 25 °C and filtered through Celite with Et_2O. Removal of the solvent *in vacuo* gave the dione **28** as a yellow solid (10 mg, 65%) which crystallized as pale yellow needles from Et_2O/pentanes, m.p. 112–113 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969, 1701, 1592, 1383, 1301 and 1075; λ_{max}(EtOH)/nm 232 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 12 100); δ_H(300 MHz; $CDCl_3$) 6.80 (1 H, s), 4.90–4.87 (2 H, m), 2.05–2.03 (4 H, m), 1.61 (3 H, s), 1.33 (3 H, s) and 1.30 (9 H, s); δ_H(300 MHz; C_6D_6) 6.27 (1 H, s), 4.79 (2 H, m), 2.12 (2 H, dd, *J* 13.3, 3.3), 1.81 (2 H, ddd, *J* 14.1, 5.6, 1.7), 1.62 (3 H, s), 1.21 (3 H, s) and 0.97 (9 H, s); δ_C(75 MHz; $CDCl_3$) 205.52 (s), 203.09 (s), 172.62 (s), 140.18 (d), 113.13 (s), 81.09 (d), 59.30 (s), 38.20 (t), 33.50 (s), 27.98 (q), 27.25 (q) and 25.03 (q); *m/z* (CI) 279 (M + 1), 263 (base), 221 and 203; (Found: C, 69.10; H, 8.04. Calc for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97%).

(±)-(7S,8R)-3-tert-*Butyl*-7,8-*isopropylidenedioxyspiro*[4.4]-*non*-2-*ene*-1,4-*dione* **29**.—(*a*) *From* **22**. Hydroxy enone **22** (66 mg, 0.24 mmol) was dissolved in anhydrous benzene (10 cm^3) and was treated with MnO_2 (400 mg, 4.6 mmol). The mixture was heated at reflux for 16 h. After this time, the solution was cooled to 25 °C and filtered through Celite with Et_2O. Removal of the solvent *in vacuo* gave the dione **29** as a yellow crystalline solid (48 mg, 73%).

(*b*) *From* **25**. Hydroxy enone **25** (26 mg, 0.093 mmol) was dissolved in anhydrous benzene (10 cm^3) and was treated with MnO_2 (400 mg, 4.6 mmol). The mixture was heated at reflux for 16 h. After this time the solution was cooled to 25 °C and filtered through Celite with Et_2O. Removal of the solvent *in vacuo* gave the dione **29** as a yellow crystalline solid (18.6 mg, 72%) which crystallized as pale yellow plates from Et_2O/pentane, m.p. 141–141.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969, 1743, 1701, 1592, 1383, 1374 and 1367; λ_{max}(EtOH)/nm 232 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 12 100); δ_H(300 MHz; $CDCl_3$) 6.87 (1 H, s), 4.90–4.87 (2 H, m), 2.06–2.02 (4 H, m), 1.61 (3 H, s), 1.33 (3 H, s) and 1.29 (9 H, s); δ_H(300 MHz; C_6D_6) 6.30 (1 H, s), 4.77 (2 H, m), 2.19 (2 H, dd, *J* 13.6, 3.6), 1.78 (2 H, ddd, *J* 14.1, 5.3, 1.5), 1.65 (3 H, s), 1.20 (3 H, s) and 0.95 (9 H, s); δ_C(75 MHz; $CDCl_3$) 206.29 (s), 202.50 (s), 170.80 (s), 141.91 (d), 113.20 (s), 81.14 (d), 59.47 (s), 38.21 (t), 33.36 (s), 28.00 (q), 27.25 (q) and 25.04 (q); *m/z* (CI) 279 (M + 1), 263 (base), 221 and 203; (Found: C, 68.89; H, 7.84. Calc. for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97%).

(±)-(7S,8R)-2-tert-*Butyl*-4-7,8-*isopropylidenedixoyspiro*[4.4]-*non*-2-*en*-1-*one* **26** *from* **28**.—A solution of dione **28** (106.6 mg, 0.38 mmol) in THF (3.0 cm^3) was cooled to −78 °C and treated

with a solution of K-Selectride (0.42 mmol) in THF (635 cm^3). After 1 h, the reaction mixture was quenched by addition of Et_2O (2.0 cm^3), aqueous NaOH (1 mol dm^{-3}; 2.0 cm^3) and 30% H_2O_2 (3.0 cm^3). The mixture was slowly warmed to 25 °C and stirred for 16 h. The mixture was diluted with Et_2O (5.0 cm^3) and the layers were separated. The aqueous layer was washed with Et_2O (5.0 cm^3). The organic layers were combined, washed with brine (5.0 cm^3), and dried ($MgSO_4$). Removal of solvent *in vacuo* followed by chromatography on silica gel with Et_2O/hexanes (1:1) gave hydroxy enone **26** (79 mg, 74%).

(±)-(7S,8R)-2-tert-*Butyl*-4-*hydroxy*-2,3-*isopropylidenedioxyspiro*[4.4]*nonan*-1-*one* **30**.—Platinum(II) oxide (2 mg, 8.8 μmol) was added to a solution of hydroxy enone **26** (100 mg, 0.357 mmol) in ethanol (2.0 cm^3). The mixture was stirred under a hydrogen atmosphere (1 atm) at 25 °C for 2 h. The reaction mixture was filtered through silica gel to remove the PtO_2 catalyst, and evaporated *in vacuo* to give the saturated hydroxy ketone **30** (94 mg, 93%) as a colourless solid which was recrystallized from $CHCl_3$ as colourless needles, m.p. 134–136 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3616, 3458, 2965, 1736 and 1071; δ_H(300 MHz; $CDCl_3$) 4.74 (2 H, m), 3.93 (1 H, dd, *J* 10.4, 6.2), 2.38–2.12 (4 H, m), 2.06 (1 H, dd, *J* 12.4, 8.1), 1.84 (1 H, br dd, *J* 14.9, 6.0), 1.69–1.41 (2 H, m), 1.54 (3 H, s), 1.31 (3 H, s) and 0.98 (9 H, s); δ_C(75 MHz; CD_3OD) 213.28 (s), 112.87 (s), 81.30 (d), 80.89 (d), 76.26 (d), 63.34 (s), 57.66 (d), 40.72 (t), 39.40 (t), 35.49 (t), 32.50 (s), 27.91 (q), 27.63 (q) and 25.32 (q); *m/z* (CI) 283 (M + 1), 267, 265, 225 and 207; (Found: C, 68.08; H, 9.27. Calc. for $C_{16}H_{26}O_4$: C, 68.04; H, 9.29%).

PtO_2 *Reduction of Hydroxy Enone* **25**.—Platinum(II) oxide (2 mg, 8.8 μmol) was added to a solution of hydroxy enone **25** (25 mg, 0.09 mmol) in ethanol (1.0 cm^3). The mixture was stirred under a hydrogen atmosphere (1 atm) at 25 °C for 3 d. The reaction mixture was filtered through silica gel to remove the PtO_2 catalyst, and the filtrate was evaporated to give a mixture of the saturated hydroxy ketones (20 mg, 98%) *trans*-**32** (33%) and *cis*-**32** (41%) determined by GC analysis. The *cis*-product was not purified.

(±)-(7S,8R)-4-*Benzoyl*-2-tert-*butyl*-7,8-*isopropylidenedioxyspiro*[4.4]*nonan*-1-*one* **31**.—A solution of the alcohol **30** (14 mg, 0.050 mmol) in chloroform (1.0 cm^3) was treated with pyridine (300 cm^3) and benzoyl chloride (160 cm^3, 1.4 mmol) and heated at reflux for 16 h. The solution was diluted with Et_2O (5.0 cm^3) and water (1.0 cm^3) and the layers were separated. The organic layer was washed with saturated aqueous Na_2CO_3 (5 × 5 cm^3), dried ($MgSO_4$) and chromatographed on a 1.0 mm silica plate, eluting with 10% EtOAc/hexanes to give the benzoate **31** (17.4 mg, 91%) as a white crystalline solid. Recrystallized from EtOH/H_2O gave colourless needles, m.p. 112–113 °C; ν_{max}-$(CHCl_3)$/ cm^{-1} 2961m, 1743s, 1717s, 1268m, 1112s and 1071s; δ_H(500 MHz; C_6D_6) 8.09 (2 H, dt, *J* 8.1, 1.9), 7.11 (1 H, dt, *J* 7.5, 1.74), 7.05 (2 H, tt, *J* 7.4, 1.5), 5.02 (1 H, dd, *J* 9.4, 6.4, H_D), 4.77 (1 H, dd, *J* 12.4, 6.8), 4.57 (1 H, dd, *J* 12.9, 6.7), 2.54 (1 H, dd, *J* 13.9, 5.9), 2.26 (1 H, ddd, *J* 14.1, 7.0, 1.4), 2.07 (1 H, ddd, *J* 12.3, 8.5, 6.4, H_C), 1.95 (1 H, dd, *J* 13.6, 5.5), 1.80 (1 H, ddd, *J* 13.9, 6.9, 1.4), 1.57 (3 H, s), 1.53 (1 H, d, *J* 8.5, H_A), 1.43 (1 H, dd, *J* 12.2, 9.4, H_B), 1.19 (3 H, s) and 0.86 (9 H, s); δ_C(75 MHz; C_6D_6) 212.28 (s), 165.73 (s), 133.35 (d), 130.44 (s), 129.71 (d), 128.83 (d), 113.19 (s), 81.74 (d), 81.41 (d), 78.62 (d), 62.09 (s), 56.30 (d), 41.33 (t), 37.24 (t), 32.56 (s), 28.72 (t), 28.02 (q), 27.79 (q) and 25.57 (q); *m/z* (EI) 386 (M^+), 370, 189, 207, 133 and 105 (base); (Found: C, 70.99; H, 7.81. Calc. for $C_{23}H_{30}O_5$: C, 71.46; H, 7.83%).

The stereochemistry of the γ-benzoyl ketone **31** was determined by an NOE experiment.

Acknowledgements

The National Institutes of Health and the Welch Foundation are thanked for their support. Dr. Vince Lynch (University of Texas at Austin) is thanked for the X-ray structural determinations.

References

1 R. T. Major. *Science*, 1967, **157**, 1270.
2 P. Michel and D. Hosford, *Ginkgolides—Chemistry, Biology, Pharmacology and Clinical Perspectives*, J. R. Prous Science Publishers, Barcelona, 1988, vol. 1, p. 1.
3 P. Braquet, *Ginkgolides—Chemistry, Biology, Pharmacology and Clinical Perspectives*, J. R. Prous Science Publishers, Barcelona, 1988, vol. 1, p. xv.
4 K. Nakanishi, *Pure Appl. Chem.*, 1967, **14**, 89.
5 N. Sakabe, S. Takada and K. Okabe, *J. Chem. Soc., Chem. Commun.*, 1967, 259.
6 K. Weinges, M. Hepp and H. Jaggy, *Liebigs Ann. Chem.*, 1987, **6**, 521.
7 K. Nakanishi, K. Habaguchi, V. Nakadaira, M. C. Woods, M. Maruyama, R. T. Major, M. Alauddin, A. R. Patel, K. Weinges and W. Bähr, *J. Am. Chem. Soc.*, 1971, **93**, 3544.
8 E. J. Corey, A. Y. Gavai, *Tetrahedron Lett.*, 1989, **30**, 6959; E. J. Corey, M.-C. Kang, M. C. Desai, A. K. Ghosh and I. N. Houpis, *J. Am. Chem. Soc.*, 1988, **110**, 649.
9 K. Weinges, W. Bähr and P. Rao, *Justus Liebigs Ann. Chem.*, 1971, **753**, 100.
10 E. B. Vilhauer and R. C. Anderson, *J. Org. Chem.*, 1987, **52**, 1186.
11 M. T. Crimmins and J. B. Thomas, *Tetrahedron Lett.*, 1989, **30**, 5997.
12 E. J. Corey and A. K. Ghosh, *Tetrahedron Lett.*, 1988, **29**, 3205.
13 E. J. Corey and A. Y. Gavai, *Tetrahedron Lett.*, 1988, **29**, 3201.
14 E. J. Corey and K. Kamiyama, *Tetrahedron Lett.*, 1990, **31**, 3995.
15 E. J. Corey and A. V. Gavai, *Tetraedron Lett.*, 1989, **30**, 6959.
16 E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989, p. 89.
17 M. F. Semmelhack, J. S. Foos and S. Katz, *J. Am. Chem. Soc.*, 1973, **95**, 7325.
18 E. Piers, K. F. Cheng and I. Nagakura, *Can. J. Chem.*, 1982, **60**, 1256.
19 A. J. Bloodworth and H. J. Eggelte, *Singlet Oxygen*, vol. 2, CRC Press, Boca Raton, 1985, ch. 4.
20 A. Scettri, G. Piancatelli, M. D'Auria and G. David, *Tetrahedron*, 1979, **35**, 135.
21 R. G. Salomon, M. F. Salomon and D. J. Coughlin, *J. Am. Chem. Soc.*, 1978, **100**, 660; R. G. Salomon, D. B. Miller, M. G. Zagorski and D. J. Coughlin, *J. Am. Chem. Soc.*, 1984, **106**, 6049; R. G. Salomon, *Acc. Chem. Res.*, 1985, **18**, 294.
22 S. Mitsui, Y. Senda and H. Saito, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 694; H. W. Thompson, E. McPherson and B. L. Lences, *J. Org. Chem.*, 1976, **41**, 2903; G. Stork and D. E. Kahne, *J. Am. Chem. Soc.*, 1983, **105**, 1072; D. A. Evans and M. M. Morrissay, *Tetrahedron Lett.*, 1984, **25**, 4637.
23 W. B. Smith and C. Gonzales, *J. Org. Chem.*, 1963, **28**, 3541.

Paper 1/02791C
Received 10*th June* 1991
Accepted 30*th July* 1991