From Griseofulvin to Substituted Xanthones via Deoxygrisans

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Abstract

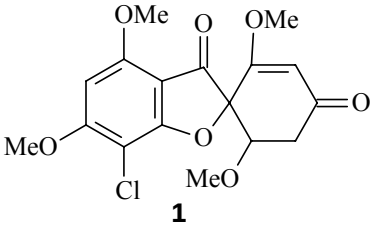
Substituted xanthones have broad spectrum of biological activities. In our search for bioactive natural and synthetic xanthones, 9-substituted xanthenes, and substituted dibenzoxanthenes, the thermal-induced rearrangement of deoxygrisans **8** and **22** and the synthesis of xanthones **10**, **15**, and **16** were undertaken. Deoxygrisan **8** was synthesised from dihydroxydiphenylmethane **7** while deoxygrisan **22** was synthesised from dihydroxydinaphthylmethane **21**. Thermolysis of **8** and **22** gave xanthone **10** and dibenzoxanthene **23**, respectively. Reduction of xanthone **10** gave xanthydrol **19** while oxidation of dibenzoxanthene **23** gave 9-methoxydibenzoxanthene **25** via dibenzoxanthylium cation **24**.

Key words: Deoxygrisans, substituted xanthones, xanthenes, thermolysis

Introduction

Natural and synthetic substituted xanthones have been shown by various investigators to have broad spectrum of biological activities namely antimalarial (Ignatushchenko, *et al*, 2000; Hay, *et al*, 2004), anti-inflammatory (Lin, *et al*, 1996), anti-tumor (Pedro, *et al*, 2002), antimycobacterial (Pickert, *et al*, 1998), antiallergic (Pfister, *et al*, 1972), cardiovascular (Chen, *et al*, 1993) and neuropharmacological effects (Marona, 1998).

Spirodienones of the types **2** and **3** are referred to as grisans and deoxygrisans, respectively, because of their structural similarities to griseofulvin **1**, an antimycotic agent from *Penicillium griseofulvum*



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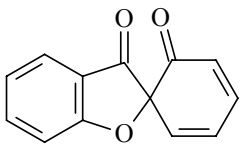

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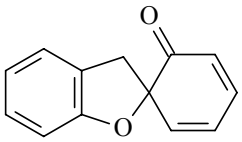

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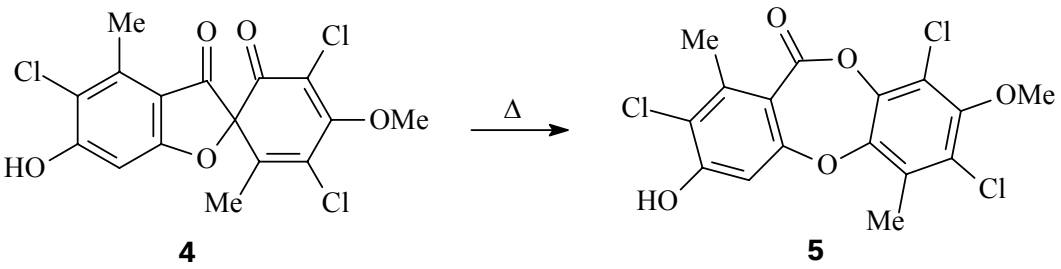
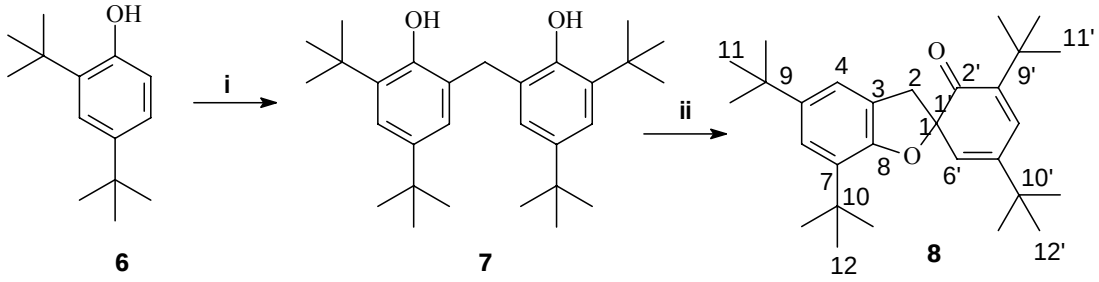
Deoxygrisans were synthesised and studied (Shode, 1980) in order to shed light on the thermal rearrangement of grisans (Sharpe, 1972; Rey, 1973). Generally, grisans of the type **2** undergo thermal rearrangement to depsidones upon heating (Sharpe, 1972). For example, grisan **4**, upon heating at its melting point, rearranges to depsidone **5**.



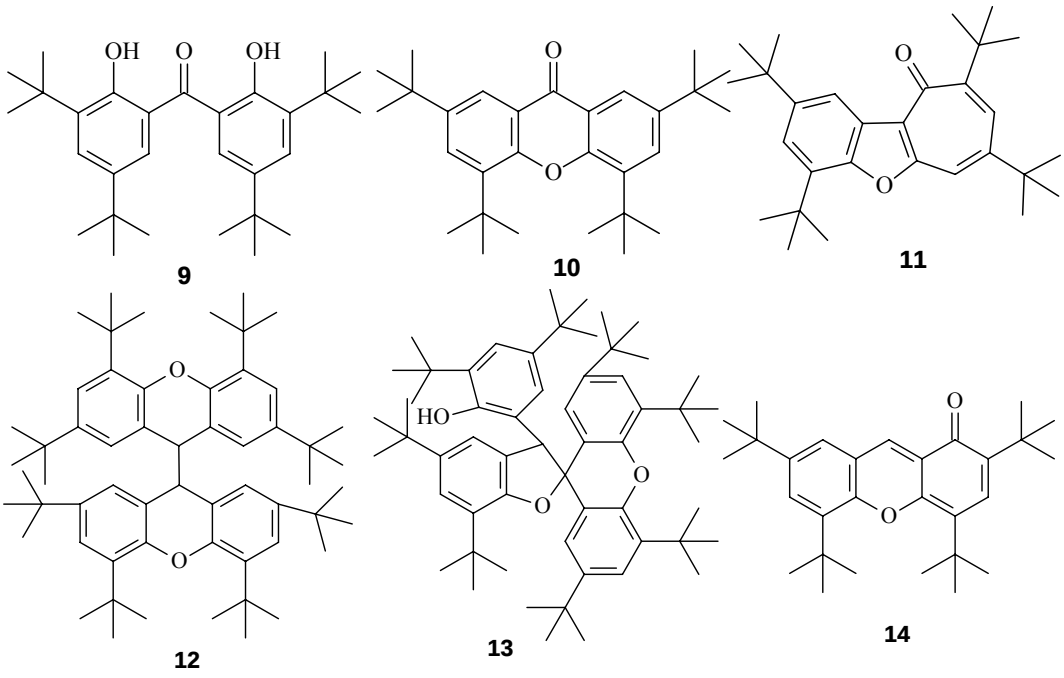
4 **5**

Deoxygrisan **8** was synthesised from dihydroxydiphenylmethane **7** which in turn was synthesised from 2,4-di-*tert*-butylphenol **6** in good yield (Muller, *et al*, 1961)(Scheme 1). Thermolysis of **8** followed by repeated column chromatography of the melt afforded seven compounds namely dihydroxydiphenylmethane **7**(4%), dihydroxybenzophenone **9**(18%), xanthone **10**(8%), benzofuranotropone **11**(7%), bixanthyl **12**(4%), spiroxanthyl **13**(10%), and isoxanthone **14**(1.5%)(Shode, 1980).



6 **7** **8**

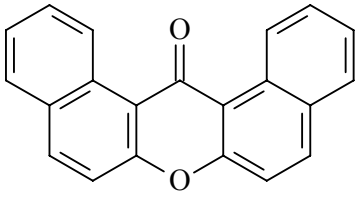
Scheme 1. Synthesis of deoxygrisan **8.** [i. HCHO/H^+ ii. KFeCN6/KOH_{aq}]



9 **10** **11**

12 **13** **14**

The search for bioactive xanthones and their derivatives made us to re-visit the thermal rearrangement of deoxygrisans specifically to produce more of **10** and xanthones **15** and **16** as precursors for their corresponding 9-substituted xanthenes as well as for biological activity evaluation. The results of our studies are reported as follows.



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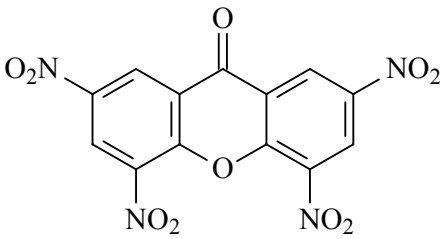

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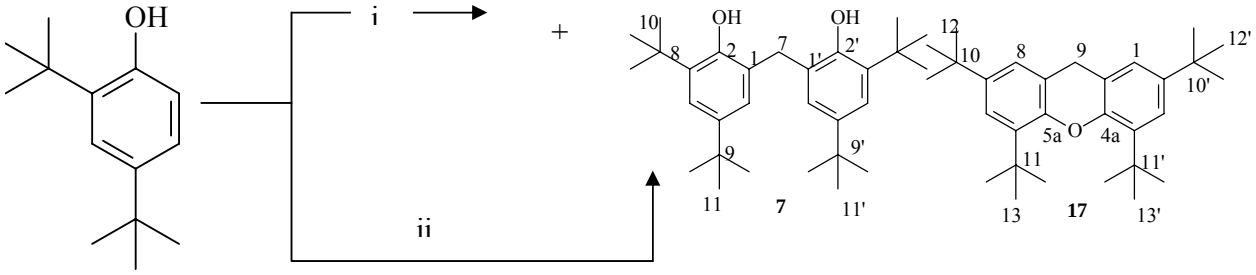
Results and Discussion

A mixture of dihydroxydiphenylmethane **7** and xanthene **17** was produced when 2,4-di-*tert*-butylphenol **6** was reacted with formalin in the presence of phosphoric acid and glacial acetic acid at 4°C for 5 days (Scheme 2)(Khoramadi-zad, *et al,* 2002). In a similar reaction, compound **7** was formed exclusively when the reaction mixture was refluxed overnight (Scheme 2). The formation of xanthene **17** from compound **6** at low temperature was a surprise but at the same time, a delightful experience to us. A critical investigation of this reaction is necessary in order to establish the mechanism of the reaction and its applicability in the synthesis of xanthenes.



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Scheme 2. Formation of compounds **7** and **17**.

i. $HCHO/H_3PO_4/AcOH$, 4°C; ii. $HCHO/H_3PO_4/AcOH$, reflux

Deoxygrisan **8** was produced from **7** and thermolysed neat. Repeated column chromatography of the melt gave xanthone **10** in 8% yield. Having obtained xanthone **10**, other synthetic methods were used to synthesise it in order to improve the yield. These methods are enumerated in Table 1.

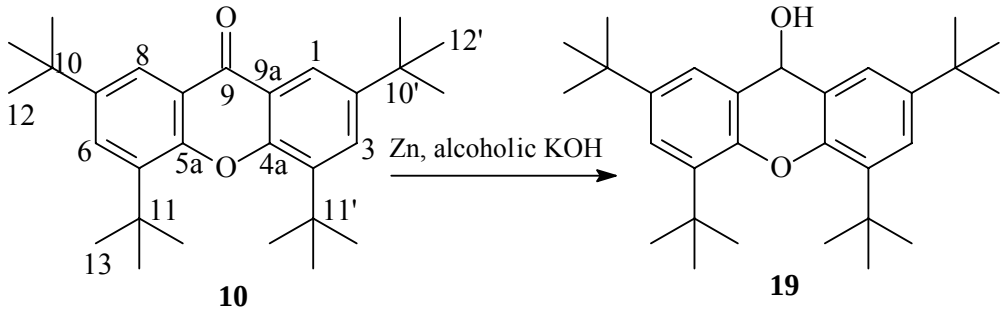
Table 1. Some synthetic methods of xanthone **10**.

Method	Reagents	Precursor	Yield
1	O_2,DMSO/Bu^{t}OH(4:1)/Bu^{t}OK, rt	**17**	quantitative
2	SeO_2	**17**	quantitative
3	$Na_2Cr_2O_7$/AcOH	**17**	quantitative
4[a]	SeO_2	**18**[b]	30%

[a] This is the first example of SeO_2 induced oxidative cyclisation of 2'-hydroxy-2'-methoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane. A provisional RSA patent no. 2003/9186 has been granted.

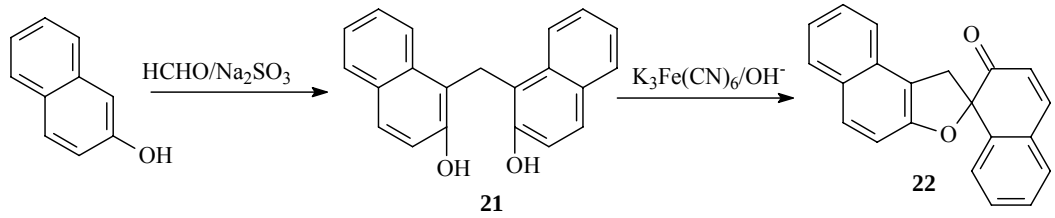
[b] This compound is 2'-hydroxy-2'-methoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane

Xanthone **10** was reduced to 9-hydroxyxanthene **19** using Zn powder in alcoholic KOH. Other 9-substituted-tetra-*tert*-butylxanthenes will be produced from compound **19**.

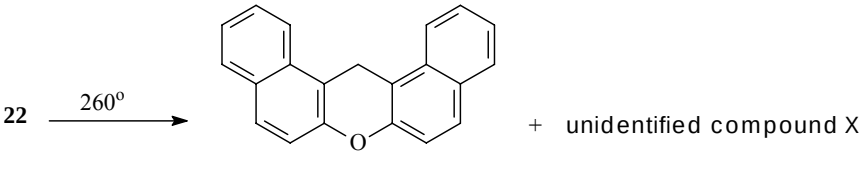


10 **19**

Deoxygrisan **22** was produced from dihydroxydinaphthylmethane **21** which in turn was made from 2-naphthol, in 50% yield. Its thermolysis yielded dibenzoxanthene **23** and an unidentified compound. The expected dibenzoxanthone **15** was not obtained. Oxidation of **23** produced a red solid which, on addition of methanol, gave compound **25** in quantitative yield. Its is conceivable that the red solid could be compound **24** or its equivalent which after nucleophilic attack by methanol gave the methoxy-compound **25**.



21 **22**



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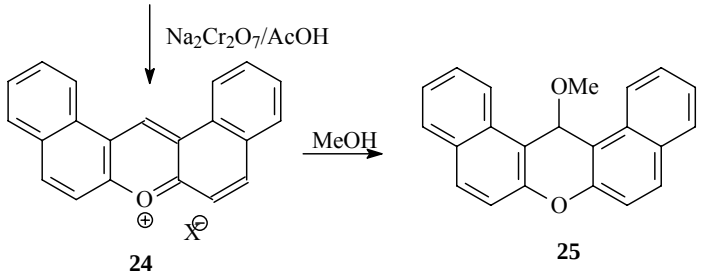

24 **25**

Conclusion

Deoxygrisans **8** and **22** have been synthesised and their thermolyses have yielded xanthone **10** and dibenzoxanthene **23**, respectively. Xanthone **10** has been reduced to xanthydrol **19** which could be exploited to synthesise 9-substituted xanthenes for various applications in medicine and polymer industry. Oxidation of dibenzoxanthene **23** has yielded 14-methoxy-14*H*-dibenzo[a,j]xanthene **25** via a dibenzoxanthylium cation. This reaction will be exploited in the synthesis of other derivatives of dibenzoxanthenes.

Experimental

General experimental procedures

Melting points (uncorrected) were determined on a Stuart Scientific SMP1 apparatus. IR spectra (KBr) were recorded on a Nicolet Impact 420 spectrophotometer. NMR spectra (both 1D and 2D) were obtained on a Varian 300 (300 MHz) spectrometer, using the residual solvent peaks as internal standards. HR-EIMS and LR-EIMS were determined on a Kratos 9/50 HRMS instrument and a MAT Finnigan GCQ spectrometer, respectively. Column chromatography was carried out using Merck Si gel 60 (70-230 mesh). Analytical TLC was carried out on pre-coated aluminium plates using Merck Si gel F254; the plates were visualised under UV light (λ 254 and 366nm) and by spraying with anisaldehyde/H_2SO_4 reagent, followed by gentle heating.

2,2'-Dihydroxy-3,3'5,5'-tetra-*tert*-butyldiphenylmethane (7)

A mixture of 2,4-di-*tert*-butylphenol (100g, 0.5 mol), conc. HCl (100ml) and formalin (40%, 37.5ml) was stirred at room temperature for 72 h. It produced a thick white solid. The solid was recrystallised from glacial acetic acid to give **7** as colourless crystals (73g. 73%); mp 136-137° C (Lit. 142-143°C) (Muller, *et al*, 1961) (Found: $M^{+\cdot}$ 424. $C_{29}H_{44}O_2$ requires M 424).

IR ν_{max}: 3500 and 1605 $cm^{-1;}$ ^{1}HNMR ($CDCl_3$): δ 7.18 (2H, *d*, J = 2.0 Hz, 2 x ArH, H-4 and H-4'), 7.14 (2H, *d*, J = 2.0 Hz, 2 x ArH, H-6 and H-6'), 5.88 (2H, s, 2 x OH, 2-OH and 2'-OH), 3.94 (2H, s, 2 x H-7), 1.40 (18H, s, 9 x H-10 and 9 x H-10') and 1.28 (18H, s, 9 x H-11 and 9 x H-11'). ^{13}C NMR ($CDCl_3$) δ135.49 (*s*, C-1 and C-1'), 149.88 (*s*, C-2 and C-2'), 142.97 (*s*, C-3 and C-3'), 125.18 (*d*, C-4 and C-4' or C-6 and C-6'), 126.07 (*s*, C-5 and C-5'), 122.56 (*d*, C-6 and C-6' or C-4 and C-4'), 32.53 (*t*, C-7), 34.64 (*s*, C-8 and C-8' or C-9 and C-9'), 34.28 (*s*, C-9 and C-9' or C-8 and C-8'), 31.59 (*q*, C-10 and C-10' or C-11 and C-11'), 30.06 (*q*, C-11 and C-11' or C-10 and C-10').

3',5,5',7-Tetra-*tert*-butyl-spiro[benzofuran-2(3H), 1'-[3,5]cyclohexadien]-2'-one (deoxygrisan) (8)

A solution of dihydroxydiphenylmethane **7** (30g, 0.15 mol) in toluene (100ml) was added over 1h to a stirred solution of potassium ferricyanide (65.8g, 0.2 mol) and potassium hydroxide (8g, 0.15 mol) in water (600ml) under nitrogen at room temperature. The solution turned green and eventually yellow during further stirring (ca. 2h). The reaction mixture was then extracted into ether (4 x 100ml), washed with water, and dried (anhydrous Na_2SO_4). Evaporation of the organic solvents gave a light brown oil which crystallised from methanol giving compound **8** as yellow crystals (25.9g, 87%), mp 154-155° (lit. 153-155°)(Muller, *et al*, 1961) (Found: $M^{+\cdot}$ 422. $C_{29}H_{42}O_2$ requires M 422);

UV λ_{max} (cyclohexane): 230 (ε 10,700), 283 (ε 5,200), 290 (ε 5,600), and 310 nm; IR ν_{max} cm^{-1}: 1690 and 1660; ^{1}H NMR ($CDCl_3$): δ 7.12 (1H, *d*, J = 1.5Hz, H-4 or H-6), 6.98 (1H, *d*, J = 1.5 Hz, H-6 or H-4), 6.85 (1H, *d*, J = 3.0Hz, H-4' or H-6'), 6.18 (1H, *d*, J = 3.5 Hz, H-6' or H-4'), 3.45 and 2.99 (2H, *q*, J_{AB} = 16.6 Hz, H_A-2 and H_B-2), 1.40, 1.28, 1.24, and 1.12 (36H, s, 4 x Bu^t).

Thermolysis of deoxygrisan 8

Deoxygrisan **8** (1g, 2.4 mmol) was heated neat at 189-192° under nitrogen for 3h. The resulting dark-red melt was dissolved in chloroform. Repeated chromatography of the residue of the above solution afforded xanthone 10 (79mg) as colourless crystals from methanol, mp 161-162°. It showed a strong light-blue fluorescence on silica gel plate under UV illumination. (Found: M+. 420. $C_{29}H_{40}O_2$ requires M 420); UV λ_{max} ($CHCl_3$): 354 (ε 7,500),

344 (ε6,900) and 274 nm (ε 11,800); 1H NMR ($CDCl_3$): δ8.32 (2H, *d*, J = 1.5 Hz, H-1 and H-8), 7.86 (2H, *d*, J = 1.5 Hz, H-3 and H-6), 1.65 (18H, *s*, 9 x H-12 and 9 x H-12'), 1.41 (18H, *s*, 9 x H-13 and 9 x H-13'); ^{13}C NMR ($CDCl_3$): δ178.3 (*s*, C-9), 145.8 (*d*, C-1 and C-8), 121.0 (*s*, C-2 and C-7), 121.9 (*d*, C-3 and C-6), 130.3 (*s*, C-4 and C-5),154.3 (*s*, C-4a and C-5a), 138.2 (*s*, C-8a and C-9a), 35.4 (*s*, C-10 and C-10' or C-11 and C-11'), 34.8 (*s*, C-11 and C-11' or C-10 and C-10'), 31.4 (*s*, C-12 and C-12' or C-13 and C-13'), 31.0 (*s*, C-13 and C-13' or C-12 and C-12').

Xanthene 17 from 2,4-di-*tert*-butylphenol 6

A mixture 2,4-di-tert-butylphenol 6 (8g, 0.034 mol), formalin (2ml), glacial acetic acid (20ml) and phosphoric acid (4 drops) was kept at 5°C for 5 days. The reaction was monitored by TLC which showed three spots at day 5. The reaction was quenched with water and the solid filtered. Chromatography of the solid gave the starting compound 6, xanthene **17**, and compound **7**. Xanthene **17** was recrystalised from methanol as colourless crystals (mp 129°C) (Found: M+. 406. $C_{29}H_{42}O_2$ requires M 406); ^1H NMR ($CDCl_3$): δ7.27 (2H, *d*, J = 2.1 Hz, H-1 and H-8), 6.88 (2H, *d*, J = 2.1 Hz, H-3 and H-6), 4.82 (2H, b*d*, J = 5.8 Hz, 2 x H-9), 1.41 (18H, *s*, 9 x H-12 and 9 x H-12'), 1.27 (18H, *s*, 9 x H-13 and H-13'); ^{13}C NMR ($CDCl_3$): δ153.13 (*s*, C-4a and C-5a), 136.53 (*s*, C-8a and C-9a), 124.13 and 124.08 (*d*, C-1 and C-8), 123.96 (*s*, C-2 and C-7), 122.63 and 122.59 (*d*, C-3 and C-6), 141.62 (*s*, C-4 and C-5), 65.92 (*t*, C-9), 34.96 (*s*, C-10 and C-10'), 34.21 (*s*, C-11 and C-11'), 31.62 (*q*, C-12 and C-12'), 29.68 (*q*, C-13 and C-13').

Xanthone 10 from 2-hydroxy-2'-methoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane 18

An intimate mixture of **18** (4g, 9.1 mmol) and selenium dioxide (2g 18 mmol) was heated at 200°C for 30min. The cooled melt was diluted with water (20ml) and extracted into ether (2 x 100ml). The etheal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solution followed by column chromatography and crystallisation from methanol gave xanthone **10** (1.1g, 30%) as colourless needles, mp 161-162°C. These crystals were identical with an authentic sample of **10**.

Oxidation of xanthene 17

a) Using O_2, DMSO/Bu^tOH(4:1)/Bu^tOK:

Oxygen was passed into a stirred solution of xanthene **17** (0.5g, 1.2 mmol) in DMSO/Bu^tOH (4:1) (25ml) containing potassium *tert*-butoxide (0.15g, 1.34 mmol) at room temperature. After the uptake of oxygen had ceased, the reaction mixture was poured into water (50ml) and extracted into ether (2 x 100ml). The ethereal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent followed by crystallisation of the residue from methanol gave xanthone **10** in quantitative yield.

b. Using SeO_2:

An intimate mixture of xanthene **17** (0.5g, 1.2 mmol) and selenium dioxide (0.5g, 4.5 mmol) was heated at 160°C for 24h. The cooled melt was diluted with water (10ml) and extracted into ether (2 x 100ml). The ethereal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent followed by crystallisation of the residue from methanol gave xanthone **10** in quantitative yield.

c. Using sodium dichromate in glacial acetic acid:

To a suspension of xanthene **17** (0.1g, 0.25 mmol) in glacial acetic acid (10ml) was added sodium dichromate (0.2g, 0.76 mmol) in one portion. The mixture was heated on a steam

bath for 2h and the cooled reaction mixture was poured into water (50ml). The insoluble solid was filtered off and recrystallised from methanol to give xanthone **10** as colourless needles, mp 161-162°C, in quantitative yield.

Reduction of xanthone 10

Deoxygrisan 22

Deoxygrisan **22** was synthesised from 2,2' dihydroxydinaphthylmethane by the method used for deoxygrisan **8**. The yield was 50%.

Thermolysis of deoxygrisan 22

Deoxygrisan **22** (1g, 3.36 mmol) was heated neat at 260°C for 15 min and the resulting dark brown melt was chloroform. TLC examination of the chloroform solution showed that it contained two major components. Preparative TLC of the solution using chloroform-hexane mixture (3:7) as eluent, gave compound **23** (4%), 14H dibenzo[a,j]xanthene, and compound **X** (40%). Compound **23** crystallised from methanol as colourless needles, mp 204-205°C (lit. 205-206°C) (Casiraghi, *et al*., 1974) (Found: $M^{+\cdot}$ 282. $C_{21}H_{14}O$ requires M 282.); ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, *d*, J = 8.0 Hz, 2 x Ar-H), 7.80 (2H, *d*, J = 8.0 Hz, 2 x Ar-H), 7.72 (2H, *d*, J = 8.9 Hz, 2 x Ar-H), 7.60 (2H, *t*, J = 8.0 Hz, 2 x Ar-H), 7.40 (2H, *t*, J = 8.0 Hz, 2 x Ar-H), 7.26 (2H, *d*, J = 8.0 Hz, 2 x Ar-H), and 4.52 (2H, *s*, -CH_2-).

Oxidation of dibenzoxanthene 23

A mixture of **23** (0.4g, 1.4 mmol), sodium dichromate (0.5g, 1.9 mmol), and acetic acid (50ml) was heated on a steam-bath for 30 min. The reaction mixture was poured into water and the resultant red solid was filtered off and washed with water. Treatment of the red solid with methanol gave 14-methoxy-14H-dibenzo[a,j]xanthene **25** as colourless solid (250mg, 58%), mp 176-177°C (Found: $M^{+\cdot}$ 312. $C_{22}H_{16}O_2$ requires M 312); ^{1}H NMR ($CDCl_3$): δ8.50 (2H, *d,* J = 8.7 Hz, 2 x Ar-H), 7.82 (4H, *d*, J = 8.7 Hz, 4 x Ar-H), 7.65 (2H, *t*, J = 7.3 Hz, 2 x Ar-H), 7.50 (2H, *t*, J = 7.3 Hz, 2 x Ar-H), 7.35 (2H, *t*, J = 8.7 Hz, 2 x Ar-H), 7.19 (1H, *s*, Ar-CH-), and 2.60 (3H, *s*, -OMe).

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